National Clinical Guideline Centre

Draft for consultation

Obesity

Identification, assessment and management of overweight and obesity in children, young people and adults

Update of CG43

Appendix G

July 2014

Draft for Consultation

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Royal College of Physicians

The Royal College of Surgeons of England

RCGP Royal College of General Practitioners

Royal College of Nursing

NICE accredited

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G.1 Very-low-calorie diets (VLCD)

G.1.1 Effectiveness

Table 1: Pavlou 1989

Study	Pavlou 1989[30]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=160)
Countries and setting	Conducted in USA; Setting: Workplace- all male, members of the Boston Police Department and the Metropolitan District Commission.
Line of therapy	1st line
Duration of study	Intervention + follow up: treatment 8 weeks, follow-up 6 + 18 months
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable:
Inclusion criteria	Not specified, however participants underwent medical history, physical examination, and usual laboratory tests and found to be euthyroid and free from any significant physical, psychological, or metabolic impairments
Exclusion criteria	Not specified
Recruitment/selection of patients	Through workplace, sample all male police officers
Age, gender and ethnicity	Age - Range: 26-52 yr. Gender (M:F): All male sample. Ethnicity: Not stated
Further population details	1. Ethnicity: Not applicable / Not stated / Unclear 2. Learning disabilities: Not applicable / Not stated / Unclear 3. T2DM: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=80) Intervention 1: Very-low-calorie diet - VLCD (<800 calories per day). Combined two VLCDs - 1. DPC-70: a 420 kcal powdered protein-carbohydrate mix derived from calcium caseinate, egg albumin, and fructose was dissolved in

Study	Pavlou 1989[30]
	water or other noncaloric liquid before intake. Fat content essentially zero. Formula fortified with vitamins and minerals. Participants instructed to mix 5 packets a day in ~30 ounces of noncaloric liquid and consume no other nutrients. 2. DPC-800: an 800 kcal diet provided in powder form, consumed similarly to the DPC-70 diet. Provided a complete mixture of nutrients. Except for slightly fewer total calories, was similar nutritionally in nearly all aspects to the BCDD diet. Duration 8 weeks treatment, 78 weeks follow-up. Concurrent medication/care: Participants were randomly assigned to one of four diets: two VLCDs (DPC-70 kcals; DPC-800 kcals) and two LCDs (BCDD-1000 kcals; PSMF-1000 kcals), and exercise/nonexercise groups for 8 weeks. A multivitamin tablet was given to all participants. Additionally, 2.8g potassium chloride was prescribed for all individuals on PSMF and DPC-70 diets. Noncaloric liquids including coffee in unrestricted amounts were allowed. Participants were asked to keep a detailed daily record of food intake and physical activity; and asked to report at least once weekly for medical monitoring. All participants attended weekly educational sessions that included instruction in behaviour modification, diet, general nutrition, and exercise. Half participants required to attend 90 min supervised exercise program conducted 3 times per week. Program consisted of a 35-60 min aerobic activity. Those that did not participate in the supervised exercise program received education but were asked to continue daily normal activity and not participate in any form of additional activity during the active phase of weight loss Further details: 1. Diet: (n=80) Intervention 2: Standard dietary advice - LCD. Combined two LCDs - 1. BCDD: Balanced caloric-deficit diet, by which 1000 kcals were selected from the usual four food groups in quantities thought to meet basic requirements (i.e. standard weight-reduction diet). 2. PSMR: protein-sparing modified fast, a ketogenic diet wherein meat, fish, and fowl were used as the only dietary source to provide an equivalent of 1.2 g of high-biologic-value protein per kilogram of ideal body weight, ~1000 kcals. Duration 8 weeks treatment, 78 weeks follow-up. Concurrent medication/care: Participants were randomly assigned to one of four diets: two VLCDs (DPC-70 kcals; DPC-800 kcals) and two LCDs (BCDD-1000 kcals; PSMF-1000 kcals), and exercise/nonexercise groups for 8 weeks. A multivitamin tablet was given to all participants. Additionally, 2.8g potassium chloride was prescribed for all individuals on PSMF and DPC-70 diets. Noncaloric liquids including coffee in unrestricted amounts were allowed. Participants were asked to keep a detailed daily record of food intake and physical activity; and asked to report at least once weekly for medical monitoring. All participants attended weekly educational sessions that included instruction in behaviour modification, diet, general nutrition, and exercise. Half participants required to attend 90 min supervised exercise program conducted 3 times per week. Program consisted of a 35-60 min aerobic activity. Those that did not participate in the supervised exercise program received education but were asked to continue daily normal activity and not participate in any form of additional activity during the active phase of weight loss Further details: 1. Diet:

Study	Pavlou 1989[30]
Funding	Study funded by industry (Supported in part by a grant from Sandoz Nutrition, Minneapolis MN)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VLCD (<800 CALORIES PER DAY) [DPC 800 & DPC 70] versus LCD [BCDD 1000 & PSMF ~1000] Protocol outcome 1: % weight change (kg) at Latest follow-up - Actual outcome: NOTE final weight (kg) at 8 weeks treatment and 78 weeks follow-up (assumed); Group 1: mean 89.82 kg (SD 5.56); n=57, Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: NOTE change weight (kg) at 8 weeks treatment and 78 weeks follow-up (assumed); Group 1: mean -11.68 kg (SD 1.679); n=57, Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: NOTE "percent of ideal weight loss" at 8 weeks treatment and 78 weeks follow-up (assumed); Group 1: mean 67.5 % (SD 15.5); n=57, Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: % drop outs at Latest follow-up - Actual outcome: NOTE number of withdrawals from start of study to end of study at 8 weeks treatment and 78 weeks follow-up (assumed); Group 1: 23/80, Group 2: 27/80; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Health related quality of life at Latest follow-up; % weight change (BMI) at Latest follow-up; Improvement in physical activity at Latest follow-up; % weight change (kg) from end of diet to end of study at Latest follow-up; % weight change (BMI) from end of diet to end of study at Latest follow-up

Table 2: Simonen 2000

Study	Simonen 2000[37]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=16)
Countries and setting	Conducted in Finland; Setting: Not specified
Line of therapy	1st line
Duration of study	Intervention + follow up: Run in 6 weeks, treatment 12 weeks, maintenance 4 months to 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable

Study	Simonen 2000[37]
Inclusion criteria	Recent diagnosis (<2 years) of type 2 diabetes (fasting blood glucose ≥7.0 mmol/L), and BMI ≥30
Exclusion criteria	Insulin therapy, diabetic microangiopathy, hepatic or thyroid disease, unstable angina pectoris or myocardial infarction, or invasive CAD treatment in the previous year.
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (SD): 52.3 (1.8). Gender (M:F): 13 men and 3 women. Ethnicity: Not stated
Further population details	1. Ethnicity: Not applicable / Not stated / Unclear 2. Learning disabilities: Not applicable / Not stated / Unclear 3. T2DM: Not applicable / Not stated / Unclear (All participants had a recent diagnosis (< 2 years) of type 2 diabetes).
Extra comments	All women were postmenopausal and none had received hormone replacement therapy.
Indirectness of population	No indirectness: Participants with recent diagnosis of T2D (<2 years)
Interventions	(n=10) Intervention 1: Very-low-calorie diet - VLCD (<800 calories per day). The VLED group ingested daily 3 servings of a VLED (97 kj/d, Cambridge Diet, Howard Foundation, Cambridge). One serving provided 14.2 g protein, 15.0 g carbohydrates, 2.7 g fat, and essential minerals, trace nutrients, and vitamins. Hypoglycemia treatment was discontinued in the VLED group.. Duration run-in: 6 weeks, treatment 12 weeks, maintenance: 4 months to 2 yr. Concurrent medication/care: During run-in period (6 week), baseline metabolic studies were completed while participants consumed an ad libitum diet at home. Weight-reduction period last 3 months. Weigh-maintenance period continued from 4 months until 2 years in both groups. The diets were individually tailored by the dietitian so that the daily energy balance was zero. Participants kept a food record for 7 d, from which the proportions of the dietary constituents were calculated. Additionally, participants were given a capsule to be taken 3 times daily with their regular meals during 7-d period. In the VLED and LED groups, respectively, 8 and 2 patients received diet therapy, 1 and 2 patients took glibenclamide, and 1 and 2 patients took both glibenclamide and biguanide. Four patients in the VLED group and 2 in the LED group took a combination of beta blockers and calcium chanel-blocking agents, 3 patients in the LED group took beta blockers only. The use of medications was maintained during the study. Further details: 1. Diet: (n=6) Intervention 2: Standard dietary advice - LCD. The LED group was advised to consume a low-fat, low-cholesterol diet. In the LED group, the dose of glibenclamide was adjusted so that blood glucose concentrations were <7.0 mmol/L and biguanide was discontinued. Duration run-in: 6 weeks, treatment 12 weeks, maintenance: 4 months to 2 yr. Concurrent medication/care: During run-in period (6 week), baseline metabolic studies were completed while participants consumed an ad libitum diet at home. Weight-reduction period last 3 months. Weigh-maintenance period continued from 4 months until 2 years in both groups. The diets were individually tailored by the dietitian so that the daily energy balance was zero. Participants kept a food record for 7 d, from which the proportions of the dietary constituents were calculated. Additionally, participants were given a capsule to be taken 3 times daily with their

Study	Simonen 2000[37]
	regular meals during 7-d period. In the VLED and LED groups, respectively, 8 and 2 patients received diet therapy, 1 and 2 patients took glibenclamide, and 1 and 2 patients took both glibenclamide and biguanide. Four patients in the VLED group and 2 in the LED group took a combination of beta blockers and calcium chanel-blocking agents, 3 patients in the LED group took beta blockers only. The use of medications was maintained during the study. Further details: 1. Diet:
Funding	Academic or government funding (Supported by grants from Helsinki University Central Hospital, the Finnish Diabetes Research Association, and The Howard Foundation, Cambridge, UK)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VLCD (<800 CALORIES PER DAY) versus LCD Protocol outcome 1: % weight change (kg) at Latest follow-up - Actual outcome: NOTE weight in kg (change score - start of study to end of follow-up) at run-in 6 weeks, treatment 12 weeks, maintenance 4 months to 2 years; Group 1: mean -6.7 kg (SD 7.81); n=10, Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: % drop outs at Latest follow-up - Actual outcome: NOTE number of withdrawals from start of study to end of study at run-in 6 weeks, treatment 12 weeks, maintenance 4 months to 2 years; Group 1: 0/10, Group 2: 0/6; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Health related quality of life at Latest follow-up; % weight change (BMI) at Latest follow-up; Improvement in physical activity at Latest follow-up; % weight change (kg) from end of diet to end of study at Latest follow-up; % weight change (BMI) from end of diet to end of study at Latest follow-up

Table 3: Viegener 1990

Study	Viegener 1990[39]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=85)
Countries and setting	Conducted in USA; Setting: Unclear
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 months (6 months intervention, follow-up at 1 year)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: overweight based on the Metropolitan Life Insurance Company tables

Study	Viegener 1990[39]
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	21-59 years of age, 25-99% overweight (based on the height-weight tables of the Metropolitan Life Insurance Company, 1983), and had obtained physician's approval to participate in weight reduction program. Prior to treatment, clients posted a $125.00 deposit that was returned based on attendance at sessions and completion of written food diaries
Exclusion criteria	Excluded if had obesity related medical disorders
Recruitment/selection of patients	Newspaper advertisements
Age, gender and ethnicity	Age - Mean (SD): Overall: 47.12 (8.21), standard diet: 47.13 (8.86), intermittent diet: 47.10 (7.49). Gender (M:F): 85 female (no male participants). Ethnicity: Not stated
Further population details	1. Ethnicity: Not applicable / Not stated / Unclear 2. Learning disabilities: Not applicable / Not stated / Unclear 3. T2DM: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=42) Intervention 1: Very-low-calorie diet - VLCD (<800 calories per day). Intermittent diet condition consisted of behaviour therapy plus an 800-calorie per day, low-fat diet used 4 days per week. Participants in the intermittent diet condition were instructed to rotate through two levels of caloric intake. Participants were expected to maintain 4 days at 800 kcal/day and 3 days at 1200 kcal/day. The sequence of low and higher calorie days was varied according to individual preference. In addition, participants were instructed to restrict their intake of dietary fats to 25% or less of their total calories on "high" calorie days and to 15% or less on "low" calorie days. Duration 12 months (6 months intervention, follow-up at 1 year). Concurrent medication/care: Treatment was conducted in eight groups of 10-12 clients by one of two teams of clinical psychology graduate students. Therapist teams were counterbalanced by treatment condition such that each team conducted two standard diet groups and two intermittent diet groups. Therapists were provided with manuals detailing session-by-session treatment procedures. In addition, all therapists participated in weekly training sessions to help ensure uniformity of treatment procedures across therapists. During the first 6 months, all participants received 26 weekly group sessions, each 2hrs. The behavioural treatment procedures included training in self-monitoring, stimulus control, self-reinforcement, cognitive modification, and problem solving. All participant's instructed to follow a program of aerobic exercise (i.e. walking or stationary cycling), with a target goal of 30 mins/day, 6 days per week. Additionally, all participants were required to: (1) purchase nutrition guidebooks to enhance familiarity with caloric and nutritional values of foods; and (2) to maintain a written daily food diary listing the type, amount, and caloric values of all foods consumed. During the second 6 months, all participant's provided with the opportunity to participate in therapist-led "maintenance" sessions that were held twice per month. All participants were taught to monitor their intake of macronutrients using both calorie counting

Study	Viegener 1990[39]
	and the exchange system of the American Diabetes Association (1986). Nutrition education was a significant focus of the VLCD condition, with a portion of each treatment session given to nutritional concepts (e.g. nutritional composition of foods). Other additional procedures were utilised: (1) low-calorie, low-fat days were conceptualised as "fat-free" days. Participants were encouraged to eliminate or reduce all visible dietary fats on these days and to restrict the use of foods with any significant fat content. (2) participants were instructed to begin with one “fat-free” day during the 2nd week of treatment and to increase to 4 “fat-free” days by the 6th week. (3) In vivo techniques were utilised to encourage adherence to the low-calorie regimen. Samples of low-fat, low-calorie foods were provided during treatment, along with recipes, meal plans and product information. (4) model the integration of low-fat alternatives in meal planning Further details: 1. Diet: (n=43) Intervention 2: Standard dietary advice - LCD. Standard treatment program consisted of behaviour therapy plus a 1200-calorie per day balanced deficit diet (nutritional recommendations: 55% carbohydrate, 30% fat, and 15% protein). Duration 12 months (6 months intervention, follow-up at 1 year). Concurrent medication/care: Treatment was conducted in eight groups of 10-12 clients by one of two teams of clinical psychology graduate students. Therapist teams were counterbalanced by treatment condition such that each team conducted two standard diet groups and two intermittent diet groups. Therapists were provided with manuals detailing session-by-session treatment procedures. In addition, all therapists participated in weekly training sessions to help ensure uniformity of treatment procedures across therapists. During the first 6 months, all participants received 26 weekly group sessions, each 2hrs. The behavioural treatment procedures included training in self-monitoring, stimulus control, self-reinforcement, cognitive modification, and problem solving. All participants instructed to follow a program of aerobic exercise (i.e. walking or stationary cycling), with a target goal of 30 mins/day, 6 days per week. Additionally, all participants were required to: (1) purchase nutrition guidebooks to enhance familiarity with caloric and nutritional values of foods; and (2) to maintain a written daily food diary listing the type, amount, and caloric values of all foods consumed. During the second 6 months, all participants provided with the opportunity to participate in therapist-led "maintenance" sessions that were held twice per month. All participants were taught to monitor their intake of macronutrients using both calorie counting and the exchange system of the American Diabetes Association (1986) Further details: 1. Diet:
Funding	Academic or government funding (Funds from the V.A. Medical Research Service (U.S. Department of Veterans Affairs))
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VLCD (<800 CALORIES PER DAY) versus LCD	

Study	Viegener 1990[39]
Protocol outcome 1: % weight change (kg) at Latest follow-up - Actual outcome: NOTE weight in kg, change score, from start of study to end of treatment at 6 months; Group 1: mean -10.2 kg (SD 5.1); n=30, Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: NOTE weight in kg, change score, from start of study to end of follow-up at 12 months; Group 1: mean -9 kg (SD 6.7); n=30, Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: % drop outs at Latest follow-up - Actual outcome: NOTE number of withdrawals from start of study to end of study at 12 months (6 months treatment + 6 months follow-up); Group 1: 12/42, Group 2: 13/43; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Health related quality of life at Latest follow-up; % weight change (BMI) at Latest follow-up; Improvement in physical activity at Latest follow-up; % weight change (kg) from end of diet to end of study at Latest follow-up; % weight change (BMI) from end of diet to end of study at Latest follow-up

Table 4: Wadden 1994

Study	Wadden 1994[40]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=49)
Countries and setting	Conducted in USA
Line of therapy	1st line
Duration of study	Intervention + follow up: 52 weeks + 26 weeks follow-up
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	At least 25 kg overweight (determined by height-weight tables of the Metropolitan Life Insurance Company)
Exclusion criteria	Recent myocardial infarction or evidence of cardiac abnormalities, history of cerebrovascular, kidney, or liver disease, cancer, type 1 diabetes, bulimia nervosa or significant psychiatric illness
Recruitment/selection of patients	Patients recruited by newspaper advertisement seeking for those at least 25 kg overweight
Age, gender and ethnicity	Age - Mean (SD): LCD: 42.86 (10.12) / VLCD: 36.82 (8.87). Gender (M:F): All women. Ethnicity: Not reported
Further population details	1. Ethnicity: Not applicable / Not stated / Unclear 2. Learning disabilities: Not applicable / Not stated / Unclear 3.

Study	Wadden 1994[40]
	T2DM: Not applicable / Not stated / Unclear
Extra comments	Height 164.38 cm, weight 106.33 kg (VLCD 107.85 SD 14.89 vs. LCD 105.43 SD 13.68), BMI 39.46 (VLCD 40.01 SD 5.73 vs. LCD 38.80 SD 5.39). All patients paid $600 for the 18 months of treatment and $300 of which was refunded at 6-month intervals for completing the program; there were 9 patients considered binge eaters in the VLCD group at baseline (BES 27+) while there were 5 in the LCD group at baseline
Indirectness of population	No indirectness
Interventions	(n=28) Intervention 1: Very-low-calorie diet - VLCD (<800 calories per day). After initial first week on 1200 kcal per day, patients had liquid formula VLCD (OPTIFAST 70, Sandoz Nutrition, Minneapolis, MN) during weeks 2 to 17 (total 16 weeks) which provided 420 kcal/d (70g protein, 30 g carbohydrates, 2 g fat, 2990 mg/d potassium and 100% of US RDA essential vitamins and minerals). During this time, patients were instructed to have at least 2 L of noncaloric fluid per day and avoid all other foods. After the 16-week VLCD, conventional foods were gradually introduced for weeks 18-23 and patients were consuming 1000 kcal/d by week 23 (this was overseen by a dietician). From week 18-27, subjects attended groups led by a dietician which provided information on food preparation and nutrition. During weeks 24-52, subjects were instructed to consume conventional reducing diet of 1200 kcal/d and record daily food intake. Duration 52 weeks + 26 weeks maintenance program. Concurrent medication/care: All arms had the same behavioural therapy and exercise. Behavioural therapy: weekly sessions in groups of 6-9 subjects led by a doctoral-level clinical psychologist or a psychology graduate student for the 52 week treatment giving instruction in traditional behavioural methods of weight control including: 1) recording eating behaviour (amounts, calories, times, etc.), 2) controlling stimuli associated with eating, 3) slowing the rate of eating, 4) modifying self-defeating thoughts and emotions, 5) eliciting social support, 6) increasing life-style activity (implementation involved problem-solving skills); Exercise programme: started at week 8 which consisted of walking for most - subjects were instructed to exercise for 10-20 minutes at 40-60% of estimated maximum heart rate for 2-3 times per week initially, then for 20-40 minutes at 60-70% of maximum heart rate for 3-5 times per week. During the maintenance program, biweekly sessions focused on instruction in basic 'upkeep' skills including graphing weight weekly, preparing low-fat meals, continuing to exercise regularly and learning to reverse small weight gains as they occurred. Subjects were also taught to prevent dietary and exercise lapses by identifying high-risk situations and given steps to take if they have an overeating episode. Further details: 1. Diet: Not applicable / Not stated / Unclear (n=21) Intervention 2: Standard dietary advice - LCD. For 52 weeks, subjects were instructed to consume 1200 kcal/d diet (15-20% protein, no more than 30% from fat and the remainder from carbohydrate); during the 26-week maintenance program, they were told to adjust their caloric intake according to their desired weight change but not to consume less than 1200 kcal/d. Duration 52 weeks + 26 week maintenance program. Concurrent medication/care: All arms had the same behavioural therapy and exercise. Behavioural therapy: weekly sessions in groups of 6-9

