Scientific Advisory Committee on Nutrition

Lower carbohydrate diets for adults with type 2 diabetes

Annexes

Contents

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

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

Energy	2500 kcal/day for men; 2000 kcal/day for women[6]
Proteins[2]	0.75g of proteins per kilogram of bodyweight[7]
Total fats[3]	Reduce to about 35% of dietary energy[8]
of which	
Saturated fats[3]	Reduce to no more than about 10% of dietary energy[9]
MUFA[3]	No specific recommendations[10]
n-6 PUFA[3]	No further increase in the average intakes and the proportion of the population consuming in excess of about 10% of energy should not increase[11]
Linoleic acid[2]	Provide at least 1% of total energy
Long chain n-3 PUFA[4]	Increase from 0.2 g/day to 0.45 g/day[12]
Alpha linolenic acid[2]	Provide at least 0.2% of total energy
Trans fats[3]	Provide no more than about 2% of dietary energy
Carbohydrates[5]	Approximately 50% of total dietary energy
of which	
Free sugars[5]	Should not exceed 5% of total dietary energy
Dietary fibre[5]	30g/day[13]

[1]Values are expressed as proportions of either total (dietary) energy or dietary energy, depending on the source report.
[2]COMA Dietary Reference Values for Food Energy and Nutrients for the United Kingdom (1991).
[3]COMA Nutritional Aspects of Cardiovascular disease (1994) recommendations.
[4] SACN Advice on fish consumption benefits and risks (2004). SACN endorsed the population recommendation (including pregnant women) to eat at least two portions of fish per week, of which one should be oily. Two portions of fish per week, one white and only oily, contain approximately 0.45 g/day long chain n-3 PUFA.
[5] SACN Carbohydrates and Health (2015) - recommendations for population aged 2 years and over.
[6] Figures are based on the UK government advice. They are not in line with SACN Dietary Reference Values for energy (2011). SACN recommended that DRVs for adult men and women should be 2605 kcal/day and 2079 kcal/day respectively; these recommendations were not adopted by the government because of issues of overweight and obesity in the UK.
[7]Reference Nutrient Intake (RNI) for adults aged 19 to 50 years (these vary depending on age, sex and whether pregnant or breastfeeding).
[8]COMA Nutritional Aspects of Cardiovascular disease (1994) - recommends a reduction in the average contribution of total fat to dietary energy in the population to about 35%.
[9]COMA Nutritional Aspects of Cardiovascular disease (1994) recommends that the [population] average contribution of saturated fatty acids to [total] dietary energy be reduced to no more than about 10%. This value was based on total dietary energy (which includes any intake from alcohol). The COMA DRV report 1991 noted

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

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

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

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

[13]DRV for adults aged 19 years and over; DRVs vary depending on age.

Annex 2: Search strategy

Table A2.1: Details of literature search

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

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

Annex 3: Selection of studies

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

Studies		Reasons for exclusion/inclusion
1st screening		
1	Clifton P, Carter S, Headland M & Keogh J (2015) Low carbohydrate and ketogenic diets in type 2 diabetes. Curr Opin Lipidol 26(6):594-595.	Non-SR/MA/PA
2	D'Arrigo T (2007) Low-fat vs. low-carb. What really works? Diabetes Forecast. 60(7):16.	Non-SR/MA/PA
3	Dena MB, Lisa S, Jane H, Harlan MK, Ingram O, Christopher DG & Dawn MB (2003) Efficacy and safety of low-carbohydrate diets: a systematic review. JAMA 289(14):1837.	Included participants with/without T2D. Studies that included individuals with T2D assessed weight loss but duration less than 12 months
4	Dyson PA (2008) A review of low and reduced carbohydrate diets and weight loss in type 2 diabetes. J Human Nutr Diet. 21(6):530-538.	Non-SR/MA/PA
5	Haugen H-K (2014) The effectiveness of a low-carbohydrate diet in management of type 2 diabetes-A systematic review of the current literature. Høgskolen i Oslo og Akershus.	Master's thesis
6	Julienne KK, Darby EG, Timothy EC, Edward WL, Mary A & Karen LM (2007) Restricted-carbohydrate diets in patients with type 2 diabetes: a meta-analysis. J Am Diet Assoc. 108:91	Same study already included (Kirk et al 2008)
7	Santos F, Esteves S, da Costa Pereira A, Yancy Jr W & Nunes J (2012) Systematic review and meta-analysis of clinical trials of the effects of low carbohydrate diets on cardiovascular risk factors. Obes Rev. 13(11):1048-1066.	Participants without T2D
8	Moore H, Summerbell C, Hooper L, Cruickshank K, Vyas A, Johnstone P et al (2004). Dietary advice for treatment of type 2 diabetes mellitus in adults. Cochrane. (2):004097.	Same study (updated) already included (Nield et al 2007)

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

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

	Studies	Reasons for inclusion/exclusion
1	Sartorius K, Sartorius B, Madiba TE & Stefan C (2018) Does high-carbohydrate intake lead to increased risk of obesity? A systematic review and meta-analysis. BMJ Open. 8(2):e018449.	Excluded: participants without T2D
2	Kwon YJ, Lee HS & Lee JW (2017) Association of carbohydrate and fat intake with metabolic syndrome. Clin Nutr. S0261-5614(17):30233-30239.	Excluded: not RCT
3	Te Morenga L, Docherty P, Williams S & Mann J (2017) The Effect of a Diet Moderately High in Protein and Fiber on Insulin Sensitivity Measured Using the Dynamic Insulin Sensitivity and Secretion Test (DISST). Nutrients. 9(12).	Excluded: study length less than 3 months
4	Zinn C, McPhee J, Harris N, Williden M, Prendergast K & Schofield G (2017) A 12-week low-carbohydrate, high-fat diet improves metabolic health outcomes over a control diet in a randomised controlled trial with overweight defence force personnel. Appl Physiol Nutr Metab 42(11):1158-1164.	Excluded: participants without T2D
5	Juraschek SP, Miller ER 3rd, Selvin E, Carey VJ, Appel LJ, Christenson RH et al (2016) Effect of type and amount of dietary carbohydrate on biomarkers of glucose homeostasis and C reactive protein in overweight or obese adults: results from the OmniCarb trial. BMJ Open Diabetes Res Care. 4(1):e000276. eCollection 2016.	Excluded: participants without T2D
6	Ruiz-González I, Fernández-Alcántara M, Guardia-Archilla T et al (2016) Long-term effects of an intensive-practical diabetes education program on HbA1c and self-care. Appl Nurs Res. 13-18.	Excluded: participants with T1D
7	Nuttall FQ, Almokayyad RM & Gannon MC (2015) Comparison of a carbohydrate-free diet vs. fasting on plasma glucose, insulin and glucagon in type 2 diabetes. Metabolism. 64(2):253-262.	Excluded: study length less than 3 months
8	Tay J, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert GA et al (2015) Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial. Am J Clin Nutr. 102(4):780-790.	Excluded: already included in Schwingshackl et al 2018 and Huntriss et al 2018

	Studies	Reasons for inclusion/exclusion
9	Martens EA, Gatta-Cherifi B, Gonnissen HK & Westerterp-Plantenga MS (2014) The potential of a high protein-low carbohydrate diet to preserve intrahepatic triglyceride content in healthy humans. PLoS One. 9(10):e109617.	Excluded: participants without T2D
10	Sacks FM, Carey VJ, Anderson CA, Miller ER 3rd, Copeland T, Charleston J et al (2014) Effects of high vs low glycemic index of dietary carbohydrate on cardiovascular disease risk factors and insulin sensitivity: the OmniCarb randomized clinical trial. JAMA. 312(23):2531-2541.	Excluded: participants without T2D
11	Luley C, Blaik A, Reschke K, Klose S & Westphal S (2011) Weight loss in obese patients with type 2 diabetes: effects of telemonitoring plus a diet combination - the Active Body Control (ABC) Program. Diabetes Res Clin Pract. 91(3):286-292.	Excluded: RCT published before the most recent SR, MA or PA
12	Tay J, Thompson CH, Luscombe-Marsh ND, Wycherley TP, Noakes M, Buckley JD et al (2018) Effects of an energy-restricted low-carbohydrate, high unsaturated fat/low saturated fat diet versus a high-carbohydrate, low-fat diet in type 2 diabetes: A 2-year randomized clinical trial. Diabetes Obes Metab.	Included: RCT not included in the SR with the most up-to-date search period
13	Saslow LR, Daubenmier JJ, Moskowitz JT, Kim S, Murphy EJ, Phinney SD et al (2017) Twelve-month outcomes of a randomized trial of a moderate-carbohydrate versus very low-carbohydrate diet in overweight adults with type 2 diabetes mellitus or prediabetes. Nutr Diabetes. 7(12):304.	Included: RCT not included in the SR with the most up-to-date search period

Annex 4: Extracted data from 8 systematic reviews with meta-analyses

Table A4.1: Summary table of eligible meta-analyses/systematic reviews/pooled analyses

Study	Methods	Included studies	**Results of meta-analyses** (weighted mean difference in change (95% CI))	**Limitations and study conclusions** (assessed by authors)
van Zuuren et al (2018) **Aim**: To compare the effects of dietary carbohydrate restriction with fat restriction on markers of metabolic syndrome and quality of life in people with T2D. **Study design**: Systematic review and meta-analysis of RCTs and controlled clinical trials (CCTs) **Countries**: Australia (2), Europe (14), Israel (2), Japan (2), Mexico (1), US and Canada (15) **Funding source**: Supported by grants from the Dutch Diabetes Foundation and Sanofi **Declarations of interest:** None	**Search period**: To 21 March 2017 **Databases searched**: Medline, PubMed, Embase, Web of Science, Cochrane Library, Cochrane Central Register of Controlled Trials, Emcare, Academic Search Premier, ScienceDirect, Latin American and Caribbean Health Science Information Database, Indice Bibliografico Espanol en Ciencias de Salud **Language restrictions**: None reported **Inclusion criteria:** • RCTs and CCTs comparing low CHO diet (≤40% TE) with low fat diet (≤30% TE) over ≥4 wk in adults (aged ≥18 y) with T2D • Data from crossover trials with washout periods of ≥4 wk between interventions. In absence of adequate wash-out period, data from these trials only included if able to extract relevant data for 1st phase **Exclusion criteria:** • Studies that included people with other chronic diseases (except hypertension or CVD) or using systemic corticosteroids, or had any progressive disease requiring hospital care • Studies that included those with an eating disorder or other disease re special dietary requirements (except sodium restriction) **Outcome measures**:	**Number of studies**: 36 (n=2161) **Study duration**: 4 wk to 7 y **Study population**: • Age range (mean): 32 to 65 y • BMI: NR • Sex: male (4), female (3), both (29) • Ethnicity: NR • Medication: insulin (5 trials), oral hypoglycaemic agents (25 trials), anti-hypertensive drugs (3 trials), lipid-lowering medications (10 trials). In 5 trials, anti-diabetic drugs discontinued or reduced; 5 trials did not provide details of medication; 2 trials, no medication use • Physical activity: 8 trials encouraged an increase in physical activity **Intervention**: **LC** (CHO ≤40% TE) • Ranged from 10 to 40% TE/<20 to <130 g **Comparator**: Low fat diet (≤30% TE) • Fat intake ranged from 10 to 30% TE • CHO intake ranged from 45 to 70% TE	**Achieved CHO intake**: NR **Retention rates**: NR **Outcomes**: <u>HbA1c (%)</u> • ≥16 to 26 wk (n=7): -0.26 (-0.50, -0.02), p=0.04, I^2=59% • >26 wk (n=4): -0.36 (-0.58, -0.14, p=0.001), I^2=0% • 2 y (n=3): 0.02 (-0.37, 0.41), p=0.93, I^2=13% <u>Weight (kg)</u> • >26 wk (n=5): -0.19 (-1.65, 1.27), p=0.80, I^2=0% • 2y (n=2): -0.14 (-1.64, 1.35), p=0.85, I^2=0% <u>Lipid profile (mmol/L)</u> <u>LDL-cholesterol</u> • ≥16 to 26 wk (n=5): 0.02 (-0.09, 0.13), p=0.75, I^2=0% • >26 wk (n=4): -0.07 (-0.23, 0.09), p=0.41, I^2=50% • 2 y (n=2): 0.06 (-0.08, 0.21), p=0.39, I^2=0% <u>HDL-cholesterol</u> • ≥16 to 26 wk (n=6): 0.09 (-0.03, 0.22), p=0.13, I^2=91% • >26 wk (n=4): 0.11 (0.05, 0.18), p<0.0007, I^2=66% • 2 y (n=2): 0.12 (0.07, 0.17), p<0.00004, I^2=0% <u>Triacylglycerols</u>	**Limitations**: High degree of clinical and methodologic heterogeneity between included studies. Energy percentage of macronutrients in prescription diets differed considerably. Numerous other aspects differed considerably between studies including calorie content, exercise prescription, provision of food by study centre and reporting of actual food intake. Inconsistent methods of quantification and reporting of medication use precluded reliable statistical analyses of changes in drug doses. **Conclusions**: Low to moderate certainty of evidence that dietary carbohydrate restriction to maximum of 40% yields slightly better metabolic control of uncertain clinical importance than reduction in fat to a maximum of 30% in people with T2D.

Study	**Methods**	**Included studies**	**Results of meta-analyses** (weighted mean difference in change (95% CI))	**Limitations and study conclusions** (assessed by authors)
	• Primary: HbA1c, whole blood and fasting plasma glucose and lipids (triacylglycerol, LDL-c, HDL-c) • Secondary: weight, BMI, waist circumference, BP, quality of life **Statistical analysis**: • Random-effects model • Heterogeneity assessed using I^2 statistic (I^2>50% indicative of substantial heterogeneity) • Several sensitivity analyses to explore sources of heterogeneity and assess robustness of data • Repeated analyses using fixed-effects model to assess influence of small-study effects on results of any meta-analyses with evidence of between study heterogeneity **Study quality**: GRADE (to assess certainty of evidence) and Cochrane risk of bias tool. **Publication bias**: Paucity of studies evaluating any of the outcomes at same timepoints did not permit assessment.	**Authors' evaluation**: Risk of bias RCTs (n=33): 19, high risk; 14, unclear risk CCTs (n=3): moderate to serious	• ≥16 to 26 wk (n=6): -0.22 (-0.37, -0.08), p=0.002, I^2=41% • >26 wk (n=5): -0.25 (-0.47, -0.04), p=0.02, I^2=73% • 2 y (n=2): -0.19 (-0.32, -0.05), p=0.007, I^2=0%	

Study	Methods	Included studies	**Results of meta-analyses** (weighted mean difference in change (95% CI))	**Limitations and study conclusions** (assessed by authors)
Korsmo-Haugen et al (2018) **Aim**: To compare the effects of low carbohydrate diets on body weight, glycaemic control, lipid profile and blood pressure with those observed on higher carbohydrate diets in adults with T2D **Study design**: Systematic review and meta-analysis of RCTs **Countries**: Australia (5), Europe (5), Israel (3), Japan (1), New Zealand (1), North America (8) **Funding source**: No particular funding received for this work **Declarations of interest**: None	**Search period**: 1983 to 31 January 2016 **Databases searched**: Medline, Embase, CINAHL, Cochrane Central Register of Controlled Trials, Food Science Source and SweMed **Language restrictions**: English, Danish, Norwegian, Swedish **Inclusion criteria**: • RCTs with more than 3 m duration comparing diet below to a diet above 40% TE from CHO • Co-morbidities accepted but studies including individuals with impaired glucose tolerance and/or T1D only included if separate data provided for T2D individuals **Exclusion criteria**: • Complex interventions consisting of elements with potential to interfere with effect of dietary interventions (eg, parenteral administration or promotion of physical activity **Outcome measures**: • Weight, HbA1c, lipids (triacylglycerol, total cholesterol, LDL-c, HDL-c), BP, compliance to dietary intervention **Statistical analysis**: • Random effects model • Lipid profile qualitatively evaluated • Heterogeneity assessed using I^2 statistic (I^2>50% or value of Cochrane Q test <0.1 associated with heterogeneity) and subgroup analyses to explore possible reasons for heterogeneity • Post hoc subgroup and sensitivity analyses to explore impact of study	**Number of studies**: 23 (n=2178) **Study duration**: 3 m to >3 y **Study population**: • Age range: NR • BMI: NR • Sex: NR • Ethnicity: NR • Medication: insulin therapy (12 trials), anti-hypertensive drugs (8 trials), lipid-lowering drugs (10 trials) and oral hypoglycaemic agents such as metformin (10), sulfonylurea (10), thiazolidinedione (4) • Physical activity: several trials promoted general recommendations for physical activity **Intervention**: LCD (CHO <40% TE) • Ranged from 5 to 40% TE **Comparator**: Variety of diets: LFD (n=8), standard diabetes care (n=4), HCD (n=3), LPD(n=1), Med (n=2), HCD/LFD (n=2), High wheat fibre (n=1), Low GI (n=2), High GI (n=1) • CHO intake ranged between 42 and 65%. **Authors' evaluation**: Risk of bias: Overall, 3 studies classified as low risk, 10 as high risk and 10 as unclear risk Publication bias: Not indicated	**Achieved CHO intake** (mean): • 9/18 studies CHO intakes in LCD were 5 TE% within prescribed intakes • 7/9 trials that observed low compliance, participants were on very low CHO diets (CHO intakes of 5 to 22% TE) **Attrition rates**: LCD vs HCD • No detectable difference in attrition rates between diets: RR=1.08 (95% CI, 0.92, 1.27; I^2=0%) **Outcomes**: HbA1c (%) (n=16) • 3 to 6 m: -0.17 (-0.27, -0.08), p=NR, I^2=0% • >12 m: 0.00 (-0.10, 0.09), p=NR, I^2=0% Weight (kg) (n=17) • 3 to 6 m: -0.87 (-1.88, 0.15), p=NR, I^2=33%, • >12 m: 0.14 (-0.29, 0.57), p=NR, I^2=0% Sensitivity analyses showed less difference between LCDs and HCDs in studies with low risk of bias than in those with high risk of bias. Lipid profile (mmol/L) Total cholesterol (n=14) • 3 to 6 m: -0.06 (-0.41, -0.30); p=NR, I^2=57%, • >12 m: 0.07 (-0.04, 0.19); p=NR, I^2=23% LDL-cholesterol (n=15) • 3 to 6 m: -0.08 (-0.29, 0.14); p=NR, I^2=50%, • >12 m: 0.03 (-0.10, 0.16); p=NR, I^2=51% HDL-cholesterol (n=16) • 3 to 6 m: -0.01 (-0.07, 0.04); p=NR, I^2=15% • >12 m: 0.06 (-0.01, 0.13);p=NR, I^2=71%	**Limitations**: Whilst there appeared to be relatively high level of compliance with LCD, the ability to follow diet with very low CHO content was generally poor. Changes in medications over time may have blurred effects of differences in diet composition. **Conclusions**: The proportion of daily energy provided by CHO intake is not an important determinant of response to dietary management, especially when considering longer-term trials.

Study	Methods	Included studies	**Results of meta-analyses** (weighted mean difference in change (95% CI))	**Limitations and study conclusions** (assessed by authors)
	duration (6 vs 12 m), varying CHO content ((VLCD 21 to 70 g vs LC diet 30 to 40% TE) and risk of bias (low vs high) **Study quality**: GRADE and Cochrane risk of bias tool. **Publication bias**: Funnel plot		Triacylglycerols (n=16) • 3 to 6 m: -0.18 (-0.36,0.00); p=NR, I^2=20% • >12 m: -0.10 (-0.23, 0.03); p=NR, I^2=61%	

Study	Methods	Included studies	**Results of meta-analyses** (weighted mean difference in change (95% CI))	**Limitations and study conclusions** (assessed by authors)
Sainsbury et al (2018) **Aim**: To compare effectiveness of carbohydrate-restricted diets with high carbohydrate diets on glycaemic control in adults with diabetes mellitus **Study design**: Systematic review and meta-analysis of RCTs **Countries**: Austria (1), Australia (6), Canada (2), Czech Republic (1), Israel (2), Japan (2), New Zealand (1), Sweden (1), UK (2), US (7) **Funding source**: Did not receive specific grant from funding agencies in public, commercial or not-for-profit sectors **Declarations of interest**: None	**Search period**: 1 January 1980 to 31 August 2016 **Databases searched**: Medline, Embase, CINAHL, Global Health, Cochrane **Language restrictions**: English **Inclusion criteria**: • RCTs comparing CHO-restricted diet (≤45% TE) to high CHO diet (>45% TE) for glycaemic control in adults (≥18 y) with T1D or T2D • Studies had to report on change in HbA1c and minimum duration of 3 m • Studies of individuals with and without diabetes only included if ≥80% had diabetes or if subgroup analysis for this group **Exclusion criteria**: • 1 intervention group included a non-dietary weight loss component (eg physical activity advice, pharmaceutical intervention) while other group did not • Trials with meal replacement drinks or enteral feeds • Studies of prediabetes, gestational diabetes, pregnant or lactating women **Outcome measures:** • Primary: HbA1c • Secondary: weight; lipid profile (triacylglycerol, total cholesterol, LDL-c, HDL-c) **Statistical analysis:** • Random-effects model to estimate HbA1c change at 3, 6, 12, 24 months. Subgroup analysis conducted at each time-point to test	**Number of studies**: 25 (n=2412) **Study duration**: 3 to 24 m **Study population**: • Age range: 52 to 63 y • BMI: 25.8 to 38.1 kg/m^2 (median, 36.7) • Sex: male and female • Ethnicity: NR • Medication: majority on diabetes medication and/or insulin (1 study, diet treatment only); 11 studies allowed medication adjustments during intervention, with 5 reporting that they accounted for this in analysis • Physical activity: 15 studies included advice (to maintain or increase level) **Intervention**: CHO-restricted diet (≤45% TE) • LC group <130 g or <26% TE) (n=10) • Moderate carbohydrate (MC) (130 to 225 g or 26 to 45% TE) (n=15) (4 studies increased % of protein, 6 increased % of fat, 4 increased % of both protein and fat as proportion of TE, 14 studies isocaloric.) **Comparator**: • HCD (>225 g or >45% TE) **Authors' evaluation**:	**Achieved CHO intake**: NR **Retention rates**: • 3 to 6 m (n=10): >70% • 12 to 24 m: 50 to 69% (n=6); ≥70% (n=8) **Outcomes**: <u>HbA1c (%)</u> (WMD) (95% CI) • 3 m (n=12): -0.19 (-0.33, -0.05), p=0.008, I^2=28% • 6 m (n=11): -0.15 (-0.31, 0.02), p=0.09, I^2=50% • 12 m (n=12): -0.09 (-0.21, 0.03), p=0.12, I^2=16% • 24 m (n=3): -0.11 (-0.38, 0.15), p=NR, I^2=NR <u>Weight change 12 m (kg)</u> (n=10): -0.43 (-0.93, 0.07), p=0.09, I^2=0% <u>Lipid profile</u> • 3 to 6 m: no change or small reductions in total cholesterol and LDL-c on both CHO-restricted diet and HC diet. Greater increase in HDL-c for CHO-restricted diet in 9/20 studies with 3 reporting significant difference between groups • 12 to 24 m: 6 studies reported significantly greater increase in HDL-c and 5 reported significantly greater reductions in triacylglycerols for CHO-restricted diet compared with HC diet.	**Limitations**: Due to high risk of performance and detection bias and inconsistency in estimates of effect across studies, the evidence of HbA1c change was graded low quality High variability in methods of analysis across studies CHO quantity based on prescribed rather than actual intake Did not consider effect that altering fat and protein proportions may have had on outcomes **Conclusion:** Over the short term (3 to 6 m) CHO-restricted diets (≤45% TE) produce greater reductions in HbA1c than high CHO diets (>45% TE). These effects primarily driven by LC diets (<26% TE) with no significant difference between MC diets (26 to 45% TE) and HC diets. The short-term glycaemic improvements on LC diets appear to be due to weight loss with no significant difference in HbA1c change between diets when restricted to studies with equal weight loss.

Study	Methods	Included studies	**Results of meta-analyses** (weighted mean difference in change (95% CI))	**Limitations and study conclusions** (assessed by authors)
	effect of different levels of CHO restriction on HbA1c • Lipid profile qualitatively evaluated • Heterogeneity assessed using I^2 statistic **Study quality**: GRADE and Cochrane risk of bias tool. **Publication bias**: Funnel plot and Egger's test	Risk of bias: Overall 9 studies classified as being low risk, 7 at high risk and 9 at unclear risk Publication bias: Present at 3 m (p=0.005) but not at 6 m (p=0.125) or 12 m (p=0.052). Not tested at 24 m (n=3)		

Study	Methods	Included studies	**Results of meta-analyses** (weighted mean difference in change (95% CI))	**Limitations and study conclusions** (assessed by authors)
Huntriss et al (2018) **Aim**: To evaluate the clinical effect of a low carbohydrate diet in the management of type 2 diabetes **Study design**: Systematic review and meta-analysis of RCTs **Countries**: NR **Funding source**: Completed within a National Institute of Health Research funded Masters in Clinical Research **Declarations of interest**: None	**Search period**: until June 2016 **Databases searched**: Medline, Embase, CINAHL, Cochrane, ISRCTN, ProQuest, opengrey.eu. Reference lists of selected papers **Language restrictions**: English **Inclusion criteria**: • RCTs in adults aged: ≥18 y with T2D • LCD group must have achieved lower CHO intake than control group • Control group usual care (on variety of diets) **Exclusion criteria**: • Studies that enrolled individuals with T1D, pre-diabetes or included pregnant women **Outcome measures**: • Primary: HbA1c • Secondary: Change in diabetes medication, weight, total cholesterol, LDL-c, HDL-c, triacylglycerol, BP, dietary adherence **Statistical analysis**: • Random-effects model • Meta-analysis performed for change in each outcome at 1 y • Studies <48 wk or with marked design heterogeneity not included in meta-analysis **Study quality**: Assessed for risk of bias using Cochrane Risk of Bias tool **Publication bias**: Not assessed	**Number of studies**: 18 (n=2204) **Study duration**: 12 wk to 4 y **Study population**: • Mean age: NR • BMI: NR • Sex: NR • Ethnicity: NR • Medication: Participants in 14/18 studies on diabetes medication; 2 studies did not include participants on medication; 2 did not report medication changes • Physical activity: NR **Intervention:** • CHO: <20 to 70 g/d /14 to 52% TE • All authors described intervention as low CHO • 10 studies prescribed LCD (<130 g/d or <26% TE) • 5 prescribed MCD (130 to 225 g/d or 26 to 45% TE) • 1 prescribed HCD (>225 g/d or 45% TE) • 1 prescribed up to 50% TE from CHOs encompassing range up to and including HCD **Comparator**: Usual care, which included variety of diets • CHO: 50 to 60% TE • Fat: ≤30% TE **Author's evaluation**:	**Dropout**: NR **Achieved CHO intake** (mean): 106 g/d **Outcomes** (1 y) HbA1c (%) (n=7) • -0.28% (-0.53, -0.02), p=0.03, I^2=54% Body weight (kg) (n=6): 0.28 (-1.37, 1.92), p=0.74, I^2=75% Blood lipids profiles (mmol/L) Total cholesterol (n=7): • -0.08 (-0.23, 0.08), p=0.35, I^2=60% LDL-c (n=5) • 0.05 (-0.10, 0.19), p=0.54, I^2=0% HDL-c (n=7) • 0.06 (0.04, 0.09), p<0.00001, I^2=1% Triacylglycerols n=7) • -0.24 (-0.35, -0.13,) p<0.0001, I^2=0% Diabetes medication: Out of 14 studies, 9 reported statistically significant reduction in diabetes medication in LCD group (p≤0.05). Dietary adherence: 12/18 trials reported CHO intake at trial end in LCD. Two reported that they achieved prescribed intake in the intervention arm, 1 that prescribed LC diet and 1 that prescribed up to and including HC diet.	**Limitations**: Varied CHO prescription across studies Lack of blinding of participants and study personnel True effect of LC group on HbA1c could not be observed due to medication adjustments Study design heterogeneity present Some studies prescribed lower calorie allowance to control group Several studies provided insufficient information and could not be included in the meta-analyses, limiting number of studies and participants that could be included in pooled analysis **Conclusion**: Statistically significant superiority of LC group in improving HbA1c, HDL-c, triacylglycerol at 1 year and in reducing diabetes medication. No difference in weight loss, total cholesterol or LDL-c at 1 year. Reducing CHO intake may promote favourable health outcomes in management of T2D in context of a healthy diet.

Study	**Methods**	**Included studies**	**Results of meta-analyses** (weighted mean difference in change (95% CI))	**Limitations and study conclusions** (assessed by authors)
		Risk of bias: 15/18 studies at high risk of bias in 1 or more of the 6 criteria [random sequence generation , allocation concealment, blinding of participants and personnel, blinding of outcome assessment), incomplete outcome data , selective reporting. 15/18 studies at high risk of performance bias.		

Study	Methods	Included studies	**Results of meta-analyses** (weighted mean difference in change (95% CI))	**Limitations and study conclusions** (assessed by authors)
Snorgaard et al (2017) **Aim**: Effect of dietary carbohydrate restriction compared with recommended diet containing 45 to 60% carbohydrate in people with type 2 diabetes. **Study design**: Systematic review and meta-analysis of RCTs **Countries**: Australia (2), Canada (1), Israel (1), Japan (1), New Zealand (1), Sweden (1), US (3) **Funding source**: Danish Health Authority **Declarations of interest**: One of the authors (A Astrup), member of advisory boards / consultant for: Lucozade Ribena Suntory, UK; McCain Foods Ltd, US; McDonalds, US; Nestle Research Centre, Switzerland; Swedish Dairy and Weight Watchers, US.	**Search period**: January 2004 to October 2014 **Databases searched**: Embase, Medline, Cochrane Library **Language restrictions**: English and Scandinavian languages **Inclusion criteria**: • RCTs comparing CHO restriction (<45% TE) to 45 to 60% CHO diet in individuals with T2D • CHO restriction could be combined with higher fat intake, higher protein intake, or both **Exclusion criteria**: • Interventions aimed at also changing GI of diet **Outcome measures**: • Primary: HbA1c and BMI after 1 y or more • Secondary: HbA1c and BMI (or weight) before 1 y, LDL-c, quality of life, dropout rates (To note: weight included in analysis of BMI not available.) **Statistical analysis**: NR **Study quality**: Guidelines/systematic reviews evaluated using GRADE and AMSTAR Risk of bias assessed using Cochrane Risk of Bias tool **Publication bias**: Not assessed	**Number of studies**: 10 (n=1376) **Study duration**: 3 to 24 m **Study population**: • Age (mean): 58 y • Sex: 49% male • BMI (mean): 26 to 37 kg/m^2 • Ethnicity: NR • Medication: Reports on glucose-lowering medication available in 7 studies • Physical activity: 5 trials advised an increase in daily physical activity equally in both groups **Intervention**: • LCD: CHO <45% TE • Prescribed CHO intake (%): average predefined target 25% TE (range 14 to 40%) **Comparator**: • Recommended diet containing 45 to 60% CHO (HCD) **Author's evaluation**: Risk of bias: overall risk, low to moderate	**Dropout**: • RR=1.13 (0.94, 1.37), I^2=0% **Achieved CHO intake** (mean): • 3 or 6 m: 30% (range 14 to 45%) • 1 y (n=5): 38% (range 27 to 45%) • 2 y (n=3): increased further compared to 1 y (42 to 48% and 27 to 31%) or remained high (45%) **Outcomes**: HbA1c (%) • 3 or 6 m (n=8): -0.34 (-0.06, -0.63), p=0.02, I^2=74% • ≥1 y (n=7): 0.04 (-0.04, 0.13), p=0.29, I^2=0% Weight (kg) (n=6) • ≥1 y: 0.2 (-0.97, 1.36), p=NR, I^2=NR LDL-cholesterol (mmol/L)) • <1y (n=8): 0.04% (-0.06, 0.13), p=NR, I^2=NR • ≥1y (n=7): -0.01 (-0.1, 0.07), p=NR, I^2=NR Diabetes medication (n=7) • 3 or 6 m: medication reduced in LCD compared to control • 1 y: numerically lower in LCD group	**Limitations**: Changes in glucose medication and variability in adherence to diet probably main factors modifying effect of LCD on glycaemic control. Other factors potentially contributing to heterogeneity of results: duration and intensity of intervention, CHO and total daily calorie intake in LCD and HCD groups, GI of CHOs, fat and protein intake, baseline HbA1c. **Conclusions**: CHO restriction (TE% < 45%) has greater effect on glycaemic control than HCD in short term. Magnitude of effect correlated to CHO intake: the greater the restriction, the greater the glucose lowering. In the long term, glucose-lowering effect of LDC and HCD similar. Isocaloric LCD and HCD had similar effects on weight and LDL-c.

Study	Methods	Included studies	Results of meta-analyses (weighted mean difference in change (95% CI))	Limitations and study conclusions (assessed by authors)
Meng et al (2017) **Aim**: To evaluate overall effect of low carbohydrate diet on weight loss, blood glucose, and blood lipid concentrations in diabetic patients. **Study design**: Systematic review and meta-analysis of RCTs **Countries**: Australia (1), Israel (1), Japan (1), Sweden (1), UK (1), US (4) **Funding source**: National Natural Science Foundation of China **Declarations of interest**: None	**Search period**: Through January 2017 **Databases searched**: Medline, Embase, Cochrane Library **Language restrictions**: None **Inclusion criteria**: • RCTs in individuals with T2D • LCD: CHO <130 g/d or 26% TE • Control: normal or HCD • Studies reporting change in weight, fasting plasma glucose, HbA1c, total cholesterol, triacylglycerol, HDL-c, LDL-c **Exclusion criteria**: NR **Outcome measures**: • Primary: body weight • Secondary: HbA1c, fasting plasma glucose, total cholesterol, triacylglycerol, HDL-c, LDL-c **Statistical analysis**: • Q tests and I^2 statistics used to assess heterogeneity: p<0.1 or I^2 >50% considered to represent significant heterogeneity and random-effects model used; otherwise fixed-effects model selected **Study quality**: Modified Jadad scale. Random sequence generation, allocation concealment, double blinding, withdrawals and dropouts evaluated. Each study received score from 0 to 7; a score of > 4 considered to be of high quality. **Publication bias**: Funnel plots and Egger linear regression test	**Number of studies**: 9 (n=734) **Study duration**: 3 to 24 m **Study population**: • Mean age: NR • Sex: NR • BMI: NR • Ethnicity: NR • Medication: NR • Physical activity: NR **Intervention**: • LCD: CHO <130 g/d or 26% TE • CHO intake <20 to 130 g/d or 5 to 20% TE **Comparator**: • Normal or HCD • CHO intake 45 to 60% TE (unclear in 3 studies) **Author's evaluation**: Study quality: 5/9 studies considered to be of high quality (modified Jadad score ≥4) Publication bias: No evidence of publication bias	**Dropout**: NR **Achieved CHO intake**: NR **Outcomes** Weight (units NR) (n=9) • >1y (n=3): -0.24 (-2.18, 1.7); p=0.57, I^2=0% HbA1c (n=9) • -0.44 (-0.61, -0.26); p=0.00I^2=19.6% Fasting plasma glucose (n=5) • -0.05 (-0.58, 0.47); p=0.84, I^2=0%; Blood lipid profiles: Triacylglycerol (n=6) • -0.33 (-0.45, -0.21); p=0.00, I^2=0% HDL-cholesterol (n=8) • 0.07 (0.03, 0.11); p=0.00, I^2=40.6%; LDL-cholesterol (n=7) • 0.04 (-0.08, 0.16); p=0.53, I^2=0.0% Total cholesterol (n=6) • 0.06 (-0.08, 0.21); p=0.33, I^2=0.0%	**Limitations**: • Only 5 studies considered to be of high quality. • CHO intake in LCD ranged from 5% to 20% of daily energy. **Conclusions**: Results suggest beneficial effect of LCD on glucose control, triacylglycerols and HDL-c in patients with T2D but no significant effect on long term weight loss, total cholesterol or LDL-c.

