Very-low calorie diets and morbidity: A systematic review of longer-term evidence

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Abstract:

Evidence from the literature supports the safe use of very-low-calorie diets for up to 3-months in supervised conditions for patients who fail to meet a target weight loss using a standard low-fat, reduced-calorie approach. There is, however, a need for longer-term outcomes on obesity and associated morbidities following a very-low-calorie diet.

This systematic review aims to investigate longer term outcomes from studies using very-low-calorie diets, with a minimum duration of 12-months, published between January 2000 and December 2010. Studies conducted in both children and adults, with mean/median body mass index of ≥28 kg/m^2 were included. PubMed, MEDLINE, Web of Science and Science Direct were searched. Reference lists of studies and reviews were manually searched. Weight loss or prevention of weight gain and morbidities were the main outcomes assessed.

A total of 32 out of 894 articles met the inclusion criteria. The duration of the studies ranged from 12 months to 5 years. Periods of VLCD ranged from 25 days to 9 months. Several studies incorporated aspects of behaviour therapy, exercise, low fat diets, low carbohydrate diet or medication. Current evidence demonstrates significant weight loss and improvements in blood pressure, waist circumference and lipid profile in the longer-term following a very-low-calorie diet. Interpretation of the results, however, was restricted and conclusions with which to guide best practice are limited due to heterogeneity between the studies.

This review clearly identifies the need for more evidence and standardised studies to assess the longer-term benefits from weight loss achieved using very-low-calorie diets.

Abbreviations: VLCD -very low calorie diet; NICE - National Institute for Health and Clinical Excellence; NoF - National Obesity Forum; BMI- body mass index; LDL- low density lipoprotein; HDL - high density lipoprotein; LCD - low calorie diet; HBA_{1C} - glycated haemoglobin; SHBG - sex hormone binding globulin; OC – osteocalcin; CTX - C terminal telopeptide of type I collagen; PTH- parathyroid hormone; BMC - bone mineral content; BMD - bone mineral density; DXA - dual-emission X-ray absorptiometry; LAGB - laparascopic gastric banding; OSAS - obstructive sleep apnoea syndrome; CPAP- continuous positive airway pressure; ODI_4 oxygen desaturation index; OSA - obstructive sleep apnoea; GSI - general symptom index; ISS- index of subjective sleepiness; FVC- flow vital capacity; FEV1- forced expiratory volume in 1 second; PEF - peak expiratory flow; BED- binge eating disorder; CBT - cognitive behavioural therapy; SD- standard deviation; Sub-BED - sub threshold binge eating disorder; BS - bariatric surgery; SWM - successful weight maintainers; USWM - unsuccessful weight maintainers; MI - myocardial infarctions

Introduction:

The use of very low calorie diets (VLCDs) has been severely criticised in the past. Current VLCDs, however, should not be confused with those from the 1970's which resulted in a number of deaths due to vitamin and mineral deficiencies and poor quality or inadequate amounts of protein (1,2). Modern VLCDs do not induce such deficiencies.

A very low calorie diet is defined as a diet of <800 kcal/day (3). A variety of synthetic and food based formula diets are available, which give energy intakes of 300-400 kcal/day designed to achieve weight loss while minimising the loss of lean body mass

by providing high levels of protein supplemented with vitamins, minerals, electrolytes and fatty acids (4).

There is sufficient evidence in the literature to ensure the safe use of VLCDs in the short-term (5,6). Based on this evidence, institutions such as the National Institute for Health and Clinical Excellence (NICE) and the National Obesity Forum (NoF) support the use of this approach for up to 3 months in supervised conditions for patients who fail to meet a target weight loss with the standard low fat, reduced calorie approach. Despite this, there are still concerns about weight regain following these diets as well as detrimental health effects due to the rapid weight loss they induce. There is a need to review the evidence of longer-term outcomes with the use of VLCDs on obesity and associated morbidity. We aim to carry out a systematic review of the literature for studies using a VLCD, with a minimum follow up of 12 months, published between January 2000 and December 2010.

Methods:

The protocol used for this systematic review follows the methods recommended by the Cochrane Collaboration (7).

Inclusion Criteria

This review is intended to assess the current literature in this field and update National Health Service R&D Health Technology Assessment systematic review of diet and lifestyle on weight loss and cardiovascular risk published by Avenell *et al* (8). Studies from January 2000 to December 2010 were evaluated. Interventions where the participants had a mean or median BMI of ≥28 kg/m^2 were included. Interventions evaluated in this review had to be of at least 12 months duration, including the period of active intervention and follow up. Studies in children and adults were included. Randomised controlled trials, non-randomised controlled trials and restrospective

studies were evaluated. The variation of time on diet using active intervention, follow up and different follow up treatments was recorded and accounted for where possible.

Types of Intervention

The focus of this review was to examine the effect of VLCDs on obesity and associated comorbidities. The types of dietary interventions evaluated were VLCDs also known as very low energy diets defined as a dietary intake of 800kcal/day or less. Case studies, however, were omitted.

Outcome Measures

Weight loss or prevention of weight gain were the main outcomes assessed from the studies included in the review. With regard to morbidity, the following outcomes were also included:

- Cardiovascular risk (Serum lipids, including total cholesterol, low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), and triacylglycerols, systolic and diastolic blood pressure, glycaemic control.)
- Liver and kidney function
- Fertility
- Bone health
- Respiratory disorders
- Eating disorders

Information about dropouts and adverse events were also gathered.

Outcome measures were considered in relation to the time of active intervention as well as the time and nature of follow up period as these varied widely between

studies (i.e 25 days -9 months of active intervention and 12 months-5 years for follow up).

Search Strategy for the Identification of Included Studies

This systematic review was restricted to studies where the full study report was available. A wide search strategy was applied to identify as many studies evaluating dietary interventions using VLCDs as possible and which were relevant to the management of obesity and morbidity. Four electronic databases were searched including PubMed, MEDLINE, Web of Science and Science Direct. The search strategy incorporated very low calorie/energy diet related terms and text terms, specific to each database. Reference lists of included studies and reviews were searched and authors contacted for further details of their trials.

Quality Assessment of Studies

Full copies of studies were assessed by 3 researchers for methodological quality. The researchers were not blinded to author, journal or institution. Differences of opinion were resolved by discussion. Trial quality and risk of bias was assessed using items known to be associated with the magnitude of results using the criteria list from Jadad et al (9) (procedure of allocation, withdrawals/drop outs, blinding of patients and outcome assessment). The protocol used by Jadad et al (9) was slightly modified where in the "withdrawals and dropouts" section, one point was given if numbers of withdrawals were mentioned and an extra point was given if the reasons for withdrawals were also described. Where no dropouts occurred, the study was attributed two points. However, for retrospective or ancillary studies, where essentially a completers analysis was carried out, the studies were attributed no points.

Identified Studies

A total of 32 out of 894 articles met the inclusion criteria and were included in the systematic review. Reasons for the exclusion of these studies is summarised in Figure 1.

Results:

Study Characteristics

There was a large amount of heterogeneity in study design for the papers meeting inclusion criteria. The studies included ranged from 12 months to 5 years in duration. Periods of VLCD ranged from 25 days to 9 months. Several studies incorporated aspects of behaviour therapy, exercise programmes, low fat diets, low carbohydrate diet, medication (Orlistat and Sibutramine) or corset treatment (Soft corsets were fitted to cover the torso from the xiphoid to the pubic region. The corset was to be used 12 – 16 hours per day, seven days per week for nine months) (Table 1).

All of the studies were designed to reduce or prevent weight gain and also examined morbidity. Results for all the studies are summarised in Table 1.

Quality Assessment

Table 2 displays the quality assessment of reported studies, separated by comorbidity and ranked from highest to lowest. The studies where drugs were used for weight maintenance generally scored the highest (≥4) (17,18,21,29,30) with the exception of those that were not randomised controlled trials (13,28).

Weight change

Thirteen studies reported significant weight change at VLCD end (4,11,14,15,19,20,22,27,29,30,32,35,39). Of these, 12 studies demonstrated significant reductions in weight at VLCD end and one study in the group combining CBT only (39). At study end, all of which had varying periods of follow up from 1-5 years, 15 reported significant changes from baseline in the VLCD groups (4,10,13,14,15,19,20,22,23,27,28,31,33,35,36). There was no clear pattern observed for period of follow up or for the means of weight maintenance method utilised in that period (exercise therapy, counselling, orlistat, intermittent/on-demand VLCD,etc). However, exercise (10,27) behaviour therapy (24,36), medication (17,18,21) and longer reintroduction phase post VLCD (25) appear to aid maintain the weight loss achieved by VLCDs (Table 2).

Cardiovascular risk

There were 24 papers identified that reported the effects of weight loss at least partially achieved with a VLCD on cardiovascular risk. We reviewed data from each study to determine if cardiovascular parameters at baseline changed significantly following dietary intervention with VLCD, (VLCD end) or at the final follow up period (study end)

Blood Pressure

Seventeen papers (4, 10-25) detailed blood pressure in participants at either VLCD end or study end. After the intervention there were a number of different approaches to follow up although most generally included a support or review process.

Overall systolic pressure trends were reported in 13 of the 17 studies following the VLCD end (4,10,11,13,14,16-23). Of the changes at VLCD end, 6 showed significant reductions from baseline (4,11,14,16,19,23), four of which sustained significant

systolic blood pressure reductions at study end (4,11,19,23). Three more studies reported a significant reduction in systolic blood pressure at study end only (13,15,25).

Study design varied substantially in all who showed significant systolic pressure reductions and thus it is difficult to determine which particular variables have the most significant impact on blood pressure.

Diastolic blood pressure information was also available from these 17 studies. At VLCD end, 11 of the studies showed diastolic reductions which were more pronounced than at study end (4,10,11,14,16,18-21,23). Only one study (19) showed a significant change from baseline which improved further between VLCD end and study end. At VLCD end, similar trends to those for systolic pressure were observed for diastolic pressure in 7 of the 17 studies (4,11,13,15,19,23,25) which demonstrated a significant improvement at study endpoint.

Overall, time of VLCD duration, time of follow up and nature of follow up (hypocaloric diet, exercise, medication, counselling etc) did not predict blood pressure outcomes in the long term.

Waist Circumference

Eighteen papers reported waist circumference data (10-14,17-25,27-30). Of the 13 papers that reported waist circumference data at VLCD end (10,11,13,18-23, 27-30), 7 studies (11,13,19,20,23,27,29) showed significant reductions at VLCD end, five of which maintained significant reductions from baseline at study end (19,20,23,27,29). (Table 3). Nine studies in total showed a significant reduction in waist circumference at study end (13,19,20,23,25,27-30).

Similarly to blood pressure, time of VLCD duration, time of follow up and nature of follow up did not predict waist circumference outcomes in the long term.

Lipid Profile

Twenty-one studies included cholesterol as primary or secondary outcomes following weight loss and intervention (4,10-14,16-25,28-32). Results for the different studies are presented in Table 4.

Triacylglycerols

Nineteen studies examined for changes in triacylglycerols through the study periods (10-14,17-25,28-32). Of all 19 studies, 4 reported significant improvements in triacylglycerols at the VLCD end (11,19,20,29) although in one study this involved combined data from VLCD and LCD interventions (11). At study end, 9 studies, including the four which had significant changes at VLCD end, showed significant reductions in triacylglycerols from baseline (11,13,19,20,25,28,29,31,32).