Study	Wadden 1994[40]
	subjects led by a doctoral-level clinical psychologist or a psychology graduate student for the 52 week treatment giving instruction in traditional behavioural methods of weight control including: 1) recording eating behaviour (amounts, calories, times, etc.), 2) controlling stimuli associated with eating, 3) slowing the rate of eating, 4) modifying self-defeating thoughts and emotions, 5) eliciting social support, 6) increasing life-style activity (implementation involved problem-solving skills); Exercise programme: started at week 8 which consisted of walking for most - subjects were instructed to exercise for 10-20 minutes at 40-60% of estimated maximum heart rate for 2-3 times per week initially, then for 20-40 minutes at 60-70% of maximum heart rate for 3-5 times per week. During the maintenance program, biweekly sessions focused on instruction in basic 'upkeep' skills including graphing weight weekly, preparing low-fat meals, continuing to exercise regularly and learning to reverse small weight gains as they occurred. Subjects were also taught to prevent dietary and exercise lapses by identifying high-risk situations and given steps to take if they have an overeating episode. Further details: 1. Diet: Comments: This arm is referred to as the BDD (balanced deficit diet) in the study
Funding	Academic or government funding (National Institute for Mental Health grants)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VLCD (<800 CALORIES PER DAY) + BEHAVIOURAL THERAPY + EXERCISE versus LCD (1200 CALORIES PER DAY) + BEHAVIOURAL THERAPY + EXERCISE Protocol outcome 1: % weight change (kg) at Latest follow-up - Actual outcome: NOTE weight in kg, change (from start of study to end of treatment) at 17 weeks; Group 1: mean -20.5 kg (SD 7.29); n=28, Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: NOTE weight in kg, change (from start of study to end of study at 78 weeks (52 weeks intervention + 26 weeks follow-up); Group 1: mean -10.94 kg (SD 9.97); n=21, Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: % drop outs at Latest follow-up - Actual outcome: NOTE number of withdrawals (from start of study to end of study) at 78 weeks; Group 1: 7/28, Group 2: 5/21; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Health related quality of life at Latest follow-up; % weight change (BMI) at Latest follow-up; Improvement in physical activity at Latest follow-up; % weight change (kg) from end of diet to end of study at Latest follow-up; % weight change (BMI) from end of diet to end of study at Latest follow-up

Table 5: Wing 1984

Study	Wing 1984[48]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=48)
Countries and setting	Conducted in USA
Line of therapy	1st line
Duration of study	Intervention + follow up: Pre-assessment 10 days, treatment 10 weeks, maintenance and follow-up 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Participants had to be aged 20-65, ≥20% overweight, not currently involved in any other weight-control programs and willing to participate in a 15-month study. An $85.00 deposit was required: $35.00 was non-refundable; $50.00 was refunded for attendance at treatment and follow-up meetings.
Exclusion criteria	Not specified
Recruitment/selection of patients	Newspaper articles and physician referrals. Those interested were invited to attend an orientation meeting
Age, gender and ethnicity	Age - Mean (SD): 44.79 (5.06). Gender (M:F): 42 female, 6 male. Ethnicity: Not specified
Further population details	1. Ethnicity: Not applicable / Not stated / Unclear 2. Learning disabilities: Not applicable / Not stated / Unclear 3. T2DM: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Very-low-calorie diet - VLCD (<800 calories per day). Participants in the intermittent low-calorie regimen were given comparable individualised goals to follow for 5 days/week. For the other 2 days of the week, participants were advised to practice 'self-control' by restricting intake to below 750 kcal/day. Participants were given two specific plans for achieving the low-calorie goal: they could either follow a prescribed low-calorie menu or could return to a combination of liquid Slender and Slender bars. It was explained to participants that both of these eating plans would simply the decisions involved in meal selection and would help reduce the stimuli associated with overeating. At the weekly treatment meeting, participant's selected the 2 self-control days for the following week. Duration pre-assessment 10 d, treatment 10 weeks, maintenance 6 months, follow-up 1 yr. Concurrent medication/care: All participants completed a 10-day assessment procedure, in which their intake and physical activity was recorded for the 4 days following the orientation meeting. Participants were instructed to maintain their normal pattern of intake and expenditure during this time. Days 5-7, participants were given an individually prescribed diet consisting of only Slender breakfast bars (137 kcal/bar) and liquid Slender in cans (225 kcals/can). A caloric goal was

Study	Wing 1984[48]
	calculated for each participant (based on weight x 12 - 1000 kcal) and the combination of bars/cans that would most closely achieve this goal was prescribed. Days 8-10, participants were instructed to return to regular foods, but to maintain their intake at or below the prescribed calorie goal. Participants who completed the assessment were randomly assigned to either treatment arm. Participant's in both attended weekly meetings for a 10 week period, each lasting 60-90 min and consisted of an individual weight-in, review, and collection of food diaries and presentation of new lesson (energy balance, strategies for increasing exercise, stimulus control, cognitive restructuring, self-reinforcement and relapse prevention). Treatments differed only in type of eating plan. Half of the participant's from each treatment were assigned to a booster maintenance schedule. To ensure participants who had been successful during initial treatment were evenly distributed, participants were blocked according to weight loss during the 10 week program (lost <10 lb, lost 10-20 lb, lost >20 lb) and randomly assigned from within blocks to one of the two booster schedules. Both conditions met 6 times. Booster condition: 6 meetings held monthly over 6-month period. Massed condition: met once at beginning and once at end of 6-month maintenance interval, with remaining 4 meetings massed during third month. Both conditions met again 12 months after initial treatment. The content of the booster sessions was similar for the two conditions (problem-solving techniques to identify difficult situations and preplan strategies for coping with these situations). Additional topics related to nutrition and exercise Further details: 1. Diet: (n=23) Intervention 2: Standard dietary advice - LCD. Participants in the standard behavioural condition were given a calorie goal (based on initial weight x 12 - 1000 kcal). They were told to self-monitor their caloric intake and to stay within the calorie goal. All participants were given calorie goals of at least 1000 kcal/day. Duration pre-assessment 10 d, treatment 10 weeks, maintenance 6 months, follow-up 1 yr. Concurrent medication/care: All participants completed a 10-day assessment procedure, in which their intake and physical activity was recorded for the 4 days following the orientation meeting. Participants were instructed to maintain their normal pattern of intake and expenditure during this time. Days 5-7, participants were given an individually prescribed diet consisting of only Slender breakfast bars (137 kcal/bar) and liquid Slender in cans (225 kcals/can). A caloric goal was calculated for each participant (based on weight x 12 - 1000 kcal) and the combination of bars/cans that would most closely achieve this goal was prescribed. Days 8-10, participants were instructed to return to regular foods, but to maintain their intake at or below the prescribed calorie goal. Participants who completed the assessment were randomly assigned to either treatment arm. Participant's in both attended weekly meetings for a 10 week period, each lasting 60-90 min and consisted of an individual weight-in, review, and collection of food diaries and presentation of new lesson (energy balance, strategies for increasing exercise, stimulus control, cognitive restructuring, self-reinforcement and relapse prevention). Treatments differed only in type of eating plan. Half of the participant's from each treatment were assigned to a booster maintenance schedule. To ensure participants who had been successful during initial treatment were evenly distributed, participants were blocked according to weight loss during the 10 week program (lost <10 lb, lost 10-20 lb, lost >20 lb) and randomly assigned from within blocks to one of the two booster schedules. Both

Study	Wing 1984[48]
	conditions met 6 times. Booster condition: 6 meetings held monthly over 6-month period. Massed condition: met once at beginning and once at end of 6-month maintenance interval, with remaining 4 meetings massed during third month. Both conditions met again 12 months after initial treatment. The content of the booster sessions was similar for the two conditions (problem-solving techniques to identify difficult situations and preplan strategies for coping with these situations). Additional topics related to nutrition and exercise Further details: 1. Diet:
Funding	Academic or government funding (Grant AM 29757-02 from the National Institute of Arthritis, Metabolism and Digestive Diseases)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VLCD (<800 CALORIES PER DAY) versus LCD Protocol outcome 1: % weight change (kg) at Latest follow-up - Actual outcome: NOTE - weight in kg (not %), change score, from start of study to end of diet treatment at preassessment:10 ds, treatment:10 weeks; Group 1: mean -8.4 kg (SD 1.4); n=24, Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: NOTE - weight in kg (not %), change score, from start of study to end of follow-up at pre-assessment, 10 ds; treatment, 10 weeks; maintenance, 6 months; follow-up at 1 year; Group 1: mean -2.7 kg (SD 2.4); n=23, Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: % drop outs at Latest follow-up - Actual outcome: NOTE number of withdrawals from start of study to end of study at pre-assessment 10 d, treatment 10 weeks, maintenance 6 months, follow-up 12 months; Group 1: 2/25, Group 2: 2/23; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Health related quality of life at Latest follow-up; % weight change (BMI) at Latest follow-up; Improvement in physical activity at Latest follow-up; % weight change (kg) from end of diet to end of study at Latest follow-up; % weight change (BMI) from end of diet to end of study at Latest follow-up

Table 6: Wing 1991

Study (subsidiary papers)	Wing 1991[50] (Wing 1997[43], Wing 1991[49])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=36)
Countries and setting	Conducted in USA; Setting: Not reported
Line of therapy	1st line

Study (subsidiary papers)	Wing 1991[50] (Wing 1997[43], Wing 1991[49])
Duration of study	Intervention + follow up: 20 week intervention + 1 year follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Ideal body weight was based on Metropolitan Life Insurance norm (participants needed to be at least 30% or more above)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	35-70 years old, 30% or more above ideal body weight (based on Metropolitan Life Insurance norm), type 2 diabetes (defined by National Diabetes Data Group)
Exclusion criteria	Liver, renal, or heart disease
Recruitment/selection of patients	Advertisement in newspaper
Age, gender and ethnicity	Age - Mean (SD): 50.6 (7.7) for VLCD vs. 51.9 (9.9) for LCD. Gender (M:F): 10 men / 26 women. Ethnicity: Not reported
Further population details	1. Ethnicity: Not applicable / Not stated / Unclear 2. Learning disabilities: Not applicable / Not stated / Unclear 3. T2DM: T2DM
Extra comments	Mean 102.1 kg (SD 11.7) VLCD vs. 104.5 kg (SD 21.5) LCD; mean BMI: 37.34 (SD 4.7) VLCD vs. 38.10 (SD 5.7) LCD; mean years diabetic: 5.7 (SD 4.2) VLCD vs. 7.8 (SD 7.5); mean HbA 10.4% (SD 2.2) VLCD vs. 10.4% (SD 2.0) LCD; mean fasting blood glucose 14.2 mmol/L (SD 4.5) VLCD vs. 12.7 mmol/L (SD 4) LCD
Indirectness of population	No indirectness
Interventions	(n=17) Intervention 1: Very-low-calorie diet - VLCD (<800 calories per day). After 4 weeks on 1000-1500 kcal/d balanced diet, participants had VLCD (400 kcal/d) for 2 months/8 weeks given as either lean meat, fish or fowl or liquid formula (Optifast 70, Sandoz Nutrition). In the fourth month (after week 16), they gradually increased the quantity and types of food until the 5th month when the patients returned to 1000-1500 kcal/d. Participants received the above in addition to behavioural therapy (see below). Duration 20 weeks. Concurrent medication/care: Participants in both arms had behaviour therapy: in groups if 8-10 and led by a team of therapists; included instruction in diet, exercise, and behaviour modification including a) exercise recommendations to start at 210 J/week weekly and increasing to 4200 J/week (i.e. approximately 10 miles per week), b) daily monitoring of caloric intake and exercise by participants, c) stimulus control techniques including strategies for removing food cues from their environment, eating slowly, separating eating from other activities, d) modification of cognitions for relapse prevention and self-reinforcement, e) subjects deposited $150 at the start of the program and earned this back weekly for meeting homework goals, f) self-monitoring of blood glucose and provision with monitoring equipment and supplies Further details: 1. Diet: Not applicable / Not stated / Unclear

Study (subsidiary papers)	Wing 1991[50] (Wing 1997[43], Wing 1991[49])
	(n=19) Intervention 2: Standard dietary advice - LCD. Participants received a 1000-1500 kcal/d balanced diet for the duration of the study in addition to behavioural therapy (see below). Duration 20 weeks. Concurrent medication/care: Participants in both arms had behaviour therapy: in groups if 8-10 and led by a team of therapists; included instruction in diet, exercise, and behaviour modification including a) exercise recommendations to start at 210 J/week weekly and increasing to 4200 J/week (i.e. approximately 10 miles per week), b) daily monitoring of caloric intake and exercise by participants, c) stimulus control techniques including strategies for removing food cues from their environment, eating slowly, separating eating from other activities, d) modification of cognitions for relapse prevention and self-reinforcement, e) subjects deposited $150 at the start of the program and earned this back weekly for meeting homework goals, f) self-monitoring of blood glucose and provision with monitoring equipment and supplies. Further details: 1. Diet: Not applicable / Not stated / Unclear
Funding	Academic or government funding (Grants from National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Western Pennsylvania Affiliate of the American Diabetes Association)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VLCD (400 CALORIES PER DAY) + BEHAVIOUR THERAPY + EXERCISE versus LCD (1000-1500 CALORIES PER DAY) + BEHAVIOUR THERAPY + EXERCISE

Protocol outcome 1: % weight change (kg) at Latest follow-up
- Actual outcome: NOTE weight in kg, change (from start of study to end of treatment) at 20 weeks; Group 1: mean -18.6 kg (SD 9.5); n=17, Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: NOTE weight in kg, change (from start of study to end of follow-up) at 72 weeks (20 weeks intervention + 52 weeks follow-up); Group 1: mean -8.6 kg (SD 9.2); n=17, Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: % drop outs at Latest follow-up
- Actual outcome: NOTE number of withdrawals (from start of study to end of study) at 72 weeks (20 weeks intervention + 52 weeks follow-up); Group 1: 0/17, Group 2: 3/19; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: % weight change (BMI) at Latest follow-up
- Actual outcome: NOTE weight in BMI, final (NOTE from start of study to end of follow-up) at 72 weeks (20 weeks intervention + 52 weeks follow-up); Group 1: mean 34.14 BMI (SD 3.62); n=17, Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: NOTE weight in BMI, change (NOTE from start of study to end of treatment) at 20 weeks intervention; Group 1: mean -6.76 BMI (SD 3.47); n=17, Risk of bias: Very high; Indirectness of outcome: No indirectness

Study (subsidiary papers)	Wing 1991[50] (Wing 1997[43], Wing 1991[49])
Protocol outcomes not reported by the study	Health related quality of life at Latest follow-up; Improvement in physical activity at Latest follow-up; % weight change (kg) from end of diet to end of study at Latest follow-up; % weight change (BMI) from end of diet to end of study at Latest follow-up

Table 7: Wing 1994

Study (subsidiary papers)	Wing 1994[45] (Wing 1994[46], Wing 1995[51], Wing 1996[44])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=93)
Countries and setting	Conducted in USA; Setting: Not clear
Line of therapy	1st line
Duration of study	Intervention + follow up: 2 years (including 48 week intervention time)
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Overweight defined as either more than 30% or more than 18 kg above ideal body weight based on Metropolitan Life Insurance Norms.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with T2D and were either more than 30% or more than 18 kg above ideal body weight based on Metropolitan Life Insurance norms and aged between 30 and 70 with no health problems that precluded use of a VLCD.
Exclusion criteria	Not reported (other than health problems the precluded use of a VLCD).
Recruitment/selection of patients	Newspaper advertisements were used to recruit people
Age, gender and ethnicity	Age - Mean (SD): VLCD: 52.3 years (10.7) vs. LCD: 51.3 years (8.7). Gender (M:F): 33/60. Ethnicity:
Further population details	1. Ethnicity: Not applicable / Not stated / Unclear 2. Learning disabilities: Not applicable / Not stated / Unclear 3. T2DM: T2DM
Extra comments	Diagnosis of diabetes for an average of 6.8 years (SD 6.2), with mean 106.8 kg (SD 18.6) and average BMI 37.9 (SD 6.3)
Indirectness of population	No indirectness
Interventions	(n=45) Intervention 1: Very-low-calorie diet - VLCD (<800 calories per day). 12 week VLCD (400-500 kcal/d) (week 1-12), then gradual introduction of LCD (1000-1200 kcal/d) over next 12 weeks, then 2nd 12-week VLCD period (400-500 kcal/d) (week 24-36) followed by 2nd 12-week LCD period (1000-1200 kcal/d). VLCD was liquid (Optifast 70, Sandoz Nutrition, Minneapolis, Minnesota) or as lean meat, fish and fowl. All were given vitamin and mineral supplementation to take daily and were seen every other week by the project physician. Duration 1 year. Concurrent

Study (subsidiary papers)	Wing 1994[45] (Wing 1994[46], Wing 1995[51], Wing 1996[44])
	medication/care: Behavioural treatment occurred over 1 year. Weekly group meetings (of around 15 subjects) were conducted by a multidisciplinary team of therapists (including behavioural therapist, health educator, nutritionist and physician). Meetings consisted of individual weigh-in, review of self-monitoring records, and a lecture and discussion concerning a topic related to nutrition, exercise or behaviour modification. Exercise lectures stressed walking and people were given weekly exercise goals which gradually increased to 10 miles each week. Behavioural lectures focused on self-monitoring of intake and exercise, goal setting, stimulus control, preplanning, relapse prevention, and modifying cognitions. There was sufficient time given for role-play of appropriate behavioural responses and to allow for individual discussion and questions. Further details: 1. Diet: Supervised VLCD (Subjects were seen weekly by the project physician.). Comments: 2 patients did not receive the 2nd VLCD as they had already reached ideal body weight. Subjects received the program free of charge but all deposited $150 at the start of treatment which was refunded in full for reaching behavioural goals and attending sessions. (n=48) Intervention 2: Standard dietary advice - LCD. LCD (1000-1200 kcal/d). Subjects were able to select food items they wished but were encouraged to spread their calories over the day and limit their dietary fat intake to less than 30% of calories.. Duration 1 year. Concurrent medication/care: Behavioural treatment occurred over 1 year. Weekly group meetings (of around 15 subjects) were conducted by a multidisciplinary team of therapists (including behavioural therapist, health educator, nutritionist and physician). Meetings consisted of individual weigh-in, review of self-monitoring records, and a lecture and discussion concerning a topic related to nutrition, exercise or behaviour modification. Exercise lectures stressed walking and people were given weekly exercise goals which gradually increased to 10 miles each week. Behavioural lectures focused on self-monitoring of intake and exercise, goal setting, stimulus control, preplanning, relapse prevention, and modifying cognitions. There was sufficient time given for role-play of appropriate behavioural responses and to allow for individual discussion and questions. Further details: 1. Diet: Not applicable / Not stated / Unclear Comments: Subjects received the program free of charge but all deposited $150 at the start of treatment which was refunded in full for reaching behavioural goals and attending sessions.
Funding	Academic or government funding (Grant from National Institutes for Health)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VLCD (400-500 CALORIES PER DAY) + BEHAVIOURAL TREATMENT versus LCD + BEHAVIOURAL TREATMENT

Protocol outcome 1: % weight change (kg) at Latest follow-up
- Actual outcome: NOTE weight in kg, change (start of study to end of treatment) (note: not % change) at 1 year; Group 1: mean -14.2 kg (SD 10.3); n=38, Group 2:

Study (subsidiary papers)	Wing 1994[45] (Wing 1994[46], Wing 1995[51], Wing 1996[44])
mean -10.5 kg (SD 11.6); n=41; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: % drop outs at Latest follow-up - Actual outcome: NOTE number of withdrawals at 1 year at 1 year; Group 1: 7/45, Group 2: 7/48; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: NOTE number of withdrawals at 2 years (use this data) at 2 years; Group 1: 9/45, Group 2: 11/48; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: % weight change (BMI) at Latest follow-up - Actual outcome: NOTE weight in BMI, change (start of study to end of treatment) (note: not % change) at 1 year; Group 1: mean -5 kg/m2 (SD 3.5); n=38, Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: % weight change (kg) from end of diet to end of study at Latest follow-up - Actual outcome: NOTE - weight in kg, change (start of study to end follow-up) (note: not % change) at 2 years; Group 1: mean -7.2 kg (SD 8); n=36, Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Health related quality of life at Latest follow-up; Improvement in physical activity at Latest follow-up; % weight change (BMI) from end of diet to end of study at Latest follow-up

G.1.2 Safety

Table 8: Arai 1992

Study	Arai 1992[2]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=45)
Countries and setting	Conducted in Japan; Setting: Not explicitly reported
Line of therapy	1st line
Duration of study	Intervention time: 4-8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: BMI
Stratum	Overall
Subgroup analysis within study	Not applicable

Study	Arai 1992[2]
Inclusion criteria	Not explicitly reported
Exclusion criteria	Not explicitly reported
Recruitment/selection of patients	Not explicitly reported
Age, gender and ethnicity	Age - Mean (SD): VLCD: 31.6 years (SD13.1), LCD: 35.3 years (SD 11.7). Gender (M:F): 12/33. Ethnicity: Japanese (study explicitly states that the participants were Japanese)
Further population details	1. Ethnicity: Asian (>80%) (All patients appeared to be Japanese). 2. Learning disabilities: Not applicable / Not stated / Unclear 3. T2DM: Not applicable / Not stated / Unclear
Extra comments	37 kg/m2 (SD 4) VLCD, 36 kg/m2 (SD 6) LCD
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Very-low-calorie diet - VLCD (<800 calories per day). VLCD with Optifast 70 providing 1757 kJ (~419 kcal/day), 70 g protein, 30 g carbohydrate and 2 g fat. Duration 1-2 months. Concurrent medication/care: None reported Further details: 1. Diet: Not applicable / Not stated / Unclear (n=25) Intervention 2: Standard dietary advice - LCD. LCD of 3515-5021 kJ/d (~839-1199 kcal/d) using 2-3 packages of Optifast 70 and 2678-3682 kj of conventional balanced meals consisting of a mixture of 88g protein, 30-80 g carbohydrate and 4-9 g of fat.. Duration 1-2 months. Concurrent medication/care: None reported Further details: 1. Diet: Not applicable / Not stated / Unclear
Funding	Equipment / drugs provided by industry (Sandoz Nutrition Company provided the Optifast products used in the study)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VLCD (<800 CALORIES PER DAY) versus LCD Protocol outcome 1: Gout at Latest follow up - Actual outcome: Serum acid levels at 8 weeks; Group 1: mean 283.2 µmol/L (SD 94.4); n=20, Group 2: mean 306.8 µmol/L (SD 64.9); n=25; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: Proportion with marked serum uric acid concentration during treatment; Group 1: 7/20, Group 2: 0/25; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Disordered eating at Latest follow up; Depression score at Latest follow up; Postural hypotension at Latest follow up; Bone density at Latest follow up; Constipation at Latest follow up; Gall stones at Latest follow up; Diarrhoea at Latest