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

Study	Methods	Included studies	**Results of meta-analyses** (weighted mean difference in change (95% CI))	**Limitations and study conclusions** (assessed by authors)
Naude et al (2014) **Aim**: To compare effects of low carbohydrate and isoenergetic balanced weight loss diets in overweight and obese adults. **Study design**: Systematic review and meta-analysis of RCTs **Countries**: Australia (3), New Zealand (1), Sweden (1) **Funding source**: Not stated **Declarations of interest**: None	**Search period**: 1966 to 19 March 2014 **Databases searched**: Medline, Embase, Cochrane **Language restrictions**: English **Inclusion criteria**: • RCTs in overweight individuals with diabetes, glucose intolerance or insulin resistance, CVD conditions or risk factors • Provided macronutrient goals as TE or could be calculated as % of TE for both groups • Intervention: 2 main variants of low CHO weight loss diets: (a) High fat variant (HFV) - LCD (<45% TE), high fat (>35% TE), high protein diet (>20% TE) or (b) high protein variant (HPV) - LCD (<45% TE), recommended fat (25 to 35% TE), high protein diet • Control diets: balanced weight loss plans with similar prescribed energy content as intervention diet **Exclusion criteria**: • RCTs <n=10 per group or duration <12 wk • Aged <18 y or pregnant/lactating women • Treatment and control diets not adequately defined/control diet 'no dietary intervention' • Diets combined with any other intervention (eg physical activity, pharmacological) • Intervention focused on energy restriction	**Number of studies**: 5 (n=720) **Study duration**: 3 to 26 m **Study population**: • Age: 30 to 78 y • Sex: Male and female • BMI: >30 kg/m^2 • Ethnicity: NR • Medication: excluded studies with this component • Physical activity: excluded studies with this component **Intervention**: • CHO: 20% TE (n=1) or 40% TE (n=4) • Fat: 30% TE (n=1) or 30% TE (n=4) • Protein: 30% TE **Comparator:** • CHO: 55 to 60% TE • Fat: 25 to 30% TE • Protein: 10 to 15% TE **Author's evaluation**: Study quality: Presence of risk of selection, performance and attrition bias in most included trials were primary reasons for the moderate grade of evidence in most outcomes. For weight loss at 3 to 6 m and 1 to 2 y follow-up, imprecision of the effect estimates resulted in further downgrading to low quality evidence.	**Dropout**: Ranged from 0 to 21% • 1 study: 0% in both groups • 3 studies: similar in both groups (9, 15 and 21%) • 1 study: 8% in LCD and 5.5% in control **Achieved CHO intake**:NR. **Outcomes**: Weight (kg) • 12 to 24 m (n=4): 0.91 (-2.08, 3.89), p=0.55, I^2=33% HbA1c (%) • 3 to 6 m (n=5) 0.19 (-0.0, 0.39), p=0.05, I^2=0% • 12 to 24 m (n=4) 0.01 (-0.28, 0.3), p=0.95, I^2=0% Blood lipid profiles (mmol/L) Triacylglycerol • 3 to 6 m (n=4) -0.20 (-0.45, 0.05), p=0.12, I^2=0% • 12 to 24 m (n=3) -0.08 (-0.43, 0.26), p=0.63, I^2=0% HDL-c • 3 to 6 m (n=5) -0.01 (-0.05, 0.04, p=0.71), I^2=0% • 12 to 24 m (n=4) 0.00 (-0.09, 0.08), p=0.91, I^2=26% LDL-c • 3 to 6 m (n=5) 0.06 (-0.11, 0.23), p=0.50, I^2=25% • 12 to 24 m (n=4) 0.10 (-0.06, 0.27), p=0.23, I^2=0% Total cholesterol • 3 to 6 m (n=5) 0.04 (-0.21, 0.30), p=0.73, I^2=43%	**Limitations**: • Risk of bias or lack of power or both in many included trials. • Adherence to dietary macronutrient goals not optimal. • Possibility of inter-trial variation in quantity and type of fat consumed. • Interpretation of many weight loss trials limited by lack of blinded ascertainment of outcome, small samples, large loss to follow-up, potentially limited generalisability and lack of data on adherence to assigned diets. **Conclusions** Little/no difference in changes in weight and CVD and diabetes risk factors with low CHO weight loss diets compared to isoenergetic balanced weight loss diets. Weight loss result of a reduction in total dietary energy intake rather than manipulation of macronutrient contribution.

Study	Methods	Included studies	**Results of meta-analyses** (weighted mean difference in change (95% CI))	**Limitations and study conclusions** (assessed by authors)
	• Substantial disparity in energy intake (>500 KJ) between control and prescribed diet **Outcome measures**: • Weight loss, BMI, HbA1c, total cholesterol, HDL-c, LDL-c, triacylglycerol **Statistical analysis**: • Random-effects model. Heterogeneity anticipated due to variation in dietary plans, follow-up length and methodology Study quality: GRADE (used to express quality of evidence and magnitude of effect. For large effects and moderate quality evidence, used the word *'probably';* for low quality, used the word '*may')* Cochrane risk of bias tool (domains include random sequence generation, allocation concealment, performance and detection bias, attrition bias, reporting bias and 'other' bias. Publication bias: Assessed with funnel plots when ≥10 studies per outcome		• 12 to 24 m (n=4) 0.10 (-0.12, 0.31), p=0.37, I^2=9%	

Table A4.2: Summary table of eligible network meta-analysis (NMA)

Study	Methods	Included studies	Results	Limitations/ Comments
Schwingshackl (2018) **Aim**: Comparative efficacy of different dietary approaches on glycaemic control in patients with type 2 diabetes. **Study design**: Network meta-analysis (NMA) of randomised trials. **Countries**: Asia (8), Australia (13), Canada (4), Europe (14), New Zealand (3), US (14) **Funding source**: NR **Declarations of interest**: No competing interests	**Search period**: Up to July 2017 **Databases searched**: PubMed, Cochrane Library, Google Scholar **Language restrictions**: None **Inclusion criteria**: • RCTs comparing different dietary approaches in adults (≥18 y) with T2D; intervention period ≥12 wk • Primary outcome, HbA1c; secondary outcome, defined fasting glucose **Exclusion criteria**: • Studies including pregnant women and patients with abnormal glucose metabolism • Studies solely based on dietary approaches or single foods, using dietary supplements as placebo, exercise or medication co-intervention not applied to all groups, those based on very low energy diets (<600 kcal/day) **Outcome measures**: • Primary: HbA1c • Secondary: Defined fasting glucose **Statistical analysis**: • Random-effects NMA • Subgroup analyses: study duration (≥12 vs <12 m), sample size (≥100 vs <100), age (≥60 vs <60 y) • Sensitivity analyses of studies at low risk of bias and excluding risk of bias trials • Relative ranking of diets, distribution of ranking probabilities and surface under cumulative ranking curves (SUCRA)	**Number of studies**: 56 (n=4937) **Duration**: 3 to 48 m **Study population**: • Mean age: 44 to 67 y • BMI: 25 to 43 kg/m^2 • Sex: NR • Ethnicity: NR • Medication: NR • Physical activity: NR **Intervention**: • LCD (CHO <25% TE; high intake protein/fat) • MCD (CHO 25 to 45% TE; 10 to 20% protein intake) • HPD (protein >20% TE; fat <35% TE) • LFD (fat <30% TE; high intake cereals/grains; protein 10 to 25% TE) • Low glycaemic index/load • Vegetarian/vegan diet • Mediterranean dietary pattern • Paleolithic diet **Control**: • No or minimal intervention **Author's evaluation:** **Risk of bias**: • 21 trials, low risk • 7 trials, high risk • 28 trials, moderate/unclear risk Credibility of evidence rated very low for LCD vs LFD, LCD vs MCD, LCD vs HPD	**Comparison**: Only results for low carbohydrate diet (LCD) and moderate carbohydrate diet (MCD) shown • LCD vs control/MCD/LFD/HPD • MCD vs control/LFD/HPD **Dropout**: NR **Achieved CHO intake:** NR **Outcomes**: Mean difference (95% CI) HbA1c (%) (contribution to estimate of direct/indirect comparisons %) • LCD vs control -0.82 (-1.11, -0.53) (0/100) • LCD vs MCD -0.23 (-0.50, 0.04) (23/77) • LCD vs LFD -0.35 (-0.56, -0.14) (83/17) • LCD vs HPD -0.33 (-0.61, -0.05) (0/100) • MCD vs control -0.59 (-0.85, -0.32) (19/81) • MCD vs LFD -0.12 (-0.31, 0.08) (57/43) • MCD vs HPD -0.10 (-0.37, 0.17) (0/100) Fasting glucose (mmol/L) (contribution to estimate of direct/ indirect comparisons %) • LCD vs control -1.23 (-1.91, -0.55) (0/100) • LCD vs MCD -0.03 (-0.68, 0.62) (20/80) • LCD vs LFD -0.24 (-0.82, 0.35) (57/43) • LCD vs HPD -0.16 (-0.88, 0.57) (0/100) • MCD vs control -1.20 (-1.69, -0.71) (25/75) • MCD vs LFD -0.20 (-0.56, 0.15) (61/39) • MCD vs HPD -0.13 (-0.69, 0.44) (0/100) Ranking of different diets: LCD ranked as best dietary approach for reducing HbA1c (SUCRA, 84%); MCD ranked 6th (SUCRA, 46%). Subgroup analyses: LCD more effective in reducing HbA1c in the shorter term (<12 m), in smaller size studies and including patients ≥60 y. Meta-regression: mean reduction in HbA1c significantly related to mean difference in weight change between different dietary approaches.	**Limitations**: • Number and quality of studies available. • Analyses based on original intended randomised design not on adherence. Adherence to dietary programme not accounted for in analyses. • Heterogeneous definition and overlap between different dietary approaches. • Statistical inconsistencies. • Significant differences in LCD compared to other dietary approaches for study duration, sample size and patients' age. **Conclusions:** LCD diets more effective in HbA1c reduction in short term compared to other diets but no superiority observed in longer term. Mediterranean diet seems to be most effective and efficacious to improve glycaemic control in T2D patients. These findings need to be seen in light of very

Study	Methods	Included studies	Results	Limitations/ Comments
	• Meta-regression analysis: association between HbA1c and mean differences in weight change Study quality: GRADE, to assess credibility of evidence; Cochrane risk of bias tool to assess methodological quality. Publication bias: assessed primarily on non-statistical considerations and funnel plot	Publication bias: comparison adjusted funnel plots for both outcomes slightly asymmetric when LFD vs other dietary approaches.		low to moderate credibility of evidence.

Annex 5: Extracted data from 48 publications in 8 SRs with MAs

Table A5.1: Study design

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

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis [per protocol (PP)/intention-to-treat (ITT)]	Inclusion/exclusion criteria, Power
Brunerova (2007) RCT, parallel Czech Republic **Funding:** VZ MSM 0021620814	To compare influence of a hypocaloric, high-fat diet enriched with MUFA and conventional diet on weight loss and metabolic parameters in obese non-diabetic and obese T2D adults over 3m. **Study duration:** 3 **Outcomes**: Weight, HbA1c, fasting glucose, triacylglycerols, HDL **[NR]**	**Inclusion criteria:** Either obese non-diabetic or T2D adults (a (i) FBG ≥7 mmol/l or random blood glucose ≥11.1 mmol/l on 2 occasions or, if on only 1 occasion, then with symptoms (polyuria, polydipsia, etc.), or blood glucose at 120 min of an oral glucose tolerance test ≥11.1 mmol/l; (ii) fasting C-peptide >800 pmol/l, (iii) negative for anti-GAD and anti IA2, and (iv) being treated with diet or with oral glucose-lowering drugs**.** **Exclusion criteria:** Presence of pancreatic, biliary or thyroid diseases. **Study power:** Estimated 13/group would provide >80% to detect difference in fasting blood glucose of 0.8mmol/L between months 0 and 3. Estimated 13/group would be needed to have 90% power to detect 0.8% mean decrease in HbA1c.
Daly (2006) RCT, parallel UK **Funding:** Diabetes UK	To examine effects of a 3 m programme of dietary advice to restrict carbohydrate intake compared with reduced-portion, low-fat advice in obese adults with poorly controlled T2D. **Study duration**: 3 **Outcomes**: Weight, HbA1c, triacylglycerols, total cholesterol, HDL **[PP]**	**Inclusion criteria:** Obese (BMI ≥30 kg/m^2) adults with poorly controlled T2D (HbA1c, 8 to 12%) with a serum creatinine <150 µmol/l. **Exclusion criteria:** Patients with unexplained weight loss or ketosis. **Study power:** 37/group [To detect 1% difference in HbA1c achieved between the 2 interventions with 80% CI. SD for change in HbA1c from feasibility studies informed power calculation.]
Davis (2009) RCT, parallel US **Funding:** Robert C. Atkins Foundation and Diabetes Research and Training Center (P60 DK020541) and by Clinical and Translational Science Award UL1 RR025750.	To compare effects of a 1 y intervention with a low carbohydrate and a low-fat diet on weight loss and glycaemic control in adults with T2D. **Study duration**: 12 **Outcomes**: Weight, HbA1c, triacylglycerols, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** Adults aged >18 y with a diagnosis of T2D for at least 6 m, BMI ≥25 kg/m^2, and HbA1c, 6 to 11%. **Exclusion criteria:** Weight change of >10 lbs within 3m of screening, kidney disease (creatinine >1.3 mg/dl), active liver or gallbladder disease, significant heart disease, history of severe (requiring hospitalisation) hypoglycaemia, or use of weight loss medications. **Study power:** 105 [80% power to detect mean (SD) difference in weight of 2 (3) kg and HbA1c of 0.7 (1.3) % between dietary arms.]

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis [per protocol (PP)/intention-to-treat (ITT)]	Inclusion/exclusion criteria, Power
De Bont (1981) RCT, parallel UK **Funding:** NR	To investigate the effect of low fat diet advice on dietary response in insulin independent diabetic Women **Study duration:** 6 **Outcomes**: Weight, HbA1c, triacylglycerols, total cholesterol, HDL **[PP]**	**Inclusion criteria:** Diabetic women, aged 35 to 64 y and free of other diseases **Exclusion criteria:** NR **Study power:** NR
Dyson (2007) RCT, parallel UK **Funding:** Medisense UK, Abbott Laboratories.	To assess impact of a low carbohydrate diet on body weight, HbA1c, ketone and lipid levels in diabetic and non-diabetic adults. **Study duration**: 3 **Outcomes**: Weight, BMI, HbA1c, triacylglycerols, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** Age >18 y, BMI >25 kg/m^2, without T2D or with T2D treated by diet alone or metformin monotherapy. **Exclusion criteria:** T1D or T2D individuals treated by insulin, sulphonylurea or thiazolidinedione, pregnant or breastfeeding women or women without adequate contraception, major psychiatric disease, including eating disorders, history of alcohol or drug abuse, serum creatinine >150 µmol/l, abnormal liver function tests, or any known malignancy. **Study power:** 10/group [9/group would give >90% power, p=0.05]
Elhayany (2010) RCT, parallel Israel **Funding:** NR	To compare effects of a low carbohydrate Mediterranean, a traditional Mediterranean, and the 2003 American Diabetic Association diet on health parameters over 12 m. **Study duration**: 12 **Outcomes**: Weight, BMI, HbA1c, fasting glucose, triacylglycerols, total cholesterol, HDL, LDL **[NR]**	**Inclusion criteria:** (i) age 30 to 65 y; (ii) T2D diagnosed within 1 to 10 y; (iii) BMI 27 to 34 kg/m^2; (iv) last HbA1c measurement 7 to 10%; (v) last plasma TG, 1.8 to 4.5 mmol/l; (vi) last serum creatinine <123.2 µmol/l; and (vii) no change in diabetes medication for at least 3 m before entering study. **Exclusion criteria:** (i) proliferative diabetic retinopathy; (ii) current insulin treatment; (iii) active oncologic or psychiatric disease; and (iv) uncontrolled hypothyroidism or hyperthyroidism. **Study power:** NR

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

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis [per protocol (PP)/intention-to-treat (ITT)]	Inclusion/exclusion criteria, Power
Facchini (2003) RCT, parallel US **Funding**: NR	To evaluate whether a carbohydrate-restricted, low-iron available, polyphenol-enriched (CR-LIPE) diet may delay and improve the outcome of diabetic nephropathy to a greater extent than standard protein restriction. **Study duration**: 47 (22) **Outcomes**: NR **[ITT]**	**Inclusion criteria:** Type 2 diabetic patients referred to nephrology clinics for various degrees of renal failure (GFR 15 ÷ 75 ml/min) and otherwise unexplained proteinuria (350 ÷ 12,000 mg/day). Nephropathy was attributed to diabetes when it satisfied the following criteria: slowly increasing serum creatinine concentration (eg, chronic renal failure), negative serological work-up (ANA, RA, HIV, hepatitis C, B, C3, C4, and serum and urine protein electrophoresis), no history of offending drug or toxin exposure, inactive sediment on urinalysis and symmetrical kidneys of normal or increased size on abdominal ultrasonography. When it subsisted a doubt (haematuria, lack of documented retinopathy, or small kidneys on ultrasonography), a renal biopsy was undertaken to confirm the diagnosis. **Exclusion criteria:** NR **Study power**: 93/group [Sample size calculation was estimated on the basis of former survival analysis from carbohydrate-restricted animal experiments and from iron depletion experiments leading to 50% reduction of insulin resistance.]
Garg (1994) RCT, cross-over US **Funding**: Pfizer Inc, New York, the National Institutes of Health grants, the Medical Research Service of the San Diego Veterans Affairs Medical Center.	To study effects of variation in carbohydrate content of diet on glycaemia and plasma lipoproteins in patients with non-insulin-dependent diabetes (NIDDM). **Study duration**: 3.5 **Outcomes**: NR **[PP]**	**Inclusion criteria:** NR **Exclusion criteria:** NR **Study power**: NR

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis [per protocol (PP)/intention-to-treat (ITT)]	Inclusion/exclusion criteria, Power
Goday (2006) RCT, parallel Spain **Funding**: Pronokal Group	To evaluate the short-term safety and tolerability of a VLCK diet (≤50 g of carbohydrate daily) in an interventional weight loss program including lifestyle and behavioural modification support (Diaprokal Method) in subjects with T2DM **Study duration:** 4 **Outcomes**: Weight, BMI, HbA1c, fasting glucose, triacylglycerols, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** Eligibility criteria for the study included age between 30 and 65 years, previous diagnosis of T2DM and body mass index between 30 and 35 kg/m^2. **Exclusion criteria:** Exclusion criteria included duration of T2DM longer than 10 years, insulin therapy, haemoglobin A1c (HbA1c) ⩾9% and fasting C-peptide <1 ng/ml. In addition, subjects presenting with impaired renal function (defined as an estimated glomerular filtration rate <60 ml/min per 1.73 m^2), impaired liver function (defined as liver enzymes greater than equal to twofold the upper normal limit), alcohol intake ⩾40 g/day for men and ⩾24 g/day for women, pregnancy, lactation, or severe eating or psychiatric disorder according to the investigator criterion were excluded from the study. **Study power:** 45/group [Sample size of 38 subjects per group was estimated necessary to validate the hypothesis that the occurrence of AE would be equivalent in the two study groups, with an alpha error of 0.05 and a statistical power of 80%. A dropout rate of 15% was anticipated in both study groups. Thus, we aimed at recruiting a total of 45 subjects per group.]
Goldstein (2011) RCT, parallel Israel **Funding:** None	To compare an Atkins-like diet to a conventional American Diabetes Association-recommended diet. **Study duration**: 12 **Outcomes**: Weight, HbA1c, fasting glucose, triacylglycerols, total cholesterol, HDL **[ITT]**	**Inclusion criteria:** Aged 35 to 75 y, BMI 30 to 9.9 kg/m^2, HbA1c >7%, not receiving insulin, microalbumin excretion <60 mg/day. **Exclusion criteria:** Serum creatinine level >1.4 mg/dl, DBP >100 mmHg or SBP >180 mmHg, liver disease, LDLc >160 mg/dl despite lipid-lowering treatment, use of psychiatric medications, osteoporosis, cancer, food allergies, consumption of a low carbohydrate diet in past 6 m. **Study power:** 20/group [>80% power to detect between group differences in loss of 3kg or more in body weight and reduction of ≥1% in HbA1c. 56 adults recruited to allow for expected drop-outs.]

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis [per protocol (PP)/intention-to-treat (ITT)]	Inclusion/exclusion criteria, Power
Guldbrand (2012) RCT, parallel Sweden **Funding:** University Hospital of Linköping, Linköping University, County Council of Östergötland, and Diabetes Research Centre of Linköping University.	To compare effects of a 2-year intervention with a low-fat diet or a low carbohydrate diet based on four group-meetings to achieve compliance. **Study duration**: 24 **Outcomes**: Weight, BMI, HbA1c, triacylglycerols, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** T2D diagnosis, treated with diet with or without additional oral anti-diabetic medication, incretin-based therapy or insulin. **Exclusion criteria:** Difficulties in understanding Swedish, suffering from severe mental disease, malignant disease or abusing drugs. **Study power:** 30/group [Power of study not reported; size of study based on earlier 6 m pilot study (n=28) randomised to same diet.]
Hockaday (1978) RCT, parallel UK **Funding:** British Diabetic Association and from the International Sugar Research Foundation Inc.	To determine the effect of low carbohydrate diet and the high carbohydrate, modified-fat diet on circulating metabolites and on diabetic complications. **Study duration**: 12 **Outcomes**: Weight, fasting glucose, triacylglycerols, total cholesterol **[ITT]**	**Inclusion criteria:** Newly diagnosed T2D patients who did not require therapy with either insulin or oral hypoglycaemic agents; aged 65 years or under. **Exclusion criteria:** People suffering from co-existent major illness; did have endocrine disease, myocardial infarction, neurological deficit following a cerebrovascular accident or liver disease. **Study power**: NR
Iqbal (2009) RCT, parallel US **Funding:** VA Merit Review Entry program	To determine whether comparable results to those of short-term, intensive interventions comparing a low-carbohydrate versus low-fat diet in obese, diabetic adults could be achieved over 24m using a low-intensity intervention that approximates what is feasible in outpatient practice. **Study duration:** 24 **Outcomes**: Weight, HbA1c, fasting glucose, triacylglycerols, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** Adults with T2D (defined as a pre-existing clinical diagnosis or by use of insulin or oral antidiabetic medications), age ≥18 y, BMI ≥30 kg/m^2. **Exclusion criteria:** Serum creatinine >1.5 mg/ dl (133 µmol/l), urine albumin to creatinine ratio >200 µg/ mg, HbA1c <6.0% or >12.0%, hypoglycaemic or hyperglycaemic episodes in past month requiring external assistance, weight loss ≥5% in past 3 m, participation in weight-loss program, or use of weight-loss medications. **Study power:** 50/group [80% power to detect 5 +/-12% greater weight loss in the LCD group. Given an anticipated drop-out rate of 35% target enrolment was set at n= 156.]

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis [per protocol (PP)/intention-to-treat (ITT)]	Inclusion/exclusion criteria, Power
Jenkins (2014) RCT, parallel Canada **Funding:** Canola Council of Canada, Agriculture and Agri-Food Canada, and Loblaw Companies Canada.	To determine the combined effect of ALA, MUFA, and low GL on glycaemic control and CVD risk factors in type 2 diabetes. **Study duration:** 3 **Outcomes**: Weight, HbA1c, fasting glucose, triacylglycerols, total cholesterol, HDL, LDL, total cholesterol:HDL ratio **[ITT]**	**Inclusion criteria:** At least a 6-month history of type 2 diabetes based on clinical criteria, were taking a stable dose of oral antihyperglycaemic agents for at least the previous 2 months, and had HbA1c values between 6.5% (48 mmol/mol) and 8.5% (69 mmol/mol) both at the initial screening and at the visit 1 week before randomisation. **Exclusion criteria:** HbA1c <6.5% or >8.5%; not on diabetes medication **Study power:** 140 participants [On the basis of data from a 12-week study in type 2 diabetes (16) from an ANCOVA model, we would require 116 completers to detect a treatment difference in HbA1c change of 0.15% with an SD of 0.48% [assuming a=0.05, 1 2 b=0.8,using r=0.8 to account for the high degree of correlation between successive measure.]
Jonasson (2014) RCT, parallel Sweden **Funding:** NR	To investigate effects of diet on inflammation in T2D by comparing a traditional low-fat diet with a low carbohydrate diet. **Study duration:** 6 **Outcomes**: BMI, HbA1c, triacylglycerols, total cholesterol, HDL, LDL **[NR]**	**Inclusion criteria:** Diagnosis of T2D treated with diet with or without oral glucose-lowering medication or insulin. **Exclusion criteria:** Difficulties in understanding the Swedish language, severe mental disease, malignant disease or drug abuse. **Study power:** 30/group [Based on an earlier 6 m pilot study of 28 participants, no. of participants was increased to at least 30/group.]

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis [per protocol (PP)/intention-to-treat (ITT)]	Inclusion/exclusion criteria, Power
Jonsson (2009) RCT, cross-over Sweden **Funding**: Crafoordska stiftelsen, Region Skåne and Lund University	To compare the effects of a Paleolithic ('Old Stone Age') diet and a diabetes diet as generally recommended on risk factors for cardiovascular disease in patients with type 2 diabetes not treated with insulin. **Study duration**: 6 **Outcomes**: Weight, BMI, HbA1c, fasting glucose triacylglycerols, total cholesterol, HDL, LDL **[NR]**	**Inclusion criteria:** Included adult patients with type 2 diabetes and a C-peptide value above zero, unaltered medical diabetes treatment and stable weight since three months before start of study, HbA1c above 5.5% by Mono-S standard, creatinine below 130 µmol/L, liver enzymes below four times their respective upper reference value, no chronic oral or injection steroid treatment and no acute coronary event or change in medication of beta blockers or thyroxin since six months before start of study. **Exclusion criteria:** During ongoing study were change in beta blocker or thyroxin medication, chronic oral or injection steroid treatment, warfarin treatment, creatinine above 130 µmol/L or liver enzymes above four times their respective upper reference value, acute coronary event, and physical or psychological illness or changes in personal circumstances which would make further study participation impossible. **Study power**: 15 participants [A pre-study power calculation showed that 15 subjects would be required to detect, with 80% power and at a significance level of 5%, a 15% reduction in AUC glucose 0 to 120.]
Krebs (2012) RCT, parallel New Zealand **Funding:** Health Research Council of New Zealand (06/337)	To compare effectiveness of low-fat high-protein and low-fat high-carbohydrate dietary advice on weight loss, using group-based interventions, among overweight adults with T2D. **Study duration:** 24 **Outcomes**: Weight, HbA1c, fasting glucose, triacylglycerols, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** Established T2D (WHO criteria), aged 30 to 76 y, BMI ≥27 kg/m^2. **Exclusion criteria:** On weight-reducing medications, weight loss of >5% in past 3 m, had psychiatric or eating disorder, HbA1c >9.5% (80 mmol/mol) or renal disease (estimated glomerular filtration rate <60 ml/min or urine albumin:creatinine ratio >30 mg/mmol), abnormal liver enzymes, heart failure, active malignancy or myocardial infarction in preceding 6 m. **Study power:** 420 participants [420 participants required to detect clinically important differences between groups of 1.9% in weight, 2 cm in waist circumference (80% power, p=0.05).]

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis [per protocol (PP)/intention-to-treat (ITT)]	Inclusion/exclusion criteria, Power
Larsen (2011) RCT, parallel Australia **Funding:** Meat and Livestock Australia (MLA)	To determine whether high-protein diets are superior to high-carbohydrate diets for improving glycaemic control in individuals with T2D. **Study duration:** 12 **Outcomes**: Weight, HbA1c, triacylglycerols, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** Adults with T2D; aged 30 to 75 y; BMI, 27 to 40 kg/m^2; HbA1c, 6.5 to 10%. **Exclusion criteria:** Significant heart disease, stroke within previous 3m, renal disease (proteinuria or serum creatinine >0.13 mmol/l), liver disease, or malignancy. **Study power:** 46/group [80% power (at 2-sided 5% level) to detect a difference of 0.5% in HbA1c between groups assuming SD of 0.85%.]
Luger (2013) RCT, parallel Austria **Funding:** NR	To determine feasibility and efficacy of a high-protein diet compared with a standard diet aiming for weight maintenance in insulin treated T2D adults on insulin requirement, body weight and metabolic parameters. **Study duration**: 3 **Outcomes:** Weight, BMI, HbA1c, fasting glucose, triacylglycerols, HDL, LDL, total cholesterol:HDL ratio **[PP]**	**Inclusion criteria:** T2D patients on insulin therapy. **Exclusion criteria:** Myocardial infarction within last 6 m, stroke, impaired renal function (creatinine >1.3 mg dl − 1), parameters of liver function 2-times higher than normal and intake of protein-rich food supplements. **Study power:** NR
Mayer (2014) RCT, parallel US **Funding:** NIH T32 grant: ST32DK007012-35. Funding for original study: Department of Veterans Affairs.	To determine glycaemic, weight, and pertinent adverse effects of two weight-loss diet plans in T2D adults and to compare the intensity of anti-glycaemic agent use. **Study duration**: 11 **Outcomes**: Weight, BMI, HbA1c, fasting glucose, triacylglycerols, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** Adults with T2D aged ≤70 y and BMI 27 to 30 kg/m^2 plus an obesity-related disease, or BMI 30 kg/m^2. **Exclusion criteria:** Adults with T1D, unstable chronic disease, or disease that would interfere with participation; serum creatinine >1.5 mg/dl in men and >1.3 mg/dl in women; HbA1c >11%. **Study power:** NR

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis [per protocol (PP)/intention-to-treat (ITT)]	Inclusion/exclusion criteria, Power
McLaughlin (2007) RCT, parallel US **Funding:** National Institutes of Health Grants RR2HLL406 and RR 000070	To determine whether weight loss or metabolic improvement differed as a function of macronutrient composition (ie, prescribed diets moderately restricted in either carbohydrate or fat). **Study duration:** 4 **Outcomes**: Weight, BMI, HbA1c, fasting glucose, triacylglycerols, total cholesterol, HDL, LDL **[NR]**	**Inclusion criteria:** BMI 27 to 36 kg/m^2, fasting plasma glucose concentration 7.2 to 8.3 mmol/l, no use of anti-hyperglycaemic medications, and stable weight for 3 months. Subjects on anti-hypertensive or cholesterol-lowering drugs or aspirin were allowed to continue their medications. **Exclusion criteria:** NR **Study power:** NR
Nielsen (2005) RCT, parallel Sweden **Funding:** Medical research committee in Blekinge, Sweden	To observe fasting blood glucose, long-term glycaemic control, body weight and BMI in obese T2D adults on low carbohydrate diet with a control group on a high carbohydrate diet. **Study duration:** 6 **Outcomes**: Weight, HbA1c, fasting glucose **[ITT]**	**Inclusion criteria:** Fasting blood glucose >6 mmol/L, HbA1c >5.6%, use of glucose-lowering medication. **Exclusion criteria:** NR **Study power:** NR
Parker (2002) RCT, parallel Australia **Funding:** Meadow Lea Foods	To determine effect of a high-protein weight loss diet compared with lower-protein diet on fat and lean tissue and fasting and postprandial glucose and insulin concentrations. **Study duration:** 3 **Outcomes**: Weight, HbA1c, fasting glucose, triacylglycerols, total cholesterol, HDL, LDL **[NR]**	**Inclusion criteria:** NR **Exclusion criteria:** NR **Study power:** NR

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

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis [per protocol (PP)/intention-to-treat (ITT)]	Inclusion/exclusion criteria, Power
Pohl (2009) RCT, parallel Germany **Funding**: NR	Stage I (Pohl et al 2005) of a pre-planned 2-stage study has provided good evidence for improved glycaemic control with a disease specific enteral formula low in carbohydrates and high in monounsaturated fatty acids (MUFAs), fish oil, chromium and antioxidants in insulin-treated T2D. The study was continued with stage II to give confirmatory proof of these beneficial effects. **Study duration**: 3 **Outcomes**: HbA1c, fasting glucose, triacylglycerols, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** Patients aged 40 y or older with insulin-treated T2D with HbA1c ≥7.0% and/or fasting blood glucose (FG) >6.7 mmol/L (>120 mg/dL) and indication for long-term tube feeding due to dysphagia caused by neurological disorders (eg, stroke, traumatic brain injury, hypoxic brain damage). **Exclusion criteria:** T1D, known allergy against ingredients of investigational products, intake of other enteral diets, parenteral nutrition, severe liver disease, renal failure, congestive heart failure, human immunodeficiency virus and systemic glucocorticoid therapy within the last 2 weeks before and/or after study admission. **Study power**: NR
Rock (2014) RCT, parallel US **Funding:** School of Medicine, UCSD	To test whether a weight loss programme promotes greater weight loss, glycaemic control, and improved CVD risk factors compared with control conditions and whether there is a differential response to higher versus lower carbohydrate intake. **Study duration:** 12 **Outcomes**: Weight, BMI, HbA1c, fasting glucose, triacylglycerols, total cholesterol, HDL, LDL **[PP and ITT]**	**Inclusion criteria:** T2D confirmed by physician; aged ≥18 y; BMI 25 to 45 kg/m^2; not pregnant/ breastfeeding or planning pregnancy; no eating disorders, food allergies, or food intolerances; no history of bariatric surgery; able to perform step test for assessing cardiopulmonary fitness. **Exclusion criteria:** Weight loss >10 lb in past 3 m; history or presence of a significant psychiatric disorder or any condition that would interfere with participation. HbA1c >11% (97 mmol/mol), fasting triacylglycerol >600 mg/dL, and serum creatinine level ≥1.4 mg/dL (women) or 1.5 mg/dL (men). **Study power:** 75/group [90% power for primary aim with dropout rate of up to 20%; also 90% power to detect between group HbA1c differences of 0.5% (6 mmol/mol).]

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis [per protocol (PP)/intention-to-treat (ITT)]	Inclusion/exclusion criteria, Power
Samaha (2003) RCT, parallel US **Funding:** Veterans Affairs Healthcare Network Competitive Pilot Project Grant	To test whether severely obese adults with high prevalence of diabetes or metabolic syndrome would have greater weight loss, without detrimental effects on risk factors for atherosclerosis, while on a carbohydrate-restricted diet than on a calorie and fat-restricted (low-fat) diet. **Study duration:** 6 **Outcomes**: Weight, HbA1c, fasting glucose **[ITT]**	**Inclusion criteria:** Age ≥18 y and BMI ≥35 kg/m^2. **Exclusion criteria:** Serum creatinine >1.5 mg/dl (132.6 µmol/L); hepatic disease; severe, life-limiting medical illness; inability of diabetic subjects to monitor their own glucose levels; active participation in a dietary programme; use of weight loss medications. **Study power:** 50/group [80% power to demonstrate a mean (+/-) weight loss that was 5±12 kg greater in low carbohydrate than in low fat group.]
Saslow (2014) RCT, parallel US **Funding:** William K. Bowes, Jr. Foundation and the Mount Zion Health Fund	Compare effects of two diets on HbA1c and other health-related outcomes in overweight/obese adults with T2D or prediabetes **Study duration:** 3 **Outcomes**: Weight, BMI, HbA1c, fasting glucose, triacylglycerols, HDL, LDL **[ITT]**	**Inclusion criteria:** Aged ≥18 y with a diagnosis of T2D (HbA1c≥6.5) or prediabetes with an HbA1c >6.0. BMI ≥25 kg/m^2. **Exclusion criteria:** non-English speaking, substance abuse, mental health or medical condition making it difficult to take part, use of oral glucocorticoids or weight loss medications; pregnant or planning pregnancy, breastfeeding or <6 m postpartum; history of or planned weight loss surgery; vegan; using insulin or taking >3 oral hypoglycaemic medications. **Study power:** NR

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis [per protocol (PP)/intention-to-treat (ITT)]	Inclusion/exclusion criteria, Power
Sato (2017) RCT, parallel Japan **Funding:** Mishima Kaiun Memorial Foundation	To compare effectiveness and safety of low carbohydrate diet with calorie restricted diet. **Study duration:** 6 **Outcomes**: Weight, BMI, HbA1c, triacylglycerols, HDL, LDL **[ITT]**	**Inclusion criteria:** Diagnosis of: proliferative retinopathy, severe neuropathy, kidney disease (serum creatinine level >2.0 mg/dL and/or with microalbuminuria), serious liver disease excluding fatty liver (aspartate aminotransferase and/or alanine aminotransferase levels >100 IU/L), acute heart failure within 3 m or apparent chronic heart failure, active malignancy, pancreatic disease, pregnancy, serious infectious disease, trauma injury, alcohol dependency. **Exclusion criteria:** Retinopathy, severe neuropathy, serious kidney disease (serum creatinine >2.0 mg/dL and/or with microalbuminuria), serious liver disease excluding fatty liver (aspartate aminotransferase and/or alanine aminotransferase >100 IU/L), acute heart failure within 3 m, active malignancy, serious pancreatic disease, pregnancy, serious infectious disease, trauma injury, alcohol dependency. **Study power:** 33/group [Estimated difference in HbA1c reduction between 2 groups of 0.4% power of 90%.]
Shai (2008) RCT, parallel Israel **Funding:** Nuclear Research Center Negev, Atkins Research Foundation, and S Daniel Abraham International Center for Health and Nutrition, Ben Gurion University.	To compare effectiveness and safety of 3 nutritional protocols: a low-fat, restricted-calorie diet; a Mediterranean, restricted-calorie diet; and a low-carbohydrate, non-restricted calorie diet. **Study duration:** 24 **Outcomes**: NR **[ITT]**	**Inclusion criteria:** Age 40 to 65 y, BMI ≥27 kg/m^2 or presence of T2D (according to the American Diabetes Association criteria) or CHD, regardless of age and BMI. **Exclusion criteria:** Pregnant or lactating, serum creatinine ≥2 mg/dl (177 µmol/L), liver dysfunction, gastro intestinal problems, cancer, or participating in another diet trial. **Study power:** 100/group [Type I error of 5%, >90% power to detect significant differences in weight loss.]

