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Do intermittent diets provide physiological benefits over continuous diets for weight loss? A systematic review of clinical trials

Radhika V Seimon\textsuperscript{a}, Jessica A Roekenes\textsuperscript{a}, Jessica Zibellini\textsuperscript{a}, Benjamin Zhu\textsuperscript{a}, Alice A Gibson\textsuperscript{a}, Andrew P Hills\textsuperscript{b}, Rachel E Wood\textsuperscript{c}, Neil A King\textsuperscript{d}, Nuala M Byrne\textsuperscript{c}, Amanda Sainsbury\textsuperscript{a}

\textsuperscript{a}The Boden Institute of Obesity, Nutrition, Exercise & Eating Disorders, Sydney Medical School, The University of Sydney, Camperdown NSW 2006, Australia
\textsuperscript{b}Centre for Nutrition and Exercise, Mater Research Institute, The University of Queensland, South Brisbane QLD 4101, Australia
\textsuperscript{c}Bond Institute of Health and Sport, Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Australia
\textsuperscript{d}Institute of Health and Biomedical Innovation and School of Exercise and Nutrition Sciences, Queensland University of Technology, Brisbane QLD 4059, Australia

\textbf{Address for correspondence:} Amanda Salis (nee Sainsbury)

The Boden Institute of Obesity, Nutrition, Exercise & Eating Disorders
Sydney Medical School
The University of Sydney
Camperdown NSW 2006
Australia

Phone: +61 4 23777801
Email: amanda.salis@sydney.edu.au
Running head: Intermittent versus continuous energy restriction

Abbreviations

ADF: Alternate day fasting
BMI: Body mass index
CER: Continuous energy restriction
DHEAS: Dehydroepiandrosterone sulphate
24-hour EE: 24-hour Energy expenditure
EI: Energy intake
ER: Energy restriction
EX: Exercise
FFM: Fat-free mass
%FM: Percent fat mass
FM: Fat mass
HbA1C: Glycated hemoglobin
Hip: Hip circumference
HOMA-IR: Homeostatic model assessment – [Insulin Resistance]
IER: Intermittent energy restriction
IGF-1: Insulin-like growth factor-1
REE: Resting energy expenditure
T3: Triiodothyronine or 3,3′,5-triiodothyronine
T4: Thyroxine or 3,5,3′,5′- tetraiodothyronine
TSH: Thyroid stimulating hormone
Waist: Waist circumference
ABSTRACT (150 words maximum)

Energy restriction induces physiological effects that hinder further weight loss. Thus, deliberate periods of energy balance during weight loss interventions may attenuate these adaptive responses to energy restriction and thereby increase the efficiency of weight loss (i.e. the amount of weight or fat lost per unit of energy deficit). To address this possibility, we systematically searched MEDLINE, PreMEDLINE, PubMed and Cinahl and reviewed adaptive responses to energy restriction in 40 publications involving humans of any age or body mass index that had undergone a diet involving intermittent energy restriction, 12 with direct comparison to continuous energy restriction. Included publications needed to measure one or more of body weight, body mass index, or body composition before and at the end of energy restriction. 31 of the 40 publications involved ‘intermittent fasting’ of 1-7-day periods of severe energy restriction. While intermittent fasting appears to produce similar effects to continuous energy restriction to reduce body weight, fat mass, fat-free mass and improve glucose homeostasis, and may reduce appetite, it does not appear to attenuate other adaptive responses to energy restriction or improve weight loss efficiency, albeit most of the reviewed publications were not powered to assess these outcomes. Intermittent fasting thus represents a valid – albeit apparently not superior – option to continuous energy restriction for weight loss.

Keywords (maximum of 6 keywords, using British spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of').

Intermittent energy restriction; alternate day fasting; appetite; energy expenditure; body composition; glucose homeostasis
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Not provided.

Highlights

Highlights are mandatory for this journal. They consist of a short collection of bullet points that convey the core findings of the article and should be submitted in a separate editable file in the online submission system. Please use 'Highlights' in the file name and include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point). See http://www.elsevier.com/highlights for examples.

- Energy restriction induces adaptive physiological responses that hinder weight / fat loss.
- Intermittent energy balance periods might reduce adaptive responses during energy restriction.
- Intermittent fasting reduces body weight and possibly appetite but not other adaptive responses.
- Intermittent fasting is an equivalent alternative to continuous energy restriction for weight loss.
1. Introduction

Recent years have seen a surge in popularity of eating patterns involving intermittent energy restriction (IER). Such eating patterns involve restricting energy intake by varying degrees for a pre-defined period of time, and eating *ad libitum* (i.e. to satisfy appetite) – or at least more than during the energy-restricted period – at all other times. The most common form of IER is ‘intermittent fasting’, where energy intake is severely restricted for short periods (typically 1 to 4 days per week). During periods of greater energy intake, there may or may not be restrictions placed on the types and amounts of foods and beverages consumed.

While IER in varying forms has been used for health and religious reasons for thousands of years (1, 2), it has more recently been popularised in a weight management context through various forms of the media. IER contrasts with the conventional approach to weight management, or continuous energy restriction (CER). The latter entails continuously trying to restrict energy intake to below weight maintenance requirements for an extended and often open-ended period of time, and usually also involves restrictions on the types of foods consumed (e.g. limiting the intake of energy-dense, nutrient-poor foods).

A question that has not been extensively addressed is whether or not IER provides physiological benefits over CER for weight management. For instance, is there a ‘metabolic advantage’ associated with IER? Specifically, does energy restriction achieved via IER result in greater weight or fat loss than the same overall amount of energy restriction achieved by CER? Or, do people who follow IER lose the same amount of weight or fat per unit of energy restriction, on
average, as those on CER? IER might be expected to result in more efficient weight loss than CER, because of the known effects of energy restriction to induce physiological responses that oppose ongoing weight loss, and because of emerging evidence that these adaptive responses can be normalised or at least attenuated by a period of energy balance (i.e. where energy intake is matched to energy requirements and weight remains constant) or by \textit{ad libitum} food intake. These considerations will be briefly reviewed in the next paragraph.

The adaptive responses to energy restriction in individuals that are overweight or obese are numerous and have been reviewed elsewhere (Sainsbury A, Seimon RV, Hills AP, Wood RE, King NA, Gibson AA, Byrne NM, submitted manuscript, (3-11). They include increased appetite (12-15), reduced physical activity (16, 17) or the energy cost of physical activity (16, 18-21), reduced energy expenditure greater than that expected from the reduction in body mass (22, 23), and hormonal effects that can adversely affect body composition by promoting the accumulation of adipose tissue (particularly central adiposity) and stimulating the loss of lean tissues (3, 24-27). Indeed, studies in lean animals and humans clearly show that negative energy balance markedly inhibits activity of the hypothalamo-pituitary-thyroid (28), -gonadotropic and -somatotropic axes (or reduces circulating insulin-like growth factor-1 [IGF-1] levels) (29), while concomitantly activating the hypothalamo-pituitary-adrenal axis (3, 26). There is little information available as to the effects of weight loss in people that are overweight or obese on the circulating concentrations of effector hormones of these neuroendocrine axes (notably thyroid hormones, sex hormones, IGF-1 and cortisol), but available evidence suggests that similar changes to those occurring during energy deficit in lean animals and humans may also occur in overweight and obese people during weight loss interventions (3, 24-27). Such changes
could conceivably hamper outcomes from weight loss interventions, by fostering a hormonal milieu known to promote accretion of adipose tissue (particularly central adiposity) while simultaneously promoting loss of lean tissues (3). Some research suggests that the greater the deficit between energy requirements and intake, the greater the magnitude of these adaptive responses (22, 23, 30-32). Interestingly, several lines of evidence from lean (33, 34) and overweight or obese (17, 24, 35-39) humans suggest that some adaptive responses to energy restriction may be deactivated or partially deactivated by well-controlled restoration of energy balance and weight maintenance at the reduced body weight, at least in some individuals. This phenomenon appears to be dependent upon restoration of true energy balance or even positive energy balance (not continued energy restriction) (24), although positive energy balance was not a panacea for all aspects of the adaptive response to energy restriction (13, 14), as reviewed elsewhere (Sainsbury A, Seimon RV, Hills AP, Wood RE, King NA, Gibson AA, Byrne NM, submitted manuscript). Deactivation of adaptive responses to energy restriction may also occur more effectively when exercise is incorporated into the weight management regime (Sainsbury A, Seimon RV, Hills AP, Wood RE, King NA, Gibson AA, Byrne NM, submitted manuscript, (16, 40-43). Taken together, this literature would suggest that deliberate periods of energy balance during weight loss interventions – as in IER – could attenuate or deactivate various adaptive responses to energy restriction and thereby increase the efficiency of weight loss. But what is the evidence for this in humans?