Total Cholesterol

Twelve studies reported changes in total cholesterol at VLCD end (4,10,11,14,18-23,29,30). Three studies (4,11,19) reported significant improvements in cholesterol at VLCD end, two of which presented a sustained significant improvement at study end (4,11). Of 15 studies, only five studies reported a significant reduction in total cholesterol at study end in at least one arm (4,11,12,14,29).

HDL cholesterol

HDL changes were examined in all 20 studies (10-14,16-25,28-32). Fourteen of these studies reported VLCD end data, 2 of which interestingly reported a significant reduction in HDL (11,19). Nine of these studies, however, showed significantly increased HDL levels in the VLCD arm at study end (11,13,14,19,20,25,28,31,32).

Only one study (29), showed an overall significant reduction in HDL. In contrast, although Paisey et al (12), showed an increase in HDL, this was only in the group who had to undertake regular exercise and standard dietary intervention and not the VLCD arm.

LDL cholesterol

14 studies reported changes in LDL (10,12,14,16-18,20-23,29-32). Of the 9 studies reporting data at VLCD end (10,14,16,18,20-23,29), one showed a significant reduction in LDL (20). From the information on the 14 studies reported at follow up, significant LDL reduction was observed in two studies (14,29) .

As observed for blood pressure and waist circumference, time of VLCD duration, time of follow up and nature of follow up did not predict lipid profile outcomes in the long term.

Insulin and Glucose Control

Fewer studies examined the effects of VLCD on diabetic control and insulin resistance. Only 4 studies reported a significant improvement in fasting glucose at VLCD end (11,16,20,23). Fasting plasma glucose data were reported at study end in 16 studies (10-16,18,19,21,23-25,28,31,32), 4 of which showed a significant reduction in fasting glucose at study end (13,20,23,25).

Of the 9 studies (10,11,14-16,21,24,31) that reported insulin levels at study end, significant improvements were observed in 3 of them (11,14,15). Five of the 9 studies (10,14,16,18,21) reported VLCD end data where no significant change was reported. HBA_{1c} also represented by fructosamine was reported in 7 studies (4,12,19,,21,23,29,33). Three studies showed significant improvements in the VLCD groups at study end (4,23,29). Interestingly Jazet et al (19), reported a significant

improvement in HBA_{1c} in the 6 patients who regained more than 5kg weight by study end (19).

We identified 4 studies where the number of patients taking daily insulin or actual insulin doses were reported (4,12,19,33). In the 3 studies that reported insulin doses at study end, reduced daily doses of insulin were noted although statistical significance was not reported (4,19,33). Only one study reported an increase in insulin users in the VLCD arm at study end (4). A large reduction in the actual number of insulin users at study end was reported in one other study although, again, statistical significance was not reported (19).

Again, time of VLCD duration, time of follow up and nature of follow up did not predict glycaemic outcomes in the long term.

Liver and Kidney Function

Of the 32 papers identified, only 2 commented about liver and kidney function (15,23). The paper by Melin et al (15), stated that at 2 years follow up, there were no significant changes in liver transaminases and plasma urate but data were not provided. Rolland et al (23), on the other hand, report significant improvements in alanine aminotransferase (U/L) (30.0 ± 17.8 vs 23.2 ± 8.9; ($p < 0.05$); alkaline phosphatase (U/L) (81.6 ± 19.6 vs 78.0 ± 22.1;($p < 0.05$); γ-Glutamyl transferase (U/L) (33.8 ± 33.7 vs 24.1 ± 17.7; ($p < 0.05$) and estimated glomerular filtration rate (mL/min) (77.1 ± 11.6 vs 79.7 ± 11.4; ($p < 0.05$) from post-screening to 9 months.

Fertility

One study examined the impact of VLCD induced weight loss on fertility and sexual function (28). Sex hormone-binding globulin (SHBG) rose significantly from 27.6 ±11.9 to 48.1 ± 23.5 nmol/l at VLCD end, ($p < 0.0001$) and remained significant

despite declining by study end (32.6 ± 12.9 nmol/l, $p < 0.001$). Free testosterone levels also increased significantly by VLCD end and remained elevated at 212 ± 84 pmol/l at 1 year ($p = 0.002$), compared to baseline (185 ± 66 pmol/l). The number of men presenting with biochemical hypoandrogenism (total testosterone < 11nmol/l) decreased significantly during the VLCD ($p < 0.001$) and at the 1 year follow up ($p = 0.002$).

Bone health

Three papers examined changes in bone mass following VLCD intervention (27,34,35). Study design is described in Table 1.

Hinton et al (35) examined the effects of both weight loss and weight maintenance on serum bone turnover by measuring osteocalcin (OC) and C terminal telopeptide of type I collagen (CTX) as markers of bone formation and resorption respectively.

Both OC and CTX showed a significant increase at VLCD end, but these were not significantly correlated suggesting an imbalance in bone resorption and formation during weight loss. At study end, OC and CTX became significantly correlated, suggesting bone formation and resorption were balanced during weight maintenance. Changes in body weight were significantly and negatively correlated with changes in CTX only at VLCD end and study end.

Fogelholm et al (27), similarly examined changes in bone mineral density (BMD) or bone mineral content (BMC), in 3 groups of post-menopausal women (Table 1). At VLCD end, total BMC remained unchanged but there was a significant reduction noted in lumbar trochanteric and radial BMD ($p < 0.05$). A reduction in total body BMC and significantly lower lumbar and femoral neck BMD were reported at study

end, with recovery of distal radius BMD. Group exercise allocation had no statistically different effect on BMD at the various sites.

In the study by Dixon et al (34), total body bone mineral content had decreased significantly in the LAGB (-0.087 ± 0.12; p = 0.002) as well as the intensive dietary weight loss group (-0.061 ± 0.9; p = 0.002) at 24 months. The changes were not significant between the two groups.

Respiratory Disorders

Sleep apnoea

Two studies investigated the effect of VLCD on the alleviation of symptoms associated with Obstructive Sleep Apnoea Syndrome (OSAS) (24,36) and one examined the effects of weight reduction in obese patients with asthma (37).

Kajaste et al (36) did not provide VLCD end data, although other time periods of 6, 12, 24 months and study end were reported. No significant differences were seen for weight loss at any point of the study. Changes in sleep apnoea were assessed by measuring the Oxygen Desaturation Index (ODI_4), the average number of oxygen desaturation events per hour of sleep exceeding 4 % from baseline. Improvements in ODI_4 from baseline were significant at 24 months. Significant correlations were seen between ODI_4 improvements and weight change at 6 and 24 months ($p < 0.001$). At the three year follow up, 5 patients reported no OSAS symptoms.

Tuomilehto et al (24) assessed changes in sleep apnoea by measuring the Apnea-Hypopnea Index (AHI). At VLCD end, the mean total AHI was statistically improved in the VLCD versus control group (p = 0.036). Based on the AHI values, 22 of 36 patients (61 %) in the intervention group, and in 12 of 38 patients (32 %) in the control group, were objectively cured (p = 0.019) at VLCD end. This change was

maintained at 1-year follow-up, where intervention group mean total AHI was 6.0 events/hour and control group 9.6 events/hour ($p = 0.043$). Changes in AHI during the 12-month follow-up were strongly associated with changes in weight and waist circumference which was independent of baseline BMI. Moreover significant improvements were observed in the intervention group as compared to the control group after 1 year for mean arterial oxygen saturation.

Asthma

Stenius-Aarniala et al (37), was the only study which investigated the effects of VLCD on obese patients with asthma. Details of the study design are given in Table 1.

Data for flow vital capacity (FVC) and forced expiratory volume in one second (FEV1) were collected. FEV_1 (% of predicted) improved significantly more in the treatment group at VLCD end, and was maintained even after a year ($p = 0.02$).There was also a significantly greater median reduction of dyspnoea in the treatment group as compared to the control group (13mm vs 1mm on VAS, $p < 0.05$). The daily use of rescue sympathomimetics decreased by significantly more in the treatment group (1.2 doses vs 0.1 doses; $p < 0.05$).

Eating Disorders

Binge Eating Disorder

Two studies reported the effect of VLCDs on binge eating disorder (BED) (38,39).

In de Zwaan et al (39), patients with BED participated in a 6 month intervention. The change in binge eating was not different between the BED only group as compared to the BED+CBT group at any time point. However, during the fasting period of VLCD, an improvement in absence of binge eating was observed in both groups (80.6 % were binge free at BED+CBT versus 80.4 % at BED-CBT, $p = 0.98$). At study

end, 47 participants were binge free and 56.3 % did not meet the criteria for BED, again with no significant difference between the groups.

A study by Raymond et al (38), investigated the influence of several factors on the diagnostic criteria of obese individuals with and without BED, 1 year after following a VLCD programme. Details of the study are given in Table 1. At baseline, 63 participants were diagnosed with BED, 36 sub threshold BED (Sub-BED) and 29 no binge eating symptoms (no BED). Of the 63 individuals with BED 36 (57 %) no longer met the criteria at 12 months. Conversely at 12 months, 16 (13%) of the BED patients moved to a more severe category. 9 of the patients (25 %) with Sub-BED and 3 (10 %) with no BED at baseline also met full BED criteria at 12 month follow up. A significant association was found between BED diagnosis and weight gained at 12 month follow up ($p = 0.0087$).

Mental Health

Two studies looked at the effects of VLCDs on mental health. One study looked at depression (40) and the other study looked at the effect of mental disorders on the maintenance of weight loss (41).

Legenbauer et al (40), investigated the effect of eating and depressive disorders on weight loss after VLCD treatments and after surgical weight reduction treatment. A greater number of participants in the VLCD group met the criteria for diagnosis of depressive disorder at baseline, as compared with the BS patients. Although lifetime history of depression did not differ between groups, history of depressive disorder (both current and lifetime) had a significant negative predictive value on longer-term weight loss in the BS but not in the VLCD group at 4 years. Conversely in the BS group, a positive association was demonstrated in patients who had a history of eating disorder, with greater weight losses achieved at study end. The authors

suggest this observation may be due to a number of limitations in their study, including the lack of randomisation, high attrition rate and the lack of evaluation of recurrence or severity of depression on long term outcomes.

Legenbauer et al (41) assessed the effect of mental disorders on maintenance of weight loss among patients who had previously successfully participated in a VLCD programme. Of 166 participants, 28.3 % maintained a weight loss of at least 5 % of their initial weight for 3 years. In the 71.7% who did not achieve these losses significantly lower levels of cognitive control, higher levels of disinhibition and higher levels of perceived hunger were reported at 3 year follow up compared to those with >5% loss.

Dropouts and adverse events

Of the 32 studies included in this review, dropout information was available for 28 (4,10,12-25,27,29-32,34,36-41). In five of these studies, no dropouts were reported (13,19,29,31,37). Dropouts were more notable during the follow up as opposed to the VLCD period. In only 3 of the remaining studies did they specify higher dropout rates during the VLCD phase as compared to the follow up period (4,12,24). For the studies that reported dropouts during the VLCD phase, this appears to be in the first few weeks (24,32). The main reasons for discontinuing the VLCD appeared to be withdrawal from study before starting the diet, distaste of products, poor compliance, work schedules (4,12,24,25,32,36). One death was recorded in the first 5 weeks of VLCD but was not linked to the VLCD diet by the authors (24). In one study where 23.7% patients dropped out in the VLCD phase only 0.1%, however, were due to adverse effects (18).