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis [per protocol (PP)/intention-to-treat (ITT)]	Inclusion/exclusion criteria, Power
Shirai (2013) RCT, parallel Japan **Funding:** Weight Control Association	To clarify usefulness of a 24-week dietary regimen using formula diet once a day in combination with conventional low-caloric diet in obese adults with T2D. **Study duration:** 6 **Outcomes**: Weight, BMI, HbA1c, fasting glucose, triacylglycerols, HDL, LDL **[PP]**	**Inclusion criteria:** T2D patients (HbA1c ≥6.0%): BMI >25 kg/m^2. **Exclusion criteria:** Massive proteinurea; malignancy; history of hepatitis, cardiovascular events, respiratory or gastrointestinal diseases; uncontrolled hypertension; pregnant or breast feeding. **Study power:** NR
Stern (2004) RCT, parallel US **Funding:** Veterans Affairs Healthcare Network Competitive Pilot Project Grant	To report findings 1 y after a low-carbohydrate diet versus low-fat weight loss diet in severely obese adults with a high prevalence of diabetes or metabolic syndrome. **Study duration**: 12 **Outcomes**: HbA1c, fasting glucose **[ITT]**	**Inclusion criteria:** Aged ≥18 y, BMI ≥35 kg/m^2. **Exclusion criteria:** Serum creatinine level >133 µmol/L (>1.5 mg/dL), hepatic disease, severe life-limiting medical illness, inability to self-monitor glucose levels, or active use of a weight loss programme or weight loss medication. **Study power:** 50/group [80% power to detect a 5kg greater mean weight loss in low carbohydrate group.]
Strychar (2009) RCT, parallel Canada **Funding:** Canadian Institutes of Health Research, Institute of Nutrition and Metabolism.	To compare the effects of a eucaloric diet higher in carbohydrate/lower in fat versus lower in carbohydrate/higher in monounsaturated fat on post-meal triacylglycerol concentrations and other CVD risk factors in non-obese subjects with T1D and in good glycaemic control. **Study duration**: 6 **Outcomes**: Weight, BMI, HbA1c, triacylglycerols, total cholesterol, HDL, LDL, total cholesterol:HDL ratio **[PP]**	**Inclusion criteria:** Adults with T1D on intensive insulin therapy were recruited. **Exclusion criteria:** BMI ≥30 kg/m^2, HbA1c ≥8.4% and major diabetes complications. **Study power:** NR

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis [per protocol (PP)/intention-to-treat (ITT)]	Inclusion/exclusion criteria, Power
Tay (2014) RCT, parallel Australia **Funding:** National Health and Medical Research Council of Australia; Agency for Science, Technology and Research, Singapore.	To compare the effects of a very low-carbohydrate, high unsaturated / low saturated fat diet with those of a high unrefined carbohydrate, low-fat diet (HC) on glycaemic control and CVD risk factors in T2D. **Study duration**: 6 **Outcomes**: Weight, BMI, HbA1c, fasting glucose, triacylglycerols, total cholesterol, HDL, LDL **[PP]**	**Inclusion criteria:** Overweight/obese adults (BMI 26 to 45 kg/m^2, age 35 to 68 y) with T2DM (previously diagnosed with HbA1c ≥7.0% [53 mmol/mol] and/or taking antiglycaemic medication). **Exclusion criteria:** T1D; proteinuria (urinary albumin to-creatinine ratio ≥30 mg/mmol); impaired renal function (eGFR ,60 mL/min); abnormal liver function (alanine aminotransferase, aspartate aminotransferase, or γ-glutamyl transferase ≥2.5 times normal upper limit); any significant endocrinopathy history of malignancy; liver, respiratory, gastrointestinal, or CVD; pregnancy/lactation; clinical depression; history of/or current eating disorder; smoking. **Study power:** NR [The trial was designed to have 80% power to detect 0.7% (7.7 mmol/mol) absolute difference in HbA1c between diets.]
Tay (2015) RCT, parallel Australia **Funding:** National Health and Medical Research Council of Australia; Agency for Science, Technology and Research, Singapore.	To compare effects of a very-low-carbohydrate, high unsaturated fat, low saturated fat (LC) diet with a high carbohydrate, low-fat (HC) diet on glycaemic control and CVD risk factors in T2D after 52 weeks. **Study duration**: 12 **Outcomes**: Weight, BMI, HbA1c, fasting glucose, triacylglycerols, total cholesterol, HDL, LDL **[PP]**	**Inclusion criteria:** Overweight and obese adults [BMI 26 to 45 kg/m^2; age: 35 to 68 y] with T2D (HbA1c ≥7.0%) or taking a diabetes medication. **Exclusion criteria:** T1D; impaired renal function, proteinuria, or abnormal liver functioning; any overt endocrinopathy (other than stable treated thyroid disease); history of malignancy; respiratory disease, gastrointestinal disease, or CVD; pregnancy or lactation; and history of or having current eating disorder or history of or current smoking. **Study power:** NR [The trial was designed to have 80% power to detect a 0.7% (7.7 mmol/mol) absolute difference in HbA1c between the diets.]

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis [per protocol (PP)/intention-to-treat (ITT)]	Inclusion/exclusion criteria, Power
Tay (2018) RCT, parallel Australia **Funding:** National Health and Medical Research Council of Australia; Agency for Science, Technology and Research, Singapore.	To examine whether a low-carbohydrate, high-unsaturated/low-saturated fat diet improves glycaemic control and CVD risk factors in overweight and obese adults with T2D. **Study duration**: 24 **Outcomes**: Weight, BMI, HbA1c, fasting glucose, triacylglycerols, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** Aged 35 to 68 y with T2D (HbA1c ≥7.0% and/or using diabetes medication including insulin) and with BMI of 26 to 45 kg/m^2. **Exclusion criteria:** T1D; renal, hepatic, respiratory, gastrointestinal or CVD; history of malignancy; any significant endocrinopathy (other than stable treated thyroid disease); pregnancy/lactation; history of or current eating disorder; or smoking. **Study power:** NR [The trial was designed to have 80% power to detect a 0.7% (7.7 mmol/mol) absolute difference in HbA1c between the diets.]
Walker (1995) RCT, cross-over Australia **Funding:** Diabetes Australia; food products supplied by Olive Oil Council and Meadow Lea Foods Australia	To examine the effects of a high-carbohydrate low-fat (HCLF) and a modified-fat diet on body weight and metabolic control in subjects with noninsulin-dependent diabetes mellitus (NIDDM) living at home. **Study duration**: 3 **Outcomes**: Weight, BMI, HbA1c, fasting glucose, triacylglycerols, total cholesterol, HDL, LDL **[PP]**	**Inclusion criteria:** NR **Exclusion criteria:** NR **Study power:** NR
Walker (1999) RCT, cross-over Australia **Funding:** The National Health and Medical Research Council of Australia	To compare effects of a high carbohydrate (high-carbohydrate) and a monounsaturated fat diet (high-MUFA) on body fat distribution and sex hormones in post-menopausal women with type 2 diabetes. **Study duration**: 6 **Outcomes**: Weight, HbA1c, fasting glucose, triacylglycerols, total cholesterol, HDL **[PP]**	**Inclusion criteria:** NR **Exclusion criteria:** NR **Study power:** NR

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis [per protocol (PP)/intention-to-treat (ITT)]	Inclusion/exclusion criteria, Power
Watson (2016) RCT, parallel Australia **Funding:** Pork Cooperative Research Centre; study foods donated by various companies.	To compare effects of a high protein diet to an isocaloric higher-carbohydrate diet on cardiometabolic risk factors for 12 weeks in energy restriction (~30% reduction) followed by 12 weeks of energy balance whilst performing regular exercise. **Study duration**: 6 **Outcomes**: Weight, BMI, HbA1c, fasting glucose, triacylglycerols, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** Diagnosed with T2D, aged 18 to 70 y, HbA1c 6.5 to 10.5%, BMI >25 kg/m^2, weight ≤135 kg, nonsmoker (>6 m), proficient in written and spoken English, age-appropriate cognitive abilities. **Exclusion criteria:** Liver, kidney, GI or CVD, respiratory disease (apart from asthma), retinopathy, malignancy (within last 6 m), proteinuria, uncontrolled hypertension (>170/100), taking medication for a neurological or psychiatric condition, neurological or psychiatric condition, history of head/brain injury, musculoskeletal injury or peripheral vascular disease sufficient to impede exercise, undertaking a weight loss programme or taking appetite suppressants, pregnant or lactating. **Study power:** NR
Westman (2008) RCT, parallel US **Funding:** Robert C Atkins Foundation	To test whether a diet lower in carbohydrate would lead to greater improvement in glycaemic control over 24 weeks in obese adults with T2D. **Study duration**: 6 **Outcomes**: Weight, BMI, HbA1c, fasting glucose, triacylglycerols, total cholesterol, HDL, LDL, total cholesterol:HDL ratio **[PP]**	**Inclusion criteria:** T2D >1 y (HbA1c >6.0%), onset of diabetes after age 15 y, no history of diabetic ketoacidosis, age 18 to 65 y, BMI 27 to 50 kg/m^2, and desire to lose weight. **Exclusion criteria:** Unstable or serious medical condition; significant co-morbid illnesses such as liver disease (AST or ALT >100 IU/L), kidney disease (serum creatinine >1.5 mg/dL), cancer; pregnancy; or nursing mothers. **Study power:** 60 participants [80% power in a completers analysis to detect a clinically meaningful change in HbA1c (absolute change of 1.0%, SD=1.5).]

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis [per protocol (PP)/intention-to-treat (ITT)]	Inclusion/exclusion criteria, Power
Wolever (2008) RCT, parallel Canada **Funding:** Canadian Institutes of Health Research; foods donated by various companies.	To compare effects of altering the glycaemic index or amount of carbohydrate on HbA1c, plasma glucose, lipids, and C-reactive protein in T2D adults. **Study duration**: 12 **Outcomes**: Weight, HbA1c, fasting glucose, triacylglycerols, total cholesterol, HDL, LDL, total cholesterol:HDL ratio **[ITT]**	**Inclusion criteria:** Men/non-pregnant women with T2D (fasting plasma glucose ≥7.0 mmol/L or plasma glucose ≥11.1 mmol/L 2 h after a 75-g oral-glucose-tolerance test) managed by diet alone. **Exclusion criteria:** Use of insulin or any hypoglycaemic or anti-hyperglycaemic medication, stroke, myocardial infarction or major surgery within 6 m of randomisation, serum triacylglycerol >10 mmol/L, any major debilitating disorder, condition or drug likely to alter nutrient absorption, use of oral steroids, substance or alcohol abuse, allergy or intolerance to >1 of study key foods. **Study power:** 42/group [80% probability and a 2-tailed p<0.05 to allow detection of difference of 0.36% in rate of change of HbA1c between low carbohydrate and low GI diets.]
Wycherley (2010) RCT, parallel Australia **Funding:** National Heart Foundation of Australia; Diabetes Australia Research Trust; Pork Cooperative Research Centre; Geroge Weston Foods donated foods.	To evaluate effects of 2 low-fat hypocaloric diets differing in the carbohydrate-to-protein ratio, with and without resistance exercise training on weight loss, body composition and CVD risk outcomes in overweight/obese adults with T2D. **Study duration**: 4 **Outcomes**: Weight, BMI, HbA1c, fasting glucose, triacylglycerols, total cholesterol, HDL, LDL **[PP]**	**Inclusion criteria:** NR **Exclusion criteria:** Proteinuria; a malignancy; history of liver, kidney, CVD, respiratory, or gastrointestinal disease; uncontrolled hypertension; pregnant or lactating; smoker; using insulin, any musculoskeletal injury or joint or peripheral vascular disease sufficient to impede exercise or had participated in regular physical exercise in 6 m prior to study. **Study power:** NR

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis [per protocol (PP)/intention-to-treat (ITT)]	Inclusion/exclusion criteria, Power
Yamada (2014) RCT, parallel Japan **Funding:** NR	To examine effects of a non-calorie-restricted, low-carbohydrate diet in Japanese patients unable to adhere to a calorie-restricted diet. **Study duration:** 6 **Outcomes**: Weight, BMI, HbA1c, fasting glucose, triacylglycerols, HDL, LDL **[PP]**	**Inclusion criteria:** Individuals with T2D who had received guidance regarding calorie restriction at least once with HbA1c 6.9 to 8.4%. **Exclusion criteria:** Proteinuria >1.0 g/day, serum creatinine >132 μmol/L (men) or 106 μmol/L (women), aspartate aminotransferase or alanine aminotransferase >3 times upper limit of normal, history of myocardial infarction or stroke within 6 m before study entry or an absolute change in the HbA1c of >1.0% within 6 m before study entry. **Study power:** 22 [90% power, α=0.05 to detect change in HBA1c over 6 m of 0.0 (5) % in arm 2 (calorie restricted) and 0.7 (0.5) in arm 1 (LC group).]

Table A5.2 Description of intervention

Author (year)	Intervention groups	Number of participants at baseline (completers)	Loss to follow-up, n (%)	Mean age in years (SD or SEM*)	Duration of known T2D in years	Inclusion criteria for diagnosis of T2D
Brehm (2003)	[1] High MUFA	62 (43)	19 (31)	NR	NR	HbA1c 6.5 to 9%; diagnosis of T2D for at least 6 m
	[2] High carbohydrate	62 (52)	10 (15)	NR		
	[All]	124 (95)	29 (23)	56.5 (0.8)*		
Brinkworth (2004)	[1] High protein	33(19)	14(42)	60.9 (1.8)*	NR	NR
	[2] Low protein	31 (19)	12(39)	62.7 (1.8)*		
	[All]	64 (38)	26 (41)	NR		
Brunerova (2007)	[1] Hypocaloric, high-fat enriched with MUFA	14	0 (0)	54.7 (3.8)	NR	Fasting blood glucose >7 mmol/l or random blood glucose >11.1 mmol/l on at least 2 occasions OR blood glucose at 120 min of an OGTT >11.1 mmol/l
	[2] Conventional	13	0 (0)	51.2 (3.3)		
	[All]	27	0 (0)	NR		

Author (year)	Intervention groups	Number of participants at baseline (completers)	Loss to follow-up, n (%)	Mean age in years (SD or SEM*)	Duration of known T2D in years	Inclusion criteria for diagnosis of T2D
Daly (2006)	[1] Low carbohydrate	51 (40)	11 (22)	58.2 (1.6)*	NR	HbA1c 8 to 12%
	[2] Low fat	51 (39)	12 (24)	59.1 (1.5)*		
	[All]	102 (79)	23 (23)	NR		
Davis (2009)	[1] Low carbohydrate	55 (47)	8 (15)	54 (6)	NR	HbA1c 6 to 11%; diagnosis of T2D for at least 6 m
	[2] Low fat	50 (44)	6 (12)	53 (7)		
	[All]	105 (91)	14 (13)	NR		
De Bont (1981)	[1] Low carbohydrate	NR (65)	NR	54 (8)	6.9	NR
	[2] Low fat	NR (71)	NR	56 (7)	6.9	
	[All]	148 (136)	12 (8)	NR	NR	
Dyson (2007)	[1] Low carbohydrate	6 (0)	0 (0)	NR	NR	NR
	[2] Diabetes UK nutritional recommendations	7 (6)	1 (14)	NR		
	[All]	13 (12)	1 (8)	54 (9)		

Author (year)	Intervention groups	Number of participants at baseline (completers)	Loss to follow-up, n (%)	Mean age in years (SD or SEM*)	Duration of known T2D in years	Inclusion criteria for diagnosis of T2D
Elhayany (2010)	[1] Low carbohydrate Mediterranean	85 (61)	24 (28)	55.5 (6.5)	5.5 (3.8)	Last HbA1c measurement 7 to 10%
	[2] Traditional Mediterranean	89 (63)	26 (29)	57.4 (6.1)	6.2 (9.9)	
	[3] American Diabetes Association 2003	85 (55)	30 (35)	56.0 (6.1)	5.1 (2.6)	
	[All]	259 (179)	80 (31)	55	NR	
Esposito (2009)	[1] Low carbohydrate Mediterranean	108 (98)	10 (9)	52.4 (11.2)	Newly diagnosed	American Diabetes Association criteria; HbA1c <11%
	[2] Low fat	107 (97)	10 (9)	51.9 (10.7)		
	[All]	215 (195)	20 (9)	NR		
Fabricatore (2011)	[1] Low GL	40 (24)	16 (40)	52.8 (1.4)*	NR	NR
	[2] Low fat	39 (26)	13 (33)	52.5 (1.3)*		
	[All]	79 (50)	29 (37)	NR		

Author (year)	Intervention groups	Number of participants at baseline (completers)	Loss to follow-up, n (%)	Mean age in years (SD or SEM*)	Duration of known T2D in years	Inclusion criteria for diagnosis of T2D
Facchini (2003)	[1] carbohydrate-restricted	100 (91)	9 (9)	59 (10)	9 (4)	NR
	[2] Standard protein restriction	91 (79)	12 (13)	60 (12)	10 (5)	
	[All]	191 (170)	21 (11)	NR	NR	
Garg (1994)	[1] High MUFA	NR	NR	NR	NR	NR
	[2] High carbohydrate	NR	NR	NR		
	[All]	42 (21)	1 (2)	54 (9)		
Goday (2006)	[1] Very low calorie ketogenic diet	45 (40)	5 (11)	54.89 (8.81)	NR	NR
	[2] Low calorie diet	44 (36)	8 (18)	54.17 (7.97)		
	[All]	99 (76)	23 (23)	54.53 (8.37)		
Goldstein (2011)	[1] Modified Atkins diet	26 (14)	12 (46)	57 (9)	7.7 (4.9)	HbA1c >7%
	[2] American Diabetes Association 2001 calorie-restricted diet	26 (16)	10 (38)	55 (8)	8.2 (5.8)	
	[All]	52 (30)	22 (42)	NR	NR	

Author (year)	Intervention groups	Number of participants at baseline (completers)	Loss to follow-up, n (%)	Mean age in years (SD or SEM*)	Duration of known T2D in years	Inclusion criteria for diagnosis of T2D
Guldbrand (2012)	[1] Low carbohydrate	30 (26)	4 (13)	61.2 (9.5)	9.8 (5.5)	NR
	[2] Low fat	31 (28)	3 (10)	62.7 (11)	8.8 (6.2)	
	[All]	61 (54)	7 (11)	NR	NR	
Hockaday (1978)	[1] Low carbohydrate	54 (54)	0 (0)	53	Newly diagnosed	NR
	[2] High carbohydrate, modified fat	39 (39)	0 (0)	50		
	[All]	93 (93)	0 (0)	NR		
Iqbal (2009)	[1] Low carbohydrate	70 (28)	42 (60)	60.0 (8.9)	NR	Defined as pre-existing clinical diagnosis or by use of insulin or oral anti-diabetic medications. Excluded if HbA1c <6% or >12%
	[2] Low fat	74 (40)	34 (46)	60.0 (9.5)		
	[All]	144 (68)	76 (53)	59.4 (9.2)		
Jenkins (2014)	[1] Wholegrain diet	70 (55)	15 (21)	59 (10)	7.6 (6.9)	HbA1c 6.5 to 8.5%
	[2] Low GL with α-linoleic acid and MUFA	71 (64)	7 (10)	59 (10)	7.5 (5.4)	
	[All]	141 (119)	22 (16)	NR	NR	

Author (year)	Intervention groups	Number of participants at baseline (completers)	Loss to follow-up, n (%)	Mean age in years (SD or SEM*)	Duration of known T2D in years	Inclusion criteria for diagnosis of T2D
Jonasson (2014)	[1] Low carbohydrate	30 (30)	0 (0)	61 (9.5)	9.8 (5.5)	NR
	[2] Low fat	31 (31)	0 (0)	63 (11)	8.8 (6.2)	
	[All]	61 (61)	0 (0)	NR	NR	
Jonsson (2009)	[1] Paleolithic diet	NR	NR	66 (6)	6	HbA1c >5.5%
	[2] The European Association for Diabetes recommendations	NR	NR	63 (6)	11	
	[All]	26 (26)	0 (0)	64 (6)	NR	
Krebs (2012)	[1] Low fat higher protein	207 (144)	63 (30)	57.7 (9.9)	8.3 (6.6)	WHO criteria
	[2] Low fat higher carbohydrate	212 (150)	62 (29)	58.0 (9.2)	8.2 (6.3)	
	[All]	419 (294)	125 (30)	57.9 (9.5)	NR	
Larsen (2011)	[1] High protein	53 (43)	10 (19)	59.6 (57.5, 61.8) [range]	8.7 (6.8, 10.5)	HbA1c 6.5 to 10%
	[2] High carbohydrate	46 (37)	9 (20)	58.8 (55.8, 61.7) [range]	8.6 (6.6, 10.6)	
	[All]	99 (80)	19 (19)	NR	NR	

Author (year)	Intervention groups	Number of participants at baseline (completers)	Loss to follow-up, n (%)	Mean age in years (SD or SEM*)	Duration of known T2D in years	Inclusion criteria for diagnosis of T2D
Luger (2013)	[1] High-protein	22 (20)	2 (9)	61.0 (5.7)	17.6 (9.4)	NR
	[2] The European Association for Diabetes recommendations	22 (22)	0 (0)	63.7 (5.2)	16.2 (9.2)	
	[All]	44 (42)	2 (5)	62.4 (5.6)	NR	
Mayer (2014)	[1] Low carbohydrate	22	NR	56.6 (7.3)	5.9 (4.4)	NR
	[2] Low fat + orlistat	24	NR	54.7 (8.4)	7.3 (8.9)	
	[All]	46	NR	NR	NR	
McLaughlin (2007)	[1] 40% carbohydrate	14 (14)	0 (0)	57 (7)	NR	Fasting plasma concentration 7.2 to 8.3 mmol/l
	[2] 60% carbohydrate	15 (15)	0 (0)	56 (7)		
	[All]	29 (29)	0 (0)	NR		
Nielsen (2005)	[1] Low carbohydrate	16 (16)	0 (0)	57.1 (6.2)	13 (5.5)	HBA1c >5.6% and fasting blood glucose >6 mmol/l
	[2] High carbohydrate	15 (15)	0 (0)	58.6 (10.1)	8.5 (5.4)	
	[All]	31 (31)	0 (0)	NR	NR	

Author (year)	Intervention groups	Number of participants at baseline (completers)	Loss to follow-up, n (%)	Mean age in years (SD or SEM*)	Duration of known T2D in years	Inclusion criteria for diagnosis of T2D
Parker (2002)	[1] High protein	36 (31)	5 (14)	Male, 63.4 (1.7)*; female, 58.7 (2.2)*	NR	NR
	[2] Lower protein	28 (23)	5 (18)	Male, 64.2 (3.8)*; female, 60.9 (2.3)*		
	[All]	64 (54)	10 (16)	NR		
Pedersen (2014)	[1] High protein to carbohydrate ratio	38(21)	NR	59.4 (2.2)*	12.4 (2.5)	NR
	[2] Standard protein diet	38(24)	NR	62.4 (1.7)*	7.9 (1.0)	
	[All]	76 (45)	31 (41)	NR	NR	
Pohl (2005)	[1] Low carbohydrate, high MUFA	39 (21)	18 (46)	71 (42, 86)	NR	HbA1c ≥7% and/or fasting blood glucose >6.66mmol/l
	[2] Standard formula	39 (23)	16 (41)	72.0 (51, 87)		
	[All]	78 (44)	34 (44)	NR		
Pohl (2009)	[1] Low carbohydrate, high MUFA	52 (34)	18 (35)	74	NR	
	[2] Standard formula	52 (21)	31 (60)	69		
	[All]	104 (55)	49 (47)	NR		

Author (year)	Intervention groups	Number of participants at baseline (completers)	Loss to follow-up, n (%)	Mean age in years (SD or SEM*)	Duration of known T2D in years	Inclusion criteria for diagnosis of T2D
Rock (2014)	[1] Lower carbohydrate	77 (67)	10 (13)	57.3 (8.6)	NR	T2D diagnosis confirmed by physician
	[2] Lower fat	74 (69)	5 (7)	55.5 (9.2)		
	[3] Usual care	76 (68)	8 (11)	56.8 (9.3)		
	[All]	227 (204)	23 (10)	NR		
Samaha (2003)	[1] Low carbohydrate	26 (17)	9 (35)	53 (9)	NR	NR
	[2] Low fat	26 (12)	14 (54)	54 (9)		
	[All]	52 (29) (includes participants with and without T2D)	23 (44)	NR		
Saslow (2014)	[1] Very low carbohydrate ketogenic	16 (15)	1 (6)	64.8 (7.7)	7.8 (7.5)	HbA1c ≥6.5%
	[2] Moderate carbohydrate, calorie restricted, low fat	18 (17)	1 (6)	55.1 (13.5)	6.4 (4.9)	
	[All]	34 (32)	2 (6)	NR	NR	

Author (year)	Intervention groups	Number of participants at baseline (completers)	Loss to follow-up, n (%)	Mean age in years (SD or SEM*)	Duration of known T2D in years	Inclusion criteria for diagnosis of T2D
Sato (2017)	[1] Low carbohydrate	33 (30)	1 (3)	60.5 (10.5)	14.0 (7.8 to 18.5) [median (IQR)]	HbA1c >7.5% for >3 m
	[2] Calorie restricted	33 (32)	3 (9)	58.4 (10.0)	13.0 (9.0 to 20.0) [median (IQR)]	
	[All]	66 (62)	4 (6)	NR	NR	
Shai (2008)	[1] Low carbohydrate, non-restricted calorie	19 (12)	7 (37)	52 (7)	NR	American Diabetes Association criteria
	[2] Mediterranean, restricted calorie	15 (13)	2 (13)	53 (6)		
	[3] Low fat, restricted calorie	12 (11)	1 (8)	51 (7)		
	[All]	46 (36)	10 (22)	52 (7)		
Shirai (2013)	[1] Formula (high protein, low carbohydrate, low fat)	120 (119)	1 (1)	50.5 (11.8)	NR	HbA1c ≥6.0%
	[2] Conventional	120 (110)	10 (8)	51.7 (10.9)		
	[All]	240 (229)	11 (5)	NR		

Author (year)	Intervention groups	Number of participants at baseline (completers)	Loss to follow-up, n (%)	Mean age in years (SD or SEM*)	Duration of known T2D in years	Inclusion criteria for diagnosis of T2D
Stern (2004)	[1] Low carbohydrate	27 (18)	9 (33)	53 (9)	NR	Fasting blood glucose >6.94 mmol/L or use of antidiabetic medications
	[2] Conventional	27 (16)	11 (41)	54 (9)		
	[All]	54 (34)	20 (37)	NR		
Strychar (2009)	[1] Low carbohydrate, high MUFA	(15)	Unclear	NR	Participants with T1D	Adults with T1D on intensive insulin therapy; HbA1c >8.4% excluded
	[2] High carbohydrate, low fat	(15)	Unclear	NR		
	[All]	(30) not clear how many were recruited initially	Unclear	37.9 (8.1)		
Tay (2014)	[1] Low carbohydrate, high unsaturated fats, low saturated fat	58 (46)	12 (21)	58 (7)	NR	HbA1c ≥7.0% or taking anti-glycaemic medication
	[2] High carbohydrate, low-fat	57 (47)	10 (18)	58 (7)		
	[All]	115 (93)	22 (19)	58 (7)		

Author (year)	Intervention groups	Number of participants at baseline (completers)	Loss to follow-up, n (%)	Mean age in years (SD or SEM*)	Duration of known T2D in years	Inclusion criteria for diagnosis of T2D
Tay (2015)	[1] Low carbohydrate, high unsaturated fats, low saturated fat	58 (41)	17 (29)	58 (7)	7 (5) [SD]	HbA1c ≥7.0% or taking diabetes medication
	[2] High carbohydrate, low-fat	57 (37)	20 (35)	58 (7)	9 (7) [SD]	
	[All]	115 (78)	37 (32)	58 (7)	NR	
Tay (2018)	[1] Low carbohydrate, high unsaturated fats, low saturated fat	58 (33)	25 (43)	58 (7)	6 (4 to 7) [CI]	HbA1c ≥7.0% or taking diabetes medication
	[2] High carbohydrate, low-fat	57 (28)	29 (51)	58 (7)	8 (6 to 10) [CI]	
	[All]	115 (61)	54 (47)	58 (7)	NR	
Walker (1995)	[1] Modified fat	NR	NR	NR	NR	NR
	[2] High carbohydrate, low fat	NR	NR	NR		
	[All]	NR (48)	NR	58.3 (2.1)		
Walker (1999)	[1] High MUFA	NR	NR	NR	3 (3)	NR
	[2] High carbohydrate	NA	NA	NR	3 (3)	
	[All]	34 (21)	13 (38)	58 (7)	NR	

Author (year)	Intervention groups	Number of participants at baseline (completers)	Loss to follow-up, n (%)	Mean age in years (SD or SEM*)	Duration of known T2D in years	Inclusion criteria for diagnosis of T2D
Watson (2016)	[1] High protein	32 (23)	9 (28)	54 (8)	7.9 (6.0) [SD]	HbA1c 6.5 to 10.5%
	[2] High carbohydrate	29 (21)	8 (28)	55 (8)	6.5 (4.2) [SD]	
	[All]	61 (44)	17 (28)	55 (8)	NR	
Westman (2008)	[1] Low carbohydrate, ketogenic	38 (21)	17 (45)	51.8 (7.3)	NR	Diagnosis >1 y (confirmed by HbA1c >6.0%); onset of T2DM after 15 y of age
	[2] Low GI, reduced calorie	46 (29)	17 (37)	51.8 (7.8)		
	[All]	84 (50)	34 (40)	NR		
Wolever (2008)	[1] Low carbohydrate, high MUFA	54 (44)	10 (19)	58.6 (1.2)*	NR	Fasting plasma glucose ≥7.0 mmol/L or ≥11.1 mmol/L 2 h after 75 g OGTT on ≥1 occasion with 2 m of randomisation
	[2] Low GI, high carbohydrate	56 (45)	11 (20)	60.6 (1.0)*		
	[3] High GI, high carbohydrate	52 (41)	11 (21)	60.4 (1.1)*		
	[All]	162 (130)	32 (20)	NR		

Author (year)	Intervention groups	Number of participants at baseline (completers)	Loss to follow-up, n (%)	Mean age in years (SD or SEM*)	Duration of known T2D in years	Inclusion criteria for diagnosis of T2D
Wycherley (2010)	[1] High protein	21 (12)	9 (43)	NR	NR	NR
	[2] Energy-restricted standard carbohydrate	19 (16)	3 (16)	NR		
	[All]	40 (28)	12 (30)	55.0 (8.4)		
Yamada (2014)	[1] Low carbohydrate	12 (12)	0 (0)	63.3 (13.5)	8.9 (3.6) [SD]	HbA1c level 6.9 to 8.4%
	[2] Conventional calorie-restricted	12 (12)	0 (0)	63.2 (10.2)	9.5 (4.8) [SD]	
	[All]	24 (24)	0 (0)	63.3 (11.7)	NR	

Table A5.3: Macronutrient intakes and details of dietary approach (including physical activity recommendations)

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

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

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

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

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

First author (year)	Intervention groups	Energy (kcal)	Carbohydrate (% total energy)	Protein (% total energy)	Fat [SFA, PUFA, MUFA] (% total energy)	Carbohydrate (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
De Bont (1981)		**Prescribed intakes**						
	[1] Low carbohydrate	NR	40	NR	NR	NR	NR	NR
	[2] Low fat	NR	NR	NR	30	NR	NR	NR
		Achieved intakes						
	[1] Low carbohydrate	1340	38	19.9	41.8 [SFA 19.9, PUFA 4.8, MUFA 16.6]	NR	NR	NR
	[2] Low fat	1197	45.7	20.3	31.1 [SFA 12, PUFA 7.8, MUFA 11.3]	NR	NR	NR
	Food-based dietary advice: Group 1: NR. Group 2: reducing dairy products and fat from meat, and substituting margarines in order to improve the saturated:polyunsaturated fat balance. **Intervention approach/intensity:** NR **Assessment of dietary adherence:** NR **Physical activity:** NR							

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

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

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

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

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

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

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

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

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

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

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

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

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

First author (year)	Intervention groups	Energy (kcal)	Carbohydrate (% total energy)	Protein (% total energy)	Fat [SFA, PUFA, MUFA] (% total energy)	Carbohydrate (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Jonsson (2009)		**Prescribed intakes**						
	[1] Paleolithic diet	NR	NR	NR	NR	NR	NR	NR
	[2] The European Association for Diabetes recommendations	NR	NR	NR	NR	NR	NR	NR
		Achieved intakes						
	[1] Paleolithic diet	1581 (295) [SD]	32 (7) [SD]	24 (3) [SD]	39 (5) [SD]	NR	NR	NR
	[2] The European Association for Diabetes recommendations	1878 (379) [SD]	42 (7) [SD]	34 (6) [SD]	20 (4) [SD]	NR	NR	NR
	Food-based dietary advice: Diabetes diet: aim at evenly distributed meals with increased intake of vegetables, root vegetables, dietary fibre, wholegrain bread and other wholegrain cereal products, fruits and berries, and decreased intake of total fat with more unsaturated fat. The majority of dietary energy should come from carbohydrates from foods naturally rich in carbohydrate and dietary fibre. The concepts of glycaemic index and varied meals through meal planning by the Plate Model were explained. Salt intake was recommended to be kept below 6 g/day. Paleolithic diet: based on lean meat, fish, fruit, leafy and cruciferous vegetables, root vegetables, eggs and nuts, while excluding dairy products, cereal grains, beans, refined fats, sugar, candy, soft drinks, beer and extra addition of salt. The following items were recommended in limited amounts: eggs (≤2 per day), nuts (preferentially walnuts), dried fruit, potatoes (≤1 medium-sized per day), rapeseed or olive oil (≤1 tablespoon per day), wine (≤1 glass per day). Intakes of other foods was not restricted and no advice given with regard to proportions of food categories (eg, animal versus plant foods). **Intervention approach/intensity:** NR **Assessment of dietary adherence:** NR **Physical activity:** Advice about regular physical activity was given equally to all subjects.							

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

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

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

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

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

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

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

First author (year)	Intervention groups	Energy (kcal)	Carbohydrate (% total energy)	Protein (% total energy)	Fat [SFA, PUFA, MUFA] (% total energy)	Carbohydrate (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Pedersen (2014)		**Prescribed intakes**						
	[1] High protein to carbohydrate ratio	1434	40	30	30 [SFA: 10]	130 to 230	90 to 120	NR
	[2] Standard protein diet	1434	50	20	30 [SFA: 10]	NR	55 to 70	NR
		Achieved intakes						
	[1] High protein to carbohydrate ratio	2004.8 (149.4) [SEM]	39.3	NR	NR	197.4 (16.3) [SEM]	130.6 (9.8) [SEM]	77.8 (6.6); SFA, 30.1 (2.7), PUFA, 12.3 (1.2); MUFA, 28.1 (2.4) [SEM]
	[2] Standard protein diet	1666.1 (87.7) [SEM]	45	NR	NR	187.6 (10.2) [SEM]	88.3 (4.0) [SEM]	63.3 (4.4); SFA, 22.9 (1.4); PUFA, 12.0 (1.2); MUFA, 22.3 (1.8) [SEM]
	Food-based dietary advice: NR **Intervention approach/intensity:** NR **Assessment of dietary adherence:** Compliance with protein prescription monitored by a daily food checklist and FFQ (at baseline, 4 and 12 months) and also assessed by 24-hour urine urea excretion (UUE). At baseline urea excretion did not differ significantly between groups. At 12 months the UUE was not significantly different compared to baseline, however adjusted urea excretion at 12 months was significantly different between groups (p=0.04) indicating compliance to the protein prescription. This was confirmed by self-reported diet data. **Physical activity:** All participants reported a moderate to low physical activity level and asked to maintain this level throughout study.							

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

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

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

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

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

First author (year)	Intervention groups	Energy (kcal)	Carbohydrate (% total energy)	Protein (% total energy)	Fat [SFA, PUFA, MUFA] (% total energy)	Carbohydrate (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Sato (2017)		**Prescribed intakes**						
	[1] Low carbohydrate	NR	NR	NR	NR	130	NR	NR
	[2] Calorie-restricted	NR	50 to 60	NR	NR	NR	1.0 to 1.2 g/kg BW	NR
		Achieved intakes						
	[1] Low carbohydrate	1371 (1161 to 1573) [median (IQR)]	43.5	NR	NR	149 (126 to 167) [median (IQR)]	64 (51 to 74) [median (IQR)]	52 (40 to 65) [SFA 15.8 (10.0 to 20.8), PUFA 10.9 (9.7 to 13.0), MUFA 18.8 (14.5 to 24.6)] [median (IQR)]
	[2] Calorie-restricted	1605 (1295 to 1847) [median (IQR)]	49.3	NR	NR	198 (161 to 234) [median (IQR)]	63 (57 to 73) [median (IQR)]	52 (43 to 60) [SFA 14.1 (10.6 to 16.4), PUFA 10.9 (8.7 to 14.3), MUFA 18.9 (15.0 to 22.8)] [median (IQR)]
	Food-based dietary advice: NR **Intervention approach/intensity:** 1:1 sessions/30 minutes at 0, 1, 2, 4 and 6 months. **Assessment of dietary adherence:** 3-day weighed/measured food record. Authors comment *'more patients of LCD group withdrew from study compared to CRD group, suggesting that adherence to LCD is difficult in some patients'*. **Physical activity:** NR							

First author (year)	Intervention groups	Energy (kcal)	Carbohydrate (% total energy)	Protein (% total energy)	Fat [SFA, PUFA, MUFA] (% total energy)	Carbohydrate (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Shai (2008)		**Prescribed intakes**						
	[1] Low carbohydrate, non-restricted calorie	NR	NR	18	30	120	NR	NR
	[2] Mediterranean, restricted calorie	1500 to 1800	NR	NR	<35	NR	NR	NR
	[3] Low fat, restricted calorie	NR	NR	NR	NR	NR	NR	NR
		Achieved intakes						
	[1] Low carbohydrate, non-restricted calorie	NR	40.4 (7.1) [SD]	21.8 (3.9) [SD]	39.1 (5.5) [SFA 12.3 (3.2)] [SD]	NR	NR	NR
	[2] Mediterranean, restricted calorie	NR	50.2 (8.6) [SD]	18.8 (3.5) [SD]	33.1 (5.5) [SFA 9.6 (2.2)] [SD]	NR	NR	NR
	[3] Low fat, restricted calorie	NR	50.7 (5.7) [SD]	19.0 (3.2) [SD]	30.0 (3.9) [SFA 9.6 (1.8)] [SD]	NR	NR	NR
	Food-based dietary advice: Group 1: participants counselled to choose vegetarian sources of fat and protein and to avoid trans-fat. Group 2: Mediterranean diet rich in vegetables and low in red meat (poultry and fish replacing beef and lamb). Main sources of added fat were 30 to 45 g olive oil and nuts (5 to 7 nuts, <20 g/d). Group 3: participants counselled to consume low-fat grains, vegetables, fruits and legumes and to limit consumption of additional fats, sweets and high-fat snacks. **Intervention approach/intensity:** Group sessions/weeks 1, 3, 5, 7 and thereafter at 6-week intervals, for a total of 18 sessions of 90 minutes each; 6 times during the 2-year intervention dietitian conducted 10 to 15 minutes motivational telephone call with participants having difficulty with adhering to diet. **Assessment of dietary adherence:** FFQ at baseline, 6, 12, 24 months. Subgroup of participants completed 2 repeated 24-hour dietary recalls to verify absolute intake. Overall rate of adherence was 95.4% at 12 months and 84.6% at 24 months. The 24 months adherence rates were 90.4% in low-fat group, 85.3% in Mediterranean diet group and 78.0% in low carbohydrate group (p=0.04 for comparison among diet groups). **Physical activity:** Used validated questionnaire to assess physical activity. Transformed physical-activity scores into metabolic equivalents per week according to amount of time spent in various forms of exercise per week, with each activity weighted in terms of its level of intensity. The amount of physical activity increased significantly from baseline in all groups, with no significant difference among groups in the amount of increase.							

