Matched weight loss through intermittent or continuous energy restriction does not lead to compensatory increases in appetite and eating behavior in a randomized controlled trial in women with overweight and obesity

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of interest.

List of abbreviations: AUC, Area under the curve; BMI, Body mass index; CER, Continuous energy restriction; CoEQ, Control of Eating Questionnaire; IER, Intermittent energy restriction; LFPQ, Leeds Food Preference Questionnaire; PAL, Physical activity level; RMR, Resting metabolic rate; SQ, Satiety quotient; TDEE, total daily energy expenditure; TFEQ, Three-Factor Eating Questionnaire; VAS, Visual analogue scales; WL, Weight loss.

Supplementary Table 1, Supplementary Table 2, and Supplementary Results are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn.

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Abstract

Background: Continuous energy restriction (CER) is purported to be problematic due to reductions in fat-free mass (FFM), compensatory motivation to overeat and weakened satiety. Intermittent energy restriction (IER) is an alternative behavioral weight loss (WL) strategy that may mitigate some of these limitations.

Objective: The objective of the DIVA study was to compare the effects of CER and IER on appetite when the degree of WL (≥5%) is matched.

Methods: Women with overweight/obesity (BMI 25.0-34.9 kg/m^2; age 18-55 years) were recruited for this controlled-feeding RCT via CER (25% daily energy restriction) or IER (alternating ad libitum and 75% energy restriction days). Probe days were conducted at baseline and post-intervention to assess body composition, ad libitum energy intake and subjective appetite in response to a fixed-energy breakfast, and eating behavior traits. Following baseline measurements, participants were allocated to CER (*n*=22) or IER (*n*=24). Per protocol analyses (≥5%WL within 12 weeks) were conducted using repeated measures ANOVA.

Results: 30 of 37 completers reached ≥5%WL [CER (*n*=18): 6.3±0.8% in 57±16 days, IER (*n*=12): 6.6±1.1% in 67±13 days; %WL *P*=0.43 and days *P*=0.10]. Fat mass (-3.9 (95%CI: -4.3, -3.4) kg) and FFM (-1.3 (95%CI: -1.6, -1.0) kg) were reduced post-WL (*P*<0.001), with no group differences. Self-selected meal size decreased post-WL in CER (*P*=0.03) but not in IER (*P*=0.19). Hunger area under the curve decreased post-WL (*P*<0.05), with no group differences. Satiety quotient remained unchanged and was similar in both groups. Both interventions improved dietary restraint, craving control, susceptibility to hunger and binge eating (*P*<0.001).

Conclusions: Controlled ≥5%WL via CER or IER did not differentially affect changes in body composition, reductions in hunger and improvements in eating behavior traits. This suggests that neither CER nor IER lead to compensatory adaptations in appetite in women with overweight/obesity.

Trial registration: Clinicaltrials.gov as NCT03447600.

Keywords: Appetite, eating behavior, body composition, weight loss, intermittent energy restriction, alternate day fasting, women with overweight/obesity

1 Introduction

Achieving weight loss (WL) through traditional continuous energy restriction (CER) has been proposed to be problematic due to reductions in fat-free mass and compensatory drive to overeat, leading individuals to regain the WL achieved (1, 2). Several studies have shown marked increases in appetite following 5-10% diet-induced WL (3-7). For example, Sumithran and colleagues showed that hunger was elevated after 10% WL with a very low energy diet (~500 kcal/day for 10 weeks) and remained elevated 1 year later (5). An increase in desire to eat was also shown with more modest diet-induced WL in women with overweight (~4.6%WL with a 700-kcal/day restriction) (8). In addition to unsought reductions in fat-free mass, which some have suggested may contribute to compensatory increases in appetite during WL (1), changes in the release of gut peptides (e.g. increase in ghrelin and decrease in peptide YY and cholecystokinin) and satiety signaling with WL have been observed (5, 9, 10). Thus, not only could diet-induced WL lead to a stronger motivation to eat, this may be accompanied by weaker satiety.

Beyond physiological factors, very few studies have examined adaptations in psychobehavioural determinants of appetite and eating behavior during diet-induced WL. Some studies have shown that moderate CER (500-700 kcal daily deficit) to 5% WL increases cognitive restraint, and reduces disinhibition and susceptibility to hunger, suggesting favorable rather than detrimental adaptations in behavior (11, 12). Another risk factor that could promote a poor response to dietary WL interventions is an elevated hedonic response to the sensory features of foods (i.e. liking, wanting or food cravings for high/low energy and sweet/savory tasting food) (13). Indeed, physiological satiety signals can be weakened by responsiveness to high energy-density, high palatability foods, and strong preferences for these foods are expressed as behavioral traits that constitute risk factors for weight gain (14). In the context of WL, we recently showed in a systematic review that food reward for high-energy food generally decreases following weight management interventions, again suggesting favorable outcomes (15).

Intermittent energy restriction (IER) has generated interest in recent years as an alternative WL strategy to CER in individuals with overweight/obesity (16, 17). Some evidence suggests that IER could mitigate the loss of fat-free mass observed during WL (18), potentially reducing compensatory adaptations in appetite leading to poor WL outcomes. However, other studies have shown that both IER and CER lead to similar WL and changes in body composition (19-21). To date, few studies have examined the effects of IER on appetite (17, 22-25). One study (25% energy intake 'fast' day, alternated with an ad libitum 'feed' day for 8 weeks to ~4% WL) found no increase in hunger but rather an increase in fullness after consuming a fixed-energy liquid meal (23). A reduction in hunger and increase in fullness at the end of a fast day have also been observed (26). However, these studies did not directly compare IER to CER. One study found that after ~12.5% WL via IER or CER (12 weeks of ~500 kcal 3 days/week or 33% daily energy restriction, respectively), there were no changes in fasting or postprandial appetite sensations (24). Interestingly, end of day hunger increased and fullness decreased on fast days after 12 months of IER only in those classified as losing ≥5% WL compared to <5% WL (25). In CER, no changes were found in hunger or fullness regardless of WL (25). However, none of these studies measured appetite responses to a standardized test meal and subsequent ad libitum energy intake to accurately assess the strength of satiety. Furthermore, inconsistent results have been found for changes in dietary restraint, with a 12-week IER study showing increases in restraint (26), and a longer term intervention of 1 year showing no change (25). The effects of IER on eating behavior traits remain to be fully understood, and potential effects on food reward and cravings are unknown.

