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Comparison of a low-energy diet and a very low-energy diet in sedentary obese individuals: a pragmatic randomized controlled trial

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Summary

There is no consensus on whether 'very low-energy diets' (VLED; <800 kcal d^{-1}) cause greater weight loss in obese individuals than 'low-energy diets' (LED; 800–1200 kcal d^{-1}). The objective was to determine whether a very low-energy formula diet would cause greater weight loss than a formula 810 kcal d^{-1} LED in older sedentary individuals. This is a pragmatic randomized controlled trial. Inclusion criteria: obesity (body mass index [BMI] > 30); age >50 years, with knee osteoarthritis. Participants were randomized to VLED (420–554 kcal d^{-1}) or LED (810 kcal d^{-1}) for 8 weeks, followed by a fixed-energy (1200 kcal d^{-1}) diet with food and two diet products daily for 8 weeks. In all, 192 participants were randomized. Mean age was 63 years (standard deviation: 6), mean weight 103.2 kg (15.0) and BMI of 37.3 kg m^{-2} (4.8) at baseline. Mean weight losses in VLED and LED groups were 11.4 kg (standard error: 0.5) and 10.7 kg (0.5) at week 8 and 13.3 kg (0.7) and 12.2 kg (0.6) at week 16. Mean differences between groups were 0.76 kg (95% confidence interval: –0.59 to 2.10; $P = 0.27$) and 1.08 kg (–0.66 to 2.81; $P = 0.22$) at 8 and 16 weeks, respectively. Loss of lean body mass was 2.1 kg (0.2) and 1.2 kg (0.4) (17% and 11% of the weight lost, respectively) at week 16 in the VLED and LED group with a mean difference of 0.85 kg (0.01 to 1.69; $P = 0.047$). Significant adverse effects comparing VLED and LED, were bad breath: 34 (35%) vs. 21 (22%), intolerance to cold: 39 (41%) vs. 17 (18%) and flatulence: 43 (45%) vs. 28 (29%) for VLED and LED at 8 weeks ($P < 0.05$ in all cases). The VLED and LED regimens were equally successful in inducing weight loss. The significantly lower loss of lean tissue in the LED group together with more frequently reported side effects in the VLED group, favours the choice of low-energy diet (LED) for the treatment of obesity.

Keywords: Obesity, weight loss, LED, VLED.

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Introduction

Osteoarthritis (OA) is a multifactorial disease with obesity as one of the main risk factors (1). Obesity and OA share pathogenetic features. The development of one disease increases the risk of the other, which may lead to a vicious circle (2,3). An important aspect in the treatment of individuals with combined obesity and OA is the practical difficulty of reducing weight by exercising. In contrast, weight loss by diet alone increases the self-reported functional status significantly – with short-term results being equal to that of a joint replacement (4). A variety of weight loss methods are available, from minimally structured self-guided approaches (5) to medically supervised very low-energy diets (VLED) (6,7) and bariatric surgery (8). The VLED (400–800 kcal d^{-1}) usually provide a low carbohydrate ketogenic diet with an energy content of around 450–800 kcal d^{-1} in the form of nutrition powders or in

the form of protein-, mineral-, trace element- and vitamin-enriched formulated meals or drinks to meet recommended daily intake for micronutrients (5,7). In a previous study, we demonstrated the feasibility of a low-energy formula diet (LED) in overweight individuals with knee OA (4).

The aim of this study was to compare a short-term VLED (415 kcal d^{-1}) and a LED (810 kcal d^{-1}) (8 weeks) in older obese individuals with concomitant knee OA, followed by an 8-week follow-up with a hypo-energetic diet of both normal food and formula meal replacements.

Methods

This was a prospective, pragmatic randomized controlled trial, with blinded outcome assessors: the CAROT study – Influence of weight loss or exercise on cartilage in obese knee osteoarthritis patients trial: a randomized controlled trial (ClinicalTrials.gov Identifier: NCT00655941). This paper is based on the first phase, initiating weight loss using dietary intervention with LED over a 16-week trial, evaluating outcomes at two pre-specified points. Participants were recruited November 2007–August 2008 from the out-patient clinic at the Department of Rheumatology, Frederiksberg Hospital, Denmark through advertisements in newspapers and on the website of the Parker Institute. Additionally, local general practitioners were informed about the possibility to assign patients to the project. All participants were prescreened via telephone using a series of standard questions about eligibility according to criteria of inclusion and exclusion. The study was designed as a pragmatic trial – a randomized controlled trial whose purpose was to inform decisions about effectiveness when used in normal practice, i.e. excluding as few participants as possible from participation and directly relevant to healthcare practitioners (9). Individuals more than 50 years of age and with confirmed knee OA based on standing radiographs were eligible for inclusion (10). They were obese as defined by a body mass index (BMI) $\geq$30 kg m^{-2}. Exclusion criteria were: lack of motivation to lose weight, inability to speak Danish, planned anti-obesity surgery, total knee alloplasty and receiving pharmacologic therapy for obesity. The participants were asked not to change any medication or nutritional supplement during the study. The study was approved by the ethics committee of the Capital Region of Denmark [H-B-2007-088] and all participants gave written informed consent.

The first phase of the study consisted of an 8-week weight reduction programme where the participants were randomized to either an all-provided VLED with 415–554 kcal d^{-1} or a LED with 810 kcal d^{-1} in a supervised dietary programme (products provided by The Cambridge Weight Plan). Participants attended the nutrition department at the Parker Institute weekly. They were weighed on a decimal scale and given nutritional and dietetic instructions by an experienced dietitian in sessions of 1.5–2 h. The VLED programme consisted of powdered formula mixture dissolved in water. Women at or below 173 cm in height were given three sachets a day (415 kcal d^{-1}, 43.2 g protein); men and women taller than 173 cm were given four sachets (554 kcal d^{-1}, 57.6 g protein). The LED programme consisted of powdered formula mixture dissolved in skimmed milk and water. Participants were given four sachets a day, three of which were dissolved in milk using 7.5 dL of milk/day and one in water (810 kcal d^{-1}, 83.9 g protein). Both programmes met all recommendations for daily intake of vitamins and minerals. Daily intake of protein was at least 43.2 g, and of essential fatty acids, linoleic and linolenic acids was 3 g and 0.4 g, respectively. Dietary fibre intake was 7.2 g d^{-1} at minimum. Participants were advised to use a fibre supplement (psyllium) to avoid constipation. The average diet composition of the 415 kcal d^{-1} diet was 41% of dietary energy from protein, 41% from carbohydrate and 18% from fat; for the 810 kcal d^{-1} diet 41% of dietary energy was from protein, 46% from carbohydrate and 13% from fat.