Study	Arai 1992[2]
	follow up; Hypoglycaemia at Latest follow up; Health related quality of life at Latest follow-up

Table 9: Riecke 2010, Christensen 2011

Study (subsidiary papers)	CAROT-study trial: Riecke 2010[32,32] (Christensen 2011[4,5])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=192)
Countries and setting	Conducted in Denmark; Setting: The Parker Institute, Frederiksberg Hospital, Frederiksberg
Line of therapy	1st line
Duration of study	Intervention time: 16 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Obesity (BMI > 30 kg/m2), > 50 years old, primary knee osteoarthritis diagnosed according to American Rheumatology criteria (clinical signs and symptoms as well as radiologically or arthroscopically verified OA in one of both knees)
Exclusion criteria	Previous or planned total knee replacement in the target knee, surgical procedures (ie. arthroscopy or injections into a knee) within 3 months of enrolment, pharmacological therapy with weight reducing drugs, lack of motivation to lose weight, inability to speak Danish fluently, mental state impeding compliance with the program, patient with other medical illnesses who could not manage transport to the outpatients clinic on their own
Recruitment/selection of patients	From November 2007 to August 2008 from the outpatient's clinic at the Department of Rheumatology at Frederiksberg Hospital, Frederiksberg. GPs were contacted and the study was advertised in newspapers and on the website of The Parker Institute.
Age, gender and ethnicity	Age - Mean (SD): 62.5 (SD 6.4) (range 50-77.9). Gender (M:F): 37 male/155 female. Ethnicity: Not reported
Further population details	1. Ethnicity: Not applicable / Not stated / Unclear 2. Learning disabilities: Not applicable / Not stated / Unclear 3. T2DM: Not applicable / Not stated / Unclear
Extra comments	Mean BMI 37.3 kg/m2 (SD4.8, range 30.1-54), mean 103.2 kg (SD15, range 76-145.3). Patients with other medical illnesses were included in the trial; the study was a pragmatic RCT; patients were asked not to change any nutritional supplements or medication for their osteoarthritis during the study; purpose of trial to treat knee osteoarthritis symptoms
Indirectness of population	No indirectness

Study (subsidiary papers)	CAROT-study trial: Riecke 2010[32,32] (Christensen 2011[4,5])
Interventions	(n=96) Intervention 1: Very-low-calorie diet - VLCD (<800 calories per day). Formula only diet with 415 kcal/d (Cambridge nutritional powder disolved into water) for 8 weeks, then 8 weeks of hypoenergetic diet (approximately 1200 kcal/d from normal food plus meal replacements). Duration 16 weeks. Concurrent medication/care: Both arms recevied nutritional instructions and behavioural therapy with experienced dietician in weekly sessions (1.5 h/wk) throughout the 16 weeks Further details: 1. Diet: Supervised VLCD (n=96) Intervention 2: Standard dietary advice - LCD. Formula only diet with 810 kcal/d for 8 weeks: The Cambridge diet including meal replacements, nutritional powder disolved in 7.5 dl of milk/d, and bars taken 3 times per day. For the next 8 weeks, hypoenergetic diet: approximately 1200 kcal/d from normal food plus meal replacements. Duration 16 weeks. Concurrent medication/care: Both arms recevied nutritional instructions and behavioural therapy with experienced dietician in weekly sessions (1.5 h/wk) throughout the 16 weeks Further details: 1. Diet: Supervised VLCD
Funding	Study funded by industry (Supported by grants from The Cambridge Health and Weight Plan UK but also The Oak Foundation, The Velux Foundation, The Danish Rheumatism Association, The Augustinus Foundation, The A.P. Moller Foundation for the Advancement of Medical Science, Erik Horslev og hustru Birgit Horslevs Fond, Aase og Ejnar Danielsens fond and Bjarne Jensens Fond (but none had involveement in the design, collection, analysis or interpretation of the data.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VLCD (415 CALORIES PER DAY) FOLLOWED BY HYPOENERGETIC DIET + BEHAVIOURAL THERAPY versus LCD (810 CALORIES PER DAY) FOLLOWED BY HYPOENERGETIC DIET + BEHAVIOURAL THERAPY Protocol outcome 1: Depression score at Latest follow up - Actual outcome: Depressive tendencies at 16 weeks; Group 1: 6/86, Group 2: 3/89; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Constipation at Latest follow up - Actual outcome: Constipation at 16 weeks; Group 1: 28/86, Group 2: 25/89; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Diarrheoa at Latest follow up - Actual outcome: Diarrhoea at 16 weeks; Group 1: 4/86, Group 2: 3/89; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Disordered eating at Latest follow up; Postural hypotension at Latest follow up; Bone density at Latest follow up; Gall stones at Latest follow up; Gout at Latest follow up; Hypoglycaemia at Latest follow up; Health related quality of life at

Study (subsidiary papers)	CAROT-study trial: Riecke 2010[32,32] (Christensen 2011[4,5])
	Latest follow-up

Table 10: Gebhard 1996

Study	Gebhard 1996[12,12]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=13)
Countries and setting	Conducted in USA; Setting: Not described
Line of therapy	1st line
Duration of study	Intervention time: 24 week programme (12 week intervention)
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Not clear how 'obese' was defined but most patients appear to be over 25 kg/m2 BMI
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Not clearly described apart from healthy, obese subjects recruited from a medical clinic weight loss program, had normal gallbladder ultrasonography
Exclusion criteria	Presence of gallstones
Recruitment/selection of patients	Recruitment from a medical clinic weight loss programme (between May 1993 to May 1994)
Age, gender and ethnicity	Age - Mean (SD): 40 (5) for VLCD and 40 (8) for LCD. Gender (M:F): 3 male/10 female. Ethnicity: Not reported
Further population details	1. Ethnicity: Not applicable / Not stated / Unclear 2. Learning disabilities: Not applicable / Not stated / Unclear 3. T2DM: Not applicable / Not stated / Unclear
Extra comments	105 kg (SD 21) for VLCD and 114 kg (SD29) for LCD; BMI 37 kg/m2 (SD 4) compared to 36 (SD 6) LCD
Indirectness of population	No indirectness
Interventions	(n=6) Intervention 1: Very-low-calorie diet - VLCD (<800 calories per day). 12 weeks on VLCD: Liquid formula containing 520 kcal/d with 50g protein, less than 2 g fat, and 30 mg cholesterol (each meal has less than 1 g of fat) (contained 100% of the USA recommendation daily allowance for vitamins and minerals)12 weeks was followed by introduction to conventional foods and reduction of liquid food so that by 18 weeks, patients were on 1000 kcal/d of solid food; this was gradually increased to 1500 kcal/d over the remaining 6 weeks. Duration 24 week. Concurrent medication/care: none Further details: 1. Diet: Not applicable / Not stated / Unclear

Study	Gebhard 1996[12,12]
	Comments: Patients were monitored medically and included in a 24-week program including weekly meetings, diary and compliance review by a single registered dietician experienced in weight loss methods and periodic evaluation by a physician. (n=7) Intervention 2: Standard dietary advice - LCD. 12 weeks on LCD: liquid formula with 900 kcal/d with 90g protein, 30g fat (source=canola oil), and 90 mg cholesterol (each preparation contained 5 g fat) (noncommercial diet prepared by Sandoz Nutrition); one daily meal consisted of two packets in 12 oz of fluid to provide one 10-g fat meal daily to stimulate maximal gallbladder emptying. (contained 100% of the USA recommendation daily allowance for vitamins and minerals)12 weeks was followed by introduction to conventional foods and reduction of liquid food so that by 18 weeks, patients were on 1000 kcal/d of solid food; this was gradually increased to 1500 kcal/d over the remaining 6 weeks. Duration 24 weeks. Concurrent medication/care: none Further details: 1. Diet: Not applicable / Not stated / Unclear Comments: Patients were monitored medically and included in a 24-week program including weekly meetings, diary and compliance review by a single registered dietician experienced in weight loss methods and periodic evaluation by a physician.
Funding	Study funded by industry (Sandoz Nutrition (Mineapolis, MN) and Department of Veterans Affairs Research Program)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VLCD (520 CALORIES PER DAY) versus LCD (900 CALORIES PER DAY) Protocol outcome 1: Gall stones at Latest follow up - Actual outcome: Gallstones at unclear; Group 1: 4/6, Group 2: 0/7; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Disordered eating at Latest follow up; Depression score at Latest follow up; Postural hypotension at Latest follow up; Bone density at Latest follow up; Constipation at Latest follow up; Gout at Latest follow up; Diarrheoa at Latest follow up; Hypoglycaemia at Latest follow up; Health related quality of life at Latest follow-up

Table 11: Wadden 1990

Study	Wadden 1990[41,42]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=15)
Countries and setting	Conducted in USA

Study	Wadden 1990[41,42]
Line of therapy	1st line
Duration of study	Intervention time: 18 weeks
Method of assessment of guideline condition	--
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Not explicitly reported
Exclusion criteria	Exclusion criteria not explicitly reported but some reasons for exclusion included recent myocardial infarction, history of cerebrovascular, kidney, or liver disease, cancer, hypo or hyperthyroidism, type I diabetes, pregnancy
Recruitment/selection of patients	Patients were drawn from a sample of 50 persons participating in a controlled trial of behavioural therapy and VLCD
Age, gender and ethnicity	Age - Other: 44.5 years (44.3 SD9 VLCD, 44.9 SD7 LCD). Gender (M:F): Define. Ethnicity: Not reported
Further population details	1. Ethnicity: Not applicable / Not stated / Unclear 2. Learning disabilities: Not applicable / Not stated / Unclear 3. T2DM: Not applicable / Not stated / Unclear
Extra comments	Weight: 107.5 kg (SD 24) in VLCD vs 118.5 kg (S 26) for LCD; BMI was 40.7 kg/m2 (SD 10) vs 44.6 kg/m2 (SD 9) in LCD group. All patient had an initial 1000-1200 kcal/d diet before randomisation to either VLCD or LCD
Indirectness of population	No indirectness
Interventions	(n=8) Intervention 1: Very-low-calorie diet - VLCD (<800 calories per day). After an initial 4-week 1000-1200 kcal/d diet (tailored to individual food preferences wit goal of 15% protein, 55% carbohydrate, 30% fat), patients were treated with 8 week VLCD. VLCD consisted of protein-sparing modified fast from 3 servings a day from a list of high-protein foods including lean meat, fish, and fowl which each consisted of 20-25g protein (60-75% daily total) and 2-8 g of fat. Participants were told to have no more than 500 kcal per day and to avoid other foods with the exception of noncaloric beverages (and bouillon to avoid salt depletion), potassium and calcium supplements daily multivitamin capsule; they were told to drink at least 1.5 liters of water per day.After 8 weeks, gradual introduction of conventional foods over 2 weeks up to 1000-1200 kcal/d (refeeding diet consisted of fruits and vegetables, breads and cereals, and fats which were introduced in this order until 1000 kcal/d was reached). Duration 8 week VLCD + 10 week LCD. Concurrent medication/care: All patients in study had behavioural therapy: weekly 90-minute group sessions of 4-7 person led by a doctoral-level clinical psychologist Further details: 1. Diet: Not applicable / Not stated / Unclear (n=7) Intervention 2: Standard dietary advice - LCD. 1000-1200 kcal/d diet tailored to individual food preferences wit goal of 15% protein, 55% carbohydrate, 30% fat. Duration 18 weeks. Concurrent medication/care: All patients in study had behavioural therapy: weekly 90-minute group sessions of 4-7 person led by a doctoral-level clinical psychologist

Study	Wadden 1990[41,42]
	Further details: 1. Diet: Not applicable / Not stated / Unclear
Funding	Study funded by industry (Sandoz Nutrition Company and NIMH Research Scientist Development Award and NIHM Career Scientist Award)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VLCD (400 CALORIES PER DAY) + BEHAVIOURAL THERAPY versus LCD (1200 CALORIES PER DAY) + BEHAVIOURAL THERAPY Protocol outcome 1: Depression score at Latest follow up - Actual outcome: Depression score (BDI) at 18 weeks; Group 1: mean 1.8 (SD 3); n=8, Group 2: mean 9 (SD 9); n=7; Beck's Depression Inventory 0 to 63 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Disordered eating at Latest follow up; Postural hypotension at Latest follow up; Bone density at Latest follow up; Constipation at Latest follow up; Gall stones at Latest follow up; Gout at Latest follow up; Diarrheoa at Latest follow up; Hypoglycaemia at Latest follow up; Health related quality of life at Latest follow-up

Table 12: Wadden 1994

Study	Wadden 1994[40,42]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=49)
Countries and setting	Conducted in USA
Line of therapy	1st line
Duration of study	Intervention + follow up: 52 weeks + 26 weeks follow-up
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	At least 25 kg overweight (determined by height-weight tables fo the Metropolitain Life Insturance Company)
Exclusion criteria	Recent myocardial infarction or evidence of cardiac abnormalities, history of cerebrovascular, kidney, or liver disease,

Study	Wadden 1994[40,42]
	cancer, type 1 diabetes, bulimia nervosa or significant psychiatric illness
Recruitment/selection of patients	Patients recruited by newspaper advertisement seeking for those at least 25 kg overweight
Age, gender and ethnicity	Age - Other: Mean 39.31 (36.82 SD 8.87 for VLCD vs 42.86 SD 10.12 LCD). Gender (M:F): All women. Ethnicity: Not reported
Further population details	1. Ethnicity: Not applicable / Not stated / Unclear 2. Learning disabilities: Not applicable / Not stated / Unclear 3. T2DM: Not applicable / Not stated / Unclear
Extra comments	Height 164.38 cm, weight 106.33 kg (VLCD 107.85 SD 14.89 vs LCD 105.43 SD 13.68), BMI 39.46 (VLCD 40.01 SD 5.73 vs LCD 38.80 SD 5.39). All patients paid $600 for the 18 months of treatment and $300 of which was refunded at 6-month intervals for completing the program; there were 9 patients considered binge eaters in the VLCD group at baseline (BES 27+) while there were 5 in the LCD group at baseline
Indirectness of population	No indirectness
Interventions	(n=28) Intervention 1: Very-low-calorie diet - VLCD (<800 calories per day). After initial first week on 1200 k/cal per day, patients had liquid formula VLCD (OPTIFAST 70, Sandoz Nutrition, Minneapolis, MN) during weeks 2 to 17 (total 16 weeks) which provided 420 kcal/d (70g protein, 30 g carbohydrates, 2 g fat, 2990 mg/d potassium and 100% of US RDA essential vitamins and minerals). During this time, patients were instructed to have at least 2 L of noncaloric fluid per day and avoid all other foods. After the 16-week VLCD, conventional foods were gradually introduced for weeks 18-23 and patients were consuming 1000 kcal/d by week 23 (this was overseen by a dietician). From week 18-27, subjects attended groups led by a dietician which provided information on food preparation and nutrition. During weeks 24-52, subjects were instructed to consume conventional reducing diet of 1200 kcal/d and record daily food intake.. Duration 52 weeks + 26 weeks maintenance program. Concurrent medication/care: All arms had the same behavioural therapy and exercise. Behavioural therapy: weekly sessions in groups of 6-9 subjects led by a doctoral-level clinical psychologist or a psychology graduate student for the 52 week treatment giving instruction in traditional behavioural methods of weight control including: 1) recording eating behaviour (amounts, calories, times, etc), 2) controlling stimuli associated with eating, 3) slowing the rate of eating, 4) modifying self-defeating thoughts and emotions, 5) eliciting social support, 6) increasing life-style activity (implementation involved problem-solving skills); Exercise programme: started at week 8 which consisted of walking for most - subjects were instructed to exercise for 10-20 minutes at 40-60% of estimated maximum heart rate for 2-3 times per week initially, then for 20-40 minutes at 60-70% of maximum heart rate for 3-5 times per week.During the maintenance program, biweekly sessions focused on instruction in basic 'upkeep' skills including graphing weight weekly, preparing low-fat meals, continuing to exercise regularly and learning to reverse small weight gains as they occurred. Subjects were also taught to prevent dietary and exercise lapses by identifying high-risk situations and given steps to take if they have an overeating episode. Further details: 1. Diet: Not applicable / Not stated / Unclear

Study	Wadden 1994[40,42]
	Comments: Cognitive-behavioural treatment was the same as in the other trial arm but materials were presented in a different order during the first 26 weeks because of the different dietary interventions. (n=21) Intervention 2: Standard dietary advice - LCD. For 52 weeks, subjects were instructed to consume 1200 kcal/d diet (15-20% protein, no more than 30% from fat and the remainder from carbohydrate); during the 26-week maintenance program, they were told to adjust their caloric intake according to their desired weight change but not to consume less than 1200 kcal/d. Duration 52 weeks + 26 week maintenance program. Concurrent medication/care: All arms had the same behavioural therapy and exercise. Behavioural therapy: weekly sessions in groups of 6-9 subjects led by a doctoral-level clinical psychologist or a psychology graduate student for the 52 week treatment giving instruction in traditional behavioural methods of weight control including: 1) recording eating behaviour (amounts, calories, times, etc), 2) controlling stimuli associated with eating, 3) slowing the rate of eating, 4) modifying self-defeating thoughts and emotions, 5) eliciting social support, 6) increasing life-style activity (implementation involved problem-solving skills); Exercise programme: started at week 8 which consisted of walking for most - subjects were instructed to exercise for 10-20 minutes at 40-60% of estimated maximum heart rate for 2-3 times per week initially, then for 20-40 minutes at 60-70% of maximum heart rate for 3-5 times per week.During the maintenance program, biweekly sessions focused on instruction in basic 'upkeep' skills including graphing weight weekly, preparing low-fat meals, continuing to exercise regularly and learning to reverse small weight gains as they occurred. Subjects were also taught to prevent dietary and exercise lapses by identifying high-risk situations and given steps to take if they have an overeating episode. Further details: 1. Diet: Not applicable / Not stated / Unclear Comments: This arm is referred to as the BDD (balanced deficit diet) in the study
Funding	Academic or government funding (National Institute for Mental Health grants)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VLCD (<800 CALORIES PER DAY) + BEHAVIOURAL THERAPY + EXERCISE versus LCD (1200 CALORIES PER DAY) + BEHAVIOURAL THERAPY + EXERCISE

Protocol outcome 1: Disordered eating at Latest follow up
- Actual outcome: Binge eating score at 52 weeks; Group 1: mean 18.32 (SD 8.18); n=23, Group 2: mean 12 (SD 6.78); n=17; Binge Eating Scale (BES; Gormally, Black, Daston & Rardin, 1982) 0 to 46 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: Numbers of severe binge eaters (BES 27+) at 52 weeks; Group 1: 5/23, Group 2: 1/17; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Depression score at Latest follow up

Study	Wadden 1994[40,42]
- Actual outcome: Depression score at 52 weeks; Group 1: mean 8.32 (SD 8.98); n=23, Group 2: mean 5 (SD 5.64); n=17; Beck Depression Inventory (BDI) 0 to 63 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Postural hypotension at Latest follow up; Bone density at Latest follow up; Constipation at Latest follow up; Gall stones at Latest follow up; Gout at Latest follow up; Diarrheoa at Latest follow up; Hypoglycaemia at Latest follow up; Health related quality of life at Latest follow-up

Table 13: Wing 1991

Study (subsidiary papers)	Wing 1991[47,50] (Wing 1997[43,47], Wing 1991[47,49])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=36)
Countries and setting	Conducted in USA; Setting: Not reported
Line of therapy	1st line
Duration of study	Intervention + follow up: 20 week intervention + 1 year follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Ideal body weight was based on Metropolitain Life Insurance norm (participants needed to be at least 30% or more above)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	35-70 years old, 30% or more above ideal body weight (based on Metropolitain Life Insurance norm), type 2 diabetes (defined by National Diabetes Data Group)
Exclusion criteria	Liver, renal, or heart disease
Recruitment/selection of patients	Advertisement in newspaper
Age, gender and ethnicity	Age - Mean (SD): 50.6 (7.7) for VLCD vs 51.9 (9.9) for LCD. Gender (M:F): Define. Ethnicity: Not reported
Further population details	1. Ethnicity: Not applicable / Not stated / Unclear 2. Learning disabilities: Not applicable / Not stated / Unclear 3. T2DM: T2DM
Extra comments	Mean 102.1 kg (SD 11.7) VLCD vs 104.5 kg (SD 21.5) LCD; mean BMI: 37.34 (SD 4.7) VLCD vs 38.10 (SD 5.7) LCD; mean years diabetic: 5.7 (SD 4.2) VLCD vs 7.8 (SD 7.5); mean HbA 10.4% (SD 2.2) VLCD vs 10.4% (SD 2.0) LCD; mean fasting blood glucose 14.2 mmol/L (SD 4.5) VLCD vs 12.7 mmol/L (SD 4) LCD
Indirectness of population	No indirectness