Therefore, the main aim of the DIVA (Diet-Induced Variability in Appetite) proof of concept study was to compare the effects of matched WL to ≥5% through individually prescribed and controlled CER and IER on appetite control in women with overweight and obesity. This design intentionally minimizes the influence of the variability in degree of WL on outcomes, and was not intended to compare the efficacy of the interventions to produce WL. Several psychobehavioural markers of appetite control were assessed, such as subjective appetite sensations, satiety efficiency of food (satiety quotient), ad libitum energy intake, eating behavior traits, food reward (liking and wanting) and food cravings, as well as body composition and resting metabolic rate (RMR). We hypothesized that IER would attenuate compensatory adaptations in appetite (e.g. increase in hunger and reduction in satiety) compared to CER.

2 Methods

2.1 Participants

Women with overweight and obesity were recruited from the University of Leeds and the surrounding area via posters and email lists. The study ran between February-December 2018. Volunteers were included if they were aged between 18-55 years and had a body mass index (BMI) between 25.0-34.9 kg/m^2. Participants taking oral contraceptives were not excluded. Participants were excluded if they had significant health problems that could affect study outcomes; had a history of eating disorders; were taking any medication or supplements known to affect appetite or weight within the past month and/or during the study; were pregnant, planning to become pregnant or breastfeeding; had known food allergies or food intolerances (including a history of anaphylaxis to food); were smokers or had recently ceased smoking (<6 months); had lost/gained >4kg in the previous 6 months; exercised >3 days/week or had significantly changed their physical activity patterns in the past 6 months or who intended to change them during the study; taking medications or treatment likely to interfere with evaluation of the study parameters (including hormone replacement therapy, and treatment for premenstrual dysphoric disorder, polycystic ovary syndrome and thyroid disorders); worked in appetite/feeding-related areas; or were shift workers.

Volunteers provided written informed consent prior to taking part and were remunerated £100 upon completion of all study procedures. The study received approval from the University of Leeds School of Psychology Research Ethics Committee (ref: PSC-238, date: 10-Jan-2018). This trial was registered at clinicaltrials.gov as NCT03447600.

2.2 Screening

Following an online pre-screening questionnaire obtaining background information and assessing general eligibility criteria, participants were invited to the laboratory for a full screening session where consent forms were signed and eligibility determined. Participants were advised not to change their physical activity habits for the duration of the study.

2.3 Randomization & blinding

This study is a parallel group controlled-feeding randomized controlled trial. Participants were unaware of the true aims of the study (i.e. comparison between CER and IER) as it was advertised as 'The effects of a personalized WL meal plan on body composition and metabolism'. Participants were told that once their baseline measurements were completed they would be informed about their 'personalized meal plan'. Upon consenting to participate, participants were randomized (randomization.com) to CER or IER on a 1:1 ratio in blocks of 6 stratified by age (18-36/37-55 years) and BMI (25.0-29.9/30.0-34.9 kg/m^2). Participants and investigators were blinded to the allocated treatment until the baseline measurements were completed. At this point, the participants were given the details of their meal plan (i.e. CER or IER) by the research dietitian who retrieved each diet allocation on a case-by-case basis from an independent co-investigator. To minimize attrition bias, the diet allocation of those that withdrew from the study were re-allocated to new participants (8 pre-diet intervention, 6 during). Outcome assessors remained blinded to the diet allocations throughout the entire intervention. Participants were debriefed about the 2 arms of the trial at the end of the intervention.

2.4 Procedure

As shown in Figure 1, at baseline and in the final week of the intervention, participants completed a free-living measures week where body weight was measured fasted and nude each morning with a scale provided (Salter scale model 9206, UK), and an online food diary was completed at the end of each day. A physical activity monitor (SenseWear Armband, described below) was worn continuously throughout this week. Upon completion of the free-living measures week, participants attended a laboratory measures day (for IER this was completed after a fast day in the final week). A measures week and measures day were also conducted in week 2 of the intervention to assess shorter-term adaptations as predictors of longer-term outcomes, but these data are not reported here.

All testing took place after a 10-12-h overnight fast. Fasting appetite and food reward, body composition, waist and hip circumference, and RMR were assessed. This was followed by a fixed breakfast (25% RMR) and three hours later an ad libitum lunch to determine the acute response in the strength of satiety (appetite ratings every 30 minutes between breakfast and lunch) and food reward (pre- and post-lunch). Participants were then provided with eating behavior questionnaires to complete at home that evening. This manuscript reports on the probe day outcomes: energy intake (primary), appetite, food reward, eating behavior traits, anthropometrics, body composition, and RMR. For full list of outcomes, see online protocol (NCT03447600).

[Figure 1 here]

2.5 Free-living measurements

2.5.1 Physical activity monitor

At baseline and in the final week of the intervention, participants were instructed to wear a SenseWear Armband (BodyMedia, Inc., Pittsburgh, USA) on their non-dominant arm over 7 days for at least 23 hours per day (awake and asleep, except for the time around showering, bathing or swimming), as previously described (27). The SenseWear Armband assesses total daily energy expenditure (TDEE), and minutes spent sleeping, sedentary and in light, moderate and vigorous physical activity. Physical activity level (PAL; TDEE/basal metabolic rate) for each participant was calculated by the software using basal metabolic rate obtained from the WHO equation (28).