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

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

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

First author (year)	Intervention groups	Energy (kcal)	Carbohydrate (% total energy)	Protein (% total energy)	Fat [SFA, PUFA, MUFA] (% total energy)	Carbohydrate (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Tay (2014)		**Prescribed intakes**						
	[1] Low carbohydrate, high unsaturated, low saturated fat	NR	14	28	58 [SFA <10%; MUFA 35%; PUFA 13%]	<50	NR	NR
	[2] High carbohydrate, low fat	NR	53	17	<30 [SFA <10%; MUFA 15%, PUFA 9%]	NR	NR	NR
		Achieved intakes						
	[1] Low carbohydrate, high unsaturated, low saturated fat	1563 (225) [SD]	13.9 (1.6) [SD]	26.7 (1.3) [SD]	54.1 (2.6) [SFA 10.0 (0.9), PUFA 12.2 (1.1), MUFA 30.4 (1.8)] [SD]	56.7 (8.0) [SD]	102.8 (14.7) [SD]	96.5 (16.5) [SD]
	[2] High carbohydrate, low fat	1587 (171) [SD]	50.1 (2.0) [SD]	18.8 (0.9) [SD]	24.5 (2.5) [SFA 7.5 (1.1), PUFA 4.1 (0.6), MUFA 11.5 (1.3)] [SD]	204.9 (22.8) [SD]	73.6 (8.3) [SD]	44.3 (7.4) [SD]
	Food-based dietary advice: Group 1: 30 g high-fibre, low GI cereal; 1 crispbread; 250 g lean chicken, pork, fish, red meat (3 to 4 times/week); 40 g almonds and 20 g pecans; 3 cups low-starch vegetables (exclude potato/sweet potato/corn); 200 mL skim (<1% fat) milk; 100 g diet yogurt; 20 g cheese; 30 g margarine/oil (MUFA, eg, canola oil/margarine). Group 2: 40 g high-fibre, low GI cereal; 5 crispbread; 1/2 cup cooked pasta/rice/potato; 2 slices wholegrain bread (70 g); 80 g lean chicken, pork, red meat (4 times/week); 80 g fish (2 times/week); 80 g legumes (1 time/week); 3 cups vegetables; 400 g fruit; 250 mL reduced-fat (1 to 2%) milk; 150 g reduced-fat yogurt; 20 g cheese; 25 g margarine/oil (MUFA, eg, canola oil/margarine). **Intervention approach/intensity:** 1:1 sessions/every 2 weeks for 12 weeks and monthly thereafter. **Assessment of dietary adherence:** Random sample of 7 consecutive days of daily weighed food records for every 14-day period. Authors note that *'reported dietary intakes were consistent with diet prescriptions'*. **Physical activity:** Exercise session attendance and accelerometry; participants undertook 60-minute classes of professionally supervised exercise in a circuit training format 3 days/week that incorporated moderate intensity aerobic/resistance exercises (encouraged to make-up any missed sessions). Physical activity assessed with 7 consecutive days of triaxial accelerometry. Exercise session attendance similar between groups. Mean activity count and time spent in moderate to vigorous physical activity from accelerometry increased similarly in both groups.							

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

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

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

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

First author (year)	Intervention groups	Energy (kcal)	Carbohydrate (% total energy)	Protein (% total energy)	Fat [SFA, PUFA, MUFA] (% total energy)	Carbohydrate (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Watson (2016)		**Prescribed intakes**						
	[1] High protein	NR	33	32	30 [SFA <10]	130-230	NR	NR
	[2] High carbohydrate	NR	51	22	22 [SFA <10]	NR	NR	NR
		Achieved intakes						
	[1] High protein	1736.9 (239.5) (phase 2); 1490.4 (147.5) (phase 1) [SEM]	33.6 (3.2) [SEM]	28.5 (2.8) [SEM]	31.6 (2.9) [SFA: 36.0 (4.4), PUFA: 17.7 (3.1), MUFA: 46.3 (2.5) 5 of total fat] [SEM]	149.2 (18.8) [SEM]	121.3 (19.6) [SEM]	62.2 (10.4) [SEM]
	[2] High carbohydrate	1666.3 (248.1) phase 2; 1420.9 (207.0), phase 1 [SEM]	47.2 (4.5) [SEM]	20.1 (1.5) [SEM]	25.1 (3.6) [SFA: 33.3 (3.9), PUFA: 21.2 (4.2), MUFA: 45.5 (3.8) 5 of total fat] [SEM]	199.3 (23.6) [SEM]	82.1 (12.5) [SEM]	47.8 (11.7) [SEM]
	Food-based dietary advice: Provided with core foods that included fresh lean pork, breakfast cereal, mixed grain bread, fat-reduced cheese (Group 1 only), and raw almonds (Group 1 only). **Intervention approach/intensity:** 1:1 sessions/every 2 weeks. Provided with core study foods corresponding to their assigned dietary pattern. **Assessment of dietary adherence:** Daily semi-quantitative food records. Analysis based on 7 consecutive days from every 2-weekly food record. Authors comment: *Based on dietary data collected, participants achieve good compliance to their allocated dietary prescription.* **Physical activity:** Asked to undertake minimum 30 minutes moderate aerobic exercise 5 times/week (150 mins/wk). Participants completed physical activity logs to monitor compliance. Both groups exceeded their requirements with no significant differences between groups.							

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

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

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

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

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Annex 6: Overlap of primary studies within SRs with MAs, grouped by outcome

Table A6.1: Overlap of primary studies — body weight (long term)

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

Table A6.2A: Overlap of primary studies — HbA1c (short term)

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

Table A6.2B: Overlap of primary studies — HbA1c (long term)

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

Table A6.3: Overlap of primary studies — fasting glucose (short and long term)

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

Table A6.4: Overlap of primary studies — serum total cholesterol (short and long term)

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

Table A6.5: Overlap of primary studies — serum triacylglycerol (short and long term)

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

Table A6.6: Overlap of primary studies — serum LDL cholesterol (short and long term)

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

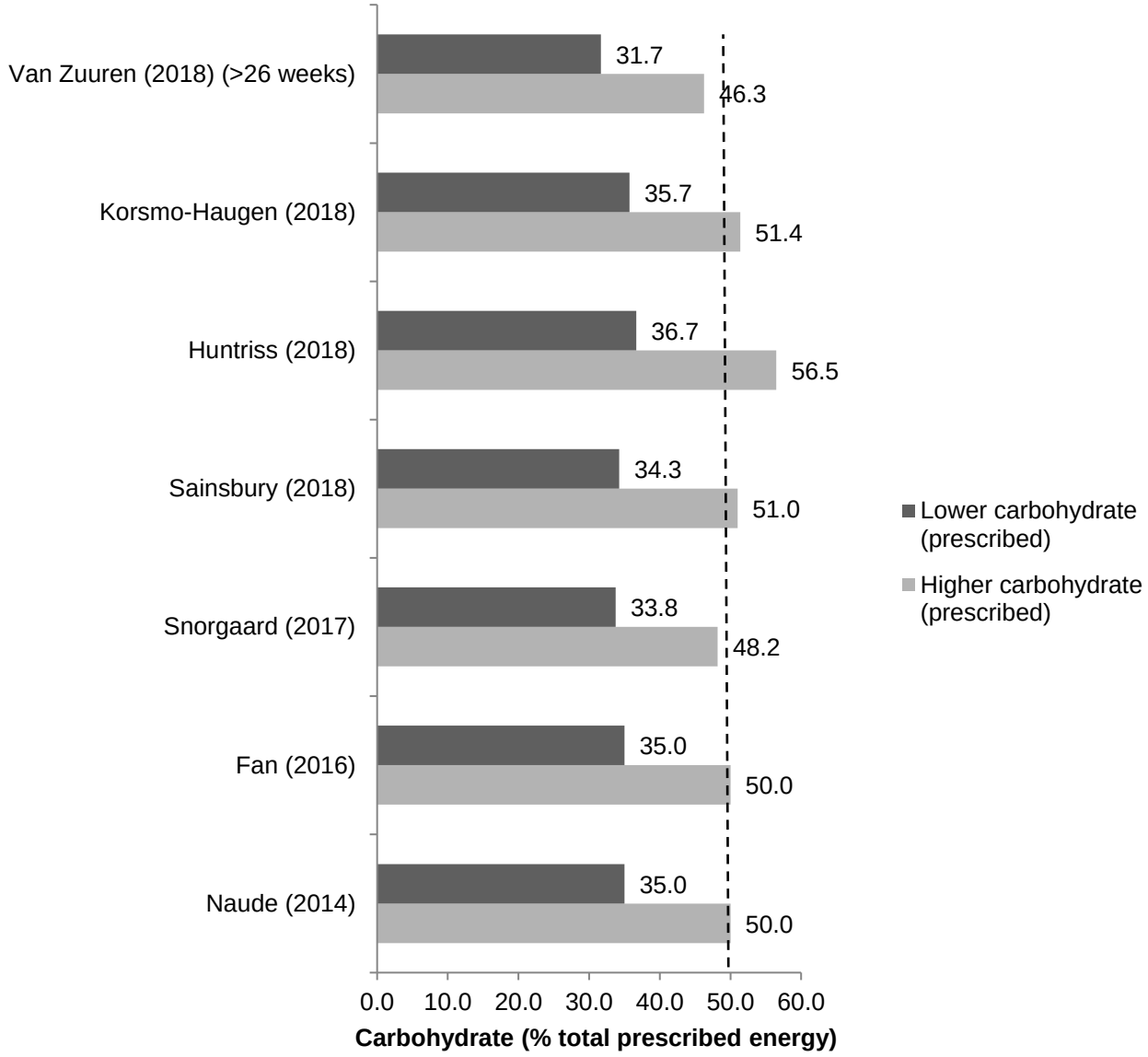
Table A6.7: Overlap of primary studies — serum HDL cholesterol (short and long term)

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

Annex 7: Macronutrient and energy intake

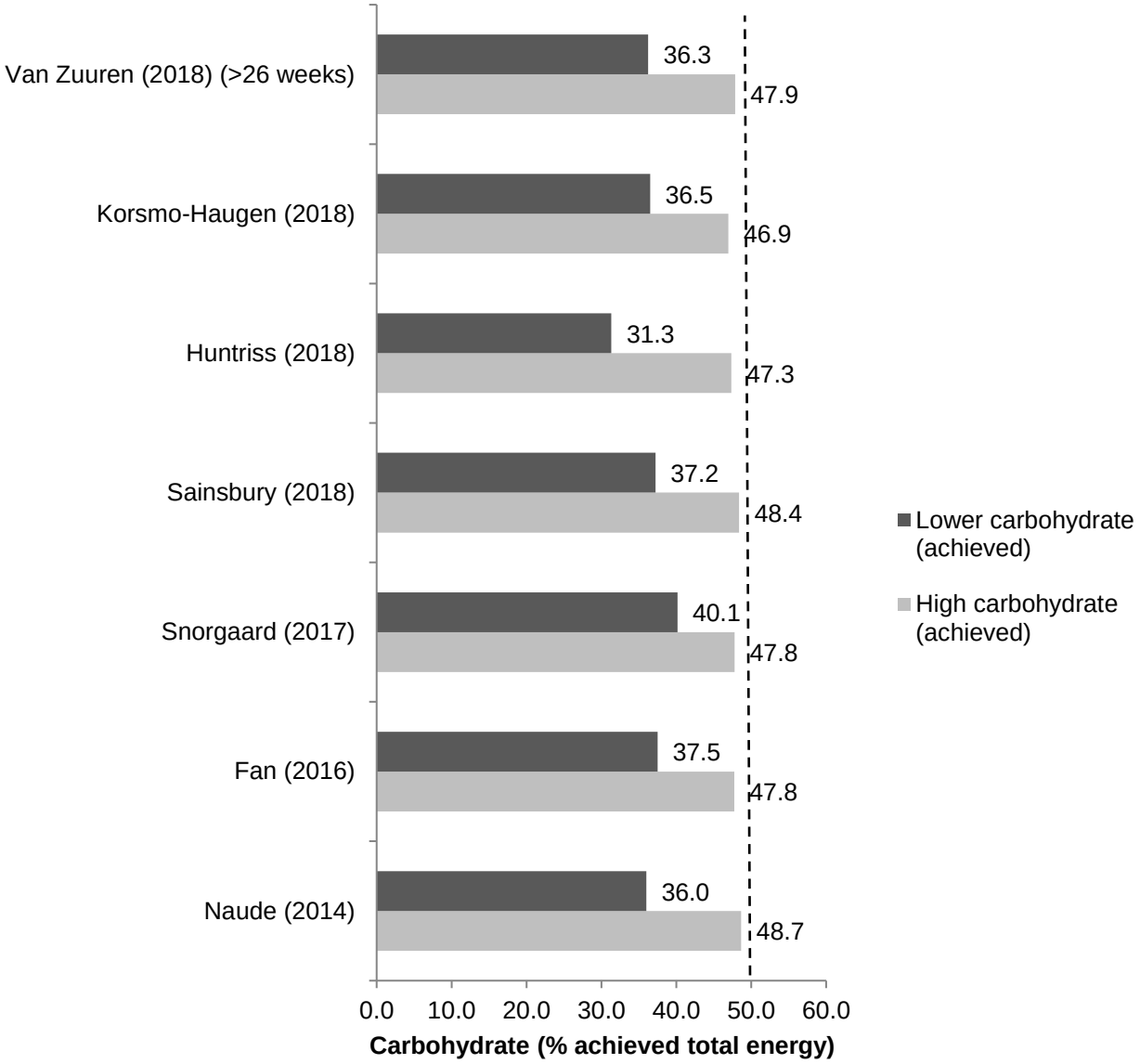
Data from meta-analyses for the outcome of body weight in longer-term studies (≥12 months) (Figures A7.1 to A7.10)

Figure A7.1: Average prescribed intakes of carbohydrate in lower and higher carbohydrate groups (% of total prescribed energy).



The vertical dashed line (---) represents the dietary reference value for total carbohydrate that should be maintained at a population average of approximately 50% of total dietary energy (SACN, 2015).

Figure A7.2: Average achieved intakes of carbohydrate in lower and higher carbohydrate groups (% of total achieved energy).



The vertical dashed line (---) represents the dietary reference value for total carbohydrate that should be maintained at a population average of approximately 50% of total dietary energy (SACN, 2015).

Figure A7.3: Difference in average prescribed carbohydrate intakes in lower and higher carbohydrate groups versus difference in average achieved carbohydrate intakes in lower and higher carbohydrate groups.

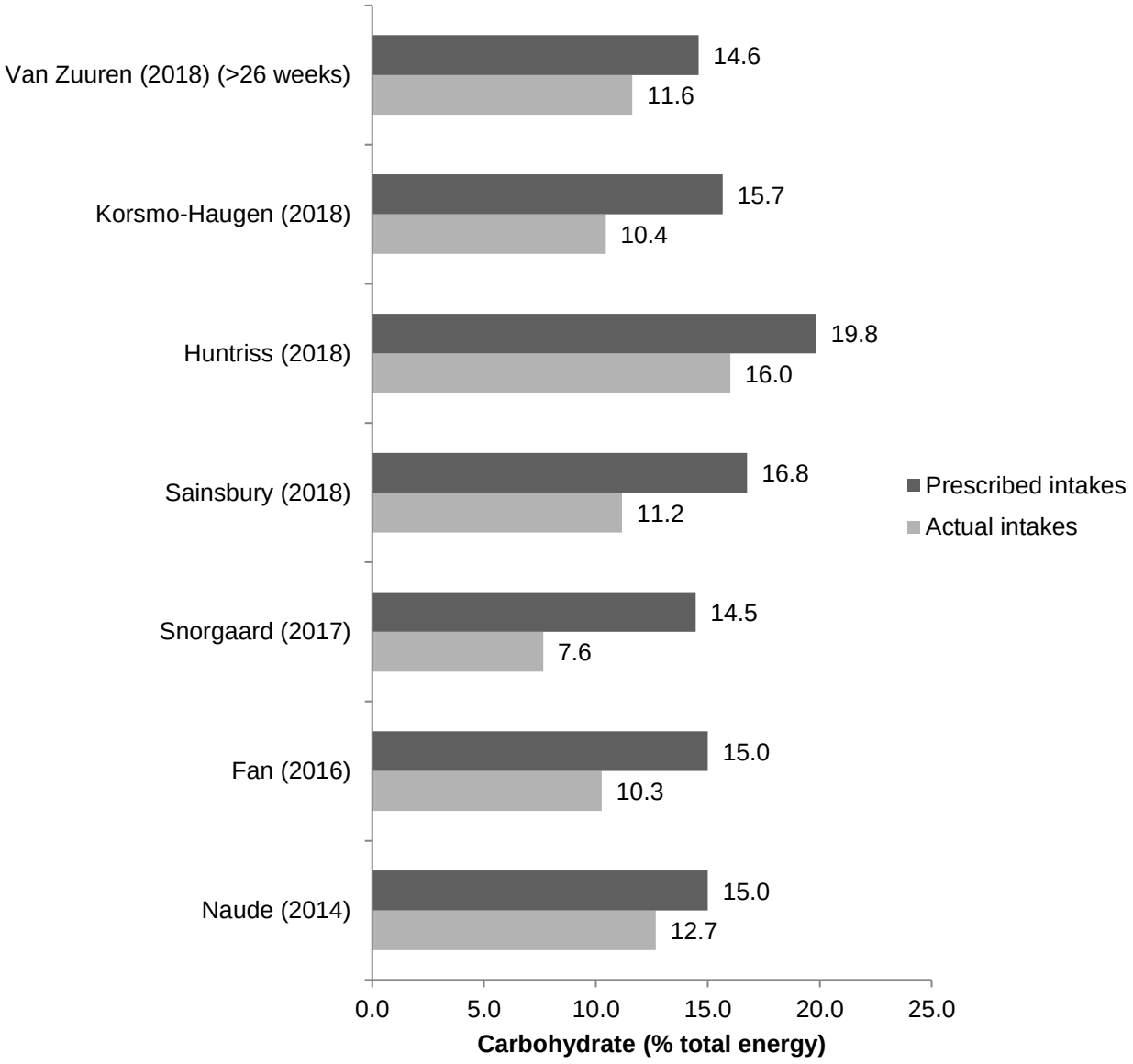
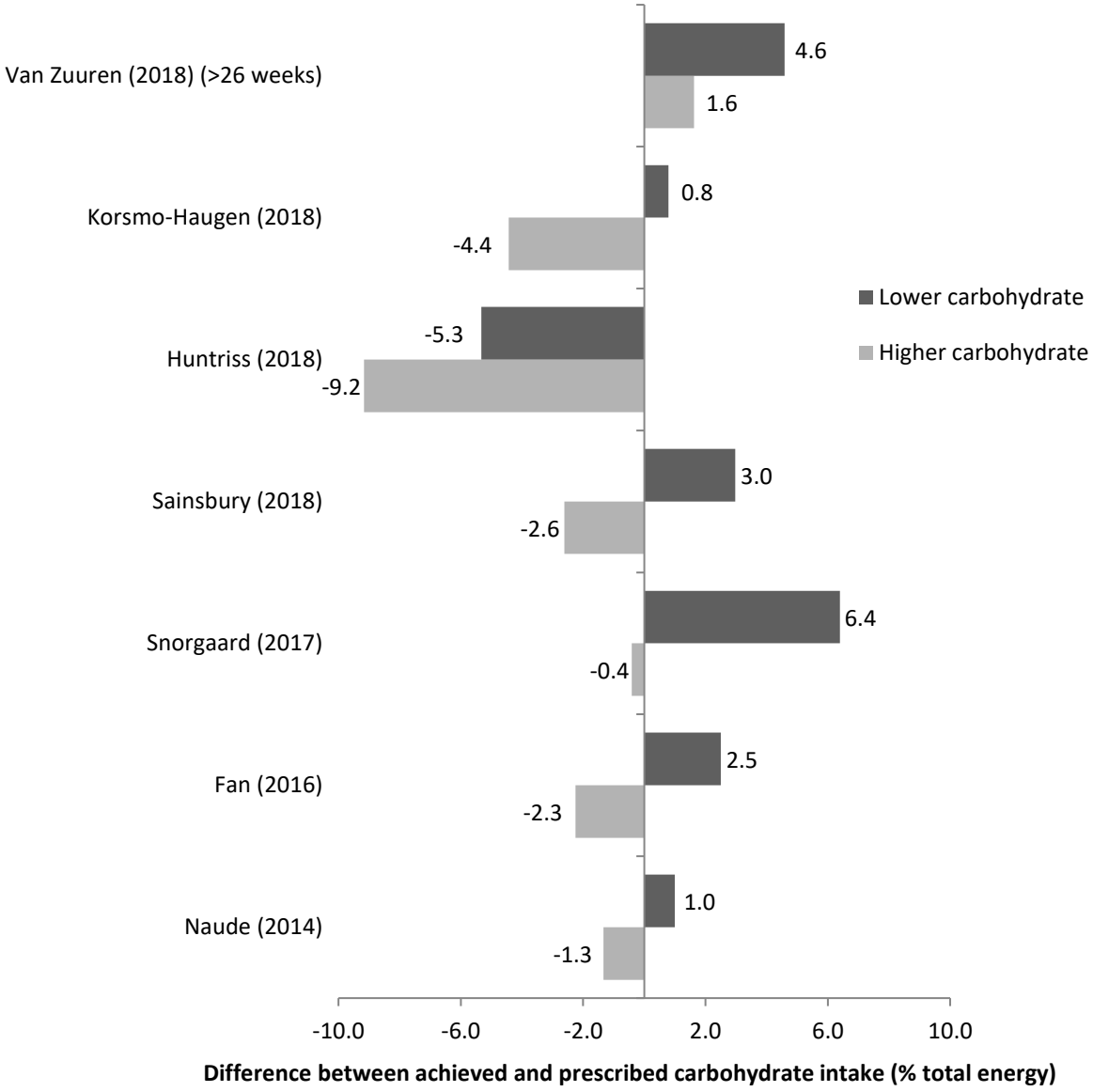


Figure A7.4: Adherence to the average prescribed intake of carbohydrate in the lower and higher carbohydrate groups.



Positive and negative values indicate that the average achieved intake was greater or lesser than the average prescribed intake, respectively.

Figure A7.5: Average achieved intakes of carbohydrate, fat and protein in lower carbohydrate groups.

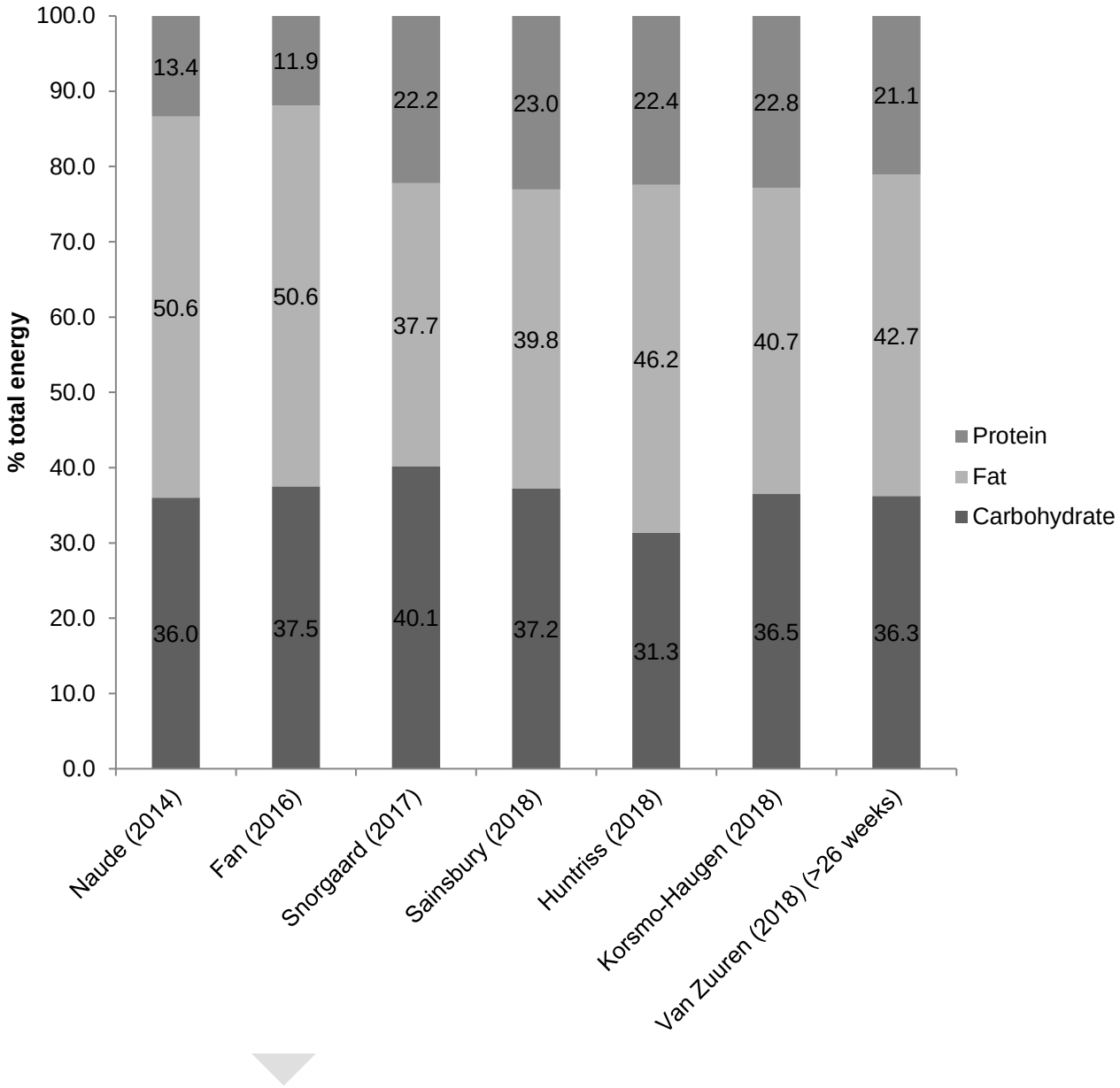


Figure A7.6: Average achieved intakes of carbohydrate, fat and protein in higher carbohydrate groups.

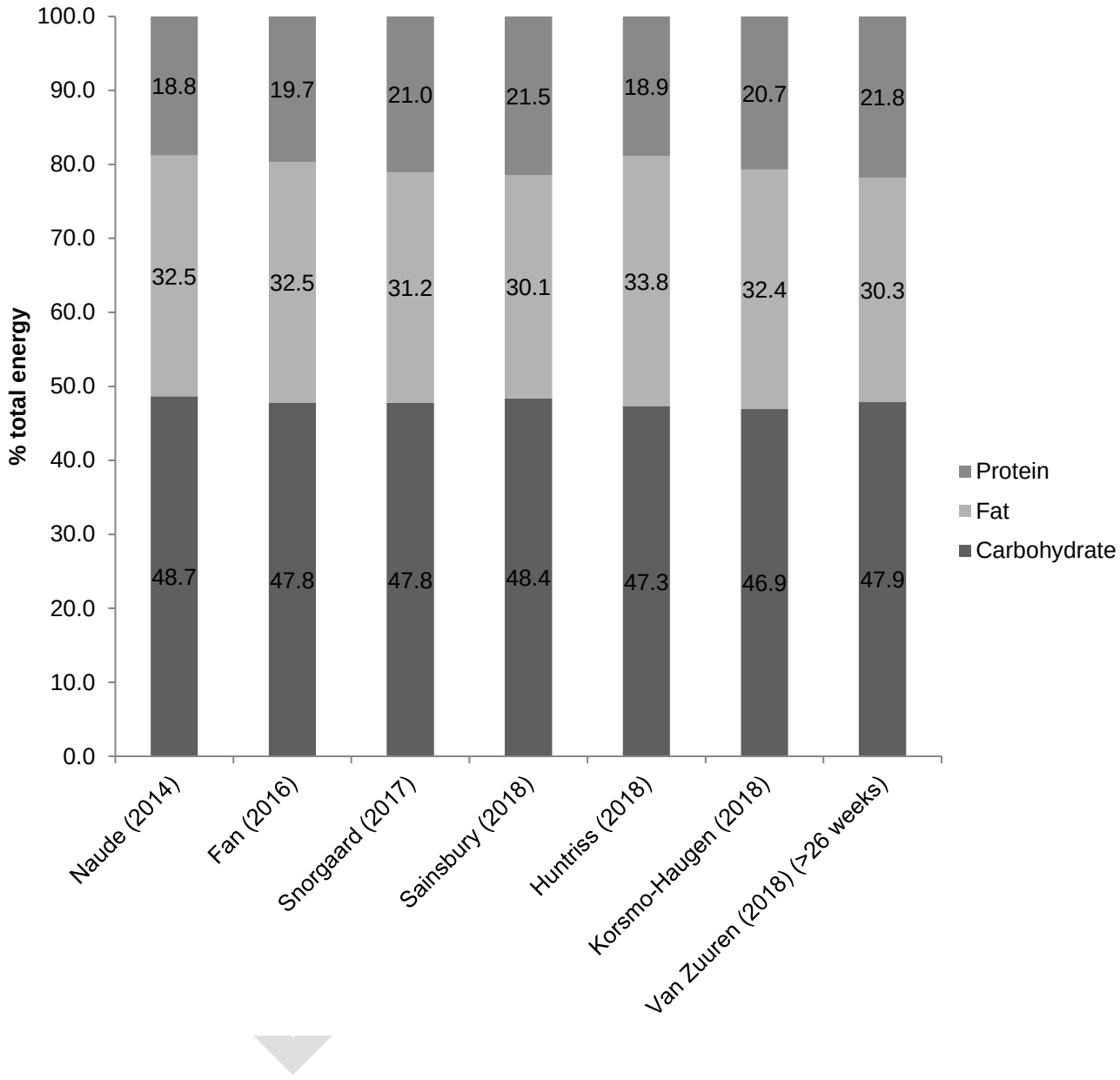
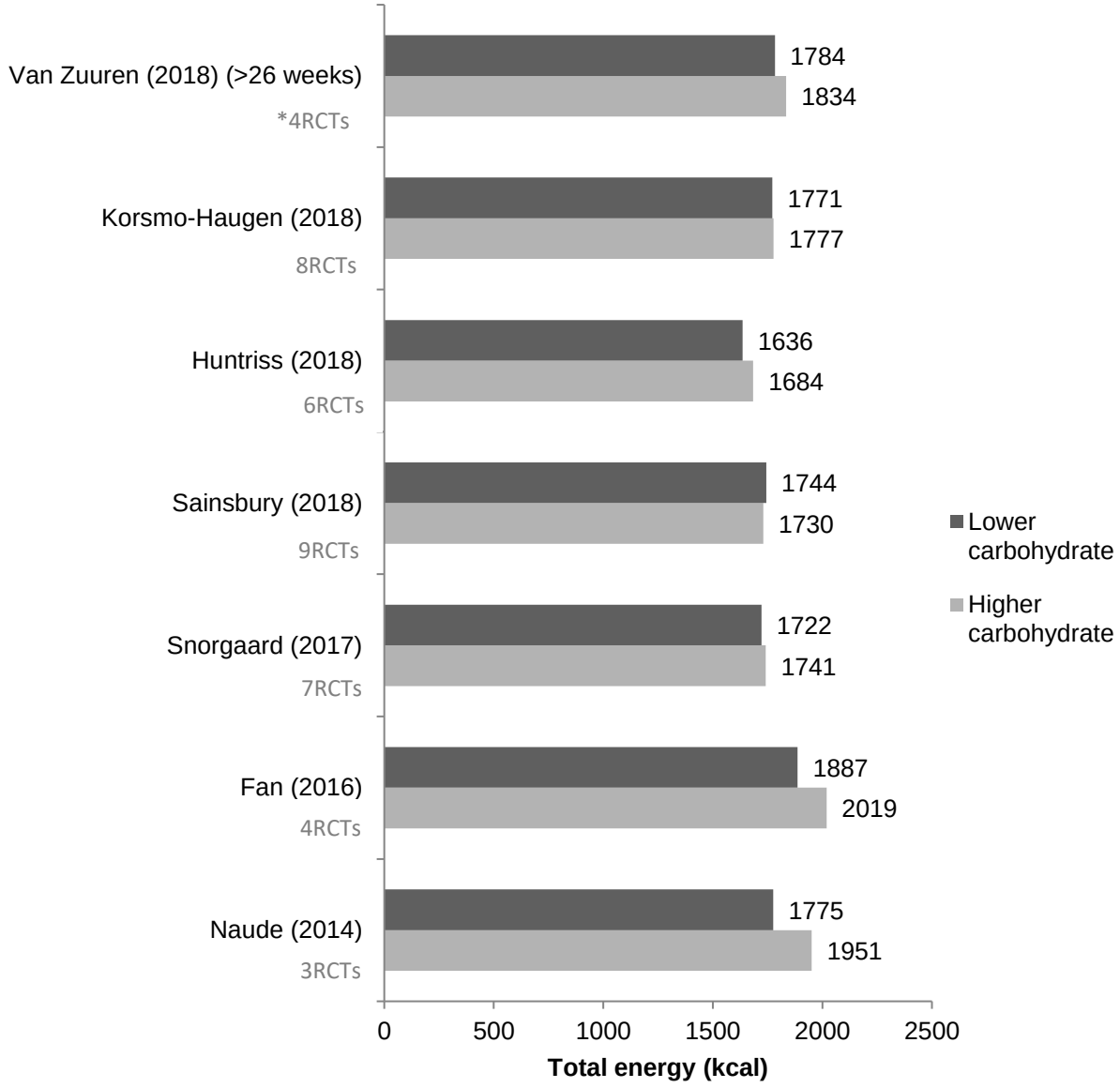
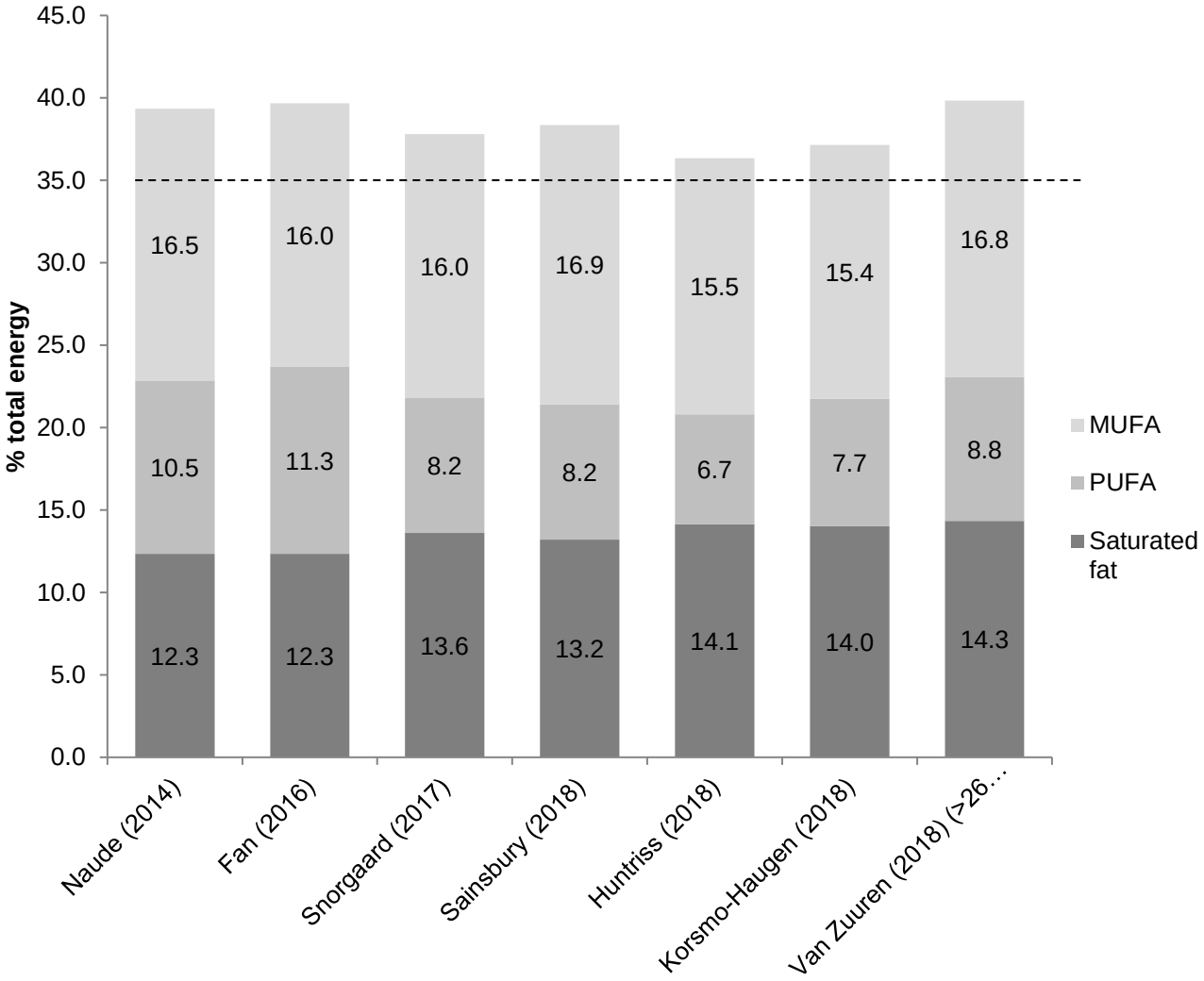


Figure A7.7: Average achieved energy intake (kcal/d) in lower and higher carbohydrate groups.