The second phase of the study, which was the same for all participants, consisted of 8 weeks' fixed energy diet programme using 1200 kcal incorporating two diet products daily. Participants continued to attend the groups to which they were initially allocated. All participants were taught to make diet plans with five to six small meals a day. The principles of the diet were in line with the guidelines for healthy eating issued by the Danish National Board of Health, i.e. low-fat, low-sugar and high-fibre. Participants were encouraged to eat at least 300 g vegetables and two pieces of fruit daily. They received a list of recommended food items and were instructed in how to use a food shopping guide promoting low-fat and high-fibre products. These guidelines encourage consumption of whole grains, legumes, vegetables and fruits that induce satiety because they may be eaten in relatively large amounts. During this phase both groups received the same nutritional education together with recipes for low-energy meals. The focus was on long-term lifestyle modifications; educational themes were: energy expenditure and energy balance, macronutrients, satiety, digestion, motivation and diet planning. The group treatment provided a combination of empathy, social support and friendly competition. In both phases of the study, the dietitian aimed to maximize adherence by reinforcing positive dietary changes and addressing barriers to adherence.

Randomization

Participants were randomly assigned to receive either a LED or a VLED for the first period of 8 weeks. Participants were included in strata of 24, giving three subgroups of eight receiving therapy, with 192 participants enrolled in

the randomization, who had an equal probability of group assignment. The *randomization* was based on minimization (11), thus randomly allocating participants to one of two groups according to important predictors: (i) sex (male vs. female); (ii) BMI/obesity category (≥30; ≥35, ≥40); and (iii) age in years. Each randomization list was drawn up by a statistician and given to the secretariat at the Parker Institute, who subsequently informed participants when to meet with the dietitian (i.e. concealed group allocation).

Participants attended in groups of eight, all receiving the same dietary treatment, and although they knew they were receiving diets in the range of 415 kcal d^{-1} to 810 kcal d^{-1}, they were not overtly aware of the dietary group to which they had been allocated. As all participants had exactly the same amount of attention from clinicians during this project, we believe the risk of performance bias was low (12). Outcome assessors who took blood samples and body composition measurements (dual energy X-ray absorptiometry [DEXA] scans) and who monitored adverse events were blinded to group allocation.

Outcomes

As part of the overall project with weight loss as a therapy for OA, the body-weight outcome, was measured weekly on digital scales (TANITA BW-800, Frederiksberg Vægtfabrik). We assessed patients' self-reported outcome by asking them to rate their wellbeing and satisfaction with dieting. This was done weekly using a Likert scale of '*Smileys*': (0) very bad (I) bad (II) reasonable (III) good and (IV) very good. Other outcomes were changes in BMI calculated by using a person's weight (in kilograms) and dividing it by the square of his or her height (in metres). Height was measured to the nearest 0.01 m. Waist circumference was measured with a tape measure midway between the lower rib and iliac crest according to WHO recommendations (13). Fasting blood glucose, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides, C-reactive protein, liver enzymes, urine – methyl ketones, blood pressure and pulse were measured at baseline, week 8 and week 16. All blood samples were analysed in a central laboratory (Frederiksberg Hospital). Body composition was determined by DEXA using a Lunar DPX IQ Full Body Bone Densitometer and was measured at baseline and after 16 weeks' diet therapy. We asked the participants to report medication changes, hospitalizations and adverse events to the study nurses on the outcome assessment days in week 8 and week 16.

Reporting of adverse events was elicited with non-leading questions according to Good Clinical Practice: all events were coded according to the Medical Dictionary for Regulatory Activities, as currently required by all regulatory authorities including the US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products. We also introduced a questionnaire with some suggestive leading questions, assessing adverse events in a generic framework using options based on OA standards as well as typical adverse effects and complications of VLED (5).

Statistical analysis

Prospectively, this study was *not* powered with a superiority design to compare the two weight loss regimen arms. The primary comparison in this study (ClinicalTrials.gov Identifier: NCT00655941) was based on the assessment of the number of obese patients with knee OA who would respond according to the Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International (OMERACT-OARSI) criterion after a 1-year maintenance programme. The maintenance programme starting from week 16 will either be (A) a weight maintenance programme, (B) an exercise programme, or (C) a control group with no attention. All data analyses were done according to a pre-specified statistical analysis plan; all analyses were done applying SAS software (v. 9.1.3 Service Pack 4; SAS Institute Inc., Cary, NC, USA). All descriptive statistics and tests were reported in accordance with the recommendations of the '*Enhancing the QUAlity and Transparency Of health Research*' (EQUATOR) network: the Consolidated Standards of Reporting Trials (CONSORT) statement (14). To evaluate the empirical distributions of the continuous outcomes, visual inspection was used to ascertain whether the assumption of normality was reasonable; the PROC UNIVARIATE statement was used for summarizing the data. All analyses were conducted by intention-to-treat, with participants analysed according to their initial assignments, i.e. baseline observation carried forward (15). Two sided significance tests were used throughout. We applied a likelihood-based approach to general linear mixed models, dealing with the repeated (longitudinal) measures in a statistical model (16). The *MIXED* procedure of the SAS® system (SAS 9.1.3; SAS Institute Inc., Cary, NC, USA) provides a rich selection of covariance structures through the *RANDOM* and *REPEATED* statements (17). If the assumption of normality was not reasonable, we analysed the data with the non-parametric *Wilcoxon Rank Sum* test using PROC NPAR1WAY; in this case the mean difference was replaced with median differences using the ROBUSTSCALE option based on the interquartile range applicable for estimating robust 95% confidence intervals (CI).

