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Systematic Review

Very-low-energy diets and morbidity: a systematic review of longer-term evidence

Y. Mulholland, E. Nicokavoura, J. Broom and C. Rolland*

Centre for Obesity Research and Epidemiology (CORE), Faculty of Heath and Social Care, Robert Gordon University, Aberdeen AB251HG, Scotland, UK

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Abstract

Evidence from the literature supports the safe use of very-low-energy diets (VLED) for up to 3 months in supervised conditions for patients who fail to meet a target weight loss using a standard low-fat, reduced-energy approach. There is, however, a need for longer-term outcomes on obesity and associated morbidities following a VLED. The present systematic review aims to investigate longer-term outcomes from studies using VLED, with a minimum duration of 12 months, published between January 2000 and December 2010. Studies conducted in both children and adults, with a mean/median BMI of $\geq 28\,kg/m^2$ 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 thirty-two out of 894 articles met the inclusion criteria. The duration of the studies ranged from 12 months to 5 years. Periods of VLED ranged from 25 d to 9 months. Several studies incorporated aspects of behaviour therapy, exercise, low-fat diets, low-carbohydrate diets or medication. Current evidence demonstrates significant weight loss and improvements in blood pressure, waist circumference and lipid profile in the longer term following a VLED. Interpretation of the results, however, was restricted and conclusions with which to guide best practice are limited due to heterogeneity between the studies. The present review clearly identifies the need for more evidence and standardised studies to assess the longer-term benefits from weight loss achieved using VLED.

Key words: Obesity: Systematic reviews: Very-low-energy diets: Morbidity

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

A VLED is defined as a diet of $< 3347\,kJ/d$ ($< 800\,kcal/d$)[3]. A variety of synthetic and food-based formula diets are available, which give energy intakes of 1255–1673 kJ/d (300–400 kcal/d) 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 VLED in the short term[5,6]. Based on this evidence, institutions such as the National Institute for Health and Clinical Excellence and the National Obesity Forum 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 a standard low-fat, reduced-energy 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 VLED on obesity and associated morbidity. We aim to carry out a systematic review of the literature for studies using a VLED, with a minimum follow-up of 12 months, published between January 2000 and December 2010.

Methods

The protocol used for the present systematic review follows the methods recommended by the Cochrane Collaboration[7].

Abbreviations: AHI, apnoea–hypopnoea index; BED, binge eating disorder; BMC, bone mineral content; BMD, bone mineral density; BP, blood pressure; CBT, cognitive behaviour therapy; CTX, C-terminal telopeptide of type I collagen; VLED, very-low-energy diet.

* **Corresponding author:** Dr C. Rolland, email c.rolland@rgu.ac.uk

Inclusion criteria

The present review is intended to assess the current literature in this field and update the 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 $\geq 28\,kg/m^2$ were included. Interventions evaluated in the present 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 retrospective 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 the present review was to examine the effect of VLED on obesity and associated co-morbidities. The types of dietary interventions evaluated were VLED, also known as VLED defined as a dietary intake of 3347 kJ/d (800 kcal/d) 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 present review. With regard to morbidity, the following outcomes were also included:

(1) Cardiovascular risk (serum lipids, including total cholesterol, LDL-cholesterol, HDL-cholesterol and TAG, systolic and diastolic blood pressure (BP) and glycaemic control)
(2) Liver and kidney function
(3) Fertility
(4) Bone health
(5) Respiratory disorders
(6) Eating disorders

Information about dropouts and adverse events was also gathered.

Outcome measures were considered in relation to the time of active intervention as well as the time and nature of the follow-up period, as these varied widely between studies (i.e. 25 d to 9 months of active intervention and 12 months to 5 years for follow-up).

Search strategy for the identification of included studies

The present 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 VLED as possible and which were relevant to the management of obesity and morbidity. For this purpose, 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 the 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 three 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 were 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/dropouts, 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 thirty-two out of 894 articles met the inclusion criteria and were included in the systematic review. Reasons for the exclusion of these studies are summarised in Fig. 1.

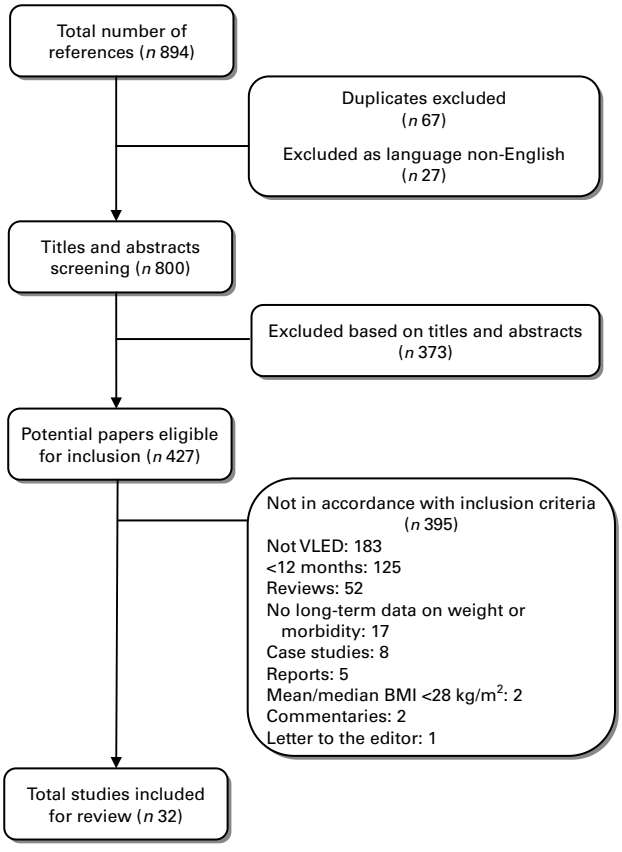

Fig. 1. Summary of the literature search. VLED, very-low-energy diets.

Results

Study characteristics

There was a large amount of heterogeneity in study design for the papers meeting the inclusion criteria. The studies included ranged from 12 months to 5 years in duration. The periods of VLED ranged from 25 d to 9 months. Several studies incorporated aspects of behaviour therapy, exercise programmes, low-fat diets, low-carbohydrate diets, 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 h/d, 7 d/week for 9 months) (Table 1).

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

Quality assessment

Table 2 displays the quality assessment of the reported studies, separated by co-morbidity and ranked from highest to lowest. The studies in which 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

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

Cardiovascular risk

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

Blood pressure

Of the identified papers, seventeen[4,10–25] detailed BP in participants at either VLED 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 thirteen of the seventeen studies following the VLED end[4,10,11,13,14,16–23]. Of the changes at VLED end, six showed significant reductions from baseline[4,11,14,16,19,23], four of which sustained significant systolic BP reductions at study end[4,11,19,23]. Also, three more studies reported a significant reduction in systolic BP at study end only[13,15,25].

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

Diastolic BP information was also available from these seventeen studies. At VLED end, eleven of the studies showed diastolic reductions which were more pronounced than at study end[4,10,11,13,14,16,18–21,23]. Only one study[19] showed a significant change from baseline which improved further between the VLED end and the study end. At VLED end, similar trends to those for systolic pressure were observed for diastolic pressure in seven of the seventeen studies[4,11,13,15,19,23,25] which demonstrated a significant improvement at study endpoint.

Overall, the time of VLED duration, the time of follow-up and the nature of follow-up (hypoenergetic diet, exercise, medication, counselling, etc.) did not predict BP outcomes in the long term.

Waist circumference

Waist circumference data were reported in eighteen papers[10–14,17–25,27–30]. Of the thirteen papers that reported waist circumference data at VLED end[10,11,13,18–23,27–30], seven studies[11,13,19,20,23,27,29] showed significant reductions at VLED end, five of which maintained significant reductions from baseline at study end[19,20,23,27,29] (Table 3). In total, nine studies showed a significant reduction in waist circumference at study end[13,19,20,23,25,27–30].

Similarly to BP, the time of VLED duration, the time of follow-up and the nature of follow-up did not predict waist circumference outcomes in the long term.

Lipid profile

Of the identified studies, twenty-one included cholesterol as primary or secondary outcomes following weight loss and intervention[4,10–14,16–25,28–32]. The results for the different studies are presented in Table 4.

TAG

There were nineteen studies identified that examined for changes in TAG throughout the study periods[10–14,17–25,28–32]. Of all the nineteen studies, four reported significant improvements in TAG at the VLED end[11,19,20,29], although in one study this involved combined data from VLED and LED interventions[11]. At study end, nine studies, including the four which had significant changes at VLED end, showed significant reductions in TAG from baseline[11,13,19,20,25,28,29,31,32].