To this end, we conducted a systematic review of original human clinical trials involving IER. We included studies with humans of any age or body mass index (BMI) incorporating a diet involving IER, with or without comparison to CER or a control arm, in order to assess any
evidence that IER may reduce or fail to induce adaptive responses to energy restriction, or improve the efficiency of weight loss. To be included in the review, publications needed to measure body weight, BMI or body composition both before commencement of the intermittent diet, as well as upon completion of the diet.

2. Methods for the systematic review of intermittent energy restriction

2.1 Inclusion and exclusion criteria

Study designs included in this review were human clinical trials (randomized controlled trials and pilot studies). Only original research studies were included; review articles, case studies, surveys, as well as abstracts and conference papers, were excluded. To be included in this systematic review, publications needed to have investigated humans of any age or BMI that had undergone a diet involving IER. Ramadan fasting as a form of IER was excluded due to the pattern of eating not matching that of common forms of intermittent diets, but Sunnah fasting (nil by mouth, sunrise to sunset, typically 2 days per week) was included, as it is of a similar format to other forms of IER. Studies that did and did not include a comparator group on CER or control conditions were included, to give a broad perspective of the wide variety of ways in which IER is being investigated.

No limit was placed on the duration of IER. Studies were excluded if participants had undergone bariatric surgery, were diagnosed with cancer, Crohn’s disease or were taking medications designed to induce weight loss. Any non-surgical, non-cancer or non-medication arms of any of the above such studies could, however, be included if they met the inclusion criteria.
To be included in this review, publications needed to measure one or more of the following parameters both before commencement of the intermittent diet, as well as at a time point upon completion of the diet: body weight, BMI or body composition. We used these broad outcome measures as inclusion criteria rather than the adaptive responses to energy restriction, because very few studies have investigated the latter outcomes (i.e. drive to eat, physical activity, energy expenditure, and circulating concentrations of thyroid, adrenal, gonadal or somatotropic hormones).

2.2 Search strategy

MEDLINE, PreMEDLINE, PubMed and Cinahl were searched from the inception date of each database to November 2014. Both medical subject headings (MeSH) and free text search terms were employed. Limitations were set so that only studies published in English and involving human participants were found. Reference lists of relevant articles as well as review articles were searched to help ensure that all relevant studies were found.

The following example shows the specific key words (or MeSH terms) used for the search of MEDLINE:

Alternate day fast*.tw OR alternat* calori* diet*.tw OR alternate day diet*.tw OR intermittent fast*.tw OR alternate day modified fast*.tw OR intermittent energy fast*.tw OR intermittent energy restrict*.tw OR intermittent energy diet*.tw OR intermittent energy restrict* diet*.tw OR (intermittent adj2 diet*).tw OR intermittent food depriv*.tw OR intermittent calori* restrict*.tw OR (intermittent adj2 restrict*).tw
The example search strategy for MEDLINE (above) was adapted to suit each database.

2.3 Data extraction and analysis

The titles and abstracts of the studies identified in the above search strategy were independently screened by two authors (JAR and JZ). The full texts of potentially relevant studies were retrieved and were independently screened by the same authors (JAR and JZ) according to the inclusion and exclusion criteria. If discrepancies between the two screening authors arose as to which studies to include or exclude, consensus was reached by consultation with a third author (RVS). Additional articles that the authors knew about from other sources, but did not come up in the search, were also included in this review.

Two authors (JAR and BZ) extracted the following data from each study, as summarized in Table 1: author, year, sample size, participant characteristics (sex, age, BMI), the percent of participants who dropped out of the intervention (as well as the percent that dropped out due to inability to adhere to the intervention), duration and design of the intervention, description of IER and CER or control arms, weight change, anthropometric changes, effects on glucose homeostasis, as well as other changes related to the adaptive responses to energy restriction. Data extraction was checked by two additional authors (RVS and AS).

Publications included in this review used different definitions, units and terminology to describe the interventions, so the following standardized definitions were applied. Durations of interventions were expressed in weeks, and all data provided in other units of time were converted to weeks (1 month = 4.3 weeks; 1 year = 52 weeks). Severe energy restriction was
defined as a prescribed or measured energy intake of less than 5,000 kJ per day (44, 45), and
moderate energy restriction was defined as a prescribed or measured energy intake of greater
than or equal to 5,000 kJ per day (32). All data that were provided in calories were converted to
kJ (1 calorie = 4.18 kJ). Energy intake (prescribed or measured) during the fast and feed days
was not reported in every publication, hence we made the following assumptions and estimations
when presenting daily energy intake. Namely, an energy-restricted intervention that prescribed a
meal replacement program was assumed to be severely energy restricted, and an intervention that
described a food-based diet emphasizing healthy food choices was assumed to be moderately
energy restricted. Additionally, some studies that did not report prescribed or measured energy
intake reported on the degree of energy intake or restriction relative to weight maintenance
requirements, and we presented these as percent energy restriction (e.g. 100% energy restriction
for an energy intake of 0% of requirements [complete fasting]; 75% energy restriction for an
energy intake of 25% of requirements). Energy restriction of 65% or more was designated as
severe energy restriction; less than that was deemed to be moderate energy restriction. Where it
was necessary to assume weight maintenance energy requirements, this was assumed to be
10,000 kJ per day for participants that were overweight or obese, and 8,700 kJ per day for those
that were lean. Data were extracted qualitatively according to the authors’ results and
conclusions about the change from baseline, with upwards arrows referring to statistically
significant increases, downwards arrows referring to statistically significant decreases, or
sideways arrows referring to no statistically significant changes from baseline. The dropout rates
reported in Table 1 were rates at the end of the total study period (including any follow up), not
the weight loss intervention period noted in the table. Also, the sample sizes reported in Table 1
represent the total number of participants enrolled in the study. These values were extracted from
the methods section of each publication and not from the abstract, as the abstract of some publications only reported on the number of participants that completed the study and not on the number of participants initially enrolled.

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Figure 1. Flow diagram for the process of publication selection, inclusion and exclusion from this systematic review

- Publications discovered through electronic database search: $n = 402$
- Number of articles screened (after duplicates removed): $n = 308$
- Full text publications retrieved after screening titles and abstracts: $n = 72$
- Publications excluded after application of inclusion and exclusion criteria: $n = 40$
  - Protocol: $n = 22$
  - Participants: $n = 5$
  - Ramadan fasting: $n = 13$
- Publications included after application of inclusion and exclusion criteria: $n = 32$
- Articles authors knew about from other sources: $n = 8$
- Publications included in the systematic review: $n = 40$
  - Publications comparing IER with CER: $n = 12$
  - Publications comparing IER to a control arm: $n = 8$
  - Publications of IER alone with no comparator arm: $n = 20$
3. Results and discussion for the systematic review of intermittent energy restriction

3.1 Search results, sample sizes and intervention characteristics

A total of 402 records were retrieved from the 4 databases searched, equating to 308 unique publications. Following screening of titles and abstracts, the full texts of 72 potentially relevant publications were retrieved and analyzed against the inclusion and exclusion criteria, resulting in the exclusion of 40 publications for the reasons shown in Figure 1. No further publications were identified from screening the reference lists of these 72 publications. As a result, 32 publications from the search, plus 8 additional articles known to the authors (39, 46-52), were included in this systematic review (Figure 1). These 40 included publications involved 32 independent clinical trials, with results from some trials being reported on in more than one publication. Twelve publications compared the effectiveness of IER to CER, 8 publications compared the effectiveness of IER to a control arm, while 20 publications examined the effect of IER alone, as shown in Figure 1 and the alphabetical listing of the included publications in Table 1.

Sample size for each publication varied from 4 to 334 participants, with the most common sample size being between 30 to 60 participants. Of the 40 publications included, 17 publications included females only, 6 included males only, while the remaining 17 publications included both males and females. The lowest included age was 17 years and the greatest was 79 years. Participants had a minimum included BMI of 20 kg/m² and maximum included BMI of 45 kg/m². In most trials, participants were overweight or obese, but 9 of the 40 publications in this review included lean participants (51, 53-60). Of these 9 publications, 1 included lean participants only in the control and not the intervention arm (60), 5 included a mixed population
of lean and overweight participants (51, 54-56, 59), and 3 included lean participants only (53, 57, 58).