Results

A total of 388 people were prescreened by telephone during the 9-month recruitment period (Fig. 1). Of these, 187 (48%) were ineligible, and 9 (2%) declined participation after the first screening visit, leaving 192 persons for ran-

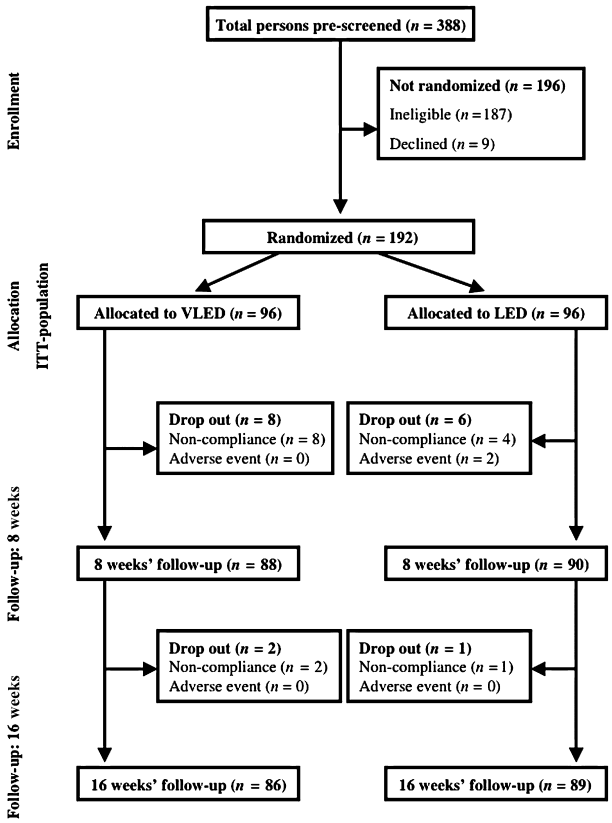

Figure 1 Trial profile. ITT, intention-to-treat; LED, low-energy diet; VLED, very low-energy diet.

domization to one of two treatment groups. Table 1 shows the characteristics of the randomized cohort. In total, 175 of 192 participants (91%) completed the study (returned for final data collection at week 16). Retention of participants was not significantly different between the two groups (VLED and LED). After randomization, 17 participants dropped out of the study. In the first 8 weeks, 14 participants dropped out: 12 due to non-compliance (VLED eight; LED four) and two due to adverse events (VLED zero; LED two). In the last 8 weeks, three participants dropped out: three due to non-compliance (VLED two; LED one) and none due to adverse events. Adherence was 91% and 94% (defined as attendance at the 8-week follow-up) for the first 8 weeks, and 90% and 93% at 16 weeks (defined as the percentage of follow-up calls that were successfully completed) for VLED and LED groups, respectively (no significant difference between the two groups; data not shown).

As pre-specified, all analyses were based on the intention-to-treat population – i.e. all randomized individuals included in the analyses. The mean age of the study population (±standard deviation:) was 63 ± 6 years. As expected, the majority of participants were women (155 of the 192). The mean weight at baseline was 103.2 ± 15.0 kg, corresponding to a BMI of 37.3 ± 4.8 kg m^{-2} and with a mean waist circumference of 111.4 ± 11.0 cm. Figure 2a shows the weight loss curves for the VLED and LED group, respectively. The primary outcome measure of this study 'weight loss' showed a tendency towards a statistical interaction with respect to *Group and Time* ($P = 0.067$), with a highly significant effect of *Time* ($P < 0.0001$) and some indication of a *Group* effect ($P = 0.098$). The 'wellbeing and satisfaction with dieting' reported by the participants showed a significant interaction between *Group and Time* ($P = 0.015$), as illustrated in Fig. 2b by a different pattern over time. Exploring the main effects of *Group* and *Time* in terms of participants' wellbeing and satisfaction revealed no indication of differences between VLED and LED ($P = 0.607$); however, there was a highly significant change over time ($P = 0.0001$).

As presented in Table 2, after the first 8 weeks the average weight loss (±standard error) in the VLED group was 11.4 ± 0.5 kg and in the LED group 10.7 ± 0.5 kg, with a non-significant group mean difference of 0.76 kg (95% CI: –0.59 to 2.10 kg; $P = 0.27$). When comparing the number of responders in each group 66 (68.8%) and 57 (59.4%) participants lost more than 10% body weight, translating into a non-significant absolute difference of 9.4% (–4.1 to 22.9%) more responders on VLED. When combined, the two groups lost 11.1 kg (95% CI: 10.4 to 11.8 kg) on average and 123 (64%) participants had a clinically significant weight loss following 8 weeks – which is highly significant from baseline ($P < 0.0001$).

At week 16 the VLED group had lost a mean of 13.3 ± 0.7 kg and the LED group 12.2 ± 0.6 kg with a non-significant group mean difference of 1.08 kg (95% CI: –0.66 to 2.81; $P = 0.22$) as shown in Table 3. The proportion of responders (i.e. those losing >10%), was the same in both groups (71 participants), which corresponds to 74% of participants having achieved a successful weight loss at week 16. The combined weight loss at week 16 was 12.8 kg (95% CI: 11.8 to 13.7 kg), which is highly significant from baseline ($P < 0.0001$).

Body composition, determined using DEXA, was measured at baseline and after 16 weeks' diet therapy. After 16 weeks the VLED group had lost a mean of 2.1 ± 0.2 kg lean body mass and the LED group 1.2 ± 0.4 kg, with a significant group mean difference in favour of LED of 0.85 kg (95% CI: 0.01 to 1.69 kg; $P = 0.047$). The fat mass was reduced by 10.3 ± 0.5 kg in the VLED group 9.8 ± 0.5 kg in the LED group. This was resulting in a non-significant group mean difference of 0.57 kg (95% CI: –0.82 to 1.95 kg; $P = 0.42$).

Safety

Table 4 shows the most frequent adverse effects reported after 8 weeks in VLED and LED: bad breath (anticipated