Table 1. Summary of the studies included in the review

Author	*n* (males)	Study	Inclusion criteria	Duration of VLED	Duration of follow-up	Weight (kg) at baseline	Weight (kg) at the end of the VLED	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 of VLED. Those who achieved ≥10 % were then randomised to either a HC or a HP for 12 months	Men and women; 18–75 years old; BMI ≥27 kg/m^2 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)** HP: Δ −17·4 (SE 0·7)**	HC: Δ −13·8 (SE 1·3)** HP: Δ −14·3 (SE 1·1)**
Dhindsa *et al.*[4]	40 (22)	Clinical trial where patients underwent 8 weeks of VLED with follow-up until 1 year. During the follow-up, participants followed a standard LED and received bi-monthly exercise advice	Obese men and women with hyperglycaemic symptoms and poorly controlled T2DM	8 weeks	1 year	119 (SD 19)	107 (SD 18)**	109 (SD 18)**
Erondu *et al.*[18]	502 (69)	Multicentre, double-blind, randomised, placebo-controlled clinical trial where patients were given VLED for 6 weeks. Patients who lost ≥6 % body weight were randomised to 52 weeks of MK-0557 or placebo with a hypoenergetic diet	Non-diabetic men and women; 18–65 years old; BMI 30–43 kg/m^2; no significant cardiovascular, pulmonary, renal, neurological, psychiatric disease or weight-altering medication	6 weeks	52 weeks	100·0 (SD 14·6)	90·6 (SD 13·3)	Placebo: 95·6 (SD 15·7) MK-0557: 91·1 (SD 14·5)‡
Fogelholm *et al.*[10]	82 (0)	Randomised controlled trial where patients followed a 3-month VLED 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 4184 kJ (1000 kcal) week with diet counselling (Walk 1) and 8368 kJ (2000 kcal) week with counselling (Walk 2). Patients were then followed up 24 months later	Women; 30–45 years old; BMI 30–45 kg/m^2; pre-menopausal; clinically healthy; not regularly taking medications other than hormonal contraceptives; weight stable; not physically active, pregnant, lactating or smokers. Not BED or bulimic	12 weeks	3 years	92·0 (SD 9·8)	Control: 80·0 (SD 9·5) Walk 1: 78·0 (SD 8·8) Walk 2: 78·2 (SD 11·6)	Control: 89·7 (SD 9·6) Walk 1: 83·9 (SD 12·2)* Walk 2: 87·4 (SD 15·3)
Gripeteg *et al.*[25]	169 (60)	Non-blind, randomised clinical trial with parallel groups where all patients were initially assigned to 12-week VLED. 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 (SD 23·0) Group 6: 124·6 (SD 25·8)	Group 1: 102·8 (SD 20·7) Group 6: 104·0 (SD 23·0)	Group 1: Δ 8·2 (SD 8·3) % Group 6: Δ 3·9 (SD 9·1) %‡
Jazet *et al.*[19]	18 (9)	Cohort study where patients were assigned to 30 d VLED followed by an 18-month follow-up	Obese men and women; T2DM, part of another intervention. All on insulin therapy	30 d	18 months	111·7 (SE 4·0)	Δ −11·7 (SE 0·7)***	Δ −13·9 (SE 2·5)***
Kukkonen-Harjula *et al.*[16]	90 (90)	A randomised trial where patients followed a VLED for 2 months and then were randomised to a walking, resistance training or control group for 6 months. All groups received similar dietary advice	Males; 35–50 years old; BMI 30–40 kg/m^2; waist circumference >100 cm; no regular medications, no regular exercise, non-smokers, no binge eaters, BP <160/105 mmHg, cholesterol <8 mmol/l, TAG <4 mmol/l, blood glucose <6·7 mmol/l	2 months	23 months	–	Combined: Δ −14·2 (SD 4·0)§	Combined: Δ −4·8 (SD 0·8)§

Table 1. *Continued*

Author	*n* (males)	Study	Inclusion criteria	Duration of VLED	Duration of follow-up	Weight (kg) at baseline	Weight (kg) at the end of the VLED	Weight (kg) at the end of the follow-up
Laaksonen *et al.*[13]	27 (13)	Longitudinal clinical intervention where patients underwent a VLED for 9 weeks followed by 1-year weight maintenance. If patients lost at least 5 % of their initial weight at the end of the VLED, 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 (SD 12·8)	86·9 (SD 10·4)	88·2 (SD 12·4)**
Lantz *et al.*[14]	334 (86)	Randomised clinical trial where patients undertook a 16-week VLED. Following this, subjects followed either a 2-week VLED every 3 months (intermittent VLED) or VLED whenever their body weight passed an individualised cut-off level (on-demand). All subjects followed hypoenergetic diet during VLED-free periods	Men and women; BMI >30·0 kg/m^2; 18–60 years old. No significant serious diseases, previous obesity surgery or drug abuse	16 weeks	2 years	Intermittent: 114·2 (SD 18·9) On-demand: 114·4 (SD 17·5)	Intermittent: Δ −20·6 (SD 18·3 %)** On-demand: Δ −22·0 (SD 19·0 %)**	Intermittent: Δ −7·0 (SD 11·0)** On-demand: Δ −9·1 (SD 9·7)**
Linna *et al.*[20]	90 (90)	Cohort study where patients underwent 2 months of VLED followed by 6-month weight maintenance during which patients were randomised into three groups: control, walking or resistance training group. They then followed an unsupervised 2 year follow-up	Men; 35–50 years old; BMI 30–40 kg/m^2; waist circumference >100 cm; not regular exercisers, binge eaters, smokers or on regular medication	2 months	31 months	105·6 (SD 10·3)	90·9 (SD 9·8)**	100·6 (SD 11·7)**
Madsen *et al.*[29]	93 (51)	Randomised clinical trial where patients underwent 8 weeks of VLED and then randomised to either orlistat or a placebo together with a 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 (95 % CI 105·1, 115) Orlistat: 109 (95 % CI 104·5, 113·8)	Placebo: 95·6 (95 % CI 91·3, 100·1)§ Orlistat: 95·8 (95 % CI 91·8, 100·1)§	Placebo: 105 (95 % CI 99·4, 110·9) Orlistat: 99·9 (95 % CI 95, 105·1)†
Madsen *et al.*[30]	68 (37)	Randomised clinical trial where patients underwent 8 weeks of VLED and then randomised to either orlistat or a placebo together with a lifestyle intervention and a hypoenergetic 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 (SD 16·1) Orlistat: 110·8 (SD 16·8)	Placebo: 98·1 (SD 12·8) Orlistat: 97·5 (SD 15·0)	Placebo: 106·2 (SD 14·6) Orlistat: 100·9 (SD 17·7)†
Mathus-Vliegen *et al.*[17]	189 (27)	Randomised clinical trial where patients underwent 3 months of VLED 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 (SD 14·6) Sibutramine: 103·7 (SD 13·1)	Placebo: 90·2 (SD 13·0) Sibutramine: 88·6 (SD 11·4)	Placebo: Δ −8·5 (SD 8·1) Sibutramine: Δ −10·7 (SD 7·5)‡

Table 1. *Continued*

Author	*n* (males)	Study	Inclusion criteria	Duration of VLED	Duration of follow-up	Weight (kg) at baseline	Weight (kg) at the end of the VLED	Weight (kg) at the end of the follow-up
Melin *et al.*[15]	43 (4)	Randomised clinical trial where patients undertook a 25 d of VLED followed by a hypoenergetic diet. Patients were divided into two groups: one group received intensive therapy every fortnight during the first year and six meetings in the second year, the second group had planned meetings every third month	Men and women; 24–60 years old; BMI 35 kg/m^2 (29–48)	25 d	2 years	Group 1: 99·8 (SE 5·5) Group 2: 93·4 (SE 4·1)	Group 1: Δ - 8·3 (SE 0·64)** Group 2: Δ −10·0 (SE 0·71)**	Group 1: Δ - 6·8 (SE 1·4)* Group 2: Δ − 8·6 (SE 1·6)*
Niskanen *et al.*[28]	58 (58)	Cohort study where patients underwent a VLED 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 (SD 15·6)	99·1 (SD 13·7)	101·0 (SD 15·8)**
Paisey *et al.*[12]	45 (18)	Randomised prospective controlled trial where patients were randomised to one of three groups: group 1 – VLED; group 2 – intensive conventional diet and exercise; group 3 – failed to follow either programme	Men and women; BMI > 30 kg/m^2; type 2 diabetes	3 months	5 years	BMI group 1: 37·7 (SD 9·9) kg/m^2 BMI group 2: 35·9 (SD 5·4) kg/m^2	–	BMI group 1: 36·1 (SD 10·7) kg/m^2 BMI group 2: 32·7 (SD 3·8) kg/m^2*
Richelsen *et al.*[21]	383 (226)	Randomised placebo-controlled study. All patients received 8 weeks of VLED. 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 30–45 kg/m^2; waist circumference ≥102 cm (men) or ≥92 cm (women). Also, diet-controlled diabetics or metabolic syndrome	8 weeks VLED	3 years	Placebo: 111·9 (SD 16) Orlistat: 110·7 (SD 17·9)	Placebo: Δ −14·3 (−12) Orlistat: Δ −14·5 (−13)	Placebo: Δ −7·2 (−6·3) Orlistat: Δ −9·4 (−8·3)‡
Rolland *et al.*[23]	120 (11)	Randomised clinical trial where patients were assigned to a 600 calorie-deficient diet for 3 months. Those who did not achieve 5 % were randomised to either a VLED or a LCHP for the following 9 months	Men and women; >18 years old; BMI ≥35 kg/m^2; no diagnosis of cancer, hepatic or renal disease; not pregnant or lactating; not on antidepressants, anti-obesity medications; no eating disorder	6·9 months (4–9 months)	–	LCHP: 110·4 (SD 12·2) LL: 129·6 (SD 23·0)	–	LCHP: 109·1 (SD 14·6) LL: 98·0 (SD 20·3)***‡‡
Simonen *et al.*[31]	16 (13)	Randomised clinical trial where patients were randomly assigned to a VLED or LED for 3 months with a 2-year follow-up	Men and women; recent diagnosis of type 2 diabetes (<2 years); BMI >30 kg/m^2; not on insulin; no diabetic microangiopathy, hepatic or thyroid disease; no unstable angina, myocardial infarctions or invasive CAD treatment in the past year	12 weeks	2 years	Combined: 93·2 (SE 3·7)	–	Combined: 87·2 (SE 3·2)*
Vasankari *et al.*[11]	77 (0)	Randomised control trial where patients underwent 12 weeks of VLED (WR) followed by a 9-month WM period where three groups were randomly assigned: high exercise; low exercise; dietary counselling (WR + WM groups were combined as there was 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	Pre-menopausal women; BMI > 29 kg/m^2; no regular medication (except contraceptives); no ischaemic 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 (SD 11·5) WR + WM: 92·2 (SD 9·8)	Control: 85·0 (SD 11·6)* WR + WM: 79·1 (SD 10·0)***	Control: not applicable WR + WM: 79·7 (SD 10·9)***§

