Intermittent fasting interventions for the treatment of overweight and obesity in adults aged 18 years and over: a systematic review and meta-analysis

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Executive summary

Background

Intermittent energy restriction encompasses dietary approaches including intermittent fasting, alternate day fasting, and fasting for two days per week. Despite the recent popularity of intermittent energy restriction and associated weight loss claims, the supporting evidence base is limited.

Objective

To examine the effectiveness of intermittent energy restriction in the treatment for overweight and obesity in adults, when compared to usual care treatment or no treatment.

Inclusion criteria

Types of participants

This review included overweight or obese (BMI ≥ 25 kg/m^2) adults (≥ 18 years).

Types of intervention(s) / phenomena of interest

Intermittent energy restriction was defined as consumption of ≤ 800 kcal on at least one day, but no more than six days per week. Intermittent energy restriction interventions were compared to no treatment (*ad libitum* diet) or usual care (continuous energy restriction ~25% of recommended energy intake). Included Interventions had a minimum duration of 12 weeks from baseline to post outcome measurements.

Types of studies

Randomized and pseudo-randomized controlled trials.

Types of outcomes

The primary outcome of this review was change in body weight. Secondary outcomes included: 1. Anthropometric outcomes (change in BMI; waist circumference; fat mass; fat free mass); 2. Cardio-metabolic outcomes (change in blood glucose and insulin, lipoprotein profiles and blood pressure; 3. Lifestyle outcomes: Diet, physical activity, quality of life and adverse events.

Search strategy

A systematic search was conducted from database inception to November 2015. The following electronic databases were searched: MEDLINE; Embase; CINAHL; Cochrane library; Clinicaltrials.gov; ISRCTN registry; and anzctr.org.au for English language published studies, protocols, and trials.

Methodological quality

Two independent reviewers evaluated the methodological quality of included studies using the standardized critical appraisal instruments from the Joanna Briggs Institute.

Data extraction

Data were extracted from papers included in the review by two independent reviewers using the standardized data extraction tool from the Joanna Briggs Institute.

Data synthesis

Effect sizes were expressed as weighted mean differences and their 95% confidence intervals were calculated for meta-analyses.

Results

Six studies were included in this review. The intermittent energy restriction regimens varied across studies and included alternate day fasting, fasting for two days, and up to four days per week. The duration of studies ranged from three to 12 months. Four studies included continuous energy restriction as a comparator intervention and two studies included a no treatment control intervention. Meta-analyses showed that intermittent energy restriction was more effective than no treatment for weight loss (-4.14 kg; 95% CI -6.30 kg to -1.99 kg; $p \leq 0.001$). Although, both treatment interventions achieved similar changes in body weight (Approximately 7 kg), the pooled estimate for studies that investigated the effect of intermittent energy restriction in comparison to continuous energy restriction revealed that no significant difference in weight loss (-1.03 kg; 95% CI -2.46 kg to 0.40 kg; $p = 0.156$).

Conclusions

Intermittent energy restriction may be an effective strategy for the treatment of overweight and obesity. Intermittent energy restriction was comparable to continuous energy restriction for short term weight loss in overweight and obese adults.

Keywords

Intermittent fasting; continuous energy restriction; obesity; overweight; weight loss

Background

The management of overweight and obesity is considered a major public health priority internationally. Prevalence estimates of overweight and obesity reported by the World Health Organization in 2014 showed that 39% (1.9 million) of adults aged 18 and over, were overweight, and of these 13% (600 million) were obese.[1] In adults there is evidence to support a persistent involuntary increase in body weight of between 0.24-0.45 kg per year in women and 0.25-0.58 kg per year in men,[2,3] with even greater weight changes observed in younger adults (>2kg annually).[3] Excess weight gain in adulthood has a negative impact on health and is associated with an increased risk of developing a number of chronic diseases including type II diabetes, cardiovascular disease, muscular skeletal disorders and some cancers.[4,5]

The burgeoning obesity epidemic and its associated health conditions not only have an adverse impact on the individual but are also an increasing financial burden to society. In the UK, the cost of treatment of obesity related conditions to the National Health Service is estimated to be £6.1 billion per year.[6] Medical expenditure in the USA has shown to be even greater with associated costs at $147 billion.[7] Furthermore, if trends in obesity continue to increase it is predicted that by 2050, 50% of the population in the UK could be obese and the total costs in managing obesity could escalate to £50 billion per year.[8] Therefore, effective approaches to the management of obesity are essential internationally.

Weight management approaches in the treatment of obesity include a wide range of lifestyle interventions (including dietary, physical activity and psychological elements) to change unhealthy behaviours, encourage weight loss, and prevent chronic weight gain. However, many approaches only achieve small changes in body weight which are insufficient to have a clinical impact on health.[9] Furthermore, there are a number of diet and weight management books published, with book sales sufficient to reach the best sellers list, however, many of these lack comprehensive evaluation and robust evidence to support their effectiveness.[10] Therefore, it is vitally important that new approaches to weight management are investigated for their potential efficacy in order to provide evidence based approaches to the treatment of obesity.

Intermittent fasting is currently a popular approach considered for weight management which has received significant media attention and hence public popularity. In the UK, this dietary approach reached the mainstream after a BBC Horizon documentary aired in August 2012, featured an intermittent fasting approach called the 5:2 diet. The diet involved five days of regular eating patterns interchanged with two days of “fasting” (daily maximum of 500kcal for women and 600kcal for men) per week. In addition to the popular 5:2 approach, there are a number of other intermittent fasting patterns used to describe this dietary treatment approach, including alternate day fasting (ADF), periodic fasting or intermittent energy restriction (IER) for two up to six days per week. The premise of this approach to dieting involves interspersing normal daily caloric intake with short periods of severe calorie

restriction/fasting. It does not involve a true fast which would consist of complete abstinence from food and/or water, intermittent fasting involves changing the "usual" daily energy intake to a much lower calorie intake. For the purpose of this review, the term IER will be used to describe all intermittent fasting regimens.

The potential health benefits and biological processes of IER are not well establised.[11,12] There is some evidence, predominantly from animal studies, to demonstrate beneficial effects from weight loss and additional improvements on cardio-metabolic risk factors. It has been hypothesised that the mechanism for the possible additional benefits were through fat utilization and nutritional stress.[13]

IER is achieved predominantly through intermittent periods of dietary intake based on a very low calorie diet (VLCD). However, currently international clinical guidance on the treatment of adult obesity does not recommend the routine use of VLCD (defined as a hypocaloric diet of 800 or less kcal/day) for the treatment of adult obesity.[4,5,14,15] Instead, continuous energy restriction (CER) involving a daily energy deficit of 600 kcal/day is recommended as part of a multi-component weight management strategy, including ongoing support, and a maximum intervention duration of 12 weeks.[4] In order for IER to be considered as an alternative approach to weight management, systematic evaluation of the current evidence base is necessary to provide support for this novel treatment over current practice (CER).

Despite the recent popularity of IER[16] and associated weight loss claims,[17] the supporting evidence base to justify the use in humans remains limited with only one published systematic review[13] at the time of the search examining the health benefits of this approach. The aim of this published review[13] was to examine the impact of IER interventions on wider health benefits including coronary artery disease risk of risk of diabetes (not specifically as a treatment approach for overweight and obesity). However, it did not examine the efficacy of studies which were consistent with clinical recommendations on a minimum 12 week intervention period, provide a critical appraisal of the methodology, or meta-analysis of weight loss outcomes. Therefore, the aim of the current review is to address these gaps in the evidence base.

This review was conducted according to an *a priori* published protocol.[18]

Objective

The objective of this study was to systematically review the available evidence and quantify the effect of intermittent energy restriction in the treatment for overweight and obesity in adults, when compared to usual care treatment (continuous energy restriction) or no treatment (*ad libitum* diet).

Inclusion criteria

Types of participants

This review considered studies that included free-living (not hospitalised) male and female adults aged 18 years and over who were overweight or obese (i.e., had a body mass index (BMI) greater than or equal to 25 or 30 kg/m^2, respectively). Participants were excluded if they had secondary or syndromic forms of obesity or were diabetic, previously had or were undergoing bariatric surgery, were pregnant or breast feeding, and were taking medication associated with weight loss (e.g. orlistat, metformin) or weight gain (e.g. steroids, antipsychotics).

Types of intervention(s)/phenomena of interest

This review considered studies that evaluated intermittent fasting interventions (defined as consumption of 800 kcal or less on at least one day, but no more than six days in a calendar week). As there is no accepted formal definition of 'fasting,' the clinically recommended[5] upper limit for a very low calorie diet was used (800 kcal) in this review based on clinical recommendations.[5] Interventions were included if they provided a follow up period of participants of at least 12 weeks from the start of the intervention.

Types of comparators

Interventions were compared to control (no intervention) or usual care (which consisted of advice to continuously follow a reduced calorie diet of approximately 25% of estimated daily energy requirements).

Types of studies

The review considered both randomized controlled and pseudo-randomized controlled trials for inclusion.

Types of outcomes

The primary outcome of the review was change in body weight. Secondary outcomes included in this review were change in BMI, waist circumference, fat mass, fat free mass, blood glucose and insulin, lipoprotein profiles, blood pressure, diet, physical activity, quality of life, and adverse events (such as physical or psychological side effects from taking part in the interventions).

Outcomes measures were only included in the meta-analysis if they were measured objectively, used validated tools and procedures.

Search strategy

The search strategy aimed to find peer reviewed published studies, clinical trials, and grey literature such as reports and conference proceedings. A three-step search strategy was utilized in this review.

An initial limited search of MEDLINE and CINAHL was undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms was undertaken across all included databases. Thirdly, the reference list of all identified reports and articles was searched for additional studies. Only studies published in English language and published up to November 2015 were considered for inclusion in this review.

The databases searched include:

Medline via OVID Host

Embase via OVID

CINAHL via EBSCO Host

Cochrane Central Register of Controlled Trials (CENTRAL)

The search for protocols and trials included:

Clinicaltrials.gov

ISRCTN registry

anzctr.org.au

Initial keywords to be used were: intermittent fasting or periodic fasting, ADF or intermittent calorie restriction, and overweight or obesity. The full search strategy is available in Appendix I.

Methodological quality of included studies

Quantitative papers selected for retrieval were assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix II). To be considered adequate quality, the randomized and pseudo-randomized trials had to achieve a minimum six out of 10 quality appraisal questions. Any disagreements that arose between the reviewers were resolved through discussion, or with a third reviewer.

Data extraction

Data were extracted from papers included in the review using the standardized data extraction tool from JBI-MAStARI (Appendix III). The data included specific details about the interventions, populations, study methods, and outcomes of significance to the review question.