The overall duration of the interventions varied from 2 to 104 weeks, with the most common duration being 12-13 weeks. The majority of included publications involved intermittent fasting regimes, with short periods (1-7 days) of severe energy restriction alternating with periods of moderate energy restriction or no energy restriction. Indeed, of the 40 publications, 31 publications used intermittent fasting regimes, 19 of which used alternate day fasting (ADF) as a means of IER (47, 53, 55, 58, 61-75), which consisted of a “fast day” (where energy intake is usually severely restricted to about 25% of energy requirements, or 75% energy restriction) alternating with a “feed day” (usually involving a prescription of ad libitum food consumption). The other 12 of the 31 publications that used intermittent fasting regimes used short periods of severe energy restriction during a “fasting phase” of 2 to 7 days per week (48, 51, 56, 57, 59, 60, 76-81). Besides these 31 publications investigating intermittent fasting regimes, a further 7 of the 40 included publications used longer periods of severe energy restriction (2-12 consecutive weeks) (39, 49, 50, 52, 82-84). Only 2 of the 40 publications reviewed used moderate energy restriction during the “fasting phase” of the IER protocol (46, 85).

3.2 Comparable dropout rates for interventions involving IER or CER

Of the 12 publications that compared IER with CER, 10 publications reported the percentage of participants that dropped out of the intervention. Of these 10 publications, 3 showed a greater dropout rate in the IER compared with the CER arm (52, 66, 79), 5 showed the opposite result (46, 48, 73, 78, 85), while 2 studies only reported the overall dropout rate of both arms combined.
(76, 84), indicating no clear difference in dropout rate with IER compared to CER. Of the 2 publications that reported on the proportion of people that dropped out due to inability to adhere to the intervention, both publications showed a greater dropout rate due to inability to adhere to the CER compared with the IER arm (78, 79). Only 4 of the 8 publications that compared IER with a non-CER control arm reported the percentage of participants who dropped out of the trial. Two publication showed a greater dropout rate in the IER than in the control arm (51, 62), one a greater dropout in the control arm (56), while another showed no between-group difference (74).

Of the 20 publications that looked at IER alone, 15 reported dropout rates (39, 47, 49, 61, 67-72, 75, 80-83), which ranged from 0-65%. Of these 15 studies, 12 reported dropout rates due to participants being unable to adhere to the diet, and this ranged from 3-10%. Reported dropout rates in the treatment of obesity are heterogeneous and range from 10 to 80% depending on the setting and type of program used (86, 87). As dropout is an indicator of non-adherence to an intervention (as well as other factors), these data provide no clear evidence that IER is easier to adhere to than other dietary weight loss approaches. Future trials of IER would benefit from documentation of dropout as well as assessment of adherence rates.

3.3 IER consistently reduces body weight, body size and adiposity

The findings from this systematic review clearly show that IER is an effective method for weight loss. All but 3 (53, 57, 58) of the 40 publications included in this review reported that IER produced weight loss, with no reports of weight gain. The minimum weight loss was 2.1 kg after 3 weeks (54), and the maximum weight loss was 16.6 kg after 20 weeks (39), with the most common weight loss being 3-5 kg after approximately 10 weeks of IER. All of the 3 publications that reported no change in weight during IER involved only lean participants (53, 57, 58). Of
these 3 studies in lean participants, 2 involved interventions of only 2 weeks, which may have been insufficient to result in weight change (53, 58). 2 of these 3 publications in lean individuals (53, 57) noted that the lack of weight loss may have been due to compensation for the fasting phases, with participants eating more abundantly during non-fasting days as per protocol instructions, or in compensation for previous restriction.

Besides body weight, IER also produced clear reductions in other indices of body size and adiposity, namely BMI, waist circumference, hip circumference, FM and FFM. Of the 32 independent trials (40 publications) included in this review, 13 reported on BMI, with 10 of these reporting a decrease following IER (39, 47, 51, 52, 56, 59, 63, 71, 77, 80), 2 reporting no change, albeit both of these studies involved lean participants (53, 57), while 1 reported a decrease in BMI following one form of IER and no change following another form of IER (61). Only 13 publications reported waist circumference: 12 reported a decrease in response to IER (39, 47-49, 63, 69, 76-79, 81, 85), and 1 reported a decrease in waist circumference following one form of IER and no change following another form of IER (61). Hip circumference was reduced by IER in all of the 3 interventions that reported it (48, 78, 79), albeit there was no effect of IER on the ratio of waist to hip circumference (66). Twenty three (23) of the 32 independent trials reported on FM, either as a percent of body weight or as absolute weight: 20 reported a decrease (39, 47, 49, 51, 55, 56, 59, 60, 63, 66, 70, 74, 76-80, 82, 83, 85), 2 trials, both in lean participants, reported no change (53, 58), while 1 reported a decrease in FM following one form of IER and no change following another form of IER (61). Finally, of the 32 independent trials included in this review, 17 reported on FFM. Of these trials, 9 reported a decrease (39, 49, 55, 64, 66, 78, 79, 82, 85), while 8 reported no change (51, 58, 59, 61, 63, 70, 74, 80) in FFM following IER. On
balance, the majority of publications reporting on various indicators of body size and composition showed reductions in indices of size and adiposity, and only approximately half of the publications showed reductions in FFM with IER.

3.4 Comparable weight loss for interventions involving IER or CER

Of the 12 publications covering 12 independent trials comparing the effectiveness of IER to CER, 9 demonstrated that IER was not significantly different from CER with respect to weight loss (46, 48, 50, 66, 73, 76, 78, 79, 85), but 1 reported a greater weight loss in the CER group compared with the IER group (64), while another 2 reported the opposite result of greater weight loss in the IER group compared with the CER group (52, 84). In the 12 publications that compared IER with CER, 7 reported on BMI, waist circumference, hip circumference or the ratio of waist to hip circumference (48, 52, 66, 76, 78, 79, 85). These publications unanimously showed that IER and CER induced equivalent reductions in BMI (52), waist circumference (48, 76, 78, 79, 85) and hip circumference (48, 78, 79), with neither intervention inducing a reduction waist to hip ratio (66). In the 12 publications that compared IER with CER, 5 reported on FM, with no difference reported between IER and CER in 4 of these publications (66, 76, 79, 85), while 1 publication reported a greater decrease in FM in the IER group (78). Of the 12 publications directly comparing IER with CER, 5 reported on FFM, with no difference reported in 4 of these publications (64, 66, 78, 79), and 1 publication reporting a greater decrease in FFM in the IER group (85). Taken together, it can be seen that IER appears to be comparable to CER with respect to weight loss and the location and composition of the body weight lost.

3.5 Effects of IER on the drive to eat and mood
Of the 32 independent trials included in this review, only 10 investigated aspects of the drive to eat. Two of these 10 independent trials compared IER against CER, with both showing a greater number of participants in the IER than the CER arm reporting hunger and/or preoccupation with food, albeit the proportion of participants affected was low (only 3-15% in the IER arm and 0-7% in the CER arm) (78, 79). Two of these 10 independent trials compared IER with a non-CER control arm (62, 74). Despite significant weight loss in both trials, 1 reported decreases from baseline in hunger and uncontrolled eating with concomitant increases in fullness, satisfaction and restrained eating (with no difference in emotional eating) in the IER but not the control group (62), and the other reported no difference from baseline in hunger and an increase in fullness and satisfaction in the IER group, with no such change in the control group (74). The other 6 publications that investigated appetite (55, 57, 67-69, 81) investigated IER without any comparator arm. Of these, 2 publications reported a decrease from baseline in appetite (as indicated by decreases in hunger and increases in fullness and/or satisfaction) despite significant weight loss (68, 69), 2 publications, one in obese (55) and one in lean participants that did not lose weight (57), reported an increase from baseline in measures of appetite (increased hunger or ‘drive to eat’ or preoccupation with food, with concomitantly reduced fullness and no change in satisfaction or the ‘desire to eat’), while 2 reported no change from baseline in appetite measures (hunger, fullness, satisfaction) with concurrent weight loss (67, 81) following IER. In sum, 4 of these 10 independent trials that investigated aspects of the drive to eat showed that IER increased measures of appetite (55, 57, 78, 79), while 6 showed that IER either decreased (62, 68, 69, 74) or had no significant effect on appetite (67, 81). It is noteworthy that these decreases or lack of change in overall appetite indices occurred despite significant weight loss in all of the 6 aforementioned IER interventions (62, 67-69, 74, 81), given that weight loss has been
associated with increases in the drive to eat (11-15). It is also noteworthy that this apparent
suppression of the drive to eat occurred despite decreased circulating levels of the appetite-
reducing hormone, leptin, following IER. Indeed, of the 8 publications that reported leptin
concentrations in IER, 7 showed significant reductions from baseline in circulating leptin levels
(39, 61, 69, 74, 78-80), with 1 of these studies showing no difference from baseline (67). Thus, it
would seem that IER may attenuate the effect of energy restriction to increase the drive to eat.