Table 1 Demographic and clinical characteristics at baseline

Characteristic/variable	VLED ($n = 96$)	LED ($n = 96$)	Total ($n = 192$)
Age, years	61.7 ± 6.2	63.3 ± 6.3	62.5 ± 6.4 (50.0–77.9)
Female, *n* (%)	78 (81.3%)	77 (80.2%)	155 (80.7%)
Current smokers, *n* (%)	12 (12.5)	7 (3.6%)	19 (9.9%)
Disease duration, years*	3 [1; 4.5]	3 [1; 4]	3 [1; 4] (1–29)
Weight, kg	104.1 ± 15.6	102.3 ± 14.4	103.2 ± 15.0 (76.0–145.3)
Height, cm	166.6 ± 7.8	166.0 ± 8.6	166.3 ± 8.2 (148.0–191.0)
Body mass index, kg m^{-1}†	37.5 ± 5.4	37.1 ± 4.1	37.3 ± 4.8 (30.1–54.0)
Waist circumference, cm	112.2 ± 12.0	110.6 ± 10.0	111.4 ± 11.0 (85.0–141.0)
Fasting glucose, mmol L^{-1}	5.9 ± 0.7	6.1 ± 1.0	6.0 ± 0.9 (4.8–11.1)
Normal (<5 mmol L^{-1}), *n* (%)	6 (6.3%)	2 (2.1%)	8 (4.2%)
Impaired (5–7 mmol L^{-1}), *n* (%)	85 (88.5%)	82 (85.4%)	167 (87.0%)
Diabetic (>7 mmol L^{-1}), *n* (%)†	5 (5.2%)	12 (12.5%)	17 (8.9%)
Total cholesterol, mmol L^{-1}	5.2 ± 0.9	5.2 ± 1.2	5.2 ± 1.1 (2.6–8.6)
LDL cholesterol, mmol L^{-1}	3.0 ± 0.8	2.9 ± 1.1	3.0 ± 0.9 (0.7–5.2)
HDL cholesterol, mmol L^{-1}	1.6 ± 0.4	1.6 ± 0.4	1.6 ± 0.4 (0.5–2.9)
Triglycerides, mmol L^{-1}*	1.19 [0.93; 1.59]	1.25 [0.96; 1.68]	1.21 [0.94; 1.66] (0.49–7.02)
C-reactive protein, mg L^{-1}*	4.1 [2.3; 8.1]	4.6 [2.4; 7.1]	4.4 [2.4; 7.7] (0.7–58.6)
Bilirubin, mmol L^{-1}	7.9 ± 3.5	8.4 ± 3.0	8.1 ± 3.3 (3.0–23.0)
ALT, IU L^{-1}*	25 [21; 32]	30 [22; 38]	26 [21; 35] (6–296)
Increased ALT >45 IU L^{-1}, *n* (%)	11 (11.5%)	16 (16.7%)	27 (14%)
ALP, IU L^{-1}	73 ± 17	75 ± 21	74 ± 19 (38–148)
Urinary ketone bodies, *n* (%)	2 (2.1%)	0	2 (1.0%)
Pulse, bpm	68 ± 10	69 ± 11	69 ± 10 (44–113)
Systolic blood pressure, mmHg	141.4 ± 18.6 (103.0–193.0)	142.3 ± 17.8 (98.0–204.0)	141.9 ± 18.2 (98.0–204.0)
Diastolic blood pressure, mmHg	85.4 ± 10.4 (62.0–123.0)	87.5 ± 9.2 (65.0–118.0)	86.4 ± 9.8 (62.0–123)
Metabolic syndrome, *n* (%)‡	67 (69.8%)	72 (75%)	139 (72.4%)
Lean body mass, kg§	50.8 ± 8.2	50.8 ± 9.1	50.8 ± 8.7 (37.1–78.4)
Fat mass, kg§	48.1 ± 10.5	46.2 ± 8.3	47.1 ± 9.5 (30.7–80.7)
Lean body mass, %§	50.2 ± 5.8 (38.0–67.7)	50.9 ± 5.5 (39.1–66.0)	50.5 ± 5.7 (38.0–67.7)
Fat mass, %§	47.1 ± 6.1 (28.8–59.7)	46.3 ± 5.7 (30.8–58.5)	46.7 ± 5.9 (28.8–59.7)

Data are mean ± standard deviation: and (minimum–maximum), except when otherwise indicated.

*Presented as median [Q_1; Q_3].

†Or use of medication for hyperglycemia.

‡The metabolic syndrome is defined according to the American Heart Association criteria.

§Lean body mass and fat mass was measured using dual energy x-ray absorptiometry.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; bpm, beats per minute; LDL, low density lipoprotein; LED, low-energy diet; HDL, high density lipoprotein; VLED, very low-energy diet.

because of ketosis: 34 [35%] and 21 [22%], respectively, $P = 0.038$), intolerance to cold (39 [41%] and 17 [18%], $P = 0.0005$) and flatulence (43 [44.8%] and 28 [29.2%], $P = 0.025$). There were trends that dry skin and hair loss were reported more frequently in the VLED group than in the LED group at week 8. After week 16 the only statistically significant side effect reported in the VLED vs. LED group was epigastric pain (12 [12.5%] and 4 [4.2%], $P = 0.037$). There was also a trend towards bad breath being more common in the VLED than in the LED group at week 16 (data not shown).

One participant in the LED group developed an allergic reaction and was excluded after the first week. This was probably because of an allergy to a component of the formulated diet; the participant was not hospitalized.

During the entire 16 weeks, five participants (2.6%) experienced a serious adverse event. These were mostly cardiovascular events as seen regularly in this age group (see Appendix).

Discussion

Our study shows that both VLED and LED can induce substantial weight loss in obese patients with knee OA, with 74% achieving a clinically significant drop in weight, i.e. more than 10%. We found that the two programmes were equally effective in inducing short-term weight loss. The most important finding of this study is that there was no difference in the weight losses between those receiving 415–554 kcal d^{-1} and those receiving 810 kcal d^{-1}. Our knee OA study therefore confirms the earlier findings of a