Data synthesis

Quantitative data were, where possible, pooled in statistical meta-analysis using Comprehensive Meta-Analysis software (Version 3.0 for Windows: Biostat, Englewood, Colorado, USA). All results were subject to double data entry. Effect sizes were expressed as weighted mean differences (WMD) (for continuous data, calculated from the last available measure) and their 95% confidence intervals were calculated for analyses. Three studies did not report the standard deviation of the mean change.[19-21] Therefore, these were calculated using an imputed correlation coefficient, calculated from the variance of pre- and post-, and change in outcome variable from available data from Bhutani *et al.*[22]. One study investigated the effects of two formats of IER in comparison to CER.[20] To create a single pair-wise comparison, and to prevent multi-comparisons and a unit-of-analysis error, IER interventions in the aforementioned study were combined. Heterogeneity was assessed statistically using the standard I-squared and tau-squared. Where possible, subgroup analyses were considered based on baseline weight status of participants (i.e., overweight [BMI: 25-29 kg/m^2], obese [BMI: 30-39 kg/m^2] & morbidly obese [BMI 40+ kg/m^2]); gender; age; length of study, and IER approach. Where statistical pooling was not possible, the findings are presented in narrative form including tables and figures to aid in data presentation where appropriate.

GRADE assessment

GRADE assessment was conducted to assess the overall quality of evidence.[23] GRADE assessment is made up of risk of bias to the internal validity of results, consistency of results across studies, directness and precision of results, and likelihood of publication bias. The overall quality of evidence is then categorised as high, moderate, low or very low. GRADE assessments were conducted for the primary outcome included in the meta-analysis (GRADE Tables are presented in Appendix IV). Two independent researchers (LA and LH) performed the GRADE assessments and consensus agreed.

Results

Literature search

The systematic search identified 69097 studies. After removing duplicate studies, 61,328 titles and abstracts were reviewed. Full text articles were sought for 119 studies and their eligibility for inclusion in this review assessed. One hundred and ten articles were excluded based on the reasons illustrated in Figure 1. Nine studies were considered eligible. Three of these studies were identified from the clinical

trials register and were considered ongoing studies, with final results not published at the time of the search. Six studies reported adequate outcome data and were included in this systematic review and meta-analysis.

INSERT Figure 1: PRISMA flow diagram of search and study selection process (Adapted from Moher *et al.*[24])

Methodological quality

Two out of the six studies were randomized controlled trials[20,22] based on the definition used by the JBI-MAStRI critical appraisal tool (Appendix II). The remaining studies were pseudo-randomized studies, as they did not clearly define the process of random allocation of participates to treatment conditions (Q1). The results for each quality assessment question by study are presented in Table 1. Three studies met the minimum six 'Yes' scores out of 10 (refer to appendix II) and therefore were considered of adequate methodological quality.[19,20,22] None of the studies blinded participants to treatment allocation (Q2) and only one study[20] clearly reported allocation to treatment groups was concealed from the allocator (Q3), with the remaining studies judged as unclear due to limited reporting of this outcome. This was consistent with blinding of outcome assessors to treatment allocation(Q5), with the aforementioned study reporting participants were not blinded and the remaining studies unclear in their reporting of this outcome. Three studies did not include outcomes of people who withdrew in the analyses.[21,25,26] One study did not meet the criteria for question six (were the control and treatment groups comparable at entry?) and one study did not fulfil question nine (Were outcomes measured in a reliable way?).[21,25] Differences in baseline characteristics between the treatment groups did not appear to be considerably different in the study by Hill *et al.*[21] However, no statistical test of differences in baseline characteristics was described, this was reviewed as unclear. Again, limited reporting, of outcome measures meant that question nine was also assessed as unclear in the study by Viegener *et al.*[25] The reviewers judged that insufficient reporting of methodology limited these studies meeting the criteria for a 'yes' in questions six and nine and likely not a limitation in the conduct of the methodology. All studies fulfilled the 'Yes' criteria for treating intervention groups identically (Q7), consistency in measuring outcomes for all interventions (Q8), and providing appropriate statistical analysis (Q10). In addition to the risk to the internal validity of studies assessed by the JBI-MAStRI critical appraisal tool, high rates of attrition ($\geq$ 20%) were reported in four out of the six studies (table 1). Rates of attrition were comparable between intervention groups with the exception of Bhutani *et al.*[22] which had no drop outs in the control intervention in comparison to nine participants from the IER intervention.

INSERT: Table 1: Assessment of methodological quality

Study characteristics

A summary of the characteristics of the six included studies is detailed in Table 2. The majority of studies were in general conducted in the USA (n=4), with the exception of two studies by Harvie and colleagues conducted in the UK.[19,20] Four studies investigated the efficacy of IER interventions in comparison to CER[19-21, 25] and two studies included a no treatment control intervention (*ad libitum* diet) as the comparator. The mean duration of the interventions was 5.6 months (range: 3 to 12 months), with only one study conducting follow up outcome measures at six months post intervention.[21] The majority of studies focused their intervention on weight loss, with only two studies including a weight maintenance phase.[20,25] In addition to examining the efficacy of calorie restriction regimens, the effects of exercise interventions were also investigated in two studies.[21,22] Bhutani *et al.*[22] included four intervention groups; ADF, exercise, combination (both exercise and ADF) and a control group, while Hill *et al.*[21] examined the efficacy of four interventions of, ADF and CER with and without exercise. As the primary aim of the review was focused on the efficacy of dietary restriction regimens, results are not presented for participants involved in the above exercise interventions. All studies measured body weight as their primary outcome. Additional anthropometric outcomes included fat mass, fat free mass, and waist circumference. BMI[26] and other circumferences measures (bust and thigh) [19,20] were reported in few studies but not included in the meta-analysis. Secondary outcome measures varied across studies; the most commonly reported were cardio-metabolic biomarkers including lipoprotein profiles, glucose, and insulin (presented in Table 3) and less commonly reported were satiety hormones (leptin and adiponectin) and inflammatory markers [including Interleukin 6 (IL-6) and Tumour Necrosis Factor Alpha (THF- α)].

INSERT Table 2: Overview of included studies.

Participant characteristics

A total of 400 participants were enrolled in the studies (excluding participants in the exercise interventions). The mean sample size was 67 participants (range: 20-115 participants) and a mean of 31 participants per intervention (range: 10 to 54 participants). The mean age of participants in each study ranged from 37 years to 49 years. Participants were overweight or obese (mean BMI range 26.0 kg/m^2 to 35.6 kg/m^2). The ethnicity of the participants was only reported in three studies.[19,20,26] The

majority of participants were Caucasian (range: 46% to 97%). Other ethnic origins included African American (46%); Afro Caribbean (2%); Hispanic (10%) and ethnic origin classified as other (2%). Socio economic status (SES) was not reported across studies. However, an indication of employment level, relevant to SES, was reported in two studies.[19,20] The majority of participants were in full time employment (range: 64% to 82%), followed by part time employment (range: 14% to 19%). Seventeen percent were reported to be retired or unemployed. The majority of studies involved only female participants with the exception of two studies which included both genders; however, females were primarily enrolled, with only 10 men participating in total across all studies.[22,26] Participants were considered in general to be healthy, and were not reported to have any obesity related health conditions such as type II diabetes or cardiovascular disease. Five participants were reported to have hypertension a condition associated with the development of chronic conditions.[19] Participants in the studies by Harvie *et al.*[19,20] were at increased risk of developing breast cancer by virtue of a positive family history but had no personal history of breast cancer.

INSERT Table 3: Change in weight, anthropometric, and cardiometabolic outcomes of primary studies.

Interventions

Dietary protocols for IER varied across studies from a minimum two days fasting per calendar week up to four days. Two studies utilized an alternative day fasting followed by a “feed day”.[22,26] Participants had to consume their total energy intake on fast days between 12pm and 2pm to allow a 24 hour fasting period. Two studies prescribed fasting on two consecutive days[19,20] and two studies included three or more days of fasting.[21,25] Hill *et al.*[21] altered the number of days of reduced energy intake from three to seven with a set pattern prescribed from weeks 1-5 and 7-12. Dietary intake on fast days was restricted to 25%-40% in four studies.[19,20,22,25,26] Daily energy restriction in the study by Hill *et al.*[21] ranged from 600 kcal to 1500 kcal.[21,25] On non-energy restriction days participants ate *ad libitum* in the ADF regimens[22,26] and energy intake was restricted to between 60% -75% of total energy intake in conjunction with estimated requirements for weight maintenance[19,20,25]. The macronutrient composition of the IER diets were primarily based on recommendations for a healthy balanced diet[27] to include 55% energy from carbohydrate, 25-30% fat, and 15-20% protein[18,19,22]. Two studies limited energy intake on fasting days solely to protein[19,20] and one study only provided recommendations on restricting dietary intake of fat to less than 15% on energy restriction days.

Energy restriction in the CER interventions ranged from 25%-30% of daily energy requirements. Macronutrient composition of prescribed diets was again based on recommendations for a healthy balanced diet[27] as discussed above. Interventions comparing IER to no treatment allowed for *ad libitum* energy intake.

In addition to the dietary interventions, two studies provided an exercise component, which ranged from advice on physical activity and providing an information booklet focused on home based activities

(including walking, strength, and flexibility exercises)[20] to a more structured exercise aerobic program with an aim of 30 minutes of walking or stationary cycling activity six days a week.[25] Exercise components were consistent across both treatment groups. Four studies did not provide any exercise component and participants were advised to maintain their habitual physical activity.[19,21,22,26] As previously mentioned, interventions which primarily focused on the efficacy of exercise were excluded from this review.

Adherence/Compliance

Measuring adherence to dietary advice is always challenging due to the subjective nature of self-report dietary intake and a lack of valid objective measurements.[28] All studies with the exception of Bhutani *et al.,*[22] utilized self-report measures of dietary intake through food diaries as a measure of adherence/ compliance to the dietary regimen. Based on the self-report measures, compliance with diets (IER and CER) was high (mean adherence range: 58% to 98%) and not different between treatments. Furthermore, adherence to IER regimens appeared not to be affected with increased number of fasting days (i.e., fasting for 2 days[19,20] or 4 days per week[21,25]).