2.5.2 Online food diary

At baseline and in the final week of the intervention, daily energy intake was assessed over a 7-day period using a validated online self-administered 24-hour dietary record tool (myfood24.org) (29). After being familiarized with the system, participants were asked to record all food items and drinks consumed, keeping their eating habits as close as possible to their normal routine (baseline) or in line with their meal plan (final week). With this tool, nutrient and energy content of foods are calculated based on the McCance and Widdowson's 6th Edition Composition of Foods UK Nutritional Dataset (30), supplemented with the nutrient content of fast food outlets and food packaging (29). Participants noted with as many details as possible when foods eaten were not in the system, and investigators manually entered the nutritional information of those foods using nutritional information provided on food packaging returned or from the manufacturer's website.

2.6 Laboratory measurements

2.6.1 Anthropometrics, body composition and resting metabolic rate

Height, waist/hip circumference, body weight and composition (BodPod, Life Measurement, Inc., Concord, USA) and resting metabolic rate (GEM indirect calorimeter; Nutren Technology Ltd, UK) were assessed as previously described (27).

2.6.2 Test meals

Participants consumed a breakfast (within 15 minutes) equal to 25% of RMR (65% carbohydrate, 15% protein, 20% fat) measured at baseline and adjusted to the equivalent energy expenditure post-WL. The ingredients consisted of muesli base (Holland & Barret), raisins and sultanas (Holland & Barret), honey (Sainsbury's) and whole milk natural yoghurt (Yeo Valley), semi-skimmed milk (Sainsbury's), and coffee (Nescafe Gold) or tea (Yorkshire Tea). Three hours after breakfast, participants consumed an ad libitum lunch consisting of risotto (Uncle Ben's Tomato & Herb Risotto; 1.51 kcal/g), yoghurt (Yeo Valley Strawberry and MyProtein Maltodextrin; 1.48 kcal/g) and water, served in excess of expected consumption (70% carbohydrate, 9% protein, 21% fat). For the lunch meal, the participants were instructed to eat as much or as little as they liked until comfortably full and that more food was available if needed. Food items were weighed before and after consumption and macronutrient intake was calculated from the manufacturers' food labels. Energy intake was subsequently calculated using energy equivalents for protein, fat and carbohydrate of 4, 9 and 3.75 kcal/g, respectively.

2.6.3 Subjective appetite ratings & satiety quotient

Hunger, fullness, desire to eat and prospective food consumption (100-mm visual analogue scales; VAS) were measured before and after food intake, and at 30-minute intervals between the breakfast and lunch meal (180 min) with a validated electronic system (31). Area under the curve (AUC) for the ratings from pre-breakfast (0 min) to post-lunch (~195 min) was calculated using the trapezoid method (32).

The satiety quotient (SQ) measures the satiating effect of food in relation to the changes in ratings of hunger before and following a meal (33, 34), and was calculated from post-breakfast (~15 min) to pre-lunch (180 min).

2.6.4 Psychometric eating behavior questionnaires

Psychometric eating behaviors were measured using the validated Three-Factor Eating Questionnaire (TFEQ) (35), Binge Eating Scale (36), and Control of Eating Questionnaire (CoEQ) (37).

2.6.5 Food reward: explicit liking and implicit wanting for high-fat relative to low-fat foods

The Leeds Food Preference Questionnaire (LFPQ) was used to measure food reward and food preferences during each test meal day, as previously described (38). It was administered in the fasted state before breakfast, and before and after lunch consumption to assess explicit liking and implicit wanting for an array of food images (adapted to the time of day; see Supplementary Table 1) chosen to be predominantly high (>40% energy) or low (<20% energy) in fat (14). Food images were individually screened to ensure familiarity and acceptability. As a measure of hedonic preference for high-fat foods relative to low-fat foods, liking/wanting fat appeal bias was calculated by subtracting low-fat scores from high-fat scores.

2.7 Diet intervention

Following baseline measurements, participants were given the specifics of their allocated meal plan (CER or IER). The research dietitian calculated energy requirements based on measured RMR × PAL obtained from the SenseWear Armband[1]. Meal plans were adapted for each participant based on requirements and food preferences, and modified on a weekly basis based on feedback from participants. Foods were all pre-portioned (except for the milk where a measuring cup was also provided) with minimal preparation required and accompanied by daily food checklists. Participants were permitted to consume coffee/tea with the milk provided by the researchers (otherwise only black coffee/tea and herbal teas were allowed) and other energy-free beverages, chew sugar-free gum, and were encouraged to drink plenty of water. Participants were instructed to note whether all foods were consumed, or specify how much was left, and the time eaten. Additionally, participants noted if any foods or drinks not on the meal plan were consumed (and if yes, to specify what and how much). Adherence to the meal plans was considered when reported energy intake in the weekly meal plan booklets did not exceed the prescribed energy intake by more than 75 kcal (39). If this occurred, that day was considered non-adherent. Adherence (%) was calculated on a weekly basis by dividing the number of adherent days by the number of prescribed meal plan days × 100 (39). Additionally, we objectively quantified average daily energy intake throughout the intervention using a

[1]For six participants (4 IER and 2 CER) measured PAL from SenseWear was >1.65; therefore a capped PAL of 1.60 was used instead subject to modification after weekly review.

previously validated energy balance equation considering final week TDEE measured with the SenseWear Armband and changes in fat-free mass and fat mass measured with air displacement plethysmography (40, 41). Two 'days off' per month were allowed.

During IER, on fast days, volunteers consumed 25% of their daily energy requirements from total diet replacement products (LighterLife Ltd, UK) provided by the researchers, whereas on the alternate days, volunteers ate ad libitum using their own foods. The calorie content (~150 kcal) and macronutrient composition (~36% carbohydrate, ~27% fat and ~37% protein) was similar for each product, and ensured a daily protein intake of 49.2±8.2 g, in line with the 50 g recommended by the European guidelines on total diet replacement products for weight management (42). There were no time restrictions on when participants could consume the food packs (ranging from 3 to 5 full packs plus an additional bar portion to make up the difference if needed); these were typically evenly distributed throughout the day. Participants were also provided milk portions for coffee/tea, if requested (and deducted from the daily allocated calories), but were required not to consume any other energetic beverages. During the weekly meetings with the dietitian, if WL was not achieved with full compliance, food intake on feed days was discussed and general guidance was offered.