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Table 1. *Continued*

Author	*n* (males)	Study	Inclusion criteria	Duration of VLED	Duration of follow-up	Weight (kg) at baseline	Weight (kg) at the end of the VLED	Weight (kg) at the end of the follow-up
Wikstrand *et al.*[32]	91 (26)	Cohort study where patients underwent 3 months of VLED and lifestyle advice group meetings. Those who attained ≥8 kg reduction weight were randomised to two groups, corset wearing and no corset, for 9 months and followed up at 24 months	Men and women; 30–60 years old; BMI ≥30– < 45 kg/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 (SD 7·0)§ Group B: Δ −4·4 (SD 7·3)§
Willi *et al.*[33]	20	Cohort study of children who undertook VLED as part of diabetic treatment. All had varying lengths of VLED (mean 60 (SD 8) d) as they continued until predefined treatment goals, i.e. a 10 % reduction in BMI, were reached. They were followed up for 24 months	Children with type 2 diabetes; BMI >30 kg/m^2	60 (SD 8) d	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 LAGB or to a dietary weight-loss programme where patients followed a VLED for 12 weeks followed by a transition phase over 4 weeks combining VLED 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; BMI 30–35 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 programme	12 weeks	24 months	LAGB: 95·8 (SD 11·3) VLED: 93·3 (SD 9·9)		LAGB: 74·9 (SD 11·5)‡‡ VLED: 87·4 (SD 11·2)
Fogelholm *et al.*[27] also in CVD risks	85 (0)	Randomised clinical trial where patients underwent 3 months of VLED 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 4184 kJ (1000 kcal) or 8368 kJ (2000 kcal) weekly. Patients were then followed up 24 months later	Women; BMI 30–46 kg/m^2; 30–45 years old; pre-menopausal; weight stable; no medications, (except hormonal contraceptives); sedentary, not pregnant or lactating; non-smokers; no BED or bulimia	3 months	3 years	92·0 (SD 9·8)	Δ −13·2 (SD 3·3)*	Δ −4·9 (SD 7·1)*
Hinton *et al.*[35]	37 (13)	Randomised cohort control study where patients were assigned to 3 months of VLED. If 10 % initial weight was lost, then patients were randomised either to a LF or LCHO for 9 months	Men and women; 19–70 years old; sedentary; BMI >27 kg/m^2; weight stable; healthy as determined from a health history questionnaire and medical examination	3 months	12 months	111·6 (SD 17·8)	90·1 (SD 14·5)*	93·4 (SD 18·3)*

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Table 1. *Continued*

Author	*n* (males)	Study	Inclusion criteria	Duration of VLED	Duration of follow-up	Weight (kg) at baseline	Weight (kg) at the end of the VLED	Weight (kg) at the end of the follow-up
Respiratory disorders								
Kajaste *et al.*[36]	31 (31)	Randomised control study where all patients received 6 weeks of VLED and 24 months of behaviour therapy. During this time, half the patients underwent treatment with CPAP, while the 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 (SD 16·0) Non-CPAP: 145·5 (SD 23·4) Combined: 140 (SD 20)	–	Combined: 134 (SD 24·1)*
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 of VLED	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 2 years or more before the age of 50 years	8 weeks	1 year	–	Control: 0·3 (no 95 % CI) Treatment: Δ - 14·2 (95 % CI 7·7, 22·1)§	Control: Δ 2·3 (no 95 % CI) Treatment: Δ −11·1 (95 % CI 1·1, 22·5)§
Tuomilehto *et al.*[24] also in CVD risks	72 (53)	Randomised controlled parallel trial where the treatment group received VLED plus lifestyle modification while the control group received lifestyle counselling only	18–65 years old; BMI $28–40\,kg/m^2$; AHI, 5–15 events/h	12 weeks	1 year	Control: 92·3 (SD 11·3) Treatment: 101·2 (SD 11·9)‡	–	Control: Δ −2·4 (SD 5·6) Treatment: Δ −10·7 (SD 6·5)‡‡
Eating disorders								
de Zwaan *et al.*[39]	71 (0)	Clinical trial where patients underwent 12 weeks of VLED, 6 weeks of food reintroduction, 6 weeks of weight maintenance. After the first 2 weeks of refeeding, half of the BED participants, were randomly assigned to an additional 10-week CBT component	Women; 18–55 years old; at least 22·7 kg above 'ideal' body weight, BED	12 weeks	12 months	BED only: 97·7 (SD 12·7) BED + CBT: 98·8 (SD 11·3)	BED only: 83·0 (SD 11·4) BED + CBT: 85·6 (SD 11·6)‡	BED only: 92·1 (SD 13·8) BED + CBT: 93·1 (SD 14·5)
Legenbauer *et al.*[40]	251 (69)	Prospective longitudinal study where patients underwent 3 months of VLED followed by 9 months refeeding. Patients were then grouped as 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 (SD 25·1)	–	USWM: 123·7 (SD 27·0)‡ SWM: 111·7 (SD 23·8)
Legenbauer *et al.*[41]	403 (124)	Longitudinal naturalistic study where those in the VLED group underwent 3 months of VLED and a 9-month refeeding period with weekly group sessions for 1 year. These patients were compared with patients who underwent 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	VLED: 121·1 (SE 1·7) BS: 148·0 (SE 2·2)	–	VLED: 114·7 (SE 1·9)* BS: 116·6 (SE 2·2)*

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Table 1. *Continued*

Author	*n* (males)	Study	Inclusion criteria	Duration of VLED	Duration of follow-up	Weight (kg) at baseline	Weight (kg) at the end of the VLED	Weight (kg) at the end of the follow-up
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 VLED, 6 weeks of food reintroduction, 6 weeks of weight maintenance. After the first 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 22·7 kg above-average body weight for their height	12 weeks	12 months	–	BED: Δ −17·5 (SD 8·4) Sub-BED: Δ −19·1 (SD 8·3) No-BED: Δ −13·8 (SD 7·9)	Percentage of weight regain: BED: 70 % (SD 86·2) Sub-BED: 71·7 % (SD 36·7) No-BED: 68·6 % (SD 54·5)

VLED, very-low-energy diet; HC, high-carbohydrate diet; HP, high-protein diet; Δ, change; LED, low-energy diet; T2DM, type 2 diabetes mellitus; MK-0557, highly selective, orally administered neuropeptide Y Y5 receptor antagonist; BED, binge eating disorder; BP, blood pressure; LCHP, low-carbohydrate, high-protein diet; LL, lighter Life; CAD, coronary artery disease; WR, weight reduction; WM, weight maintenance; ECG, electrocardiogram; IDDM, insulin-dependent diabetes; GI, gastrointestinal; LAGB, laparoscopic gastric band; LF, low fat; LCHO, low carbohydrate; CPAP, continuous airway positive pressure; ODI_4, oxygen desaturation index; N/A, not available; AHI, apnoea–hypopnoea index; CBT, cognitive behaviour therapy; SWM, successful weight maintainers; USWM, unsuccessful weight maintainers; BS, bariatric paper.
Mean values were significantly different from baseline: * $P<0·05$, ** $P<0·001$, *** $P<0·0001$.
Mean values were significantly different from VLED end: † $P<0·05$.
Mean values were significantly different between groups: ‡ $P<0·05$, ‡‡ $P<0·001$.
§ No *P* value provided in original paper.

Total cholesterol

There were twelve studies that reported changes in total cholesterol at VLED end[4,10,11,14,18–23,29,30]. Of these, three studies[4,11,19] reported significant improvements in cholesterol at VLED end, two of which presented a sustained significant improvement at study end[4,11]. Of fifteen 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 twenty studies[10–14,16–25,28–32]. Of these studies, fourteen reported VLED end data, two of which interestingly reported a significant reduction in HDL[11,19]. Of these, nine, however, showed significantly increased HDL levels in the VLED 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 in the VLED arm.

LDL-cholesterol

Changes in LDL were reported in fourteen studies[10,12,14,16–18,20–23,29–32]. Of the nine studies reporting data at VLED end[10,14,16,18,20–23,29], one showed a significant reduction in LDL[20]. From the information on the fourteen studies reported at follow-up, significant LDL reduction was observed in two studies[14,29].

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

Insulin and glucose control

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

Of the nine studies[10,11,14–16,18,21,24,31] that reported insulin levels at study end, three showed significant improvements[11,14,15] while five[10,14,16,18,21] reported VLED end data which showed no significant change.