Effects of interventions

Primary outcome change in body weight

Meta-analysis was conducted for four studies that included CER as a comparator intervention.[19-21,25] Both interventions achieved comparable weight losses and there were no significant differences in change in body weight between interventions (WMD: -1.03 kg; 95% CI -2.46 kg to 0.40 kg; p = 0.156; Figure 2). Statistical heterogeneity was not present (Q (3) 1.2, P = 0.76 I^2 = 0.0%). Only one study examined the efficacy of IER at 12 months, illustrating that weight loss could be sustained long term equivalent to that following CER.[25]

INSERT Figure 2: Weighted mean difference in body weight (kg) between the intermittent energy restriction interventions and continuous energy restriction interventions.

Secondary anthropometric outcome

Secondary outcomes of interest in this review were other measures of body composition and cardio-metabolic markers. Few studies consistently reported anthropometric outcomes. The results for change in outcomes are primarily from the studies conducted by Harvie and colleagues.[19,20] Pooled effect sizes

across these studies revealed significant reductions in waist circumference (WMD: -2.14 cm; 95% CI -3.53 cm to -0.75 cm; p = 0.002) and in fat mass (WMD: -1.38 kg; 95% CI -2.47 kg to -0.28 kg; p = 0.014) for the IER intervention in comparison to CER (Table 4).

Secondary cardio-metabolic outcomes

Summary effect estimates for cardio-metabolic outcomes were only included for outcomes which were reported by two or more studies. Results again were primarily reported from the studies led by Harvie *et al.*[19,20] Effect sizes for cardio-metabolic outcomes are presented in Table 4. There was a significant effect of IER in comparison to CER for improvements in insulin concentrations (WMD: -4.66 pmol/l -9.12 pmol/l to -0.19 pmol/l; p = 0.041). However, there were no significant between group differences for IER in comparison to CER for lipoprotein profiles (Total cholesterol, LDL and HDL cholesterol and Triglycerides) or glucose concentrations. It is important to note that due to the limited number of studies included in this analysis of cardio-metabolic outcomes (n = 2; total cholesterol n = 3), results should be interpreted with caution.

INSERT Table 4: Pooled effect sizes (WMD) of secondary outcomes.

IER compared to no treatment control

Primary outcome change in body weight

Two studies assessed the efficacy of IER interventions in comparison to a no treatment control group. There was a significant difference between the IER interventions and no treatment (WMD: -4.14 kg; 95% CI -6.30 kg to -1.99 kg; p ≤ 0.001; Figure 3). There was significant statistical heterogeneity in effect sizes (Q (1) 2.9, p = 0.09 I^2 = 65.7%). The within group analysis revealed that in the study by Bhutani *et al.*[22] the significant differences were due to a significant decrease in body weight in the IER regimen and no change in body weight following no treatment. Within group differences were not reported in the study by Varady *et al.*[26]

INSERT FIGURE 3: WMD in body weight (kg) between the IER interventions and control interventions.

Secondary anthropometric outcomes

In addition to change in body weight, there was a significant between group effect of IER compared to no treatment on change in fat mass (WMD: -3.24 kg; 95% CI -4.55 kg to -1.92 kg; p ≤ 0.001).

Secondary cardio-metabolic outcomes

The study by Varady *et al.*[26] measured cardio-metabolic outcomes including lipoprotein profiles, however, due to the limited number of studies utilizing a control comparator, pooled effect sizes could not be calculated. The results revealed that there was no significant between group differences for total cholesterol, LDL and HDL cholesterol or triglycerides for the IER intervention in comparison to no treatment. Meta-analysis was conducted for blood pressure, with both studies reporting changes in systolic and diastolic pressures.[22,26] There was no significant effect of IER in comparison to no treatment in changing either blood pressure measurement (table 4).

Lifestyle outcomes

Meta-analyses were not conducted to assess any change in diet, due to limited reliability of reporting and a lack of valid objective measurements. This was also applicable to measures of physical activity. Only three studies measured physical activity through self-report methodologies, using the International Physical Activity Questionnaire[19] and physical activity diaries.[20,25] In the study by Viegener *et al.*[25] recording of physical activity in a diary was included as an outcome. There were minimal and non-significant changes reported with no between group differences. Quality of life was only assessed in two studies[19,20] and the methodology across studies was not consistent (RAND SF-36 and Profile of Mood Scores). Irrespective of methodology used, improvements in quality of life were comparable across dietary treatments. However, there was a significant increase in the mental health component summary score and indicating a slight improvement in quality of life in the CER group in comparison to the IER intervention in the study by Harvie *et al.*[19]

Adverse events

No serious adverse events were reported across studies. Three studies reported minor physical and psychological effects.[19,20,26] These were in general reported for a small number of participants and were reported in both dietary interventions. The physiological effects included headaches (IER 8%), reduced energy levels (IER 4.9%; CER 5%), feeling cold (IER 4.8%; CER 3%), constipation (IER 6.4%; CER 3%). Light headiness and bad breath was reported on IER days for 3% and 8% of participants, respectively. Psychological effects in both interventions included a lack of concentration, pre-occupation with food, and mood swings (IER: range 3-15%; CER: range 3-7%). Adverse events were not reported in studies utilizing a no treatment control intervention.[22,25]

Discussion

Principle findings

This systematic review aimed to examine the efficacy of IER as an approach to weight management in comparison to current clinical practice (CER) or no treatment. Based on current evidence, the primary results of the meta-analysis revealed that IER is as effective as CER for short term weight loss. Both conditions led to a comparable and substantial weight loss (~5-10 kg). However, the duration of the interventions was short (mean duration: 5.6 months; range: 3 months to 12 months) with only one study comprising a 12 month intervention in accordance with current clinical guidance.[4,5,14,15] Results from this longer term study revealed that change in body weight was sustainable in both IER and CER conditions.[25] There was a significant intervention effect of IER on waist circumference and body fat, in comparison to current CER. Raised waist circumference was the best anthropometric predictor of visceral fat, and signals both high BMI and central fat distribution.[29] These results are promising as reductions in waist circumference or central fat distribution reduce cardiovascular risk.[30] The reduction in waist circumference may partially explain the decrease in fasting insulin, though this is also likely to be associated with the periods of acute energy restriction, particularly in the IER group. Waist changes of close to 9 cm reflect a clinically important weight change of close to 9 kg.[30] However, the efficacy of changes in secondary anthropometric outcomes should be interpreted cautiously due to the limited number of studies. Future studies are required to assess the long term effects of IER as a treatment approach to weight management.

The second element of the comparison is for the two studies for which IER was compared with a control group. Both studies prescribed an ADF approach to intermittent fasting. As expected when offering no treatment as a comparator intervention, there was a significant effect of IER in comparison to the control intervention. A significant between group difference was also replicated in secondary anthropometric outcomes, waist circumference and percentage body fat. These results are consistent with the majority of weight management interventions.[31]

Clinical effectiveness

Clinical guidelines have concluded that in overweight and obese adults, a reduction in body weight of 5-10% of initial body weight (or approximately 5-10 kg) was associated with improvements in health risk factors.[4,5] None of the included studies investigating IER in comparison to CER reported percentage weight change as an outcome and whether or not participants achieved sufficient weight loss associated with improvements in health risk factors. However, weight loss based on between group changes in mean body weight revealed that mean weight loss (~ 7 kg) was of sufficient magnitude to be associated with clinical benefits in both the IER and CER interventions. This is an important finding illustrating that participants may have lost equivalent or even greater than the 5-10% target amount and thus provides

evidence that the IER may be a clinically important approach for weight management. For studies investigating the efficacy of IER in comparison to no treatment, mean percentage weight change was only reported in one study.[20] Mean percentage weight change in this study was not of a magnitude associated with clinical benefits. Future studies, should aim to report percentage weight change and in particular weight change associated with improvements in health risk factors.

Despite not reporting clinically important weight loss, studies reported measuring changes in cardio-metabolic risk factors. The results for the efficacy of IER on cardio-metabolic outcomes in comparison to CER was primarily investigated by the two studies by Harvie *et al.*[19,20] Summary estimates revealed that there was a significant reduction in insulin concentrations following IER in comparison to CER. A significant reduction in fasting insulin may potentially be explained in part due to the concomitant significant reduction in total body fat and central adiposity. Although the mechanisms of fasting on improvements on metabolic outcomes are yet to be defined, the improvement in insulin sensitivity is most likely to be associated with periods of acute energy restriction particularly on fasting days. However, moderate weight loss (-7% body weight) in obese adults without acute periods of energy restriction, has also shown improvements in insulin sensitivity after fasting via changes in cytokines, which are altered after weight loss.[32] Therefore there is insufficient evidence to determine the acute mechanistic effects of fasting, though the mediator for these changes is moderate weight loss.[33]

There was no significant difference in treatment approach on lipoprotein profiles or plasma glucose. Despite a lack of between group effect, both studies reported significant changes in concentrations from pre- to post-intervention. Although the significance of the change in cardio-metabolic outcome was reported, clinically meaningful changes were not. Comparison of change in outcomes with clinically important definitions (based on guidelines from evidence based practice[4,5] and previous research examining clinical risk factor changes in patients with type II diabetes)[34] revealed that in general changes in cardio-metabolic outcomes in these studies were not sufficient to offer health improvements with the exception of changes in total cholesterol[21] and LDL cholesterol.[26] It is important to note that the limited findings of clinical benefits should be interpreted with caution, as few studies consistently measured cardio-metabolic outcomes and limited reporting of outcomes prevented inclusion of all outcomes in the analysis. Furthermore, there were a number of additional biomarkers that were not included in the meta-analysis as they were only measured in one study. For example, IER appeared to affect the production of adiponectin this has a crucial role in insulin sensitivity, cancer progression, and development. However, due to the limited number of studies and sample sizes of studies, conclusions on the potential health benefits of IER are limited and future studies are warranted to elucidate the potential metabolic effects of IER. The evidence to date does not support any additional metabolic benefit of IER.

Maintenance of body weight following a period of weight loss is an essential component to weight management. Evidence has demonstrated that individuals who have sustained changes in body weight

have been able to adhere to the new healthy lifestyle choices and remain at a reduced risk of adverse health conditions associated with weight gain.[4,5] Only two of the interventions in this review included a weight maintenance phase of varying durations; of one month[20] and six months.[25] Weight loss was maintained in both interventions, providing evidence that IER might also be an effective strategy for preventing weight gain, following a period of weight loss. However, future studies with a weight maintenance period of adequate duration such as a minimum six months as recommended by clinical guidance is required to elucidate the long term effects on sustainability of weight loss and improvements in health risk factors.