Study (subsidiary papers)	Wing 1991[47,50] (Wing 1997[43,47], Wing 1991[47,49])
Interventions	(n=17) Intervention 1: Very-low-calorie diet - VLCD (<800 calories per day). After 4 weeks on 1000-1500 kcal/d balanced diet, participants had VLCD (400 kcal/d) for 2 months/8 weeks given as either lean meat, fish or fowl or liquid formula (Optifast 70, Sandoz Nutrition). In the fourth month (after week 16), they gradually increased the quantity and types of food until the 5th month when the patients returned to 1000-1500 kcal/d. Participants received the above in addition to behavioural therapy (see below). Duration 20 weeks. Concurrent medication/care: Participants in both arms had behaviour therapy: in groups if 8-10 and led by a team of therapists; included instruction in diet, exercise, and behaviour modification including a) exercise recommendations to start at 210 J/wk weekly and increasing to 4200 J/wk (ie. approximately 10 miles per week), b) daily monitoring of caloric intake and exercise by participants, c) stimulus control techniques including strategies for removing food cues from their environment, eating slowly, separating eating from other activities, d) modification of cognitions for relapse prevention and self-reinforcement, e) subjects deposited $150 at the start of the program and earned this back weekly for meeting homework goals, f) self-monitoring of blood glucose and provision with monitoring equipment and supplies Further details: 1. Diet: Not applicable / Not stated / Unclear (n=19) Intervention 2: Standard dietary advice - LCD. Participants received a 1000-1500 kcal/d balanced diet for the duration of the study in addition to behavioural therapy (see below). Duration 20 weeks. Concurrent medication/care: Participants in both arms had behaviour therapy: in groups if 8-10 and led by a team of therapists; included instruction in diet, exercise, and behaviour modification including a) exercise recommendations to start at 210 J/wk weekly and increasing to 4200 J/wk (ie. approximately 10 miles per week), b) daily monitoring of caloric intake and exercise by participants, c) stimulus control techniques including strategies for removing food cues from their environment, eating slowly, separating eating from other activities, d) modification of cognitions for relapse prevention and self-reinforcement, e) subjects deposited $150 at the start of the program and earned this back weekly for meeting homework goals, f) self-monitoring of blood glucose and provision with monitoring equipment and supplies. Further details: 1. Diet: Not applicable / Not stated / Unclear
Funding	Academic or government funding (Grants from National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Western Pennsylvania Affiliate fo the American Diabetes Association)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VLCD (400 CALORIES PER DAY) + BEHAVIOUR THERAPY + EXERCISE versus LCD (1000-1500 CALORIES PER DAY) + BEHAVIOUR THERAPY + EXERCISE

Protocol outcome 1: Depression score at Latest follow up

Study (subsidiary papers)	Wing 1991[47,50] (Wing 1997[43,47], Wing 1991[47,49])
- Actual outcome: Depression score (Beck Depression Inventory) at 4 and 5 months; Group 1: mean 5 (SD 6.3); n=16, Group 2: mean 2.9 (SD 2.8); n=15; Becks Depression Inventory (BDI) 0 to 63 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Disordered eating at Latest follow up; Postural hypotension at Latest follow up; Bone density at Latest follow up; Constipation at Latest follow up; Gall stones at Latest follow up; Gout at Latest follow up; Diarrheoa at Latest follow up; Hypoglycaemia at Latest follow up; Health related quality of life at Latest follow-up

G.1.3 Maintenance

Table 14: Agras 1996

Study	Agras 1996[1]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n= 194)
Countries and setting	Conducted in USA; Setting: not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 9 month intervention + 6 month follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Not clear; participants had all received 12-week VLCD + behavior therapy and included in study if they had lost 5% or more of their initial weight
Exclusion criteria	Recent myocardial infarction, major cardiac arrhythmia or stroke, type II diabetes not controlled with oral hypoglycemic agents, bleeding peptic ulcer, other serious disorders that may complicate dieting (i.e. liver or kidney disease, evidence of serious mental disorder like current psychosis or alcohol or drug abuse, current bulimia nervosa, pregnancy, taking any medication that may affect appetite)
Recruitment/selection of patients	Of 201 who entered into the VLCD, 194 were randomised into different maintenance treatments (6 dropped out of VLCD - no reason stated - and 1 did not meet entry criteria for the maintenance phase)
Age, gender and ethnicity	Age - Mean (SD): 43.7 (10). Gender (M:F): Women only. Ethnicity: Not reported
Further population details	1. Ethnicity: Not applicable / Not stated / Unclear 2. Learning disabilities: Not applicable / Not stated / Unclear 3.

Study	Agras 1996[1]
	T2DM: Not applicable / Not stated / Unclear
Extra comments	Average age of reported onset of overweight: 19.4 years (SD 11.7), weight on entry to VLCD: 100.3 kg (SD14) and BMI: 36.6 kg/m2 (SD4.4). VLCD: 800 kcal/day with Optifast 800 (Sandoz Nutrition, Minneapolis, MN); participants consumed 5 packets throughout the day and were carefully monitored during treatment; Behaviour therapy: provided major behavioural change elements associated with weight loss programs - modifying their own food intake, increased physical activity levels in a graded manner, learned to eat slower, learned to choose foods low in fat and high in complex carbs when fully varied diet was introduced; 3 patients did not have complete data to analyse but it was not clear which group these patients were in
Indirectness of population	No indirectness
Interventions	(n= 50) Intervention 1: Maintenance strategy - diet. Behaviour therapy + refeeding with standard food (time dependent): each patient was prescribed a set of meal plans providing different meals each day with the correct number of kcal for each phase - regular food gradually replace the VLCD, starting with one meal/day (350 kcal replacing 2 Optifast packets) for 2 weeks, 2 meals/day (700 kcal added replacing 2 Optifast packets) for the 3rd week, and 3 meals/day for the fourth and subsequent weeks (1200 kcal replacing final Optifast packet). Duration 9 months. Concurrent medication/care: Not reported Further details: 1. Diet: Comments: Behaviour therapy weekly for first 3 months, fortnightly for the next 3 months and then monthly for the last 3 months of treatment. (n= 47) Intervention 2: Maintenance strategy - diet. Behaviour therapy + refeeding with standard food (weight dependent): regular food gradually replaced the VLCD but only if weight was stable or declining with maximum period of 1 month (resulting in food being completely replaced in 3 months) - the phases were as follows: starting with one meal/day (350 kcal replacing 2 Optifast packets) for 2 weeks, 2 meals/day (700 kcal added replacing 2 Optifast packets) for the 3rd week, and 3 meals/day for the fourth and subsequent weeks (1200 kcal replacing final Optifast packet). Duration 9 months. Concurrent medication/care: Not reported Further details: 1. Diet: Comments: Behaviour therapy weekly for first 3 months, fortnightly for the next 3 months and then monthly for the last 3 months of treatment. (n= 45) Intervention 3: Maintenance strategy - diet. Behaviour therapy + refeeding with prepackaged food (stimulus narrowing & time dependent) - use of limited number of prepackaged foods selected to provide the same number of calories and fat, carbs, and protein composition in the same timing as the regular food conditions - this occurred as one meal per day in the first week, a second (but different) prepackaged food each day for the second week, and a third meal in prepackaged form in the third week - participants were encouraged to continue this prescribed limited

Study	Agras 1996[1]
	selection of meals for the remaining 2 months. Duration 9 months. Concurrent medication/care: Not reported Further details: 1. Diet: Comments: Behaviour therapy weekly for first 3 months, fortnightly for the next 3 months and then monthly for the last 3 months of treatment. (n= 49) Intervention 4: Maintenance strategy - diet. Behaviour therapy + refeeding with prepackaged food (stimulus narrowing & time dependent) - prepackaged food gradually replaced the VLCD but only if weight was stable or declining with maximum period of 1 month (resulting in food being completely replaced in 3 months); the phases were as follows: use of limited number of prepackaged foods selected to provide the same number of calories and fat, carbs, and protein composition in the same timing as the regular food conditions - this occurred as one meal per day in the first week, a second (but different) prepackaged food each day for the second week, and a third meal in prepackaged form in the third week - participants were encouraged to continue this prescribed limited selection of meals for the remaining 2 months. Duration 9 months. Concurrent medication/care: Not reported Further details: 1. Diet: Comments: Behaviour therapy weekly for first 3 months, fortnightly for the next 3 months and then monthly for the last 3 months of treatment.
Funding	Equipment / drugs provided by industry (Sandoz Corporation provided Optifast-800 (study was funded by National Institutes for Health))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BEHAVIOUR THERAPY + STANDARD FOOD REFEEDING (TIME DEPENDENT) versus BEHAVIOUR THERAPY + STANDARD FOOD REFEEDING (WEIGHT DEPENDENT)

Protocol outcome 1: % weight change (kg) at Latest follow-up
- Actual outcome: NOTE - weight change in kg not % change at 18 months; Group 1: mean -8.2 kg (SD 12.3); n= 45, Group 2: mean -8.6 kg (SD 11.4); n= 41; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: % withdrawals at Latest follow-up
- Actual outcome: % withdrawals at 18 months; Group 1: 3/50, Group 2: 2/47; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BEHAVIOUR THERAPY + STANDARD FOOD REFEEDING (TIME DEPENDENT) versus BEHAVIOUR THERAPY + PREPACKAGED FOOD REFEEDING (WEIGHT DEPENDENT)

Protocol outcome 1: % weight change (kg) at Latest follow-up

Study	Agras 1996[1]
- Actual outcome: NOTE - weight change in kg not % change at 18 months; Group 1: mean -8.2 kg (SD 12.3); n= 45, Group 2: mean -2.8 kg (SD 18.3); n= 42; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: % withdrawals at Latest follow-up - Actual outcome: % withdrawals at 18 months; Group 1: 3/50, Group 2: 5/49; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BEHAVIOUR THERAPY + STANDARD FOOD REFEEDING (WEIGHT DEPENDENT) versus BEHAVIOUR THERAPY + PREPACKAGED FOOD REFEEDING (WEIGHT DEPENDENT) Protocol outcome 1: % weight change (kg) at Latest follow-up - Actual outcome: NOTE - weight change in kg not % change at 18 months; Group 1: mean -8.6 kg (SD 11.4); n= 41, Group 2: mean -2.8 kg (SD 18.3); n= 42; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: % withdrawals at Latest follow-up - Actual outcome: % withdrawals at 18 months; Group 1: 2/47, Group 2: 5/49; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BEHAVIOUR THERAPY + PREPACKAGED FOOD REFEEDING (TIME DEPENDENT) versus BEHAVIOUR THERAPY + PREPACKAGED FOOD REFEEDING (WEIGHT DEPENDENT) Protocol outcome 1: % weight change (kg) at Latest follow-up - Actual outcome: NOTE - weight change in kg not % change at 18 months; Group 1: mean -6 kg (SD 11.1); n= 34, Group 2: mean -2.8 kg (SD 18.3); n= 42; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: % withdrawals at Latest follow-up - Actual outcome: % withdrawals at 18 months; Group 1: 7/45, Group 2: 5/49; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Health related quality of life at Latest follow-up; % change in BMI at Latest follow-up; % weight change including lead in (kg) at Latest follow-up; % weight change including lead in (BMI) at Latest follow-up; Improvement in physical activity at Latest follow-up

Table 15: Borg 2002

Study (subsidiary papers)	Borg 2002[3] (Kukkonen-harjula 2005[18])
Study type	RCT (Patient randomised; Parallel)

Study (subsidiary papers)	Borg 2002[3] (Kukkonen-harjula 2005[18])
Number of studies (number of participants)	(n= 82)
Countries and setting	Conducted in Finland; Setting: not clear
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 6 month intervention + 23 month unsupervised follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Men aged 35-50 years with BMI 30-40 kg/m2, waist circumference over 100 cm
Exclusion criteria	Men who used regular medication, were physically active (leisure-time physical exercise more than once weekly), were smokers or binge eaters (symptom scores > 20 on Bulimic Investigatory Test of Edinburgh)
Recruitment/selection of patients	Newspaper advertisement (of 214 who answered the advert, 90 fulfilled the criteria, 82 finished the weight reduction phase)
Age, gender and ethnicity	Age - Mean (SD): 42.6 (4.6). Gender (M:F): Define. Ethnicity: not reported
Further population details	1. Ethnicity: Not applicable / Not stated / Unclear 2. Learning disabilities: Not applicable / Not stated / Unclear 3. T2DM: Not applicable / Not stated / Unclear
Extra comments	Men had mean BMI 32.9 kg/ m2 (range: 28.5-40), mean waist circumference 112.5cm (range 98-132) before starting the VLCD; mean weight reduction after weight reduction phase was 14.3 kg (range -26.1 to -5.1) with a BMI decrease of 4.4 kg/m2 (range -7.5 to -1.8). The 2 month weight reduction phase included a low energy diet (1200 kcal/day) for the first and last week, and a VLED (500 kcal/day; Nutrilett, Leiras Oy, Turku, Finland) for the remaining weeks. During this time, they had weekly meetings in small groups (5-12 participants) which were led by a nutritionist and included instructions on both diets, general knowledge on diet and weight management, and the basics of relapse prevention techniques (using the LEARN program).
Indirectness of population	No indirectness
Interventions	(n= 25) Intervention 1: Maintenance strategy - diet and exercise. Dietary counselling and walking program. Walking program consisting to 3 sessions of 45 minutes weekly - sessions were preceded by 45 minutes of warm up and followed by 5 minutes of stretching and cool down. (one weekly session was attended by an exercise instructor). Target intensity of walking was 60-70% maximum 02 consumption measured in a treadmill test by heart rate monitors. Estimated gross energy expenditure of one session was average 400 kcal (1.7 MJ).Dietary counselling: All patients had weekly meetings in small groups during the maintenance period where problems with diet and prevention of relapses were discussed. Patients were instructed to follow a low-fat and high carb diet; they received

Study (subsidiary papers)	Borg 2002[3] (Kukkonen-harjula 2005[18])
	written educational material monthly. Duration 6 months. Concurrent medication/care: Not reported Further details: 1. Diet: Not applicable / Not stated / Unclear Comments: Participants were not given specific instructions about physical activity after the intervention and during follow-up. (n= 28) Intervention 2: Maintenance strategy - diet and exercise. Dietary counselling and weight resistance training. Resistance training consisting to 3 session of 45 minutes weekly - sessions were preceded by 45 minutes of warm up and followed by 5 minutes of stretching and cool down. (one weekly session was attended by an exercise instructor). Target intensity of walking was 60-80% of repetitive maximum with 8 repetitions and three sets in each exercise. Estimated gross energy expenditure of one session was average 300 kcal (1.2 MJ).Dietary counselling: All patients had weekly meetings in small groups during the maintenance period where problems with diet and prevention of relapses were discussed. Patients were instructed to follow a low-fat and high carb diet; they received written educational material monthly. Duration 6 months. Concurrent medication/care: Not reported Further details: 1. Diet: Comments: Participants were not given specific instructions about physical activity after the intervention and during follow-up. (n= 29) Intervention 3: Standard dietary advice - control. Dietary counselling and advise not to increase physical activity. Dietary counselling: All patients had weekly meetings in small groups during the maintenance period where problems with diet and prevention of relapses were discussed. Patients were instructed to follow a low-fat and high carb diet; they received written educational material monthly. Duration 6 months. Concurrent medication/care: none reported Further details: 1. Diet: Comments: Participants were not given specific instructions about physical activity after the intervention and during follow-up.
Funding	Other (Leiras Oy (Industry - pharmaceutical company), Finland by Emil Aaltonen Foundation, the Ministry of Education, the Ministry of Social Affairs and Health, Juho Vainio Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIETARY COUNSELLING + WALKING versus DIETARY COUNSELLING + RESISTANCE TRAINING

Protocol outcome 1: % weight change (kg) at Latest follow-up
- Actual outcome: NOTE - weight in kg (final) not % at 31 months; Group 1: mean 102 kg (SD 13.5); n= 20, Group 2: mean 99.9 kg (SD 10.9); n= 26; Risk of bias: High; Indirectness of outcome: No indirectness

Study (subsidiary papers)	Borg 2002[3] (Kukkonen-harjula 2005[18])
Protocol outcome 2: % withdrawals at Latest follow-up - Actual outcome: % withdrawals at 31 months; Group 1: 5/25, Group 2: 2/28; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIETARY COUNSELLING + WALKING versus CONTROL (DIETARY COUNSELLING) Protocol outcome 1: % weight change (kg) at Latest follow-up - Actual outcome: NOTE - weight in kg (final) not % at 31 months; Group 1: mean 102 kg (SD 13.5); n= 20, Group 2: mean 100.7 kg (SD 13.5); n= 22; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: NOTE - mean difference in kg (ANCOVA) not % at 31 months; MD -0.5 (95%CI -5 to 4); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: % withdrawals at Latest follow-up - Actual outcome: % withdrawals at 31 months; Group 1: 5/25, Group 2: 7/29; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIETARY COUNSELLING + RESISTANCE TRAINING versus CONTROL (DIETARY COUNSELLING) Protocol outcome 1: % weight change (kg) at Latest follow-up - Actual outcome: NOTE - weight in kg (final) not % at 31 months; Group 1: mean 99.9 kg (SD 10.9); n= 26, Group 2: mean 100.7 kg (SD 11.4); n= 22; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: NOTE - mean difference in kg (ANCOVA) not % at 31 months; MD 0.8 (95%CI -4 to 5.6); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: % withdrawals at Latest follow-up - Actual outcome: % withdrawals at 31 months; Group 1: 2/28, Group 2: 7/29; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Health related quality of life at Latest follow-up; % change in BMI at Latest follow-up; % weight change including lead in (kg) at Latest follow-up; % weight change including lead in (BMI) at Latest follow-up; Improvement in physical activity at Latest follow-up

Table 16: Delbridge 2009

Study	Delbridge 2009[6]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n= 180)
Countries and setting	Conducted in Australia; Setting: Hospital (Royal Melbourne and Austin Hospitals)

Study	Delbridge 2009[6]
Line of therapy	1st line
Duration of study	Intervention + follow up: 15 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women aged ≥18 to ≤75 years, BMI ≥30 or ≥27 with comorbidities
Exclusion criteria	Individuals with a history or presence of significant disease, endocrine disorder, psychiatric illness, and alcohol or drug abuse were excluded. Women who were lactating, pregnant, or planned to become pregnant during the study were excluded
Recruitment/selection of patients	Recruited by newspaper advertisement and word of mouth
Age, gender and ethnicity	Age - Mean (SD): High carb diet: 44 (1.1). High protein diet: 43.7 (1.4). Gender (M:F): High carb diet: 70 (35m / 35f). High protein diet: 71 (35m / 36f). Ethnicity: Not specified
Further population details	1. Ethnicity: 2. Learning disabilities: 3. T2DM:
Indirectness of population	No indirectness
Interventions	(n= 70) Intervention 1: Maintenance strategy - diet. Participants were counselled to consume an energy intake consistent with weight maintenance, and this information was reinforced at each monthly visit attended during phase 2. Participants bought and prepared their own food, received meal plans and recipes and invited to attend group cooking classes appropriate to their dietary group. HC participants were instructed to consume 15% of their intake as protein. Both groups were recommended to consume lean red meat 3-4 times/wk to meet recommended intakes or iron and zinc in line with Australian Dietary Guidelines. Both groups were advised to reduce fat intake to <30% of their intake, particular emphasis on reducing saturated fat. Carbohydrates with low glycemic index were recommended to both. Counselling sessions provided (comfort eating, etc.). Participants encouraged to practice healthy behaviours such as aerobic exercise ≥3 times/wk. Duration 1 year. Concurrent medication/care: During phase 1, participants were provided with a commercially available VLED (Optifast; Nestle Nutrition, Frankfurt, Germany). The VLED was consumed 3 times/d as a meal replacement for a 12wk period. Participants were also permitted to consume up to 2 cups of low starch vegetables daily with a small amount of oil (5 mL) and a minimum of 2L water or low-energy drinks. This provided participants with ~500-550 kcal/d. Participants attended clinic each fortnight to be weighed, counselled on the use of the VLED and be provided with a 2wk supply. Participants were required to lose ≥10% body weight during phase 1. Further details: 1. Diet:

Study	Delbridge 2009[6]
	(n= 71) Intervention 2: Maintenance strategy - diet. Participants were counselled to consume an energy intake consistent with weight maintenance, and this information was reinforced at each monthly visit attended during phase 2. Participants bought and prepared their own food, received meal plans and recipes and invited to attend group cooking classes appropriate to their dietary group. HP participants were instructed to consume 30% of their intake as protein. Both groups were recommended to consume lean red meat 3-4 times/wk to meet recommended intakes or iron and zinc in line with Australian Dietary Guidelines. Both groups were advised to reduce fat intake to <30% of their intake, particular emphasis on reducing saturated fat. Carbohydrates with low glycemic index were recommended to both. Counselling sessions provided (comfort eating, etc.). Participants encouraged to practice healthy behaviours such as aerobic exercise ≥3 times/wk. Duration 1 year. Concurrent medication/care: During phase 1, participants were provided with a commercially available VLED (Optifast; Nestle Nutrition, Frankfurt, Germany). The VLED was consumed 3 times/d as a meal replacement for a 12wk period. Participants were also permitted to consume up to 2 cups of low starch vegetables daily with a small amount of oil (5 mL) and a minimum of 2L water or low-energy drinks. This provided participants with ~500-550 kcal/d. Participants attended clinic each fortnight to be weighed, counselled on the use of the VLED and be provided with a 2wk supply. Participants were required to lose ≥10% body weight during phase 1. Further details: 1. Diet:
Funding	Study funded by industry (Study supported in part by Meat and Livestock Australia)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH-PROTEIN DIET versus HIGH-CARBOHYDRATE DIET