Few reasons were given for dropout during the follow up phase, however, it was observed that younger patients and patients with higher baseline BMI were

significantly more likely to dropout (32,40) while those receiving behaviour therapy were more likely to be retained (39).

Of the 32 studies, 14 monitored for adverse events (4,12,15,16,18,19,24,25,31-33,36,40,41). Two of these studies stated that no adverse effects were reported (31,33). Of the remaining studies, 5 reported minor transient adverse events including nausea, vomiting, diarrhoea, biliary colic, elevation of liver function enzymes, dry skin, hair loss and dizziness (4,12,18,24,32).

Seven studies commented on major adverse events throughout the study period (12,19,24,25,36,40,41). In 3 studies, significant cardiac events were noted, none of which were reported as being directly related to the VLCD intervention. In summary one death was attributable to MI (36) and 1 from heart failure at 35 weeks post VLCD (42). Paisey et al reported one non-fatal MI in the VLCD group but also a non-fatal MI in the conventional diet group. In this study, however, one patient was able to have coronary bypass as a result of weight loss achieved through the VLCD. Finally, 1 case of acute coronary syndrome (19) was also reported in the VLCD arm. Seven other deaths were reported over 3 studies (24,40,41), although cause of death was not reported. In 2 of the studies which included type 2 diabetic patients, 1 other death occurred from primary biliary cirrhosis (12) and a case of prostate cancer was also diagnosed (19). In another study five patients were lost to follow up due to illness but type of illness was not specified (40). Overall, none of the major adverse effects noted in any of these studies were reported to be related to the VLCD itself.

Discussion:

This review suggests that long term weight loss and improvements in comorbidities ranging from cardiovascular risk to respiratory disorders can be advised in the longer-term using VLCDs. These improvements, however, are more likely associated with the weight loss induced, rather than the way in which the weight loss is achieved.

Previous studies have argued that despite greater initial reductions in weight loss with VLCD, weight regain is similar to a conventional diet (33). In accordance with the meta-analysis by Andeson et al (43), our review suggests that significant weight loss appears to be sustained in the longer-term following a VLCD for obese and overweight individuals with co-morbidities. Our systematic review also demonstrates that in the longer term, and in agreement with previously reported evidence, significant weight loss maintenance following a VLCD was demonstrated mainly in the groups who used conventional diet with exercise or adjuncts such as Orlistat (12,21).

Cardiovascular risk

Jazet et al (19) suggest that cardiovascular risk factors may be reduced, irrespective of weight loss or regain, in the long-term following a VLCD (19). In this review, however, significant reductions in systolic and diastolic blood pressure were generally associated with significant weight loss (4,12,15,19,23,25,26) as were improvements in waist circumference (19,20,23,25,26,28).

Lipid data appear to conflict and study design is significantly varied. Rolland et al (44), recently reported the effects of VLCDs on HDL where an improvement is often seen during weight maintenance, although not necessarily at VLCD end (45). This is in keeping with our findings on review of long-term evidence.

Although changes in plasma glucose were associated with significant weight reduction, insulin levels also improved regardless of significant weight losses, but again may be influenced by additional factors in study design. Few studies reported insulin requirements, but the results suggested reduced doses at study end.

Fertility

The limited long-term evidence we currently have for the use of VLCDs for improving fertility does not allow us to make any concrete conclusions. An interesting case study of an obese type 2 diabetic and hypertensive patient (46) who followed a VLCD to improve her likelihood of conceiving demonstrated the usefulness of VLCDs for pregnant control of glucose metabolism and blood pressure. In addition, short-term evidence does suggest that weight loss improves fertility in obese women with PCOS (47,48). This warrants the need for further investigation into the use of VLCDs for improving fertility in the longer term.

Bone Health

There has been concern expressed on the effect of weight loss on bone health (49-55). Very little is currently known of the long-term effects of weight loss on bone turnover. The limited evidence for VLCDs suggests imbalanced turnover during the VLCD phase, which resumes balance during weight maintenance. The imbalance observed during the VLCD phase may simply be due to the reduced energy intake (56), or may reflect a delay in osteoblast formation relative to osteoclastic resorption (35). The evidence also suggests that, in long-term weight loss, total body bone mineral content is significantly decreased regardless of whether exercise is included in the weight maintenance phase (27) or if the weight loss is achieved through surgical or dietary means (34). Nevertheless, more evidence is required to fully

understand the effects of VLCDs on bone health, perhaps by looking at bone mineral density directly as well as serum markers of bone formation and breakdown.

Respiratory disorders

The long-term use of VLCDs in the treatment of sleep apnoea demonstrates an improvement in the disease where greater weight loss is associated with greater improvements. These benefits may be further improved through the administration of behaviour therapy. More research is required to determine the optimal duration of VLCD or extent of weight loss which is required for the resolution of apnoeic events in obese individuals.

Eating disorders

VLCDs have been criticised in the past for increasing occurrence of BED. The long-term evidence remains unclear as one study demonstrated improvements in BED while the other study reported varied outcomes with some patients improving and others worsening. The role of CBT in the treatment of BED in conjunction with VLCD also remains unclear. One study by Svendsen et al (57), was not included in this review as long-term weight loss was not described in the paper. Nevertheless, they showed that 36 months after having followed a VLCD for 8 weeks, decreased binge eating was a predictor of sustained weight maintenance whilst weight loss was associated with decreases in binge eating. More research and evidence is required to elucidate the effects of VLCDs on BED.

Drop outs and adverse events

Recent reviews have concluded that, in the long term, VLCDs have no worse outcomes or adverse effects than standard diets (58). Previous studies have argued that VLCDs are associated with high cost and high attrition rates (59). Our findings suggest that dropouts are higher during the follow up phase and are rarely due to the

VLCD itself. Few studies suggest reasons for this and future studies may provide more information on reasons for high attrition in the follow up period.

In our review we found that few papers reported significant adverse events. The minor adverse events outlined were as expected when following a ketotic diet (60). Few deaths and major adverse events such as myocardial infarctions were reported. There appears, however, to be a lack of rigor in reporting of adverse events. Standardisation of adverse events reporting would be beneficial in providing further evidence of short and long term safety outcomes.

Strengths and Limitations

This review represents a detailed systematic review of an important area of controversy. Despite the complexity of this review, due to the high variation in study design of reviewed papers, we have attempted to separate effects attributable to VLCDs and other interventions. The heterogeneity in study design, particularly in terms of VLCD period, length of follow up and additional interventions, however, makes interpretation of results difficult and conclusions with which to guide best practice limited. A meta-analysis was planned but not able to be completed because of the inconsistent protocols. In addition, study quality was variable where 62.5% of the studies had a score of 2 or less. However, this may simply reflect the way in which the quality was assessed, as studies were scored for double blinding, which is not possible to achieve in behavioural studies. Perhaps a different method of assessment investigating sample size, conduct of study, detail of follow up analysis and interpretation would have been more suitable for the assessment of these papers.

There remains limited evidence on the effects of VLCDs on specific disease groups, which is partially due to the strict safety protocols which accompany this dietary

approach. Although evidence is mounting for use in some groups at higher cardiovascular risk, such as type 2 diabetics, there is little evidence of outcomes in other obesity related secondary diseases, such as non-alcoholic fatty liver disease. Future areas of research may provide more information on the outcomes of VLCDs dependent on age, gender, ethnicity and specific disease. There is need, however, for clarification of nutritional completeness of different VLCDs used in research. With the exception of energy intake, current VLCDs should either be nutritionally complete or include supplements to avoid any deficiencies. Of the 32 studies investigated, only four comment about the nutritional completeness (21,34,35,37), two comment on the use of a supplement (16,31). When we looked for manufacturer information about the different VLCDs used, these were all stated to be nutritionally complete. Only one paper made no comment of the VLCD that was used or its nutritional completeness (13).

The data presented in this review are often conflicting. There is a greater need for consistency in the design of study to allow accurate data extrapolation, and long-term studies to show sustained outcomes. Long term information on the use of intermittent or on demand VLCD is an area which has not been explored in many studies. The 'yo-yo' effect of rapid weight loss and regain associated with VLCD's has previously been criticised (61). However, several studies have demonstrated that intermittent VLCD use does not have any detrimental effect on metabolic parameters such as RMR, fasting insulin, Insulin resistance, leptin, inflammatory markers, lipids or BP (61-64).

The role of VLCD combined with varying intensity of exercise, and also behaviour modification through counselling, needs to be explored in more depth. This is consistent with the findings of a recent systematic review which stated that VLCDs were more efficacious if combined with behaviour modification and active follow up

(65). In the long-term, weight regain may occur, but the VLCD may instigate behaviours which facilitate longer-term changes for prevention of weight regain and overall health and well being. The use of behaviour therapy may be particularly useful for those individuals with a history of eating and mental health disorders who appear to have more difficulty in maintaining long-term weight loss.

Conclusion

Overall, this review suggests that long-term weight loss, improvements in cardiovascular risk, fertility, and respiratory disorders are achievable with the use of VLCDs, particularly in conjunction with behaviour therapy and exercise. There is currently little evidence to suggest any detriment to bone health, liver or kidney function, but data assessing these factors remain limited. We clearly identify that there is a need for further standardised research of VLCD use in healthy and at risk groups, the results of which could better inform best practice.

Conflicts of interest: Professor Iain Broom is the medical director for LighterLife Ltd.

Author contributions: YM, CR and EN carried out the literature search, data extraction and were involved in the interpretation of the results and writing of the manuscript. IB provided scientific expertise and was involved in the review and writing of the final manuscript.