During CER, participants consumed 75% of their daily energy requirements each day from commercially available products provided by the researchers, estimated to induce a similar WL based on current clinical nutrition practices (43). The macronutrient composition of the diet was 50-55% carbohydrate, 30-35% fat and 15-20% protein, in line with national guidelines (44). Three main meals and snacks were provided, and similar to IER, no time restrictions or specific number of eating episodes were given for the consumption of the foods. During the weekly meetings with the dietitian, if WL was not achieved or plateaued with full adherence, prescribed daily food intake was reduced for the following week by 50-100 kcal.

WL was monitored each week, and energy intake adjusted if needed. Upon reaching ~5% WL at a weekly weigh in, participants repeated a final measures week while continuing the dietary intervention and emailed their fasted body weight each day to the research dietitian. Participants were included in the per protocol analysis (≥5% WL within 12 weeks) if self-reported body weight was ≥5% WL on at least 4/7 days leading to the last measures day and objectively confirmed during the final measures day. Participants who did not achieve the ≥5% WL criterion were still tested at 12 weeks but not included in the per protocol analyses.

2.7.1 Statistical analyses

Descriptive data in the text are presented as mean ± SD, and in the figures as mean ± SEM. Data were analyzed per protocol (≥5% WL; CER *n*=18, IER *n*=12), in the completers (CER *n*=19, IER *n*=18) with repeated measures ANOVA in SPSS (version 25, IBM, USA) and intention-to-treat (ITT) in those who only completed baseline measurements (CER *n*=22, IER *n*=24) using a repeated measures linear mixed model to account for missing data with time, treatment and their interaction as fixed factors and subject as the random factor using the lme4 package (45) in R statistics. Chi-square tests were conducted to compare participant attrition and achievement of per protocol criteria between groups. Baseline data were analyzed with independent samples t-tests for randomized, completers and per protocol participants. Baseline to post-WL changes were analyzed with repeated measures ANOVA with group as the between-subject factor and time as the within-subject factor. Where appropriate, Greenhouse-Geisser probability levels were used to adjust for non-sphericity, and post hoc analyses were performed using the Bonferroni adjustment for multiple comparisons. Alongside *P*-values, effect sizes are reported as partial eta-squared (η_p^2) for the ANOVAs and marginal R^2 for the linear mixed models and estimated marginal mean differences (M_Δ) with their 95% confidence intervals (95%CI).

Power calculations (G*Power v3.1) estimated that a sample size of 34 would be required to detect an interaction in self-selected meal size (ad libitum energy intake; η_p^2=0.06) between 2 groups and 2 repeated measurements (r=0.5, based on data from a prior 12-week intervention (46)) with α=0.05 and 1-β=0.8.

3 Results

3.1 Participant flow

Participant flow is shown in Figure 2. There were no differences in attrition between groups (CER: 14% vs IER: 25%; *P*=0.33) but there were more completers achieving ≥5% WL within 12 weeks in CER than in IER (95% vs. 67% respectively; *P*=0.03). There were no serious harms or unintended effects reported in either group.

[Figure 2 here]

3.2 Baseline characteristics

As shown in Table 1, there were no baseline differences between those randomized/allocated to a treatment arm, those that completed the intervention and those that achieved the ≥5%WL criteria (per protocol). Three of the randomized participants were post-menopausal (2 CER and 1 IER), 1 participant was peri-menopausal (IER), and the remaining were pre-menopausal. The following sections report on the per protocol analyses, and completers and ITT analyses can be found in Supplementary Materials.

3.3 Adherence to the interventions and reported energy intake

Mean final WL for CER was 6.3±0.8% in 57±16 days and for IER was 6.6±1.1% in 67±13 days as measured on the final probe day. There were no differences in % WL (*P*=0.43) or days until final measures day (*P*=0.10) between groups. The 7 participants who did not reach ≥5% WL had a final WL of 3.6±2.0%.

There were no differences in mean weekly adherence, as measured by the weekly meal plan booklets, between groups (CER: 89.0±9.7%, IER: 81.4±14.6%; *P*=0.13). Mean calculated daily energy requirements (RMR × PAL) for CER was 2155±399 kcal and for IER was 2196±358 kcal (*P*=0.78). Mean energy prescription for CER was 71.0±4.7% energy requirements (including any adjustments for WL plateauing) and for IER was 24.8±0.3% energy requirements on the fast days. When the estimated energy intake throughout the intervention was calculated (intake balance method using SenseWear Armband and air displacement plethysmography), these data indicated that average energy intake during the intervention in CER was 1592±306 kcal/day, and in IER it was 1678±336 kcal/day (*P*=0.49). This was equivalent to 70.4±8.7% of TDEE in CER and 71.6±10.3% in IER (*P*=0.75). These data support data from the weekly meal plan booklets regrading dietary adherence, and suggest the prescribed diets were effective in achieving the same level of energy deficit.

Baseline self-reported energy and macronutrient intake did not differ between groups (*P*≥0.26; Table 2). Both groups' reported energy intake did not differ from the meal plan in the final week of the intervention (CER *P*=0.11, IER *P*=0.41; Table 2). IER participants' baseline energy intake was also not different to the reported energy intake on feed days in the final week of the intervention (*P*=0.20; Table 2). In terms of macronutrient composition of the prescribed diets, the percentage of daily energy from carbohydrates, fat and protein differed from baseline in both CER and IER (*P*≤0.008) and between CER and IER in the final week (*P*<0.001). Macronutrient composition for IER at baseline and during the feed day in the final week did not change (*P*≥0.46).

Baseline physical activity (minutes of light, moderate, vigorous and total physical activity) and TDEE did not differ between CER and IER (all *P*≥0.36; data not shown). Total physical activity did not change from baseline to the final week of the intervention (*P*=0.37).

3.4 Anthropometrics, body composition and RMR after ≥5% WL

For BMI, body mass, fat mass, fat-free mass, body fat percentage, waist circumference, and hip circumference, there was a main effect of time, with all reducing from baseline to post-WL (*P*<0.001; Table 3), but no differences between groups or interaction effects. There were no changes in waist-to-hip ratio or RMR (*P*≥0.63).