A decrease in hunger or increase in fullness or satiety – or no change in these parameters from
baseline despite significant weight loss and reduced leptin levels – is in keeping with the finding
that participants on IER protocols involving severe energy restriction exhibited no change from
baseline in fasting (55, 67) or meal-induced (54) circulating concentrations of the hunger-
promoting hormone, ghrelin, albeit there was a significant increase in fasting ghrelin levels
during fast days in one trial (79), and is also in keeping with the increase (55, 57, 67, 79) or non-
significant trend (P = 0.07) to an increase (53) in circulating concentrations of the ketone body,
β-hydroxybutyrate, that was observed in all but one (78) of the 6 trials that measured ketone
bodies. We have recently shown in a meta-analysis that ketogenic diets (severely energy
restricted VLEDs or very low carbohydrate ketogenic diets) significantly reduce the drive to eat
– or do not increase it – despite significant weight loss (88). The mechanism for this is unknown,
but may be due to elevated circulating concentrations of ketone bodies associated with such
diets, among other possible factors (88). Thus, the severe energy restriction used in intermittent
fasting protocols may contribute to the observed appetite suppression as indicated by subjective
measures. Besides subjective measures, 2 studies provided objective evidence of reduced drive to
eat in response to IER involving severe energy restriction (55, 68). In 1 such study, an ADF
protocol, it was hypothesized that participants would increase their energy intake on feed days to approximately 125% of their baseline energy requirements. However, no such response was observed, with participants only consuming an average of 95% of their calculated energy needs on feed days, resulting in overall weight loss (68). In the other study, which also constituted an ADF protocol involving total fasting, participants were asked to double their energy intake on feed days to maintain energy balance. However, participants did not consume enough food on the feed days to maintain their weight, and in turn lost weight (55). It therefore seems likely that IER has an effect to reduce food intake even after the fast day has ended, contrary to expectations that such diets would lead to compensatory overeating.

As changes in the drive to eat can moderate moods such as anxiety or contentedness, we therefore examined information on mood in the publications reviewed, notwithstanding that IER could conceivably also have direct effects on mood. Only 5 of the 32 independent trials in 40 publications reported mood in response to IER (56, 57, 67, 78, 79). Of these 5 trials and publications, 2 had a direct comparison of IER to CER (78, 79), with inconsistent results. While one of these 2 publications showed a lower number of participants in the IER (32%) than the CER (46%) arm reporting improved mood, with a greater number in IER than CER reporting bad temper (79), the other showed that there was no difference between IER and CER in the number of participants reporting improved mood and vigour, or in self-reported tension, depression and anger, and there was a smaller number of participants in the IER (3%) than the CER (5%) arm reporting mood swings / bad temper, albeit the proportion of participants affected was low (78).

The 3 other studies reporting on mood showed similarly mixed effects. While 2 studies involving severe energy restriction showed positive effects of IER on mood, as indicated by reductions in
mood disturbance, tension, anger and confusion (56), or improved mood (67), the other study, which was in lean participants but also involving severe energy restriction, reported a worsening of mood during the fast days of IER compared with baseline, with concomitant increases in irritability, fatigue and concentration difficulties, along with increases in hunger, preoccupation with food and the drive to eat (57). With only 5 out of 40 publications reporting on mood, and given the inconsistent results from these studies where mood was not a primary outcome, it is not possible to draw conclusions about the effects of IER on mood.

3.6 No evidence that current IER protocols reduce other adaptive responses to energy restriction

The publications included in the current review showed no clear evidence that current IER protocols reduce any effect of energy restriction and weight loss to decrease physical activity or energy expenditure, or to alter hormone concentrations, as outlined below.

In the 3 publications that reported on physical activity, 2 found no change from baseline in participants on IER (53, 68), and the other study observed significant decreases in physical activity in response to CER and one form of IER (severe ER on fast days, no restriction on feed days), but not the other (ad libitum bread, water, coffee, tea on fast days, no restriction on feed days), with no difference between groups (64). A finding of decreased physical activity with IER is in keeping with the greater feeling of fatigue reported by participants on IER in one publication involving severe energy restriction (57), albeit that publication only included lean individuals. In the 2 studies that compared subjectively rated energy levels in people on IER versus CER (78)(79), there was no indication of IER being superior. Indeed, one of these 2 studies (79) showed that more people on IER than CER reported feeling a lack of energy, and
that fewer people on IER than CER reported feeling increased energy. The other one of these 2
studies (78) showed no difference between IER and CER with respect to the number of people
that reported feeling a lack of energy or fatigue.

Of the 32 independent trials included in this review, only 6 reported on energy expenditure. Of
these, 3 showed a decrease in 24-hour EE and / or REE – either in absolute values (58, 64, 66) or
adjusted for FFM (64), while 3 showed no change in REE (55, 83, 85) or REE adjusted for FFM
(55, 66, 83) relative to baseline following IER. Of these 6 publications that reported on energy
expenditure, 3 made a direct comparison between IER and CER (64, 66, 85). One such article
reported no difference from baseline in REE and no difference between the IER and CER groups
(85), one showed that with IER there was a decrease from baseline in absolute and adjusted
values of 24-hour EE and REE, with the decrease being greater, less than or no different from
that in the CER group depending on the parameter under investigation (64), while the third
article showed that the reduction in REE from baseline was similar between IER and CER (66).
Taken together, there was no evidence to suggest that the effect of energy restriction to reduce
energy expenditure was abated by IER.

In terms of hormonal effects, IER induced a decrease in circulating concentrations of the thyroid
hormone T3 (triiodothyronine or 3,3′,5-triiodothyronine) compared to baseline (57), similar to
changes that have been observed with CER in separate publications (11). In keeping with this,
there was no difference between IER and CER with respect to circulating concentrations of
thyroid stimulating hormone, thyroid hormones (or cortisol) when measured at the end of the
intervention (58). IER also induced apparently similar effects as CER to inhibit the gonadal axis
Indeed, IER and CER induced similar decreases in circulating concentrations of testosterone, the free androgen index, androstenedione and prolactin, albeit IER induced a lesser decrease in that of DHEAS (dehydroepiandrosterone sulphate, a metabolic intermediate in the biosynthesis of the androgen and estrogen sex steroids), and similar increases in that of sex hormone binding globulin (79). Interestingly, menstrual cycle length was significantly longer in women on a 26-week IER than a CER intervention (79). IER also induced similar effects to CER to inhibit the somatrotropic axes (as indicated by similar increases in the circulating concentrations of IGF-1 binding proteins 1 and 2) (79), albeit with no change from baseline in circulating IGF-1 levels in either group (78, 79). Another study, this one with no CER or control comparator arm, showed a significant reduction in circulating IGF-1 concentrations with one form of IER but not the other form (81). Taken together, these studies suggest that the effect of energy restriction and weight loss to induce adaptive changes in neuroendocrine status may not be different in current IER interventions compared to that observed with CER, albeit there is very little research available to assess this.

A finding that currently reviewed IER protocols did not reduce the adaptive response to energy restriction relative to the effects of CER would perhaps not be surprising when considering that attenuation of these adaptive responses appears to be dependent upon restoration of true energy balance or even positive energy balance (not continued energy restriction) (Sainsbury A, Seimon RV, Hills AP, Wood RE, King NA, Gibson AA, Byrne NM, submitted manuscript) (24), and that a significant proportion of IER interventions hereby reviewed did not attain neutral or positive energy balance at any time during the intervention. Although all interventions involved periods of energy restriction interspersed with periods of relatively greater actual or prescribed energy
intake, 14 of the 40 publications included in this review (35%) prescribed a degree of energy restriction even during these relative ‘feasts’ (50-52, 56, 59, 60, 66, 76, 78-82, 84). In other studies, even though participants were instructed to increase their energy intake during ‘feast’ days, participants consumed less than prescribed or expected. This was observed in 7 publications using protocols where energy intake during ‘feast’ times had been estimated from food diary analysis and found to be below energy prescriptions or energy balance requirements (47, 54, 55, 61, 69-71). This phenomenon of consuming less energy than the prescribed or weight maintenance energy intake, which likely also occurred in other studies where food diaries were not analysed, was possibly due to an effect of severe IER to reduce the drive to eat, as discussed in Section 3.5, or a sentiment amongst participants that restricting energy intake would maximise weight loss, a motivator for enrolling in a clinical weight loss trial in the first place. Therefore, it seems unlikely that the ‘feast’ periods in commonly studied intermittent dieting protocols involved sufficient energy intake to deactivate adaptive responses to energy restriction.