Protocol outcome 1: % weight change (kg) at Latest follow-up
- Actual outcome: NOTE - weight change (rand to end) in kg, not % at 1 year; Group 1: mean 3 kg (SD 1.1); n= 42, Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 2: % withdrawals at Latest follow-up
- Actual outcome: % withdrawals at 1 year; Group 1: 29/71, Group 2: 30/70; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: % weight change including lead in (kg) at Latest follow-up
- Actual outcome: NOTE - weight change (start to end) in kg, not % at 1 year; Group 1: mean -14.8 kg (SD 1.5); n= 42, Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Health related quality of life at Latest follow-up; % change in BMI at Latest follow-up; % weight change including lead in (BMI) at Latest follow-up; Improvement in physical activity at Latest follow-up

Table 17: Fogelholm 2000

Study (subsidiary papers)	Fogelholm 2000[10] (Fogelholm 2001[9], Fogelholm 1999[11])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n= 85)
Countries and setting	Conducted in Finland; Setting: not clear
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 40 week maintenance intervention + 2 year follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Premenopausal women with BMI between 30 and 45, aged between 30 and 45, clinically healthy who had not been regularly using medication (other than hormonal contraceptives), with stable weight (within 3 kg for the previous 3 months)
Exclusion criteria	Physically active women (2 or more times per week of leisure-time physical exercise), pregnancy, lactating, smoker, suspected binge eaters (greater than 20 symptom score on Bulimic Investigatory Test of Edinburgh [BITE])
Recruitment/selection of patients	Advertisement in newspapers (207 responded, 125 were invited to medical history screening, physical examination, and exercise test). Of 85 patients who participated in weight reduction phase (including a VLCD), only 82 completed the diet and were randomised to maintenance arms.
Age, gender and ethnicity	Age - Mean (SD): 40 years (SD not reported); range: 30-45 years. Gender (M:F): All women. Ethnicity: not reported
Further population details	1. Ethnicity: Not applicable / Not stated / Unclear 2. Learning disabilities: Not applicable / Not stated / Unclear 3. T2DM: Not applicable / Not stated / Unclear
Extra comments	Women had mean BMI 34 kg/m2 (SD3.6) (range: 29.1-45.6), mean weight 92.0 kg (SD9.8) (range 75.2-125.6); mean weight reduction after weight reduction phase was 13.1 kg (SD3.5) (range 4.5-20.8). The initial weight reduction phase (including VLCD) was 12 weeks: 1 week low energy diet (meal-exchange system), 8 weeks on VLED (Nutrilett, Nycomed-Pharma AS, Oslo, Norway) and remaining 3 weeks on low energy diet). During this time, they had weekly meetings in small groups (5-12 participants) which were overseen by a nutritionist and included instructions on diets and weight management, and relapse prevention (these were educational more than supportive).
Indirectness of population	No indirectness
Interventions	(n= 26) Intervention 1: Maintenance strategy - diet and exercise. Dietary counselling and walking program. Walking program: targeted to expend 1000 kcal per week (4.2 MJ) (on average, 2-3 hours weekly); participants were prescribed exercise that was 50-60% of their individual heart rate reserve (maximal minus resting heart rate) added to

Study (subsidiary papers)	Fogelholm 2000[10] (Fogelholm 2001[9], Fogelholm 1999[11])
	their resting heart rate (weekly walking time was calculated as target energy expenditure divided by energy expenditure corresponding to their target heart rate); participants wore heart-rate monitors during all walking sessions. Dietary counselling: All patients had weekly meetings in small groups during the maintenance period which was conducted by an exercise instructor where problems with diet and prevention of relapses were discussed. Patients were instructed to follow a low-fat diet; they received educational material monthly and were asked to monitor high-risk situations for overeating. Duration 40 weeks. Concurrent medication/care: not reported Further details: 1. Diet: (n= 27) Intervention 2: Maintenance strategy - diet and exercise. Dietary counselling and walking program. Walking program: targeted to expend 2000 kcal/wk (8.4 MJ) (on average, 4 to 6 hours weekly); participants were prescribed exercise that was 50-60% of their individual heart rate reserve (maximal minus resting heart rate) added to their resting heart rate (weekly walking time was calculated as target energy expenditure divided by energy expenditure corresponding to their target heart rate); participants wore heart-rate monitors during all walking sessions. Dietary counselling: All patients had weekly meetings in small groups during the maintenance period which was conducted by an exercise instructor where problems with diet and prevention of relapses were discussed. Patients were instructed to follow a low-fat diet; they received educational material monthly and were asked to monitor high-risk situations for overeating. Duration 40 weeks. Concurrent medication/care: Not reported Further details: 1. Diet: (n= 29) Intervention 3: Standard dietary advice - control. Dietary counselling (unspecified but appear to be weekly meetings as during VLCD). Duration 40 weeks. Concurrent medication/care: none reported Further details: 1. Diet:
Funding	Other (Pharmaceutical companies: Nycomed-Pharma AS (Oslo, Norway) (of VLCD diet), Leiras Oy (Turku, Finland); other: Ministry of Education, Helsinki, Finland and Yrjo Jahnsson Foundation, Helsinki)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIETARY COUNSELLING + EXERCISE (TARGET 1000KCAL) versus DIETARY COUNSELLING + EXERCISE (TARGET 2000 KCAL)

Protocol outcome 1: % weight change (kg) at Latest follow-up
- Actual outcome: NOTE - weight in kg (final) not % at 2 years; Group 1: mean 83.9 kg (SD 12.2); n= 24, Group 2: mean 87.4 kg (SD 15.3); n= 23; Risk of bias: High; Indirectness of outcome: Serious indirectness

Protocol outcome 2: % withdrawals at Latest follow-up

Study (subsidiary papers)	Fogelholm 2000[10] (Fogelholm 2001[9], Fogelholm 1999[11])
- Actual outcome: % withdrawals at 2 years; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIETARY COUNSELLING + EXERCISE (TARGET 1000KCAL) versus CONTROL (DIETARY COUNSELLING) Protocol outcome 1: % weight change (kg) at Latest follow-up - Actual outcome: NOTE - weight in kg (final) not % at 2 years; Group 1: mean 83.9 kg (SD 12.2); n= 24, Group 2: mean 89.7 kg (SD 9.6); n= 27; Risk of bias: High; Indirectness of outcome: Serious indirectness - Actual outcome: NOTE - mean difference in final values (ANCOVA) not % weight change at 2 years; MD -3.5 (95%CI -6.8 to -0.2); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: % withdrawals at Latest follow-up - Actual outcome: % withdrawals at 2 years; Group 1: 2/26, Group 2: 2/29; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Improvement in physical activity at Latest follow-up - Actual outcome: Number of daily steps at 1 year; MD 25700 (95%CI 770 to 4370); Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIETARY COUNSELLING + EXERCISE (TARGET 2000 KCAL) versus CONTROL (DIETARY COUNSELLING) Protocol outcome 1: % weight change (kg) at Latest follow-up - Actual outcome: NOTE - weight in kg (final) not % at 2 years; Group 1: mean 87.4 kg (SD 15.3); n= 23, Group 2: mean 89.7 kg (SD 9.6); n= 27; Risk of bias: High; Indirectness of outcome: Serious indirectness - Actual outcome: NOTE - mean difference in final values (ANCOVA) not % weight change at 2 years; MD -0.2 (95%CI -3.6 to 3.1); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: % withdrawals at Latest follow-up - Actual outcome: % withdrawals at 2 years; Group 1: 4/27, Group 2: 2/29; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Improvement in physical activity at Latest follow-up - Actual outcome: Number of daily steps at 2 years; MD 3040 (95%CI 1110 to 4970); Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Health related quality of life at Latest follow-up; % change in BMI at Latest follow-up; % weight change including lead in (kg) at Latest follow-up; % weight change including lead in (BMI) at Latest follow-up

Table 18: Lecheminant 2005

Study	Lecheminant 2005[19]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n= 157)
Countries and setting	Conducted in Unknown multicentre, USA; Setting: Not specified
Line of therapy	1st line
Duration of study	Intervention + follow up: 1 year (VLCD: 12w, re-feeding: 4w, maintenance: 36w)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	19-70 years of age, overweight or obese (BMI ≥28 kg/m2), non-smokers, and able to exercise (i.e. walk)
Exclusion criteria	Individuals with any unstable medical conditions (i.e. undiagnosed diabetes or hypertension), seeking treatment for depression or eating disorders, or a woman who was pregnant or lactating were excluded
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (SD): Female completers: 49.9 (10.0) / male completers: 53.7 (9.6). Gender (M:F): At week 16: N= 147 (107 female / 40 male). Ethnicity: Not specified
Further population details	1. Ethnicity: 2. Learning disabilities: 3. T2DM:
Indirectness of population	No indirectness
Interventions	(n= 90) Intervention 1: Maintenance strategy - diet. Structure meal replacement programme: plan included a level of energy intake calculated to maintain weight and incorporated a diet low in fat (20-30% of total energy intake) and a fruit/vegetable consumption of at least 35 per week. Meal replacement: received 2 meal replacements per day that were incorporated into the structure meal plan. Meal replacements had an energy value from 150-270 per meal replacement. Duration 1 year. Concurrent medication/care: Clinics conducted in group format and included instruction in lifestyle modification, physical activity, and nutrition. Weekly for first 26 weeks and bi-weekly for the second 26 weeks. Meeting included weighing, report of weekly data, and topic presentation. Staff included dietitians, exercise physiologists, and behavioural therapists. Goal was for participants to exercise at least 300 min per week and maintain that level after week 26 Further details: 1. Diet: (n= 67) Intervention 2: Maintenance strategy - anti-obesity drugs. Structure meal replacement programme: plan included a level of energy intake calculated to maintain weight and incorporated a diet low in fat (20-30% of total

Study	Lecheminant 2005[19]
	energy intake) and a fruit/vegetable consumption of at least 35 per week. Orlistat: received medication that was prescribed twice daily at 120 mg per dose. The twice daily dosage was based on previous clinical experience of authors and participant feedback. Duration 1 year. Concurrent medication/care: Clinics conducted in group format and included instruction in lifestyle modification, physical activity, and nutrition. Weekly for first 26 weeks and bi-weekly for the second 26 weeks. Meeting included weighing, report of weekly data, and topic presentation. Staff included dietitians, exercise physiologists, and behavioural therapists. Goal was for participants to exercise at least 300 min per week and maintain that level after week 26 Further details: 1. Diet:
Funding	Study funded by industry (Research supported by Health Management Resources, Boston, MA)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIET - MEAL REPLACEMENT versus ANTI-OBESITY DRUGS - ORLISTAT Protocol outcome 1: % weight change (kg) at Latest follow-up - Actual outcome: NOTE - weight final value (kg, not %) at 1 year; Group 1: mean 88.1 kg (SD 16.5); n= 56, Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: % withdrawals at Latest follow-up - Actual outcome: % withdrawals at 1 year; Group 1: 34/90, Group 2: 31/67; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Health related quality of life at Latest follow-up; % change in BMI at Latest follow-up; % weight change including lead in (kg) at Latest follow-up; % weight change including lead in (BMI) at Latest follow-up; Improvement in physical activity at Latest follow-up

Table 19: Lejeune 2005

Study	Lejeune 2005[20]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n= 140)
Countries and setting	Conducted in Netherlands
Line of therapy	1st line
Duration of study	Intervention + follow up: 13m (1 m VLCD, 6m maintenance, 6m follow-up) [note ambig, confirmed with MW]

Study	Lejeune 2005[20]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	Recruited by advertisements in local newspapers
Age, gender and ethnicity	Age - Mean (SD): 45.1 (10.4). Gender (M:F): Define. Ethnicity: Not specified
Further population details	1. Ethnicity: 2. Learning disabilities: 3. T2DM:
Extra comments	Mean BMI 29.3 (2.5)
Indirectness of population	No indirectness
Interventions	(n= 53) Intervention 1: Maintenance strategy - diet. Habitual diet, additional 30g protein per day. Duration 13m. Concurrent medication/care: VLCD to initiate weight loss (4 weeks, approx. 500 kcal), carbohydrate - protein - fat 42:44:14 energy percentage. Modifast, Novartis Nutrition. Provided in three sachets daily that dissolved in water. Vegetables and fruit were allowed in addition to Modifast. Aim weight loss of at least 4kg. Maintenance (6m): assessed 6 times (measurements, dietitian, dietary counselling). Followed habitual diet again. Provided additional 30g protein per day. Provided as a sachet of pure protein to be dissolved in water (contained no carbohydrate or fat). Consumed protein drink at lunch or in the afternoon. Aimed energy intake comprising 18-20% protein/d, depending on participant's usual protein intake. Further details: 1. Diet: (n= 60) Intervention 2: Standard dietary advice - control. Habitual diet. Duration 13m. Concurrent medication/care: VLCD to initiate weight loss (4 weeks, approx. 500 kcal), carbohydrate - protein - fat 42:44:14 energy percentage. Modifast, Novartis Nutrition. Provided in three sachets daily that dissolved in water. Vegetables and fruit were allowed in addition to Modifast. Aim weight loss of at least 4kg. Maintenance (6m): no additional protein, no placebo was used for this control group Further details: 1. Diet:
Funding	Study funded by industry (Study supported by Novartis CH, Consumer Health Ltd, Switzerland)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIET - HIGH PROTEIN versus CONTROL	

Study	Lejeune 2005[20]
Protocol outcome 1: % withdrawals at Latest follow-up - Actual outcome: % withdrawals at 13 months; Group 1: 22/53, Group 2: 21/60; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: % weight change including lead in (kg) at Latest follow-up - Actual outcome: NOTE - weight change in kg, not % at 13m (VLCD: 1m / maintenance: 6m / follow-up: 6m); Group 1: mean -5.5 kg (SD 0.9); n= 31, Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	% weight change (kg) at Latest follow-up; Health related quality of life at Latest follow-up; % change in BMI at Latest follow-up; % weight change including lead in (BMI) at Latest follow-up; Improvement in physical activity at Latest follow-up

Table 20: Pasman 1997

Study	Pasman 1997[29]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n= 48)
Countries and setting	Conducted in Netherlands; Setting: Not specified
Line of therapy	1st line
Duration of study	Intervention + follow up: 18m (VLCD: 2m / maintenance 16m)
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: No mention of how obesity was assessed
Stratum	Overall
Subgroup analysis within study	Post-hoc subgroup analysis
Inclusion criteria	Not specified
Exclusion criteria	Not specified
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (SD): 41.4 (7.4). Gender (M:F): All female population. Ethnicity: Not specified
Further population details	1. Ethnicity: 2. Learning disabilities: 3. T2DM:
Extra comments	All female population
Indirectness of population	No indirectness
Interventions	(n= 25) Intervention 1: Maintenance strategy - diet. Consume 10g of guar gum fibre twice daily (20g in total). Duration

Study	Pasman 1997[29]
	14m. Concurrent medication/care: VLCD: approx. 477 kcals, for 2 months. Maintenance: fibre supplement was an enzymatically modified guar gum (Benefiber, Sandoz Nutrition), which has the same characteristics as the native form. Participants were asked to consume 10g of fibre in the afternoon and 10g in the evening. The fibre supplement was dissolved in 200ml solution. Further details: 1. Diet: (n= 14) Intervention 2: Standard dietary advice - control. Non-treatment group. Duration 14m. Concurrent medication/care: VLCD: approx. 477 kcals, for 2 months. Maintenance: no placebo for this fibre supplement was available. Further details: 1. Diet:
Funding	Study funded by industry (Financially support by Sandoz Nutrition Ltd, Switzerland)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIET - HIGH FIBRE versus CONTROL Protocol outcome 1: % weight change (kg) at Latest follow-up - Actual outcome: NOTE - weight kg (final score), not % at 16 months; Group 1: mean 87 kg (SD 11.78); n= 20, Group 2: mean 85 kg (SD 12); n= 11; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: % withdrawals at Latest follow-up - Actual outcome: % drop out at 16 months; Group 1: 5/25, Group 2: 3/14; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: % change in BMI at Latest follow-up - Actual outcome: NOTE - weight in BMI (final), not % at 16 months; Group 1: mean 32.75 kg (SD 4.421); n= 20, Group 2: mean 31.4 kg (SD 5.1); n= 11; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Health related quality of life at Latest follow-up; % weight change including lead in (kg) at Latest follow-up; % weight change including lead in (BMI) at Latest follow-up; Improvement in physical activity at Latest follow-up

Table 21: Richelsen 200, Madsen 2008, Madsen 2009, Svendsen 2009

Study (subsidiary papers)	trial: Richelsen 2007[31] (Madsen 2008[23], Madsen 2009[22], Svendsen 2009[38])
Study type	RCT (Patient randomised; Parallel)

Study (subsidiary papers)	trial: Richelsen 2007[31] (Madsen 2008[23], Madsen 2009[22], Svendsen 2009[38])
Number of studies (number of participants)	1 (n= 383)
Countries and setting	Conducted in Multiple countries; Setting: Research centres
Line of therapy	2nd line
Duration of study	Intervention + follow up: 8 week VLED followed by 3 year follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: Stratified according to sex, centre, and degree of weight loss after VLED
Subgroup analysis within study	Not stratified but pre-specified: Sex difference in weight loss
Inclusion criteria	Aged 18-65, with abdominal obesity (defined as BMI between 30 and 45 kg/m2 and waist circumference ≥102cm men / ≥92cm women), one or more risk factors (impaired fasting glucose, diet-related T2D or dyslipidaemia and/or serum triglycerides)
Exclusion criteria	Body weight loss of ≥5% during VELD was a prerequisite for randomisation into the 3-year weight maintenance period. Patients whose A1C level exceeded 10% after maximal metformin treatment (2g daily), the participant was withdrawn. At inclusion, treatment for lipid-lowering drugs was not allowed.
Recruitment/selection of patients	Patients recruited at nine clinical research centres in Scandinavia
Age, gender and ethnicity	Age - Mean (SD): Experimental group (orlistat): 47.2 (20-64) / Control group (placebo): 46.7 (19-63). Gender (M:F): Men: 152 / Female: 157. Ethnicity: Not specified
Further population details	1. Ethnicity: Not applicable / Not stated / Unclear 2. Learning disabilities: Not applicable / Not stated / Unclear 3. T2DM:
Indirectness of population	No indirectness
Interventions	(n= 156) Intervention 1: Maintenance strategy - anti-obesity drugs. Treatment with orlistat capsules (120 mg t.i.d.). Duration 3 years. Concurrent medication/care: Participants were prescribed a VLED (Modifast; Novartis, Basel, Switzerland or Nutrilett; Nycomed Pharma, Oslo, Norway) of 600-300 kcal/day for 8 weeks. During 8 weeks, patients were followed weekly by a dietitian. A body weight loss of ≥5% was a prerequisite for randomisation (309 of 383 patients, 80.7%). After VLED, patients were instructed to follow a standard energy restricted diet (600 kcal daily deficit) during the following 3 years. Patients were monitored every month for the first 18 months and then at 3-month intervals. Dietician provided dietary and lifestyle advice to reduce fat to ~30% of total energy, in particular saturated fat by limiting dairy fats and oils and substituting poultry, fish, and lean meats for fatty meats and increasing the intake of fruits and vegetables and limiting sweets, cookies, and desserts. Advice to increase daily physical activity was also given Further details: 1. Diet:

Study (subsidiary papers)	trial: Richelsen 2007[31] (Madsen 2008[23], Madsen 2009[22], Svendsen 2009[38])
	(n= 153) Intervention 2: Standard dietary advice - control. Placebo capsules. Duration 3 years. Concurrent medication/care: Participants were prescribed a VLED (Modifast; Novartis, Basel, Switzerland or Nutrilett; Nycomed Pharma, Oslo, Norway) of 600-300 kcal/day for 8 weeks. During 8 weeks, patients were followed weekly by a dietician. A body weight loss of ≥5% was a prerequisite for randomisation (309 of 383 patients, 80.7%). After VLED, patients were instructed to follow a standard energy restricted diet (600 kcal daily deficit) during the following 3 years. Patients were monitored every month for the first 18 months and then at 3-month intervals. Dietician provided dietary and lifestyle advice to reduce fat to ~30% of total energy, in particular saturated fat by limiting dairy fats and oils and substituting poultry, fish, and lean meats for fatty meats and increasing the intake of fruits and vegetables and limiting sweets, cookies, and desserts. Advice to increase daily physical activity was also given Further details: 1. Diet:
Funding	Study funded by industry (Clinical trial was investigator initiated and sponsored by Roche Scandinavia)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORLISTAT versus PLACEBO Protocol outcome 1: % weight change (kg) at Latest follow-up - Actual outcome: NOTE - weight loss from end of VLCD to end of study, kg not % at 36 months; Group 1: mean 4.6 kg (SD 8.6); n= 156, Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: % withdrawals at Latest follow-up - Actual outcome: % withdrawals at 36 months; Group 1: 58/156, Group 2: 51/153; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: % weight change including lead in (kg) at Latest follow-up - Actual outcome: NOTE - weight loss from start of study to end, kg not % at 38 months; Group 1: mean -9.4 kg (SD -8.3); n= 156, Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Health related quality of life at Latest follow-up; % change in BMI at Latest follow-up; % weight change including lead in (BMI) at Latest follow-up; Improvement in physical activity at Latest follow-up