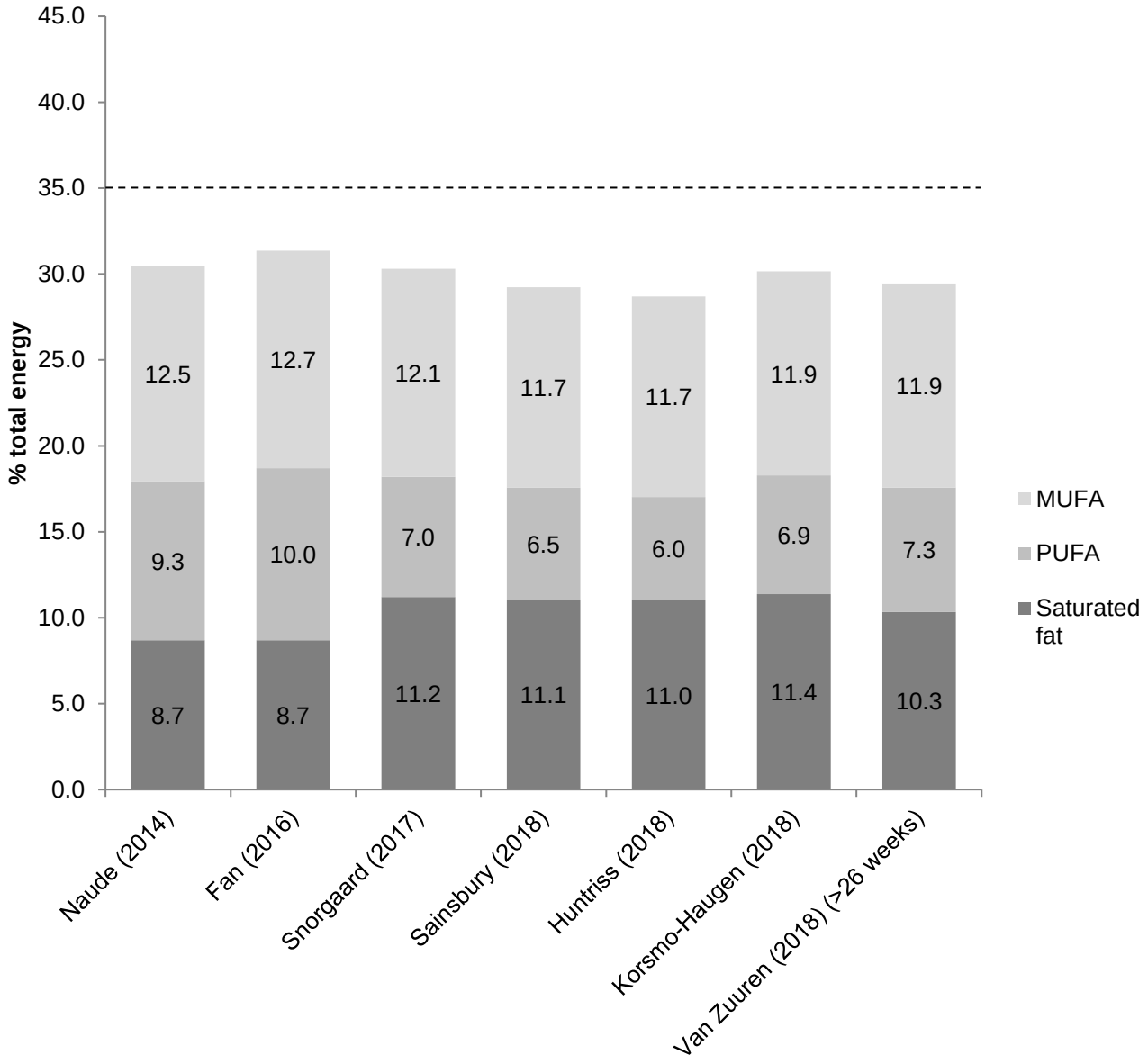
*Indicates the number of RCTs the average energy intakes are based on. Note that not all RCTs included in the meta-analyses reported energy intakes.

Figure A7.8: Average achieved fat intake in lower carbohydrate groups.



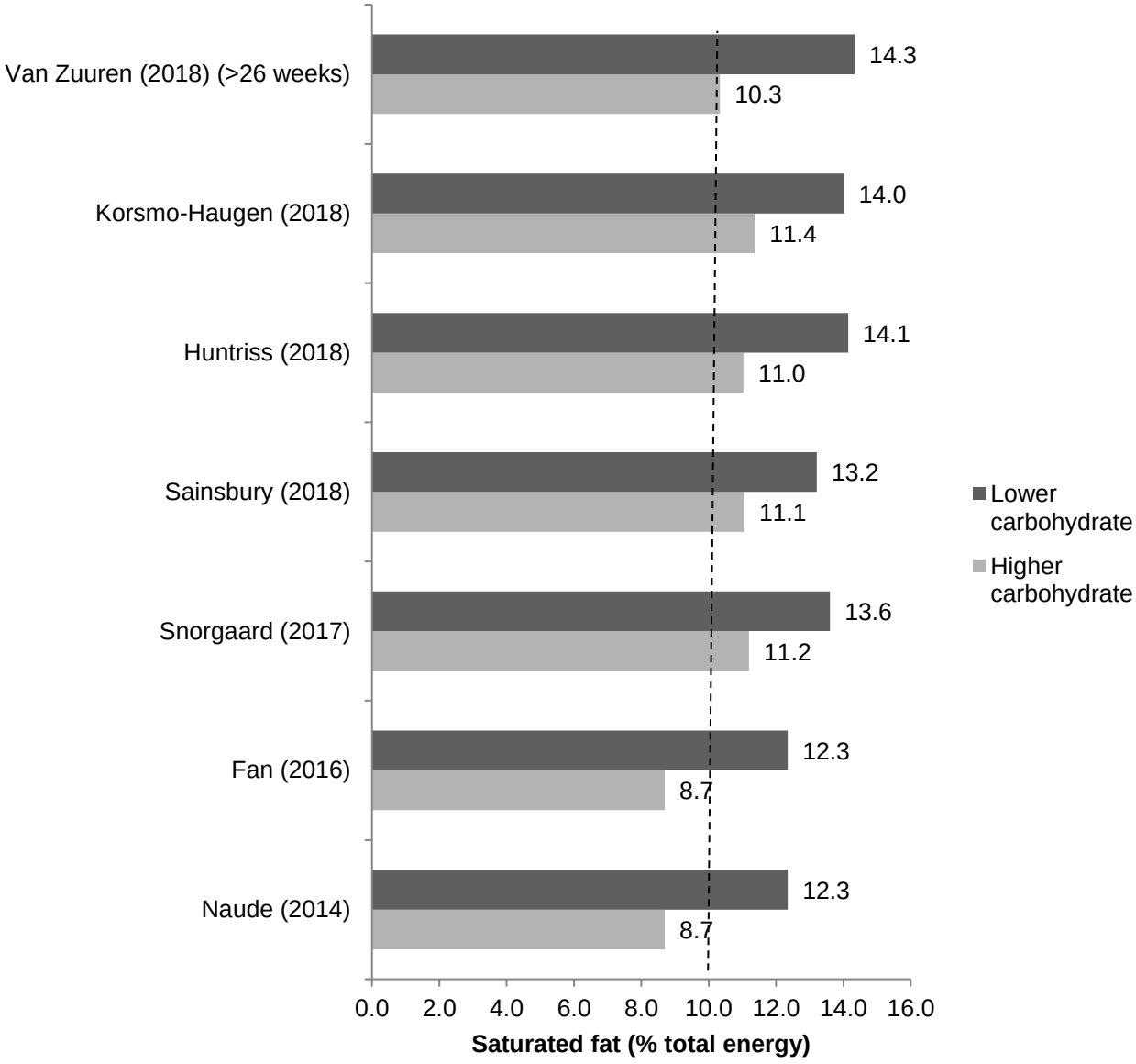
Recommendations for saturated fats: 10% of total dietary energy; recommendations for polyunsaturated fatty acids (PUFA): not exceeding 10% of total dietary energy; recommendations for monounsaturated fatty acids (MUFA): around 12% of total dietary energy. The horizontal dashed line (---) represents the dietary reference value for total fat that the average contribution of total fat to dietary energy should be 35% (DH, 1994).

Figure A7.9: Average achieved fat intake in higher carbohydrate groups.



Recommendations for saturated fats: 10% of total dietary energy; recommendations for polyunsaturated fatty acids (PUFA): not exceeding 10% of total dietary energy; recommendations for monounsaturated fatty acids (MUFA): around 12% of total dietary energy.] The horizontal dashed line (---) represents the dietary reference value for total fat that the average contribution of total fat to dietary energy should be 35% (DH, 1994).

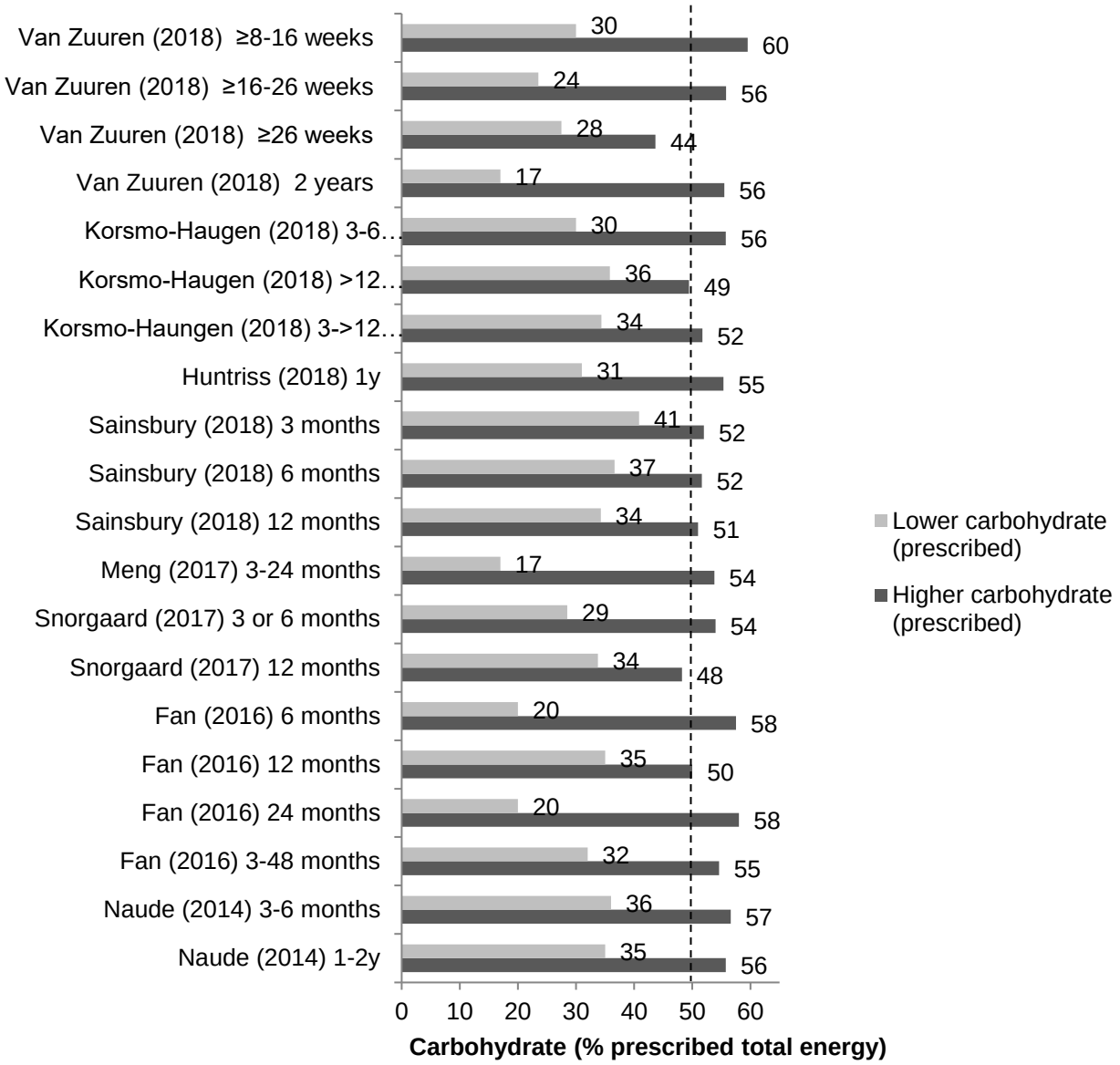
Figure A7.10: Average achieved intakes of saturated fats in lower and higher carbohydrate groups.



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

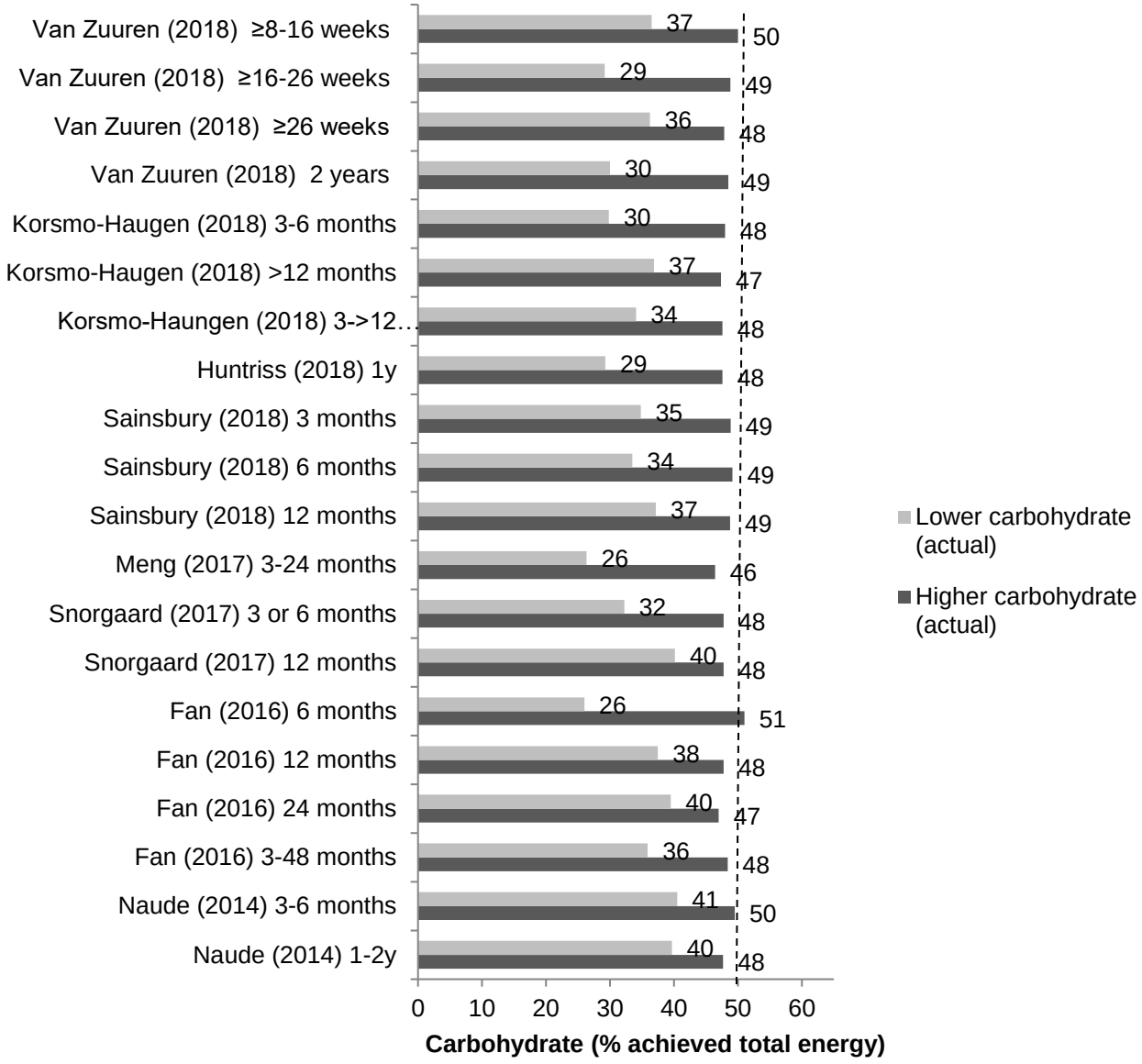
Data presented from meta-analyses for the outcome of HbA1c (Figures A7.11 to A7.20)

Figure A7.11: Average prescribed intakes of carbohydrate in lower and higher carbohydrate groups.



The vertical dashed line (---) represents the dietary reference value for total carbohydrate that should be maintained at a population average of approximately 50% of total dietary energy (SACN, 2015).

Figure A7.12: Average achieved intakes of carbohydrate in lower and higher carbohydrate groups.



The vertical dashed line (---) represents the dietary reference value for total carbohydrate that should be maintained at a population average of approximately 50% of total dietary energy (SACN, 2015).

Figure A7.13: Difference in average prescribed carbohydrate intakes in lower and higher carbohydrate groups versus difference in average achieved carbohydrate intakes in lower and higher carbohydrate groups.

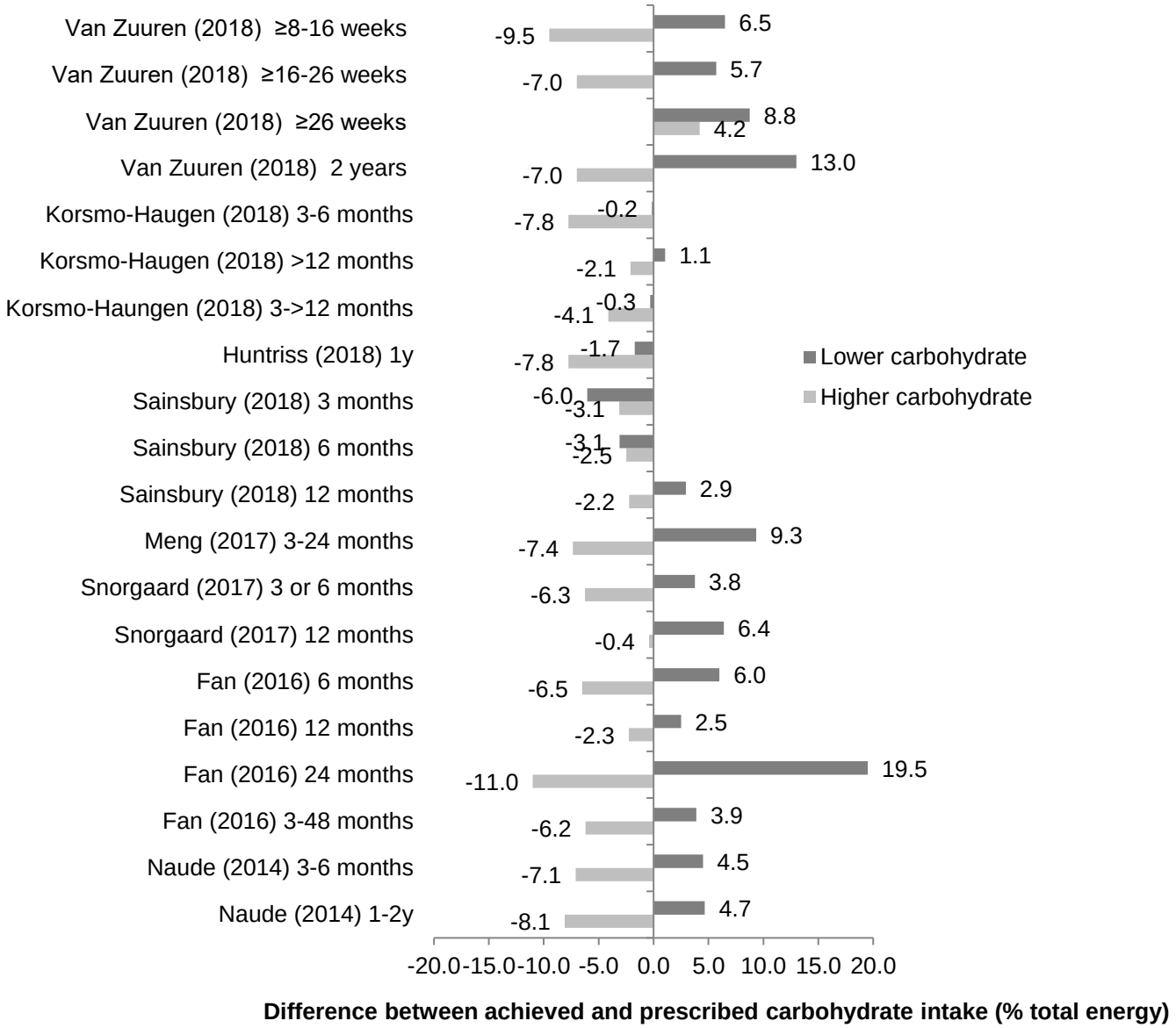
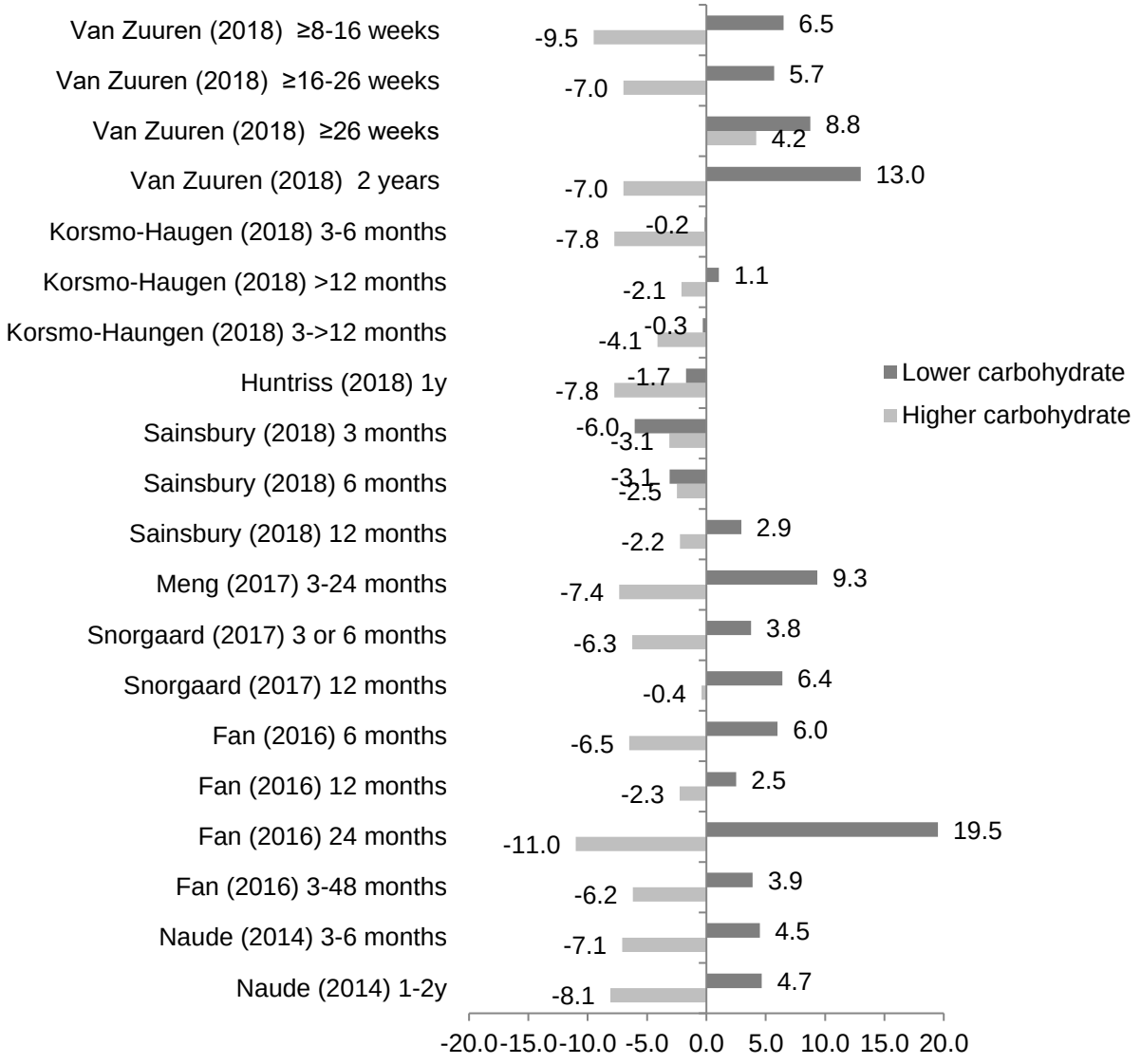


Figure A7.14: Adherence to the average prescribed intake of carbohydrate in the lower and higher carbohydrate groups.



Positive and negative values indicate that the average achieved intake was greater or lesser than the average prescribed intake, respectively.

Figure A7.15: Average achieved intakes of carbohydrate, fat and protein in lower carbohydrate groups.

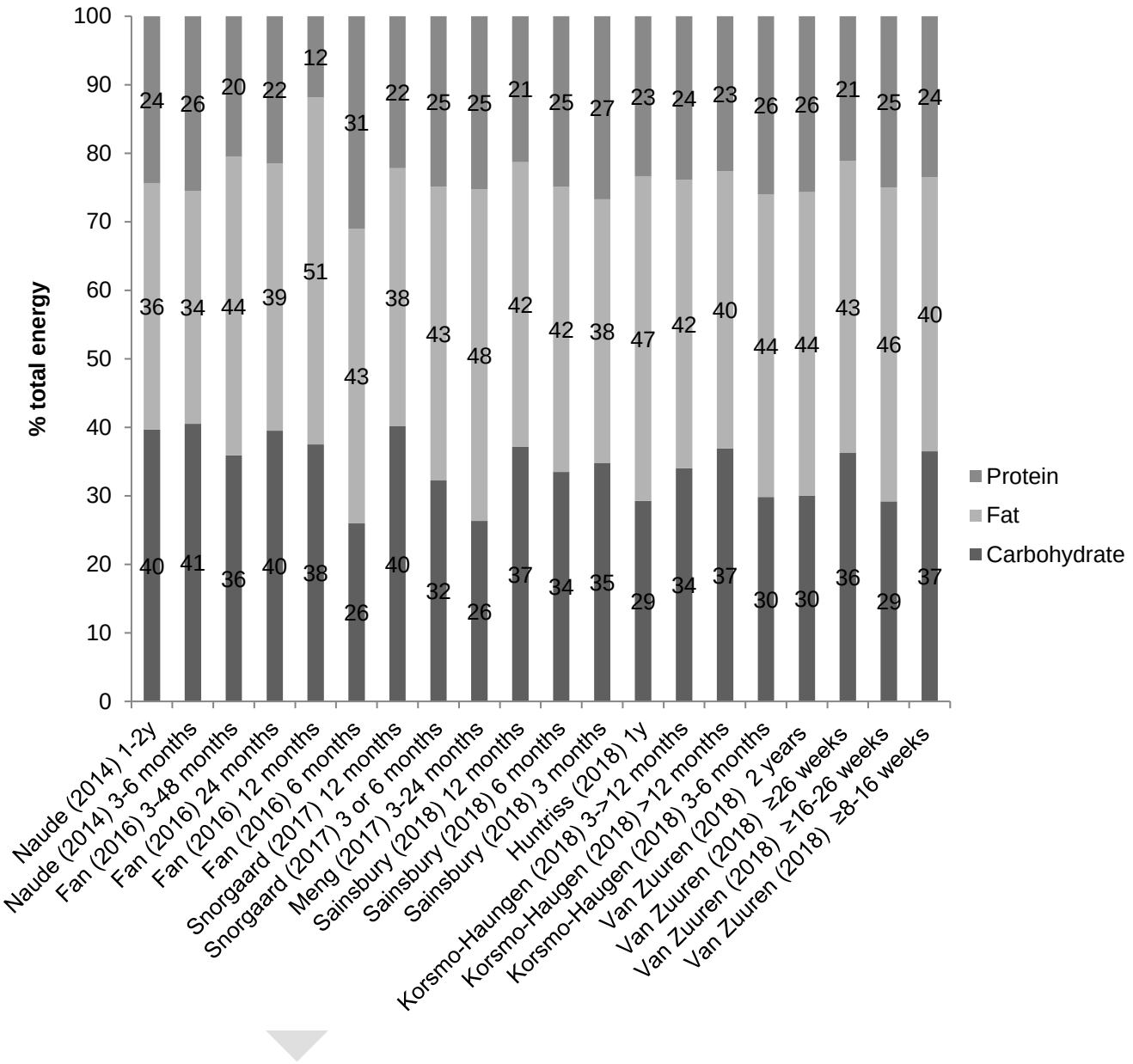


Figure A7.16: Average achieved intakes of carbohydrate, fat and protein in higher carbohydrate groups.

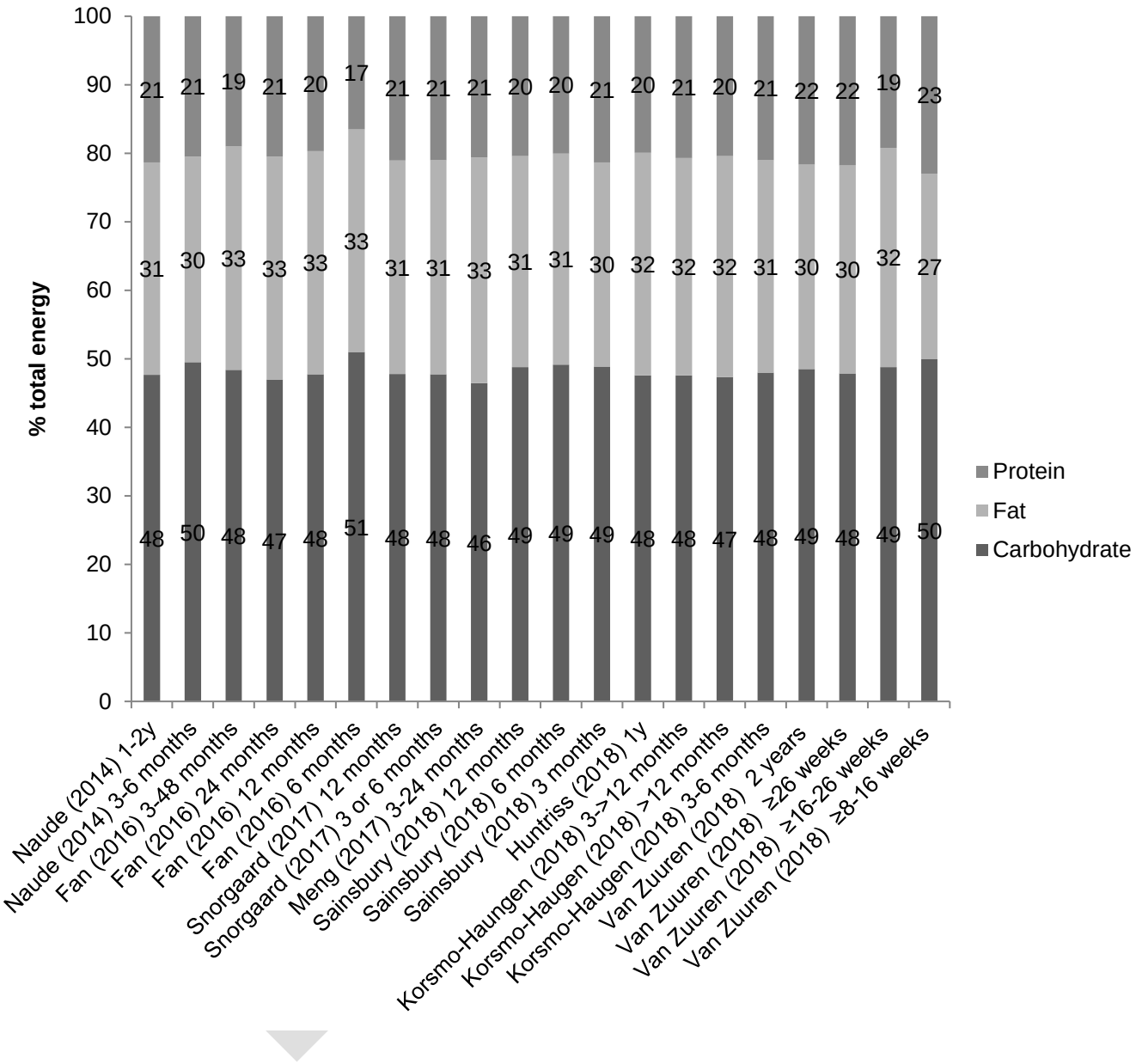
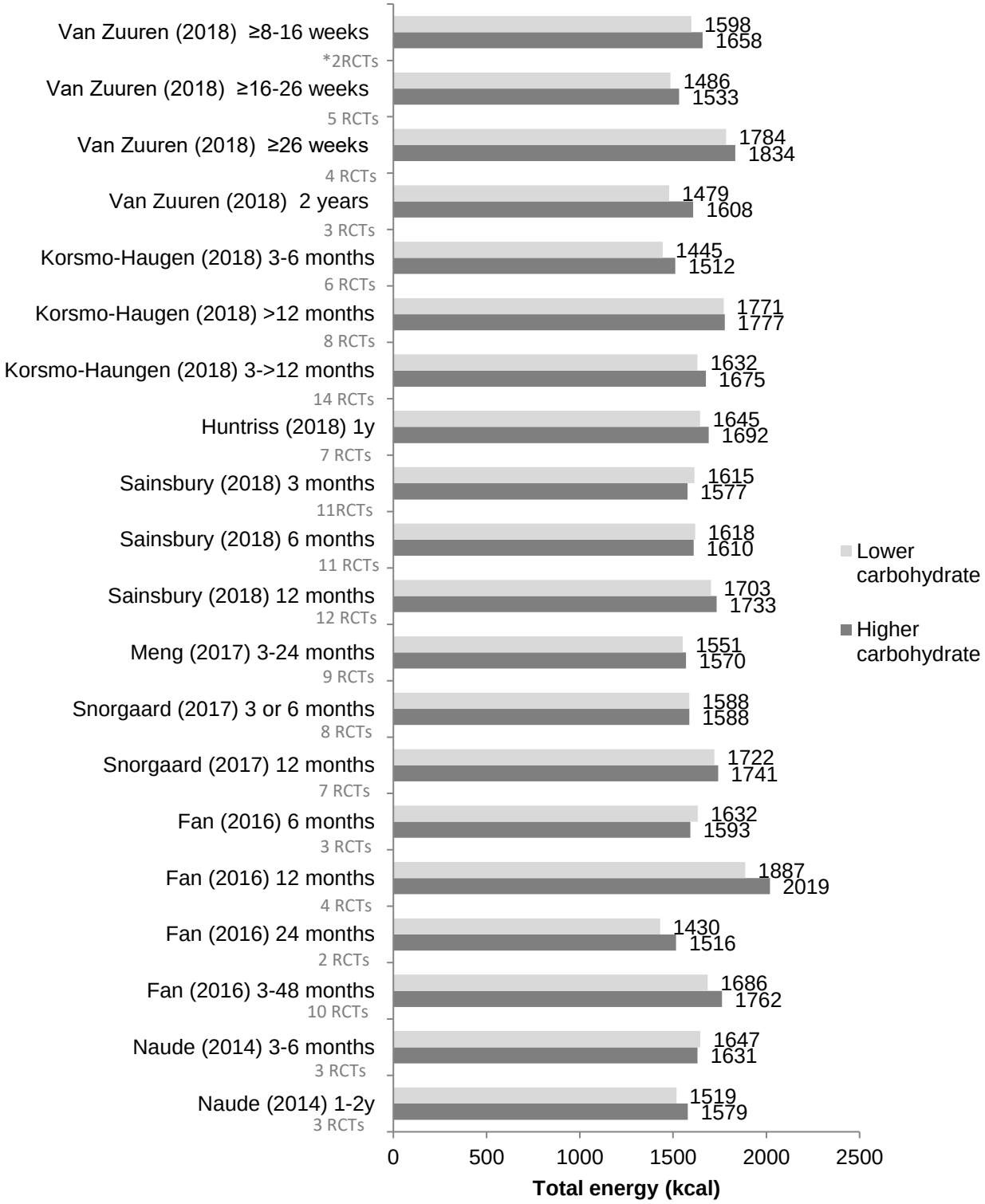
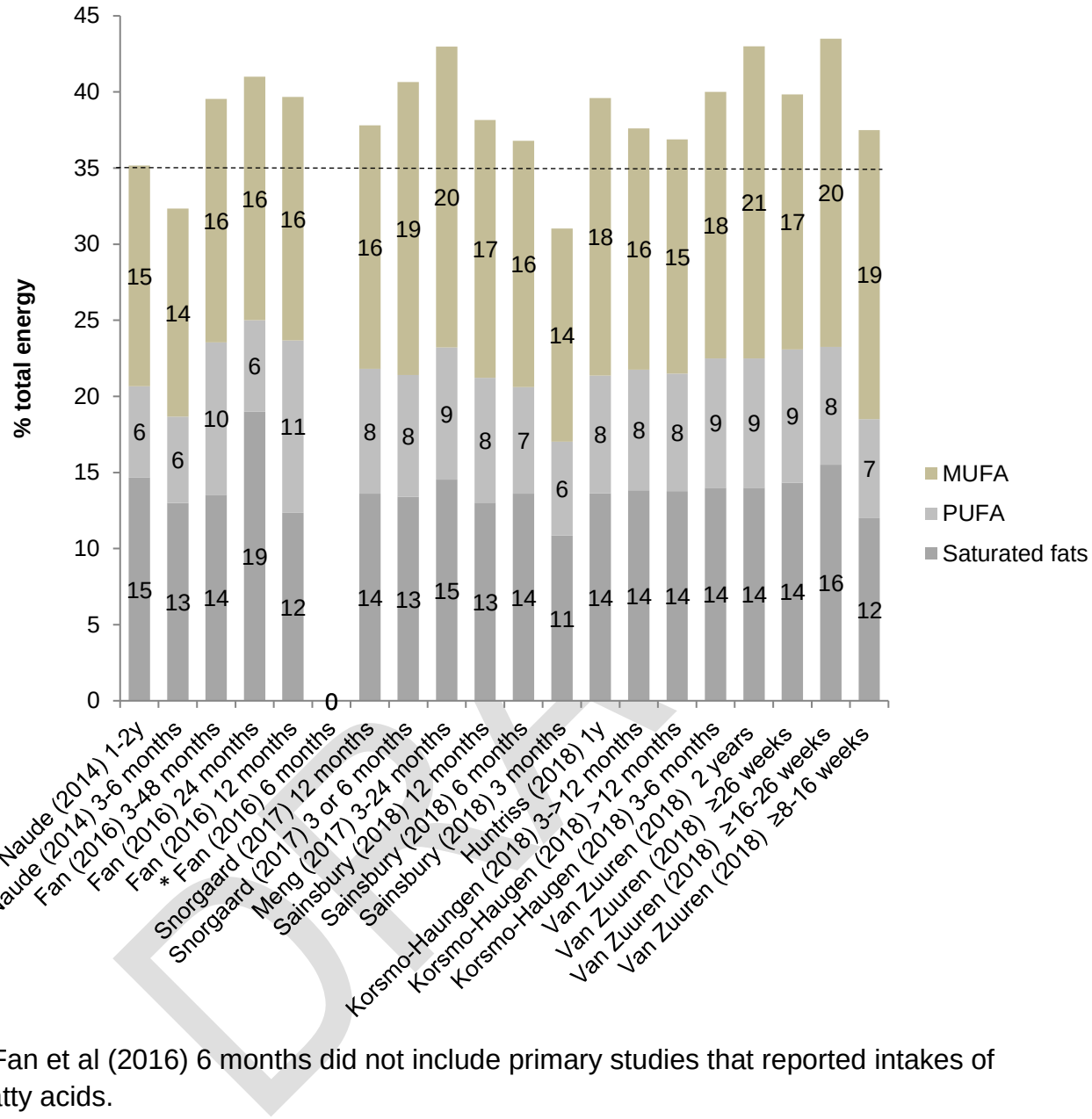


Figure A7.17: Average achieved energy intake (kcal/d) in lower and higher carbohydrate groups.