3.5 Test meal energy intake after ≥5% WL

There were no differences in breakfast energy intake between baseline and post-WL (fixed to 25% RMR and re-adjusted post-WL; *P*=0.22). Overall breakfast intake was 357±48 kcal.

For ad libitum energy intake at lunch (Figure 3), there was no effect of WL or group, but there was an interaction between WL and group (*P*=0.02; η_p^2=0.19). Post hoc analyses revealed that CER consumed more than IER at baseline (*P*=0.046, η_p^2=0.14) and reduced intake post-WL (*P*=0.03, η_p^2=0.17), to a similar amount as IER, who slightly increased intake post-WL (*P*=0.19, η_p^2=0.06).

[Figure 3 here]

3.6 Appetite ratings & satiety quotient after ≥5% WL

Hunger throughout the measures day (from morning until early afternoon) decreased overall post-WL (M_{Δ}=3 (95%CI: -7, -0.03) mm, *P*=0.048, η_p^2=0.13), with no differences between groups or interactions (*P*≥0.25, η_p^2≤0.05). Hunger AUC (from pre-breakfast to post-lunch, Figure 4A) decreased post-WL (*P*=0.02, η_p^2=0.18), with no differences between groups or interactions (*P*≥0.75, η_p^2≤0.004).

There were no changes in fullness or fullness AUC (Figure 4B) post-WL, differences between groups or interactions (*P*≥0.10, η_p^2≤0.08).

For desire to eat, there was a reduction post-WL (M_{Δ}=-4 (95%CI: -7, 0.03) mm, *P*=0.05, η_p^2=0.13), but no differences between groups or interactions (*P*≥0.12, η_p^2≤0.56). Desire to eat AUC decreased post-WL (*P*=0.02, η_p^2=0.19; Figure 4C), with no differences between groups, or interactions (*P*≥0.93, η_p^2=0.00).

For prospective food consumption, there was no effect of WL (*P*=0.47, η_p^2=0.02), but there was a time by WL interaction (*P*=0.01, η_p^2=0.09), with post hoc analyses showing that prospective food consumption increased at the first time point (M_{Δ}=6 (95%CI: -0.2, 13) mm, *P*=0.056, η_p^2=0.12) and decreased before lunch (M_{Δ}=8 (95%CI: -16, -0.2) mm, *P*=0.045, η_p^2=0.14) post-WL. There were no changes in prospective food consumption AUC post-WL, group differences or interactions (*P*≥0.17, η_p^2≤0.07; Figure 4D).

[Figure 4 here]

There were no changes in SQ post-WL, group differences or interactions (*P*≥0.26, η_p^2≤0.05; Figure 5).

[Figure 5 here]

3.7 Eating behavior traits after ≥5% WL

As shown in Table 4, dietary restraint increased post-WL (*P*<0.001, η_p^2=0.55) but there were no group or interaction effects (*P*≥0.39, η_p^2≤0.03). Disinhibition decreased post-WL (*P*=0.001, η_p^2=0.32), there was also a main effect of group where IER had greater scores compared to CER (*P*=0.03, η_p^2=0.15; group differences were not apparent at baseline with t-test *P*=0.21, *d*=0.5), and a WL by group interaction was apparent (*P*=0.08, η_p^2=0.11). Post hoc analyses revealed that disinhibition decreased post-WL only in CER (*P*<0.001, η_p^2=0.40), and post-WL, was greater in IER compared to CER (*P*=0.009, η_p^2=0.22). Susceptibility to hunger decreased post-WL (*P*<0.001, η_p^2=0.43), with no group or interaction effects (*P*≥0.81, η_p^2≤0.002). Binge eating score decreased post-WL (*P*<0.001, η_p^2=0.39), with no group or interaction effects (*P*≥0.44, η_p^2≤0.02).

Craving control improved post-WL (*P*<0.001, η_p^2=0.60), with no group or interaction effects (*P*≥0.32, η_p^2≤0.04). Craving for sweet foods decreased post-WL (*P*=0.001, η_p^2=0.35), with no effect of group or interaction (*P*≥0.20, η_p^2≤0.06). Craving for savory foods decreased post-WL (*P*<0.001, η_p^2=0.41), and there was a main effect of group, with IER having greater cravings for savory foods than CER (*P*=0.008, η_p^2=0.23; group differences were also apparent at baseline with t-test *P*=0.003, *d*=1.2), but there was no interaction (*P*=0.10, η_p^2=0.09).

3.8 Liking and wanting for high-fat relative to low-fat foods after ≥5% WL

At the fasted (pre-breakfast) LFPQ, liking or wanting fat bias did not change post-WL, differ between groups, nor were there any interactions (P≥0.11, η_p^2≤0.07; data not shown). At the pre- and post-lunch LFPQ, liking or wanting fat bias also did not change post-WL, differ between groups, nor where there any interactions (P≥0.14, η_p^2=0.06; data not shown).

4 Discussion

In this study, we examined the appetite responses to matched moderate WL to ≥5% through CER or IER to test the hypothesis that IER would mitigate compensatory adaptations promoting poor WL outcomes. Diets were individually prescribed, participants were monitored each week and food for the energy restriction aspect of the intervention was provided (fast days for IER and daily for CER). Appetite parameters were measured under controlled laboratory conditions. Overall, both groups achieved similar changes in body composition with WL without any compensatory increases in hunger or food intake, or weakening of satiety. Rather, there was a reduction in hunger and desire to eat after WL in both groups. This was accompanied by favorable adaptations in eating behavior traits: dietary restraint and craving control increased, and susceptibility to hunger and binge eating score decreased in both groups. Liking and wanting for high-fat relative to low-fat foods did not change during the WL interventions. Contrary to our hypothesis, IER did not result in better outcomes in appetite control compared to CER. Several factors could have contributed to these outcomes. Firstly, while we expected to observe compensatory adaptations after CER, it is possible that controlled WL of ~5% was not sufficient to elicit a response. Previous research has shown appetite-related compensation after weight loss (5, 7) but these reported greater amounts of weight loss, ~8-11%. Secondly, the very controlled nature of the present intervention with all foods provided in CER, but unrestricted feed days in IER may have also influenced the results. Thirdly, the final measurements were conducted immediately after the intervention, when the participants were still in negative energy balance. It is unknown whether compensatory responses would have been detectable in either group if the measures were taken after a weight stabilization period. Nevertheless, the lack of differences between groups suggests that neither intervention resulted in unfavorable outcomes.