Table 22: Ryttig 1995

Study	Ryttig 1995[34]
Study type	RCT (Patient randomised; Parallel)

Study	Ryttig 1995[34]
Number of studies (number of participants)	1 (n= 114)
Countries and setting	Conducted in Sweden; Setting: Karolinska Hospital, Sweden
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 weeks lead in / 52 weeks maintenance - 64 weeks total
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Obese patients (≥30kg/m2), from the waiting list of the obesity unit at Karolinska Hospital. Age 19-65 years. Stable body weight (fluctuations less than 3kg) within the last 2 months before commencing treatment
Exclusion criteria	Patients with known history of renal, cardiac, cerebrovascular, gastrointestinal ulcer, or gall-bladder diseases; patients with diabetes mellitus type 1, gout and porphyria; and patients with psychiatric disturbances. Treatment with the following drugs: anti-hypertensives, antidepressants, anorectics and lithium, oral contraceptives and oestrogen substitution therapy; and pregnancy, breastfeeding, vegetarian diet and lack of informed consent
Recruitment/selection of patients	Via waiting list of the obesity unit at Karolinksa Hospital, Sweden.
Age, gender and ethnicity	Age - Mean (SD): 41.5 (11.1). Gender (M:F): Group 1: N= 23 (male 4, female 19), Group 2: N= 22 (male 5, female 17). Ethnicity: Not specified
Further population details	1. Ethnicity: 2. Learning disabilities: 3. T2DM:
Extra comments	. Patients instructed to maintain the same physical and smoking habits during the whole trial period
Indirectness of population	No indirectness
Interventions	(n= 31) Intervention 1: Maintenance strategy - diet. Normal, hypocaloric diet containing 1600 kcal day, of which 220 kcal was provided by two sachets of the Cambridge diet. Duration 64 weeks. Concurrent medication/care: VLCD: Initial treatment for all patients during the first 12 weeks, consisted of one sachet of Cambridge diet, three times daily as the sole source of nourishment. Patients encouraged to drink as much water or low caloric beverage as they could, at least 2.5 l daily. Total energy intake during this period was 330 kcal. Maintenance: Instructed to use one sachet 30 min before two of their main meals of the day. The average energy distribution in the hypocaloric diet was approximately 20% protein, 30% fat and 50% carbohydrate. The programme was free of charge for all patients. A dietitian instructed the patients in group sessions during the transition period and intermittently during the maintenance period Further details: 1. Diet: (n= 29) Intervention 2: Standard dietary advice - control. Same daily energy intake provided by the same principal diet

Study	Ryttig 1995[34]
	as group receiving hypocaloric diet (i.e. hypocaloric diet of 1600 kcal daily) [note: not clear in text]. Duration 64 weeks. Concurrent medication/care: VLCD: Initial treatment for all patients during the first 12 weeks, consisted of one sachet of Cambridge diet, three times daily as the sole source of nourishment. Patients encouraged to drink as much water or low caloric beverage as they could, at least 2.5 l daily. Total energy intake during this period was 330 kcal. Maintenance: same daily energy intake provided by the same principal diet as group 1 for the rest of the treatment period. The programme was free of charge for all patients. A dietitian instructed the patients in group sessions during the transition period and intermittently during the maintenance period Further details: 1. Diet:
Funding	Equipment / drugs provided by industry (Financial support provided by The Howard Foundation and Cambridge Kuren Danmark. Tricum AB, Sweden, provided the dietary fibre supplement)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIET - HYPOCALORIC DIET WITH VLCD versus DIET - STANDARD HYPOCALORIC DIET Protocol outcome 1: % weight change (kg) at Latest follow-up - Actual outcome: NOTE - weight change (kg) not % change at 64 weeks; Group 1: mean 8 kg (SD 8.2); n= 31, Group 2: mean 12.3 kg (SD 9.7); n= 29; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: % withdrawals at Latest follow-up - Actual outcome: % withdrawals at 64 weeks; Group 1: 5/31, Group 2: 2/29; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: % weight change including lead in (kg) at Latest follow-up - Actual outcome: % weight change, including lead in at 64 weeks; Group 1: mean 9.3 % (SD 9.4); n= 31, Group 2: mean 12.3 % (SD 10); n= 29; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Health related quality of life at Latest follow-up; % change in BMI at Latest follow-up; % weight change including lead in (BMI) at Latest follow-up; Improvement in physical activity at Latest follow-up

Table 23: Ryttig 1997

Study	Ryttig 1997[33]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n= 81)

Study	Ryttig 1997[33]
Countries and setting	Conducted in Sweden; Setting: Obesity unit at Karolinska Hospital, Sweden
Line of therapy	1st line
Duration of study	Intervention + follow up: Up to 28 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Stable body weight (fluctuations ≤3kg) within the last two months before commencing the treatment. Only patients, who were able to complete a visual analogue scale concerning hunger feelings at 3pm daily during a two week run-in period were included
Exclusion criteria	Patients with known history of renal, cardiac, cerebrovascular, gastrointestinal ulcer, or gallbladder diseases. Patients suffering from IDDM, gout and porphyria. Patients with psychiatric disturbances (depression, schizophrenia and behavior disorders such as alcoholism and drug abuse). Treatment with the following drugs: antihypertensives, antidepressants, anorectics and lithium, oral contraceptives and estrogen substitution therapy. Pregnancy, lactation, vegetarian diet and lack of informed consent were also exclusion criteria
Recruitment/selection of patients	Participants from the obesity unit at Karolinska Hospital were invited to participate in the trial
Age, gender and ethnicity	Age - Mean (SD). Gender (M:F): 81 patients: 44 female, 37 male. Group a: female 14, male 13 / group b & c: female 30, male 23 (note this only give total pop of 80, not 81). . Ethnicity: Not specified
Further population details	1. Ethnicity: 2. Learning disabilities: 3. T2DM:
Extra comments	group a: 39.5 (±10) / group b & c: 44.0 (±10)
Indirectness of population	No indirectness
Interventions	(n= 27) Intervention 1: Standard dietary advice - control. Hypocaloric diet (1606 kcal) for 26m. Duration 28 months (VLCD: 2m, maintenance: 26m). Concurrent medication/care: VLCD: consisted of five sachets Nutrilett (422 kcal) as sole source of nourishment during 2m period. Maintenance: after one week transition period, with gradually increased intake of normal food, this VLCD group received a hypocalorc diet (1606 kcal) using different recipes together with behavior modification during the whole treatment period. The energy content of the hypocaloric diet was approx. 75g protein, 60g fat and 180g carbohydrate. Patients encouraged to drink as much water or non-caloric beverage as able to, at least 2.5l daily. Supplemented with capsule containing recommended daily intake of vitamins, minerals and essential fatty acids, ingested daily in VLCD and when needed in dietary fibre supplement Further details: 1. Diet: (n= 27) Intervention 2: Maintenance strategy - diet. Hypocaloric diet (1606 kcal), plus three sachets of Nutrilett/d (238

Study	Ryttig 1997[33]
	kcal) for 26m. Duration 28 months (VLCD: 2m, maintenance: 26m). Concurrent medication/care: VLCD: consisted of five sachets Nutrilett (422 kcal) as sole source of nourishment during 2m period. Maintenance: after one week transition period, with gradually increased intake of normal food, this VLCD group was prescribed a hypocaloric diet (1606 kcal) and 238 kcal provided as three sachets of Nutrilett/d. The VLCD was taken to prevent loss of food intake control, in practice in the evening. The powder was dissolved in a glass of water (approx. 250ml) and ingested. The energy content in each sachet was 12.3g protein, 1.2g fat and 6.1g carbohydrate. Patients encouraged to drink as much water or non-caloric beverage as able to, at least 2.5l daily. Supplemented with capsule containing recommended daily intake of vitamins, minerals and essential fatty acids, ingested daily in VLCD and when needed in dietary fibre supplement Further details: 1. Diet:
Funding	Study funded by industry (Nycimed Pharma AS, Oslo, Norway supported the project and Tricum AB, Hoganas, Sweden provided the dietary fibre supplement)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CONTROL - HYPOCALORIC DIET versus CONTROL - HYPOCALORIC DIET PLUS VLCD Protocol outcome 1: % weight change (kg) at Latest follow-up - Actual outcome: NOTE - weight in kg (final) not % at 26 months; Group 1: mean 107.3 kg (SD 15.1); n= 16, Group 2: mean 107.5 kg (SD 16.9); n= 15; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: % withdrawals at Latest follow-up - Actual outcome: % withdrawals at 26 months; Group 1: 16/27, Group 2: 12/27; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: % weight change including lead in (kg) at Latest follow-up - Actual outcome: % weight change, including lead in (i.e. from start of study, to end) at VLCD 2m, maintenance 26m; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Health related quality of life at Latest follow-up; % change in BMI at Latest follow-up; % weight change including lead in (BMI) at Latest follow-up; Improvement in physical activity at Latest follow-up

G.2 Bariatric surgery in people with type 2 diabetes

Table 24: Dixon 2008

Study	Adjustable gastric banding and conventional therapy for T2DM trial: Dixon 2008[7,8]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Australia; Setting: Hospital
Line of therapy	2nd line
Duration of study	Intervention + follow up: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age between 20 and 60 years, had a BMI of 30 to 40, had been diagnosed with clearly documented type 2 diabetes within the previous 2 years, had no evidence of renal impairment or diabetic retinopathy, and were able to understand and comply with the study process
Exclusion criteria	History of type 1 diabetes, diabetes secondary to a specific disease, or previous bariatric surgery, a history of medical problems (such as mental impairment, drug or alcohol addiction), recent major vascular event, internal malignancy, or portal hypertension; or a contraindication for either study group, failure to attend 2 initial information visits
Recruitment/selection of patients	Via newspaper advertisement. Run-in period of 3 months undertaken to ensure maximise current diabetes management. Endocrinologist independently determined when a patient was ready for randomisation. Randomisation was computer derived, with blocking into 3 groups to allow for orderly recruitment into both study groups. Study unblinded
Age, gender and ethnicity	Age - Mean (SD): Surgery group: 46.6 (7.4) and conventional therapy group: 47.1 (8.7). Gender (M:F): Male: 28 (15 surgery group / 13 non-surgery group) Female: 32 (15 surgery group / 17 non-surgery group). Ethnicity: Not specified
Further population details	1. Diabetes treatment: Not applicable / Not stated / Unclear (Appear some are on insulin but not clear how many). 2. Ethnicity: Not applicable / Not stated / Unclear 3. Sex: Mixed
Extra comments	None
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Surgery - Gastric band. Surgical group underwent placement of a laparoscopic adjustable gastric band via the pars flaccida technique by 1 of 2 experienced surgeons within 1 month of randomisation. . Duration 2

Study	Adjustable gastric banding and conventional therapy for T2DM trial: Dixon 2008[7,8]
	years. Concurrent medication/care: Surgery was in addition to conventional therapy. Progress was reviewed by the bariatric surgical team every 4 to 6 weeks throughout the study, and adjustments to band volume were made using standard clinical criteria Further details: 1. Exercise: 2. Medical - Dietician: 3. Medical - VLCD: 4. Surgery: (n=30) Intervention 2: Diet and exercise - Diet and exercise general. Patients had open access to a GP, dietitian, nurse, and diabetes educator, and had visits with at least 1 team member every 6 weeks throughout the 2 years. Duration 2 years. Concurrent medication/care: Medical therapies, including pharmaceutical agents, were determined by an experienced diabetologist on an individual basis. Lifestyle modification programs were individually structured to reduce energy intake, to reduced intake of fat (<30%) and saturated fats, and to encourage intake of low glycaemic index and high-fibre foods. Physical activity: 10,000 steps per day and 200 minutes per week of structured activity, including moderate intensity aerobic activity and resistance exercise. Very low calorie diets and medications were discussed with all patients and used after consultation Further details: 1. Exercise: 2. Medical - Dietician: 3. Medical - VLCD: 4. Surgery:
Funding	Study funded by industry (Study funded by Monash University, which has received an unrestricted grant from Allergan Health. The bands (Allergan Health) and ports (Allergan Medical) were provided without charge by the manufacturers. Allergan Health and Allergan Medical had no role in the design and conduct of the study, the collection, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GASTRIC BAND versus DIET AND EXERCISE GENERAL

Protocol outcome 1: % Weight change (BMI) at 1 year
- Actual outcome: % weight change at 2 years; Group 1: mean 20 % (SD 9.4); n=29, Group 2: mean 1.4 % (SD 4.9); n=26; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Improvement (glycaemic control, i.e. HBA1C) at 1 year
- Actual outcome: HBA1C < 6.2% at 2 years; Group 1: 24/29, Group 2: 6/26; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: Improvement in glycaemic control (continuous) at 2 years; Group 1: mean 6 % HbA1C (SD 0.82); n=30, Group 2: mean 7.21 % HbA1C (SD 1.39); n=30; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Mortality at 1 year
- Actual outcome: Mortality at 2 years; Group 1: 0/29, Group 2: 0/26; Risk of bias: Very high; Indirectness of outcome: No indirectness

Study	Adjustable gastric banding and conventional therapy for T2DM trial: Dixon 2008[7,8]
Protocol outcome 4: Weight change (kg) at 1 year - Actual outcome: Weight in kg at 2 years; Group 1: mean 84.6 kilograms (SD 15.8); n=30, Group 2: mean 104.8 kilograms (SD 15.3); n=30; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 5: Remission of T2D at 1 year - Actual outcome: Remission of T2D at 2 years; Group 1: 22/29, Group 2: 4/26; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 6: Medication reduction at 1 year - Actual outcome: Proportion using diabetic medication after follow-up at 2 years; Group 1: 3/29, Group 2: 18/26; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at 1 year

Table 25: Mingrone 2012

Study	Bariatric surgery versus conventional medical therapy for T2D trial: Mingrone 2012[25,26]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Italy; Setting: Hospital
Line of therapy	2nd line
Duration of study	Intervention + follow up: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age between 30 to 60 years, a BMI of 35 or more, history of T2D of at least 5 years, a glycated haemoglobin level of 7% or more
Exclusion criteria	History of type 1 diabetes, diabetes secondary to a specific disease or glucocorticoid therapy, previous bariatric surgery, pregnancy, other medical condition requiring short-term hospitalisation, severe diabetes complications, other severe medical conditions, and geographic inaccessibility
Recruitment/selection of patients	Patients enrolled at a hospital for metabolic diseases and diabetology
Age, gender and ethnicity	Age - Mean (SD): usual care: 43.45 (7.27) / gastric sleeve 42.75 (8.06) / gastric bypass 43.90 (7.57). Gender (M:F):

Study	Bariatric surgery versus conventional medical therapy for T2D trial: Mingrone 2012[25,26]
	Male: 28 (10 medical therapy / 10 biliopancreatic diversion / 8 gastric bypass) Female: 32 (10 medical therapy / 10 biliopancreatic diversion / 12 gastric bypass) . Ethnicity: Not specified
Further population details	1. Diabetes treatment: 2. Ethnicity: 3. Sex:
Extra comments	. None
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Diet and exercise - Diet and exercise general. Patients evaluated by a multidisciplinary team (diabetologist, dietitian, nurse) at baseline and at 1, 3, 6, 9, 12, and 24 months after surgery. Duration 2 years. Concurrent medication/care: Oral hypoglycaemic agents and insulin doses were optimised on an individual basis with the aim of reaching a glycated haemoglobin level of less than 7%Programs for diet and lifestyle modification were designed by an experienced diabetologist with assistance from a dietitian, included: reduced overall energy and fat intake (<30% total fat, <10% saturated fat, and high fibre content), increased physical exercise (≥30 mins daily of brisk walking, possibly associated with moderate-intensity aerobic activity twice a week) Further details: 1. Exercise: 2. Medical - Dietician: 3. Medical - VLCD: 4. Surgery: (n=20) Intervention 2: Surgery - Gastric bypass. Two teams of bariatric surgeons, one with expertise in laparoscopic gastric bypass and the other with expertise in open biliopancreatic diversion, performed the procedures. Duration 2 years. Concurrent medication/care: Patients evaluated by a multidisciplinary team (diabetologist, dietitian, nurse) at baseline and at 1, 3, 6, 9, 12, and 24 months after surgery. Medical therapy was adjusted according to the seven-point glycaemic profile during the first 3 months and according to glycated haemoglobin levels thereafter. Discontinuation of medical therapy was considered in cases of normalisation of the glycaemic profile, glycated haemoglobin levels or both. Daily multivitamin and mineral supplementation was prescribed Further details: 1. Exercise: 2. Medical - Dietician: 3. Medical - VLCD: 4. Surgery: (n=20) Intervention 3: Surgery - Biliopancreatic diversion. Two teams of bariatric surgeons, one with expertise in laparoscopic gastric bypass and the other with expertise in open biliopancreatic diversion, performed the procedures. Duration 2 years. Concurrent medication/care: Patients evaluated by a multidisciplinary team (diabetologist, dietitian, nurse) at baseline and at 1, 3, 6, 9, 12, and 24 months after surgery. Medical therapy was adjusted according to the seven-point glycaemic profile during the first 3 months and according to glycated haemoglobin levels thereafter. Discontinuation of medical therapy was considered in cases of normalisation of the glycaemic profile, glycated haemoglobin levels or both. Daily multivitamin and mineral supplementation was prescribed Further details: 1. Exercise: 2. Medical - Dietician: 3. Medical - VLCD: 4. Surgery: Comments: Advice from AO 280114: biliopancreatic diversion is categorised in protocol as gastric sleeve. Specifically, gastric sleeve plus the exclusion of the small bowl. Procedure is entirely malabsorptive and not widely carried out in

Study	Bariatric surgery versus conventional medical therapy for T2D trial: Mingrone 2012[25,26]
	the UK. Procedure known as BPD.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GASTRIC BYPASS versus DIET AND EXERCISE GENERAL

Protocol outcome 1: % Weight change (BMI) at 1 year
- Actual outcome: Weight in BMI at 2 years; Group 1: mean 29.31 BMI (SD 2.64); n=20, Group 2: mean 43.07 BMI (SD 6.44); n=20; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: % weight change at 2 years; Group 1: mean -33.31 % (SD 7.88); n=19, Group 2: mean -4.74 % (SD 6.37); n=18; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Mortality at 1 year
- Actual outcome: Mortality at 2 years; Group 1: 0/20, Group 2: 0/20; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 3: Weight change (kg) at 1 year
- Actual outcome: Weight in kg at 2 years; Group 1: mean 84.29 kilos (SD 13.35); n=20, Group 2: mean 128.06 kilos (SD 19.77); n=20; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 4: Remission of T2D at 1 year
- Actual outcome: Difference in the rate of remission of T2D, defined as A). fasting plasma glucose level of less than 100 mg per decilitre at 2 years; Group 1: mean 5.69 mmol/litre (SD 3.07); n=20, Group 2: mean 7.83 mmol/litre (SD 1.66); n=20; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome: Difference in the rate of remission of T2D, defined as B). glycated haemoglobin level of less than 6.5% for at least 1 year without active pharmacologic therapy at 2 years; Group 1: mean 6.35 percentage (SD 1.42); n=20, Group 2: mean 4.95 percentage (SD 0.49); n=20; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome: Remission of T2D at 2 years; Group 1: 15/20, Group 2: 0/20; Risk of bias: Very high; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GASTRIC SLEEVE versus DIET AND EXERCISE GENERAL

Protocol outcome 1: % Weight change (BMI) at 1 year
- Actual outcome: Weight in BMI at 2 years; Group 1: mean 29.19 BMI (SD 4.9); n=20, Group 2: mean 43.07 BMI (SD 6.44); n=20; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: % weight change at 2 years; Group 1: mean -33.82 % (SD 10.17); n=19, Group 2: mean -4.74 % (SD 6.37); n=18; Risk of bias: Very high; Indirectness of outcome: No indirectness

Study	Bariatric surgery versus conventional medical therapy for T2D trial: Mingrone 2012[25,26]

Protocol outcome 2: Improvement (glycaemic control, i.e. HBA1C) at 1 year
- Actual outcome: Improvement in glycaemic control (continuous) at 2 years; Group 1: mean 6.35 % HbA1c (SD 1.42); n=19, Group 2: mean 7.69 % HbA1c (SD 0.57); n=18; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Mortality at 1 year
- Actual outcome: Mortality at 2 years; Group 1: 0/20, Group 2: 0/20; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 4: Weight change (kg) at 1 year
- Actual outcome: Weight in kg at 2 years; Group 1: mean 89.53 kilos (SD 17.84); n=20, Group 2: mean 128.06 kilos (SD 19.77); n=20; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 5: Remission of T2D at 1 year
- Actual outcome: Difference in the rate of remission of T2D, defined as A). fasting plasma glucose level of less than 100 mg per decilitre at 2 years; Group 1: mean 3.89 mmol/litre (SD 0.67); n=20, Group 2: mean 7.83 mmol/litre (SD 1.66); n=20; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome: Difference in the rate of remission of T2D, defined as B). glycated haemoglobin level of less than 6.5% for at least 1 year without active pharmacologic therapy at 2 years; Group 1: mean 4.95 percentage (SD 0.49); n=20, Group 2: mean 7.69 percentage (SD 0.57); n=20; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome: Remission of T2D at 2 years; Group 1: 19/20, Group 2: 0/20; Risk of bias: Very high; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GASTRIC SLEEVE versus GASTRIC BYPASS