3.7 Comparable improvements in glucose homeostasis for interventions involving IER or CER

Overweight and obesity are major risk factors for the development of type 2 diabetes. As modest weight loss is associated with improvements in glucose homeostasis in overweight or obese individuals, including those with type 2 diabetes or pre-diabetes, we also compared the effects of IER and CER on glucose homeostasis. In the 32 independent trials reported on in this review, 20 investigated various aspects of glucose homeostasis, with 17 reporting specifically on fasting circulating glucose concentrations. Of these, 11 reported no change from baseline in fasting glucose levels following IER (39, 47, 49, 53, 55, 59, 63, 67, 77, 78, 84), 4 reported a decrease from baseline (52, 79, 80, 85), while 2 reported an increase from baseline (60, 66) following
IER. Similarly to fasting glucose levels, results for HbA1c—which reflects longer-term circulating glucose levels—showed inconsistent results, with 2 articles reporting no change (78, 84) and 2 reporting a decrease (52, 76) in HbA1c compared with baseline following IER. With respect to the 13 independent trials that measured fasting circulating insulin concentrations, 4 found no change in this parameter relative to baseline following IER (53, 66, 67, 84), while 8 reported a decrease (39, 49, 52, 55, 60, 63, 78, 79) and 1 reported a decrease following one form of IER and no change following another form of IER (80). This finding of little or no reduction in fasting circulating glucose concentrations in response to IER in the face of a possible decrease in fasting insulin suggests that insulin sensitivity may be increased following IER. In keeping with this possibility, of the 5 independent trials that assessed homeostatic model assessment—[Insulin Resistance] (HOMA-IR), an index of insulin resistance, 4 reported a decrease from baseline with IER (39, 49, 78, 79), while one reported no change (63).

Of the 12 articles that compared IER against a CER comparator arm, 7 investigated aspects of glucose homeostasis. Only 2 of these reported a greater decrease from baseline in fasting glucose (79, 85), and only 1 reported a greater decrease from baseline in fasting insulin (79) and HOMA-IR (79) with IER compared to CER. The remaining 5 publications found no difference in fasting circulating levels of glucose (52, 66, 78, 84), HbA1c (52, 76, 78, 84) or insulin (52, 66, 84) between the IER and CER groups, while one reported a greater decrease in fasting insulin and HOMA-IR with one form of IER compared with the other form of IER and CER (78). This suggests that following an IER there are improvements in glucose homeostasis, but no more so than in response to CER.
3.8 Impact of exercise on effects of IER

Of the 32 independent trials included in this review, 3 trials (in 4 publications) combined IER with exercise (62, 63, 66, 73). Two of these trials (in 3 publications) involved a direct comparison between IER with and without exercise (62, 63, 66), while 1 trial included an exercise only group as a comparison arm (73). Of the former 2 independent trials (62, 63, 66), both showed that when IER was combined with exercise, even greater weight loss was achieved – approximately 3 kg more than when achieved by IER alone. In the 1 publication that reported BMI and waist circumference, the addition of exercise to IER decreased these parameters to a greater extent from baseline than the IER intervention alone (63). In the 2 independent trials in 2 publications that reported on body composition (63, 66), the IER plus exercise intervention produced greater reductions in %FM or FM when compared with IER alone, although there was no difference in FFM between IER administered with or without exercise. In addition, the combination of IER and exercise reduced emotional eating when compared with IER or exercise alone (62). Apart from a decrease in emotional eating, which may suggest a manifestation of a reduction in the drive to eat, there was no clear evidence that exercise attenuated other aspects of the drive to eat, or other adaptive responses to energy restriction, as has been suggested elsewhere (Sainsbury A, Seimon RV, Hills AP, Wood RE, King NA, Gibson AA, Byrne NM, submitted manuscript). This is indicated by the observation that IER was no different from IER plus exercise in terms of reducing uncontrolled eating and increasing restrained eating (62). In fact, whereas hunger was decreased and fullness and satisfaction were increased by IER relative to baseline, no such changes from baseline were seen when IER was combined with exercise (62). Additionally, there were no differences in REE or REE adjusted for FFM reported with IER or CER alone versus IER or CER with exercise added to the intervention (66).
3.9 Limitations and future directions

There are a number of limitations to this systematic review that need to be addressed. Only 12 of the 40 publications included in this review directly compared IER with CER: the lack of direct comparison makes it difficult to determine whether IER is superior to CER, or for whom. Another limitation is that 14 of the 40 publications included in this review were performed by the same research group (47, 61-63, 68-75, 80, 81). Additionally, differences in study design, intervention form, and participant characteristics and numbers makes it difficult to clarify which form(s) of IER is (are) the most effective for weight loss. For example, although we were able to categorize interventions as IER or CER, the diets were highly variable with respect to the levels of prescribed energy intake, macronutrient composition, and timing of the ‘fast’ and ‘feast’ phases. Furthermore, there is currently insufficient data to support the notion that IER influences body weight, FM, FFM, adaptive responses to energy restriction or glucose homeostasis any differently to CER, as most studies were not powered to specifically investigate these parameters, with most having moderate sample sizes of 30-50 participants. Finally, only 5 of the 40 included publications followed up participants at 52 weeks or more after commencement of the diet (48, 49, 52, 76, 85), so the longer-term impact of several weeks or months of IER on body weight, body composition, or the adaptive responses to energy restriction is not precisely known. Further investigation from more researchers is required, with larger sample sizes and longer durations, to fully investigate the potential of IER versus the conventional approach of CER for weight management.

4. Summary and conclusions
Apart from a possible decrease in the drive to eat, likely associated with ketosis or other factors concomitant with severe energy restriction, this work found no evidence that IER, as applied in the clinical trials hereby reviewed, reduced adaptive responses to energy restriction relative to effects of CER. While very little research has been done in this domain, this finding is in keeping with the observation that a significant proportion of the IER interventions reviewed (most of which were intermittent fasting regimes) did not attain neutral or positive energy balance at any time during the intervention, and given that attenuation of adaptive responses to energy restriction is likely to be dependent upon relief from negative energy balance. Consistent with this is the finding that IER and CER produced apparently equivalent outcomes in terms of the amount of weight, waist or hip circumference, FM or FFM lost, the improvements in parameters related to glucose homeostasis, as well as the proportion of people dropping out of the intervention. Intermittent diets, notably the intermittent fasting diets that comprised the bulk of the trials hereby reviewed, thus represent an alternative and equivalent option to more conventional diets involving CER as a means of weight reduction.
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References