HbA_{1c} also represented by fructosamine was reported in seven studies[4,12,19,21,23,29,33]. Of these, three studies showed significant improvements in the VLED groups at study end[4,23,29]. Interestingly, Jazet *et al.*[19] reported a significant improvement in HbA_{1c} in six patients who regained more than 5 kg weight by the study end[19].

We identified four studies where the number of patients taking daily insulin or actual insulin doses were reported[4,12,19,33]. In the three studies that reported insulin doses at study end, reduced daily doses of insulin were

Table 2. Quality assessment of the reported studies, separated by co-morbidity 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-Aarniala *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

noted although statistical significance was not reported[4,19,33]. Only one study reported an increase in insulin users in the VLED 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, the time of VLED duration, the time of follow-up and the nature of follow-up did not predict glycaemic outcomes in the long term.

Liver and kidney function

Of the thirty-two papers identified, only two commented on 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, reported significant improvements in alanine aminotransferase (30·0 (SD 17·8) *v.* 23·2 (SD 8·9) U/l; $P<0·05$); alkaline phosphatase (81·6 (SD 19·6) *v.* 78·0 (SD 22·1) U/l; $P<0·05$); γ-glutamyl transferase (33·8 (SD 33·7) *v.* 24·1 (SD 17·7) U/l; $P<0·05$) and estimated glomerular filtration rate (1·29 (SD 11·6) *v.* 1·33 (SD 0·19) ml/s; $P<0·05$) from post-screening to 9 months.

Fertility

In one study, the impact of VLED-induced weight loss on fertility and sexual function was examined[28]. Sex hormone-binding globulin rose significantly from 27·6 (SD 11·9) to 48·1 (SD 23·5) nmol/l at VLED end ($P<0·0001$) and remained significant despite declining by study end (32·6 (SD 12·9) nmol/l; $P<0·001$). Free testosterone levels also increased significantly by VLED end and remained elevated at 212 (SD 84) pmol/l at 1 year ($P=0·002$), compared with baseline (185 (SD 66) pmol/l). The number of men presenting with biochemical hypoandrogenism (total testosterone <11 nmol/l) decreased significantly during the VLED ($P<0·001$) and at the 1-year follow-up ($P=0·002$).

Table 3. Summary of the results for blood pressure and waist circumference

		Systolic blood pressure (mmHg)			Diastolic blood pressure (mmHg)			Waist circumference (cm)		
Study	Patient groups	Pre-VLED	Post-VLED	Study end	Pre-VLED	Post-VLED	Study end	Pre-VLED	Post-VLED	Study end
Delbridge *et al.*[22]	All	–	Δ −13·2 (SE 1·4)**	Δ −11·1 (SE 1·7)**	–	Δ −8·5 (SE 1·1)**	Δ −5·2 (SE 1·3)**	–	Δ −14·2 (SE 0·5)**	Δ −16·0 (SE 1·1)**
	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)‡	–	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 (SD −17)	Δ −10*	No value*	82 (SD −9)	Δ −6a	No value*	–	–	–
Erondu *et al.*[18]	Placebo	125·3 (SD −14·2)	116 (SD −12·2)	121·4 (SD −14·1)	80·6 (SD −7·9)	75·7 (SD −8·1)	77·9 (SD −8·8)	109·8 (SD −11·3)	102·2 (SD −10·7)	103·7 (SD −11·4)
	MK-0557	124 (SD −13·9)	115·1 (SD −12·8)	121·4 (SD −14·9)	79·6 (SD −8·4)	74·7 (SD −8·9)	76·3 (SD −9·2)	108·5 (SD −11·7)	99·9 (SD −11·2)	100 (SD 12·0)‡
Fogelholm *et al.*[10]	Control	119 (SD −10)	115 (SD −12)	125 (SD −13)	78 (SD −7)	77 (SD −8)	81 (SD −7)	102 (SD −9)	91·1 (SD −8·2)	98·1 (SD −9)
	Walk 1	119 (SD −10)	116 (SD −11)	127 (SD −12)	78 (SD −7)	80 (SD −8)	81 (SD −8)	102 (SD −9)	90·1 (SD −7·1)	93·4 (SD −11·3)
	Walk 2 + counselling	119 (SD −10)	114 (SD −8)	123 (SD −13)	78 (SD −7)	78 (SD −6)	79 (SD −9)	102 (SD −9)	89·8 (SD −9·6)	95·3 (SD −10·8)
Fogelholm *et al.*[27]	All	–	–	–	–	–	–	102 (SD −9)	Δ −12 (SD 4)*	Δ −7 (SD 8)*
Gripeteg *et al.*[25]	1-week refeeding	–	128·8 (SD −16·4)	No value§	–	84 (SD −10·3)	–	–	124·8 (SD −14·8)	No value§
	6-week refeeding	–	130·8 (SD −16·5)	No value§	–	85·7 (SD −12·7)	No value§	–	125·5 (SD −15·9)	No value§
Jazet *et al.*[19]	All	169 (SD −8)	Δ −27 (SE 6)*	Δ −27 (SE 7)*	96 (SD −4)	Δ −14 (SE 4)*	Δ −17 (SE 4)*	122 (SD 2·2)	Δ −8·6 (SE 0·9)***	Δ −5·8 (SE 2·1)*
Kukkonen-Harjula *et al.*[16]	All	131 (SD −13)	Δ −6 (95 % CI −8, −4)	Δ 2 (95 % CI −1, 5)	84 (SD −11)	Δ −8 (95 % CI −10, −6)	Δ 2 (95 % CI −0, 4)	–	–	–
	Control	129 (SD −13)	–	132 (SD −15)	82 (SD −21)	–	84 (SD −10)	–	–	–
	Walk	130 (SD 14)	–	131 (SD −19)	82 (SD −12)	–	84 (SD −10)	–	–	–
	Resistance	132 (SD −13)	–	136 (SD −15)	85 (SD −9)	–	87 (SD −10)	–	–	–
Laaksonen *et al.*[13]	All	129·4 (SD − 8·6)	119·9 (SD − 8·4)	126·5 (SD 8·5)**	79·4 (SD − 5·9)	74·4 (SD − 5·6)	77·8 (SD 6·8)***	115 (SD − 8)	103 (SD − 8)	103 (SD 10)**
Lantz *et al.*[14]	All	134 (SD −19)	Δ −6 (95 % CI −9, −3)	Δ 0 (95 % CI −3, 3)	80 (SD −11)	Δ −4 (95 % CI −6, −2)	Δ 0 (95 % CI −2, 2)	120·6 (SD −11·4)	–	Δ −6·7 (95 % CI −8·4, 5·1)
Linna *et al.*[20]	All	131·0 (SD −12·6)	124·8 (SD 14·2)**	133·3 (SD 16·0)**	83·6 (SD −10·9)	76·1 (SD 9·3)**	85·1 (SD 9·9)**	112·1 (SD −7)	97·5 (SD 8·1)**	106·7 (SD 10·1)**
	Subgroup 1	131·2 (SD −13·9)	128·4 (SD −15·7)	132·6 (SD 17·5)*	83·5 (SD −12·2)	76·3 (SD 9·8)*	82·4 (SD 10·3)*	111·7 (SD −5·1)	95·7 (SD 7·1)**	98·3 (SD 8·1)*
	Subgroup 2	130·9 (SD −12·3)	123·3 (SD 13·5)**	133·7 (SD 15·7)**	84 (SD −10·2)	76·2 (SD 9·2)**	86·6 (SD 9·3)**	112·7 (SD −8·1)	98·3 (SD 8·4)**	110·3 (SD 8·7)**‡‡
Madsen *et al.*[29]	Orlistat	–	–	–	–	–	–	117·4 (95 % CI 114, 121)	106·5 (95 % CI 103·3, 109·9	108·7 (95 % CI 104·7, 112·8)†
	Placebo	–	–	–	–	–	–	117·4 (95 % CI 114, 121·6)	105·9 (95 % CI 102·4, 109·4	112·2 (95 % CI 107·7, 116·8)
Madsen *et al.*[30]	Orlistat	–	–	–	–	–	–	118·4 (SD −11·6)	107·4 (SD −9·7)	109·7 (SD 12·6)‡
	Placebo	–	–	–	–	–	–	119·5 (SD −11)	107·8 (SD −9·8)	114·1 (SD −12)
Mathus-Vliegen *et al.*[17]	Sibutramine	137 (SD −14·8)	Δ −14·9 (SD −14·2)	–	84·1 (SD −7·2)	Δ −7·0 (SD −7·3)	–	–	–	Δ −3·4 (No SD)‡
	Placebo	136·2 (SD −13)	Δ −14·6 (SD −14·2)	–	84·2 (SD −6·6)	Δ −5·9 (SD −7·7)	–	–	–	Δ −5·4 (No SD)
Melin *et al.*[15]	Intensive therapy	129 (SE 3·6)	–	Δ −9·8 (SE 4·2)*	83·2 (SE 1·6)	–	Δ −6·6 (SE 2·3)*	–	–	–
	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 (SD −19)	–	–	97 (SD −11)	–	–	121 (SD −10)	108 (SD −9)	108 (SD 12)**
Paisey *et al.*[12]	VLED	139 (SD −17)	–	143 (SD −13)	76 (SD −10)	–	77 (SD −11)	117 (SD −24)	–	114 (SD −20)
	Diet and exercise	142 (SD −22)	–	130 (SD −20)	85 (SD −13)		74 (SD 13)**	113 (SD −13)	–	108 (SD −4)
Richelsen *et al.*[21]	Orlistat	144 (SD −19·3)	Δ −13	Δ −7·8	90·8 (SD −11·6)	Δ −7·2	Δ −3·7	119 (SD −12·1)	Δ −12	Δ −5·4
	Placebo	144 (SD −17·3)	Δ −12	Δ −8·2	90·7 (SD −11·6)	Δ −7·6	Δ −4·7	119 (SD −10·9)	Δ −12	Δ −7·7e
Rolland *et al.*[23]	LCHP	136·7 (SD −22)	132 (SD −18·6)	133·1 (SD −16·6)	89 (SD −9·6)	87·7 (SD −8·2)	86·6 (SD −8·4)	122·6 (SD −9·9)	119·1 (SD 10·0)§	119 (SD 10·8)§