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

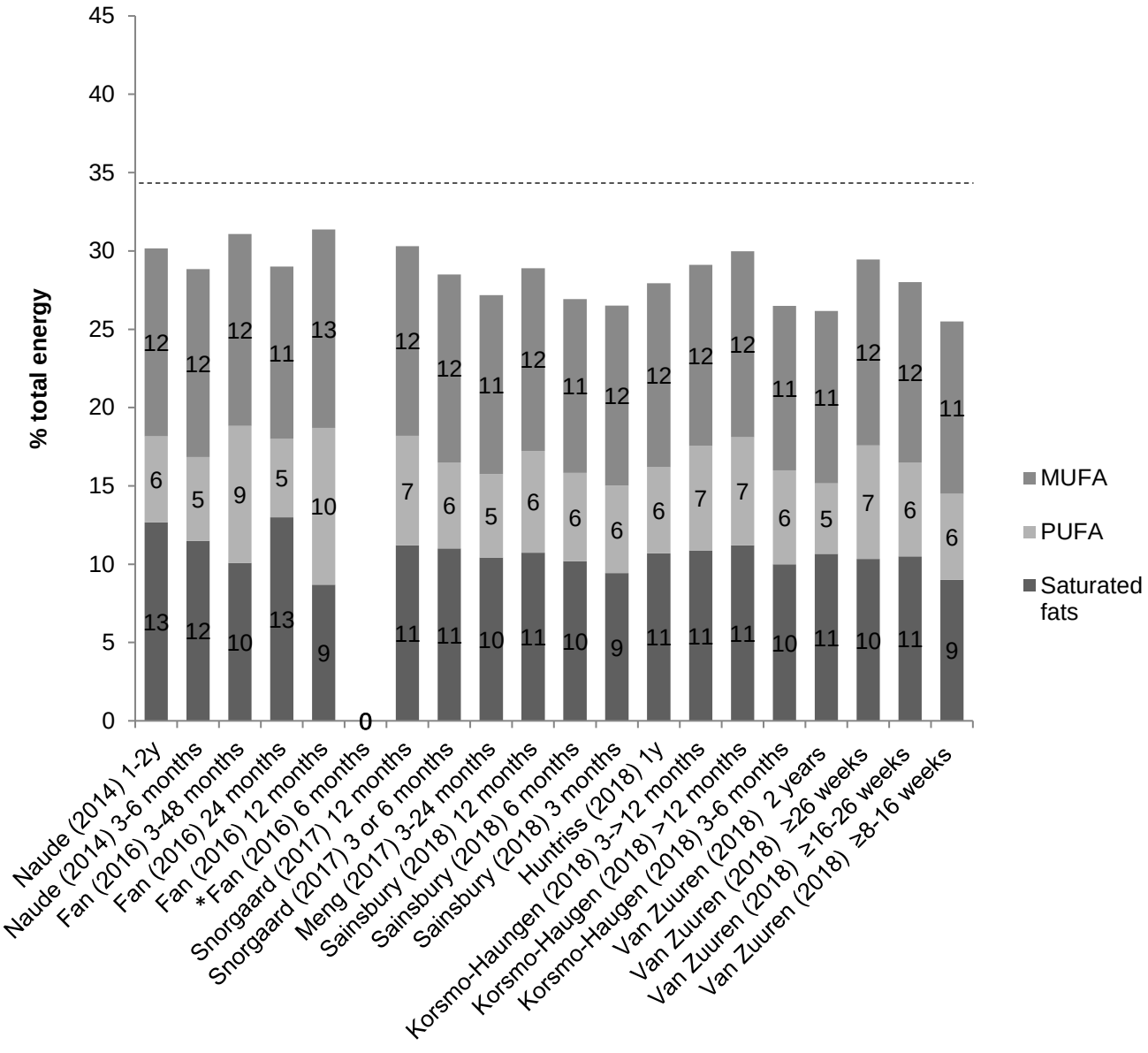
Figure A7.18: Average achieved fat intake in lower carbohydrate groups.



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

Recommendations for saturated fats: 10% of total dietary energy; recommendations for polyunsaturated fatty acids (PUFA): not exceeding 10% of total dietary energy; recommendations for monosaturated fatty acids (MUFA): around 12% of total dietary energy. The horizontal dashed line (---) represents the dietary reference value for total fat that the average contribution of total fat to dietary energy should be 35% (DH, 1994).

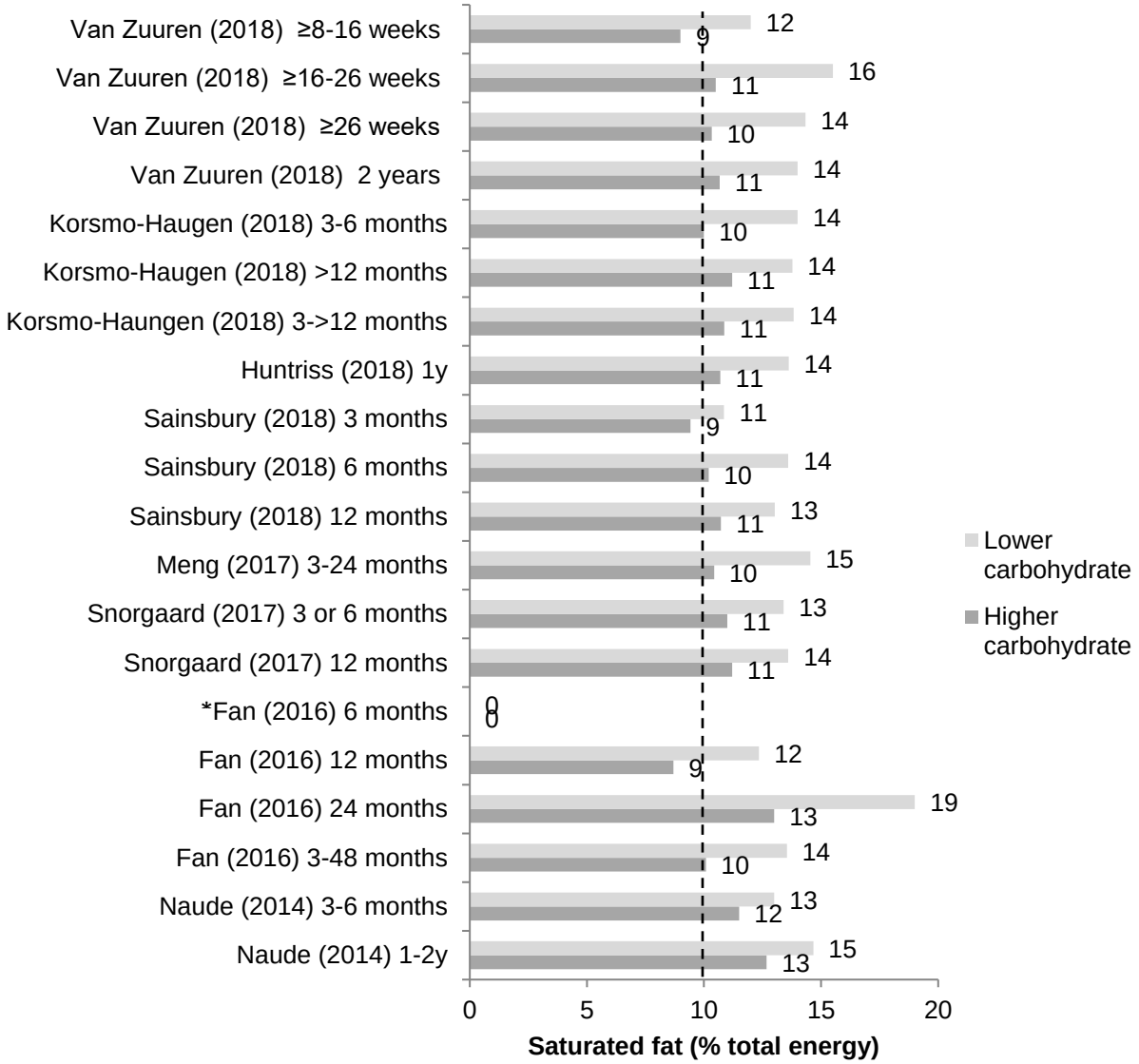
Figure A7.19: Average achieved fat intake in higher carbohydrate groups.



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

Recommendations for saturated fats: 10% of total dietary energy; recommendations for polyunsaturated fatty acids (PUFA): not exceeding 10% of total dietary energy; recommendations for monounsaturated fatty acids (MUFA): around 12% of total dietary energy. The horizontal dashed line (---) represents the dietary reference value for total fat that the average contribution of total fat to dietary energy should be 35% (DH, 1994).

Figure A7.20: Average achieved intakes of saturated fats in lower and higher carbohydrate groups.



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

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

Annex 8: AMSTAR 2 assessment

Table A8.1: Summary of the results of AMSTAR 2 assessment

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

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

Annex 9: Overview and limitations of the non-prioritised SRs and NMA

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

Overview

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

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

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

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

Schwingshackl et al (2018) (56 RCTs, 4397 participants) compared the efficacy of 9 different dietary approaches on HbA1c (primary outcome) and fasting glucose (secondary outcome). Only the comparisons relating to low carbohydrate (defined as

<25% TE [low]) and moderate carbohydrate (defined as 25 to 40% TE [low to moderate]) interventions were considered here. A low carbohydrate diet was compared with a control diet (no/minimal intervention) (all indirect comparisons), a moderate carbohydrate diet (77% indirect comparisons), a low-fat diet (defined as <30% TE) (17% indirect comparisons), or a high protein diet (defined as >20% TE) (all indirect comparisons). A moderate carbohydrate diet was compared to a control diet (81% indirect comparisons), a low-fat diet (43% indirect comparisons) and a high protein diet (all indirect comparisons). NMA was performed for both outcomes; subgroup analysis explored the effect of study duration (≥12 versus <12 m), sample size (≥100 versus <100) and age (≥60 versus <60 y). Sensitivity analyses were conducted for studies considered to be at low risk of bias.

Limitations

Meng et al (2017): most of the studies were of shorter duration, with only 3 out of the 9 RCTs (n=734) in the MA for weight were ≥12 months duration. Although a subgroup analysis was carried out for studies ≥12 versus <12 months duration, 1 of the RCTs in the ≥12 months subgroup had a duration of 24 weeks. Insufficient detail was provided in the risk of bias analysis. Only 1 primary study included in this SR with MA was not included in more recent 4 SRs with MAs.

Snorgaard et al (2017): no information was provided on statistical analysis; although 7 studies were ≥12 months duration, only 6 were included in the MA for weight and these were not specified. In the MA for weight, it was not clear if the results were differences between groups in weight change or in actual weight at study end. In the MA for HbA1c, difference between groups in HbA1c change were mixed with differences in actual HbA1c. Only 1 primary study included in this SR with MA was not included in more recent 4 SRs with MAs.

Fan et al (2016): the results were not clearly presented and were not the same in the text (weighted mean difference) and forest plots (standard mean difference). One RCT was included twice in the MA because it had 3 intervention arms (resulting in double-counting of participants in the lower carbohydrate group). Only 2 primary studies included in this SR with MA were not included in more recent 4 SRs with MAs.

Naude et al (2014): included a small number of studies (4 RCTs, 492 participants) which were all covered in the more recent MAs. In the MA of weight change, differences between groups in weight change were mixed with differences in actual weight at study end.

Annex 10: Primary and secondary outcomes considered in prioritised SRs

Table A10.1: Various markers and clinical outcomes of T2D considered in prioritised SRs with MAs contributing to the grading of evidence

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

Annex 11: Risk of bias analysis

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

Table A11.1: Risk of bias (RoB) reported in the prioritised 4 SRs

Systematic review (lead author, year)			
Huntriss, 2018	**Korsmo-Haugen, 2018**	**Sainsbury, 2018**	**van Zuuren, 2018**
Domains for assessment 1. Random sequence generation 2. Allocation concealment 3. Blinding of participants and personnel 4. Blinding of outcome assessment 5. Incomplete outcome data 6. Selective reporting **RoB of included studies:** • 15 out of 18 studies (83%) considered at high risk of performance bias (due to nature of intervention, authors had difficulty in blinding participants and study personnel).	**Domains for assessment** 1. Random sequence generation 2. Allocation concealment 3. Blinding of participants and personnel 4. Blinding of outcome assessment 5. Incomplete outcome data 6. Selective reporting 7. Other sources of bias **Overall RoB criteria** Low risk: No high RoB and not more than 2 unclear RoB High risk: 2 or more high RoB, 1 high and more than one unclear risk, or more than 4 unclear RoB Unclear risk: remaining articles classified as unclear RoB	**Domains for assessment** 1. Selection bias 2. Performance bias 3. Detection bias 4. Reporting bias 5. Attrition bias **Overall RoB criteria** Criteria for low risk, high risk and unclear risk per the Cochrane Handbook for Systematic Reviews of Interventions was used (2011). **RoB of included studies**: 15 studies reported using random sequence generation; remaining studies did not provide sufficient information. • Allocation concealment poorly reported across majority of studies (n=22). • Due to inherent difficulties in blinding	**Domains for assessment** RoB for each RCT assessed with the use of the Cochrane Collaboration's domain-based assessment tool. **Overall RoB criteria** Low risk: All domains assessed as low risk (plausible bias unlikely to seriously alter results). High risk: ≥1 domain judged as being at high risk (plausible bias that seriously weakens confidence in results). Unclear risk: ≥1 domain classified as an unclear risk (plausible bias that raises some doubt about results). **For non-randomised controlled trials**: used ROBINS-I (7-domain tool) to assess RoB. An overall RoB assigned on basis of assessment of each domain

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

Table A11.2: Overall risk of bias (RoB) in publications in MAs (36 publications)

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

H, high risk of bias; L, low risk of bias; U, unclear risk of bias; S, serious risk of bias; N/A = not applicable.

Annex 12: Medication

Table A12.1: Reported medication use in 36 publications (32 RCTs) included in MAs of prioritised 4 SRs

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

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

Study (year) (number of baseline / completers); duration	Medication type at baseline	Changes	Comments	Summary

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

de Bont (1981) (n=148/136); 6 m	• Oral hypoglycaemic drugs • Insulin	• Oral hypoglycaemic drugs: in LC group, n=10 received increased dosage • Insulin: in LC group, n=3 commenced		Descriptive
Elhayany (2010) (n=259/179); 12 m	Inclusion criteria specified no change in diabetes medication for at least 3 m before entering study. Exclusion criteria specified current insulin treatment.	NR		NR

Study (year) (number of baseline / completers); duration	Medication type at baseline	Changes	Comments	Summary
Esposito (2009) (n=215/195); 48 m	Only recruited newly diagnosed T2D individuals who had never been treated with anti-hyperglycaemic drugs. Exclusion criteria specified use of agents affecting glycaemic control. • Anti-hypertensive therapy: LC, 24%; HC, 23% • Lipid-lowering therapy: LC, 15%; HC, 16%	Significant difference between groups in need for anti-hyperglycaemic drug therapy • At 18 months: LC, 12% (95% CI 8, 16); HC 24% (95% CI, 18, 31) required treatment • At trial end: LC, -44% (95% CI, 34, 53); HC, 70% (95% CI, 62, 79) • Hazard ratio (HR)=0.63 (95% CI, 0.51, 0.86; p<0.001); HR adjusted for weight, 0.70 (95% CI, 0.59, 0.90; p<0.001)	Primary outcome measure was time to introduction of anti-hyperglycaemic drug therapy. Participants with HbA1c >7% given additional 3 m to reinforce dietary guidance and physical activity. If HbA1c remained >7%, a drug regimen was introduced.	Statistical: between-group, greater reduction in LC group
Fabricatore (2011) (n=79/50); 9 m	• Anti-diabetic medications (did not specify)	At 20 or 40 weeks: no difference between groups in % of participants who increased, decreased, did not change intensity of their diabetes medication regimen.	Medication use tracked throughout study and changes in anti-diabetic medications quantified: new medication or increased dosage from baseline (+1); no change in medications or dosages from baseline (0); or discontinued medication or decreased dosage from baseline (-1).	Descriptive
Facchini (2003) (n=191/170); 3.9 y	• Insulin: LC, 49%; HC, 51% • Metformin: LC, 6%; HC, 5% • Sulfonylurea: LC, 23%; HC, 26% • Statins LC, 9%; HC, 8% Also listed aspirin, ASI, calcium antagonist, central adrenergic blocker, β-blocker, α-blocker, diuretics	• Insulin: LC, 47%; HC, 54% • Metformin: LC, 7%; HC, 8% • Sulphonylurea: LC, 19%; HC, 21% • Statins: LC, 10%; HC, 12%	All participants had various degrees of kidney failure.	Descriptive
Goday (2016) (n=89/76) 4 m	Exclusion criteria specified T2D participants receiving insulin Oral anti-diabetic drugs: LC group, 73%; HC group, 86%	• LC group: significant decrease in number of participants taking anti-diabetic drugs (73% to 50%; p=0.027 • HC group, not significant (86% to 83%; p=0.7)		Statistical: within-group, reduction in LC group, no change in HC group

Study (year) (number of baseline / completers); duration	Medication type at baseline	Changes	Comments	Summary
Goldstein (2011) (n=52/30); 12 m	Inclusion criteria specified T2D participants not receiving insulin. • Anti-diabetic medication (did not specify).	Anti-diabetic medication not held constant during study and treatment changes differed modestly between groups.	In discussion, authors note 'Fear of hypoglycaemia necessitated the reduction of medication, limiting our ability to identify the effect of the diets on glucose values.'	Descriptive
Guldbrand (2012) (n=61/54); 24 m Note: this is the same RCT as reported by Jonasson (2014).	• Anti-diabetic medication (metformin, glibenclamide) • Insulin • Lipid-lowering (simvastatin, atorvastatin) At baseline, n=15 in LC group and n=13 in HC group on oral anti-diabetic medication only; 11 in HC group and 10 in LC were treated with insulin and oral medication.	• Anti-diabetic medication: no significant difference between groups • Insulin: no significant difference between groups in total dose. Reduction in insulin dose significant only in LC group at 6 months and between the 2 groups (p=0.046) • Lipid-lowering medications: no significant difference between groups	Reductions in oral anti-diabetic medication and insulin dose were made consecutively to avoid hypoglycaemia. Hypo-lipidaemic and anti-hypertensive medication adjusted to avoid CVD in study by physician for each patient at primary healthcare centre.	Statistical: within-group, no change in LC or HC group; between-groups, no difference
Hockaday (1978) (n=93/93); 12 m	Inclusion criteria specified T2D adults who did not require either insulin or oral hypoglycaemic agents.	Not applicable	Not applicable	Not applicable
Jenkins (2014) (n=141/119); 3 m	• Anti-hyperglycaemic (all; 100%) • Includes metformin sulfonylurea, thiazolidinedione, injectable GLP-1 analogue • Cholesterol-lowering: LC group, 71%; HC group, 71% • Blood pressure lowering: LC group, 56%; HC group, 61%	• Oral anti-glycaemic medication: no significant difference between groups • Lipid-lowering medications: no significant difference between groups		Statistical: between-group, no difference

Study (year) (number of baseline / completers); duration	Medication type at baseline	Changes	Comments	Summary
Jonasson (2014) (n=61/61); 6 m Note: this is the same RCT as reported by Guldbrand (2012).	• Oral glucose-lowering medications: 50% LC group; 42% HC group • Insulin: 10% LC group; 16% HC group • Oral glucose-lowering and insulin: 33% LC group; 35% HC group • Lipid-lowering: 73% LC group; 77% HC group	• Oral glucose-lowering medication: no change • Insulin: dose significantly reduced in LC group but not in HC group • Lipid-lowering: during study period, statin therapy initiated in 2 LC participants; hence n=24 in each group treated with statins at 6 m		Statistical: within-group, reduction in LC group, no change in HC group
Krebs (2012) (n=419/294); 24 m	• Diet only: LC, 19.3%; HC, 13.9%); all, 16.6% • Oral agents only: LC, 56%; HC, 57.4%; all, 56.7% • Insulin and oral agents: LC, 24.6%; HC, 28.7%; all, 26.7%	NR	For HbA1c and plasma glucose: differences over time estimated controlling for changes in glucose-lowering medication. For cholesterol, LDL, triacylglycerols, HDL: differences over time estimated controlling for changes in lipid-lowering medication.	NR
Larsen (2011) (n=108/99); 12 m	• None: LC, n=5 (9%); HC, n=5 (11%) • Insulin: LC, n=10 (19%); HC, n=7 (15%) • Oral anti-diabetic medication (did not specify): LC, n=38 (72%); HC, n=34 (74%)	Significantly greater reduction (p=0.05) in diabetes medication in LC group (mainly insulin and sulphonylurea).	Commonly cited reason for decreasing medication dosage was frequency of hypoglycaemic episodes. After adjusting for changes in medication, the between-group difference in HbA1c remained non-significant.	Statistical: between-group, greater reduction in LC group
Luger (2013) (n=44/42); 3 m	• Insulin therapy: all • Additional oral anti-diabetic medication (n=31) • Lipid-lowering agents (n=26) • Blood pressure medication (n=40) • Anti-coagulants (n=19)	Insulin requirement significantly reduced in LC group (p=0.01) and slightly increased in HC group after 12 weeks and significantly different between groups (p=0.007). Combining study groups, weight loss over 12 weeks was associated with changes in insulin dose (p=0.000; r=0.6). No change in concomitant medications.		Statistical: within-group, reduction in LC group, no change in HC group; between-group, greater reduction in LC group

Study (year) (number of baseline / completers); duration	Medication type at baseline	Changes	Comments	Summary
Mayer (2014) (n=46); 11 m	• Insulin +/- oral agents: LC group, n=7 (31.8%); HC group, n=8 (33.3%) • Oral agents only: LC group, n=12 (54.6%); HC group, n=14 (58.3%) • No agents: LC group, n=3 (13.6%); HC group, n=2 (8.3%)	Estimated medication effect score (MES). LC group led to greater reduction in anti-glycaemic medications. MES decreased by -1.24 (95% CI -1.80, -0.69) in LC group versus -0.82 (95% CI -1.33, -0.31) in HC+O group (p=0.27). Of the participants with complete medication data (LC, n=17; HC+O, n=23) 70.6% of LC versus 30.4% of HC+O had decreases in MES ≥50% (p=0.01).	In both arms anti-glycaemic medications were individually adjusted following an algorithm to prevent hypoglycaemia. A MES assessed overall utilisation of anti-glycaemic agents (based on medication potency and total daily dose). MES was a primary outcome of study.	Statistical: within-group, reduction in LC group and in HC group; between-group, no difference
McLaughlin (2007) (n=29/29); 3m	Inclusion criteria specified 'no use of anti-hyperglycaemic medications'.	Not applicable		NR

Nielsen (2005) (n=31/31); 6 m	• Insulin: LC, n=11; HC, n=6
	• Metformin LC, n=11; HC, n=10
	• Sulfonylurea: LC, n=5; HC, n=5
		• Insulin requirement
		  ○ LC: mean requirement decreased from 60 ± 33 to 39 ± 21 IU/d in 1st week and n=2 able to discontinue insulin within 24 weeks. Average requirement after 24 weeks was 18 ± 11 IU/d
		  ○ HC group: slight increase in mean insulin requirement during the 24 weeks
		• Sulphonylurea
		  ○ LC: n=2 discontinued, other 3 reduced doses because of episodes of hypoglycaemia
		  ○ HC group: n=1 discontinued
		• Metformin: NR
				Descriptive

Parker (2002) (n=64/54); 3 m Note: this is the same RCT as reported by Brinkworth (2004).	• Oral hypoglycaemic agents (metformin, sulfonylureas or combination of both): 48% • Insulin: 7% • Anti-hypertensive or lipid- lowering medications (% NR)	Hypoglycaemic medications: decreases in dosage occurred in 8 participants at weeks 4 and 8 (LC, n=5; HC, n=3).	Participants on anti-hypertensive or lipid-lowering medication asked to maintain the same dose throughout the study.	Descriptive

Study (year) (number of baseline / completers); duration	Medication type at baseline	Changes	Comments	Summary
Pedersen (2014) (n=76/45); 12 m	• Oral blood glucose lowering medicine and/or insulin: metformin (n=17), metformin + sulfonylurea (n=10), metformin + glitazones (n=2), metformin + sulfonylurea + glitazones (n=3), metformin + insulin glargine (n=6), metformin+sulfonylurea + insulin Novomix + mixtard (n=3) • Statins: monotherapy (n=38), both statin and ezetimibe (n=5), ezetimibe monotherapy (n=1)	• Oral blood glucose lowering medications o LC: 3 stopped, 3 decreased dose, 4 increased dose; 4 changed to other medication o HC: 4 decreased, 4 increased; 2 changed to other medication • Statins: dose decreased n=1 (LC), increased n=4 (1 LC and 3 HC), stopped n=5 (3 LC and 2 HC); changed to other medication n=3 (2 LC; 1 HC	When data for LDL cholesterol analysis confined to those who did not change medication, no effect of diet seen on LDL cholesterol.	Descriptive
Samaha (2003) (n=52/29); 6 m	• Hypoglycaemic agents: sulfonylurea (LC, 11%; HC, 16%), metformin (LC, 17%; HC, 13%) • Insulin (LC, 9%; HC, 4%) • Anti-hypertensive medications (LC, 64%; HC, 57%) • Peroxisome proliferator–activated receptor gamma agonist (LC, 2%; HC, 2%) • Lipid-lowering medication: statins (LC, 42%; HC, 37%), gemfibrozil (LC, 3%; HC, 0%)	• Hypoglycaemic agents or insulin: at 6 m, n=7 in LC group had dose reductions in oral hypoglycaemic agents or insulin; in comparison 1 participant in HC group had a dose reduction in insulin and 1 began oral therapy • Lipid-lowering medications: no changes in HC group, n=2 in LC started taking a statin and 1 stopped • Anti-hypertensive medications: no change		Descriptive
Saslow (2014) (n=34/32); 3 m	Excluded individuals using insulin or more than 3 hypoglycaemic medications. • Metformin only (LC, 31%; MC, 44%) • Metformin and another oral diabetes agent (sulfonylurea, thiazolidinediones) (LC, 44%; HC, 28%)	Discontinued 1 or more oral diabetes medications: LC (44%; n=7) versus HC (11%; n=2) (p=0.03).		Statistical: between-group, more discontinued in LC group

Study (year) (number of baseline / completers); duration	Medication type at baseline	Changes	Comments	Summary
Shai (2008) (n=46/36); 24 m	• Insulin (1%) • Oral glycaemic control medications (8%) • Lipid-lowering (26%) • Anti-hypertensive (30%)	Little change in medication use. No significant differences among groups in amount of change. • Glycaemic control: n=5 initiated medications for glycaemic control and n=1 reduced dosage • Lipid-lowering: n=4 initiated and n=3 stopped • Anti-hypertensive: n=20 initiated treatment		Statistical: between-group, no difference
Stern (2004) (n=54/34); 12 m	• Diabetes medications: sulfonylureas (LC, 11%; HC, 16%), metformin (LC, 17%, HC, 13%), insulin (LC, 9%, HC, 6%), peroxisome proliferator-activated receptor-γ agonist (LC, 2%; HC, 2% • Anti-hypertensive drugs: LC, 64%; HC, 57% • Hyperlipidaemia medications: statins (LC, 42%, HC, 37%), gemfibrozil (LC, 3%, HC, 2%)	NR		NR
Tay (2014) (n=115/93); 6 m	• Insulin • Oral anti-diabetic medication: metformin, sulfonylureas, thiazolidinediones, GLP-1 agonists, DPP-4 inhibitors • Lipid-lowering medication • Anti-hypertensive medication	• Anti-glycaemic MES ○ 2-fold greater reduction in LC versus HC group; more participants in LC group experienced reduction >20% compared with HC group (p<0.005) • Lipid-lowering medication: ○ LC, n=4 decreased, n=3 increased ○ HC, n=2 increased, n=2 increased • Anti-hypertensive medication: ○ LC, n=10 decreased, n=3 increased ○ HC, n=1 decrease, n=3 increased	Changes in diabetes medication requirements quantified by anti-glycaemic MES, which was computed on basis of potency and dosage of diabetes medications. At baseline, medication use and anti-glycaemic MES were similar in both groups.	Statistical: between-group, greater reduction in LC group

Study (year) (number of baseline / completers); duration	Medication type at baseline	Changes	Comments	Summary

Tay (2015) (n=115/78); 12 m	As above	• Anti-glycaemic MES:
		  ○ Greater reduction in LC versus HC group (p=0.02); LC, 52% and HC, 21% experienced ≥20% in anti-glycaemic MES (p<0.01)
		• Lipid-lowering medication:
		  ○ LC, n=4 decreased, n=3 increased
		  ○ HC, n=6 increased, n=1 increased
		• Anti-hypertensive medication:
		  ○ LC, n=13 decreased, n=2 increased
		  ○ HC, n=8 decrease, n=1 increased
			As above	Statistical: between-group, greater reduction in LC group

Tay (2018) (n=115/61); 24 m	As above	• Anti-glycaemic MES:
		  ○ Greater reduction in LC group, -0.5 (95% CI -0.6, -0.3) versus HC group -0.2 (95% CI -0.4, -0.02) (p=0.03)
		  ○ Over twice the number of LC participants (n=22) had a 20% reduction in MES compared to HC participants (n=9)
			As above	Statistical: between-group, greater reduction in LC group

Watson (2016) (n=61/44); 6 m	• Oral anti-diabetic medications: metformin (LC, 58%; HC, 64%), sulfonylureas (LC, 16%; HC, 18%), GLP-1 agonists (LC, 7%; HC, 7%), DPP-4 inhibitors (LC, 7%; HC, 11%) • Insulin (LC, 19%; HC, 21%) • Lipid-lowering (LC, 52%; HC, 64%) • Anti-hypertensive (LC, 61%; HC, 43%)	• Diabetes medication: MES decreased over time (p=0.02), with no significant difference between the groups (p=0.43) • Lipid-lowering medication: LC, n=1 decreased, n=1 increased; HC, n=3 decreased • Anti-hypertensive medication: dosage reduced (LC, n=5; HC, n=2) and increased for n=1 in HC group	Changes in medication use quantified by MES (basis for this not given).	Statistical: within-group, reduction in LC and in HC groups; between-group, no difference

Study (year) (number of baseline / completers); duration	Medication type at baseline	Changes	Comments	Summary
Westman (2008) (n=84/50); 6 m	• Hypoglycaemic medications: ○ LC (n=20; 95.2%) (insulin only, n=4, oral agents only, n=12; insulin and oral agents n=4) ○ HC (n=22; 75.9%) (insulin only, n=3, oral agents only, n=19)	20/21 (95%) participants in LC group eliminated or reduced medication compared with 18/29 (62%) in HC group (p<0.01). 5 individuals (LC, n=4; HC, n=1) who were taking >20 units of insulin at baseline were no longer taking insulin at end of study.		Statistical: between-group, more eliminated/reduced in LC group
Wolever (2008) (n=162/130); 12 m	Exclusion criteria specified insulin or hypoglycaemic / anti-hyperglycaemic medication use. • Anti-hypertensive: ACE inhibitor (48%); diuretic (16%); calcium channel blocker (12%); angiotensin-receptor blocker (11%); β-blocker (9%); α-blocker (3%) • Lipid-lowering medication (43%)	Doses of lipid-lowering drugs were adjusted.	Doses of lipid-lowering drugs adjusted during run-in for optimal control, then kept constant unless changes required for clinical reasons. Participants whose dose of statin changed during study (n=15) were excluded from analysis of blood lipids and lipoproteins.	Descriptive
Wycherley (2010) (n=40/28); 4 m	• Hypoglycaemic (LC, n=7; HC, n=11) • Lipid-lowering (LC, n=5; HC, n=9) • Anti-hypertensive (LC, n=4; HC, n=9)	• Hypoglycaemic medication: difference between groups not significant • Lipid-lowering medication: no change • Anti-hypertensive medication: no change	Lipid-lowering and anti-hypertensive medications encouraged to remain constant throughout the intervention.	Statistical: between-group, no difference
Yamada (2014) (n=24/24); 6 m	• Glucose-lowering drugs (LC/HC): ○ Insulin (25/33%) ○ Oral agents: metformin (42/8%); sulfonylurea (42/67%), glinide (8/0%), thiazolidinedione (33/50%), α-glucosidase inhibitor (17/0%), DPP-4 inhibitor (17/25%).	In LCD group, n=3 treated with a sulfonylurea or insulin, experienced symptomatic hypoglycaemia; the events did not recur after adjusting the medications.	Did not change medications unless hypoglycaemia occurred.	Descriptive

Table A12.2 Observations from 3 prioritised SRs with MAs* on medication change

Systematic review	Narrative summary of medication changes
Sainsbury et al (2018)	Reported that carbohydrate restriction either reduced the dosage of oral medications and/or insulin or eliminated medication for participants across all studies that reported on medication outcomes. They noted that many studies allowed medication changes throughout the intervention due to potential for hypoglycaemic episodes on carbohydrate-restricted diets. While some studies recognised the potential confounding effect of medication change and corrected for this in analysis, the majority either did not specify or stated they did not make adjustments for medication change. This may have attenuated the positive effect of carbohydrate restriction on glycaemic control. They concluded that although there were inconsistencies in the measurement and reporting of diabetes medications across studies, the results suggested that carbohydrate-restricted diets are associated with a reduction in medication dosage.
Korsmo-Haugen et al (2018)	Reported that the limited information from the included studies suggested there was a greater reduction in use of diabetes medication (mainly insulin) that may have masked a more positive impact on glycaemic control than shown in their MA. Some studies repeated their analyses adjusting for difference in medication and found it did not alter the conclusions.
van Zuuren et al (2018)	Reported that medication regimes (glucose-, blood pressure and lipid-lowering) were modified in some studies but remained unchanged in others. Some studies included medication naïve patients while others did not document medication details adequately. Out of 5 studies that included patients taking medication and that adequately reported changes,4 reported that glucose-lowering drug doses were reduced in participants on lower carbohydrate diets but not in those on higher carbohydrate diets. Inconsistent methods of quantification and reporting precluded reliable statistical analysis of changes in drug doses.

*Huntriss et al (2018) not included here because it considered medication change as an outcome (see chapter 6 in report, paragraphs 6.190 to 6.194).