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<tr>
<th>Author, year (Ref)</th>
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<tr>
<td>Arguin et al. (2012) (85)</td>
<td>(n=25) Female, mean age 60.5±6.0 years, obese, postmenopausal Dropout: 15% IER; 25% CER</td>
<td>34 weeks IER 29 weeks CER (4 weeks weight maintenance plus 5 weeks ER plus 15-20 weeks of IER or CER plus 5 weeks weight maintenance), follow up at 52 weeks from start</td>
<td>IER ((n=13)): 2 cycles of 5 weeks of weight maintenance plus 5 weeks of moderate ER (20 weeks) CER ((n=12)): 15 weeks of moderate ER (15 weeks)</td>
<td>↓IER ≅ ↓CER Follow up versus baseline ↓IER ≅ ↓CER</td>
<td>Waist, %FM, FM: ↓IER ≅ ↓CER FFM: ↓IER &gt; ↓CER Follow up versus baseline Waist, %FM, FM: ↓IER ≅ ↓CER</td>
<td>Glucose: ↓IER, ↔CER Follow up versus baseline REE: ↔IER, ↔CER</td>
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<td>Ash et al. (2003) (76)</td>
<td>(n=51) Male, aged &lt;70 years, overweight/obese ((\text{BMI} 25-40 \text{ kg/m}^2)), type 2 diabetes Dropout: 53% overall</td>
<td>12 weeks, follow up at 78 weeks from start</td>
<td>IER ((n=14)): 4 consecutive days/week of severe ER ((4180 \text{ kJ/day prescribed})), 3 days/week of moderate ER ((6000-7000 \text{ kJ/day prescribed})) CER: 1) CER A ((n=20)): Moderate ER via pre-portioned meals ((6900 \text{ kJ/day allotted})) 2) CER B ((n=17)): Moderate ER via self-selected meals ((6000-7000 \text{ kJ/day prescribed}))</td>
<td>↓IER ≅ ↓CER A ≅ ↓CER B Follow up versus baseline ↔IER, ↔CER A, ↔CER B</td>
<td>Waist: ↓IER ≅ ↓CER A ≅ ↓CER B %FM: ↓IER ≅ ↓CER A &gt; ↓CER B Follow up versus baseline Waist, %FM: ↔IER, ↔CER A, ↔CER B</td>
<td>HbA(_1C): ↓IER ± ↓CER A, ↓CER B Follow up versus baseline HbA(_1C): ↔IER, ↔CER A, ↔CER B</td>
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<td>de Groot et al. (1989) (64)</td>
<td>(n=27) Female, aged 21-46 years, overweight ((\text{BMI} &gt;24.9 \text{ kg/m}^2))</td>
<td>5 weeks (1 week weight maintenance plus 4 weeks IER or CER)</td>
<td>IER: ADF 1) IER A ((n=10)): Severe ER ((4886 ± 465 \text{ kJ/day measured})) on fast days, no restriction ((9772 ± 929 \text{ kJ/day measured})) on feed days 2) IER B ((n=10)): Ad libitum bread, water, coffee, tea on fast days ((\text{energy intake not measured})), no restriction ((9772 ± 929 \text{ kJ measured})) on feed days CER ((n=7)): Moderate to severe ER ((4886 ± 465 \text{ kJ/day measured}))</td>
<td>↓IER A ≅ ↓IER B &lt; ↓CER</td>
<td>FFM: ↓IER A ≅ ↓IER B ≅ ↓CER</td>
<td>Physical activity: ↓IER A ≅ ↓CER, ↔IER B 24-hour EE, REE (sleeping): ↓IER A ≅ ↓IER B &lt; ↓CER 24-hour EE adjusted: ↓IER A ≅ ↓IER B ≅ ↓CER REE (sleeping) adjusted: ↔IER A, ↓IER B &gt;</td>
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<td>Harvie et al. (2011) (79)</td>
<td>$n=107$ Female, aged 30-45 years, overweight/ obese (mean BMI 30.6±5.1 kg/m$^2$), premenopausal Dropout: 19% IER (4% unable to adhere); 13% CER (6% unable to adhere)</td>
<td>26 weeks</td>
<td>IER ($n=53$): 75% ER (2060-2266 kJ/day prescribed) on 2 days/week, CER diet on 5 days/week CER ($n=54$): 25% ER (~6276 kJ/day prescribed)</td>
<td>↓IER ≅ ↓CER</td>
<td>↑Waist, hip, %FM, FM, FFM; ↓IER ≅ ↓CER</td>
<td>Glucose: ↓IER ≅ ↓CER Insulin, HOMA-IR: ↓IER &gt; ↓CER</td>
<td>↓Leptin, free androgen index, testosterone, androstenedione, prolactin: ↓IER ≅ ↓CER IGF-1: ↔IER, ↔CER Ghrelin, sex hormone binding globulin, IGF-1 binding proteins 1, 2: ↑IER ≅ ↑CER β-hydroxybutyrate#: ↑IER, ↔CER DHEAS: ↓IER &lt; ↓CER Menstrual cycle length: IER &gt; CER N° of participants reporting hunger, preoccupation with food, lack of energy, feeling cold, headaches, constipation, lack of concentration, bad temper: IER &gt; CER N° of participants reporting increased energy, improved mood: IER &lt; CER</td>
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<td>Harvie et al. (2013) (78)</td>
<td>n=115 Female, aged 20-69 years, overweight (BMI 24-45 kg/m²) Dropout: 11% IER A; 26% IER B (3% unable to adhere); 33% CER (8% unable to adhere)</td>
<td>17 weeks (13 weeks IER or CER plus 4 weeks weight maintenance)</td>
<td>IER: 1) IER A (n=37): 70% ER (2500-2717 kJ/day prescribed) on 2 days/week, CER diet on 5 days/week 2) IER B (n=38): IER plus 250 g protein-rich food (total of 5000 kJ/day prescribed) on 2 days/week, CER diet on 5 days/week CER (n=40): 25% ER (6000 kJ/day prescribed)</td>
<td>↓IER A ≅ ↓IER B ≅ ↓CER</td>
<td>Waist, hip, FFM: ↓IER A ≅ ↓IER B ≅ ↓CER FM: ↓IER A ≅ ↓IER B</td>
<td>Glucose, HbA1c: ↔IER A, ↔IER B, ↔CER Insulin, HOMA-IR: ↓IER A &gt; ↓IER B (↓IER B ≅ ↓CER)</td>
<td>Leptin: ↓IER A ≅ ↓IER B ≅ ↓CER β-hydroxybutyrate, IGF-1: ↔IER A, ↔IER B, ↔CER N° of participants reporting preoccupation with food, headaches, constipation, feeling light-headed: IER &gt; CER N° of participants reporting lack of concentration, mood swings, bad temper, feeling cold: IER &lt; CER N° of participants reporting decreased energy levels, tension, depression, anger, fatigue and confusion, increased vigour, improved mood: IER ≅ CER</td>
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<td>Hill et al. (1989) (66)</td>
<td>n=40 Female, mean age 37±8 years, obese (mean BMI 30±3 kg/m²) Dropout: 40% IER; 0% IER+EX; 20% CER; 20% CER+EX</td>
<td>12 weeks, follow up at 26 weeks from start</td>
<td>IER (n=6): ADF Severe ER (2512 kJ/day prescribed) on fast days, moderate ER (7536 kJ/day prescribed) on feed days CER (n=8): moderate ER (5024 kJ/day prescribed) IER+EX (n=10): IER plus moderate aerobic training on 5 days/week</td>
<td>↓IER ≅ ↓CER &lt; (↓IER+EX ≅ ↓CER+EX)</td>
<td>Waist hip ratio: ↑IER ≅ ↑IER+EX ≅ ↑CER+EX</td>
<td>Glucose: ↑IER ≅ ↑IER+EX ≅ ↑CER+EX Insulin: ↔IER, ↔CER, ↔IER+EX, ↔CER+EX REE: ↑IER ≅ ↑CER ≅ ↑IER+EX ≅ ↑CER+EX REE adjusted: →IER, →CER, →IER+EX, →CER+EX</td>
<td>↔REE: →IER, →CER, →IER+EX, →CER+EX</td>
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Seimon et al, 2015