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Table 3. *Continued*

Study	Patient groups	Systolic blood pressure (mmHg)			Diastolic blood pressure (mmHg)			Waist circumference (cm)		
		Pre-VLED	Post-VLED	Study end	Pre-VLED	Post-VLED	Study end	Pre-VLED	Post-VLED	Study end
	VLED	134·8 (SD −18·4)	127·8 (SD 15·2)§	128·2 (SD 8·0)§	87·7 (SD −13)	81·8 (SD 10·8)‡‡§	83·2 (SD 12·4)§	126·3 (SD 14·9)	119·1 (SD 16·4)§	114·5 (SD 16·0)‡§
Tuomilehto *et al.*[24]	Control	130 (SD −12·8)	–	Δ −1·1 (SD −19·6)	80·7 (SD −7·8)	–	Δ −0·4 (SD −12·6)	105·3 (SD −8·3)	–	Δ −3·0 (SD −6)
	Intervention	131·2 (SD −10·2)	–	Δ −1·7 (SD −14·7)	81·8 (SD −8·9)	–	Δ −1·9 (SD −10·6)	112·5 (SD −8·7)	–	Δ −11·6 (SD 6·6)‡‡
Vasankari *et al.*[11]	All	119 (SD −10)	113 (SD 16)***	121 (SD 10)**	78 (SD −7)	71 (SD 10)***	79 (SD 7)***	102 (SD −8·5)	90·3 (SD 8·3)***	90·1 (SD −9·2)
Wikstrand *et al.*[32]	Corset	136 (SD −20)	–	–	79 (SD −14)	–	–	–	–	–
	No corset	134 (SD −18)	–	–	79 (SD −10)	–	–	–	–	–

VLED, very-low energy diet; Δ, change; HC, high-carbohydrate diet; HP, high-protein diet; MK-0557, highly selective, orally administered neuropeptide Y Y5 receptor antagonist; LCHP, low-carbohydrate, high-protein diet.
Mean values were significantly different from baseline: * $P<0·05$, ** $P<0·001$, *** $P<0·0001$.
Mean values were significantly different from VLED end: † $P<0·05$.
Mean values were significantly different between groups: ‡ $P<0·05$, ‡‡ $P<0·001$.
§ Statistical significant difference from baseline stated but no P value given.

Bone health

In three papers, changes in bone mass following a VLED intervention were examined[27,34,35]. The 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 and C-terminal telopeptide of type I collagen (CTX) as markers of bone formation and resorption, respectively.

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

Fogelholm *et al.*[27] similarly examined changes in bone mineral density (BMD) or bone mineral content (BMC) in three groups of postmenopausal women (Table 1). At VLED end, total BMC remained unchanged; however, 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 the 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 BMC had decreased significantly in the laparoscopic gastric band (−0·087 (SD 0·12); $P=0·002$) as well as the intensive dietary weight-loss group (−0·061 (SD 0·9); $P=0·002$) at 24 months. The changes were not significant between the two groups.

Respiratory disorders

Sleep apnoea. In two studies, the effect of VLED on the alleviation of symptoms associated with the obstructive sleep apnoea syndrome was investigated[24,36] and in one study the effects of weight reduction in obese patients with asthma were examined[37].

Kajaste *et al.*[36] did not provide VLED end data, although other time periods of 6, 12, 24 months and study end were reported. No significant differences were observed for weight loss at any point of the study. Changes in sleep apnoea were assessed by measuring the oxygen desaturation index, the average number of oxygen desaturation events per h of sleep exceeding 4 % from baseline. Improvements in oxygen desaturation index from baseline were significant at 24 months. Significant correlations were observed between oxygen desaturation index improvements and weight change at 6 and 24 months ($P<0·001$). At the 3-year follow-up, five patients reported no obstructive sleep apnoea syndrome symptoms.

Tuomilehto *et al.*[24] assessed changes in sleep apnoea by measuring the apnoea–hypopnoea index (AHI). At VLED end, the mean total AHI was statistically improved in the VLED *v.* control group ($P=0·036$). Based on the AHI values, twenty-two of the thirty-six patients (61 %) in the intervention