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Figure 1: Summary of literature search

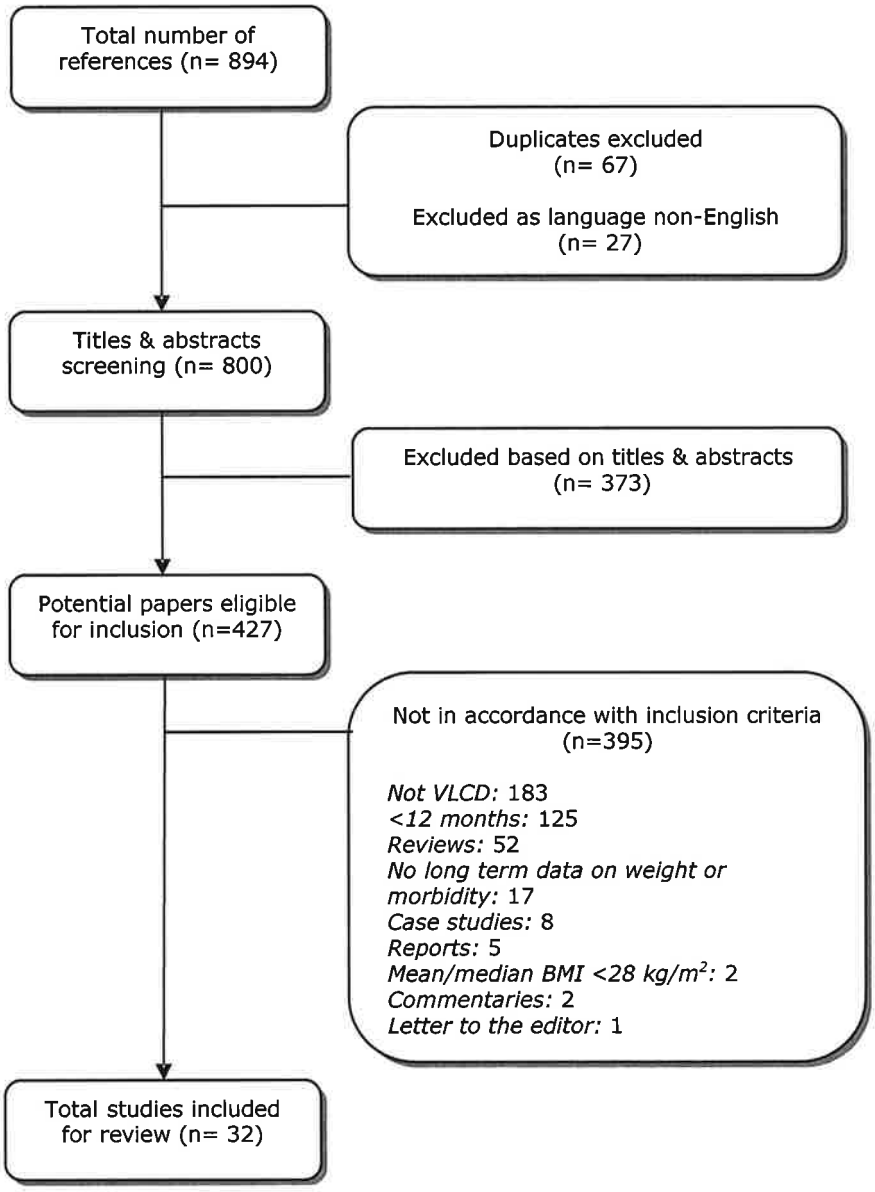

Table 1: Quality assessment of reported studies, separated by comorbidity and ranked from highest to lowest.

	Randomisation	Double blinded	Withdrawals and dropouts	Total
Cardiovascular risk				
Mathus-Vliegen et al (17)	2	2	2	6
Richelsen et al (21)	2	2	2	6
Erondu et al (18)	2	1	2	5
Madsen et al (29)	1	2	1	4
Madsen et al (30)	1	2	1	4
Delbridge et al (22)	1	0	2	3
Melin et al (15)	1	0	2	3
Rolland et al (23)	1	0	2	3
Simonen,et al (31)	1	0	2	3
Tuomilehto et al (24)	1	0	2	3
Dhindsa et al (4)	0	0	2	2
Fogelholm et al (10)	1	0	1	2
Fogelholm et al (27)	1	0	1	2
Gripeteg et al (25)	1	0	1	2
Jazet et al (19)	0	0	2	2
Kukkonen-Harjula et al (16)	1	0	1	2
Laaksonen et al (13)	0	0	2	2
Lantz et al (14)	1	0	1	2
Linna et al (20)	1	0	1	2
Niskanen et al (28)	1	1	0	2
Paisey et al (12)	0	0	2	2
Wikstrand et al (32)	1	0	1	2
Vasankari et al (11)	1	0	0	1
Willi et al (33)	0	0	0	0
Liver and Kidney				
Melin et al (15)		*See CVD section*		
Rolland et al (23)		*See CVD section*		
Fertility				
Niskanen et al (28)		*See CVD section*		
Bone health				
Dixon et al (34)	1	0	1	2
Fogelholm et al (27)		*See CVD section*		
Hinton et al (35)	1	0	0	1
Respiratory disorders				
Stenius- Aarnalia et al (37)	2	0	2	4
Kajaste et al (36)	1	0	2	3
Tuomilehto et al (24)		*See CVD section*		
Eating disorders				
de Zwaan et al (39)	1	0	1	2
Legenbauer et al (40)	0	0	2	2
Legenbauer et al (41)	0	0	2	2
Raymond et al (38)	1	0	1	2

Table 2: Summary of studies included in the review.

Author	N (males)	Study	Inclusion Criteria	Duration of VLCD	Duration of follow up	Weight (kg) at baseline	Weight (kg)at the end of the VLCD	Weight (kg)at the end of the follow up
Cardiovascular risk								
Delbridge et al (22)	141 (70)	Randomised parallel trial where patients underwent 3 months VLCD. Those who achieved ≥10% were then randomised to either a high carbohydrate (HC) or a high protein (HP) diet for 12 months.	Men and women; 18-75 years old; BMI ≥ 27 with co-morbidities or ≥ 30 kg/m^2; no history or presence of significant disease, endocrine disorder, psychiatric illness, and alcohol or drug abuse; not pregnant or lactating.	3 months	12 months	HC: 109.4 (SE 2.6) HP: 114.0 (SE 3.0)	HC: Δ -17.6 (SE 0.8) [b] HP: Δ -17.4 (SE 0.7) [b]	HC: Δ -13.8 (SE 1.3) [b] HP: Δ – 14.3 (SE 1.1) [b]
Dhindsa et al (4)	40 (22)	Clinical trial where patients underwent 8 weeks of VLCD with follow up until 1 year. During follow up participants followed a standard LCD and received bi-monthly exercise advice.	Obese men and women with hyperglycaemic symptoms and poorly controlled T2DM..	8 weeks	1 year	119 (19)	107 (18)[b]	109 (18) [b]
Erondu et al (18)	502 (69)	Multicentre, double blind, randomised, placebo controlled clinical trial where patients were given VLCD for 6 weeks. Patients who lost ≥6% body weight were randomised to 52 weeks MK-0557 or placebo with hypocaloric diet.	Non diabetic men and women; 18-65 years old; BMI 30 -43kg/m^2; no significant cardiovascular, pulmonary, renal, neurological, psychiatric disease or weight altering medication.	6 weeks	52 weeks	100.0 (14.6)	90.6(13.3)	Placebo: 95.6 (15.7) MK-0557: 91.1(14.5) [e]
Fogelholm et al (10)	82 (0)	Randomised controlled trial where patients followed a 3 month VLCD	Women; 30 -45 years old; BMI 30 -45 kg/m^2; premenopausal; clinically	12 weeks	3 years	92.0 (9.8)	Control: 80.0 (9.5)	Control: 89.7(9.6)

		following which they were randomised to a 9 month maintenance programme consisting of a control group who received diet counselling but no increase in habitual exercise; and two exercise groups targeted to expend 1000kcal/week with diet counselling (Walk-1) and 2000kcal/week with counselling (Walk-2). Patients were then followed up 24 months later.	healthy; not regularly taking medications other than hormonal contraceptives; weight stable; not physically active, pregnant, lactating or smokers. Not binge eating disorder or bulimic.				Walk 1: 78.0 (8.8) Walk 2: 78.2(11.6)	Walk 1: 83.9 (12.2)[a] Walk 2: 87.4 (15.3)
Gripeteg et al (25)	169 (60)	Non blinded, Randomised clinical trial with parallel groups where all patients were initially assigned to 12 week VLCD. Those who lost >10% weight were randomised to a 1 or 6 week refeeding programme where they returned to energy-reduced diets for 40 weeks.	Men and women; 18-60 years old, BMI >30.0 kg/m^2.	12 weeks	52 weeks	Group 1: 122.9 (23.0) Group 6: 124.6 (25.8)	Group 1: 102.8 (20.7) Group 6: 104.0 (23.0)	Group 1: Δ 8.2 (8.3)% Group 6: Δ 3.9 (9.1)%[e]
Jazet et al (19)	18 (9)	Cohort study where patients were assigned to 30 day VLCD followed by an 18 months follow up.	Obese men and women; type 2 diabetes mellitus, part of another intervention. All on insulin therapy.	30 days	18 months	111.7 (SE 4.0)	Δ -11.7 (SE 0.7) [c]	Δ -13.9 (SE 2.5) [c]
Kukkonen-Harjula et al (16)	90 (90)	A randomised trial where patients followed a VLCD for 2 months then were randomised to a walking, resistance training or	Males; 35-50 years old; BMI 30-40 kg/m^2; waist circumference >100cm; no regular medications, no regular exercise, non-	2 months	23 months	-	Combined: Δ -14.2 (4.0) [g]	Combined: Δ – 4.8 (0.8) [g]

		control group for 6 months. All groups received similar dietary advice.	smokers, no binge eaters, BP <160/105, cholesterol <8mmol/L, Triacylglycerol <4mmol/L, blood glucose <6.7 mmol/L.					
Laaksonen et al (13)	27 (13)	Longitudinal clinical intervention where patients underwent a VLCD for 9 weeks followed by 1 year weight maintenance. If patients lost at least 5% of their initial weight at the end of the VLCD, they were randomised to receive either orlistat or a placebo. (results were combined).	Men and women; BMI 30-45 kg/m^2; metabolic syndrome. No poorly controlled diabetics, no IHD; no psychiatric history; no significant renal disease.	9 weeks	1 year	102.5 (12.8)	86.9 (10.4)	88.2 (12.4) [b]
Lantz et al (14)	334 (86)	Randomised clinical trial where patients undertook a 16 week VLCD. Following this, subjects followed either a 2 week VLCD every 3 months (intermittent VLCD) or VLCD whenever their body weight passed an individualised cut-off level (on-demand). All subjects followed hypocaloric diet during VLCD-free periods.	Men and women; BMI> 30.0kg/m^2; 18 -60 years old. No significant serious diseases, previous obesity surgery or drug abuse.	16 weeks	2 years	Intermittent : 114.2 (18.9) On-demand: 114.4 (17.5)	Intermittent: Δ -20.6 (18.3%) [b] On-demand: Δ -22.0 (19.0%) [b]	Intermittent: Δ -7.0 (11.0) [b] On-demand: Δ – 9.1 (9.7) [b]
Linna et al (20)	90 (90)	Cohort study where patients underwent 2 months of VLCD followed with 6 month weight maintenance during which patients were randomised into 3 groups: control,	Men; 35-50 years old; BMI 30-40kg/m^2; waist circumference >100cm; not regular exercisers, binge eaters, smokers or on regular medication.	2 months	31 months	105.6 (10.3)	90.9 (9.8) [b]	100.6 (11.7) [b]