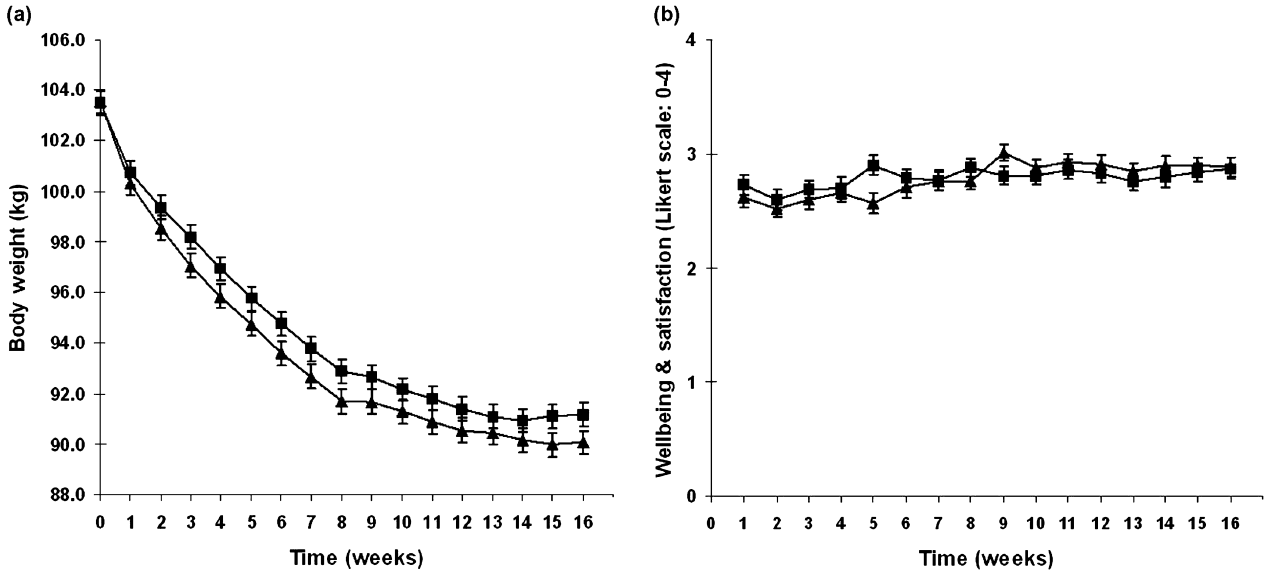

Figure 2 Data are values for patients attending the scheduled visits at the nutrition department. Values are mean ± standard error; ▲ very low-energy diet, ■ low-energy diet. (a) Mean drop in body weight from baseline. (b) Patients self-reported wellbeing and satisfaction with dieting using a Likert scale 0–4.

Table 2 Changes following intervention. Efficacy data: short-term (8 weeks)

Characteristic/variable	VLED (n = 96)	LED (n = 96)	Mean difference (95% CI)	*P*-value
Δ Weight, kg	–11.4 ± 0.5	–10.7 ± 0.5	0.76 (–0.59 to 2.10)	0.27
Δ Body mass index, kg m^{-1}†	–4.1 ± 0.2	–3.9 ± 0.2	0.24 (–0.22 to 0.71)	0.30
Δ Waist circumference, cm	–8.6 ± 0.5	–8.1 ± 0.5	0.53 (–0.89 to 1.95)	0.46
Δ Fasting glucose, mmol L^{-1}	–0.33 ± 0.06	–0.43 ± 0.07	–0.10 (–0.28 to 0.09)	0.32
Normal (<5 mmol L^{-1}), *n* (%)*	12 (12.5%)	6 (6.3%)	–6.3% (–14.4 to 19.0)	0.14
Impaired (5–7 mmol L^{-1}), *n* (%)*	83 (86.5%)	84 (87.5%)	1% (–8.5 to 10.6)	0.83
Diabetic (>7 mmol L^{-1}), *n* (%)*,†,¶	1 (1.0%)	6 (6.3%)	5.2% (0.0 to 10.5)	0.12
Δ Total Cholesterol, mmol L^{-1}	–0.73 ± 0.07	–0.84 ± 0.09	–0.12 (–0.35 to 0.11)	0.31
Δ LDL Cholesterol, mmol L^{-1}	–0.49 ± 0.06	–0.51 ± 0.07	–0.02 (–0.19 to 0.16)	0.84
Δ HDL Cholesterol, mmol L^{-1}	–0.15 ± 0.03	–0.18 ± 0.03	–0.03 (–0.11 to 0.05)	0.48
Δ Triglycerides, mmol L^{-1}‡	–0.06 [–0.36; 0.05]	–0.13 [–0.53; 0.00]	–0.07 (–0.18 to 0.04)	0.23
Δ C-reactive protein, mg L^{-1}‡	–0.3 [–2.0; 0.3]	–0.6 [–2.7; 0.0]	–0.3 (–0.7 to 0.1)	0.17
Δ Bilirubin, mmol L^{-1}	1.41 ± 0.34	1.19 ± 0.31	–0.22 (–1.12 to 0.69)	0.63
Δ ALT, IU L^{-1}‡	3 [–2; 13]	2 [–4; 17]	–1 (–13 to 11)	0.87
Increased ALT >45 IU L^{-1}, *n* (%)*	26 (27.0%)	34 (35.4%)	8.3% (–4.7 to 21.4)	0.21
Δ ALP, IU L^{-1}	–7.98 ± 1.01	–4.76 ± 1.14	3.22 (0.21 to 6.23)	0.036
Urinary ketone bodies, *n* (%)*,**	17 (17.7%)	7 (7.2%)	–10.4% (–19.7 to –1.2)	0.03
Δ Pulse, bpm	–5.4 ± 0.9	–6.2 ± 1.0	–0.75 (–3.47 to 1.97)	0.59
Δ Systolic blood pressure, mmHg	–11.1 ± 1.9	–11.7 ± 1.7	–0.6 (–5.5 to 4.4)	0.82
Δ Diastolic blood pressure, mmHg	–5.5 ± 0.9	–6.9 ± 1.1	–1.4 (–4.2 to 1.5)	0.35
Metabolic syndrome, *n* (%)*,§	49 (51%)	48 (50%)	–1% (–15.2 to 13.1)	0.89
Patients achieving ≥10% WL, *n* (%)*	66 (68.8%)	57 (59.4%)	–9.4% (–22.9 to 4.1)	0.17

Data are mean (±standard error), except when otherwise indicated. All changes between the groups were analysed as the difference of means using an unpaired *t*-test with unequal variance and using the non-parametric test Kruskal–Wallis test for skewed data.

*Presented as proportions; mean difference is estimated via the risk difference.

†Or use of medication for hyperglycemia.

‡Presented as median [Q_1; Q_3]; the 'mean difference' is estimated as the difference in medians.

§The metabolic syndrome is defined according to the American Heart Association criteria.

¶Analysed using Fisher's exact (two-sided) test.

**Analysed using chi-square test.

ALP, alkanine phosphatase; ALT, alanine aminotransferase; bpm, beats per minute; CI, confidence interval; LDL, low density lipoprotein; LED, low-energy diet; HDL, high density lipoprotein; VLED, very low-energy diet; WL, weight loss.