Protocol outcome 1: % Weight change (BMI) at 1 year
- Actual outcome: Weight in BMI at 2 years; Group 1: mean 29.19 BMI (SD 4.9); n=20, Group 2: mean 29.31 BMI (SD 2.64); n=20; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Improvement (glycaemic control, i.e. HBA1C) at 1 year
- Actual outcome: Improvement in glycaemic control (continuous) at 2 years; Group 1: mean 4.95 % HbA1c (SD 0.49); n=19, Group 2: mean 7.69 % HbA1c (SD 0.57); n=18; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Mortality at 1 year
- Actual outcome: Mortality at 2 years; Group 1: 0/20, Group 2: 0/20; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 4: Weight change (kg) at 1 year

Study	Bariatric surgery versus conventional medical therapy for T2D trial: Mingrone 2012[25,26]
- Actual outcome: Weight in kg at 2 years; Group 1: mean 89.53 kilos (SD 17.84); n=20, Group 2: mean 84.29 kilos (SD 13.35); n=20; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Remission of T2D at 1 year - Actual outcome: Difference in the rate of remission of T2D, defined as A). fasting plasma glucose level of less than 100 mg per decilitre at 2 years; Group 1: mean 3.89 mmol/litre (SD 0.67); n=20, Group 2: mean 5.69 mmol/litre (SD 3.07); n=20; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: Difference in the rate of remission of T2D, defined as B). glycated haemoglobin level of less than 6.5% for at least 1 year without active pharmacologic therapy at 2 years; Group 1: mean 4.95 percentage (SD 0.49); n=20, Group 2: mean 6.35 percentage (SD 1.42); n=20; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: Remission of T2D at 2 years; Group 1: 19/20, Group 2: 15/20; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at 1 year; Medication reduction at 1 year

Table 26: Liang 2013

Study	Effect of LRYG on T2D with hypertension trial: Liang 2013[21,21]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=108)
Countries and setting	Conducted in China; Setting: Hospital
Line of therapy	2nd line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	BMI >28kg/m2 (WHO Asia-Pacific classification for obesity), T2D of 5-10 years with hypertension, insulin therapy in combination with oral administration of drugs for 12 months, glycated haemoglobin (HbA1c) >7%, age 30-60yrs, seronegative for antibodies against insulin, islet cells and gluamic acid decarboxylase, C-peptide level ≥ 0.3 mg/L
Exclusion criteria	People without diabetes; Type 1 diabetes, presence of autoimmune diabetes indicated by antibodies to insulin, islet cells, and GAD, and gestational diabetes; patients with heart, liver or renal function impairment; presence of severe infections or cerebrovascular disease; fasting serum insulin was less than 1/3 normal value; diabetes of more than 10yrs duration, age >60 or <30yrs

Study	Effect of LRYG on T2D with hypertension trial: Liang 2013[21,21]
Recruitment/selection of patients	Patients enrolled at hospital. No specific mention of how recruitment was carried out
Age, gender and ethnicity	Age - Mean (SD): Usual care: 51.75 (6.70) / usual care plus exenatide treatment: 50.94 (5.89) / surgery: 50.81 (5.44). Gender (M:F): Male: 70 (22 surgery group / 24 usual care plus exenatide group / 24 usual care group) Female: 31 (9 surgery group / 10 usual care plus exenatide group / 12 usual care group). Ethnicity: Not specified
Further population details	1. Diabetes treatment: Insulin 2. Ethnicity: Not applicable / Not stated / Unclear 3. Sex: Mixed
Extra comments	None
Indirectness of population	No indirectness
Interventions	(n=31) Intervention 1: Surgery - Gastric bypass. Using a standard 5-port laparoscopic technique, the greater and lesser curvatures of the stomach were separated, the gastric cavity closed with disposable closure device, and a gastric pouch created that was completely separated from the gastric remnant and anastomosed to the jejunum. An entero-entero anastomosis was created between the pancreatobiliary limb and alimentary limb 100cm distally from the gastrojejunostomy. Duration 1 year. Concurrent medication/care: Postoperative treatment was identical to that of a routine gastrointestinal operation. Clinical evaluations were carried out at baseline, 3, 6, 9, and 12 months after study entry. Discontinuation of medical therapy was considered in cases of normalisation of the glycaemic profile, HbA1c, or blood pressure. Further details: 1. Exercise: 2. Medical - Dietician: 3. Medical - VLCD: 4. Surgery: (n=34) Intervention 2: Diet and exercise - Diet and exercise general. Patients were assessed and treated by a multidisciplinary team that included an endocrinologist, a dietitian, a cardiologist, and a nurse. Medical therapy was adjusted according to the seven-point glycaemic profile during the first 3 months and according to HbA1c levels thereafter. The dose or oral hypoglycaemic medications, antihypertensive drugs and insulin was optimised on an individual basis with the aim of reaching HbA1c <7% and blood pressure ≤140/90 mmHg. Duration 1 year. Concurrent medication/care: The nutrition goal was based on an individual energy intake and reducing fat intake to <30%, saturated fat to <10% and increasing fibre intake and for physical exercise ≥30 min of brisk walking daily associated with moderate-intensity aerobic activity twice a week Further details: 1. Exercise: 2. Medical - Dietician: 3. Medical - VLCD: 4. Surgery: (n=36) Intervention 3: Diet and exercise and GRP1 analogues - Diet and exercise and incretin. Exenatide was give 1 h before breakfast or dinner. Patients were injected with 0.5g Exenatide subcutaneously twice daily for 1 month, then increased to 1.0 twice daily if tolerated. Duration 1 year. Concurrent medication/care: Assume same as usual care group - Patients were assessed and treated by a multidisciplinary team that included an endocrinologist, a dietitian, a cardiologist, and a nurse. Medical therapy was adjusted according to the seven-point glycaemic profile during the first 3 months and according to HbA1c levels thereafter. The dose or oral hypoglycaemic medications, antihypertensive

Study	Effect of LRYG on T2D with hypertension trial: Liang 2013[21,21]
	drugs and insulin was optimised on an individual basis with the aim of reaching HbA1c <7% and blood pressure ≤140/90 mmHg. The nutrition goal was based on an individual energy intake and reducing fat intake to <30%, saturated fat to <10% and increasing fibre intake and for physical exercise ≥30 min of brisk walking daily associated with moderate-intensity aerobic activity twice a week Further details: 1. Exercise: 2. Medical - Dietician: 3. Medical - VLCD: 4. Surgery:
Funding	Academic or government funding (Study supported by research grants from the National Natural Science Foundation of China)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GASTRIC BYPASS versus DIET AND EXERCISE GENERAL

Protocol outcome 1: % Weight change (BMI) at 1 year
- Actual outcome: Weight in BMI at 1 year; Group 1: mean 24.51 BMI (SD 0.91); n=31, Group 2: mean 30.38 BMI (SD 1.66); n=34; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Mortality at 1 year
- Actual outcome: Adverse event that resulted in death at 1 year; Group 1: 0/31, Group 2: 0/34; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Remission of T2D at 1 year
- Actual outcome: Diabetes remission at 1 year; Group 1: 28/31, Group 2: 0/34; Risk of bias: Very high; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GASTRIC BYPASS versus DIET AND EXERCISE AND INCRETIN

Protocol outcome 1: % Weight change (BMI) at 1 year
- Actual outcome: Weight in BMI at 1 year; Group 1: mean 24.51 BMI (SD 0.91); n=31, Group 2: mean 26.84 BMI (SD 1.21); n=36; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Mortality at 1 year
- Actual outcome: Adverse event that resulted in death at 1 year; Group 1: 0/31, Group 2: 0/36; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Remission of T2D at 1 year
- Actual outcome: Diabetes remission at 1 year; Group 1: 28/31, Group 2: 0/36; Risk of bias: Very high; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIET AND EXERCISE GENERAL versus DIET AND EXERCISE AND INCRETIN

Study	Effect of LRYG on T2D with hypertension trial: Liang 2013[21,21]
Protocol outcome 1: % Weight change (BMI) at 1 year - Actual outcome: Weight in BMI at 1 year; Group 1: mean 30.38 BMI (SD 1.66); n=34, Group 2: mean 26.84 BMI (SD 1.21); n=36; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Mortality at 1 year - Actual outcome: Adverse event that resulted in death at 1 year; Group 1: 0/34, Group 2: 0/36; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Remission of T2D at 1 year - Actual outcome: Diabetes remission at 1 year; Group 1: 0/36, Group 2: 0/36; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Improvement (glycaemic control, i.e. HBA1C) at 1 year; Quality of life at 1 year; Weight change (kg) at 1 year; Medication reduction at 1 year

Table 27: Palikhe 2013

Study	Palikhe 2013[27]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=31)
Countries and setting	Conducted in India; Setting: Single-centre at Post Graduate Institute of Medical Education and Research.
Line of therapy	1st line
Duration of study	Follow up (post intervention): Mean 12.5 months (SD 5), median 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	T2D aged between 20 and 75 with BMI 27.5 kg/m2 or greater
Exclusion criteria	Use of GLP-1 agonist therapy in previous 3 months, acute coronary syndrome and/or stroke within previous 6 months, hepatic or renal dysfunction, past history of pancreatitis, active malignancy and previous bariatric surgery or complex abdominal surgery
Recruitment/selection of patients	Between January 2011 and July 2012 (no further details)
Age, gender and ethnicity	Age - Mean (SD): Sleeve: 47 (12), medical therapy: 52 (12) years. Gender (M:F): 1/13 sleeve gastrectomy versus 7/10

Study	Palikhe 2013[27]
	for medical therapy group. Ethnicity: Not reported
Further population details	1. Diabetes treatment: Mixed (50% (7) of sleeve and 47% (8) of medical therapy group were insulin users). 2. Ethnicity: Not applicable / Not stated / Unclear 3. Sex: Mixed
Extra comments	BMI 37.9 (SD 5.3) kg/m2, mean duration of diabetes 8.5 (SD 6.1) years, mean weight was 94.5 kg (SD 11.1), HbA1c was 8.6% (SD 1.3). Study was ongoing at time of publication: patients included in this report were those with at least 6 months follow-up.
Indirectness of population	Serious indirectness: Mean duration of diabetes less than 10 years but SD would mean that many patients were over 10 years.
Interventions	(n=14) Intervention 1: Surgery - Gastric sleeve. After 2 week run in period with 600 kcal liquid VLCD diet, all patients had sleeve gastrectomy. Sleeve size was calibrated using 36F bougie and gastric transection was done with endo-GIA stapler (ETHICON, Johnson&Johnson). Intraoperative leak test was done prior to closing port sites.. Duration Surgical. Concurrent medication/care: Insulin was used during the hospital stay for glycaemic control. After discharge, patients were shifted to oral antidiabetic drugs and/or insulin depending on the blood glucose profile. Metaformin was given to all patients and, if required, insulin detemir and alph-glucosidase inhibitor was added. Multiple dose insulin regimens were prepared in the case of poor glycaemic control with target HbA1c < 7%). All patients received multivitamin, calcium iron and vitamin D supplementation. Blood pressure and dyslipidemia were managed according to American Diabetes Association guidelines. Further details: 1. Exercise: Not applicable / Not stated / Unclear 2. Medical - Dietician: Not applicable / Not stated / Unclear 3. Medical - VLCD: Very-low-calorie diet (600 kcal for 2 weeks pre-operatively; no details about postoperative diet.). 4. Surgery: Gastric sleeve Comments: Sulphonylurea, pioglitazone and DPP-4 inhibitor were prohibited (n=17) Intervention 2: Diet and exercise - Diet and exercise general. After a 2-week run-in period of 1000 kcal diet, patients started intensive medical therapy with exenatide (Exapride, Sun Pharmaceuticals, India), 5 ug twice daily with increasing dose of 10 ug twice daily after 2 weeks (patients stayed on 1000 kcal during medical therapy).. Duration Unclear. Concurrent medication/care: Metaformin was given to all patients and, if required, insulin detemir and alph-glucosidase inhibitor was added. If glycaemic control was inadequate even with these drugs, short-acting insulin (analogue or regular) was initiated along with detemir. Further details: 1. Exercise: Not applicable / Not stated / Unclear 2. Medical - Dietician: Not applicable / Not stated / Unclear 3. Medical - VLCD: Low-calorie diet (1000 kcal in 2 weeks prior to treatment and during treatment). 4. Surgery: Not applicable / Not stated / Unclear Comments: Sulphonylurea, pioglitazone and DPP-4 inhibitor were prohibited

Study	Palikhe 2013[27]
Funding	Equipment / drugs provided by industry (Sun Pharmaceutics, India provided exenatide (Exapride); unclear about any other funding sources)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GASTRIC SLEEVE versus EXENATIDE AND LOW CALORIE DIET Protocol outcome 1: % Weight change (BMI) at 1 year - Actual outcome: % weight change at Mean 12.5 months; Group 1: mean -27.9 % (SD 6.9); n=14, Group 2: mean -9.4 % (SD 7.7); n=17; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: Weight in BMI at Mean 12.5 months; Group 1: mean 29.1 kg/m2 (SD 4); n=14, Group 2: mean 32.5 kg/m2 (SD 5.8); n=17; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Improvement (glycaemic control, i.e. HBA1C) at 1 year - Actual outcome: HbA1c < 7% at Mean 12.5 months; Group 1: 8/14, Group 2: 7/17; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: Improvement in glycaemic control (continuous) at Mean 12.5 months; Group 1: mean 6.7 % HbA1C (SD 1.4); n=14, Group 2: mean 7.1 % HbA1C (SD 1.2); n=17; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Mortality at 1 year - Actual outcome: Mortality at Mean 12.5 months; Group 1: 0/14, Group 2: 0/17; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 4: Weight change (kg) at 1 year - Actual outcome: Weight in kg at Mean 12.5 months; Group 1: mean 71.5 kg (SD 10.8); n=14, Group 2: mean 81.9 kg (SD 10.4); n=17; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 5: Remission of T2D at 1 year - Actual outcome: Remission of T2D / resolution of diabetes at Mean 12.5 months; Group 1: 5/14, Group 2: 0/17; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at 1 year; Medication reduction at 1 year
Study (subsidiary papers)	**STAMPEDE trial: Schauer 2012[36,36] (Kashyap 2010[16,16], Kashyap 2013[16,17], Malin 2013[24], Schauer 2014[35,36])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in USA; Setting: Single centre, patients screened from from the Cleveland Clinic, US from March 2007 to

Study	Palikhe 2013[27]
	January 2011
Line of therapy	Mixed line
Duration of study	Follow up (post intervention): 3 years follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Type 2 Diabetes diagnosied by glycated hemoglobin level, >7.0%
Stratum	Overall
Subgroup analysis within study	Not applicable: None
Inclusion criteria	Age of 20-60 years, a diagnosis of T2D and a BMI of 27-43
Exclusion criteria	If had undergone previous bariatric surgery or other complex abdominal surgery or had poorly controlled medical or psychiatric disorders
Recruitment/selection of patients	Recruitment by use of electronic medical records and advertisement in local media. Patients providing written informed consent entered a 12 week screening period and underwent repeated physical and laboratory evaluation to confirm eligibility
Age, gender and ethnicity	Age - Mean (SD): Medical therapy group: 49.7 (7.4); Bypass group: 48.3 (8.4); Sleeve gastrectomy: 47.9 (8). Gender (M:F): 66% female. Ethnicity: White race = 73%
Further population details	1. Diabetes treatment: Mixed (44% (22/50) of those with medical therapy, 44% (22) of those with gastric bypass and 44% (22) of those with sleeve gastrectomy used insulin). 2. Ethnicity: Mixed (72-74% white in arms). 3. Sex: Mixed (58% (29) with gastric bypass, 62% (31) with medical therapy and 78% (39) with sleeve gastrectomy were women).
Extra comments	None
Indirectness of population	Serious indirectness: Mean duration of diabetes less than 10 years but SD would mean that many patients were over 10 years.
Interventions	(n=50) Intervention 1: Surgery - Gastric bypass. Intensive medical treatment and gastric bypass. Procedure performed laparoscopically by a single surgeon with the use of instruments provided by Ethicon Endo-Surgery. Consisted of the creation of a 15-20-ml gastric pouch, a 150 cm Roux limb and a 50 cm biliopancreatic limb. Evaluated by surgical nutrition, and psychology services as necessary. Vitamin and nutrient supplementation included a multivitamin, iron, vitamin B12, calcium citrate with vitamin D. Patients were assessed for nutritional deficiencies within 12 months after surgery. Duration 12 months. Concurrent medication/care: Intensive medical therapy as defined by American Diabetes Association (ADA) guidelines, including lifestyle counselling, weight management, frequent home glucose monitoring and the use of newer drug therapies (e.g. incretin analogues) approved by the food and Drug Administration. Every 3 months for the first 12 months, patients returned for study visits with a diabetes specialist at the Cleveland clinic. Patients were counselled by a diabetes educator and evaluated for bariatric surgery by a psychologist and encouraged to participate in the Weight Watchers program. The goal of medical management was

Study	Palikhe 2013[27]
	modification of diabetes medication until the patient reached the therapeutic goal of a glycated haemoglobin level of 6.0% or less or became introleratnt toeh medical treatment. All patients were treated with lipid-lowering and antihypertensive medications, according to ADA guidelines, with the following targets: systolic blood pressure, 130 mm Hg or less; and low density lipo-proptein (LDL) cholesterol, 100 mg per decilitre (2.6mmol per litre) or less Further details: 1. Exercise: Not applicable / Not stated / Unclear 2. Medical - Dietician: Not applicable / Not stated / Unclear 3. Medical - VLCD: Not applicable / Not stated / Unclear 4. Surgery: Gastric bypass (n=49) Intervention 2: Surgery - Gastric sleeve. Intensive medical therapy and sleeve gastrectomy, performed laparoscopically by a single surgeon whit the use of instruments provided by Ethicon Endo-Surgery. Involved a gastric-volume reduction of 75 to 80% by resecting the stomach alongside a 30 French endoscope beginning 3cm from the pylorus and ending at the angle of HIS. Evaluated by surgical nutrition, and psychology services as necessary. Vitamin and nutrient supplementation after sleeve gastrectomy included a multivitamin and vitamin B12. Patients were assessed for nutritional deficiencies within 12 months after surgery. Duration 12 months. Concurrent medication/care: Intensive medical therapy as defined by American Diabetes Association (ADA) guidelines, including lifestyle counselling, weight management, frequent home glucose monitoring and the use of newer drug therapies (e.g. incretin analogues) approved by the food and Drug Administration. Every 3 months for the first 12 months, patients returned for study visits with a diabetes specialist at the Cleveland clinic. Patients were counselled by a diabetes educator and evaluated for bariatric surgery by a psychologist and encouraged to participate in the Weight Watchers program. The goal of medical management was modification of diabetes medication until the patient reached the therapeutic goal of a glycated hemoglobin level of 6.0% or less or became intolerant to the medical treatment. All patients were treated with lipid-lowering and antihypertensive medications, according to ADA guidelines, with the following targets: systolic blood pressure, 130 mm Hg or less; and low density lipo-proptein (LDL) cholesterol, 100 mg per decilitre (2.6mmol per litre) or less Further details: 1. Exercise: Not applicable / Not stated / Unclear 2. Medical - Dietician: Not applicable / Not stated / Unclear 3. Medical - VLCD: Not applicable / Not stated / Unclear 4. Surgery: Gastric sleeve (n=41) Intervention 3: Diet and exercise - Diet and exercise general. Intensive medical therapy as defined by American Diabetes Association (ADA) guidelines, including lifestyle counselling, weight management, frequent home glucose monitoring and the use of newer drug therapies (e.g. incretin analogues) approved by the food and Drug Administration. Every 3 months for the first 12 months, patients returned for study visits with a diabetes specialist at the Cleveland clinic. Patients were counselled by a diabetes educator and evaluated for bariatric surgery by a psychologist and encouraged to participate in the Weight Watchers program. The goal of medical management was modification of diabetes medication until the patient reached the therapeutic goal of a glycated haemoglobin level of 6.0% or less or became intolerant to the medical treatment. All patients were treated with lipid-lowering and antihypertensive medications, according to ADA guidelines, with the following targets: systolic blood pressure, 130

Study	Palikhe 2013[27]
	mm Hg or less; and low density lipo-proptein (LDL) cholesterol, 100 mg per decilitre (2.6mmol per litre) or less. Duration 12 months. Concurrent medication/care: Intensive medical therapy alone Further details: 1. Exercise: Not applicable / Not stated / Unclear 2. Medical - Dietician: Not applicable / Not stated / Unclear 3. Medical - VLCD: Not applicable / Not stated / Unclear 4. Surgery: Not applicable / Not stated / Unclear
Funding	Study funded by industry (Grant from Ethicon Endo-Surgery, a grant from the National Institutes of Health, additional support from LifeScan and The Cleveland Clinic.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GASTRIC BYPASS + INTENSIVE MEDICAL THERAPY versus INTENSIVE MEDICAL THERAPY