Annex 13: Results of MAs in prioritised 4 SRs with MAs

Table A13.1: Change in body weight (≥12 months)

Author (year)/analysis	Results mean difference (MD) change (kg) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments (secretariat)
Sainsbury et al (2018)				
Main analysis	-0.43 (-0.93, 0.07), p=0.09; I^2=0% 10 RCTs (n=1484)	No	high (1), low (4), unclear (4), missing (1)	Participant numbers not included in forest plots (estimated here from table of included studies). 1 RCT in MA (Brinkworth, 2004) not included in Description of studies table or RoB analysis.
Subgroup analysis (by carbohydrate quantity)	low vs high carbohydrate (13% weight) 0.58 (-0.83, 1.99), p=0.42; I^2=0% 3 RCTs (n=281)	No	unclear (1), low (2)	In the *low* vs *high* carbohydrate subgroup analysis achieved carbohydrate intakes were *moderate* vs *high* in 2 out of 3 RCTs (9% of MA); 1 RCT *low* vs *high* (4% of MA).
	moderate vs high carbohydrate (87% weight) -0.58 (-1.11, -0.04), p=0.04; I^2=0%, 7 RCTs (n=1203)	Yes	high (1), unclear (3), low (2), missing (1)	In the *moderate* vs *high* carbohydrate subgroup analysis achieved carbohydrate intakes were *high* vs *high* in 2 out of 7 RCTs; *moderate* vs *high* in 3 RCTs and 1 RCT *moderate* vs *moderate* (1 NR).
Korsmo-Haugen et al (2018)				
Subgroup analysis (by study duration; 56% weight)	0.14 (-0.29, 0.57), p-value NR; I^2=0% 10 RCTs (n=1163)	No	high (1), low (3), unclear (6)	
Huntriss et al (2018)				
Main analysis	0.28 (-1.37, 1.92), p=0.74; I^2=75% 6 RCTs (n=567)	No	high in 15 of 18 studies in ≥1 of 6 criteria. High risk of performance bias in 15/18 (83%) studies.	
van Zuuren et al (2018)				
Main analysis	-0.19 (-1.65, 1.27), p=0.80; I^2=0% 5 RCTs (n=483)	No	unclear (4), high (1)	
Sensitivity analysis (excluding studies at high risk of bias)	0.12 (-1.53, 1.76), p=0.69; I^2= 0% 4 RCTs (n=367)	No	unclear (4)	

Table A13.2A: Change in HbA1c (≥3 to <12 m)

Author (year)/analysis	Results mean difference (MD) change (%) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments (secretariat)
Sainsbury et al (2018)				
3 m Main analysis	-0.19 (-0.33, -0.05), p=0.008; I^2=28% 12 RCTs (n=953)	Yes	high (4); low (3); unclear (5)	
Subgroup analysis (by carbohydrate quantity)	low vs high carbohydrate (26% weight) -0.47 (-0.71, -0.23), p=0.0001; I^2=0% 4 RCTs (n=321)	Yes	high (1); low (2); unclear (1)	Out of 4 RCTs in *low* carbohydrate subgroup, achieved carbohydrate intakes were *moderate* in 2 RCTs.
	moderate vs high carbohydrate (74% weight) -0.06 (-0.17, 0.06), p=0.33; I^2=0% 8 RCTs (n=632)	No	high (3); low (1); unclear (4)	Out of 8 RCTs in *moderate* carbohydrate subgroup, achieved carbohydrate intakes were *high* in 2 RCTs (1 did not report achieved intakes).
Sensitivity analysis (excluding studies with significantly greater weight loss on lower carbohydrate diet)	-0.05 (-0.17, 0.06), p =0.35; I^2=0% 7 RCTs (n=588)	No	high (3); low (1); unclear (3)	
Sensitivity analysis (excluding studies at high RoB)	-0.25 (-0.42, -0.07), p-value NR; I^2=NR 8 RCTs (n=614)	Yes	low (3); unclear (5)	
Subgroup analysis (excluding studies at high RoB)	low vs high carbohydrate (% weight, NR) -0.45 (-0.69, -0.20), p-value NR; I^2=NR 3 RCTs (n=-237)	Yes	low (2); unclear (1)	Details of studies in this analysis not included so unable to check achieved carbohydrate intakes in *low* and *high* categories.
	moderate vs high carbohydrate (% weight, NR) -0.09 (-0.24, 0.06), p-value NR; I^2=NR% 5 RCTs (n=377)	No	low (1); unclear (4)	

Author (year)/analysis	Results mean difference (MD) change (%) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments (secretariat)
Sainsbury et al (2018)				
6 m Main analysis	-0.19 (-0.35, -0.02), p-value NR; I^2=44% 10 RCTs (n=1173)	Yes	high (2); low (4); unclear (4)	
Subgroup analysis (by carbohydrate quantity)	low vs high carbohydrate (26% weight) -0.36 (-0.62, -0.09), p=0.008; I^2=0% 5 RCTs (n=328)	Yes		In the *low* vs *high* subgroup analysis, achieved carbohydrate intakes were *moderate* in 3 out of the 5 RCTs. Results of subgroup analysis for *moderate* vs *high* carbohydrate not reported here because included 1 RCT of adults with T1D (Strychar, 2009).
6 m Sensitivity analysis (excluding studies at high risk of bias)	-0.21(-0.38, -0.05), p-value NR; I^2=NR 8 RCTs (n=927)	Yes	low (4); unclear (4)	6 m sensitivity analysis *(omitting studies with significantly greater weight loss on lower carbohydrate diet*) not included because Strychar (2009) included (see above).
Subgroup analysis (by carbohydrate quantity)	low vs high carbohydrate (% weight, NR) -0.31 (-0.59, -0.04), p-value NR; I^2=NR 4 RCTs (n=244)	Yes	low (2); unclear (2)	
	moderate vs high carbohydrate (% weight, NR) -0.17 (-0.42, 0.09), p-value NR; I^2=NR 4 RCTs (n=683)	No	low (2); unclear (2)	Forest plots not included for these so not clear which studies were in subgroup analyses.

Author (year)/analysis	**Results** mean difference (MD) change (%) (95% CI), p-value; I^2 number of studies (participants)	**Significant**	**Risk of bias (RoB)** (author assessment)	**Comments** (secretariat)
van Zuuren et al (2018)				
4 to 6 m Main analysis	-0.26% (-0.50, -0.02), p=0.04; I^2 =59% 7 RCTs (n=539)	Yes	serious (1); unclear (6)	
Sensitivity analysis (fixed-effects model)	-0.23% (-0.38, -0.09), p=0.001; I^2 =59% 7 RCTs (n=539)	Yes	serious (1); unclear (6)	
Sensitivity analysis (excluding studies causing substantial heterogeneity)	-0.42% (-0.61, -0.24), p<0.00001; I^2 =0% 5 RCTs (n=310)	Yes	serious (1); unclear (4)	
Sensitivity analysis (excluding studies at high RoB)	-0.20% (-0.44, 0.04), p=0.1; I^2 =55% 6 RCTs (n=508)	No	unclear (6)	
Korsmo-Haugen et al (2018)				
3 to 6 m Subgroup analysis by duration (46.8% weight)	-0.17% (-0.27, -0.08), p-value: NR; I^2= 0% 6 RCTs (n=395)	Yes	high (5), unclear (1)	Also performed subgroup analysis with *low* and *moderate* carbohydrate studies separated but combined results of shorter and longer-term studies.

Author (year)/analysis	Results mean difference (MD) change (%) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments (secretariat)
Huntriss et al (2018)	Did not perform MA at 3 and 6 m			
3 m Main analysis	5 out of 7 RCTs reported average difference of ≥0.2% favouring lower carbohydrate diet with 3 of these reporting a difference of ≥0.5%. Remaining 2 studies reported no difference between groups. 2 studies reported a statistically significant difference in favour of the low carbohydrate group ($p<0.05$); however, when 1 of these studies adjusted results for differences in baseline HbA1c, statistical significance was lost ($p=0.06$).	N/A	high in 15 of 18 studies in ≥1 of the 6 criteria. High risk of performance bias in 15/18 (83%) studies	
6 m Main analysis	7 out of 8 RCTs reported improvement of ≥0.2% in favour of lower carbohydrate diet with 3 reporting improvements ≥0.5%. The remaining study reported no difference between groups. 4 studies reported a statistically significant difference between groups in favour of the lower carbohydrate diet; 1 study reported that statistical significance lost after taking account of differences in baseline HbA1c.	N/A	as above	

Table A13.2B: Change in HbA1c (≥12 months)

Author (year)/analysis	Results mean difference (MD) change (%) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments (secretariat)
Sainsbury et al (2018)				
12 m Main analysis	-0.09 (-0.21, 0.03), p=0.12; I^2=16% 12 RCTs (n=1600)	No	high (1), low (5), unclear (4); missing (2)	Sample size estimated from primary papers because not reported in forest plot. 2 RCTs included here that are not listed in table of included studies (Stern 2004, Brinkworth 2004); Stern and Brinkworth also missing from RoB analysis.
Subgroup analysis (by carbohydrate quantity)	low vs high carbohydrate (18% weight) -0.17 (-0.44, 0.09), p=0.19; I^2=0% 4 RCTs (n=335)	No	low (2), unclear (1), missing (1)	In *low* vs *high* subgroup analysis, actual intake was *moderate* in 3 out of the 4 RCTs.
	moderate vs high carbohydrate (82% weight) -0.08 (-0.23, 0.06), p=0.25; I^2=30% 8 RCTs (n=1265)	No	high (1), low (3), unclear (3), missing (1)	In *moderate* vs *high* subgroup analysis, actual intake was *high* in 2 out of the 8 RCTs.
Sensitivity analysis (excluding studies at high RoB)	-0.13 (-0.26, -0.01), p-value NR; I^2=NR 11 RCTs (n=1438)	Yes	how (5), unclear (4); missing (2)	
	low vs high CHO (% weight NR) -0.17 (-0.44, 0.09), p-value NR; I^2=NR 4 RCTs (n= 335)	No	low (2), unclear (1); missing (1)	Details of which studies in this analysis not included so unable to check achieved carbohydrate intakes in the *low* and *moderate* categories.
	moderate vs high CHO (% weight NR) -0.13 (-0.30, 0.03), p-value NR; I^2=NR 7 RCTs (n=1103)	No	low (3), unclear (3), missing (1)	High risk of bias study (Wolever, 2008) is deleted for this sensitivity analysis.
24 m Main analysis	-0.11 (-0.38, 0.15), p=NR; I^2=NR 3 RCTs (n=NR)	No	NR	Results reported in narrative; details not provided.
Korsmo-Haugen et al (2018) **≥12 m** Subgroup analysis by duration (53% weight)	0.00 (-0.10, 0.09), p-value: NR; I^2=0% 10 RCTs (n=1030)	No	low (3), unclear (7)	
Huntriss et al (2018) **12 m** Main analysis	-0.28 (-0.53, -0.02), p=0.03; I^2=54% 7 RCTs (n= 645)	Yes	high in 15 of 18 studies in ≥ 1 of the 6 criteria. High risk of performance bias in 15/18 (83%) studies.	

Author (year)/analysis	Results mean difference (MD) change (%) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments (secretariat)
van Zuuren et al (2018)				
≥12 m Main analysis	-0.36% (-0.58, -0.14), p=0.001; I^2=0% 4 RCTs (n=390)	Yes	high (1), unclear (3)	
Sensitivity analysis (excluding studies at high RoB)	-0.25 (-0.66, 0.15), p=0.22; I^2=0% 3 RCTs (n=274)	No	unclear (3)	
24 m Main analysis	0.02 (-0.37, 0.41), p=0.93; I^2=13% 3 RCTs (n=199)	No	unclear (3)	
Sensitivity analysis (fixed-effects model)	0.06 (-0.27, 0.39), p=0.74; I^2=13% 3 RCTs (n=199)	No	unclear (3)	

Table A13.3: Fasting plasma glucose

Author (year)/analysis	Results mean difference (MD) change (mmol/L) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments (secretariat)
Shorter-term studies (≥3 to <12 m)				
van Zuuren et al (2018)				
4 to 6 m Main analysis	-0.51 (-0.91, -0.12), p=0.01; I^2 =71%, 6 RCTs (n=396)	Yes	serious (1), unclear (5)	
Sensitivity analysis (fixed-effects model)	-0.27 (-0.38, -0.16), p<0.00001; I^2 =71% 6 RCTs (n=396)	Yes	serious (1), unclear (5)	Unclear why sensitivity analysis was carried out using fixed-effects model when I^2=92%.
Sensitivity analysis (excluding studies causing substantial heterogeneity)	-0.76 (-1.05, -0.47), p<0.00001; I^2 =0% 4 RCTs (n=167)	Yes	serious (1), unclear (3)	
Sensitivity analysis (excluding studies at high RoB)	-0.41 (-0.78, -0.03), p=0.03; I^2 =67% 5 RCTs (n=365)	Yes	unclear (5)	
Longer-term studies (≥12 m)				
van Zuuren et al (2018)				
≥12 m Main analysis	-0.37 (-1.22, 0.48), p=0.39; I^2= 92% 4 RCTs (n=340)	No	high (1), unclear (3)	
Sensitivity analysis (fixed-effects model)	-0.51 (-0.72, -0.30), p<0.00001; I^2= 92% 4 RCTs (n=340)	Yes	high (1), unclear (3)	Unclear why sensitivity analysis was carried out using fixed-effects model when I^2=92%.
Sensitivity analysis (excluding studies causing substantial heterogeneity)	Results not considered (only 2 primary studies in MA)	N/A	N/A	
Sensitivity analysis (excluding studies at high RoB)	-0.05 (-1.11, 1.02), p=0.93; I^2= 92% 3 RCTs (n=224)	No	unclear (3)	
24 m Main analysis	Results not considered (only 2 primary studies in MA)	N/A	N/A	

Table A13.4: Serum total cholesterol

Author (year)/analysis	Results mean difference (MD) change (mmol/L) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments (secretariat)
Shorter-term studies (≥3 to <12 m)				
Korsmo-Haugen et al (2018) **3 to 6 m** Subgroup analysis by duration (24% weight)	-0.06 (-0.41, 0.30), p-value: NR; I^2= 57% 4 RCTs (n=279)	No	high (2), unclear (2)	
Longer-term studies (≥12 m)				
Korsmo-Haugen et al (2018) **>12 m** Subgroup analysis by duration (76% weight)	0.07 (-0.04, 0.19), p-value: NR; I^2= 23% 10 RCTs (n=1094)	No	high (1), low (3), unclear (6)	
Huntriss et al (2018) **12 m** Main analysis	-0.08 (-0.23, 0.08), p=0.35; I^2=60% 7 RCTs (n=645)	No	high in 15 of 18 studies in ≥ 1 of the 6 criteria. High risk of performance bias in 15/18 (83%) studies.	

Table A13.5: Serum triacylglycerol

Author (year)/analysis	Results mean difference (MD) change (mmol/L) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments (secretariat)
Shorter-term studies (≥3 to <12 m)				
van Zuuren et al (2018)				
4 to 6 m Main analysis	-0.22 (-0.37, -0.08), p=0.002; I^2=41% 6 RCTs (n=508)	Yes	unclear (6)	
Sensitivity analysis (fixed-effects model)	-0.22 (-0.32, -0.11), p<0.0001; I^2=41% 6 RCTs (n=508)	Yes	unclear (6)	
Korsmo-Haugen et al (2018)				
3 to 6 m Subgroup analysis by duration (31% weight)	-0.18 (-0.36, 0.00), p-value: NR; I^2=20% 7 RCTs (n=424)	-	high (5), unclear (2)	Significance not reported in paper. To note: upper CI=0.
Longer-term studies (≥12 m)				
Korsmo-Haugen et al (2018)				
>12 m Subgroup analysis by duration (69% weight)	-0.10 (-0.23, 0.03), p-value: NR; I^2=61% 9 RCTs (n=967)	No	low (3), unclear (6)	
Huntriss et al (2018)				
12 m Main analysis	-0.24 (-0.35, -0.13), p<0.0001; I^2=0% 7 RCTs (n=645)	Yes	high in 15 of 18 studies in ≥1 of the 6 criteria. High risk of performance bias in 15/18 (83%) studies.	

Author (year)/analysis	Results mean difference (MD) change (mmol/L) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments (secretariat)
van Zuuren et al (2018)				
≥12 m Main analysis	-0.25 (-0.47, -0.04), p=0.02; I^2= 73% 5 RCTs (n=468)	Yes	high (1), unclear (4)	
Sensitivity analysis (fixed-effects model)	-0.25 (-0.36, -0.15), p<0.00001; I^2= 73% 5 RCTs (n=468)	Yes	high (1), unclear (4)	
Sensitivity analysis (excluding studies causing substantial heterogeneity)	-0.14 (-0.26, -0.02), p=0.02; I^2= 0% 4 RCTs (n=352)	Yes	unclear (4)	
Sensitivity analysis (excluding studies at high RoB)	As above	Yes	unclear (4)	
24 m Main analysis	Results not considered (**only 2 RCTs in MA**)	N/A	N/A	

Table A13.6: Serum LDL cholesterol

Author (year)/analysis	Results mean difference (MD) change (mmol/L) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments (secretariat)
Shorter-term studies (≥3 to <12 m)				
van Zuuren et al (2018)				
4 to 6 m Main analysis	0.02 (-0.09, 0.13), p=0.75; I^2= 0% 5 RCTs (n=372)	No	unclear (5)	
Korsmo-Haugen et al (2018)				
3 to 6 m Subgroup analysis by duration (34% weight)	-0.08 (-0.29, 0.14), p-value: NR; I^2= 50% 6 RCTs (n=345)	No	high (4), unclear (2)	
Longer-term studies (≥12 m)				
Korsmo-Haugen et al (2018)				
>12 m Subgroup analysis by duration (66% weight)	0.03 (-0.10, 0.16), p-value: NR; I^2= 51% 9 RCTs (n=1064)	No	high (1), low (3), unclear (5)	
Huntriss et al (2018)				
12 m Main analysis	0.05 (-0.10, 0.19), p=0.54; I^2=0% 5 RCTs (n=389)	No	high in 15 of 18 studies in ≥ 1 of the 6 criteria. High risk of performance bias in 15/18 (83%) studies.	
van Zuuren et al (2018)				
≥12 m Main analysis	-0.07 (-0.23, 0.09), p=0.41; I^2= 50% 4 RCTs (n=375)	No	high (1), unclear (3)	
Sensitivity analysis (fixed-effects model)	-0.08 (-0.20, 0.03), p=0.15; I^2= 50% 4 RCTs (n=375)	No	high (1), unclear (3)	
Sensitivity analysis (excluding studies causing substantial heterogeneity/high RoB)	0.00 (-0.14, 0.15), p=0.95; I^2= 0% 3 RCTs (n=259)	No	unclear (3)	

Table A13.7: Serum HDL cholesterol

Author (year)/analysis	Results mean difference (MD) change (mmol/L) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments (secretariat)
Shorter-term studies (≥3 to <12 m)				
van Zuuren et al (2018)				
4 to 6 m Main analysis	0.09 (-0.03, 0.22), p=0.13; I^2=91% 6 RCTs (n=508)	No	unclear (6)	
Sensitivity analyses (fixed-effects model)	-0.01 (-0.04, 0.02), p=0.43; I^2=91% 6 RCTs (n=508)	No	unclear (6)	
Sensitivity analysis (excluding studies causing substantial heterogeneity)	0.17 (0.11, 0.23), p<0.00001; I^2=0% 4 RCTs (n=283)	Yes	unclear (4)	
Sensitivity analysis (excluding studies at high RoB)	0.09 (-0.03, 0.22), p=0.13; I^2=91% 6 RCTs (n=508)	No	unclear (6)	
Korsmo-Haugen et al (2018)				
3 to 6 m Subgroup analysis by duration (34% weight)	-0.01 (-0.07, 0.04), p-value: NR; I^2=15% 6 RCTs (n=345)	No	high (4), unclear (2)	
Longer-term studies (≥12 m)				
Korsmo-Haugen et al (2018)				
>12 m Subgroup analysis by duration (68% weight)	0.06 (-0.01, 0.13), p-value: NR; I^2=71% 10 RCTs (n=1093)	No	high (1), low (3), unclear (6)	
Huntriss et al (2018)				
12 m Main analysis	0.06 (0.04, 0.09), p<0.00001; I^2=1% 7 RCTs (n=645)	Yes	high in 15 of 18 studies in ≥ 1 of the 6 criteria. High risk of performance bias in 15/18 (83%) studies.	

Author (year)/analysis	Results mean difference (MD) change (mmol/L) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments (secretariat)
van Zuuren et al (2018)				
≥12 m Main analysis	0.11 (0.05, 0.18), p<0.0007; I^2= 66% 4 RCTs (n=375)	Yes	high (1), unclear (3)	
Sensitivity analysis (fixed-effects model)	0.13 (0.10, 0.17), p<0.00001; I^2=66% 4 RCTs (n= 375)	Yes	high (1), unclear (3)	
Sensitivity analysis (excluding studies causing substantial heterogeneity)	0.08 (0.03, 0.13), p=0.001; I^2=0% 3 RCTs (n=259)	Yes	unclear (3)	
Sensitivity analysis (excluding studies at high RoB)	as above	Yes	unclear (3)	
24 m Main analysis	Results not considered (**only 2 RCTs in MA**)	N/A	N/A	

Annex 14: Grading analysis for all outcomes

Table A14:1: Change in body weight in longer-term studies (≥12 months)	
MA with largest number of RCTs/sample size	Korsmo-Haugen and Sainsbury included largest number of RCTs (10 RCTs) and largest sample sizes (n=1163 and n=1484, respectively).
Results of MA (mean difference in change, kg)	No difference in effect between lower and higher carbohydrate groups. Korsmo-Haugen: 0.14 (-0.29, 0.57); p=NR Sainsbury: -0.43 (-0.93, 0.07); p=0.09
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	Agreement • Results from the 2 other MAs (Huntriss and van Zuuren) in agreement (no difference in effect). • Results from 1 subgroup analysis by Sainsbury *moderate* vs *higher* carbohydrate group, not in agreement: significantly greater reduction in weight in the *moderate* compared to *higher* carbohydrate group: -0.58 (-1.11, -0.04), p=0.04, I^2=0% Heterogeneity • I^2=0% in both Korsmo-Haugen and Sainsbury Overlap 8/10 RCTs in both Korsmo-Haugen and Sainsbury; 4/6 RCTs in van Zuuren, in Korsmo-Haugen and Sainsbury (same RCTs for both); 3/6 RCTs in Huntriss, in Korsmo-Haugen and Sainsbury.
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA (higher vs poorer quality RCTs) • risk of bias (assessed by publication author)	Risk of bias • Korsmo-Haugen, *unclear* or *high* in 7 RCTs • Sainsbury, *unclear* or *high* in 5 RCTs (*missing* for 1 RCT) Analysis Korsmo-Haugen, ITT in 30% of RCTs; Sainsbury, ITT in 60% of RCTs.
Comments	
Difference in effect/Overall grade	**No difference in effect/Adequate**

Table A14:2: Change in HbA1c in shorter-term studies (≥3 to <12 months)	
MA with largest number of RCTs/sample size	Sainsbury had the largest number of RCTs at 3 m (12 RCTs, n=953) and at 6 m (10 RCTs, n=1173).
Results of MA (mean difference in change, %)	Significantly greater reduction in HbA1c in the lower carbohydrate group. At 3 m: -0.19 (-0.33, -0.05), p=0.008 At 6 m: -0.19 (-0.35, -0.02), p=NR
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	Agreement • Results from Korsmo-Haugen (6 RCTs, n=395) and van Zuuren (7 RCTs, n=539) in agreement (significantly greater reduction). • Results from **subgroup analyses** by Sainsbury (3 and 6 m) *lower* vs *higher* carbohydrate diet in agreement with main analysis (significantly greater reduction); *moderate* vs *higher* carbohydrate diet (3 m) disagreed: -0.06 (-0.17, 0.06), p=0.33, I^2=0%. [Note, *moderate* vs *higher* carbohydrate diet (6 m) not reported because 1 RCT with T1D] • Results from **sensitivity analyses** by Sainsbury (3 and 6 m) after exclusion of RCTs at *high* risk of bias, in agreement with main analyses. • Results from **sensitivity analyses** by Sainsbury (3 m) after exclusion of RCTs with greater weight, disagreed with main analysis: -0.05 (-0.17, 0.06), p =0.35, I^2=0%. Heterogeneity • Sainsbury at 3 m, I^2=28%; at 6 m, I^2=44% Overlap 0 RCTs in all 3 MAs; Korsmo-Haugen: 3/6 RCTs in Sainsbury; van Zuuren: 1/7 RCTs in Sainsbury, 0/7 RCTs in Korsmo-Haugen.
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA • risk of bias (assessed by publication author)	Risk of bias 9/12 RCTs were either at *unclear* or *high* risk of bias. Analysis Sainsbury at 3 m, ITT in 42% of RCTs; at 6 m, ITT in 70% of RCTs.
Comments	
Difference in effect/Overall grade	**Significantly greater reduction in the lower carbohydrate group/Adequate**

Table A14:3: Change in HbA1c in longer-term studies (≥12 months)	
MA with largest number of RCTs/sample size	Sainsbury had the largest number of RCTs (12 RCTs) and participants (n=1600).
Results of MA (mean difference in change, %)	No difference in effect between lower and higher carbohydrate groups. -0.09 (-0.21, 0.03), p=0.12
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	<u>Agreement</u> • Agreed with results of 2nd largest MA, Korsmo-Haugen (10 RCTs, 1030 participants) (no difference in effect): 0.00 (-0.10, 0.09), p=NR • Disagreed with results from 2 smaller MAs (significantly greater reduction in HbA1c in lower CHO group): Huntriss: 7 RCTs, n=645, -0.28 (-0.53, -0.02), p=0.03 van Zuuren: 4 RCTs, n=390, -0.36 (-0.58, -0.14), p=0.001 • Disagreed with results from **sensitivity analysis** by Sainsbury; after exclusion of RCTs at *high* risk of bias, significantly greater reduction in HbA1c with the lower CHO diet: -0.13 (-0.26, -0.01), p=NR; 11 RCTs, n=1438. However, separate subgroup analyses by carbohydrate quantity (*lower* vs *higher* and *moderate* vs *higher)* showed no difference in effect. <u>Heterogeneity</u> • Sainsbury, I^2=16%; Korsmo-Haugen, I^2=0%; Huntriss, I^2=54%, van Zuuren, I^2=0%. <u>Overlap</u> 8 RCTs in both Korsmo-Haugen and Sainsbury; 2 RCTs in all 4 MAs; 2 RCTs in Korsmo-Haugen, Sainsbury, van Zuuren; in van Zuuren, 4/4 RCTs in both Korsmo-Haugen and Sainsbury; in Huntriss, 4/7 RCTs in Korsmo-Haugen, 4/7 RCTs in Sainsbury.
Quality (risk of bias, type of analysis). Consider: • RCTs within each MA • risk of bias (assessed by publication author)	<u>Risk of bias</u> 5/12 RCTs in Sainsbury were either at *unclear* or *high* risk of bias. Risk of bias was not reported for 2 RCTs. <u>Analysis</u> Sainsbury, ITT in 75% of RCTs.
Comments	Agreement between 2 largest MAs (Sainsbury and Korsmo-Haugen) Disagreement between Sainsbury main analysis and sensitivity analysis (removal of 1 RCT at high risk of bias) MAs. All 4 RCTs in van Zuuren included in Sainsbury and Korsmo-Haugen; Huntriss included 2 RCTs uniquely (Esposito with actual intakes 44% TE in low-CHO vs 52% in comparator and Mayer with orlistat prescribed in comparator only).
Difference in effect/Overall grade	**Inconsistent**

Table A14:4: Change in fasting glucose in shorter-term studies (≥3 to <12 months)	
MA with largest number of RCTs/sample size	Only 1 MA (van Zuuren) reported on fasting glucose and included 6 RCTs (n=396).
Results of MA (mean difference in change, %)	Significantly greater reduction in the lower carbohydrate group: -0.51 (-0.91, -0.12), p=0.01
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	<u>Agreement</u> • Results from **sensitivity analyses** in agreement with the main results. <u>Heterogeneity</u> • I^2=71% <u>Overlap</u> N/A
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA • risk of bias (assessed by publication author)	<u>Risk of bias</u> 6/6 RCTs were either at *unclear* or *serious* risk of bias. <u>Analysis</u> ITT in 50% of RCTs.
Comments	Only 1 MA of 6 RCTs with 396 participants; includes 1 non-randomised trial (Nielsen, n=31) reported as at 'serious' risk of bias. van Zuuren included only RCTs that compared low carbohydrate diets specifically with low fat (≤30% TE intake).
Difference in effect/Overall grade	**Significantly greater reduction in the lower carbohydrate group/Moderate**

Table A14:5: Change in fasting glucose in longer-term studies (≥12 months)	
MA with largest number of RCTs/sample size	Only 1 MA (van Zuuren) reported on fasting plasma glucose and included 4 RCTs (n=340).
Results of MA (mean difference in change, %)	No difference in effect between lower and higher carbohydrate groups: -0.37 (-1.22, 0.48), p=0.39
Agreement with results from other MAs, additional sub-group and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	Agreement • Results of **sensitivity analysis** excluding studies at high risk of bias (1 RCT Elhayany, quasi randomised), in agreement with main results. • Disagreement with the results of a fixed-effects model but unclear why fixed-effects model used because of high heterogeneity (main analysis=random-effects model). Heterogeneity • van Zuuren, I^2=92% Overlap N/A
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA • risk of bias (assessed by publication author)	Risk of bias 4/4 RCTs were either at *unclear* or *high* risk of bias. Analysis ITT in 75% of RCTs.
Comments	Downgraded because only 1 MA of 4 RCTs (n=340) (including Nielson, n=31) a non-randomised study reported at 'serious' risk of bias), with very high heterogeneity (92%).
Difference in effect/Overall grade	**Insufficient**

Table A14:6: Change in serum total cholesterol in shorter-term studies (≥3 to <12 months)	
MA with largest number of RCTs/sample size	Only 1 MA (Korsmo-Haugen) reported on serum total cholesterol and included 4 RCTs (n=279).
Results of MA (mean difference in change, mmol/L)	No difference in effect between lower and higher carbohydrate groups: Korsmo-Haugen: -0.06 (-0.41, 0.30), p=NR
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	<u>Agreement</u> N/A <u>Heterogeneity</u> Korsmo-Haugen, I^2=57%. <u>Overlap</u> N/A
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA • risk of bias (assessed by publication author)	<u>Risk of bias</u> 4/4 RCTs were either at *unclear* or *high* risk of bias. <u>Analysis</u> ITT, 1 RCT; PP, 1 RCT; 2/4 RCTs did not report.
Comments	Only 1 MA with very small sample size (n=279).
Difference in effect/Overall grade	**No difference in effect/Moderate**

Table A14:7: Change in serum total cholesterol in longer-term studies (≥12 months)	
MA with largest number of RCTs/sample size	Korsmo-Haugen had the largest number of RCTs (10 RCTs, n=1094).
Results of MA (mean difference in change, mmmol/L)	No difference in effect between lower and higher carbohydrate groups: 0.07 (-0.04, 0.19), p=NR
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	Agreement • Results from Huntriss in agreement (no difference in effect). Heterogeneity • I^2=23% Overlap 4 RCTs in both.
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA • risk of bias (assessed by publication author)	Risk of bias 7/10 RCTs were either at *unclear* or *high* risk of bias. Analysis ITT in 80% of RCTs.
Comments	
Difference in effect/Overall grade	**No difference in effect/Adequate**

Table A14:8: Change in serum triacylglycerol in shorter-term studies (≥3 to <12 months)	
MA with largest number of RCTs/sample size	van Zuuren included 6 RCTs and had most participants (n=508).
Results of MA (mean difference in change, mmol/L)	Significantly greater reduction in serum triacylglycerol with the lower carbohydrate diet: -0.22 (-0.37, -0.08), p=0.002
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	Agreement • Consistent with results from Korsmo-Haugen, 7 RCTs (n=424): -0.18 (-0.36, 0.00), p=NR. **Note**: upper CI=0 and publication did not report significance. Heterogeneity • van Zuuren, I^2=41%; Korsmo-Haugen, I^2=20%. Overlap 1 RCT in both MAs (Yamada, 2014).
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA • risk of bias (assessed by publication author)	Risk of bias van Zuuren: *unclear* in 6/6 RCTs; Korsmo-Haugen: *unclear* or *high* in 7/7 RCTs. Analysis van Zuuren, ITT in 50% of RCTs; Korsmo-Haugen, ITT in 14% of RCTs.
Comments	Although there is agreement between the 2 MAs, Korsmo-Haugen did not report significance (upper CI=0).
Difference in effect/Overall grade	**Significantly greater reduction in the lower carbohydrate group/Adequate**

Table A14:9: Change in serum triacylglycerol in longer-term studies (≥12 months)	
MA with largest number of RCTs/sample size	Korsmo-Haugen had the largest number of RCTs (9 RCTs) and participants (n=967).
Results of MA (mean difference in change, mmol/L)	No difference in effect between lower and higher carbohydrate groups: -0.10 (-0.23, 0.03), p=NR, I^2=61%
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	<u>Agreement</u> • Disagreed with results of other MAs which reported significantly greater reduction in lower carbohydrate group: Huntriss: -0.24 (-0.35, -0.13), p<0.0001; 7 RCTs, n=645 van Zuuren: -0.25 (-0.47, -0.04), p=0.02; 5 RCTs; n=468 <u>Heterogeneity</u> • Korsmo-Haugen, I^2=61%; Huntriss, I^2=0%; van Zuuren, I^2=73%. <u>Overlap</u> 2 RCTs in all 3 MAs (Davis and Guldbrand); Korsmo-Haugen and Huntriss: 4 (4/7 RCTs in Huntriss, included in Korsmo-Haugen); Korsmo-Haugen and van Zuuren: 4 (4/5 RCTs in van Zuuren, included in Korsmo-Haugen); Huntriss and van Zuuren: 2 RCTs.
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA • risk of bias (assessed by publication author)	<u>Risk of bias</u> Korsmo-Haugen: *unclear* in 6/9 RCTs, *low* in 3/9 RCT; van Zuuren, *high* or *unclear* in 5/5 RCTs. <u>Analysis</u> Korsmo-Haugen, ITT in 78% of RCTs; Huntriss, ITT in 86% RCTs; van Zuuren, ITT in 75% of RCTs.
Comments	Downgraded because MAs did not agree. Huntriss, only MA to include RCT by Esposito (carried 62% weight in MA).
Difference in effect/Overall grade	**Inconsistent**

Table A14:10: Change in serum LDL cholesterol in shorter-term studies (≥3 to <12 months)	
MA with largest number of RCTs/sample size	van Zuuren included 5 RCTs (n=372).
Results of MA (mean difference in change, mmol/L)	No difference in effect between lower and higher carbohydrate groups: -0.02 (-0.09, 0.13), p=0.75
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	Agreement • Results from Korsmo-Haugen in agreement (6 RCTs, n=345): -0.08 (-0.29, 0.14), p=NR. Heterogeneity • van Zuuren, I^2=0%; Korsmo-Haugen, I^2=50%. Overlap 1 RCT in both MAs (Yamada).
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA • risk of bias (assessed by publication author)	Risk of bias van Zuuren: *unclear* in 5/5 RCTs; Korsmo-Haugen: *unclear* or *high* in 6/6 RCTs. Analysis van Zuuren, ITT in 60% of RCTs; Korsmo-Haugen, ITT in 17% of RCTs.
Comments	
Difference in effect/Overall grade	**No difference in effect/Adequate**

Table A14:11: Change in serum LDL cholesterol in longer-term studies (≥12 months)	
MA with largest number of RCTs/sample size	Korsmo-Haugen had largest number of RCTs (9 RCTs, n=1064).
Results of MA (mean difference in change, mmol/L)	No difference in effect between lower and higher carbohydrate groups: 0.03 (-0.10, 0.16), p=NR
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	<u>Agreement</u> • Results from 2 other MAs in agreement (no difference in effect): Huntriss: 0.05 (-0.10, 0.19), p=0.54; 5 RCTs, n=389 van Zuuren: -0.07 (-0.23, 0.09), p=0.41; 4 RCTs, n=375 <u>Heterogeneity</u> • Korsmo-Haugen, I^2=51%. <u>Overlap</u> 2 RCTs in all MAs (Davis and Guldbrand).
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA • risk of bias (assessed by publication author)	<u>Risk of bias</u> Korsmo-Haugen: *unclear* or *high* in 6/9 RCTs. <u>Analysis</u> Korsmo-Haugen, ITT in 78% of RCTs.
Comments	
Difference in effect/Overall grade	**No difference in effect/Adequate**

Table A14:12: Change in serum HDL cholesterol in shorter-term studies (≥3 to <12 months)	
MA with largest number of RCTs/sample size	van Zuuren included 6 RCTs (n=508).
Results of MA (mean difference in change, mmol/L)	No difference in effect between lower and higher carbohydrate groups: 0.09 (-0.03, 0.22), p=0.13
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	<u>Agreement</u> • Results from Korsmo-Haugen (6 RCTs, n=345) in agreement (no difference in effect): -0.01 (-0.07, 0.04), p=NR. • Results from a **sensitivity analysis** by van Zuuren excluding RCTs causing substantial heterogeneity (de Bont and Goday) disagreed with the main results (significantly greater increase): 0.17 (0.11, 0.23), p<0.00001, I^2=0%. <u>Heterogeneity</u> • van Zuuren main analysis, I^2=91%; Korsmo-Haugen, I^2=15%. <u>Overlap</u> 1 RCT in both MAs (Yamada).
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA • risk of bias (assessed by publication author)	<u>Risk of bias</u> van Zuuren, *unclear* in 6/6 RCTs; Korsmo-Haugen: *unclear* or *high* in 6/6 RCTs. <u>Analysis</u> van Zuuren, ITT in 50% of RCTs; Korsmo-Haugen, ITT in 17% of RCTs.
Comments	Downgraded because of disagreement with sensitivity analysis and high heterogeneity in largest MA (91%).
Difference in effect/Overall grade	**Inconsistent**

Table A14:13: Change in serum HDL cholesterol in longer-term studies (≥12 months)	
MA with largest number of RCTs/sample size	Korsmo-Haugen had largest number of RCTs (10 RCTs, n=1093).
Results of MA (mean difference in change, mmol/L)	No difference in effect between lower and higher carbohydrate groups: 0.06 (-0.01, 0.13), p=NR
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	<u>Agreement</u> • Results from the 2 other MAs disagreed (significantly greater increase): Huntriss: 0.06 (0.04, 0.09), p<0.00001; 7 RCTs, n=645 van Zuuren: 0.11 (0.05, 0.18), p<0.0007; 4 RCTs, n=375 <u>Heterogeneity</u> • Korsmo-Haugen, I^2=71%, Huntriss, I^2=1%, van Zuuren, I^2=66%. <u>Overlap</u> 2 RCTs in all MAs (Davis and Guldbrand); van Zuuren: 4/4 RCTs in KH; Huntriss: 4/7 RCTs in Korsmo-Haugen.
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA • risk of bias (assessed by publication author)	<u>Risk of bias</u> Korsmo-Haugen: *unclear* or *high* in 7/10 RCTs; van Zuuren: *unclear* or *high* in 4/4 RCTs. <u>Analysis</u> Korsmo-Haugen, ITT in 80% of RCTs; Huntriss, ITT in 86% of RCTs; van Zuuren, ITT in 75% of RCTs.
Comments	Downgraded because largest MA (10 RCTs, n=1093) did not agree with 2 smaller MAs (7 RCTs, n=645; 4 RCTs, n=375). Note: all 4 RCTs in smallest MA (van Zuuren) also in largest MA. Note: 1 RCT (Esposito) weighted 73% in Huntriss MA.
Difference in effect/Overall grade	**Inconsistent**

Annex 15: Within-group analyses for primary and secondary outcomes

The 4 prioritised SRs did not provide MAs for within-group analyses for any outcomes except for Sainsbury et al (2018), which reported separate MAs for within-group analyses of change in HbA1c (reported below). A narrative summary of publications included in MAs for other outcomes has been provided.