Limited evidence suggests that WL through IER may improve satiety, with an increase in postprandial fullness following a fixed-energy liquid breakfast (23). Our data show that in response to a fixed energy breakfast (25% of RMR), there were no changes in satiety (SQ) but a small reduction in hunger and desire to eat after CER and IER to ≥5% WL. Interestingly, while this reduction in hunger was not as apparent in the completers, the completers had an increase in fullness AUC in response to the test meal, with IER having greater fullness overall than CER (but there was no time by group interaction). These findings show that contrary to prior proposals (2-7), hunger did not increase and satiety did not weaken in those achieving ≥5% WL with the present WL interventions. Other IER studies have also shown no changes in postprandial hunger with 4% WL (23), and following ~12.5% WL via IER or CER, Coutinho and colleagues found no changes in fasting or postprandial subjective appetite (24). To our knowledge, one other study has also shown a reduction in hunger in response to a test meal following an 8-week low-energy diet to 8% WL (47). These results show that compensatory adaptations that increase the motivation to eat are not inevitable following diet-induced WL. The distinct findings in hunger between the participants achieving ≥5% WL and the completers may explain why the former were successful at reaching the WL target, as closer examination of the data revealed that mean hunger (and prospective food consumption) AUC in the 7 participants who did not reach ≥5% WL increased rather than decreased. However, fullness AUC also increased in these non-successful individuals; therefore, it is difficult to clearly interpret these findings. Nevertheless, a reduction in the sensation of hunger is a viable mechanism for successful WL (48, 49) and this is consistent with the present study findings. A further issue is whether changes in hunger after WL have an impact on subsequent weight regain, and this will be examined in future work.

While hunger was lower after both IER and CER following WL, only CER reduced self-selected meal size at the ad libitum test meal. Of note, baseline energy intake was greater in CER than IER, and post-WL values were not different between CER and IER. The reduction in CER aligns with one study showing that 24-hour ad libitum energy intake measured in a metabolic chamber decreased after a 15-week CER (+fenfluramine/placebo) intervention to ~10% WL (7). Another study found no changes in ad libitum meal size after a 12-week CER (+probiotic/placebo) intervention to ~4% WL (50). Habituation to smaller portions may have resulted in the reduction in self-selected meal size after WL. In contrast, IER consumed their habitual diet on feed days, without specific restrictions or guidelines, which could have contributed to the lack of observed effect on meal size. Future studies should examine the mechanisms responsible for any potential changes in satiation with diet-induced WL.

There was an overall improvement in most eating behavior traits after WL in both groups, with an increase in restraint and craving control, and a reduction in susceptibility to hunger, binge eating score and cravings for sweet and savory foods. This is in line with other diet-induced WL interventions (11, 12, 50-53). These suggest that cognitive control over eating can be improved with prescribed diet-induced WL, or as proposed by Urbanek and colleagues regarding restraint, could be an 'adaptive strategy necessary for successful weight control' (11). Westenhoefer and colleagues suggest that distinct dimensions of restraint affect WL outcomes differently: rigid control relating to an 'all-or-nothing approach to eating, dieting, and weight', and flexible control relating to a 'more graduated approach to eating, dieting, and weight, in which "fattening" foods are eaten in limited quantities without feelings of guilt' (54 (p.54)). The latter was associated with more successful WL (54). Indeed, in women, rigid restraint has been found to be positively associated with disinhibition and markers of adiposity, whereas flexible restraint was not associated with disinhibition and was inversely associated with body fat (55). IER studies have shown increases in restraint over the medium-term (12 weeks) (26) but no changes after 1 year (25). In the current study, restraint increased in both groups. Further examinations of the data (≥5% WL participants) revealed some trends suggesting that IER increased rigid restraint to a greater extent than CER, whereas CER increased flexible restraint to a greater extent than IER, and CER had greater post-WL values in flexible restraint than IER (see Supplementary Table 2). The implications for these particular responses in eating behaviors with IER and CER remain to be elucidated.

Interestingly, disinhibition reduced in CER but not IER after WL. This is in contrast to another study that showed a reduction in uncontrolled eating measured following 12-weeks of IER that included dietary counselling for healthier eating (26). Disinhibition is characterized by the tendency of an individual to overeat and to eat opportunistically (35). Furthermore, it may be that the ‘fast’ and ‘feed’ dietary pattern of the current IER intervention led to more uncontrolled eating on ‘feed’ days for some individuals. This could have contributed to the different energy intake response observed between CER and IER. Moreover, it may explain why fewer participants in IER achieved ≥5% WL within 12 weeks or took longer to reach their target weight. Several features of the IER group independent of the intervention may have also contributed to these effects. IER participants had greater disinhibition ratings overall, and the time by group interaction was stronger in the completers analysis than the ≥5% WL analysis. Another characteristic of the IER completers was poorer overall craving control and greater cravings for sweet and savory foods that was not observed in the ≥5% WL participants, but there was no time by group interaction in response to the intervention, suggesting underlying differences. It should be noted that the aim of the current study was not to examine the efficacy of either intervention to produce WL but the effect of ≥5% WL on compensatory adaptations. Examining predictors of WL success with IER would add to the limited understanding of the suitability and efficacy of this intervention for weight management (25).

An unexpected finding was that no changes in liking or wanting for high-fat relative to low-fat foods were observed after ≥5% WL in the current study, contrary to the reduction in food reward found in our recent systematic review of WL interventions with a median WL of 5% (range 2-10%) (15). Further analyses will investigate individual changes in reward for each food category of the LFPQ (high-fat, low-fat, sweet and savory) to better understand this result. A greater understanding of the impact of different dietary WL approaches on food reward and eating behavior traits, and their role in weight management is warranted.