Comparison with previous research

To the author's knowledge, this is the first review to solely include randomized or pseudorandomized controlled trials. Previous reviews[13,35,36] have included heterogeneous study designs and observational studies which induce bias such as un-measurable confounding factors and reverse causality. Randomized controlled trials are considered the criterion method to examining the effectiveness of an intervention[37] and therefore, this review adds to the quality of the current evidence base. Furthermore, this review aimed to fill the gap reported by previous reviews by providing a more reliable estimate of the effect size of IER interventions through the inclusion of meta-analyses. The findings of the meta-analyses are consistent with the conclusions of previous narrative reviews, in providing support for IER as an effective approach to weight management. Overall conclusions from the current evidence base and this review advocate the need for further high quality, randomized controlled trials to examine the long term efficacy and adverse effects of this dietary intervention in comparison to current clinical practice.

Methodological limitations

A limitation of the available literature is in relation to the study quality. Only two studies sufficiently described the process of allocation concealment to intervention groups and were considered to be truly randomized. Furthermore, most studies provided insufficient detail to determine whether outcome assessors were blinded to treatment allocation. Unblinded outcomes have shown to introduce bias in terms of exaggerating the effect size of interventions.[38] Future studies should provide an adequate description of the procedures of randomization and conduct single blinded studies to ensure and confirm that studies are at reduced risk of potential bias.

High attrition rates were evident in the IER intervention. This is comparable to previous reviews of weight management interventions,[9,39-41] reporting attrition rates of between 30-60%. Attrition rates less than 20% indicate an intervention is acceptable and contributed in addition to rigorous study design (as assessed in the critical appraisal of the included studies) to a high quality study.[42] The attrition rates were in general comparable across treatment groups, however, four studies reported greater than 20%

attrition. This is concerning due to the short duration of studies. Only one study reported attrition rate at 12 months (IER 30.2%; CER 28.6%).[25] This was not greater than the studies reporting attrition rates in general at three months. This illustrates that adherence to energy restriction periods of four days per week is not less than less intensive, two day energy restriction regimens.

Sensitivity and subgroup analysis could not be performed due to the small number of studies included in this review. This prevented insight in particular into the optimum IER approach. However, the results suggest comparable post intervention weight losses across studies irrespective of dietary regimen. This is an important finding, although further research is necessary to investigate the optimum approach to deliver an IER regime. Given the complexity of weight management it is unlikely that a 'one size fits all' approach will work. This review therefore provides data to suggest that IER may provide an alternative approach for individuals who struggle with daily energy restriction. As compliance was measured by total weight change and was also comparable between IER and CER approaches, it suggests this may be an acceptable dietary regime.

Generalizability of results

The majority of participants included in this review were female. Two studies in particular were carried out on a specific group of women, who were at primary risk of developing breast cancer.[16,17] The increased health risk in these women may have elevated their motivation, and thus may have achieved greater weight loss results than a less homogeneous group. There was also a lack of male participants (only 10 in the entire analysis),[22,26] which highlights the need for more research on IER in this population. This gender imbalance was consistent with findings from a recent review.[43] which supported the assertion that participants engaged in weight management programs are predominately female. Furthermore, the mean age range of participants was 37 years to 49 years and included primarily a homogeneous group of women. This raises question as to the generalizability of the findings to younger and older populations. This is important as young adults aged 18-24 years have been shown to be at an increased risk of weight gain as they transition from adolescence to adulthood.[44] There is also a trend demonstrating increased onset of obesity in later life,[45] yet despite the absence of an no upper age limit for inclusion of participants in the included studies, no older adults (≥ 65 years) participated. Further research examining the acceptability and effectiveness of IER in these population groups is certainly warranted.

Examining potential health inequalities is paramount in any weight management program given the established links between low SES and poor uptake and high attrition.[46] However, the studies included in this review provided very limited socio-economic data for their participants. A report on poverty in the UK[47] suggested that individuals with short term outlooks on life, enforced due to financial and other pressures, are less likely to be motivated to participate in interventions such as weight management. Therefore, consideration must be given to encourage uptake from a broader cross

section of society in order to evaluate efficacy in all populations, not just those who are most likely to engage. This is important in terms of wider roll out and ensuring that new interventions narrow, not broaden existing inequalities.

Current evidence only provides data for populations from the UK and USA. As different countries and cultures may experience different motivators and barriers to weight management, it is important that further IER research is conducted across a more geographically diverse population before the international applicability of the findings can be fully evaluated.

Research implications

This systematic review provides evidence for the efficacy of IER (which can be considered a 'complex' intervention) as an approach to short term weight management. Recent guidelines by the Medical Research Council (MRC) on developing and evaluating interventions advocate that new treatment approaches should undertake a program of research from feasibility testing (including process evaluation and economic evaluations) to rigorous randomized controlled trials to examine the efficacy of the intervention.[37,48] The studies in this review were not of high quality and had low methodological rigor and short intervention and follow-up duration. Future studies are required to determine the efficacy of IER under more quality assured conditions, including blinding of outcome measures, adequate description of randomization procedures, and reporting of outcome measures. Research recommendations from this review include the need for more adequately powered, high quality, large scale randomized control trials conducted in different countries with a more heterogeneous mix of participating genders and age ranges. Feasibility testing should investigate methods to maintain motivation throughout the interventions and prevent high attrition rates. The studies in this review were predominantly focused on examining the efficacy of the interventions in relation to their primary and secondary outcomes, and thus valuable measures in relation to the processes of delivering these dietary interventions were not investigated. Indeed, process evaluation has been highlighted of increasing importance in advancing the understanding of complex interventions.[49] Process evaluations provide opportunities to identify the successful and unsuccessful components of an intervention and are often enriched by utilizing qualitative methods.[50,51] Future IER research would benefit from more detailed process evaluation to identify barriers and facilitators to this approach, and which populations may gain most benefit and why.

As research in this field continues, it is hoped some of the limitations of the current evidence base will be addressed. This review identified three ongoing studies which met the inclusion criteria for this review. One study was conducted in the USA [(NCT00960505, 2016) which had not reached completion] and two conducted in Norway [(NCT02169778, 2016) (NCT02480504, 2016) which had reached completion but had not published any findings], which will help address the international application of this approach. The three ongoing studies focus on IER regimens including ADF

(NCT00960505, 2016); 5:2 (NCT02480504, 2016) and 3 days (NCT02169778, 2006) with two studies comparing IER to CER, and one comparing IER to no treatment control (NCT00960505, 2016). Two studies [(NCT02480504, 2016), (NCT02169778, 2006)] appeared to adhere to clinical guidelines and measured outcomes at 12 months and included body weight and cardio-metabolic outcomes. Thus, the results of these will add to the current body of research and may potentially help elucidate the long term effects and sustainability of IER and any changes in weight loss and health risk factors.

As the popularity in IER increases, clear definition on what IER actually constitutes needs to be established. For the purpose of this review, IER was defined as energy restriction periods of up to six days per week. However, additional studies identified during the systematic search, found that studies also explored longer term IER regimens (greater than one week). Future reviews should consolidate the evidence base on longer term periods of IER and whether they are an effective approach to weight management.

Clinical implications

The main aim of any dietary intervention is for it to become implemented in routine practice. Currently there is insufficient evidence to make any firm recommendations as to the routine use of IER, given the small number of variable quality studies, with very little follow up and limited generalizability. However, further studies will help to examine the long termer impact of this approach, providing more robust data to determine whether the short term changes and benefits that have been demonstrated in this evidence synthesis and meta-analysis, are persistent over time, and across different populations. As clinical guidelines require interventions that are deemed both clinically and cost effective[4], economic evaluations of this approach are also required.

Conclusion

This systematic review provides an update on the available evidence for the efficacy of IER as an approach to weight management. Few studies met the inclusion criteria which aimed to reflect current practice for the management of obesity. Furthermore, studies were of variable quality with inadequate follow up and limited generalizability. Meta-analyses revealed that both IER and CER resulted in similar weight loss, therefore, IER is as effective as CER and for short term weight loss in overweight and obese adults. IER was shown to be more effective than no treatment, however, this should be interpreted cautiously due to the small number of studies and future research is warranted to confirm the findings of this review.

Acknowledgements

The authors would like to thank Dr Shannon Robalino for her advice in the early search strategy development and Dr Samantha Harrison.

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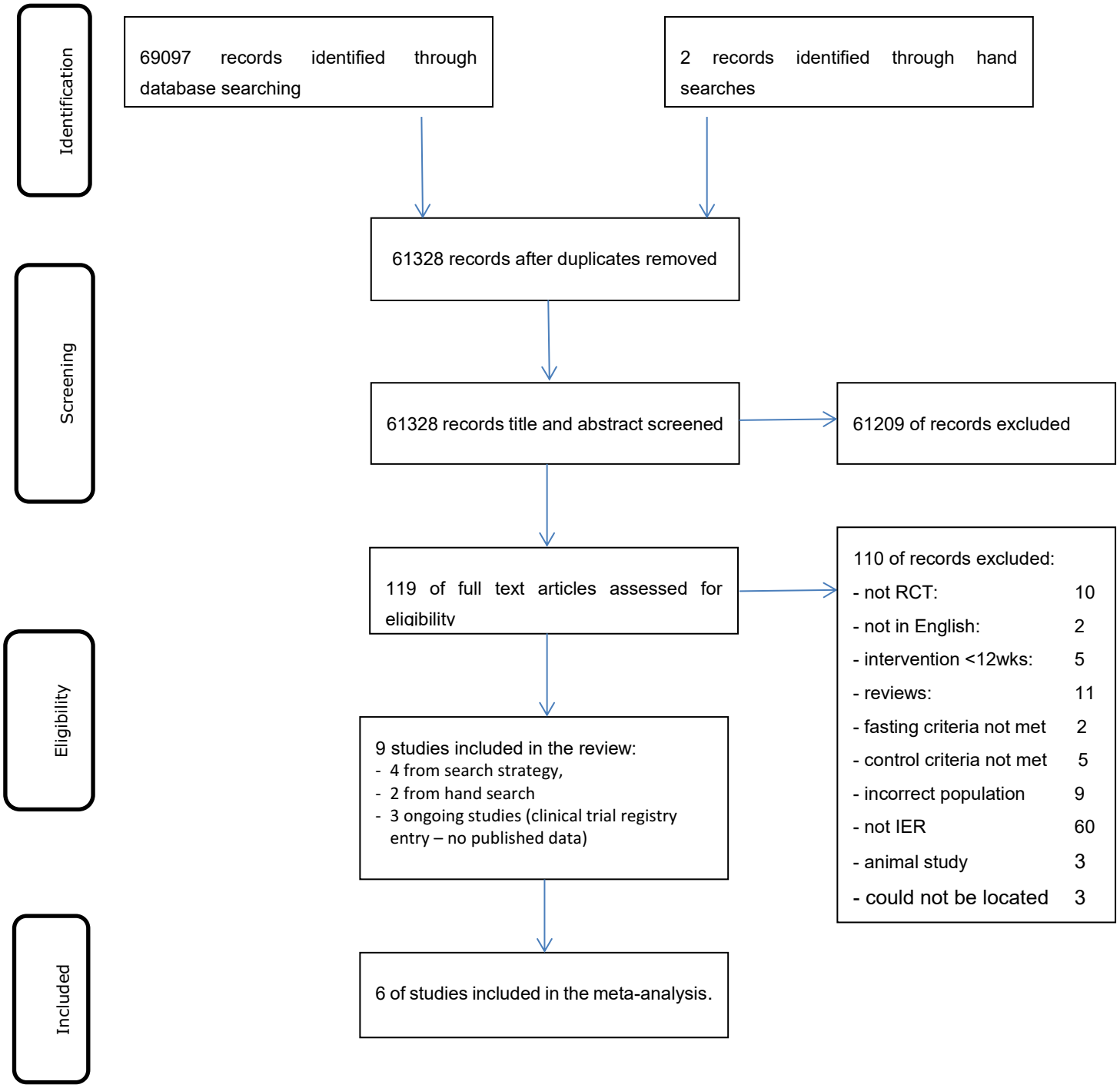