Protocol outcome 1: % Weight change (BMI) at 1 year
- Actual outcome: % weight change at 3 years; Group 1: mean -24.5 % (SD 9.1); n=48, Group 2: mean -4.2 % (SD 8.3); n=40; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Improvement (glycaemic control, i.e. HBA1C) at 1 year
- Actual outcome: HbA1c < 6% at 3 years; Group 1: 18/48, Group 2: 2/40; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome: HbA1c < 7% at 3 years; Group 1: 31/48, Group 2: 16/40; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome: Improvement in glycaemic control (continuous) at 3 years; Group 1: mean 6.7 % HbA1C (SD 1.3); n=48, Group 2: mean 8.4 % HbA1C (SD 2.2); n=40; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Mortality at 1 year
- Actual outcome: Mortality at 3 years; Group 1: 0/48, Group 2: 0/40; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Weight change (kg) at 1 year
- Actual outcome: Weight in kg at 3 years; Group 1: mean 80.6 kg (SD 15.5); n=48, Group 2: mean 100.2 kg (SD 16.6); n=40; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Remission of T2D at 1 year
- Actual outcome: Remission of T2D (Hba1c < 6% and no diabetes medications) at 3 years; Group 1: 17/48, Group 2: 0/40; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 6: Medication reduction at 1 year
- Actual outcome: Number of diabetes medications used at 3 years; Group 1: mean 0.48 number of medications (SD 0.8); n=48, Group 2: mean 2.6 number of medications (SD 1.1); n=40; Risk of bias: High; Indirectness of outcome: No indirectness

Study	Palikhe 2013[27]
- Actual outcome: Proportion taking diabetes medications at 3 years; Group 1: 15/48, Group 2: 39/40; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GASTRIC SLEEVE versus INTENSIVE MEDICAL THERAPY Protocol outcome 1: % Weight change (BMI) at 1 year - Actual outcome: % weight change at 3 years; Group 1: mean -21.1 % (SD 8.9); n=49, Group 2: mean -4.2 % (SD 8.3); n=40; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Improvement (glycaemic control, i.e. HBA1C) at 1 year - Actual outcome: HbA1c < 6% at 3 years; Group 1: 12/49, Group 2: 2/40; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: HbA1c < 7% at 3 years; Group 1: 32/49, Group 2: 16/40; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome: Improvement in glycaemic control (continuous) at 3 years; Group 1: mean 7 % HbA1C (SD 1.3); n=49, Group 2: mean 8.4 % HbA1C (SD 2.2); n=41; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Mortality at 1 year - Actual outcome: Mortality at 3 years; Group 1: 0/49, Group 2: 0/40; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Weight change (kg) at 1 year - Actual outcome: Weight in kg at 3 years; Group 1: mean 79.3 kg (SD 15.1); n=49, Group 2: mean 100.2 kg (SD 16.6); n=40; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 5: Remission of T2D at 1 year - Actual outcome: Remission of T2D (Hba1c < 6% and no diabetes medications) at 3 years; Group 1: 10/49, Group 2: 0/40; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 6: Medication reduction at 1 year - Actual outcome: Number of diabetes medications used at 3 years; Group 1: mean 1.02 number of diabetes medications (SD 1.01); n=49, Group 2: mean 2.6 number of diabetes medications (SD 1.1); n=40; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: Proportion taking diabetes medications at 3 years; Group 1: 28/49, Group 2: 39/40; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at 1 year

Table 28: Ikramuddin 2013

Study	The Diabetes Surgery Study: Ikramuddin 2013[13,14]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Taiwan, USA; Setting: 4 sites: the University of Minnesota, Columbia University Medical Centre, 2 academic clinics in Taiwan (National Taiwan University Hospital and Min Sheng General Hospital), the Mayo Clinic in Rochester, Minnesota
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 30 to 67 years, under a physician's care for T2D for at least 6 months, HbQ1C levels 8% or higher, serum C-peptide level higher than 1.0 ng/mL (to convert C-peptide level to nanomoles per liter, multiply by 0.331) 90 minutes after a liquid mixed meal (250 calories, 6g fat, 40 g carbohydrate, and 9 g protein); BMI 30-39.9 and willingness to accept randomisation to either treatment
Exclusion criteria	Conditions that contraindicate surgery including serious cardiovascular disease, previous gastrointestinal surgery, psychological concerns, or history of malignancy
Recruitment/selection of patients	Between April 2008 and December 2011, patients who were participating in an intensive lifestyle and medical management weight control program were randomised to continuing with the program or surgery. Patients were recruited through mass media advertisements, contact with professional groups, presentations at public events, and a practice-based database.
Age, gender and ethnicity	Age - Mean (SD): Bypass: 49 years (SD 9), lifestyle and medical management: 49 (SD 8). Gender (M:F): Bypass: 22/38, medical and lifestyle: 26/34. Ethnicity: Bypass: 55% Non-Hispanic white, 27% East Asian, 8% Non-Hispanic black, 7% Hispanic, 3% Native American, 0% other; medical and lifestyle: 50% Non-Hispanic white, 28% East Asian, 10% Non-Hispanic black, 7% Hispanic, 2% Native American, 3% other
Further population details	1. Diabetes treatment: Mixed (Bypass: 62% (37) and lifestyle and medical management: 43% (26)). 2. Ethnicity: Mixed (Bypass: 55% Non-Hispanic white, 27% East Asian, 8% Non-Hispanic black, 7% Hispanic, 3% Native American, 0% other; lifestyle and medical management: 50% Non-Hispanic white, 28% East Asian, 10% Non-Hispanic black, 7% Hispanic, 2% Native American, 3% other). 3. Sex: Mixed
Extra comments	Baseline BMI was 34.9 kg/m2 (SD 3) in bypass group and 34.3 kg/m2 (SD 3.1) in medical&lifestyle group (60% and

Study	The Diabetes Surgery Study: Ikramuddin 2013[13,14]
	58%, respectively had BMI 30-34.0 kg/m2)
Indirectness of population	Serious indirectness: Mean duration of diabetes less than 10 years but SD would mean that many patients were over 10 years.
Interventions	(n=60) Intervention 1: Surgery - Gastric bypass. After LCD with meal replacements for 2 weeks before the operation, patients had laparoscopic Roux-en-Y gastric bypass performed by a surgeon with extensive experience (> 300 cases). At one site 2 surgeons performed the procedure. The technique was standardised across all sites and performed by constructing a 20 mL lesser curvature gastric pouch, a 100 cm biliopancreatic limb, and an antecolic 150 cm Rouz limb with closure of all mesenteric defects. 1 day after surgery, patients had routine upper GI contrast study and initiated a clear liquid diet if the study showed no leak and continued on this for 1 week with food gradually being introduced (pureed and then solid foods). They were discharged after 2 days. . Duration 12 months post-surgery. Concurrent medication/care: All patients were on lifestyle modification and medical management before being randomised with the aim to produce maximum achievable weight loss and medications to control glycaemia and cardiovascular disease risk factors. Lifestyle modification was modelled after the Diabetes Prevention Program and the Look AHEAD protocols: patients weight themselves and recorded eating and exercise behaviours on a daily basis. They were advised to progressively increase moderate-intensity physical activity to 325 minutes per week with targets of 1200, 1500, or 1800 kcal per day, depending on body weight with the aim of losing 1-2 pounds per week. Patients had portion-controlled diets with meal replacement, structured menus, and used calorie counting. Counselling sessions with a trained interventionist occurred weekly over 24 meetings for 6 months, biweekly between months 7 and 9, and then monthly between months 10 and 12. They discussed strategies for facilitating weight management and increasing physical activity (including self-monitoring, stimulus control, problem solving, social support, cognitive behaviour modification, recipe modification, eating away from home, and relapse prevention).Medical therapy was used if interventions did not produce adequate weight loss: orlistat could be added and sibutramine was also used until it was withdrawn from the US market. Medications for glycaemic control were added in the following order: metformin, a glucagon-like peptide-1 analog or dipeptidyl peptidase 4 inhibitor, sulfonylurea or pioglitazone and insulin. Low-density lipoprotein cholesterol control was achieved with HMG-CoA reductase inhibitors first, then ezetimibe, if necessary. Blood pressure medications were used in the following order: ACE inhibitor or angiotensin receptor II blocker, diuretic, beta blocker and additional agents. Triglyceride levels were controlled with fenofibrate or fish oil if they remained higher than 300 mg/dl. Smoking cessation was strongly recommended. ACE or ARB inhibitors were provided for all with microalbuminuria or macroalbuminuria. Aspirin was added, when not contraindicated, to be consistent with evolving recommendations from the ACA. Further details: 1. Exercise: Advice on physical exercise (Patients were advised to progressively increase moderate-intensity physical activity to 325 minutes per week with targets of 1200, 1500, or 1800 kcal per day, depending on body weight with the aim of losing 1-2 pounds per week.). 2. Medical - Dietician: Not applicable / Not stated / Unclear 3. Medical - VLCD: Low-calorie diet (Patients had low-calorie diet with 2 meal replacements for 2 weeks before the

Study	The Diabetes Surgery Study: Ikramuddin 2013[13,14]
	operation). 4. Surgery: Gastric bypass Comments: Patients in the surgery group delayed the lifestyle intervention protocol until after they could tolerate solid foods (around 3-4 months after surgery), did not have calorie ceilings during the period of rapid weight loss and received additional instructions regarding food volume and adequate protein intake; also, medications for glycaemic controls, dyslipidemia and blood pressure were reduced or discontinued immediately after surgery because of fluid and caloric decreases soon after surgery but were restarted as necessary to accomplish treatment goals. Patients were not required to pay for any component of the intervention but at one site (NY), patients were required by law to make standard copayments for medications. (n=60) Intervention 2: Diet and exercise - Diet and exercise general. Patients continued on lifestyle and medical management (see below). Duration 12 months. Concurrent medication/care: All patients were on lifestyle modification and medical management before being randomised with the aim to produce maximum achievable weight loss and medications to control glycaemia and cardiovascular disease risk factors. Lifestyle modification was modelled after the Diabetes Prevention Program and the Look AHEAD protocols: patients weight themselves and recorded eating and exercise behaviours on a daily basis. They were advised to progressively increase moderate-intensity physical activity to 325 minutes per week with targets of 1200, 1500, or 1800 kcal per day, depending on body weight with the aim of losing 1-2 pounds per week. Patients had portion-controlled diets with meal replacement, structured menus, and used calorie counting. Counselling sessions with a trained interventionist occurred weekly over 24 meetings for 6 months, biweekly between months 7 and 9, and then monthly between months 10 and 12. They discussed strategies for facilitating weight management and increasing physical activity (including self-monitoring, stimulus control, problem solving, social support, cognitive behaviour modification, recipe modification, eating away from home, and relapse prevention).Medical therapy was used if interventions did not produce adequate weight loss: orlistat could be added and sibutramine was also used until it was withdrawn from the US market. Medications for glycaemic control were added in the following order: metformin, a glucagon-like peptide-1 analog or dipeptidyl peptidase 4 inhibitor, sulfonylurea or pioglitazone and insulin. Low-density lipoprotein cholesterol control was achieved with HMG-CoA reductase inhibitors first, then ezetimibe, if necessary. Blood pressure medications were used in the following order: ACE inhibitor or angiotensin receptor II blocker, diuretic, beta blocker and additional agents. Triglyceride levels were controlled with fenofibrate or fish oil if they remained higher than 300 mg/dl. Smoking cessation was strongly recommended. ACE or ARB inhibitors were provided for all with microalbuminuria or macroalbuminuria. Aspirin was added, when not contraindicated, to be consistent with evolving recommendations from the ACA. Further details: 1. Exercise: 2. Medical - Dietician: 3. Medical - VLCD: 4. Surgery: Comments: Patients were not required to pay for any component of the intervention but at one site (NY), patients were required by law to make standard copayments for medications.

Study	The Diabetes Surgery Study: Ikramuddin 2013[13,14]
Funding	Academic or government funding (Grants from National Centre for Advancing Translational Sciences, National Institutes of Health)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GASTRIC BYPASS AND LIFESTYLE&MEDICAL MANAGEMENT versus LIFESTYLE&MEDICAL MANAGEMENT

Protocol outcome 1: % Weight change (BMI) at 1 year
- Actual outcome: % weight change at 12 months; Group 1: mean -26.1 % (SD 8.7); n=56, Group 2: mean -7.9 % (SD 7.8); n=59; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: Weight in BMI at 12 months; Group 1: mean 25.8 kg/m2 (SD 3.5); n=56, Group 2: mean 31.6 kg/m2 (SD 3.7); n=59; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Improvement (glycaemic control, i.e. HBA1C) at 1 year
- Actual outcome: HBA1c < 7% at 12 months; Group 1: 43/57, Group 2: 18/57; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: HBA1c < 6% at 12 months; Group 1: 25/57, Group 2: 5/57; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome: Improvement in glycaemic control (continuous) at 12 months; Group 1: mean 6.3 % HbA1C (SD 0.9); n=57, Group 2: mean 7.8 % HbA1C (SD 1.5); n=57; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Mortality at 1 year
- Actual outcome: Mortality at 12 months; Group 1: 0/57, Group 2: 0/57; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 4: Weight change (kg) at 1 year
- Actual outcome: Weight in kg at 12 months; Group 1: mean 73 kg (SD 13.6); n=57, Group 2: mean 90.1 kg (SD 17); n=57; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 5: Remission of T2D at 1 year
- Actual outcome: Composite end point of HbA1c <7%, LDL cholesterol <100 ml/dL, and systolic blood pressure < 130 mm Hg at 12 months; Group 1: 28/56, Group 2: 11/59; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 6: Medication reduction at 1 year
- Actual outcome: Medications for control of glycaemia, dyslipidemia and blood pressure at 12 months; Group 1: mean 1.7 Number of medications used (SD 1.8); n=57, Group 2: mean 4.8 Number of medications used (SD 2.1); n=57; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at 1 year

G.3 Follow-up care packages after bariatric surgery

Table 29: Kalarchian 2012

Study	Kalarchian 2012[15]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=36)
Countries and setting	Conducted in USA; Setting: Academic medical centre in US
Line of therapy	2nd line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Contacted patients bariatric surgeon to provide historical information
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients > 21years old were eligible to participate if they had undergone bariatric surgery 3 or more years before the study enrollment and had lost less than 50% excess weight from before surgery to study enrollment.
Exclusion criteria	BMI less than 30 kg/m2; participation in a weight management program in the 6 months before study; psychiatric problems sufficiently severe to require immediate treatment; pregnancy or lactation in the previous 6 months or planning to become pregnant; taking a medication known to affect body weight in the previous 6 months; mental retardation or psychosis; participation in a conflicting research protocol in the previous 6 months
Recruitment/selection of patients	Recruited using flyers distributed to local bariatric surgeons and newspaper advertisements. Those who appeared to be interested and eligible were invited to attend an informational meeting
Age, gender and ethnicity	Age - Mean (SD): Intervention: 51.0 (7.6); Comparison: 53.9 (6.6). Gender (M:F): Male/Female: 11/89%. Ethnicity: Reported 75% white
Further population details	1. Ethnicity: 2. T2D: 3. Type of surgery:
Extra comments	None. Written clearance obtained from primary care physician
Indirectness of population	No indirectness: None
Interventions	(n=18) Intervention 1: Care package - Nutritional monitoring and avoiding weight regain and specialist educational support. Behavioural intervention: objective to decrease caloric intake through diet and increase energy expenditure through a physical activity. Participants were given a calorie range of 1200-1400 calories daily and instructed to

Study	Kalarchian 2012[15]
	maintain a balanced diet using the Food Guide Pyramid and postoperative dietary guidelines. The patients were prescribed an exercise programme according to their choice of activity. Strategies for increasing lifestyle activity and increasing involvement in activities of daily living were emphasised. The participants were assisted in self-monitoring and setting small, incremental goals for lifestyle change. Key adaptions included information about how surgery facilitates weight loss and their role of long-term self-management; addressing specific postoperative eating behaviours associated with poor weight loss (e.g. binge eating); using the group to enhance social support for behaviour change. Intervention entailed a combination of face to face group meetings and telephone coaching to minimise the intensity of counselling. The intervention occurred in 12 weekly group meetings followed by 5 bi-weekly telephone coaching sessions, extending for approximately 6 months. The group meeting lasted 1 hour and consisted of a weigh-in , review of the self-monitoring records and homework, and a didactic presentation. The telephone coaching was shorter (15-20 minutes). The interventionists were master's level therapists who had received training in obesity treatment and bariatric surgery. . Duration 12 months (6 months intervention and 6 months follow up). Concurrent medication/care: None Comments: None (n=18) Intervention 2: Usual care - Nutritional monitoring only. Wait list control. Duration 12 months. Concurrent medication/care: None Comments: None
Funding	Academic or government funding (Supported by 2007 Research Grant Award from the American Society for Metabolic and Bariatric Surgery)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NUTRITIONAL MONITORING AND AVOIDING WEIGHT REGAIN AND SPECIALIST EDUCATIONAL SUPPORT versus NUTRITIONAL MONITORING ONLY Protocol outcome 1: Percentage weight loss at Latest follow-up - Actual outcome for Adults (18 years or older): Percentage excess weight loss at 12 months; Group 1: mean 5.8 Percentages (SD 3.5); n=13, Group 2: mean 0.9 Percentages (SD 3.2); n=16; Percentages 0-100 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults (18 years or older): Mean weight change at 12 months; Group 1: mean -3.6 Kg (SD 9.6); n=13, Group 2: mean -0.6 Kg (SD 6.7); n=16; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Development of at least one micronutrient deficiency at Latest follow-up; Health-related quality of life at Latest follow-up; Re-operation rate at Latest follow-up; Mortality at Latest follow-up; Reduction in medication use at Latest follow-up; Psychological well-being at Latest follow-up

Table 30: Papalazarou 2010

Study	**Papalazarou 2010[28]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in Greece; Setting: Patients recruited from 'Evagelismos' general hospital (where they had vertical banded gastroplasty)
Line of therapy	Not applicable
Duration of study	Intervention time: 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Obesity measured with level of BMI (all patients were severely obese: > 40 kg/m2)
Stratum	Adults (18 years or older)
Subgroup analysis within study	Not applicable
Inclusion criteria	Severely obese female patients who underwent vertical banded gastroplasty between Jan 2005 and Jan 2006; BMI > 40 kg/m2, history of multiple, failed previous attempts for weight loss and absence of psychiatric illness (determined by psychiatric profiles conducted by a hospital psychiatrist)
Exclusion criteria	Not specified
Recruitment/selection of patients	consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Intervention: 32.7 (7.7) vs Usual care: 33.4 (6.2) (overall range: 21 to 45 years). Gender (M:F): All female. Ethnicity: Not explicitly reported but presumed mostly Greek origin
Further population details	1. Ethnicity: Not applicable / Not stated / Unclear 2. T2D: Not applicable / Not stated / Unclear 3. Type of surgery: Banding (vertical banded gastroplasty).
Indirectness of population	Serious indirectness: Patients had previously had vertical banded gastroplasty which is currently not performed in the UK
Interventions	(n=15) Intervention 1: Usual care - Nutritional monitoring only. An appropriately trained dietician saw patients and instructed them to take liquid very low calorie diet (665 kcal, 66g protein/day, 100% of recommended dietary allowance for vitamins and minerals) for 4 weeks after surgery. Soft and solid foods were then gradually introduced into the diet with return to conventional dietary habits usually obtained by 6 months. Patients seen regularly for the next 3 years to give general information on adopting healthier eating and physical habits in the following (total 30 sessions over 3 years):- weekly for the first 3 months postoperatively- fortnightly for the following 3 months- monthly for the last 6

	months of the first postoperative year- every 3 months in the 2nd postoperative year- every 6 months in the 3rd postoperative year. Duration 3 years. Concurrent medication/care: none Comments: Patients received advice on exercise as well as diet; unclear how long the 30 sessions were; unclear how many patients in each arm (assumed to be 1:1 allocation ratio) (n=15) Intervention 2: Care package - Nutritional monitoring and avoiding weight regain and specialist educational support. In addition to care received by usual care group, patients received a lifestyle intervention to help patients overcome barriers and regulate their body weight, adopting healthier eating habits and being less sedentary, using a patient-centred collaborative approach and behaviour modification techniques. As part of this intervention, patients attended additional 40-minute individualised sessions with the dietician during their 30 visits over the 3 years which consisted of 3 parts:1. nutritional education (information provided about nutritional value of food and benefits of a balanced diet, dietary guidelines for Greeks was the goal), 2. dietary intake, 3. physical activity (the American College of Sports Medicine guidelines for physical activity were the goal - patients were encouraged to adopt a more physically active lifestyle with around 150 minutes of moderate intensity exercise per week). Behavioural techniques used included self-monitoring, self-evaluation, goal setting, stimulus control, reinforcement, and relapse control. Duration 3 years. Concurrent medication/care: none Comments: Package did not include social support; Unclear how many patients in each arm (assumed to be 1:1 allocation ratio)
Funding	Funding not stated (however, authors declare no conflicts of interest)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NUTRITIONAL MONITORING AND AVOIDING WEIGHT REGAIN AND SPECIALIST EDUCATIONAL SUPPORT versus NUTRITIONAL MONITORING ONLY Protocol outcome 1: Percentage weight loss at Latest follow-up - Actual outcome for Adults (18 years or older): % excess weight loss at 36 months; Group 1: mean 74.8 % (SD 14.7); n=15, Group 2: mean 49.1 % (SD 14.7); n=15; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults (18 years or older): Weight (kg) at 36 months; Group 1: mean 84.2 kg (SD 12.78); n=15, Group 2: mean 102.5 kg (SD 13.55); n=15; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Development of at least one micronutrient deficiency at Latest follow-up; Health-related quality of life at Latest follow-up; Re-operation rate at Latest follow-up; Mortality at Latest follow-up; Reduction in medication use at Latest follow-up; Psychological well-being at Latest follow-up

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