		walking group or resistance training. They then followed an unsupervised 2 year follow up.						
Madsen et al (29)	93 (51)	Randomised clinical trial where patients underwent 8 weeks of VLCD and then randomised to either orlistat or a placebo together with lifestyle intervention for further 3 years.	Men and women; 18-65 years old; BMI 30-45 kg/m^2; metabolic syndrome.	8 weeks	3 years	Placebo: 109.9 (CI 105.1; 115) Orlistat: 109 (CI 104.5; 113.8)	Placebo: 95.6 (CI 91.3; 100.1)[g] Orlistat: 95.8 (CI 91.8; 100.1)[g]	Placebo: 105 (CI 99.4; 110.9) Orlistat: 99.9 (CI 95; 105.1)[d]
Madsen et al (30)	68 (37)	Randomised clinical trial where patients underwent 8 weeks of VLCD and then randomised to either orlistat or a placebo together with lifestyle intervention and hypocaloric diet for further 3 years.	Men and women; 18-65 years old; BMI 30-45 kg/m^2; metabolic syndrome.	8 weeks	3.2 years	Placebo: 113.1 (16.1) Orlistat: 110.8 (16.8)	Placebo: 98.1 (12.8) Orlistat: 97.5 (15.0)	Placebo: 106.2 (14.6) Orlistat: 100.9 (17.7)[d]
Mathus-Vliegen et al (17)	189 (27)	Randomised clinical trial where patients underwent 3 months VLCD and then randomised to sibutramine or placebo for the following 12 months. Each group combined with exercise and diet to maintain weight loss.	Men and women; 18-65 years old; BMI 30-45 kg/m^2; no weight loss medication in the last 6 months; no surgical treatment for weight reduction.	3 months	18 months	Placebo: 105.5 (14.6) Sibutramine: 103.7 (13.1)	Placebo: 90.2 (13.0) Sibutramine: 88.6 (11.4)	Placebo: Δ -8.5 (8.1) Sibutramine: Δ -10.7 (7.5)[e]
Melin,et al (15)	43 (4)	Randomised clinical trial where patients undertook a 25 day VLCD followed by hypocaloric diet. Patients were divided into 2 groups: one group received intensive therapy	Men and women; 24-60 years old; BMI 35kg/m^2 (29-48).	25 days	2 years	Group 1: 99.8 (SE 5.5) Group 2:93.4 (SE 4.1)	Group 1: Δ - 8.3 (SE 0.64) [b] Group 2: Δ -10.0 (SE 0.71) [b]	Group 1: Δ - 6.8 (SE 1.4)[a] Group 2: Δ -8.6 (SE 1.6)[a]

		every fortnight during the first year and six meetings in the second year,the second group had planned meetings every third month.						
Niskanen et al (28)	58 (58)	Cohort study where patients underwent a VLCD for 9 weeks. Following this, those who lost >5% body weight were randomised to Orlistat or placebo for 12 months.	Males; BMI 30-45 kg/m^2; diabetes mellitus or metabolic syndrome.	9 weeks	12 months	115.7 (15.6)	99.1 (13.7)	101.0 (15.8) [b]
Paisey et al (12)	45 (18)	Randomised prospective controlled trial where patients were randomised to one of three groups: Group 1 : VLCD Group 2: Intensive Conventional Diet and Exercise Group 3: failed to follow either programme.	Men and women; BMI>30; type 2 diabetes.	3 months	5 years	BMI group 1: 37.7 (9.9) kg/m^2 BMI group 2: 35.9 (5.4) kg/m^2	-	BMI group 1: 36.1 (10.7) kg/m^2 BMI group 2: 32.7 (3.8) kg/m^2 [a]
Richelsen et al (21)	383 (226)	Randomised placebo controlled study. All patients received 8 weeks VLCD. Those who lost ≥5% of their body weight(309)were randomised to either lifestyle counselling for 3 years with either orlistat or placebo.	Men and women; 18-65 years old; BMI 30-45kg/m^2; waist circumference ≥102cm (men) or ≥92cm (women). Also diet controlled diabetics or metabolic syndrome.	8 weeks VLCD ,	3 years	Placebo: 111.9 (16) Orlistat: 110.7 (17.9)	Placebo: Δ -14.3 (-12) Orlistat: Δ-14.5 (-13)	Placebo: Δ-7.2 (-6.3) Orlistat: Δ-9.4 (-8.3) [e]
Rolland et al (23)	120 (11)	Randomised clinical trial where patients were	Men and women; >18 years old; BMI	6.9 months (4-	-	LCHP: 110.4 (12.2)	-	LCHP: 109.1 (14.6)

		assigned to a 600 calorie diet for 3 months. Those who did not achieve a 5% were randomised to either: VLCD or low carbohydrate/high protein (LCHP) for the following 9 months.	≥35kg/m^2; no diagnosis of cancer, hepatic or renal disease; not pregnant or lactating; not on antidepressants, anti-obesity medications; no eating disorder.	9 months)		LL: 129.6 (23.0)		LL: 98.0 (20.3) [c,f]
Simonen,et al (31)	16 (13)	Randomised clinical trial where patients were randomly assigned to a VLCD or LCD for 3 months with a 2 year follow up.	Men and women; recent diagnosis of type 2 diabetes (<2 years);BMI>30kg/m^2; not on insulin; no diabetic microangiopathy, hepatic or thyroid disease; no unstable angina, MI or invasive CAD treatment in past year.	12 weeks	2 years	Combined: 93.2 (SE 3.7)	-	Combined: 87.2 (SE 3.2)[a]
Vasankari et al (11)	77 (0)	Randomised control trial where patients underwent 12 weeks VLCD (WR) followed by a 9 month weight maintenance (WM) period where 3 groups were randomly assigned: high exercise, low exercise, dietary counselling (WR+WM groups were combined as no difference in body weights). A control group was also assessed at 0 and 3 months but who did not participate in any intervention other than assessment of measurements at time points.	Premenopausal women; BMI>29kg/m^2 ; no regular medication (except contraceptives); no ischemic ECG changes in a maximal treadmill test; no musculoskeletal or other contraindications to walking training; weight stable; normal lipid profile; no signs of a binge-eating syndrome; little regular exercise ;non-smoking; not pregnant and no intention of becoming pregnant during the next 3 years.	12 weeks	9 months	Control: 86.8 (11.5) WR+WM : 92.2 (9.8)	Control: 85.0 (11.6) [a] WR+WM: 79.1 (10.0) [c]	Control: Not applicable WR+WM: 79.7 (10.9) [c, g]

Wikstrand et al (32)	91 (26)	Cohort study where patients underwent 3 months VLCD and lifestyle advice group meetings. Those who attained ≥8kg reduction weight were randomised to 2 groups a) Corset wearing b) No corset for 9 months and followed up at 24 months.	Men and women; 30-60-years old; BMI≥30 - <45kg/m^2; not pregnant or breast feeding; not diabetic (IDDM); no serious dermatology problems; no GI, kidney, liver, lung, cardiovascular, psychiatric disease, cancer, drug abuse, nor eating disorders.	12 weeks	24 months	-	-	Group A: Δ -6.1(7.0)[g] Group B: Δ -4.4(7.3)[g]
Willi et al (33)	20	Cohort study of children who undertook VLCD as part of diabetic treatment. All had varying lengths of VLCD (mean 60±8 days) as they continued until predefined treatment goals, ie 10% reduction in BMI, were reached. They were followed up for 24 months.	Children with type 2 diabetes; BMI>30kg/m^2.	60 ± 8 days	24 months	BMI (kg/m^2): 44.2 (SE 2.3)		BMI: (kg/m^2): 41.2 (SE 2.1)
Liver and Kidney function								
Melin,et al (15)				*See CVD section*				
Rolland et al (23)				*See CVD section*				
Fertility								
Niskanen et al (28)				*See CVD section*				
Bone Health								

Dixon et al (34)	61 (15)	Randomised clinical trial where patients were either assigned to a laparoscopic gastric band (LAGB) or to a dietary weight loss program where patients followed a VLCD for 12 weeks followed by a transition phase over 4 weeks combining VLCD with normal meals and orlistat until the completion of the intensive 6 month phase. This 6 month phase was then followed by continual behaviour, dietary and exercise advice.	Men and women; 20-50 years old; BMI30-35 kg/m^2; identifiable problems associated with their obesity; history of attempts of weight reduction; able to understand options offered and the randomisation process; willing to comply with the requirements of each program.	12 weeks	24 months	LAGB: 95.8 (11.3) VLCD: 93.3 (9.9)		LAGB: 74.9 (11.5)[f] VLCD: 87.4 (11.2)
Fogelholm et al (27) *also in CVD risks	85 (0)	Randomised clinical trial where patients underwent 3 months of VLCD followed by 9 months where they were randomised to one of three groups: a control group with no increase in habitual exercise; and two exercise groups with walking training targeted to expend 1000 kcal or 2000 kcal weekly. Patients were then followed up 24 months later.	Women; BMI 30-46 kg/m^2; 30-45 years old; premenopausal; weight stable; no medications, (except hormonal contraceptives); sendentary, not pregnant or lactating; non smokers; no binge eating disorder or bulimia.	3 months	3 years	92.0 (9.8)	Δ -13.2 (3.3) [a]	Δ -4.9 (7.1) [a]
Hinton et al (35)	37 (13)	Randomised cohort control study where patients were assigned to 3 months of VLCD. If 10% initial weight was lost then patients were randomised either to a	Men and women; 19-70 years old; Sedentary; BMI >27kg/m^2; weight stable; healthy as determined from health history questionnaire and	3 months	12 months	111.6 (17.8)	90.1 (14.5) [a]	93.4 (18.3) [a]

		low fat (LF) or low carbohydrate (LCHO) for 9 months.	medical exam.					
Respiratory disorders								
Kajaste et al (36)	31 (31)	Randomised control study where all patients received 6 weeks of VLCD and 24 months of behaviour therapy. During this time, half the patients underwent treatment with CPAP while ther others did not (Non- CPAP).	Men; BMI >35 kg/m^2; 30-60 years old; subjective symptoms of obstructive sleep apnoea syndrome, and ODI_4 >10.	6 weeks	36 months	CPAP: 135.3 (16.0) Non CPAP: 145.5 (23.4) Combined: 140 (20)	-	Combined: 134 (24.1) [a]
Stenius-Aarniala et al (37)	38 (N/A)	Randomised parallel trial where all patients received group sessions for 14 weeks. The treatment group also received 8 weeks VLCD.	Women able to cope with the study protocol; BMI 30-42 kg/m^2; 18-60 years old, previously diagnosed asthma with a spontaneous diurnal variation or a bronchodilator response of 15% or more; non smoker or having stopped smoking for two years or more before age 50.	8 weeks	1 year	-	Control: 0.3 (No CI) Treatment: Δ - 14.2 (CI 7.7; 22.1)[g]	Control: Δ 2.3 (No CI) Treatment: Δ -11.1 (CI 1.1; 22.5)[g]
Tuomilehto et al (24) *also in CVD risks	72 (53)	Randomized controlled parallel trial where the treatment group received VLCD plus lifestyle modification while the control group received lifestyle counselling only.	18–65 years old; BMI 28–40 kg/m^2; apnea–hypopnea index (AHI), 5–15 events/hour.	12 weeks	1 year	Control: 92.3 (11.3) Treatment: 101.2(11.9) [e]	-	Control: Δ -2.4 (5.6) Treatment: Δ -10.7 (6.5)[f]
Eating disorders								
de Zwaan et al (39)	71 (0)	Clinical trial where patients underwent 12	Women; 18-55 years old; at least 22.7kgs	12 weeks	12 months	BED only: 97.7 (12.7)	BED only: 83.0 (11.4)	BED only: 92.1 (13.8)

		weeks VLCD, 6 weeks food reintroduction, 6 weeks weight maintenance. After the fist 2 weeks of refeeding, half of the BED participants, were randomly assigned to an additional 10 week CBT component.	above "ideal" body weight, binge eating disorder.			BED + CBT: 98.8 (11.3)	BED+CBT: 85.6 (11.6) [e]	BED+CBT: 93.1 (14.5)
Legenbauer,et al (40)	251 (69)	Prospective longitudinal study where patients underwent 3 months VLCD followed by 9 months refeeding. Patients were then grouped as successful weight maintainers (SWM) if they maintained >5% weight loss of initial weight. If they achieved <5% weight loss of initial weight, they were grouped as unsuccessful weight maintainers (USWM).	Men and women; 18-65 years.	3 months	3 years	117.7 (25.1)	-	USWM: 123.7 (27.0) [e] SWM: 111.7 (23.8)
Legenbauer et al (41)	403 (124)	Longitudinal naturalistic study where those in the VLCD group underwent 3 months VLCD and a 9 month refeeding period with weekly group sessions for 1 year. These patients were compared to patients who underwent bariatric surgery (BS).	Caucasian men and women; 18-65 years old; BMI $\geq$ 30 kg/m^2; no diagnosis of psychotic disorder or dementia; women not having given birth within the past year, or lactating; no use of drugs with known influence on weight; understanding the German language.	3 months	4 years	VLCD: 121.1 (SE 1.7) BS : 148.0 (SE 2.2)	-	VLCD: 114.7 (SE 1.9) [a] BS: 116.6 (SE 2.2) [a]