Figure 1: PRISMA flow diagram of search and study selection process (Adapted from Moher *et al.*[24])

Reference	Intermittent energy restriction (IER)		Continuous energy restriction (CER)		Mean difference (95% CI)
	Mean (SD)	N	Mean (SD)	N	
Harvie *et al.*[19]	-5.70 (5.00)	42	-4.50 (6.40)	47	-1.20 (-3.61 to 1.21)
Harvie *et al.*[20]	-5.30 (5.29)	75	-3.80 (5.95)	40	-1.50 (-3.62 to 0.62)
Hill *et al.*[21]	-7.20 (10.10)	14	-9.50 (8.70)	9	2.30 (-5.73 to 10.33)
Viegener *et al.*[25]	-8.98 (6.73)	30	-8.96 (7.27)	30	-0.02 (-3.57 to 3.53)
Pooled Estimate (Random Effect)		161		126	-1.03 (-2.46 to 0.40)
Tests for heterogeneity: p = 0.76, I^2 = 0.0%, T^2 = 0.0					

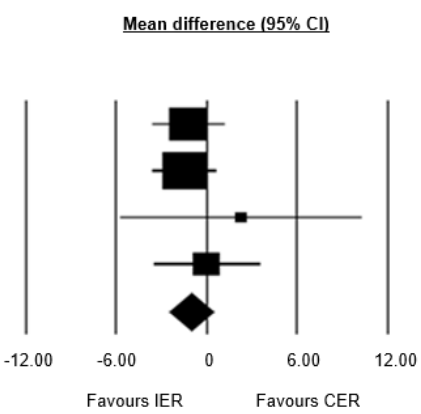

Figure 2: Weighted mean difference in body weight (kg) between the intermittent energy restriction interventions and continuous energy restriction interventions.

Reference	Mean difference (95% CI)
Bhutani *et al.*[22]	-3.00 (-4.88 to -1.19)
Varady *et al.*[26]	-5.20 (-6.88 to -3.52)
Pooled Estimate (Random Effect)	-4.14 (-6.30 to -1.99)
Tests for heterogeneity: p = 0.09, I^2 = 65.7%, T^2 = 1.6	

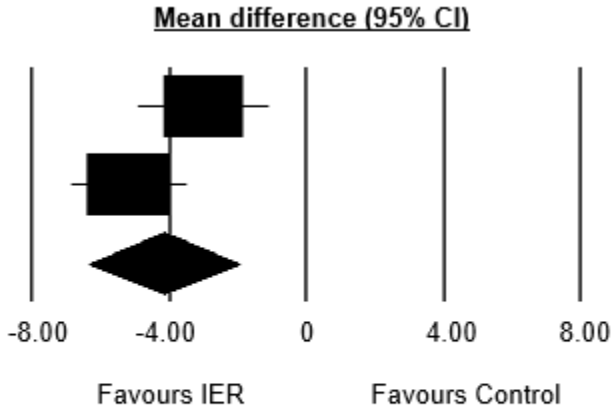

Figure 3: Weighted mean difference in body weight (kg) between the intermittent energy restriction (IER) interventions and control interventions.

Table 1: Assessment of methodological quality.

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Total
	Y	N	U	U	U	Y	Y	Y	Y	Y	6
Harvie *et al.*[19]	U	N	U	Y	U	Y	Y	Y	Y	Y	6
Harvie *et al.*[20]	Y	N	Y	Y	N	Y	Y	Y	Y	Y	8
Hill *et al.*[21]	U	N	U	N	U	U	Y	Y	Y	Y	4
Varady *et al.*[26]	U	N	U	N	U	Y	Y	Y	Y	Y	5
Viegener *et al.*[25]	U	N	U	N	U	Y	Y	Y	U	Y	4
%	33.33	0.00	16.67	33.33	0.00	83.33	100.00	100.00	83.33	100.00	

Y = Yes; N = No; U = Unclear

Q1. Was the assignment to treatment groups truly random?

Q2. Were participants blinded to treatment allocation?

Q3. Was allocation to treatment groups concealed from the allocator?

Q4. Were the outcomes of people who withdrew described and included in the analyses?

Q5. Were those assessing outcomes blind to treatment allocation?

Q6. Were the control and treatment groups comparable at entry?

Q7. Were groups treated identically other than for the named interventions?

Q8. Were outcomes measured in the same way for all groups?

Q9. Were outcomes measured in a reliable way?

Q10. Were appropriate statistical analyses used?

1 **Table 2: Overview of included studies.**

2

Reference	Study population			Intervention		Study duration (Months)	Attrition		
		IER	CER/ Control	IER	CER/Control			IER	CER
Bhutani *et al.*[22]	Weight (kg):	94.0 ± 3.0	93.0 ± 5.0	**ADF:** 75% energy restriction on fast days (24h) consumed between 12 pm & 2 pm & ad libitum on each alternating feed day (24 h).	**Control:** Ad libitum dietary intake	Weight loss: 3	Enrolled:	n = 25	n =16
	BMI (kg/m^2):	35.0 ± 1.0	35.0 ± 1.0				Completed:	n = 16	n = 16
	Age (years):	42.0 ± 2.0	49.0 ± 2.0				Attrition rate:	36.0%	0.0%
	Gender (F/M):	24/1	15/1						
				Macronutrient composition:					

				55% CHO; 25% FAT; 20% PRO (food provided on fast days for controlled feeding phase weeks 1-4)					
Harvie *et al.*[19]	Weight (kg): BMI (kg/m^2): Age (years): Gender (F/M):	81.5 (13.1) 30.7 (5.0) 40.1 (4.1) 53/0	84.4 (16.4) 30.5 (5.2) 40.0 (3.9) 42/0	**IER: 2** consecutive fast days (75% restriction. ~500 kcal/day) & to consume estimated requirements for weight maintenance for the remaining **5** days **Macronutrient composition:** 50 g PRO/day	**CER:** Daily 25% restriction (~ 1200-1800 kcal /day) **Macronutrient composition:** 45 % CHO; 30% FAT; 25% PRO	Weight loss: 6	Enrolled: Completed: Attrition rate:	n = 53 n = 42 20.8%	n = 54 n = 47 13.0%

Harvie *et al.*[20]		**IER**		**IER: 2** consecutive fast days (70% restriction, ~ 600-650 kcal /day) & **5** days (25% restriction. ~ 1200 - 1800 kcal /day) **Macronutrient composition** 250 g PRO/day & restricted 40g CHO **IER+PF:** Energy requirements as for IER with addition of ad libitum PRO/FAT	**CER:** Daily 25% restriction (~ 1200-1800 kcal /day) **Macronutrient composition:** 45% CHO; 30% FAT; 25% PRO	Weight loss: 3 Weight maintenance: 1	Enrolled: Completed: Attrition rate:	IER n = 37 n = 33 10.8%	n = 38 n = 28 26.3%
	Weight (kg):	79.4 (14.7)	86 (17.3)							
	BMI (kg/m^2):	29.6 (4.1)	32.2 (5.6)							
	Age (years):	45.6 (8.3)	47.9 (7.7)							
	Gender (F/M):	37/0	38/0							
		IER+PF						IER+PF		
	Weight (kg):	82.4 (16.4)					Enrolled:	n = 40		
	BMI (kg/m^2):	31.0 (5.7)					Completed:	n = 27		
	Age (years):	48.6 (7.3)					Attrition rate:	32.5%		
	Gender (F/M):	40/0								

Hill *et al.*[21]	Weight (kg): BMI (kg/m^2): Age (years): Gender (F/M):	85.8 (NR) 31.0 (2.0) 40.0 (5.0) 10/0	86.3 (NR) 31.0 (3.0) 37.0 (11.0) 10/0	Energy intake altered between 600 kcal/d &1500 kcal/day on a weekly regimen of fasting from **3** to **7** days/week. **Macronutrient composition:** 55% CHO; 25% FAT; 20% PRO	**CER**: Daily restriction of 1200 kcal/day.	Weight loss: 3 Follow Up: 6	Enrolled: Completed: Attrition rate: Completed: Attrition rate:	n = 10 n = 6 40.0% Follow up n = 4 60.0%	n = 10 n = 8 20% Follow up n = 3 70%
Varady *et al.*[26]	Weight (kg): BMI (kg/m^2): Age (years): Gender (F/M):	77.0 ± 3.0 26.0 ± 1.0 47.0 ± 3.0 10/5	77.0 ± 3.0 26.0 ± 1.0 48.0 ± 2.0 12/3	**ADF:** 75% energy restriction on fast days (24h) consumed between 12 pm & 2 pm & ad libitum on each alternating feed day (24 h)	**Control:** Ad libitum dietary intake	Weight loss: 3	Enrolled: Completed: Attrition rate:	n = 16 n = 15 6.3%	n = 16 n = 15 6.3%

				Macronutrient composition: 55% CHO; 30% FAT; 15% PRO				
Viegener *et al.*[25]	Weight (kg): BMI (kg/m^2): Age (years): Gender (F/M):	94.7 (12.7) 35.0 (NR) 47.1 (7.49) 43/0	98.6 (15.9) 35.6 (NR) 47.1 (8.86) 42/0	**4** days/ per week at 800 kcal & **3** days/per week at 1200 kcal **Macronutrient composition** Restrict intake of FAT to ≤25% on 1200 kcal days & to ≤15% 800 kcal days.	**CER:** Maintenance of 1200 kcal /day **Macronutrient composition** 55% CHO; 30% FAT; 15% PRO	Weight loss: 6 Weight maintenance: 6	Enrolled: Completed: Attrition rate:	n = 43 n = 30 30.2%	n = 42 n = 30 28.6%

Values represent Mean ± SEM; Mean (SD). IER = Intermittent energy restriction; IER+PF = Intermittent energy restriction with *ad libitum* protein nad fat intake;CER = Continuous energy restriction; CHO = Carbohydrate; F = Female; M = Male; NR = Not reported; PRO = Protein

Question: Intermittent energy restriction compared to usual care for treatment for overweight and obesity in adult population

Setting:

Bibliography:

Quality assessment							№ of patients		Effect	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intermittent energy restriction	usual care	Absolute (95% CI)		
Weight (kg)											
4	randomised trials	serious [a]	not serious	serious [b]	serious [c]	all plausible residual confounding would reduce the demonstrated effect dose response gradient	161	126	MD **1.03 lower** (2.46 lower to 0.1 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

a. Two out of the four included studies present high risk of bias for: performance, detection and attrition

b. There was a serious risk of indirectness due to the limited age range of participants and gender distribution.

c. There was serious imprecision considering the small number of studies and events and wide confidence interval.