Some limitations to the current study need to be acknowledged. While food packs were provided in IER for the fast days, the absence of food provision for the feed days may have impacted some of the outcome measures; however, both groups received similar amounts of diet replacement products each week. The macronutrient composition of CER and IER diets differed, but are similar to what would be followed during typical clinical or commercial weight management interventions. Along those lines, it is not possible for us to dissect the observed effects of the WL interventions from the foods that were provided and structure of the intervention. Furthermore, menstrual cycle was not taken into consideration for testing. As the final measures day occurred after 5% WL was achieved and not after a given timeline, timing of the menstrual cycle with the measures day would not have been possible. The inclusion of 4 peri/post-menopausal women may have also affected the results; however, the 2 allocated in IER did not achieve the 5% WL criterion so were not included in the per protocol analyses and 1 in CER withdrew in the second week of the intervention due to issues with the foods in the meal plan. Analyses excluding the remaining post-menopausal woman in CER revealed: IER took longer to achieve ≥5% WL than CER (67 days vs. 56 days; P=0.046), a stronger effect of ≥5% WL on reductions in hunger and desire to eat throughout the measures day (P=0.02; η_p^2=0.18 and P=0.03, η_p^2=0.17; respectively), but similar effects on body composition, test meal energy intake, SQ, eating behavior traits and food reward. Finally, as our intervention was in a relatively small number of women, up to 12 weeks in duration and designed to induce only modest WL, our results may not be generalizable to larger, longer and more intensive interventions. A larger randomized controlled trial is warranted to confirm our findings.

To conclude, CER and IER to ≥5% WL in women with overweight and obesity led to similar improvements in body composition without compensatory increases in hunger, satiety efficiency of food or energy intake. Hunger decreased, satiety remained unchanged, and eating behavior traits generally improved. Differences between interventions were sparse - disinhibition reduced in CER and remained unchanged in IER, while self-selected meal size reduced post-WL in CER with no changes observed in IER (energy intake was similar between groups post-WL). These differences, in addition to determinants of successful WL with IER, remain to be fully explored. Overall, the current study shows that both CER and IER did not lead to any detrimental compensatory adaptations in appetite and eating behavior following ≥5% WL in women with overweight and obesity.

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Figure legends

Figure 1 Schematic of the trial. Anthro, anthropometrics; Bfast, breakfast; BW, body weight; EBQ, eating behavior questionnaires; LFPQ, Leeds Food Preference Questionnaire; RMR, resting metabolic rate; SWA, SenseWear Armband; VAS, visual analogue scales for appetite ratings; WL, Weight loss.

Figure 2 Consort flow diagram. CER, continuous energy restriction; IER, intermittent energy restriction; WL, weight loss.

Figure 3 Changes in ad libitum test meal energy intake at lunch from baseline to ≥5% WL in women with overweight/obesity who underwent CER (n=18) and IER (n=12). Values are means ± SEMs.* P<0.05 (Post hoc analyses using Bonferroni corrections). CER, continuous energy restriction; IER, intermittent energy restriction; WL, weight loss.

Figure 4 A) Hunger area under the curve (AUC), B) fullness AUC, C) desire to eat AUC, and D) prospective food consumption AUC calculated from pre-breakfast (0') to post-lunch (~195') at baseline and after ≥5% WL in women with overweight/obesity who underwent CER (n=18) and IER (n=12). Values are means ± SEMs. * P<0.05 (Main effect of WL using repeated measures ANOVA). AUC, area under the curve; CER, continuous energy restriction; IER, intermittent energy restriction; WL, weight loss.

Figure 5 Satiety quotient (SQ) after the individually fixed breakfast (25% RMR) at baseline and after ≥5% WL in women with overweight/obesity who underwent CER (n=18) and IER (n=12). Values are means ± SEMs. Bfast, breakfast; CER, continuous energy restriction; IER, intermittent energy restriction; WL, weight loss.

Table 1 Baseline group characteristics of women with overweight or obesity who completed baseline measurements, completed 12 weeks of the intervention, and reached ≥5% WL within 12 weeks[1-2]

	CER	**IER**	***P*-value[3]**
Randomized	***n*=22**	***n*=24**	
Age (years)	34 ± 9	35 ± 11	0.59
Body mass (kg)	78.6 ± 10.0	81.2 ± 13.0	0.45
Height (m)	1.65 ± 0.7	1.66 ± 0.9	0.64
BMI (kg/m^2)	28.9 ± 2.3	29.4 ± 2.5	0.50
Fat mass (kg)	32.3 ± 7.6	34.5 ± 8.7	0.37
Fat-free mass (kg)	46.3 ± 5.5	46.7 ± 5.9	0.78
Body fat (%)	40.8 ± 5.7	42.0 ± 4.6	0.42
RMR (kcal/day)	1434 ± 209	1459 ± 223	0.70
Completers	***n*=19**	***n*=18**	
Age (years)	34 ± 9	36 ± 11	0.55
Body mass (kg)	79.6 ± 10.3	80.1 ± 11.1	0.90
Height (m)	1.65 ± 0.8	1.66 ± 0.9	0.90
BMI (kg/m^2)	29.1 ± 2.4	29.1 ± 2.2	0.97
Fat mass (kg)	32.8 ± 8.1	33.5 ± 6.7	0.76
Fat-free mass (kg)	46.9 ± 5.4	46.6 ± 6.0	0.87
Body fat (%)	40.7 ± 6.1	41.6 ± 4.1	0.60
RMR (kcal/day)	1456 ± 208	1435 ± 185	0.74
Per protocol (≥5%WL)	***n*=18**	***n*=12**	
Age (years)	35 ± 9	34 ± 10	0.80
Body mass (kg)	79.2 ± 10.4	81.1 ± 12.2	0.64
Height (cm)	1.65 ± 0.8	1.67 ± 0.9	0.58
BMI (kg/m^2)	29.1 ± 2.4	29.1 ± 2.5	0.95

Fat mass (kg)	32.5 ± 8.3	34.0 ± 7.2	0.60
Fat-free mass (kg)	46.7 ± 5.5	47.1 ± 6.6	0.85
Body fat (%)	40.6 ± 6.2	41.7 ± 4.1	0.60
RMR (kcal/day)	1456 ± 214	1441 ± 201	0.85

[1]Values are means ± SDs.