Raymond et al (38)	128 (0)	Clinical intervention including patients with BED, sub threshold BED, no BED who underwent a 24 week intervention with 12 weeks of VLCD, 6 weeks food reintroduction, 6 weeks weight maintenance. After the fist 2 weeks of refeeding, half of the BED participants, were randomly assigned to an additional 10 week CBT component.	Women; 18-50 years; at least 22.7kg above average body weight for their height.	12 weeks	12months	-		BED: Δ -17.5 (8.4) Sub-BED: Δ -19.1 (8.3) No-BED: Δ -13.8 (7.9)	Percentage of weight regain BED: 70%(86.2) Sub-BED: 71.7% (36.7) No-BED: 68.6% (54.5)

Abbreviations: BED – binge eating disorder; BMI – body mass index; CAD – coronary artery disease; CBT – cognitive behaviour therapy; CI – 95% confidence interval; CPAP – continuous airway positive pressure; CVD – cardiovascular disease; GI- gastro intestinal; IHD – ischaemic heart disease; MI – myocardial infarction; MK-0557 - highly selective, orally administered neuropeptide Y Y5 receptor antagonist; VLCD – very low calorie diet; SEM – standard error measurement

Values are reported as means with standard deviations in brackets unless stated otherwise

Δ represents a change

a - $p < 0.05$ from baseline

b - $p < 0.001$ from baseline

c - $p < 0.0001$ from baseline

d - $p < 0.05$ from VLCD end

e - $p < 0.05$ between groups

f - $p < 0.001$ between groups

g - no p value provided in original manuscript

Table 3: Summary of results for blood pressure and waist circumference

		Systolic Blood pressure (mmHg)			Diastolic Blood Pressure (mmHg)			Waist circumference (cm)		
Author	**Patient Groups**	**Pre**	**Post VLCD**	**Study end**	**Pre**	**Post VLCD**	**Study end**	**Pre**	**Post VLCD**	**Study end**
Delbridge et al (22)	All	-	Δ-13.2 (SE 1.4)[b]	Δ -11.1 (SE 1.7)[b]	-	Δ-8.5 (SE 1.1)[b]	Δ -5.2 (SE 1.3)[b]	-	Δ-14.2 (SE 0.5)[b]	Δ -16.0 (SE 1.1)[b]
	HC	-	Δ-12.3 (SE 2.1)	Δ -5.0 (SE 1.6)	-	Δ-7.4 (SE 1.4)	Δ- 3.1 (SE 1.4)	-	Δ-14.3 (SE 0.8)	Δ- 14.1 (SE 1.1)
	HP	-	Δ-14.9 (SE 2.1)	Δ- 11.7 (SE 1.8)[e]	-	Δ-9.8 (SE 1.8)	Δ- 6.3 (SE 1.5)	-	Δ-15.2 (SE 0.7)	Δ- 14.5 (SE 1.1)
Dhindsa et al (4)	All	152 (17)	Δ -10[a]	no value[a]	82 (9)	Δ -6[a]	no value[a]	-	-	-
Erondu et al (18)	Placebo	125.3 (14.2)	116.0 (12.2)	121.4 (14.1)	80.6 (7.9)	75.7 (8.1)	77.9 (8.8)	109.8 (11.3)	102.2 (10.7)	103.7 (11.4)
	MK-0557	124.0 (13.9)	115.1 (12.8)	121.4 (14.9)	79.6 (8.4)	74.7 (8.9)	76.3 (9.2)	108.5 (11.7)	99.9 (11.2)	100.0 (12.0)[e]

Fogelholm et al(10)	Control	119 (10)	115 (12)	125 (13)	78 (7)	77 (8)	81 (7)	102 (9)	91.1 (8.2)	98.1 (9.0)
	Walk 1	119 (10)	116 (11)	127 (12)	78 (7)	80 (8)	81 (8)	102 (9)	90.1 (7.1)	93.4 (11.3)
	Walk 2 + counselling	119 (10)	114 (8)	123 (13)	78 (7)	78 (6)	79 (9)	102 (9)	89.8 (9.6)	95.3 (10.8)
Fogelholm et al (27)	All	-	-	-	-	-	-	102 (9)	Δ -12 (4)[a]	Δ -7 (8)[a]
Gripteg et al (25)	1 week refeeding	-	128.8 (16.4)	no value[h]	-	84 (10.3)	-	-	124.8 (14.8)	no value[h]
	6 week refeeding	-	130.8 (16.5)	no value[h]	-	85.7 (12.7)	no value[h]	-	125.5 (15.9)	no value[h]
Jazet et al (19)	All	169 (8)	Δ -27 (SE 6)[a]	Δ-27 (SE 7)[a]	96 (4)	Δ -14 (SE 4)[a]	Δ-17 (SE 4)[a]	122 (2.2)	Δ -8.6 (SE 0.9)[c]	Δ -5.8 (SE 2.1)[a]

Kukkonen-Harjular et al (16)	All	131 (13)	Δ -6 (CI -8; -4)	Δ 2 (CI-1;5)	84 (11)	Δ -8 (CI-10; -6)	Δ 2 (CI-0; 4)	-	-	-
	Control	129 (13)	-	132 (15)	82 (21)	-	84 (10)	-	-	-
	Walk	130 (14)	-	131 (19)	82 (12)	-	84 (10)	-	-	-
	Resistance	132 (13)	-	136 (15)	85 (9)	-	87 (10)	-	-	-
Laaksonen et al (13)	All	129.4 (8.6)	119.9 (8.4)	126.5 (8.5)[b]	79.4 (5.9)	74.4 (5.6)	77.8 (6.8)[c]	115 (8)	103 (8)	103 (10)[b]
Lantz et al (14)	All	134 (19)	Δ -6 (CI -9; -3)	Δ 0 (CI -3; 3)	80 (11)	Δ -4 (CI -6; -2)	Δ 0 (CI -2; 2)	120.6 (11.4)	-	Δ -6.7 (CI -8.4; 5.1)
Linna et al (20)	All	131.0 (12.6)	124.8 (14.2)[b]	133.3 (16.0)[b]	83.6 (10.9)	76.1 (9.3)[b]	85.1 (9.9)[b]	112.1 (7.0)	97.5 (8.1)[b]	106.7 (10.1)[b]
	Subgroup 1	131.2 (13.9)	128.4 (15.7)	132.6 (17.5)[a]	83.5 (12.2)	76.3 (9.8)[a]	82.4 (10.3)[a]	111.7 (5.1)	95.7 (7.1)[b]	98.3 (8.1)[a]
	Subgroup 2	130.9 (12.3)	123.3 (13.5)[b]	133.7 (15.7)[b]	84.0 (10.2)	76.2 (9.2)[b]	86.6 (9.3)[b]	112.7 (8.1)	98.3 (8.4)[b]	110.3 (8.7)[b,f]

Madsen et al (29)	Orlistat	-	-	-	-	-	-	117.4 (CI 114; 121)	106.5 (CI 103.3; 109.9	108.7 (CI 104.7; 112.8)[d]
	Placebo	-	-	-	-	-	-	117.4 (CI 114; 121.6)	105.9 (CI 102.4; 109.4	112.2 (CI 107.7; 116.8)
Madsen et al (30)	Orlistat	-	-	-	-	-	-	118.4 (11.6)	107.4 (9.7)	109.7 (12.6)[e]
	Placebo	-	-	-	-	-	-	119.5 (11)	107.8 (9.8)	114.1 (12)
Mathus-Vliegen et al (17)	Sibutramine	137.0 (14.8)	Δ -14.9 (14.2)	-	84.1 (7.2)	Δ-7.0 (7.3)	-	-	-	Δ -3.4 (No SD)[e]
	Placebo	136.2 (13.0)	Δ -14.6 (14.2)	-	84.2 (6.6)	Δ-5.9 (7.7)	-	-	-	Δ -5.4 (No SD)
Melin et al (15)	Intensive therapy	129.0 (SE 3.6)	-	Δ -9.8 (SE 4.2)[a]	83.2 (SE 1.6)	-	Δ -6.6 (SE 2.3)[a]	-	-	-
	Normal therapy	127.4 (SE 2.7)	-	Δ 2.2 (SE 3.9)	84.3 (SE 1.7)	-	Δ 1.3 (SE 2.2)	-	-	-
Niskanen et al (28)	All	154 (19)	-	-	97 (11)	-	-	121 (10)	108 (9)	108 (12)[b]

Paisey et al (12)	VLCD	139 (17)	-	143 (13)	76 (10)	-	77 (11)	117 (24)	-	114 (20)
	Diet & exercise	142 (22)	-	130 (20)	85 (13)		74 (13)[b]	113 (13)		108 (4)
Richelsen et al (21)	Orlistat	144 (19.3)	Δ -13	Δ -7.8	90.8 (11.6)	Δ -7.2	Δ -3.7	119 (12.1)	Δ -12	Δ -5.4
	Placebo	144 (17.3)	Δ -12	Δ -8.2	90.7 (11.6)	Δ -7.6	Δ -4.7	119 (10.9)	Δ -12	Δ -7.7[e]
Rolland et al (23)	LCHP	136.7 (22.0)	132.0 (18.6)	133.1 (16.6)	89.0 (9.6)	87.7 (8.2)	86.6 (8.4)	122.6 (9.9)	119.1 (10.0)[h]	119.0 (10.8)[h]
	VLCD	134.8 (18.4)	127.8 (15.2)[h]	128.2 (8.0)[h]	87.7 (13.0)	81.8 (10.8)[f,h]	83.2 (12.4)[h]	126.3 (14.9)	119.1 (16.4)[h]	114.5 (16.0)[e,h]
Tuomilhehto et al (24)	Control	130 (12.8)	-	Δ -1.1 (19.6)	80.7 (7.8)	-	Δ -0.4 (12.6)	105.3 (8.3)	-	Δ -3.0 (6.0)
	Intervention	131.2 (10.2)	-	Δ -1.7 (14.7)	81.8 (8.9)	-	Δ -1.9 (10.6)	112.5 (8.7)	-	Δ -11.6 (6.6)[f]
Vasankari et al (11)	All	119 (10)	113 (16)[c]	121 (10)[b]	78 (7)	71 (10)[c]	79 (7)[c]	102 (8.5)	90.3 (8.3)[c]	90.1 (9.2)
Wikstrand et al (32)	Corset	136 (20)	-	-	79 (14)	-	-	-	-	-
	No corset	134 (18)	-	-	79 (10)	-	-	-	-	-