Question: Intermittent energy restriction compared to no treatment control for treatment overweight or obesity in adults

Setting:

Bibliography:

Quality assessment							№ of patients		Effect	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intermittent energy restriction	no treatment	Absolute (95% CI)		
Weight (kg)											

Quality assessment							№ of patients		Effect	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intermittent energy restriction	no treatment	Absolute (95% CI)		
2	randomised trials	serious [a]	very serious [b]	serious [c]	serious [d]	strong association all plausible residual confounding would reduce the demonstrated effect dose response gradient	31	31	- MD **4.14 mean difference lower** (6.30 lower to 1.99 lower)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

a. There was high risks of bias including: performance and detection bias

b. There was serious inconsistency with high and significant heterogeneity

c. There was a serious risk of indirectness due to the limited age range of participants and gender distribution

d. There was serious imprecision considering the small number of studies and events and wide confidence interval.

Table 3: Change in weight, anthropometric, and cardiometabolic outcomes of primary studies.

Reference	Weight change (kg)		Anthropometric changes		Cardiometabolic changes	
	IER	CER/ Control	IER	CER/ Control	IER	CER/ Control
Bhutani *et al.*[22]			**Waist circumference (cm)**		**Systolic blood pressure (mm/Hg)**	
	-3.0 (0.0)*	0.0 (0.0)NS	-5.0 ±1.0*	-1.0 ± 1.0 NS	-3.0 ± 1.0+	-2.0 ± 3.0 NS
			Fat mass (kg)		**Diastolic blood pressure (mm/Hg)**	
			-2.0 ± 1.0+	0.0 ± 1.0 NS	-2.0 ± 2.0+	-2.0 ± 3.0 NS
Harvie *et al.*[19]			**Waist circumference (cm)**		**Glucose (mmol/l)**	
	Pre		**Pre**		**Pre**	
	81.5 (77.5-85.4)	84.4 (79.7-89.1)	101.5 (97.8-105.2)	102.5 (98.7-106.3)	4.8 (4.7-4.9)	4.8 (4.6-4.9)
	Post		**Post**		**Post**	
	75.8 (71.4-0.2)+	79.9 (74.6-85.2)+	95.4 (91.3-99.5)+	98.6 (94.2-102.9) +	4.7 (4.6-4.8) +	4.7 (4.6-4.9)NS
			Fat mass (kg)		**Insulin (mU/ml)**	
			Pre		**Pre**	
			33.6 (30.9-36.4)	35.3 (31.9-38.7)	7.3 (6.3-8.4)	7.4 (6.4-8.6)
			Post		**Post**	
			29.1 (26-32.3) +	31.7 (27.9-35.5) +	5.2 (4.5-6.0) +	6.3 (5.4-7.4) +
			Lean Mass (kg)		**Systolic blood pressure (mm/Hg)**	
			Pre		**Pre**	
			47.6 (46.3-49.0)	49.1 (47.7-50.5)	115.2 (111.2-119.2)	116.8 (113.1-120.4)

		Post			**Post**
		46.4 (44.9-47.9) +		48.3 (46.7-49.9) +	111.5 (107.7-115.2) +
					109.3 (105.3-113.2) +
				Diastolic blood pressure (mm/Hg)	
				Pre	
				76.7 (73.9-79.4)	75.4 (72.3-78.4)
				Post	
				72.4 (68.9-76) +	69.7 (66.4-72.9)+
				Total cholesterol (mmol/l)	
				Pre	
				5.1 (4.9-5.4)	5.2 (5.0-5.4)
				Post	
				4.8 (4.5-5.0) +	4.7 (4.5-5.0) +
				HDL cholesterol (mmol/l)	
				Pre	
				1.5 (1.4-1.5)	1.6 (1.4-1.7)
				Post	
				1.5 (1.4-1.6)NS	1.5 (1.4-1.6) +
				LDL cholesterol (mmol/l)	

							Pre		
							3.1 (2.9-3.3)		3.1 (2.8-3.3)
							Post		
							2.8 (22.6-3.1) [+]		2.8 (2.6-3.0) [+]
							Triglycerides (mmol/l)		
							Pre		
							Pre 1.2 (1.0-1.4)		Pre 1.3 (1.1-1.4)
							Post		
							1.0 (0.9-1.2) [+]		1.0 (0.8-1.2) [+]
	IER	**IER+PF**	**CER**	**IER**	**IER+PF**	**CER**	**IER**	**IER+PF**	**CER**
Harvie *et al.*[20] (NR)				**Waist circumference (cm)**			**Glucose (mmol/l)**		
		Pre			**Pre**			**Pre**	
	79.4 (74.6-84.1)	82.4 (77.2-87.6)	86.0 (60.6-91.3)	100.5 (96.6-104.5)	104.1 (99.0-109.1)	106.0 (101.9-110.2)	4.9 (4.7-5.0)	5.0 (4.8-5.1)	5.0 (4.8-5.1)
		Post			**Post**			**Post**	
	73.9 (69.4-78.5)	77.3 (72.5-82.1)	82.2 (76.9-87.5)	94.4 (90.5-98.3)	98.8 (94.1-103.6)	102.4 (98.0-106.8)	4.8 (4.6-5.0)	4.9 (4.7-5.1)	4.9 (4.7-5.0)

Fat mass (kg)			Insulin (mmol/l)		
	Pre			**Pre**	
31.0 (27.9-34.2)	33.5 (29.9-37.0)	35.7 (32.3-39.2)	43.2 (35.4-52.8)	50.4 (42.6-60.0)	49.8 (42.0-59.4)
	Post			**Post**	
26.7 (23.9-29.5)	29.4 (26.3-32.6)	33.2 (29.7-36.7)	34.2 (28.2-41.4)	45.0 (38.4-52.2)	45.0 (36.6-54.6)

Lean Mass (kg)			Systolic blood pressure (mm/Hg)		
	Pre			Pre	
48.5 (46.4-50.5)	49.0 (47.2-50.9)	50.3 (48.2-52.3)	114.9 (111.0-125.0)	129.5 (115.0-138.0)	124.0 (116.0-131.0)
	Post			**Post**	
47.2 (45.1-49.3)	47.9 (46.1-49.6)	48.7 (46.5-50.8)	111.9 (108.0-118.0)	112.8 (108.0-121.0)	113.3 (107.0-125.0)

Total cholesterol (mmol/l)		
Pre		
5.3 (5.0-5.6)	5.7 (5.3-6.1)	5.3 (5.0-5.7)
Post		
5.1 (4.7-5.4)	5.5 (5.1-5.9)	5.3 (5.0-5.5)

		HDL cholesterol (mmol/l)		
		Pre		
		1.4 (1.3-1.5)	1.4 (1.3-1.5)	1.3 (1.2-1.4)
		Post		
		1.4 (1.2-1.5)	1.4 (1.3-1.6)	1.4 (1.3-1.5)
		LDL cholesterol (mmol/l)		
		Pre		
		3.3 (3.0-3.6)	3.7 (3.4-4.1)	3.4 (3.1-3.6)
		Post		
		3.2 (2.9-3.5)	3.6 (3.2-3.9)	3.3 (3.1-3.5)
		Triglycerides (mmol/l)		
		Pre		
		1.0 (0.9-1.2)	1.1 (0.9-1.2)	1.1 (0.9-1.3)
		Post		
		0.9 (0.8-1.0)	0.9 (0.8-1.1)	1.0 (0.9-1.2)
Hill *et al.*[21]		**Total cholesterol (mmol/l)**		
		Pre		

	-7.2 ± 2.7	-9.5 ± 2.9		5.5 ± 0.3	5.1 ± 0.2
(NR)					
				Post	
				4.7 ± 0.2	4.8 ± 0.3
Varady *et al.*[26]			Fat mass (kg)	Systolic blood pressure (mm/Hg)	
	-5.2 ± 0.9[*]		*-3.6 ± 0.7*[NS]	-7.0 ± 2.0[+]	1.0 ± 3.0[NS]
				Diastolic blood pressure (mm/Hg)	
				-6.0 ± 2.0[+]	2.0 ± 6.0 [NS]
				Total cholesterol (mg/dl)	
				-26.0 ± 6.0[+]	-9.0 ± 5.0 [NS]
				HDL cholesterol (mg/dl)	
				-2.0 ± 3.0[NS]	1.0 ± 2.0 [NS]
				LDL cholesterol (mg/dl)	
				-18.0 ± 6.0[+]	-9.0 ± 4.0 [NS]
				Triglycerides (mg/dl)	
				-22.0 ± 11.0[NS]	10.0 ± 7.0 [NS]
Viegener *et al.*[25]	-9.0 (6.7)	-9.0 (7.3)			

Results are presented for within group changes. Values represent mean ± SEM; mean (SD)

NR: Within group statistics not reported (Harvie *et al.*[20]; Hill *et al.*[21])

Varady *et al.*[26] Between group differences for weight and fat mass

*Significance at p = <0.001 [+]Significance at p = <0.05 [NS] Not significant p = > 0.05

Table 4: Pooled effect sizes (Weighted Mean Difference) of secondary outcomes.