Body weight

Shorter-term studies (3 months) (12 RCTs): 3 RCTs reported significant reductions in body weight within both lower (range, -3.1 to -5.9 kg) and higher (range, -1.0 to -5.1 kg) carbohydrate groups; and 9 did not report within-group analyses (Table A15.1).

Shorter-term studies (>3 to <12 months) (17 RCTs): 5 RCTs reported significant reductions in body weight within both lower (range, -2.1 to -11.1 kg) and higher (range, -1.0 to -7.0 kg) carbohydrate groups; 1 reported a significant reduction within the lower carbohydrate group only (-14.7 kg); 1 reported non-significant reductions in body weight within both groups; and 10 did not report within-group analyses (Table A15.2).

Longer-term studies (≥12 months) (16 publications): 5 RCTs reported a significant reduction in average body weight in both the lower (range, -1.9 to -3.8 kg) and higher (range, -2.1 to -5.4 kg) carbohydrate groups; 1 reported non-significant reductions in both groups; 10 did not report within-group changes (Table A15.3).

HbA1c

Sainsbury et al (2018) conducted separate MAs of within-group analyses in HbA1c at 3, 6, 12 and 24 months.

Shorter-term studies (3 months): There were significant reductions in HbA1c within both lower (weighted mean within-group change: -0.77%, 95% CI -1.15 to -0.40, p=NR; I^2=NR, type of statistical model NR; 10 RCTs, NR participants), and higher carbohydrate groups (weighted mean within-group change: -0.50%, 95% CI -0.77 to -0.22, p=NR; I^2=NR, type of statistical model NR; 10 RCTs, NR participants).

Shorter-term studies (6 months): There were significant reductions in HbA1c within both lower (weighted mean within-group change: -0.52%, 95% CI -0.82 to -0.21, p=NR; I^2=NR, type of statistical model NR; 11 RCTs, NR participants) and higher carbohydrate groups (weighted mean within-group change: -0.28%, 95% CI -0.51 to -0.05, p=NR; I^2=NR, type of statistical model NR; 11 RCTs, NR participants).

Longer-term studies (≥12 months): There were non-significant reductions in HbA1c within both lower (weighted mean within-group change: -0.43%, 95% CI -0.98 to 0.02, p-value NR; I^2=NR, type of statistical model NR; 11 RCTs, NR participants) and

higher carbohydrate groups (weighted mean within-group change: -0.21%, 95% CI -0.76 to 0.34, p=NR; I^2=NR, type of statistical model NR; 11 RCTs, NR participants).

Longer-term studies (≥24 months): There were non-significant reductions in HbA1c within both lower (weighted mean within-group change: -0.29%, 95% CI -1.07 to 0.49, p-value NR; I^2=NR, type of statistical model NR; 3 RCTs, NR participants) and higher carbohydrate groups (weighted mean within-group change: -0.05%, 95% CI -0.51 to 0.41, p-value NR; I^2=NR, type of statistical model NR; 3 RCTs, NR participants.

Fasting plasma glucose

Shorter-term studies (≥3 to <12 months) (6 RCTs): 1 RCT reported a significant reduction in fasting plasma glucose within the lower carbohydrate group only (-1.6 mmol/L); 1 reported non-significant changes within both groups; and 3 did not report within-group analyses (Table A15.4).

Longer-term studies (≥12 months) (4 RCTs): 1 RCT reported significant reductions in fasting plasma glucose in both lower (-3.4 mmol/L) and higher carbohydrate groups (-4.9 mmol/L); and 3 did not report within-group analyses (Table A15.4).

One RCT (Shai et al, 2008) reported only 14% of participants with T2D, which was outside of the inclusion criteria so data was not included at 6 or 12 months.

Serum total cholesterol

Shorter-term studies (≥3 to <12 months) (4 RCTs): 1 RCT reported a significant reduction in serum total cholesterol within the lower carbohydrate group only (-0.3 mmol/L); 3 reported non-significant changes in serum total cholesterol within both groups (Table A15.5).

Longer-term studies (≥12 months) (12 RCTs): 7 RCTs reported non-significant changes in serum total cholesterol within both groups; and 6 did not report within-group analyses (Table A15.5).

Serum triacylglycerol

Shorter-term studies (≥3 to <12 months) (12 RCTs): 4 RCTs reported significant reductions in serum triacylglycerol within lower carbohydrate groups only (range, --0.15 to -0.76 mmol/L); 1 reported significant reductions within both lower (-0.52 mmol/L) and higher (-0.55 mmol/L) carbohydrate groups; 2 reported non-significant changes within both groups; and 4 did not report within-group analyses (Table A15.6).

Longer-term studies (≥12 months) (13 RCTs): 7 RCTs reported non-significant changes within both groups; and 6 did not report within-group analyses (Table A15.6).

Serum LDL cholesterol

Shorter-term studies (≥3 to <12 months) (10 RCTs): 1 RCT reported significant reductions in serum LDL cholesterol within the lower carbohydrate group only (-0.20 mmol/L); 7 reported non-significant reductions within both groups; and 2 did not report within-group analyses (Table A15.7).

Longer-term studies (≥12 months) (12 RCTs): 1 RCT reported significant reductions in serum LDL cholesterol within both lower (-0.30 mmol/L) and higher (-0.30 mmol/L) carbohydrate groups (at 24 months); 5 reported non-significant reductions within both groups; and 5 did not report within-group analyses (Table A15.7).

Serum HDL cholesterol

Shorter-term studies (≥3 to <12 months) (11 RCTs): 1 RCT reported a significant increase in serum HDL cholesterol within both the lower (0.12 mmol/L) and higher (0.01 mmol/L) carbohydrate groups; 2 reported significant increases within lower carbohydrate groups only (0.10 and 0.15 mmol/L); 1 reported a significant reduction within the lower carbohydrate group only (-0.03 mmol/L); 4 reported non-significant changes within both groups; and 3 did not report within-group analyses (Table A15.8).

Longer-term studies (≥12 months) (13 RCTs): 2 RCTs reported significant increases in serum HDL cholesterol within both lower (range, 0.11 to 0.23 mmol/L) and higher (range, 0.08 to 0.15 mmol/L) carbohydrate groups; 1 reported a significant increase in the lower carbohydrate group only (0.23 mmol/L); 3 reported non-significant changes within both groups; and 7 did not report within-group analyses (Table A15.8).

Table A15.1: Within-group change in body weight in primary publications included in SRs with MA (3 m)

Primary publication, lead author (year)	Timepoint	Lower carbohydrate (LC) group	Higher carbohydrate (HC) group	Within-group difference (reported statistics only)
		Mean weight reduction in each group, kg		
Brehm (2009)	4 m	-4.5	-3.9	NR
Brunerova (2007)	3 m	-5.9	-5.1	p<0.01
Daly (2006)	3 m	-3.6	-0.9	NR
Davis (2009)	3 m	-5.2	-3.2	NR
Larsen (2011)	3 m	-2.8	-3.1	NR
Luger (2013)	3 m	-3.1	-1.0	LC: p=0.000; HC: p=0.03
Parker (2002)	3 m	-5.5	-4.8	NR
Saslow (2014)	3 m	-5.5	-2.6	LC: p<0.01; HC: p<0.05
Watson (2016)	3 m	-8.0	-7.6	NR
Westman (2008)	3 m	-8.3	-4.2	NR
Wolever (2008)	3 m	NR	NR	NR
Wycherley (2010)	4 m	NR	NR	NR

SR with MA, lead author (year), number of RCTs and participants	Timepoint	Lower carbohydrate group	Higher carbohydrate group	Summary of within-group difference
		Mean weight reduction, kg (range, smallest to largest reduction)		
Sainsbury (2018), based on 9 out of12 RCTs, which provided data at 3 months; 953 participants	3 m	-5.3 (-2.8 to -8.3)	-3.6 (-0.9 to -7.6)	3 RCTs: significant reduction in weight within both groups 9 RCTs: did not report within-group statistical analysis

Table A15.2: Within-group change in body weight in primary publications included in SRs with MAs (>3 and <12 m)

Primary publication, lead author (year)	Timepoint	Lower carbohydrate (LC) group	Higher carbohydrate (HC) group	Within-group difference (reported statistics only)
		Mean weight reduction in each group, kg		
Brehm (2009)	8 m	-4.5	-3.9	NR
Daly (2006)	3 m	-3.6	-0.9	NR
Davis (2009)	6 m	-4.8	-4.4	NR
de Bont (1981)	6 m	-0.9	-2.7	NR
Goday (2016)	4 m	-14.7	-5.1	LC: p<0.0001
Guldbrand (2012)	6 m	-3.9	-4.6	p<0.001
Jenkins (2014)	3 m	-2.1	-1.6	p<0.05
Jonasson (2014)	6 m	NR	NR	NR
Krebs (2012)	6 m	-3.2	-3.2	NR
Luger (2013)	3 m	-3.1	-1.0	LC: p=0.000; HC: p=0.03
McLaughlin (2007)	4 m	-5.9	-7.0	p<0.001
Nielsen (2005)	6 m	-11.4	-1.8	NR
Tay (2014)	6 m	-12.0	-11.5	NR
Watson (2016)	6 m	-8.9	-7.7	NR
Westman (2008)	6 m	-11.1	-6.9	p<0.05
Wolever (2008)	6 m	NR	NR	NR
Yamada (2014)	6 m	-2.6	-1.4	non-significant

SR with MA, lead author (year), number of RCTs and participants	Timepoint	Lower carbohydrate group	Higher carbohydrate group	Summary of within-group difference
		Mean weight reduction, kg (range, smallest to largest reduction)		
Sainsbury (2018), based on 8 out of 9 RCTs (Strychar et al, 2009 excluded because study of patients with T1D), 1484 participants	6 m	-5.8 (-2.6 to -11.1)	-4.7 (-1.4 to -7.7)	2 RCTs: significant reduction in weight within both groups 1 RCT: non-significant reduction in weight within both groups 5 RCTs: did not report within-group statistical analysis
van Zuuren (2018), 7 RCTs, 537 participants	4 to 6 m	-7.2 (-0.9 to -14.7)	-4.5 (-1.4 to -11.5)	1 RCT: significant reduction in weight within both groups 1 RCT: significant reduction in weight within LC group only 1 RCT: non-significant reduction in weight within both groups 4 RCTs: did not report within-group statistical analysis
Korsmo-Haugen (2018), 7 RCTs, 424 participants	3 to 6 m	-4.7 (-2.1 to -11.1)	-3.1 (-0.9 to -7.0)	4 RCTs: significant reduction in weight within both groups 1 RCT: non-significant reduction in weight within both groups 2 RCTs: did not report within-group statistical analysis

Table A15.3: Within-group change in body weight in primary publications included in SRs with MAs (≥12 m)

Primary publication, lead author (year)	Lower carbohydrate (LC) group	Higher carbohydrate (HC) group	Within-group difference (reported statistics only)
	Mean weight change in each group, kg		
Brehm (2009)	-4.0	-3.8	NR
Brinkworth (2004)	-3.8	-2.1	p<0.01
Davis (2009)	-3.1	-3.1	NR
Elhayany (2010)	-8.9	-7.4	NR
Esposito (2009)	-6.2	-4.2	NR
Facchini (2003)	-2.0	-1.0	non-significant
Goldstein (2011)	-3.4	-5.4	p<0.001
Guldbrand (2012)	-1.9	-3.9	p<0.001
Guldbrand (2012)	-2.0	-2.9	LC: p=0.02; HC: p=0.002
Hockaday (1978)	-3.8	-4.6	p<0.001
Krebs (2012)	-3.2	-2.4	NR
Larsen (2011)	-2.2	-2.2	NR
Mayer (2014)	-7.5	-8.1	NR
Pedersen (2014)	-7.8	-5.7	NR
Tay (2015)	-9.8	-10.1	NR
Wolever (2008)	-0.4	2.8	NR

SR with MA, lead author (year), number of RCTs and participants	Lower carbohydrate group	Higher carbohydrate group	Summary of within-group difference
	Mean weight change, kg (range, smallest to largest reduction)		
Korsmo-Haugen (2018) 10 RCTs, 1163 participants	-3.8 (-0.4 to -8.9)	-3.3 (-7.6 to 2.8)	6 RCTs: significant reduction in weight within both groups 1 RCT: non-significant reduction in weight within both groups 1 RCT: did not report within-group analysis
Sainsbury (2018) 10 RCTs, 1484 participants	-4.5 (-0.4 to -9.8)	-3.8 (-10.1 to 2.8)	2 RCTs: significant reduction in weight within both groups 8 RCTs: did not report within-group analysis
van Zuuren (2018) 5 RCTs, 483 participants	-3.6 (-0.4 to -8.9)	-3.2 (-7.4 to 2.8)	2 RCTs: significant reduction in weight within both groups 3 RCT: did not report within-group analysis
Huntriss (2018) 6 RCTs, 567 participants	-4.1 (-7.5 to -1.9)	-4.5 (-8.1 to -2.2)	2 RCTs: significant reduction in weight within both groups 4 RCTs: did not report within-group analysis

Table A15.4: Within-group change in fasting plasma glucose in primary publications included in SRs with MAs

Primary publication, lead author (year)	Timepoint	Lower carbohydrate (LC) group	Higher carbohydrate (HC) group	Within-group difference (reported statistics only)
		Mean change in fasting plasma glucose, mmol/L		
de Bont (1981)	6 m	-0.50	-0.30	NR
Elhayany (2010)	12 m	-4.29	-3.50	NR
Goday (2016)	4 m	-1.55	-0.95	LC: p<0.0001
Hockaday (1978)	12 m	-3.40	-4.90	p<0.001
Nielsen (2005)	6 m	-3.40	-0.60	NR
Shai (2008)1	6 m/12 m	Data excluded as only 14% of study population had type T2D.		
Tay (2014)	6 m	-1.10	-1.60	NR
Wolever (2008)	12 m	NR	NR	NR
Yamada (2014)	6 m	-0.78	0.44	non-significant

SR with MA, lead author (year), number of RCTs and participants	Timepoint	Lower carbohydrate group	Higher carbohydrate group	Summary of within-group difference
		Mean change in fasting plasma glucose, mmol/L (range)		
van Zuuren (2018) based on 5 out of 6 RCTs (Shai et al, 2008 excluded because only 14% of study participants with T1D), 396 participants	4 to 6 m	-1.47 (-3.40 to -0.50)	-0.60 (-1.60 to 0.44)	1 RCT: significant reduction in fasting glucose within LC group only 1 RCT: non-significant changes in fasting glucose within both groups 3 RCTs: did not report within-group statistical analysis
van Zuuren (2018) based on 3 out of 4 RCTs (Shai et al, 2008 excluded because only 14% of study participants with T1D), 340 participants	≥12 m	-3.85 (-4.29 to -3.40)	-4.20 (-4.90 to -3.50)	1 RCT: significant reduction in fasting glucose within both groups 2 RCTs: did not report within-group statistical analysis

Table A15.5: Within-group change in serum total cholesterol in primary publications included in SRs with MAs

Primary publication, lead author (year)	Timepoint	Lower carbohydrate (LC) group	Higher carbohydrate (HC) group	Within-group difference (reported statistics only)
		Mean change in serum total cholesterol, mmol/L		
Brinkworth (2004)	16 m	0.08	0.35	non-significant
Davis (2009)	12 m	0.10	-0.13	NR
Elhayany (2010)	12 m	-0.88	-0.96	NR
Esposito (2009)	12 m	-0.39	-0.15	NR
Facchini (2003)	48 m	0.30	-0.20	non-significant
Goldstein (2011)	12 m	-0.21	-0.05	non-significant
Guldbrand (2012)	12 m	0.20	0.00	non-significant
Guldbrand (2012)	24 m	-0.10	-0.30	non-significant
Jenkins (2014)	3 m	-0.30	0.04	LC: p<0.05
Jonasson (2014)	6 m	-0.10	-0.10	non-significant
Krebs (2012)	24 m	-0.24	-0.17	non-significant
Larsen (2011)	12 m	-0.15	0.01	NR
Mayer (2014)	11 m	-0.05	-0.28	NR
McLaughlin (2007)	4 m	-0.18	-0.05	non-significant
Pedersen (2014)	12 m	0.00	-0.10	non-significant
Tay (2015)	12 m	-0.10	-0.10	NR
Westman (2008)	6 m	-0.11	-0.15	non-significant
Wolever (2008)	12 m	-0.02	-0.05	non-significant

SR with MA, lead author (year), number of RCTs and participants	Timepoint	Lower carbohydrate group	Higher carbohydrate group	Summary of within-group difference
		Mean change in serum total cholesterol, mmol/L (range)		
Korsmo-Haugen (2018) 4 RCTs, 279 participants	3 to 6 m	-0.17 (-0.30 to -0.10)	-0.07 (-0.15 to 0.04)	1 RCT: significant reduction in serum total cholesterol within LC group only 3 RCTs: non-significant changes in serum total cholesterol within both groups
Korsmo-Haugen (2018) 10 RCTs, 1094 participants	≥12 m	-0.11 (-0.88 to 0.30)	-0.16 (-0.96 to 0.35)	7 RCTs: non-significant changes in serum total cholesterol within both groups 3 RCTs: did not report within-group statistical analysis
Huntriss (2018) 7 RCTs, 645 participants	12 m	-0.14 (-0.39 to 0.10)	-0.10 (-0.28 to -0.01)	2 RCTs: non-significant changes in serum total cholesterol within both groups 5 RCTs: did not report within-group statistical analysis

Table A15.6: Within-group change in serum triacylglycerol in primary publications included in SRs with MAs

Primary publication, lead author (year)	Timepoint	Lower carbohydrate (LC) group	Higher carbohydrate (HC) group	Within-group difference (reported statistics only)
		Mean change in serum triacylglycerol, mmol/L		
Brinkworth (2004)	64 w	0.06	-0.13	non-significant
Daly (2006)	3 m	-0.67	-0.25	NR
Davis (2009)	6 m	-0.02	0.04	NR
Davis (2009)	12 m	-0.15	-0.01	NR
De Bont (1981)	6 m	-0.11	-0.03	NR
Elhayany (2010)	12 m	-1.52	-1.46	NR
Esposito (2009)	12 m	-0.44	-0.22	NR
Goday (2016)	6 m	-0.41	0.20	LC: p=0.004
Goldstein (2011)	12 m	-0.45	-0.05	non-significant
Guldbrand (2012)	6 m	-0.20	0.00	non-significant
Guldbrand (2012)	12 m	-0.30	-0.10	non-significant
Guldbrand (2012)	24 m	-0.20	-0.10	non-significant
Hockaday (1978)	12 m	-0.10	0.00	non-significant
Jenkins (2014)	3 m	-0.15	-0.01	LC: p<0.05
Jonasson (2014)	6 m	-0.20	0.00	non-significant
Krebs (2012)	24 m	-0.04	-0.01	non-significant
Larsen (2011)	12 m	-0.47	-0.30	NR
Luger (2013)	3 m	-0.57	-0.15	p=0.01
Mayer (2014)	12 m	-0.4	-0.10	NR
McLaughlin (2007)	4 m	-0.52	-0.55	LC: p=0.008; HC: p=0.007
Pedersen (2014)	12 m	-0.6	-0.30	NR
Tay (2014)	6 m	-0.50	-0.10	NR
Tay (2015)	12 m	-0.4	-0.01	NR
Westman (2008)	6 m	-0.76	-0.22	LC: p<0.05
Wolever (2008)	12 m	0.14	0.30	non-significant
Yamada (2014)	6 m	-0.66	-0.08	LC: p=0.02

SR with MA, lead author (year), number of RCTs and participants	Timepoint	Lower carbohydrate (LC) group	Higher carbohydrate (HC) group	Summary of within-group difference
		Mean change in serum triacylglycerol, mmol/L (range)		
Korsmo-Haugen (2018), 7 RCTs, 424 participants	3 to 6 m	-0.50 (-0.76 to -0.15)	-0.18 (-0.55 to 0.00)	4 RCTs: significant reduction in serum triacylglycerol within LC group only 1 RCT: significant reduction in serum triacylglycerol within both groups 1 RCT: non-significant changes within both groups 1 RCT: did not report within-group statistical analysis

van Zuuren (2018), 6 RCTs, 508 participants	4 to 6 m	-0.32 (-0.66 to -0.02)	-0.06 (-0.20 to 0.04)	1 RCT: significant reduction in serum triacylglycerol within LC group only 2 RCTs: non-significant changes within both groups 3 RCTs: did not report within-group statistical analysis
Korsmo-Haugen (2018), 9 RCTs, 967 participants	≥12 m	-0.36 (-1.52 to 0.14)	-0.23 (-1.46 to 0.30)	5 RCTs: non-significant changes in serum triacylglycerol within both groups 4 RCTs: did not report within-group statistical analysis
Huntriss (2018), 7 RCTs, 645 participants	12 m	-0.37 (-0.47 to -0.15)	-0.12 (-0.30 to -0.01)	2 RCTs: non-significant changes in serum triacylglycerol within both groups 5 RCTs: did not report within-group statistical analysis
van Zuuren (2018), 5 RCTs, 468 participants	≥12 m	-0.39 (-1.52 to 0.14)	-0.14 (-0.88 to 0.30)	3 RCTs: no significant change within both groups 2 RCT: did not report within-group statistical analysis

Table A15.7: Within-group change in serum LDL cholesterol in primary publications included in SRs with MAs

Primary publication, lead author (year)	Timepoint	Lower carbohydrate (LC) group	Higher carbohydrate (HC) group	Within-group difference (reported statistics only)
		Mean change in serum LDL cholesterol, mmol/L		
Brinkworth (2004)	16	-0.19	0.27	non-significant
Davis (2009)	6	-0.10	-0.25	NR
Davis (2009)	12	-0.04	-0.18	NR
Elhayany (2010)	12	-0.61	-0.37	NR
Facchini (2003)	48	0.07	-0.12	non-significant
Goday (2016)	4	-0.05	-0.07	non-significant
Guldbrand (2012)	6	-0.20	-0.10	non-significant
Guldbrand (2012)	12	-0.20	-0.10	non-significant
Guldbrand (2012)	24	-0.30	-0.30	LC: p=0.02; HC: p=0.017
Jenkins (2014)	3	-0.20	0.04	LC: p<0.05
Jonasson (2014)	6	-0.20	-0.10	non-significant
Krebs (2012)	24	-0.17	-0.20	non-significant
Larsen (2011)	12	-0.05	0.04	NR
Luger (2013)	3	-0.11	-0.13	non-significant
Mayer (2014)	12	-0.02	-0.27	NR
McLaughlin (2007)	4	-0.13	0.00	non-significant
Pedersen (2014)	12	0.10	0.00	non-significant
Tay (2014)	6	-0.30	-0.30	NR
Tay (2015)	13	-0.10	-0.20	NR
Westman (2008)	6	0.03	-0.07	non-significant
Wolever (2008)	12	-0.13	-0.10	non-significant
Yamada (2014)	6	-0.12	-0.04	non-significant

SR with MA, lead author (year), number of RCTs and participants	Timepoint	Lower carbohydrate group	Higher carbohydrate group	Summary of within-group difference
		Mean change in serum LDL cholesterol, mmol/L (range)		
van Zuuren (2018), 5 RCTs, 372 participants	4 to 6 m	-0.15 (-0.30 to -0.05)	-0.15 (-0.30 to -0.04)	3 RCTs: non-significant reductions in serum LDL cholesterol within both groups 2 RCTs: did not report within-group statistical analysis
Korsmo-Haugen (2018), 6 RCTs, 345 participants	3 to 6 m	-0.12 (-0.20 to 0.03)	-0.05 (-0.13 to 0.04)	1 RCT: significant reduction in serum LDL cholesterol within LC group only 5 RCTs: non-significant change within both groups

van Zuuren (2018), 4 RCTs, 375 participants	≥12 m	-0.25 (-0.61 to -0.04)	-0.19 (-0.37 to -0.10)	1 RCT: non-significant changes in serum LDL cholesterol within both groups 3 RCTs: did not report within-group statistical analysis
Huntriss (2018), 5 RCTs, 389 participants	>12 m	-0.08 (-0.20 to -0.02)	-0.14 (-0.27 to 0.04)	2 RCTs: non-significant changes in serum LDL cholesterol in both arms 3 RCTs: did not report within-group statistical analysis
Korsmo-Haugen (2018), 9 RCTs, 1064 participants	>12 m	-0.15 (-0.61 to 0.10)	-0.11 (-0.37 to 0.27)	1 RCT: significant reductions in serum LDL cholesterol within both groups 5 RCTs: non-significant changes within both groups 3 RCTs: did not report within-group statistical analysis

Table A15.8: Within-group change in serum HDL cholesterol in primary publications included in SRs with MAs

Primary publication, lead author (year)	Timepoint	Lower carbohydrate (LC) group	Higher carbohydrate (HC) group	Within-group difference (reported statistics only)
		Mean change in serum HDL cholesterol, mmol/L		
Brinkworth (2004)	16 m	0.16	0.15	p<0.001
Davis (2009)	6 m	0.16	-0.01	NR
Davis (2009)	12 m	0.16	0.06	NR
de Bont (1981)	6 m	-0.19	-0.09	NR
Elhayany (2010)	12 m	0.13	-0.05	NR
Esposito (2009)	12 m	0.10	0.03	NR
Facchini (2003)	48 m	0.23	-0.05	LC: p<0.05
Goday (2016)	4 m	-0.04	-0.07	non-significant
Goldstein (2011)	12 m	0.11	0.14	non-significant
Guldbrand (2012)	6 m	0.12	0.01	LC: p<0.001, HC: p=0.002
Guldbrand (2012)	12 m	0.11	0.08	LC: p=0.024; HC: p=0.004
Guldbrand (2012)	24 m	0.23	0.11	LC: p<0.001; HC: p=0.002
Jenkins (2014)	3 m	-0.03	0.00	LC: p<0.05
Jonasson (2014)	6 m	0.10	0.00	LC: p<0.05
Krebs (2012)	24 m	-0.01	0.02	non-significant
Larsen (2011)	12 m	0.08	0.08	NR
Luger (2013)	3 m	0.02	0.04	non-significant
Mayer (2014)	12 m	0.07	0.03	NR
McLaughlin (2007)	4 m	0.05	0.05	non-significant
Pedersen (2014)	12 m	0.10	0.10	NR
Tay (2014)	6 m	0.20	0.05	NR
Tay (2015)	13 m	0.10	0.06	NR
Westman (2008)	6 m	0.15	0.00	LC: p<0.05
Wolever (2008)	12 m	0.05	-0.05	non-significant
Yamada (2014)	6 m	0.14	-0.11	non-significant

SR with MA, lead author (year), number of RCTs and participants	Timepoint	Lower carbohydrate group	Higher carbohydrate group	Summary of within-group difference
		Mean change in serum HDL cholesterol, mmol/L (range)		
van Zuuren (2018), 6 RCTs, 508 participants	4 to 6 m	0.07 (-0.19 to 0.20)	-0.04 (-0.11 to 0.05)	1 RCT: significant increases in serum HDL cholesterol within both groups 2 RCTs: non-significant changes within both groups 3 RCTs: did not report within-group statistical analysis
Korsmo-Haugen (2018), 6 RCTs, 345 participants	3 to 6 m	0.07 (-0.03 to 0.15)	0.00 (-0.11 to 0.05)	3 RCTs: significant change in HDL cholesterol within LC group only 3 RCTs: non-significant changes within both groups

van Zuuren (2018), 4 RCTs, 375 participants	≥12 m	0.11 (0.05 to 0.16)	0.01 (-0.05 to 0.08)	1 RCT: significant increases in serum HDL cholesterol within both groups 1 RCT: non-significant changes within both groups 2 RCTs: did not report within-group statistical analysis
Huntriss (2018), 7 RCTs, 645 participants	>12 m	0.10 (0.07 to 0.16)	0.07 (0.03 to 0.14)	1 RCT: significant increases in serum HDL cholesterol within both groups 1 RCT: non-significant changes within both groups 5 RCTs: did not report within-group statistical analysis
Korsmo-Haugen (2018), 10 RCTs, 1093 participants	>12 m	0.12 (-0.01 to 0.23)	0.05 (-0.05 to 0.15)	2 RCTs: significant increases in serum HDL cholesterol within both groups 1 RCT: significant increase within LC group 3 RCTs: non-significant changes within both groups 4 RCTs: did not report within-group statistical analysis

Annex 16: Shorter-term analysis of change in weight in prioritised 4 SRs with MAs

Table A16.1: Change in weight (≥3 to <12 months)

Author (year)/analysis	Results mean difference (MD) change (kg) (95% CI), p-value; I^2 number of studies (number of participants)	Significant	Risk of bias (RoB) (author assessment)	Comments (secretariat)
Sainsbury et al (2018)				
3 m Main analysis	-1.08 (-1.93, -0.23), p=0.01, I^2=69% 12 RCTs (n=953)	Yes	high (4), low (3), unclear (5)	Participant numbers not included in forest plots (estimated here from table of included studies).
Subgroup analysis (by carbohydrate quantity)	low vs high carbohydrate (32.5% weight in MA) -2.47 (-3.33, -1.60), p<0.00001; I^2=0% 4 RCTs (n=321)	Yes	high (1), low (2), unclear (1)	In the *low* vs *high* carbohydrate subgroup analysis achieved carbohydrate intakes were *low* vs *moderate* in 2 RCTs; *moderate* vs *moderate* in 1 RCT and *moderate* vs *high* in 1 RCT.
	moderate vs high carbohydrate (67.5% weight) 0.14 (-0.30, 0.59), p=0.53; I^2=0%, 8 RCTs (n=632)	No	high (3), low (1), unclear (4)	In the *moderate* vs *high* carbohydrate subgroup analysis achieved carbohydrate intakes were *high* vs *high* in 2 out of 7 RCTs (1 NR); *moderate* vs *high* in 5 RCTs.
Sainsbury et al (2018)				
6 m Main analysis	-0.14 (-0.94, 0.65), p=0.72, I^2=48% 9 RCTs (n=1070)	No	high (3), low (2), unclear (4)	Includes 1 RCT (Strychar et al, 2009) of participants with T1D (n=30, 11.7% weight).
Subgroup analysis (by carbohydrate quantity)	low vs high carbohydrate (32.5% weight) -1.07 (-2.52, 0.37), p=0.14; I^2=33% 4 RCTs (n=274)	No	high (1), low (1), unclear (2)	In the *low* vs *high* carbohydrate subgroup analysis achieved carbohydrate intakes were *moderate* vs *high* in 3 out of 4 RCTs.
	moderate vs high carbohydrate (67.5% weight) 0.29 (-0.60, 1.17), p=0.52; I^2=48% 5 RCTs (n=796)	No	high (2), low (1), unclear (2)	Includes Strychar er al, 2009, see above. In the *moderate* vs *high* carbohydrate subgroup analysis achieved carbohydrate intakes were *high* vs *high* in 2 out of 4 RCTs.

van Zuuren et al (2018)				
>4 to 6 m Main analysis	-2.51 (-5.42, 0.40), p=0.09; I^2=88% 7 RCTs (n=537)	No	serious (1), unclear (6)	1 RCT (de Bont et al, 1981) carried 59.5% weight in MA. All RCTs report at 6 m except Goday et al, 2016, which reports at 4 m.
Sensitivity analysis (fixed-effects model)	-0.24 (-1.01, 0.53), p=0.54; I^2=88% 7 RCTs (n=537)	No	serious (1), unclear (6)	
Sensitivity analysis (excluding studies causing substantial heterogeneity)	0.52 (-0.28, 1.33), p=0.20, I^2=0% 5 RCTs (n=417)	No	unclear (5)	Goday et al, 2016 and Nielsen et al, 2005 excluded from analysis.
Sensitivity analysis (excluding studies at high RoB)	-1.69 (-4.57, 1.18), p=0.25, I^2=88% 6 RCTs (n=506)	No	unclear (6)	Nielsen e al, 2005 excluded from analysis.
Korsmo-Haugen et al (2018)				
3 to 6 m Subgroup analysis (by study duration; 43.8% weight)	-0.87 (-1.88, 0.15), p-value NR; I^2=33% 7 RCTs (n=424)	No	high (5), unclear (2)	Main analysis combined longer- and shorter-term studies.
Huntriss et al (2018)	Did not perform MA at 3 m and 6 m: [a] **3 months**: 3 out of 5 RCTs reported statistically significant difference in weight change in favour of lower carbohydrate group; 2 reported no significant difference between groups. [b] **6 months**: 4 out of 8 RCTs reported statistically significant difference in weight change in favour of lower carbohydrate group; 4 reported no significant difference between groups.		high in 15 of 18 studies in ≥1 of the 6 criteria; high risk of performance bias in 15/18 (83%) studies	

Annex 17: Adverse events

Table A17.1: Adverse events reported in primary studies from prioritised 4 SRs with MAs

Primary study lead author (year)	Adverse events reported
Brunerova, 2007	No gastro-intestinal or other adverse events reported.
Daly, 2006	No adverse events reported.
Esposito, 2009	Mild: gastroenteritis (9/13; lower carbohydrate/higher carbohydrate), nausea (5/3), vomiting (3/2), headache (4/6), fever (3/1), fatigue (5/4). Serious: atrial fibrillation (1/0), pneumonia (0/1). The incidence of adverse events during the treatment phase was similar in both groups: 23 participants (21%) in the lower carbohydrate group and 25 participants (23%) in the higher carbohydrate group reported at least 1 adverse event.
Goday, 2016	No serious adverse events reported. Mild adverse events reported by 80% of the lower carbohydrate group compared with 41% of the participants in the higher carbohydrate group ($p<0.001$). Among the pre-defined adverse events: asthenia, headache, nausea and vomiting were more common in the lower carbohydrate group at 2 weeks (all $p<0.05$). The number of participants reporting these adverse events in the lower carbohydrate group declined at last follow-up. At the end of the study, constipation ($p<0.005$) and orthostatic hypotension ($p<0.05$) were more commonly referred by participants in the lower carbohydrate group (respectively, n=8 and n=6) compared with higher carbohydrate group subjects (both, n=0). Not pre-defined adverse events were more frequent in the lower carbohydrate group at 2 weeks but not at 4 months. Only 1 participant in the lower carbohydrate group discontinued the study because of an adverse event (nausea) associated with ketosis.
Guldbrand, 2012	No serious adverse events reported.
Jenkins, 2014	No serious adverse events reported. Five participants (3/2; lower carbohydrate/higher carbohydrate) reported experiencing hypoglycaemic episodes.
Krebs, 2012	No important adverse events reported.
Pedersen, 2014	No adverse events reported.
Samaha, 2003	One participant in the lower carbohydrate group was hospitalised with chest pain. One participant in the lower carbohydrate diet died from complications of hyperosmolar coma, which was thought to be due to poor compliance with drug therapy for diabetes.
Tay, 2014	Two participants in the lower carbohydrate group reported gastrointestinal disorders (constipation and diverticulitis).
Tay, 2015	Three participants (2/1; lower carbohydrate/higher carbohydrate) reported gastrointestinal disorders (constipation and diverticulitis).
Westman, 2008	No significant differences between groups in reported symptomatic adverse events. The most common symptoms experienced at any point during the study were headache (53.1%/46.3%; lower carbohydrate/higher carbohydrate), constipation (53.1%/39.0%), diarrhoea (40.6%/36.6%), insomnia (31.2%/19.5%), and back pain (34.4%/39.0%) ($p>0.05$ for all comparisons).
Wycherley, 2010	No adverse events reported.
Yamada, 2014	Side effects from medication not from diet.

Abbreviations list

ACE	angiotensin-converting enzyme
ADA	American Diabetes Association
AMSTAR	A Measurement Tool to Assess systematic Reviews
anti-GAD	antibodies to glutamic acid decarboxylase
anti-IA2	antibodies to islet antigen 2
ASI	angiotensin system inhibition
BMI	body mass index
BP	blood pressure
BW	body weight
CCT	controlled clinical trial
COMA	Committee of Medical Aspects of Food Policy
CHO	carbohydrate
CI	confidence interval
CRP	C-reactive protein
CVD	cardiovascular disease
DBP	diastolic blood pressure
df	degree of freedom
DP	degree of polymerisation
DPP-4	dipeptidyl peptidase 4
DRV	dietary reference value
eGFR	estimated glomerular infiltration rate
FBG	fasting blood glucose
FFQ	food frequency questionnaire
GI	glycaemic index
GL	glycaemic load
GLP-1	glucagon-like peptide
GRADE	Grading of Recommendations Assessment Development and Evaluations
HbA1c	glycated haemoglobin
HC	higher carbohydrate
HCLF	high-carbohydrate low-fat
HDL	high density lipoprotein cholesterol
IQR	interquartile range
kcal	kilocalorie

kJ	kilojoule
LC	lower carbohydrate
LCD	lower carbohydrate diet
LDL	low density lipoprotein cholesterol
LFD	low fat diet
LPD	low protein diet
MA	meta-analysis
MES	medication effect score
mJ	megajoule
MODY	maturity onset diabetes of the young
MUFA	monounsaturated fatty acids
NICE	National Institute for Health and Care Excellence
NIDDM	Noninsulin-dependent diabetes mellitus
NMA	network meta-analysis
NR	not reported
OGTT	oral glucose tolerance test
PA	pooled analysis
PHE	Public Health England
PUFA	polyunsaturated fatty acids
QoL	quality of life
RCT	randomised controlled trial
RNI	reference nutrient intake
RoB	risk of bias
RR	relative risk
SACN	Scientific Advisory Committee on Nutrition
SBP	systolic blood pressure
SD	standard deviation
SFA	saturated fatty acids
SI	International System of Units
SIGN	Scottish Intercollegiate Guidelines Network
SR	systematic review
T1D	type 1 diabetes
T2D	type 2 diabetes
TE	total energy
TG	triacylglycerol

VLCD	very low calorie diet
vs	versus
WG	working group
WMD	weighted mean difference