Abbreviations: CI – 95% confidence interval; cm – centimetres; HC – high carbohydrate diet; HP – high protein diet; LCHP – low carbohydrate, high protein diet; MK-0557 - highly selective, orally administered neuropeptide Y Y5 receptor antagonist; SE – standard error measurement; VLCD – very low calorie diet

Values are reported as means with standard deviations (SD) in brackets unless stated otherwise
Δ represents a change
a - $p<0.05$ from baseline
b - $p<0.001$ from baseline
c - $p<0.0001$ from baseline
d - $p<0.05$ from VLCD end
e - $p<0.05$ between groups
f - $p<0.001$ between groups
g - no p value provided in original manuscript for baseline, VLCD end, study end or between groups
h - statistical significant difference from baseline stated but no p value given

Table 4: Summary of blood lipid results

		Triacylglycerols (mmol/L)			Total cholesterol (mmol/L)			HDL (mmol/L)			LDL (mmol/L)		
Author	**Patient Groups**	**Pre**	**Post VLCD**	**Study end**	**Pre**	**Post VLCD**	**Study end**	**Pre**	**Post VLCD**	**Study end**	**Pre**	**Post VLCD**	**Study en**
Delbridge et al (22)	All	-	Δ -0.90 (SE 0.19)[b]	Δ -0.74 (SE 0.13)[b]	-	Δ -0.65 (SE 0.08)[b]	Δ -0.39 (SE 0.09)[b]	-	Δ -0.00 (SE 0.02)	Δ 0.20 (SE 0.02)[b]	-	Δ 0.14 (SE 0.05)	Δ -0.3((SE 0.09
	HC	-	Δ -0.87 (SE 0.16)	Δ -0.62 (SE 0.13)	-	Δ -0.65 (SE 0.11)	Δ -0.22 (SE 0.10)	-	Δ -0.02 (SE 0.02)	Δ0.11 (SE 0.03)	-	Δ 0.59 (SE 0.92)	Δ -0.1((SE 0.09
	HP	-	Δ -0.62 (SE 0.13)	Δ -0.56 (SE 0.12)	-	Δ -0.59 (SE 0.09)	Δ -0.28 (SE 0.09)	-	Δ -0.00 (SE 0.03)	Δ 0.14 (SE 0.03)	-	Δ -0.33 (SE 0.09)	Δ -0.1 (SE 0.0
Dhindsa et al (4)	T2DM, obese	3.4 (1.7)	-	-	6.0 (1.2)	no value[a]	no value[a]	-	-	-	-	-	-
Erondu et al(18)	Placebo	3.26 (1.8)	2.40 (1.06)	2.87 (1.35)	5.31 (0.84)	4.32 (0.83)	5.11 (0.95)	1.45 (0.34)	1.26 (0.25)	1.48 (0.37)	3.14 (0.74)	2.52 (0.73)	3.00 (0.82)
	MK-0557	1.34 (0.8)	1.08 (0.5)	1.14 (0.6)	5.23 (0.9)	4.31 (0.8)	5.04 (0.9)	1.41 (0.36)	1.22 (0.29)	1.48 (0.40)	3.12 (0.77)	2.56 (0.72)	2.97 (0.73)
Fogelholm et al (10)	Control	1.30 (0.50)	0.96 (0.26)	1.31 (0.72)	5.0 0.9)	4.6 (0.8)	5.4 (0.8)	1.22 (0.24)	1.12 (0.18)	1.34 (0.28)	5.0 (0.9)	4.6 (0.8)	5.4 (0.8)
	Walk 1	1.30 (0.50)	1.02 (0.36)	1.17 (0.45)	5.0 (0.9)	4.2 (0.7)	5.1 (0.8)	1.22 (0.24)	1.12 (0.27)	1.41 (0.31)	5.0 (0.9)	4.2 (0.7)	5.1 (0.8)
	Walk 2 + counselling	1.30 (0.50)	0.96 (0.34)	1.20 (0.45)	5.0 (0.9)	4.1 (0.7)	5.0 (0.9)	1.22 (0.24)	1.13 (0.19)	1.36 (0.23)	5.0 (0.9)	4.1 (0.7)	5.0 (0.9)

Gripteg et al (25)	1 week refeeding	1.6 (0.8)	-	no value[h]	-	-	- -	1.3 (0.2)	-	no value[h]	-	-	-
	6 weeks refeeding	1.5 (0.7)	-	no value[h]	-	-		1.3 (0.3)	-	no value[h]	-	-	-
Jazet et al (19)	All	3.5 (SE 0.8)	Δ-1.7 (SE 0.7)[a]	Δ-0.9 (SE 0.5)[a]	5.6 (SE 0.04)	Δ-0.9 (SE 0.3)[a]	Δ-0.03 (SE 0.3)	1.1 (SE 0.06)	Δ -0.1 (SE 0.04)[a]	Δ 0.2 (SE 0.06)[a]	-	-	-
Kukkonen-Harjular et al (16)	All	-	-	-	-	-	-	1.18 (0.25)	Δ 0.01 (CI -0.00; 0.04)	Δ 0.01 (CI 0.05; 0.11)			
	Control	-	-	-	-	-	-	1.18 (0.23)	-	1.27 (0.27)	- - - -	- - - -	- - - -
	Walk	-	-	-	-	-	-	1.19 (0.23)	-	1.25 (0.20)			
	Resistance	-	-	-	-	-	-	1.15 (0.27)	-	1.24 (0.31)			
Laaksonen et al (13)	Orlistat + Placebo combined	Median 2.2 (IQ 1.6, 2.8)	Median 1.0 (IQ 0.8, 1.4)	Median 1.4 (IQ 1.2, 1.8)[b]	-	-	-	1.09 (0.18)	1.17 (0.22)	1.22 (0.26)[b]	-	-	-
Lantz et al (14)	All	1.7 (0.9)	Δ -0.4 (CI -0.5; -0.2)	Δ -0.1 (CI -0.3; 0.2)	5.6 (1.1)	Δ -0.5 (CI -0.6; -0.3)	Δ -0.1 (CI -0.3; 0.07)	1.2 (0.3)	Δ 0.0 (CI -0.04; 0.05)	Δ 0.2 (CI 0.1; 0.2)[h]	3.6 (0.9)	Δ -0.3 (CI -0.5; -0.2)	Δ -0.2 (CI -0.4; -0.08)[h]

Linna et al (20)	All	-	Δ -28% (CI 22.9; 33.8)[b]	Δ -5% (CI -6.3; 16.7)[a,f]	-	Δ -21% (CI 17.9; 23.2)[b]	No Δ	-	No Δ	Δ 8% (CI 4.6; 11.0)[b,f]	-	Δ -23% (CI 19.9; 26.1)[b]	No Δ
	Subgroup 1	-	-	Δ -23% (CI 13.3-32.8)[b,e]	-	-	No Δ[e]	-	Δ 16% (CI 9.7; 23.4)[b]	Δ 12% (CI -6.6; 17.7)[b,e]	-	Δ -17% (CI -3.3; 12.1)	No Δ
	Subgroup 2	-	-	No Δ	-	-	No Δ	-	Δ 15% (CI 10.0; 19.4)[b]	Δ 6% (CI -2.1; 9.1)[a]	-	Δ -25% (CI 17.9; 31.2)	No Δ
Madsen et al (29)	All	-	-	Δ -12% (CI -1.3; 21.5)[a]	-	-	Δ -7.5% (CI -2.9; -11.8)[a]	-	-	Δ -1.6% (CI -6.1; 2.7)	-	-	Δ-10.5% (CI -4.1; 16.4)[a]
	Orlistat	2 (CI 1.7; 2.3)	1.5 (CI 1.2; 1.7)	1.8 (CI 1.5; 2.1)	6 (CI 5.5; 6.4)	4.9 (CI 4.5; 5.3)	5.6 (CI 5.2; 5.9)	1.15 (CI 1.07; 1.23)	1.09 (CI 1.01; 1.17)	1.14 (CI 1.05; 1.24)	3.8 (CI 3.4; 4.1)	3 (CI 2.8; 3.4)	3.4 (CI 3.1; 3.8)
	Placebo	2.2 (CI 1.8; 2.6)	1.5 (CI 1.3; 1.8)	1.9 (CI 1.6; 2.3)	5.8 (CI 5.4; 6.3)	4.5 (CI 4.2; 4.9)	5.4 (CI 5.1; 5.8)	1.16 (CI 1.08; 1.25)	1.08 (CI 1; 1.17)	1.17 (CI 1.06; 1.28)	3.5 (CI 3.2; 3.9)	2.7 (CI 2.4; 3)	3.2 (CI 2.9; 3.5)

Madsen et al (30)	Orlistat	2.2 (0.8)	1.6 (0.7)	2.0 (0.9)	6.0 (1.2)	5.0 (1.1)	5.5 (1.0)	1.16 (0.28)	1.1 (0.3)	1.2 (0.3)	3.9 (1.1)	3.2 (0.9)	3.5 (0.9)
	Placebo	2.5 (1.4)	1.7 (0.8)	2.2 (1.1)	5.9 (1.2)	4.7 (1.0)	5.4 (0.9)	1.16 (0.22)	1.1 (0.2)	1.2 (0.3)	3.6 (1.0)	2.8 (0.8)	3.2 (0.9)
Mathus-Vliegen et al (17)	Sibutramine	-	-	Median % Δ 2.6	-	-	Median % Δ 13.1	-	-	Median % Δ 20.5	-	-	Median % Δ 7.1
	Placebo	-	-	Median % Δ 5.9	-	-	Median % Δ 12.7	-	-	Median % Δ 19.9	-	-	Median % Δ 9.7
Niskanen et al (28)	All	Median 2.0 (IR 1.7, 2.7)	Median 1.1 (IR 0.9, 1.8)	Median 1.7 (IR 1.3, 2.4)[b]	-	-	-	1.08 (0.23)	1.16 (0.26)	1.16 (0.27)[a]	-	-	-
Paisey et al (12)	VLCD	3.9 (3.4)	-	2.9 (2.3)	6.8 (1.2)	-	5.7 (1.3)[a]	1.20 (0.39)	-	1.26 (0.47)	3.85 (1.57)	-	3.42 (1.38)
	Diet & exercise	2.4 (1.3)	-	2.5 (1.5)	5.9 (1.3)	-	5.3 (1.5)	1.10 (0.32)	-	1.78 (0.26)[a]	3.83 (0.73)	-	3.25 (0.65)
Richelsen et al (21)	Orlistat	2.36 (1.24)	Δ -0.89	Δ -0.38	5.91 (-1.26)	Δ-1.2	Δ-0.46	1.13 (0.26)	Δ -0.05	Δ 0.04	3.71 (1.04)	Δ -0.75	Δ -0.34
	Placebo	2.5 (1.41)	Δ -0.94	Δ -0.43	6.02 (-1.08)	Δ-1.2	Δ-0.46	1.15 (0.26)	Δ -0.07	Δ 0.06	3.77 (0.94)	Δ -0.8	Δ -0.38