Outcomes	K	Pooled estimate (95% CI)	p-value	Heterogeneity		
				Q (p-value)	I^2	T^2
IER vs CER						
Waist circumference (cm)	2	-2.14 (-3.53 to -0.75)	0.002	0.01 (0.938)	0.0%	0.00
Fat mass (kg)	2	-1.38 (-2.47 to -0.28)	0.014	0.49 (0.483)	0.0%	0.00
Fat free mass (kg)	2	-0.02 (-0.80 to 0.76)	0.958	1.90 (0.168)	47.5%	0.15
Glucose (mmol/l)	2	0.00 (-0.05 to 0.05)	1.000	0.00 (1.000)	0.0%	0.00
Insulin (pmol/l)	2	-4.66 (-9.12 to -0.19)	0.041	2.57 (0.109)	61.1%	6.36
Total cholesterol (mmol/l)	3	-0.14 (-0.50 to 0.23)	0.458	27.33 (<0.001)	92.7%	0.10
LDL cholesterol (mmol/l)	2	-0.05 (-0.15 to 0.05)	0.343	1.08 (0.298)	7.7%	0.00

HDL cholesterol (mmol/l)	2	0.03 (-0.10 to 0.16)	0.645	6.59 (0.010)	84.8%	0.01
Triglyceride (mmol/l)	2	-0.03 (-0.10 to 0.03)	0.314	0.690 (0.406)	0.0%	0.00
IER vs Control						
Fat mass (kg)	2	-3.24 (-4.55 to -1.92)	<0.001	1.12 (0.290)	10.7%	0.14
Systolic BP (mmHg)	2	-4.29 (-11.13 to 2.56)	0.220	2.13 (0.144)	53.1%	13.00
Diastolic BP (mmHg)	2	-3.81 (-11.64 to 4.02)	0.340	2.78 (0.095)	64.1%	20.50

IER = Intermittent energy restriction; CER = Continuous energy restriction; K = number of studies; CI = confidence interval; Q = heterogeneity statistic for the model; I^2 = index of heterogeneity beyond within-study sampling error; T^2 = estimate of the between-study variance; LDL = Low density lipoprotein; HDL = High density lipoprotein.

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Appendix I: Search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to 2015 November 21>

Search Strategy:

---

1 exp Obesity/

2 obes*.tw.

3 body mass.tw.

4 exp Body Composition/

5 body composition.tw.

6 exp Body Size/

7 body siz*.tw.

8 bodysiz*.tw.

9 exp Body Weight/

10 body weight.tw.

1 11 fat.tw.

2 12 fatness.tw.

3 13 exp Overnutrition/

4 14 overnutrition.tw.

5 15 exp Overweight/

6 16 overweight.tw.

7 17 over weight.tw.

8 18 weight.tw.

9 19 exp Weight Gain/

10 20 weight gain.tw.

11 21 weight maintenance.tw.

12 22 weight management.tw.

13 23 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
14 or 20 or 21 or 22

15 24 exp Fasting/

16 25 intermittent fast*.tw.

17 26 alternate-day fast*.tw.

18 27 intermittent energy restriction*.tw.

19 28 intermittent calori* restriction*.tw.

20 29 intermittent restrictive diet*.tw.

21 30 continuous energy restriction*.tw.

22 31 continuous calori* restriction*.tw.

1	32	continuous restrictive diet*.tw.
2	33	fasting calorie restriction intervention*.tw.
3	34	very low calorie diet*.tw.
4	35	periodic fasting*.tw.
5	36	extreme diet*.tw.
6	37	800* kcal.tw.
7	38	500 calorie*.tw.
8	39	sporadic fast*.tw.
9	40	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
10	41	23 and 40
11	42	exp Adiposity/
12	43	exp Adipose Tissue/
13	44	(adverse adj (event* or inciden*)).tw.
14	45	bio-impedance.tw.
15	46	bioimpedance.tw.
16	47	bioelectrical impedance analysis.tw.
17	48	exp Blood Glucose/
18	49	blood glucose.tw.
19	50	exp Blood Pressure/
20	51	blood pressure*.tw.
21	52	exp Body Mass Index/

1	53	body mass index.tw.
2	54	BMI.tw.
3	55	bodpod.tw.
4	56	exp Cholesterol/
5	57	cholesterol.tw.
6	58	exp Diet/
7	59	diet.tw.
8	60	exp Absorptiometry, Photon/
9	61	dexa scan*.tw.
10	62	dxa.tw.
11	63	exp Exercise/
12	64	exercise.tw.
13	65	hydrostatic.tw.
14	66	exp Magnetic Resonance Imaging/
15	67	magnetic resonance imag*.tw.
16	68	MRI.tw.
17	69	exp Skinfold Thickness/
18	70	skin-fold.tw.
19	71	exp Waist Circumference/
20	72	waist circumference.tw.
21	73	exp Weight Loss/

1 74 weight loss.tw.

2 75 slim.tw.

3 76 slimming.tw.

4 77 thin.tw.

5 78 thinness.tw.

6 79 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58
7 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or
8 76 or 77 or 78

9 80 23 and 40 and 79

10 81 limit 80 to english language

11 82 80 not 81

12 83 exp Randomized Controlled Trials as Topic/

13 84 exp Randomized Controlled Trial/

14 85 exp Random Allocation/

15 86 exp Double-Blind Method/

16 87 exp Single-Blind Method/

17 88 exp Clinical Trial/

18 89 clinical trial, phase i.pt.

19 90 clinical trial, phase ii.pt.

20 91 clinical trial, phase iii.pt.

21 92 clinical trial, phase iv.pt.

22 93 controlled clinical trial.pt.

1	94	randomized controlled trial.pt.
2	95	multicenter study.pt.
3	96	clinical trial.pt.
4	97	exp Clinical Trials as topic/
5	98	or/83-97
6	99	(clinical adj trial*).tw.
7	100	((singl* or doubl* or treb* or tripl*) adj (blind* or mask*)).tw.
8	101	exp Placebos/
9	102	placebo$.tw.
10	103	randomly allocated.tw.
11	104	(allocated adj2 random$).tw.
12	105	or/99-104
13	106	98 or 105
14	107	case report.tw.
15	108	letter/
16	109	historical article/
17	110	or/107-109
18	111	106 not 110
19	112	81 and 111
20		

Database: Embase <1974 to 2016 January 08>

Search Strategy:

1	1	exp obesity/
2	2	obes*.tw.
3	3	exp body mass/
4	4	body mass.tw.
5	5	exp body composition/
6	6	body composition.tw.
7	7	exp body size/
8	8	body siz*.tw.
9	9	bodysiz*.tw.
10	10	exp body weight/
11	11	body weight.tw.
12	12	exp fat body/
13	13	fat.tw.
14	14	fatness.tw.
15	15	exp overnutrition/
16	16	overnutrition.tw.
17	17	overweight.tw.
18	18	over weight.tw.

1 19 weight.tw.

2 20 exp weight gain/

3 21 weight gain.tw.

4 22 weight maintenance.tw.

5 23 weight management.tw.

6 24 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
7 or 20 or 21 or 22 or 23

8 25 exp diet restriction/

9 26 fasting.tw.

10 27 intermittent fast*.tw.

11 28 alternate-day fast*.tw.

12 29 exp caloric restriction/

13 30 intermittent energy restriction*.tw.

14 31 intermittent calori* restriction*.tw.

15 32 intermittent restrictive diet*.tw.

16 33 continuous energy restriction*.tw.

17 34 continuous calori* restriction*.tw.

18 35 continuous restrictive diet*.tw.

19 36 fasting calorie restriction intervention*.tw.

20 37 very low calorie diet*.tw.

21 38 periodic fasting*.tw.

22 39 extreme diet*.tw.

1 40 800* kcal.tw.

2 41 500 calorie*.tw.

3 42 sporadic fast*.tw.

4 43 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
5 or 42

6 44 24 and 43

7 45 adiposity.tw.

8 46 exp adipose tissue/

9 47 (adverse adj (event* or inciden*)).tw.

10 48 bio-impedance.tw.

11 49 bioimpedance.tw.

12 50 bioelectrical impedance analysis.tw.

13 51 exp glucose blood level/

14 52 blood glucose.tw.

15 53 exp blood pressure/

16 54 blood pressure*.tw.

17 55 body mass index.tw.

18 56 BMI.tw.

19 57 bodpod.tw.

20 58 exp cholesterol/

21 59 cholesterol.tw.

22 60 exp diet/

1	61	diet.tw.
2	62	exp photon absorptiometry/
3	63	exp dual energy X ray absorptiometry/
4	64	dexa scan*.tw.
5	65	dxa.tw.
6	66	exp exercise/
7	67	exercise.tw.
8	68	hydrostatic.tw.
9	69	exp nuclear magnetic resonance imaging/
10	70	magnetic resonance imag*.tw.
11	71	MRI.tw.
12	72	exp skinfold thickness/
13	73	skin-fold.tw.
14	74	exp waist circumference/
15	75	waist circumference.tw.
16	76	exp weight reduction/
17	77	weight loss.tw.
18	78	slim.tw.
19	79	slimming.tw.
20	80	thin.tw.
21	81	thinness.tw.

1 82 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61
2 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or
3 79 or 80 or 81

4 83 24 and 43 and 82

5 84 limit 83 to english

6 85 83 not 84

7 86 limit 83 to (conference abstract or conference paper or conference proceeding or "conference
8 review")

9 87 83 not 86

10 88 clinical trial/

11 89 randomized controlled trial/

12 90 exp randomization/

13 91 single blind procedure/

14 92 double blind procedure/

15 93 crossover procedure/

16 94 exp placebo/

17 95 randomi?ed controlled trial*.tw.

18 96 RCT.tw.

19 97 random allocation.tw.

20 98 randomly allocated.tw.

21 99 allocated randomly.tw.

22 100 (allocated adj2 random).tw.