Table 4. Summary of the blood lipid results

Study	Patient groups	TAG (mmol/l)			Total cholesterol (mmol/l)			HDL (mmol/l)			LDL (mmol/l)		
		Pre-VLED	Post-VLED	Study end	Pre-VLED	Post-VLED	Study end	Pre-VLED	Post-VLED	Study end	Pre-VLED	Post-VLED	Study end
Delbridge *et al.*[22]	All	–	Δ −0·90 (SE 0·19)**	Δ −0·74 (SE 0·13)**	–	Δ −0·65 (SE 0·08)**	Δ −0·39 (SE 0·09)**	–	Δ −0·00 (SE 0·02)	Δ 0·20 (SE 0·02)**	–	Δ 0·14 (SE 0·05)	Δ −0·30 (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)	Δ 0·11 (SE 0·03)	–	Δ 0·59 (SE 0·92)	Δ −0·16 (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 −0·17 (SE 0·09)
Dhindsa *et al.*[4]	T2DM, obese	3·4 (SD 1·7)	–	–	6·0 (SD 1·2)	No value*	No value*	–	–	–	–	–	–
Erondu *et al.*[18]	Placebo	3·26 (SD 1·8)	2·40 (SD 1·06)	2·87 (SD 1·35)	5·31 (SD 0·84)	4·32 (SD 0·83)	5·11 (SD 0·95)	1·45 (SD 0·34)	1·26 (SD 0·25)	1·48 (SD 0·37)	3·14 (SD 0·74)	2·52 (SD 0·73)	3·00 (SD 0·82)
	MK-0557	1·34 (SD 0·8)	1·08 (SD 0·5)	1·14 (SD 0·6)	5·23 (SD 0·9)	4·31 (SD 0·8)	5·04 (SD 0·9)	1·41 (SD 0·36)	1·22 (SD 0·29)	1·48 (SD 0·40)	3·12 (SD 0·77)	2·56 (SD 0·72)	2·97 (SD 0·73)
Fogelholm *et al.*[10]	Control	1·30 (SD 0·50)	0·96 (SD 0·26)	1·31 (SD 0·72)	5·0 (SD 0·9)	4·6 (SD 0·8)	5·4 (SD 0·8)	1·22 (SD 0·24)	1·12 (SD 0·18)	1·34 (SD 0·28)	5·0 (SD 0·9)	4·6 (SD 0·8)	5·4 (SD 0·8)
	Walk 1	1·30 (SD 0·50)	1·02 (SD 0·36)	1·17 (SD 0·45)	5·0 (SD 0·9)	4·2 (SD 0·7)	5·1 (SD 0·8)	1·22 (SD 0·24)	1·12 (SD 0·27)	1·41 (SD 0·31)	5·0 (SD 0·9)	4·2 (SD 0·7)	5·1 (SD 0·8)
	Walk 2 + counselling	1·30 (SD 0·50)	0·96 (SD 0·34)	1·20 (SD 0·45)	5·0 (SD 0·9)	4·1 (SD 0·7)	5·0 (SD 0·9)	1·22 (SD 0·24)	1·13 (SD 0·19)	1·36 (SD 0·23)	5·0 (SD 0·9)	4·1 (SD 0·7)	5·0 (SD 0·9)
Gripeteg *et al.*[25]	1-week refeeding	1·6 (SD 0·8)	–	No value§	–	–	–	1·3 (SD 0·2)	–	No value§	–	–	–
	6-week refeeding	1·5 (SD 0·7)	–	No value§	–	–	–	1·3 (SD 0·3)	–	No value§	–	–	–
Jazet *et al.*[19]	All	3·5 (SE 0·8)	Δ −1·7 (SE 0·7)*	Δ −0·9 (SE 0·5)*	5·6 (SE 0·04)	Δ −0·9 (SE 0·3)*	Δ −0·03 (SE 0·3)	1·1 (SE 0·06)	Δ −0·1 (SE 0·04)*	Δ 0·2 (SE 0·06)*	–	–	–
Kukkonen-Harjula *et al.*[16]	All	–	–	–	–	–	–	1·18 (SD 0·25)	Δ 0·01 (95 % CI −0·00, 0·04)	Δ 0·01 (95 % CI 0·05, 0·11)	–	–	–
	Control	–	–	–	–	–	–	1·18 (SD 0·23)	–	1·27 (SD 0·27)	–	–	–
	Walk	–	–	–	–	–	–	1·19 (SD 0·23)	–	1·25 (SD 0·20)	–	–	–
	Resistance	–	–	–	–	–	–	1·15 (SD 0·27)	–	1·24 (SD 0·31)	–	–	–
Laaksonen *et al.*[13]	Orlistat + placebo combined	Median 2·2 (IR 1·6, 2·8)	Median 1·0 (IR 0·8, 1·4)	Median 1·4 (IR 1·2, 1·8)**	–	–	–	1·09 (SD 0·18)	1·17 (SD 0·22)	1·22 (SD 0·26)**	–	–	–
Lantz *et al.*[14]	All	1·7 (SD 0·9)	Δ −0·4 (95 % CI −0·5, −0·2)	Δ −0·1 (95 % CI −0·3, 0·2)	5·6 (SD 1·1)	Δ −0·5 (95 % CI −0·6, −0·3)	Δ −0·1 (95 % CI −0·3, 0·07)	1·2 (SD 0·3)	Δ 0·0 (95 % CI −0·04, 0·05)	Δ 0·2 (95 % CI 0·1, 0·2)§	3·6 (SD 0·9)	Δ −0·3 (95 % CI −0·5, −0·2)	Δ −0·2 (95 % CI −0·4, −0·08)§
Linna *et al.*[20]	All	–	Δ −28 % (95 % CI 22·9, 33·8)**	Δ −5 % (95 % CI −6·3, 16·7)*‡‡	–	Δ −21 % (95 % CI 17·9, 23·2)**	No Δ	–	No Δ	Δ 8 % (95 % CI 4·6, 11·0)**‡‡	–	Δ −23 % (95 % CI 19·9, 26·1)**	No Δ
	Subgroup 1	–	–	Δ −23 % (95 % CI 13·3 − 32·8)**‡	–	–	No Δ‡	–	Δ 16 % (95 % CI 9·7, 23·4)**	Δ 12 % (95 % CI −6·6, 17·7)**‡	–	Δ −17 % (95 % CI −3·3, 12·1)	No Δ
	Subgroup 2	–	–	No Δ	–	–	No Δ	–	Δ 15 % (95 % CI 10·0, 19·4)**	Δ 6 % (95 % CI −2·1, 9·1)*	–	Δ −25 % (95 % CI 17·9, 31·2)	No Δ
Madsen *et al.*[29]	All	–	–	Δ −12 % (95 % CI −1·3, 21·5)*	–	–	Δ −7·5 % (95 % CI −2·9, −11·8)*	–	–	Δ −1·6 % (95 % CI −6·1, 2·7)	–	–	Δ −10·5 % (95 % CI −4·1, 16·4)*
	Orlistat	2 (95 % CI 1·7, 2·3)	1·5 (95 % CI 1·2, 1·7)	1·8 (95 % CI 1·5, 2·1)	6 (95 % CI 5·5, 6·4)	4·9 (95 % CI 4·5, 5·3)	5·6 (95 % CI 5·2, 5·9)	1·15 (95 % CI 1·07, 1·23)	1·09 (95 % CI 1·01, 1·17)	1·14 (95 % CI 1·05, 1·24)	3·8 (95 % CI 3·4, 4·1)	3 (95 % CI 2·8, 3·4)	3·4 (95 % CI 3·1, 3·8)
	Placebo	2·2 (95 % CI 1·8, 2·6)	1·5 (95 % CI 1·3, 1·8)	1·9 (95 % CI 1·6, 2·3)	5·8 (95 % CI 5·4, 6·3)	4·5 (95 % CI 4·2, 4·9)	5·4 (95 % CI 5·1, 5·8)	1·16 (95 % CI 1·08, 1·25)	1·08 (95 % CI 1, 1·17)	1·17 (95 % CI 1·06, 1·28)	3·5 (95 % CI 3·2, 3·9)	2·7 (95 % CI 2·4, 3)	3·2 (95 % CI 2·9, 3·5)
Madsen *et al.*[30]	Orlistat	2·2 (SD 0·8)	1·6 (SD 0·7)	2·0 (SD 0·9)	6·0 (SD 1·2)	5·0 (SD 1·1)	5·5 (SD 1·0)	1·16 (SD 0·28)	1·1 (SD 0·3)	1·2 (SD 0·3)	3·9 (SD 1·1)	3·2 (SD 0·9)	3·5 (SD 0·9)
	Placebo	2·5 (SD 1·4)	1·7 (SD 0·8)	2·2 (SD 1·1)	5·9 (SD 1·2)	4·7 (SD 1·0)	5·4 (SD 0·9)	1·16 (SD 0·22)	1·1 (SD 0·2)	1·2 (SD 0·3)	3·6 (SD 1·0)	2·8 (SD 0·8)	3·2 (SD 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)**	–	–	–	1·08 (SD 0·23)	1·16 (SD 0·26)	1·16 (SD 0·27)*	–	–	–
Paisey *et al.*[12]	VLED	3·9 (SD 3·4)	–	2·9 (SD 2·3)	6·8 (SD 1·2)	–	5·7 (SD 1·3)*	1·20 (SD 0·39)	–	1·26 (SD 0·47)	3·85 (SD 1·57)	–	3·42 (SD 1·38)

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Table 4. *Continued*

Study	Patient groups	TAG (mmol/l)			Total cholesterol (mmol/l)			HDL (mmol/l)			LDL (mmol/l)		
		Pre-VLED	Post-VLED	Study end	Pre-VLED	Post-VLED	Study end	Pre-VLED	Post-VLED	Study end	Pre-VLED	Post-VLED	Study end
	Diet and exercise	2·4 (SD 1·3)	–	2·5 (SD 1·5)	5·9 (SD 1·3)	–	5·3 (SD 1·5)	1·10 (SD 0·32)	–	1·78 (SD 0·26)*	3·83 (SD 0·73)	–	3·25 (SD 0·65)
Richelsen *et al.*[21]	Orlistat	2·36 (SD 1·24)	Δ −0·89	Δ −0·38	5·91 (SD −1·26)	Δ −1·2	Δ −0·46	1·13 (SD 0·26)	Δ −0·05	Δ 0·04	3·71 (SD 1·04)	Δ −0·75	Δ −0·34
	Placebo	2·5 (SD 1·41)	Δ −0·94	Δ −0·43	6·02 (SD −1·08)	Δ −1·2	Δ −0·46	1·15 (SD 0·26)	Δ −0·07	Δ 0·06	3·77 (SD 0·94)	Δ −0·8	Δ −0·38
Rolland *et al.*[23]	LCHP	1·7 (SD 1·1)	1·5 (SD 0·8)	1·5 (SD 0·9)	5·5 (SD 1·0)	5·4 (SD 0·9)	5·3 (SD 1·0)	1·45 (SD 0·32)	1·44 (SD 0·32)	1·44 (SD 0·35)	3·3 (SD 0·8)	3·3 (SD 0·8)	3·2 (SD 0·8)
	VLED	1·3 (SD 0·7)	1·2 (SD 0·7)	1·1 (SD 0·7)§	5·1 (SD 0·9)	4·6 (SD 1·1)‡§	4·8 (SD 1·0)§	1·31 (SD 0·22)	1·25 (SD 0·22)‡§	1·38 (SD 0·25)§	3·1 (SD 0·8)	2·9 (SD 0·9)‡§	2·9 (SD 0·9)§
Simonen *et al.*[31]	All	3·79 (SE 0·56)	–	2·64 (SE 0·36)*	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)
Tuomilehto *et al.*[24]	Control	1·59 (SD 0·92)	–	Δ −0·06 (SD 0·65)	–	–	–	1·11 (SD 0·37)	–	Δ 0·05 (SD 0·22)	–	–	–
	Intervention	1·74 (SD 1·17)	–	Δ −0·48 (SD 1·13)	–	–	–	1·02 (SD 0·23)	–	Δ 0·14 (SD 0·22)	–	–	–
Vasankari *et al.*[11]	All	1·29 (SD 0·46)	1·00 (SD 0·34)**	1·22 (SD 0·67)	4·98 (SD 0·83)	4·33 (SD 0·77)**	4·72 (SD 0·88)**	1·22 (SD 0·25)	1·13 (SD 0·21)**	1·36 (SD 0·26)**	–	–	–
Wikstrand *et al.*[32]	Corset	1·60 (SD 0·77)	–	1·02 (SD 0·49)**	5·4 (SD 0·9)	–	5·2 (SD 0·91)	1·45 (SD 0·30)	–	1·64 (SD 0·30)*	3·14 (SD 0·85)	–	3·02 (SD 0·89)
	No corset	1·58 (SD 0·74)	–	1·26 (SD 0·77)*	5·6 (SD 0·9)	–	5·6 (SD 0·9)	1·61 (SD 0·77)	–	1·57 (SD 0·24)	3·25 (SD 0·63)	–	3·31 (SD 0·83)

VLED, very-low energy diet; Δ, change; HC, high-carbohydrate diet; HP, high-protein diet; T2DM, type 2 diabetes mellitus; MK-0557, highly selective, orally administered neuropeptide Y Y5 receptor antagonist; IR, interquartile range; LCHP, low-carbohydrate, high-protein diet.
Mean values were significantly different from baseline: * $P<0·05$, ** $P<0·001$.
Mean values were significantly different between groups: ‡ $P<0·05$, ‡‡ $P<0·001$.
§ Statistical significant difference from baseline stated but no *P* value given.

group, and in twelve of the thirty-eight patients (32 %) in the control group, were objectively cured ($P=0·019$) at VLED end. This change was maintained at the 1-year follow-up, where the mean total AHI in the intervention group was 6·0 events/h and that in the control group was 9·6 events/h ($P=0·043$). 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 in mean arterial oxygen saturation were observed in the intervention group when compared with the control group after 1 year.