Table 3 Changes following intervention. Efficacy data: intermediate term (16 weeks)

Characteristic/variable	VLED (n = 96)	LED (n = 96)	Mean difference (95% CI)	*P*-value
Δ Weight, kg	−13.3 ± 0.7	−12.2 ± 0.6	1.08 (−0.66 to 2.81)	0.22
Δ Body mass index, kg m^{-1}†	−4.8 ± 0.2	−4.4 ± 0.2	0.35 (−0.27 to 0.96)	0.27
Δ Waist circumference, cm	−10.6 ± 0.6	−9.9 ± 0.6	0.68 (−0.93 to 2.28)	0.41
Δ Fasting glucose, mmol L^{-1}	−0.28 ± 0.05	−0.35 ± 0.06	−0.07 (−0.22 to 0.08)	0.39
Normal (<5 mmol L^{-1}), *n* (%)*,**	14 (14.6%)	7 (7.3%)	−7.3% (−16.1 to 1.5)	0.11
Impaired (5–7 mmol L^{-1}), *n* (%)*	79 (82.3%)	84 (87.5%)	5.2% (−4.9 to 15.3)	0.31
Diabetic (>7 mmol L^{-1}), *n* (%)*,†	3 (3.1%)	5 (5.2%)	2.1% (−3.6 to 7.7)	0.47
Δ Total Cholesterol, mmol L^{-1}	−0.34 ± 0.08	−0.39 ± 0.08	−0.05 (−0.28 to 0.17)	0.64
Δ LDL Cholesterol, mmol L^{-1}	−0.20 ± 0.07	−0.22 ± 0.07	−0.02 (−0.21 to 0.18)	0.88
Δ HDL Cholesterol, mmol L^{-1}	−0.04 ± 0.03	−0.07 ± 0.03	−0.03 (−0.12 to 0.05)	0.43
Δ Triglycerides, mmol L^{-1}‡	−0.08 [−0.45; 0.09]	−0.07 [−0.49; 0.09]	0.01 (−0.21 to 0.23)	0.93
Δ C-reactive protein, mg L^{-1}‡	−0.5 [−2.0; 0.0]	−0.5 [−2.5; 0.3]	0.0 (−0.5 to 0.5)	0.68
Δ Bilirubin, mmol L^{-1}	0.73 ± 0.31	0.23 ± 0.32	−0.5 (−1.37 to 0.37)	0.26
Δ ALT, IU L^{-1}‡	−2 [−7; 2]	−1 [−13; 2]	1 (−1 to 3)	0.33
Increased ALT >45 IU L^{-1}, *n* (%)*	9 (9.4%)	13 (13.5%)	4.2% (−4.8 to 13.2)	0.36
Δ ALP, IU L^{-1}	−2.31 ± 1.21	0.91 ± 1.32	3.22 (−0.32 to 6.76)	0.07
Urinary ketone bodies, *n* (%)*	0	1 (1.0%)	1.0% (−1.0 to 3.1)	0.31
Δ Pulse, bpm	−6.0 ± 0.8	−4.9 ± 0.9	1.08 (−1.28 to 3.44)	0.37
Δ Systolic blood pressure, mmHg	−9.6 ± 1.8	−11.2 ± 1.8	−1.6 (−6.5 to 3.4)	0.53
Δ Diastolic blood pressure, mmHg	−5.0 ± 0.9	−6.9 ± 1.1	−2.0 (−4.8 to 0.9)	0.18
Metabolic syndrome, *n* (%)*,§	44 (46%)	48 (50%)	4.2% (−10.0 to 18.3)	0.56
Δ Lean body mass, kg¶	−2.1 ± 0.2	−1.2 ± 0.4	0.85 (0.01 to 1.69)	0.047
Δ Fat mass, kg¶	−10.3 ± 0.5	−9.8 ± 0.5	0.57 (−0.82 to 1.95)	0.42
Patients achieving ≥10% WL, *n* (%)*	71 (74%)	71 (74%)	0.0% (−12.4 to 12.4)	1.00

Data are mean (±standard error), except when otherwise indicated. All changes between the groups were analysed as the difference of means using an unpaired *t*-test with unequal variance and using the non-parametric test Kruskal–Wallis test for skewed data.

*Presented as proportions; mean difference is estimated via the Risk Difference.

†Or use of medication for hyperglycemia.

‡Presented as median [Q_1; Q_3]; the 'mean difference' is estimated as the difference in medians.

§The metabolic syndrome is defined according to the American Heart Association criteria.

¶Lean body mass and fat mass were measured using dual energy x-ray absorptiometry.

**Analysed using chi-square test.

ALP, alkanine phosphatase; ALT, alanine aminotransferase; bpm, beats per minute; CI, confidence interval; LDL, low density lipoprotein; LED, low-energy diet; HDL, high density lipoprotein; VLED, very low-energy diet; WL, weight loss.

smaller study by Foster *et al.* and also the recently published study by Lin *et al.* (18,19). Our results show that there is no weight loss advantage in using a diet providing 415–554 kcal d^{-1} compared with a diet providing 810 kcal d^{-1}. This may have been due to lowering of basal metabolic rate rather more in the VLED group than in the LED group, and less good dietary compliance in the VLED than the LED group (20,21).

Macronutrients: the protein content was 83.9 g d^{-1} in the LED and between 43.2 and 57.6 g d^{-1} in the VLED programme. Proteins are believed to be more satiating and to have a bigger effect on diet-induced thermogenesis, than fat and carbohydrates do (22,23). Micronutrients: a recent paper by Christensen *et al.* (24) shows that dietary calcium impairs the absorption of dietary fat and increases fecal fat excretion; which could be anticipated as resulting in more body-weight lost. The LED group consumed 7.5 dL of milk daily (860 mg calcium), and the VLED group consumed only water. The higher intake of protein and calcium in the LED group may have contributed to a greater weight loss in this group.

There has been concern about the loss of lean body mass during VLED and LED treatments.

Several studies have shown that with the use of LED, the lean body mass: fat-mass ratio of the lost mass is approximately 25:75 (25). In a Swedish study by Lantz *et al.* (26) the participants had lost 20.16 kg at week 24, where the first 16 weeks were VLED. The loss of lean body mass was 4.53 kg corresponding to 22.5%. The loss of lean body mass in our study was 17% and 11% of total weight loss in the VLED and LED groups, respectively. The LED group lost significantly less lean tissue than did the VLED group, which may be explained by the higher energy intake as well as the higher protein intake. Dietary protein has two roles in nutrition, a specific role as source of nitrogen and amino acids and a non-specific role as an energy source. The lower than expected lean body mass losses in our study may reflect a relatively high increase in muscle activity from

Table 4 Self-reported adverse events among patients in the intention-to-treat population (questionnaire)