[2]BMI, body mass index; CER, continuous energy restriction; IER, intermittent energy restriction; RMR, resting metabolic rate; WL, weight loss.

[3]Result of independent sample t-test.

Table 2 Self-reported (baseline and final week of intervention) and prescribed (final week of intervention) energy and macronutrient intake in women with overweight/obesity who achieved ≥5%WL with CER and IER[1-2]

	CER reported baseline	**CER prescribed final week**	**CER reported final week**	**IER reported baseline**	**IER prescribed final week**	**IER reported final week - fast day**	**IER reported final week - feed day**
EI (kcal/d)	1951 ± 374	1475 ± 220	1400 ± 309	1783 ± 438	543 ± 89	582 ± 163	1608 ± 321
CHO (g/d)	221 ± 46	197 ± 32	180 ± 41	199 ± 58	53.4 ± 8.8	60.9 ± 21.6	178 ± 35
CHO (% daily EI)	42.6 ± 6.3	49.9 ± 2.3*,†	48.3 ± 2.4	41.5 ± 5.0	36.9 ± 0.3*	39.0 ± 3.8	42.2 ± 7.6
Fat (g/d)	78.6 ±16.3	49.0 ± 6.9	49.2 ±10.0	74.4 ±15.5	16.3 ± 2.6	16.6 ± 2.4	65.6 ±15.5
Fat (% daily EI)	36.5 ± 5.7	30.0 ± 1.9*,†	31.9 ± 3.2	37.9 ± 3.2	26.9 ± 0.3*	26.4 ± 2.9	36.8 ± 4.4
Protein (g/d)	77.8 ±18.7	73.8 ± 12.0	62.9 ±17.8	71.5 ± 26.5	49.1 ± 8.2	46.7 ± 9.1	62.0 ± 18.4
Protein (% daily EI)	16.0 ± 2.8	20.0 ± 1.2*,†	17.9 ± 2.2	15.9 ± 3.8	36.2 ± 0.5*	32.8 ± 6.3	15.2 ± 2.3

[1]Values are means ± SDs; *n*=18 (CER) or 12 (IER).

[2]CER, continuous energy restriction; CHO, carbohydrate; EI, energy intake; IER, intermittent energy restriction.

*Different from baseline within each group (repeated measures ANOVA), $P<0.001$

†Different from IER prescribed final week (repeated measures ANOVA), $P<0.001$

Table 3 Changes in anthropometrics, body composition and RMR after ≥5%WL in women with overweight/obesity who underwent CER and IER[1-2]

	CER baseline	**CER post-WL**	**IER baseline**	**IER post-WL**
BMI (kg/m^2)	29.1 ± 2.4	27.3 ± 2.3*	29.2 ± 2.5	27.2 ± 2.4*
Body mass (kg)	79.2 ± 10.4	74.2 ± 10.0*	81.1 ± 12.2	75.8 ± 11.3*
Fat mass (kg)	32.5 ± 8.3	28.8 ± 7.7*	34.1 ± 7.2	30.0 ± 6.8*
Fat-free mass (kg)	46.7 ± 5.5	45.4 ± 5.5*	47.1 ± 6.6	45.8 ± 6.3*
Body fat (%)	40.6 ± 6.2	38.4 ± 6.4*	41.7 ± 4.1	39.3 ± 4.8*
WC (cm)	91.7 ± 9.0	87.5 ± 8.6*	93.5 ± 7.4	90.1 ± 7.8*
HC (cm)	109.0 ± 6.6	105.2 ± 6.0*	111.0 ± 7.2	106.5 ± 7.2*
W:H ratio	0.84 ± 0.08	0.83 ± 0.08	0.84 ± 0.06	0.85 ± 0.06
RMR (kcal/day)	1456 ± 214	1432 ± 202	1441 ± 201	1473 ± 180

[1]Values are means ± SDs; *n*=18 (CER) or 12 (IER)

[2]CER, continuous energy restriction; HC, hip circumference; IER, intermittent energy restriction; RMR, resting metabolic rate; W:H ratio, waist-to-hip ratio; WC, waist circumference; WL, weight loss.

*Different from baseline (repeated measures ANOVA), P<0.001.

Table 4 Changes in eating behaviors traits in after ≥5%WL after ≥5%WL in women with overweight/obesity who underwent CER and IER[1-2]

	CER baseline	**CER post-WL**	**IER baseline**	**IER post-WL**
TFEQ Restraint	9 ± 5	13 ± 5*	8 ± 3	12 ± 4*
TFEQ Disinhibition	9 ± 3	6 ± 3*,†	10 ± 3	10 ± 3
TFEQ Susceptibility to hunger	7 ± 4	4 ± 3*	6 ± 3	4 ± 2*
Binge eating score	15 ± 9	9 ± 7*	16 ± 7	12 ± 5*
CoEQ Craving control	49 ± 21	71 ± 19*	42 ± 16	65 ± 20*
CoEQ Craving sweet	38 ± 23	23 ± 21*	49 ± 30	32 ± 22*
CoEQ Craving savory	34 ± 22†	23 ± 17*,†	61 ± 22	36 ± 26*

[1]Values are means ± SDs (no units for all variables); *n*=18 (CER) or 12 (IER);

[2]CER, continuous energy restriction; CoEQ, Control of Eating Questionnaire; IER, intermittent energy restriction; TFEQ, Three-Factor Eating Questionnaire; WL, weight loss.

*Different from baseline (repeated measures ANOVA), $P \leq 0.001$

†Different from IER (repeated measures ANOVA), $P < 0.01$