Rolland et al (23)	LCHP	1.7 (1.1)	1.5 (0.8)	1.5 (0.9)	5.5 (1.0)	5.4 (0.9)	5.3 (1.0)	1.45 (0.32)	1.44 (0.32)	1.44 (0.35)	3.3 (0.8)	3.3 (0.8)	3.2 (0.8)
	VLCD	1.3 (0.7)	1.2 (0.7)	1.1 (0.7)[h]	5.1 (0.9)	4.6 (1.1)[e,h]	4.8 (1.0)[h]	1.31 (0.22)	1.25 (0.22)[e,h]	1.38 (0.25)[h]	3.1 (0.8)	2.9 (0.9)[e,h]	2.9 (0.9)[h]
Simonen et al (31)	All	3.79 (SE 0.56)	-	2.64 (SE 0.36)[a]	5.94 (SE 0.18)	-	6.06 (SE 0.17)	0.85 (SE 0.05)	-	0.94 (SE 0.06)	3.20 (SE 0.20)	-	3.33 (SE 0.19)
Tuomhileto et al (24)	Control	1.59 (0.92)	-	Δ -0.06 (0.65)	-	-	-	1.11 (0.37)	-	Δ 0.05 (0.22)	-	-	-
	Intervention	1.74 (1.17)	-	Δ -0.48 (1.13)	-	-	-	1.02 (0.23)	-	Δ 0.14 (0.22)	-	-	-
Vasankari et al (11)	All	1.29 (0.46)	1.00 (0.34)[b]	1.22 (0.67)	4.98 (0.83)	4.33 (0.77)[b]	4.72 (0.88)[b]	1.22 (0.25)	1.13 (0.21)[b]	1.36 (0.26)[b]	-	-	-
Wikstrand et al (32)	Corset	1.60 (0.77)	-	1.02 (0.49)[b]	5.4 (0.9)	-	5.2 (0.91)	1.45 (0.30)	-	1.64 (0.30)[a]	3.14 (0.85)	-	3.02 (0.89)
	No corset	1.58 (0.74)	-	1.26 (0.77)[a]	5.6 (0.9)	-	5.6 (0.9)	1.61 (0.77)	-	1.57 (0.24)	3.25 (0.63)	-	3.31 (0.83)

Abbreviations: CI – 95% confidence interval; HP – high protein diet; HC – high carbohydrate diet; HDL – high density lipoprotein cholesterol; IR – interquartile range; LCHP – low carbohydrate, high protein diet; LDL – Low density cholesterol; MK-0557 - highly selective, orally administered neuropeptide Y Y5 receptor antagonist; SE – standard error measurement; VLCD – very low calorie diet;

Values are reported as means with standard deviations in brackets unless stated otherwise
Δ represents a change

a - $p<0.05$ from baseline
b - <0.001 from baseline
c - $p<0.0001$ from baseline
d - $p<0.05$ from VLCD end
e- $p<0.05$ between groups
f - $p<0.001$ between groups
g - no p value provided in original manuscript for baseline, VLCD end, study end or between groups
h - statistical significant difference from baseline stated but no p value given

Table 5: Summary of glycaemia results.

Author	Patient Groups	Fasting glucose (mmol/L)			Fasting insulin (mU/L)			HBA_{1c} %			Fructosamine (µM)		
		Pre	Post VLCD	Study end	Pre	Post VLCD	Study end	Pre	Post VLCD	Study end	Pre	Post VLCD	Study end
Dhindsa et al (22)	T2DM, obese	-	-	-	-	-	-	-	-	-	387 (71)	346 (49)[b]	371 (41)[b]
Erondu et al (18)	Placebo	5.2 (0.6)	5.0 (0.6)	5.2 (0.7)	12.7 (7.0)	7.7 (5.2)	11.3 (12.6)	-	-	-	-	-	-
	MK-0557	5.2 (0.6)	5.1 (0.6)	5.3 (0.7)	13.0 (12.1)	7.0 (5.0)	11.2 (12.1)						
Fogelholm et al (10)	Control	5.1 (0.5)	5.0 (0.4)[g]	5.5 (1.1)[g]	10.9 (4.5)	6.8 (2.3)[g]	10.4 (5.3)[g]	-	-	-	-	-	-
	Walk 1	5.1 (0.5)	4.8 (0.3)[g]	5.3 (0.4)[g]	10.9 (4.5)	6.5 (2.2)[g]	8.4 (3.5)[g]	-	-	-	-	-	-
	Walk 2 + counselling	5.1 (0.5)	4.9 (0.3)[g]	5.4 (0.5)[g]	10.9 (4.5)	6.5 (2.0)[g]	11.1 (10.9)[g]	-	-	-	-	-	-
Gripteg et al (25)	1 week refeeding	-	5.5 (1.3)	No value[h]	-	21.7 (14.3)	-	-	-	-	-	-	-
	6 weeks refeeding	-	5.4 (1.3)	No value[h]	-	25.2 (25.4)	-	-	-	-	-	-	-
Jazet et al (19)	All	11.9 (1.0)	Δ -1.5 (1.3)	Δ -0.7 (1.4)	-	-	-	8.0 (0.3)	Δ -0.3 (0.2)	Δ-0.3 (0.2)	-	-	-

Kukkonen-Harjular et al (16)	All	5.10 (0.49)	Δ -0.32 (CI -0.44 to -0.21)	Δ -0.05 (CI -0.15 to 0.04)	14.4 (5.6)	Δ -5.5 (CI -6.7 to -4.4)	Δ -3.4 (CI -4.8 to-2.0)	-	-	-	-	-	-
	Control	5.1 (0.6)	-	5.1 (0.5)[g]	14 (4.0)	-	10.5 (5.7)[g]	-	-	-	-	-	-
	Walk	5.1 (0.3)	-	5.0 (0.5)[g]	14.3 (6.8)	-	10.5 (5.7)[g]	-	-	-	-	-	-
	Resistance	5.1 (0.5)	-	5.0 (0.4)[g]	14.3 (6.4)	-	10.1 (7.2)[g]	-	-	-	-	-	-
Laaksonen et al (13)	Orlistat + Placebo	6.2 (1.8)	5.5 (0.6)	5.3 (0.8)[b]	-	-	-	-	-	-	-	-	-
Lantz et al (14)	All	4.8 (2.0)	Δ -0.4 (CI-0.6: -0.2)	Δ 0.0 (CI-0.3: 0.2)	20.6 (12.3)	Δ -9.0 (CI-10.9: -7.0)	Δ -4.9 (CI -7.0: -2.8)[h]	-	-	-	-	-	-
Linna et al (20)	All	5.1 (0.5)	4.7 (0.4)[b]	5.0 (0.5)[b]	-	-	-	-	-	-	-	-	-
	Subgroup 1	5.2 (0.7)	4.7 (0.4)[a]	5.0 (0.6)[a]	-	-	-	-	-	-	-	-	-
	Subgroup 2	5.1 (0.4)	4.7 (0.4)[b]	5.1 (0.4)[b]	-	-	-	-	-	-	-	-	-

Madsen et al (29)	Orlistat + placebo		-	-	-	-	-	-	-	Δ -13.1% (CI -11.3; -14.9)[b]	-	-	-
Mathus-Vliegen et al (17)	Sibutramine	-	-	Median % Δ 8.0	-	-	-	-	-	-	-	-	-
	Placebo	-	-	Median % Δ 2.2	-	-	-	-	-	-	-	-	-
Melin et al (15)	Intensive counselling	4.7 (0.2)	-	Δ 0.08 (0.24)	21.1 (4.6)	-	Δ -9 (1.23)[a]	-	-	-	-	-	-
	Normal counselling	5.2 (0.4)	-	Δ -0.5 (0.26)	10.2 (1.2)	-	Δ -5.0 (1.37)[a]	-	-	-	-	-	-
Niskanen et al (28)	All	6.2 (1.7)	5.4 (0.6)	5.4 (0.7)[b]	-	-	-	-	-	-	-	-	-
Paisey et al (12)	VLCD	12 (5)	-	13 (5)	-	-	-	-	-	-	352 (84)	-	348 (59)
	Diet & exercise	13 (5)	-	14 (4)	-	-	-	-	-	-	385 (98)	-	357 (88)

Richelsen et al (21)	Orlistat	6.4 (1.8)	Δ -1.1	Δ-0.49	16.7 (9.4)	Δ -6.91	Δ -3.74	6.3 (0.9)	Δ -0.5	Δ -0.7	-	-	-
	Placebo	6.3 (1.5)	Δ -0.95	Δ-0.32	16.4 (8.4)	Δ -6.48	Δ -1.73	6.3 (0.6)	Δ -0.5	Δ -0.5	-	-	-
Rolland et al (23)	LCHP	5.4 (0.8)	5.4 (0.8)	5.3 (0.8)[h]	-	-	-	5.7 (0.5)	5.6 (0.4)	5.6 (0.4)	-	-	-
	VLCD	5.2 (0.6)	4.8 (0.5)[f,h]	4.9 (0.4)[e,h]	-	-	-	5.6 (0.4)	5.5 (0.3)[h]	5.4 (0.4)[e,h]	-	-	-
Simonen et al (31)	All	8.4 (0.6)	-	7.2 (0.5)[a]	17.0 (1.0)	-	13.1 (1.5)	-	-	-	-	-	-
Toumhileto et al (24)	Control	6.1 (1.6)	-	Δ -0.4 (1.4)	10.9 (4.7)	-	Δ -1.2 (3.4)	-	-	-	-	-	-
	Intervention	6.3 (2.5)	-	Δ -0.6 (2.3)	13.5 (7.0)	-	Δ -5.9 (7.0)[f]	-	-	-	-	-	-
Vasankari et al (11)	All	5.1 (0.5)	4.9 (0.4)[b]	4.9 (0.4)[b]	11.2 (4.4)	6.8 (2.8)[b]	7.8 (2.6)[b]	-	-	-	-	-	-

Wikstrand et al (32)	Corset	5.2 (0.9)	-	4.8 (0.5)[a]	-	-	-	-	-	-	-	-	-
	No corset	5.3 (2.2)	-	4.7 (0.6)	-	-	-	-	-	-	-	-	-
Willi et al (33)	All	-	-	-	-	-	-	8.8 (0.6)	7.4 (0.6)[a]	8.9 (0.8)[a]	-	-	-

Abbreviations: CI – 95% confidence interval; LCHP – low carbohydrate, high protein diet; HP – high protein diet; HC – high carbohydrate diet; MK-0557 - highly selective, orally administered neuropeptide Y Y5 receptor antagonist; VLCD – very low calorie diet;

Values are reported as means with standard deviations in brackets unless stated otherwise
Δ represents a change
a - $p<0.05$ from baseline
b- $p<0.001$ from baseline
c - $p<0.0001$ from baseline
d - $p<0.05$ from VLCD end
e - $p<0.05$ between groups
f - $p<0.001$ between groups
g - no p value provided in original manuscript for baseline, VLCD end, study end or between groups
h - statistical significant difference from baseline stated but no p value given