Asthma. Stenius-Aarniala *et al.*[37] was the only study which investigated the effects of VLED on obese patients with asthma. The details of the study design are given in Table 1.

Data for flow vital capacity and forced expiratory volume in 1 s were collected. Forced expiratory volume in 1 s (percentage of predicted) improved significantly more in the treatment group at VLED end, and was maintained even after 1 year ($P=0·02$). There was also a significantly greater median reduction of dyspnoea in the treatment group when compared with the control group (13 *v.* 1 mm on the visual analogue scale; $P<0·05$). The daily use of rescue sympathomimetics decreased significantly more in the treatment group (1·2 *v.* 0·1 doses; $P<0·05$).

Eating disorders

Binge eating disorder. In two studies, the effect of VLED on binge eating disorder (BED) was reported[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 when compared with the BED + CBT group at any time point. However, during the fasting period of VLED, an improvement in the absence of binge eating was observed in both groups (80·6 % were binge free in the BED + CBT group *v.* 80·4 % in the BED − CBT group; $P=0·98$). At study end, forty-seven 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 VLED programme. The details of the study are given in Table 1. At baseline, sixty-three participants were diagnosed with BED, thirty-six with sub-threshold BED and twenty-nine with no binge eating symptoms (no BED). Of the sixty-three individuals with BED, thirty-six (57 %) no longer met the criteria at 12 months. Conversely, at 12 months, sixteen (13 %) of the BED patients moved to a more severe category. At 12-month follow-up, nine of the patients (25 %) with sub-threshold BED and three (10 %) with no BED at baseline also met the full BED criteria. A significant association was found between BED diagnosis and weight gained at 12-month follow-up ($P=0·0087$).

Mental health. The effects of VLED on mental health were investigated in two studies. In one study, depression was

Table 5. Summary of the glycaemia results

		Fasting glucose (mmol/l)			Fasting insulin (mU/l)§§			HBA_{1c} (%)			Fructosamine (μM)		
Study	Patient groups	Pre-VLED	Post-VLED	Study end	Pre-VLED	Post-VLED	Study end	Pre-VLED	Post-VLED	Study end	Pre-VLED	Post-VLED	Study end
Dhindsa *et al.*[22]	T2DM, obese	–	–	–	–	–	–	–	–	–	387 (SD 71)	346 (SD 49)**	371 (SD 41)**
Erondu *et al.*[18]	Placebo	5·2 (SD 0·6)	5·0 (SD 0·6)	5·2 (SD 0·7)	12·7 (SD 7·0)	7·7 (SD 5·2)	11·3 (SD 12·6)	–	–	–	–	–	–
	MK-0557	5·2 (SD 0·6)	5·1 (SD 0·6)	5·3 (SD 0·7)	13·0 (SD 12·1)	7·0 (SD 5·0)	11·2 (SD 12·1)						
Fogelholm *et al.*[10]	Control	5·1 (SD 0·5)	5·0 (SD 0·4)§	5·5 (SD 1·1)§	10·9 (SD 4·5)	6·8 (SD 2·3)§	10·4 (5·3)§	–	–	–	–	–	–
	Walk 1	5·1 (SD 0·5)	4·8 (SD 0·3)§	5·3 (SD 0·4)§	10·9 (SD 4·5)	6·5 (SD 2·2)§	8·4 (SD 3·5)§	–	–	–	–	–	–
	Walk 2 + counselling	5·1 (SD 0·5)	4·9 (SD 0·3)§	5·4 (SD 0·5)§	10·9 (SD 4·5)	6·5 (SD 2·0)§	11·1 (SD 10·9)§	–	–	–	–	–	–
Gripteg *et al.*[25]	1-week refeeding	–	5·5 (SD 1·3)	No value‖	–	21·7 (SD 14·3)	–	–	–	–	–	–	–
	6-week refeeding	–	5·4 (SD 1·3)	No value‖	–	25·2 (SD 25·4)	–	–	–	–	–	–	–
Jazet *et al.*[19]	All	11·9 (SD 1·0)	Δ −1·5 (SD 1·3)	Δ −0·7 (SD 1·4)	–	–	–	8·0 (SD 0·3)	Δ −0·3 (SD 0·2)	Δ−0·3 (SD 0·2)	–	–	–
Kukkonen-Harjular *et al.*[16]	All	5·10 (SD 0·49)	Δ −0·32 (95 % CI −0·44, −0·21)	Δ −0·05 (95 % CI −0·15, 0·04)	14·4 (SD 5·6)	Δ −5·5 (95 % CI −6·7, −4·4)	Δ −3·4 (95 % CI −4·8, −2·0)	–	–	–	–	–	–
	Control	5·1 (SD 0·6)	–	5·1 (SD 0·5)§	14 (SD 4·0)	–	10·5 (SD 5·7)§	–	–	–	–	–	–
	Walk	5·1 (SD 0·3)	–	5·0 (SD 0·5)§	14·3 (SD 6·8)	–	10·5 (SD 5·7)§	–	–	–	–	–	–
	Resistance	5·1 (SD 0·5)	–	5·0 (SD 0·4)§	14·3 (SD 6·4)	–	10·1 (SD 7·2)§	–	–	–	–	–	–
Laaksonen *et al.*[13]	Orlistat + Placebo	6·2 (SD 1·8)	5·5 (SD 0·6)	5·3 (SD 0·8)**	–	–	–	–	–	–	–	–	–
Lantz *et al.*[14]	All	4·8 (SD 2·0)	Δ −0·4 (95 % CI −0·6, −0·2)	Δ 0·0 (95 % CI −0·3, 0·2)	20·6 (SD 12·3)	Δ −9·0 (95 % CI −10·9, −7·0)	Δ −4·9 (95 % CI −7·0, −2·8)‖	–	–	–	–	–	–
Linna *et al.*[20]	All	5·1 (SD 0·5)	4·7 (SD 0·4)**	5·0 (SD 0·5)**	–	–	–	–	–	–	–	–	–
	Subgroup 1	5·2 (SD 0·7)	4·7 (SD 0·4)*	5·0 (SD 0·6)*	–	–	–	–	–	–	–	–	–
	Subgroup 2	5·1 (SD 0·4)	4·7 (SD 0·4)**	5·1 (SD 0·4)**	–	–	–	–	–	–	–	–	–
Madsen *et al.*[29]	Orlistat + placebo		–	–	–	–	–	–	–	Δ −13·1 % (95 % CI −11·3, −14·9)**	–	–	–
Mathus-Vliegen *et al.*[17]	Sibutramine	–	–	Median % Δ 8·0	–	–	–	–	–	–	–	–	–
	Placebo	–	–	Median % Δ 2·2	–	–	–	–	–	–	–	–	–
Melin *et al.*[15]	Intensive counselling	4·7 (SD 0·2)	–	Δ 0·08 (SD 0·24)	21·1 (SD 4·6)	–	Δ −9 (SD 1·23)*	–	–	–	–	–	–
	Normal counselling	5·2 (SD 0·4)	–	Δ −0·5 (SD 0·26)	10·2 (SD 1·2)	–	Δ −5·0 (SD 1·37)*	–	–	–	–	–	–
Niskanen *et al.*[28]	All	6·2 (SD 1·7)	5·4 (SD 0·6)	5·4 (SD 0·7)**	–	–	–	–	–	–	–	–	–
Paisey *et al.*[12]	VLED	12 (SD 5)	–	13 (SD 5)	–	–	–	–	–	–	352 (SD 84)	–	348 (SD 59)
	Diet and exercise	13 (SD 5)	–	14 (SD 4)	–	–	–	–	–	–	385 (SD 98)	–	357 (SD 88)
Richelsen *et al.*[21]	Orlistat	6·4 (SD 1·8)	Δ −1·1	Δ−0·49	16·7 (SD 9·4)	Δ −6·91	Δ −3·74	6·3 (SD 0·9)	Δ −0·5	Δ −0·7	–	–	–
	Placebo	6·3 (SD 1·5)	Δ −0·95	Δ−0·32	16·4 (SD 8·4)	Δ −6·48	Δ −1·73	6·3 (SD 0·6)	Δ −0·5	Δ −0·5	–	–	–
Rolland *et al.*[23]	LCHP	5·4 (SD 0·8)	5·4 (SD 0·8)	5·3 (SD 0·8)‖	–	–	–	5·7 (SD 0·5)	5·6 (SD 0·4)	5·6 (SD 0·4)	–	–	–
	VLED	5·2 (SD 0·6)	4·8 (SD 0·5)‡‖	4·9 (SD 0·4)‡‖	–	–	–	5·6 (SD 0·4)	5·5 (SD 0·3)‖	5·4 (SD 0·4)‡‖	–	–	–
Simonen *et al.*[31]	All	8·4 (SD 0·6)	–	7·2 (SD 0·5)*	17·0 (SD 1·0)	–	13·1 (SD 1·5)	–	–	–	–	–	–
Toumhileto *et al.*[24]	Control	6·1 (SD 1·6)	–	Δ −0·4 (SD 1·4)	10·9 (SD 4·7)	–	Δ −1·2 (SD 3·4)	–	–	–	–	–	–
	Intervention	6·3 (SD 2·5)	–	Δ −0·6 (SD 2·3)	13·5 (SD 7·0)	–	Δ −5·9 (SD 7·0)‡‡	–	–	–	–	–	–
Vasankari *et al.*[11]	All	5·1 (SD 0·5)	4·9 (SD 0·4)**	4·9 (SD 0·4)**	11·2 (SD 4·4)	6·8 (SD 2·8)**	7·8 (SD 2·6)**	–	–	–	–	–	–
Wikstrand *et al.*[32]	Corset	5·2 (SD 0·9)	–	4·8 (SD 0·5)*	–	–	–	–	–	–	–	–	–
	No corset	5·3 (SD 2·2)	–	4·7 (SD 0·6)	–	–	–	–	–	–	–	–	–
Willi *et al.*[33]	All	–	–	–	–	–	–	8·8 (SD 0·6)	7·4 (SD 0·6)*	8·9 (SD 0·8)*	–	–	–