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<tr>
<td>Keogh et al. (2014) (48)</td>
<td>n=75 Female, overweight/obese IER: mean age 59.5±8.7 years, mean BMI 33.3±3.8 kg/m² CER: mean age 60.8±12.5 years, mean BMI 33.0±7.5 kg/m² Dropout: 35% IER; 44% CER (40% overall)</td>
<td>8 weeks, follow up at 52 weeks from start</td>
<td>IER (n=39): Alternating weeks of severe ER (5500 kJ/day less than weight maintenance requirements prescribed) for 1 week followed by 1 week of <em>ad libitum</em> consumption CER (n=36): severe ER (5500 kJ/day less than weight maintenance requirements prescribed)</td>
<td>↓IER ≅ ↓CER Follow up versus baseline ↓IER ≅ ↓CER</td>
<td>FFM: ↓IER ≅ ↓CER ≅ ↓IER+EX ≅ ↓CER+EX</td>
<td>Waist, hip: ↓IER ≅ ↓CER Follow up versus baseline Waist, hip: ↓IER ≅ ↓CER</td>
<td>←↔CER+EX</td>
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<td>Rössner (1998) (50)</td>
<td>n=101 Male and female, aged 21-60 years, obese (BMI &gt; 30 kg/m²)</td>
<td>18 weeks, follow up at 14 and 26 weeks from start</td>
<td>IER A (n=20): 3 cycles of 2 weeks severe ER (1757 kJ/day prescribed) separated by 4 weeks moderate ER (6592 kJ/day prescribed) IER B (n=29): 3 cycles of 2 weeks severe ER (2218 kJ/day prescribed) separated by 4 weeks moderate ER (6592 kJ/day prescribed) CER A (n=20): 6 weeks of severe ER (1757 kJ/day prescribed) CER B (n=32): 6 weeks of severe ER (2218 kJ/day prescribed)</td>
<td>↓IER A ≅ ↓CER A ↓IER B ≅ ↓CER B</td>
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<td>Varady et al. (2011) (73)</td>
<td>n=60 Male and female, aged 35-65 years, overweight/obese (BMI 30-39.9 kg/m²) Dropout: 13% IER; 20% CER; 20% EX;</td>
<td>12 weeks</td>
<td>IER (n=15): ADF Severe ER (75%) prescribed on fast days, <em>ad libitum</em> intake on feed days CER (n=15): Moderate ER (25%) prescribed Exercise (EX) (n=15): Moderate intensity training 3 times/week Control (n=15): maintained current lifestyle</td>
<td>↓IER ≅ ↓CER ≅ ↓EX, ↔Control</td>
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<td>Williams et al. (1998) (84)</td>
<td>n=54 Male and female, aged 30-70 years, obese, type 2 diabetes Dropout: 13% overall</td>
<td>20 weeks</td>
<td>IER: Both groups on severe ER (1675-2512 kJ/day prescribed) for 20 days over 20 weeks, moderate ER (6280-7536 kJ/day prescribed) at all other times 1) IER A (n=18): In week 2, 5 consecutive days of severe ER then severe ER for 1 day/week for next 15 weeks 2) IER B (n=18): In week 2, 5 consecutive days of severe ER, then again every 5 weeks, a total of 4 times CER (n=18): Moderate ER (6280-7536 kJ/day prescribed) for 20 weeks</td>
<td>↓IER A ≅ ↓IER B &gt; ↓CER</td>
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<td>Glucose, HbA1c, Insulin: ↔IER A, ↔IER B, ↔CER</td>
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<td>Wing et al. (1994) (52)</td>
<td>n=93 Male and female, obese, type 2 diabetes IER: mean age 52.3±10.7 years, mean BMI 37.4±6.1 kg/m² CER: mean age 51.3±8.7 years, mean BMI 38.3±6.5 kg/m² Dropout: 16% IER; 15% CER</td>
<td>50 weeks, follow up at 103 weeks from start</td>
<td>IER (n=45): Severe ER (1675-2093 kJ/day prescribed) from weeks 1-12 and weeks 24-36. After week 12, prescribed intake increased over a 4 week period until participants consumed 4187-5024 kJ/day. CER (n=48): Moderate ER (4187-5024 kJ/day prescribed), dietary fat intake limited to less than 30% of calories</td>
<td>↓IER &gt; ↓CER Follow up versus baseline ↓IER ≅ ↓CER</td>
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<td>Glucose, HbA1c, insulin: ↓IER ≅ ↓CER Follow up versus baseline Glucose, HbA1c, insulin: ↔IER, ↔CER</td>
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<td>Wing et al. (2003) (46)</td>
<td>n=142 Male and female, mean age 42.6±9.3 years, obese (mean BMI 33.1±3.3 kg/m²) Dropout: 32% IER LB; 30% IER SB; 36% CER</td>
<td>20 weeks of IER and 14 weeks of CER, follow up at both of 20 and 48 weeks from start</td>
<td>IER: 1) IER A: “Long break” (n=47): 7 weeks of moderate ER, 6 week break*, 7 weeks of moderate ER 2) IER B: “Short break” (n=47): 3 cycles of 3 weeks of moderate ER, 2 week break*, then 5 weeks of moderate ER *weight loss stopped during breaks CER (n=48): 14 weeks of moderate to severe ER (4187-6280 kJ/day prescribed)</td>
<td>↓IER A ≅ ↓IER B ≅ ↓CER</td>
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<tr>
<td>Bhutani et al. (2013) (62)</td>
<td>n=83 Male and female, aged 25-65 years, obese (BMI 30-39.9 kg/m²) Dropout: 36% IER; 0% Control; 11% IER+EX; 33% EX</td>
<td>12 weeks</td>
<td>IER (n=25): ADF Severe ER (75%) prescribed on fast days, ad libitum intake on feed days. 4-week controlled feeding phase (all fast day meals were provided), then 8-week self-selected feeding phase (participants chose and prepared own meals based on a dietary prescription) IER+EX (n=18): IER plus moderate intensity exercise 3 times/week EX (n=24): moderate intensity exercise 3 times/week Control (n=16): Maintained current lifestyle</td>
<td>↓IER ≡ ↓EX, ↔IER+EX, ↔Control</td>
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<td>Hussin et al. (2013)</td>
<td>n=32 Male, aged 59.7±6.3</td>
<td>13 weeks</td>
<td>IER (n=16): Moderate ER (25% prescribed) plus 2 days/week of Sunnah fasting (nil by</td>
<td>↓IER, ↔Control</td>
<td>BMI: ↓IER, ↔Control</td>
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<tr>
<td>Seimon et al, 2015 (56)</td>
<td>years, lean/overweight (mean BMI 26.7±2.2 kg/m²) Dropout: 0% IER; 6% Control</td>
<td>≥ 8 weeks (2 weeks of IER plus 2 weeks of Control, separated by ≥ 4 weeks) in randomized crossover design</td>
<td>IER (n=8); ADF Severe ER (100%) prescribed on fast days, no restriction (11108 kJ/day median prescribed energy intake) on feed days Control (same participants as IER): Energy intake equivalent to IER feed days</td>
<td>↔IER, ↔Control</td>
<td>FM, FFM: ↔IER, ↔Control</td>
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<td>Soeters et al. (2009) (58)</td>
<td>n=8 Male, median age 23.5 years, lean (median BMI 21.3 kg/m²)</td>
<td>≥ 8 weeks</td>
<td>Control (n=16): maintained current lifestyle</td>
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<tr>
<td>Teng et al. (2011) (51)</td>
<td>n=28 Male, aged 50-79 years, lean/overweight (BMI 23-29.9 kg/m²) Dropout: 14% IER; 7% Control</td>
<td>12 weeks</td>
<td>IER (n=14): 5 days a week of moderate ER (1256-2093 kJ/day less than habitual intake prescribed) plus 2 days/week Sunnah fasting (nil by mouth, sunrise to sunset, ad libitum intake outside fasting hours) Control (n=14): Maintained current lifestyle</td>
<td>↓IER, ↔Control</td>
<td>BMI, % FM, FM: ↓IER, ↔Control</td>
<td>FU, TSH, T4, T3, reverse T3, cortisol (measured at end of intervention only): IER ≅ Control</td>
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<tr>
<td>Teng et al. (2013) (59)</td>
<td>n=56 Male, aged 50-70 years, lean/overweight (BMI 23-29.9 kg/m²)</td>
<td>12 weeks</td>
<td>IER (n=28): 5 days/week of moderate ER (1256-2093 kJ/day less than habitual intake prescribed) plus 2 days/week Sunnah fasting (nil by mouth, sunrise to sunset, ad libitum intake outside fasting hours) Control (n=28): Maintained current lifestyle</td>
<td>↓IER, ↔Control</td>
<td>BMI: ↓IER, ↔Control %FM, FM: ↓IER, ↑Control FFM: ↔IER, ↔Control</td>
<td>Glucose: ↔IER, ↔Control</td>
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<tr>
<td>Varady et al. (2013) (74)</td>
<td>n=32 Male and female, aged 35-65 years, overweight/obese (BMI 20-29.9 kg/m²) Dropout: 7% IER; 7% Control</td>
<td>12 weeks</td>
<td>IER (n=15); ADF Severe ER (75%) prescribed on fast days, ad libitum intake prescribed on feed days Control (n=15): Maintained current lifestyle</td>
<td>↓IER, ↔Control</td>
<td>FM: ↓IER, ↔Control FFM: ↔IER, ↔Control</td>
<td>Leptin: ↓IER, ↔Control Hunger: ↔IER, ↔Control Fullness, satisfaction: ↑IER, ↔Control</td>
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<tr>
<td>Vondra et al. (1976) (60)</td>
<td>n=31 Female IER: mean age 32.8 years (range 17-49 IER)</td>
<td>6.3 weeks (1 week preparatory period plus 5.3 weeks IER)</td>
<td>IER (n=21): 4 cycles of 5 fast days of severe ER (100%) then 3 days of severe ER (2093 kJ/day prescribed), followed by 5 fast days Control (n=10): Maintained current lifestyle</td>
<td>↓IER (Control data not reported)</td>
<td>FM: ↓IER (Control data not reported)</td>
<td>Glucose: ↑IER</td>
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<td>Ball et al. (1970) (82)</td>
<td>n=4 Female, mean age 34±8 years, overweight/obese (mean weight 126.1±22.2 kg) Dropout: 0%</td>
<td>16 weeks</td>