Variable	Safety data: short-term (8 weeks)		
	VLED ($n = 96$)	LED ($n = 96$)	Risk difference (95% CI)
Abdominal and intestinal symptoms			
Nausea	9 (9.4%)	9 (9.4%)	0 (–8.2 to 8.2)
Diarrhoea	8 (8.3%)	7 (7.3%)	1.0 (–6.5 to 8.6)
Constipation	41 (42.7%)	40 (41.7%)	1.0 (–12.9 to 15.0)
Flatulence	43 (44.8%)	28 (29.2%)	15.6 (2.1 to 29.1)*
Epigastric pain	11 (11.5%)	5 (5.2%)	6.3 (1.5 to 14.0)
Vomiting	4 (4.2%)	4 (4.2%)	0.0 (–5.7 to 5.7)
Abdominal pain	10 (10.4%)	5 (5.2%)	5.2 (–2.3 to 12.8)
Heartburn	7 (7.3%)	4 (4.2%)	3.1 (–3.4 to 9.7)
Biliary symptoms	2 (2.1%)	3 (3.1%)	1.0 (–5.5 to 3.5)
Musculoskeletal symptoms			
Cramps	7 (7.3%)	6 (6.3%)	1.0 (–6.1 to 8.1)
Joint paint	11 (11.5%)	13 (13.5%)	–2.1 (–11.4 to 7.3)
Back pain	8 (8.3%)	6 (6.3%)	2.1 (–5.3 to 9.4)
Swollen joints	2 (2.1%)	7 (7.3%)	–5.2 (–11.1 to 0.7)
Sciatic pain	8 (8.3%)	8 (8.3%)	0.0 (–7.8 to 7.8)
Central nervous system and psychiatric symptoms			
Dizziness	25 (26.0%)	18 (18.8%)	7.3 (–4.5 to 19.0)
Headache	19 (19.8%)	13 (13.5%)	6.3 (–4.3 to 16.8)
Anxiety	4 (4.2%)	3 (3.1%)	1.0 (–4.3 to 6.3)
Sleeplessness	11 (11.5%)	6 (6.3%)	5.2 (–2.8 to 13.2)
Fatigue	20 (20.8%)	15 (15.6%)	5.2 (–5.7 to 16.1)
Mood changes	10 (10.4%)	7 (7.3%)	3.1 (–4.9 to 11.1)
Depressive tendencies	7 (7.3%)	4 (4.2%)	3.1 (–3.4 to 9.7)
Skin and subcutaneous symptoms			
Dry skin	22 (22.9%)	12 (12.5%)	10.4 (–0.3 to 21.1)
Allergic rash	5 (5.2%)	5 (5.2%)	0.0 (–6.3 to 6.3)
Redness	5 (5.2%)	4 (4.2%)	1.0 (–4.9 to 7.0)
Eczema	3 (3.1%)	4 (4.2%)	–1.0 (–6.3 to 4.3)
Perianal itching	4 (4.2%)	5 (5.2%)	–1.0 (–7.0 to 4.9)
Skin irritation	11 (11.5%)	7 (7.3%)	4.2 (–4.1 to 12.4)
Urticaria	3 (3.1%)	2 (2.1%)	1.0 (–3.5 to 5.5)
Miscellaneous symptoms			
Sensitive to cold	39 (40.6%)	17 (17.7%)	22.9 (10.5 to 35.4)*
Influenza	6 (6.3%)	6 (6.3%)	0.0 (–6.8 to 6.8)
Hair loss	7 (7.3%)	2 (2.1%)	5.2 (–0.7 to 11.1)
Bad breath	34 (35.4%)	21 (21.9%)	13.5 (0.9 to 26.2)*
Toothache	8 (8.3%)	8 (8.3%)	0.0 (–7.8 to 7.8)

Data are presented as proportions no. %; mean difference is estimated via the risk difference.
*Analysed using chi-square; $P < 0.05$.
CI, confidence interval; LED, Low-Energy Diet; VLED, Very Low-Energy Diet.

baseline and thus preservation of lean body mass as a consequence of the reduced pain and improved ability to walk following weight loss.

In a paper by Sowers *et al.*, women with knee OA had less lean body mass per unit of fat mass than women without knee OA (27). From this study it is also obvious that the women with OA knees are much fatter than the women without OA. The dietary treatment in our study had the effect in a short space of time of switching our participants back towards a much healthier body composition after both VLED and LED.

Generally weight loss is known to be associated with improvements in liver enzymes and improvements of non-alcoholic fatty liver disease. This study was consistent with the literature showing that transient mild increases in liver enzymes can be observed in some patients immediately after a VLED or LED period. The increments were observed at week 8 in women only. At week 16 the values had returned to normal in most patients. The consequences of the changes are believed to be benign if the enzyme elevation is transient (28).

As described in the statistical analysis section this trial was not explicitly designed as a superiority trial, nor was it designed as a non-inferiority trial. Thus, we need to recognize that the truth about a potential difference in weight loss between VLED and LED might still be possible.

Obviously if we wanted to claim non-inferiority (VLED = LED) the primary objective of showing that the response to the LED product is not clinically inferior to VLED had to be emphasized a priori (29).

However, if we are to interpret the potential sample size limitation (not being a non-inferiority trial after all) we consider the upper limit of the 95% CI after 16 weeks (≤2.81 kg), indicating that the true difference between VLED and LED could be as much as 2.8 kg after 16 weeks. Apparently, a weight loss of this magnitude would probably be considered trivial to the patient (30), and of no interest for the pharmaceutical industry (31) – thus as the VLED evidently cause participants to lose more lean body mass than the LED, we are confident that a trial with a proper sample size in terms of non-inferiority, is not necessary.

Our study has two major strengths. The first being that this trial is the largest to date comparing the properties of two low-energy formula diets to induce weight loss; the second is the very low drop-out rate of less than 9%. The programme used in this study could be administered to patients of all ages, and in our experience concurrent medical diseases were no obstacle to the proposed dietary treatment. Formula LED present only one major challenge to the treating physician: to reduce dosage of antihypertensive and anti-diabetic medications, appropriately, effectively and safely.

In conclusion, we found that the dietary treatments LED and VLED were equally successful in inducing weight loss, improving blood pressure, decreasing waist circumference and improving blood variables in older obese individuals with knee OA. The significantly lower loss of lean tissue in the LED group together with the more frequently reported side effects of bad breath, intolerance towards cold, and flatulence in the VLED group, favours the choice of low-energy formula diet (LED) for the treatment of obesity.

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Conflict of Interest Statement

Anthony R. Leeds is employed as medical director of the Cambridge Manufacturing Company (Cambridge Diet ®). Pia Christensen, Henning Bliddal, Birgit Falk Riecke, Robin Christensen and Arne Astrup received travel grants to attend scientific meetings from the Cambridge Manufacturing Company.

Financial disclosures

None reported.