HBA_{1C}, glycated Hb; VLED, very-low-energy diet, T2DM, type 2 diabetes mellitus; MK-0557, highly selective orally administered neuropeptide Y Y5 receptor antagonist; Δ, change; LCHP, low-carbohydrate, high-protein diet.
Mean values were significantly different from baseline: * $P<0·05$, ** $P<0·001$.
Mean values were significantly different between groups: ‡ $P<0·05$, ‡‡ $P<0·001$.
§ No *P* value provided for baseline, VLED end, study end or between groups.
‖ Statistically significant difference from baseline provided but no *P* value given.
§§ The conversion factor for fasting insulin is: 1 mU/l = 6·00 pmol/l.

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examined[40] and in another study the effect of mental disorders on the maintenance of weight loss was investigated[41].

Legenbauer *et al.*[40] investigated the effect of eating and depressive disorders on weight loss after VLED treatments and after surgical weight reduction treatment. A greater number of participants in the VLED group met the criteria for diagnosis of depressive disorder at baseline, when compared with bariatric surgery patients. Although a lifetime history of depression did not differ between the groups, history of depressive disorder (both current and lifetime) had a significant negative predictive value on longer-term weight loss in the bariatric surgery group but not in the VLED group at 4 years. Conversely, in the bariatric surgery 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 suggested that 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 the maintenance of weight loss among the patients who had previously successfully participated in a VLED programme. Of the 166 participants, 28·3 % maintained a weight loss of at least 5 % of their initial weight for 3 years. In 71·7 % of the participants who maintained a loss of less than 5% of their pretreatment weight, lower levels of cognitive control, higher levels of disinhibition and higher levels of perceived hunger were reported at the 3-year follow-up compared with those with >5 % loss.

Dropouts and adverse events

Of the thirty-two studies included in the present review, dropout information was available for twenty-eight studies[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 VLED period. In only three of the remaining studies did they specify higher dropout rates during the VLED phase when compared with the follow-up period[4,12,24]. For the studies that reported dropouts during the VLED phase, this appears to be in the first few weeks[24,32]. The main reasons for discontinuing the VLED appeared to be withdrawal from the study before starting the diet, distaste of products, poor compliance and work schedules[4,12,24,25,32,36]. There was one death recorded in the first 5 weeks of a VLED but this was not linked to the VLED diet by the authors[24]. In one study where 23·7 % of the patients dropped out in the VLED 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 drop out[32,40] while those receiving behaviour therapy were more likely to be retained[39].

Of the thirty-two studies, fourteen monitored for adverse events[4,12,15,16,18,19,24,25,31–33,36,40,41]. Of these studies, two stated that no adverse effects were reported[31,33]. Of the remaining studies, five 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].

A total of seven studies commented on major adverse events throughout the study period[12,19,24,25,36,40,41]. In three studies, significant cardiac events were noted, none of which was reported as being directly related to the VLED intervention. In summary, one death was attributable to myocardial infarctions[36] and one from heart failure at 35 weeks post-VLED[25]. Paisey *et al.* reported one non-fatal myocardial infarction in the VLED group but also a non-fatal myocardial infarction in the conventional diet group. In this study, however, one patient was able to have a coronary bypass as a result of weight loss achieved through the VLED. Finally, one case of acute coronary syndrome[19] was also reported in the VLED arm. In another three studies, seven other deaths were reported[24,40,41], although the cause of death was not reported. In two of the studies which included type 2 diabetic patients, one 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 the type of illness was not specified[40]. Overall, none of the major adverse effects noted in any of these studies was reported to be related to the VLED itself.

Discussion

The present review suggests that long-term weight loss and improvements in co-morbidities ranging from cardiovascular risk to respiratory disorders can be advised in the longer term using VLED. These improvements, however, are more likely to be 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 VLED, weight regain is similar to a conventional diet[33]. In accordance with the meta-analysis by Anderson *et al.*[42], the present review suggests that significant weight loss appears to be sustained in the longer-term following a VLED for obese and overweight individuals with co-morbidities. The present systematic review also demonstrates that in the longer term, and in agreement with previously reported evidence, significant weight-loss maintenance following a VLED was demonstrated mainly in the groups who used a conventional diet with exercise or adjuncts such as orlistat[12,21].

Cardiovascular risk

Jazet *et al.*[19] suggested that cardiovascular risk factors may be reduced, irrespective of weight loss or regain, in the long term following a VLED[19]. In the present review, however, significant reductions in systolic and diastolic BP 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.*[43] recently reported the effects of VLED on HDL where an improvement is often seen during weight

maintenance, although not necessarily at VLED end[44]. This is in keeping with our findings on the 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 the study design. Few studies reported insulin requirements, but the results suggested reduced doses at study end.

Fertility

The limited long-term evidence that we currently have for the use of VLED 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[45] who followed a VLED to improve her likelihood of conceiving demonstrated the usefulness of VLED for pregnant control of glucose metabolism and BP. In addition, short-term evidence does suggest that weight loss improves fertility in obese women with polycystic ovary syndrome[46,47]. This warrants the need for further investigation into the use of VLED for improving fertility in the longer term.

Bone health

There has been concern expressed about the effect of weight loss on bone health[48–54]. Very little is currently known of the long-term effects of weight loss on bone turnover. The limited evidence for VLED suggests an imbalanced turnover during the VLED phase, which resumes balance during weight maintenance. The imbalance observed during the VLED phase may simply be due to the reduced energy intake[55], or may reflect a delay in osteoblast formation relative to osteoclastic resorption[35]. The evidence also suggests that, in long-term weight loss, the total body BMC 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 VLED on bone health, perhaps by looking at BMD directly as well as serum markers of bone formation and breakdown.

Respiratory disorders

The long-term use of VLED 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 VLED or the extent of weight loss which is required for the resolution of apnoeic events in obese individuals.

Eating disorders

VLED have been criticised in the past for increasing the 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 VLED also remains unclear. A study by Svendsen *et al.*[56] was not included in the present review as long-term weight loss was not described in the paper. Nevertheless, they showed that 36 months after having followed a VLED for 8 weeks, decreased binge eating was a predictor of sustained weight maintenance while weight loss was associated with decreases in binge eating. More research and evidence are required to elucidate the effects of VLED on BED.

Dropouts and adverse events

Recent reviews have concluded that, in the long term, VLED have no worse outcomes or adverse effects than standard diets[57]. Previous studies have argued that VLED are associated with high cost and high attrition rates[58]. Our findings suggest that dropouts are higher during the follow-up phase and are rarely due to the VLED itself. Few studies suggested reasons for this and future studies may provide more information on reasons for high attrition in the follow-up period.

In the present review, we found that few papers reported significant adverse events. The minor adverse events outlined were as expected when following a ketotic diet[59]. Few deaths and major adverse events such as myocardial infarctions were reported. There appears, however, to be a lack of rigour in the 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

The present review represents a detailed systematic review of an important area of controversy. Despite the complexity of the present review, due to the high variation in the study design of the reviewed papers, we have attempted to separate the effects attributable to VLED and other interventions. The heterogeneity in study design, particularly in terms of the VLED period, length of follow-up and additional interventions, however, makes the interpretation of the 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, details 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 VLED 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 VLED dependent on age, sex, ethnicity and specific disease. There is need, however, for clarification of nutritional completeness of different VLED used in research. With the exception of energy intake, current VLED should either be nutritionally complete or include supplements to avoid any deficiencies. Of the thirty-two studies investigated, only four commented on nutritional completeness[21,34,35,37] and two commented on the use of a supplement[16,31]. When we looked for the manufacturer's information about the different VLED used, these were all stated to be nutritionally complete. Only one paper made no comment of the VLED that was used or its nutritional completeness[13].

The data presented in the present review are often conflicting. There is a great need for consistency in the design of studies to allow accurate data extrapolation, and long-term studies to show sustained outcomes. Long-term information on the use of intermittent or on-demand VLED is an area which has not been explored in many studies. The 'yo-yo' effect of rapid weight loss and regain associated with VLED has previously been criticised[60]. However, several studies have demonstrated that intermittent VLED use does not have any detrimental effect on metabolic parameters such as RMR, fasting insulin, insulin resistance, leptin, inflammatory markers, lipids or BP[60–63].

The role of VLED 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 VLED were more efficacious if combined with behaviour modification and active follow-up[64]. In the long term, weight regain may occur, but the VLED may instigate behaviours which facilitate longer-term changes for the 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, the present review suggests that long-term weight loss and improvements in cardiovascular risk, fertility and respiratory disorders are achievable with the use of VLED, 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 VLED use in healthy and at-risk groups, the results of which could better inform best practice.

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