<td><strong>IER</strong>: 3 cycles of 16 fast days of severe ER (100%), alternating with 3 cycles of 16 days of severe ER (3347 kJ/day prescribed), followed by 16 fast days</td>
<td>↓IER</td>
<td>↓IER</td>
<td>(Control data not reported)</td>
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<tr>
<td>Belza et al. (2009) (39)</td>
<td>n=41 Male and female, aged 24-62 years, overweight/obese (BMI 28-40 kg/m²) Dropout: 12% (10% unable to adhere)</td>
<td>20 weeks</td>
<td><strong>IER</strong>: 8 weeks of severe ER 1 (3400 kJ/day liquid diet prescribed) plus 4 weeks of weight maintenance plus 4 weeks of severe ER 2 (4200 kJ/day liquid diet plus 750 kJ/day free choice prescribed) plus 4 weeks of weight maintenance</td>
<td>↓IER</td>
<td>↓IER</td>
<td>BMI, waist, FM, FFM: ↓IER</td>
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<tr>
<td>Bhutani et al. (2010) (61)</td>
<td>n=20 Male and female, aged 35-65 years, obese (BMI 30-39.9 kg/m²) Dropout: 20% (10% unable to adhere)</td>
<td>10 weeks (2 weeks weight maintenance plus 4 weeks IER A then 4 weeks IER B) for all participants</td>
<td><strong>IER</strong>: ADF 1) IER A: Controlled feeding Severe ER (75%) prescribed (2098±117 kJ/day measured) on fast days, <em>ad libitum</em> food intake prescribed on feed days (7540±950 kJ/day measured), all fast day meals were provided 2) IER B: Self-selected feeding Same as IER A, but participants chose and prepared their own meals at home based on a dietary prescription</td>
<td>↓IER A ≅ ↓IER B</td>
<td>BMI, waist, FM: ↓IER B FFM: ↓IER A, ↔IER B</td>
<td>Leptin: ↓IER A, ↓IER B</td>
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<td>Eshghinia et al. (2013) (77)</td>
<td>$n=15$ Female, mean age 33.5±5.9 years, overweight/obese (mean BMI 33.2±5.2 kg/m$^2$)</td>
<td>8 weeks (2 weeks weight maintenance plus 6 weeks IER)</td>
<td>IER: 6 x 1-week cycles of severe ER (70-75%) prescribed on 3 days, then 3 days of moderate ER (∼7536 kJ/day prescribed), based on the Key Recommendations of Dietary Guidelines for Americans, then $ad$ libitum intake for 1 day</td>
<td>↓IER</td>
<td>BMI, waist, %FM: ↓IER</td>
<td>Glucose: ←→IER</td>
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<td>Halberg et al. (2005) (53)</td>
<td>$n=8$ Male, mean age 25.0±0.1 years (standard error), lean (mean BMI 25.7±0.4 kg/m$^2$, standard error)</td>
<td>2 weeks</td>
<td>IER: ADF Severe ER (100%) for 20 hours on fast days, $ad$ libitum intake on feed days and at all other times</td>
<td>→↔IER</td>
<td>BMI, %FM: ↔IER</td>
<td>Glucose, insulin: ↔IER</td>
<td>$β$-hydroxybutyrate, physical activity: ↔IER</td>
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<tr>
<td>Heilbronn et al. (2005) (55)</td>
<td>$n=16$ Male and female, aged 23-53 years, lean/overweight (BMI 20-30 kg/m$^2$)</td>
<td>3 weeks</td>
<td>IER: ADF Severe ER (100%) on fast days, instructions to double usual intake on feed days</td>
<td>↓IER</td>
<td>FM, FFM: ↓IER</td>
<td>Glucose: ↔IER Insulin: ↓IER</td>
<td>Hunger, $β$-hydroxybutyrate: ↑IER Fullness: ↑IER Satisfaction, desire to eat, ghrelin, thirst, REE, REE adjusted: ↔IER</td>
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Seimon et al, 2015
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<tr>
<td>Johnson et al. (2007) (67)</td>
<td>n=14 Male and female, age not reported, overweight/obese (BMI &gt; 30 kg/m²) Dropout: 36% (7% unable to adhere)</td>
<td>8 weeks</td>
<td>IER: ADF  Severe ER (&gt;80%) on fast days (1339 kJ/day prescribed for females; 1590 kJ/day prescribed for males), ad libitum intake on feed days</td>
<td>↓IER</td>
<td></td>
<td>Glucose, insulin: ↔IER</td>
<td>Leptin, hunger, ghrelin: ↔IER β-hydroxybutyrate, mood, energy, quality of life: ↑IER</td>
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<tr>
<td>Klempel et al. (2012) (80)</td>
<td>n=60 Female, aged 35-65 years, overweight/obese (BMI 30-39.9 kg/m²) Dropout: 7% IER A (3% unable to adhere); 13% IER B (7% unable to adhere)</td>
<td>10 weeks (2 weeks weight maintenance plus 8 weeks IER)</td>
<td>IER: 1) IER A (n=26): 6 days/week of moderate to severe ER (4680-5520 kJ/day prescribed) using partial meal replacement liquid formulae, 1 fast day/week of severe ER (502 kJ of juice powder provided) 2) IER B (n=28): Same as IER A, but food was used instead of partial meal replacement liquid formulae</td>
<td>↓IER A &gt; ↓IER B</td>
<td>BMI, FM: ↓IER A ≅ ↓IER B FFM: ↔IER A, ↔IER B</td>
<td>Glucose, insulin: ↓IER A ≅ ↓IER B</td>
<td>Leptin: ↓IER A ≅ ↓IER B</td>
</tr>
<tr>
<td>Klempel et al. (2013) (70)</td>
<td>n=35 Female, aged 25-65 years, obese (BMI 30-39.9 kg/m²) Dropout: 12% IER A (6% unable to adhere); 6% IER B (6% unable to adhere)</td>
<td>10 weeks (2 weeks weight maintenance plus 8 weeks of IER A or IER B)</td>
<td>IER: ADF 1) IER A (n=17): Severe ER (75%) prescribed for fast days, 125% of energy requirements prescribed for feed days, using diet of 45% fat, 40% carbohydrate, 15% protein 2) IER B (n=18): same as IER A but using diet of 25% fat, 60% carbohydrate, 15% protein</td>
<td>↓IER A ≅ ↓IER B</td>
<td>FM: ↓IER A ≅ ↓IER B FFM: ↔IER A, ↔IER B</td>
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<td>Laessle et al. (1996) (57)</td>
<td>n=9 Female, mean age 22.2±1.5 years, lean (mean BMI 20.3±1.4 kg/m²)</td>
<td>4 weeks</td>
<td>IER: 4 consecutive days/week of severe ER (maximum 2512 kJ/day prescribed), 3 days/week of ad libitum food intake</td>
<td>↔IER</td>
<td>BMI: ↔IER</td>
<td>Hunger, preoccupation with food, drive to eat, β-hydroxybutyrate, irritability, concentration difficulty, fatigue (fast days): ↑IER</td>
<td>T3, mood (fast days): ↓IER</td>
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<tr>
<td>Lantz et al. (2003) (49)</td>
<td>n=334 Male and female, aged 18-60 years, obese (BMI &gt;30 kg/m²) Dropout: 65% IER A; 65% IER B</td>
<td>104 weeks</td>
<td>16 weeks of severe ER (1883 kJ/day prescribed), followed by 3-weeks re-feeding period prior to randomization IER A (n=161): 2 weeks of severe ER (1883 kJ/day prescribed) every third month for remaining treatment period (up to 2 years) IER B (n=173): Severe ER (1883 kJ/day prescribed) whenever body weight passed an individualized cut-off level</td>
<td>↑IER A ≅ ↓IER B</td>
<td>BMI, waist, FM: ↑IER A ≅ ↓IER B</td>
<td>FFM: ↑IER A &lt; ↓IER B</td>
<td>Glucose: ↔IER A, ↔IER B Insulin, HOMA-IR: ↑IER A ≅ ↓IER B</td>
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Table 1: All ages and BMI have been expressed as mean ± standard deviation where provided, or as mean or as a range, unless otherwise specified. “Follow up” time points refer to the number of weeks from the start of the intervention. Differences in outcome measures refer to the difference between post intervention and baseline values, unless a different comparison is specified (e.g. follow up versus baseline). ↓: statistically significantly decreased; ↑: statistically significantly increased; ↔: not statistically significantly different from baseline as reported by the publication authors. The meaning of the >, < and ≅ are as in the following examples: ↓IER > ↓CER, the reduction from baseline in the IER group is statistically significantly greater than the reduction from baseline in the CER group; ↓IER < ↓CER, the reduction from baseline in the IER group is statistically significantly less than the reduction from baseline in the CER group; ↓IER ≅ ↓CER, the reduction from baseline in the IER group is not statistically significantly different from the reduction from baseline in the CER group. All analytes (e.g. glucose, insulin, ghrelin) were measured in the circulation in the fasting state unless otherwise stated. #Assay included acetoacetone as well as β-hydroxybutyrate. ADF: alternate day fasting; BMI: body mass index; CER: continuous energy restriction; DHEAS: dehydroepiandrosterone sulphate; 24-hour EE: 24-hour energy expenditure; 24-hour EE adjusted: 24-hour energy expenditure adjusted for FFM. ER: energy restriction; EX: exercise; FFM, fat-free mass; FM: fat mass; %FM: percent fat mass; HbA1c: glycated haemoglobin; Hip: hip circumference; HOMA-IR: homeostatic model assessment – [Insulin Resistance]; IER: intermittent energy restriction; IGF-1: insulin-like growth factor-1; REE: absolute resting energy expenditure; REE adjusted: resting energy expenditure adjusted for FFM; REE (sleeping): absolute sleeping energy expenditure; REE (sleeping) adjusted: sleeping energy expenditure adjusted for FFM; Waist: waist circumference; TSH, thyroid stimulating hormone; T3 triiodothyronine or 3,3′,5-triiodothyronine; T4, thyroxine or 3,5,3′,5′- tetraiodothyronine.