Author contribution

Dr Robin Christensen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Additional contributions

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References

1. Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. *Lancet* 2005; **365:** 965–973.
2. Bliddal H, Christensen R. The management of osteoarthritis in the obese patient: practical considerations and guidelines for therapy. *Obes Rev* 2006; **7:** 323–331.
3. Felson DT. Clinical practice. Osteoarthritis of the knee. *N Engl J Med* 2006; **354:** 841–848.
4. Christensen R, Astrup A, Bliddal H. Weight loss: the treatment of choice for knee osteoarthritis? A randomized trial. *Osteoarthritis Cartilage* 2005; **13:** 20–27.
5. Astrup A. Dietary approaches to reducing body weight. *Baillieres Best Pract Res Clin Endocrinol Metab* 1999; **13:** 109–120.

6. National Task Force on the Prevention and Treatment of Obesity. Very low-calorie diets. National Task Force on the Prevention and Treatment of Obesity, National Institutes of Health. *JAMA* 1993; **270:** 967–974.
7. Gilden TA, Wadden TA. The evolution of very-low-calorie diets: an update and meta-analysis. *Obesity (Silver Spring)* 2006; **14:** 1283–1293.
8. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, Schoelles K. Bariatric surgery: a systematic review and meta-analysis. *JAMA* 2004; **292:** 1724–1737.
9. Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B, Oxman AD, Moher D. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ* 2008; **337:** a2390.
10. Altman RD. The classification of osteoarthritis. *J Rheumatol Suppl* 1995; **43:** 42–43.
11. Altman DG, Bland JM. Treatment allocation by minimisation. *BMJ* 2005; **330:** 843.
12. Juni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ* 2001; **323:** 42–46.
13. WHO Technical Report Series. Obesity: Preventing and managing the Global Epidemic – Report of a WHO Consultation on Obesity. 3–5 June 1997, Geneva. No 894. 2000. Ref Type: Report.
14. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, Gotzsche PC, Lang I. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001; **134:** 663–694.
15. Ware JH. Interpreting incomplete data in studies of diet and weight loss. *N Engl J Med* 2003; **348:** 2136–2137.
16. Diggle PJ. An approach to the analysis of repeated measurements. *Biometrics* 1988; **44:** 959–971.
17. Littell RC, Pendergast J, Natarajan R. Modelling covariance structure in the analysis of repeated measures data. *Stat Med* 2000; **19:** 1793–1819.
18. Foster GD, Wadden TA, Peterson FJ, Letizia KA, Bartlett SJ, Conill AM. A controlled comparison of three very-low-calorie diets: effects on weight, body composition, and symptoms. *Am J Clin Nutr* 1992; **55:** 811–817.
19. Lin WY, Wu CH, Chu NF, Chang CJ. Efficacy and safety of very-low-calorie diet in Taiwanese: a multicenter randomized, controlled trial. *Nutrition* 2009; **25:** 1129–1136.
20. Hall KD. Predicting metabolic adaptation, body weight change and energy intake in humans. *Am J Physiol Endocrinol Metab* 2009; **298:** E449–E466.
21. Bosy-Westphal A, Kossel E, Goele K, Later W, Hitze B, Settler U, Heuer M, Gluer CC, Heymsfield SB, Muller MJ. Contribution of individual organ mass loss to weight loss-associated decline in resting energy expenditure. *Am J Clin Nutr* 2009; **90:** 993–1001.
22. Veldhorst M, Smeets A, Soenen S, Hochstenbach-Waelen A, Hursel R, Diepvens K, Lejeune M, Luscombe-Marsh N, Westerterp-Plantenga M. Protein-induced satiety: effects and mechanisms of different proteins. *Physiol Behav* 2008; **94:** 300–307.
23. Lejeune MP, Westerterp KR, Adam TC, Luscombe-Marsh ND, Westerterp-Plantenga MS. Ghrelin and glucagon-like peptide 1 concentrations, 24-h satiety, and energy and substrate metabolism during a high-protein diet and measured in a respiration chamber. *Am J Clin Nutr* 2006; **83:** 89–94.
24. Christensen R, Lorenzen JK, Svith CR, Bartels EM, Melanson EL, Saris WH, Tremblay A, Astrup A. Effect of calcium from dairy and dietary supplements on faecal fat excretion: a meta-analysis of randomized controlled trials. *Obes Rev* 2009; **10:** 475–486.
25. Saris WH. Very-low-calorie diets and sustained weight loss. *Obes Res* 2001; **9** (Suppl. 4)**:** 295S–301S.
26. Lantz H, Peltonen M, Agren L, Torgerson JS. Intermittent versus on-demand use of a very low calorie diet: a randomized 2-year clinical trial. *J Intern Med* 2003; **253:** 463–471.
27. Sowers MF, Yosef M, Jamadar D, Jacobson J, Karvonen-Gutierrez C, Jaffe M. BMI vs. body composition and radiographically defined osteoarthritis of the knee in women: a 4-year follow-up study. *Osteoarthritis Cartilage* 2008; **16:** 367–372.
28. Gasteyger C, Larsen TM, Vercruysse F, Astrup A. Effect of a dietary-induced weight loss on liver enzymes in obese subjects. *Am J Clin Nutr* 2008; **87:** 1141–1147.
29. Lewis JA. Statistical principles for clinical trials (ICH E9): an introductory note on an international guideline. *Stat Med* 1999; **18:** 1903–1942.
30. Christensen R, Bartels EM, Astrup A, Bliddal H. Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2007; **66:** 433–439.
31. Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. *Lancet* 2007; **370:** 1706–1713.

Appendix

Serious adverse events.

In the LED group one participant had a stroke. This was considered unrelated to the diet as the person had previously had two strokes. The participant's cardio-vascular state was well-managed on study entry. After the event the participant dropped out of the study. Another participant in the LED group, who had lost 14 kg in 8 weeks, was briefly hospitalized with bradycardia. After adjustment of the dosage of metoprolol medication, the person was discharged with no further bradycardia and continued in the study. A third participant from the LED group was briefly hospitalized to investigate abdominal pain and pyrexia. The colonoscopy was normal, and no diagnostic label was attached. The event passed without complications. One participant in the VLED group was hospitalized and treated with a percutaneous coronary intervention. The person was known to have angina pectoris, high blood pressure and a previous episode of acute myocardial infarction but was well-managed on study entry; the participant continued in the study. Another participant (VLED) was hospitalized for treatment of an atrial-ventricular-nodal reentry. The person was known to have had episodes of supraventricular tachycardia over the 2 years up to study entry; the participant continued in the study.