1	101	single blind*.tw.
2	102	double blind*.tw.
3	103	(treble adj blind*).tw.
4	104	(triple adj blind*).tw.
5	105	placebo*.tw.
6	106	exp prospective study/
7	107	or/88-106
8	108	exp case study/
9	109	case report.tw.
10	110	abstract report/ or letter/
11	111	or/108-110
12	112	107 not 111
13	113	87 and 112
14		

Database: CINAHL (Cumulative Index of Nursing and Allied Health Literature <1981 to 2015 November 21>

Search Strategy:

S1	(MH "Obesity+")
S2	TI obes* OR AB obes*
S3	TI body mass OR AB body mass
S4	(MH "Body Composition+")
S5	TI body composition OR AB body composition
S6	(MH "Body Size")
S7	TI body siz* OR AB body siz*
S8	TI bodysiz* OR AB bodysiz*
S9	(MH "Body Weight+")
S10	TI body weight OR AB body weight
S11	TI fat OR AB fat
S12	TI fatness OR AB fatness
S13	TI overnutrition OR AB overnutrition
S14	TI overweight OR AB overweight
S15	TI over weight OR AB over weight
S16	TI weight OR AB weight
S17	(MH "Weight Gain+")
S18	TI weight gain OR AB weight gain

1	S19	(MH "Weight Control")
2	S20	TI weight maintenance OR AB weight maintenance
3	S21	TI weight management OR AB weight management
4	S22	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR
5	S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21	
6	S23	(MH "Fasting")
7	S24	TI intermittent fast* OR AB intermittent fast*
8	S25	TI alternate-day fast* OR AB alternate-day fast*
9	S26	(MH "Restricted Diet+")
10	S27	TI intermittent energy restriction* OR AB intermittent energy restriction*
11	S28	TI intermittent calori* restriction* OR AB intermittent calori* restriction*
12	S29	TI intermittent restrictive diet* OR AB intermittent restrictive diet*
13	S30	TI continuous energy restriction* OR AB continuous energy restriction*
14	S31	TI continuous calori* restriction* OR AB continuous calori* restriction*
15	S32	TI continuous restrictive diet* OR AB continuous restrictive diet*
16	S33	TI fasting calorie restriction intervention* OR AB fasting calorie restriction intervention*
17	S34	TI very low calorie diet* OR AB very low calorie diet*
18	S35	TI periodic fasting* OR AB periodic fasting*
19	S36	TI extreme diet* OR AB extreme diet*
20	S37	TI 800* kcal OR AB 800* kcal
21	S38	TI 500 calorie* OR AB 500 calorie*
22	S39	TI sporadic fast* OR AB sporadic fast*

S40 S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39

S41 S22 AND S40

S42 TI adiposity OR AB adiposity

S43 (MH "Adipose Tissue+")

S44 TI "adverse event*" OR AB "adverse event*"

S45 TI "adverse inciden*" OR AB "adverse inciden*"

S46 TI bio-impedance OR AB bio-impedance

S47 TI bioimpedance OR AB bioimpedance

S48 TI bioelectrical impedance analysis OR AB bioelectrical impedance analysis

S49 (MH "Blood Glucose")

S50 TI blood glucose OR AB blood glucose

S51 (MH "Blood Pressure+")

S52 TI blood pressure* OR AB blood pressure*

S53 (MH "Body Mass Index")

S54 TI "body mass index" OR AB "body mass index"

S55 TI BMI OR AB BMI

S56 TI bodpod OR AB bodpod

S57 (MH "Cholesterol+")

S58 TI cholesterol OR AB cholesterol

S59 (MH "Diet+")

S60 TI diet OR AB diet

1	S61	(MH "Absorptiometry, Photon")
2	S62	TI dexa scan* OR AB dexa scan*
3	S63	TI dxa OR AB dxa
4	S64	(MH "Exercise+")
5	S65	TI exercise OR AB exercise
6	S66	TI hydrostatic OR AB hydrostatic
7	S67	(MH "Magnetic Resonance Imaging+")
8	S68	TI magnetic resonance imag* OR AB magnetic resonance imag*
9	S69	TI MRI OR AB MRI
10	S70	(MH "Skinfold Thickness")
11	S71	TI skin-fold OR AB skin-fold
12	S72	(MH "Waist Circumference")
13	S73	TI waist circumference OR AB waist circumference
14	S74	(MH "Weight Loss+")
15	S75	TI weight loss OR AB weight loss
16	S76	TI slim OR AB slim
17	S77	TI slimming OR AB slimming
18	S78	TI thin OR AB thin
19	S79	TI thinness OR AB thinness
20	S80	S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR
21	S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64	

OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79

S81 S22 AND S40 AND S80

1	Database: Cochrane Library	
2	Date Run:	21/11/15 17:51:35.234
3	Description:	
4		
5	ID	Search Hits
6	#1	MeSH descriptor: [Obesity] explode all trees
7	#2	obes*:ti,ab
8	#3	body mass:ti,ab
9	#4	MeSH descriptor: [Body Composition] explode all trees
10	#5	body composition:ti,ab
11	#6	MeSH descriptor: [Body Size] explode all trees
12	#7	body siz*:ti,ab
13	#8	bodysiz*:ti,ab
14	#9	MeSH descriptor: [Body Weight] explode all trees
15	#10	body weight:ti,ab
16	#11	fat:ti,ab
17	#12	fatness:ti,ab
18	#13	MeSH descriptor: [Overnutrition] explode all trees
19	#14	overnutrition:ti,ab
20	#15	MeSH descriptor: [Overweight] explode all trees
21	#16	overweight:ti,ab

1	#17	over weight:ti,ab
2	#18	weight:ti,ab
3	#19	MeSH descriptor: [Weight Gain] explode all trees
4	#20	weight gain:ti,ab
5	#21	weight maintenance:ti,ab
6	#22	weight management:ti,ab
7	#23	{or #1-#22}
8	#24	MeSH descriptor: [Fasting] explode all trees
9	#25	intermittent fast*:ti,ab
10	#26	alternate-day fast*:ti,ab
11	#27	intermittent energy restriction*:ti,ab
12	#28	intermittent calori* restriction*:ti,ab
13	#29	intermittent restrictive diet*:ti,ab
14	#30	continuous energy restriction*:ti,ab
15	#31	continuous calori* restriction*:ti,ab
16	#32	continuous restrictive diet*:ti,ab
17	#33	fasting calorie restriction intervention*:ti,ab
18	#34	very low calorie diet*:ti,ab
19	#35	periodic fasting*:ti,ab
20	#36	extreme diet*:ti,ab
21	#37	800* kcal:ti,ab

1	#38	500 calorie*:ti,ab
2	#39	sporadic fast*:ti,ab
3	#40	{or #24-#39}
4	#41	#23 and #40
5	#42	MeSH descriptor: [Adiposity] explode all trees
6	#43	MeSH descriptor: [Adipose Tissue] explode all trees
7	#44	adverse event*:ti,ab
8	#45	adverse inciden*:ti,ab
9	#46	bio-impedance:ti,ab
10	#47	bioimpedance:ti,ab
11	#48	bioelectrical impedance analysis:ti,ab
12	#49	MeSH descriptor: [Blood Glucose] explode all trees
13	#50	blood glucose:ti,ab
14	#51	MeSH descriptor: [Blood Pressure] explode all trees
15	#52	blood pressure*:ti,ab
16	#53	MeSH descriptor: [Body Mass Index] explode all trees
17	#54	body mass index:ti,ab
18	#55	BMI:ti,ab
19	#56	bodpod:ti,ab
20	#57	MeSH descriptor: [Cholesterol] explode all trees
21	#58	cholesterol:ti,ab

1	#59	MeSH descriptor: [Diet] explode all trees
2	#60	diet:ti,ab
3	#61	MeSH descriptor: [Absorptiometry, Photon] explode all trees
4	#62	dexa scan*:ti,ab
5	#63	dxa:ti,ab
6	#64	MeSH descriptor: [Exercise] explode all trees
7	#65	exercise:ti,ab
8	#66	hydrostatic:ti,ab
9	#67	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
10	#68	magnetic resonance imag*:ti,ab
11	#69	MRI:ti,ab
12	#70	MeSH descriptor: [Skinfold Thickness] explode all trees
13	#71	skin-fold:ti,ab
14	#72	MeSH descriptor: [Waist Circumference] explode all trees
15	#73	waist circumference:ti,ab
16	#74	MeSH descriptor: [Weight Loss] explode all trees
17	#75	weight loss:ti,ab
18	#76	slim:ti,ab
19	#77	slimming:ti,ab
20	#78	thin:ti,ab
21	#79	thinness:ti,ab

1	#80	{or #42-#79}
2	#81	#23 and #40 and #80

3

Appendix II: Appraisal instruments

MAStARI appraisal instrument

JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was the assignment to treatment groups truly random?	☐	☐	☐	☐
2. Were participants blinded to treatment allocation?	☐	☐	☐	☐
3. Was allocation to treatment groups concealed from the allocator?	☐	☐	☐	☐
4. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
5. Were those assessing outcomes blind to the treatment allocation?	☐	☐	☐	☐
6. Were the control and treatment groups comparable at entry?	☐	☐	☐	☐
7. Were groups treated identically other than for the named interventions	☐	☐	☐	☐
8. Were outcomes measured in the same way for all groups?	☐	☐	☐	☐
9. Were outcomes measured in a reliable way?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐
	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

Appendix III: Data extraction instruments

MAStARI data extraction instrument

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer _____ Date _____

Author _____ Year _____

Journal _____ Record Number _____

Study Method

RCT ☐ Quasi-RCT ☐ Longitudinal ☐

Retrospective ☐ Observational ☐ Other ☐

Participants

Setting _____

Population _____

Sample size

Group A _____ Group B _____

Interventions

Intervention A _____

_____

Intervention B _____

_____

Authors Conclusions:

_____

_____

_____

Reviewers Conclusions:

_____

_____

_____

1

Study results

Dichotomous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Continuous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

1
2

Appendix IV: GRADE Assessments

Question: Intermittent energy restriction compared to usual care for treatment for overweight and obesity in adult population

Quality assessment							№ of patients		Effect	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intermittent energy restriction	usual care	Absolute (95% CI)		
Weight (kg)											
4	randomised trials	serious [a]	not serious	serious [b]	serious [c]	all plausible residual confounding would reduce the demonstrated effect dose response gradient	161	126	MD **1.03 lower** (2.46 lower to 0.1 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

a. Two out of the four included studies present high risk of bias for: performance, detection and attrition

b. There was a serious risk of indirectness due to the limited age range of participants and heterogeneous gender distribution.

c. There was serious imprecision considering the small number of studies and events and wide confidence interval.

Question: Intermittent energy restriction compared to no treatment control for treatment overweight or obesity in adults

Quality assessment							№ of patients		Effect	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intermittent energy restriction	no treatment	Absolute (95% CI)		
Weight (kg)											
2	randomised trials	serious [a]	very serious [b]	serious [c]	serious [d]	strong association all plausible residual confounding would reduce the demonstrated effect dose response gradient	31	31	- MD **4.22 mean difference lower** (5.48 lower to 2.97 lower)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

a. There was high risks of bias including: performance and detection bias

b. There was serious inconsistency with high and significant heterogeneity

c. There was a serious risk of indirectness due to the limited age range of participants and heterogeneous gender distribution

d. There was serious imprecision considering the small number of studies and events and wide confidence interval.

Appendix V: Excluded studies

Reason for exclusion: Not a randomised control trial study design (n = 10)

1. Anderlova K, Kremen J, Dolezalova R, Housovaj J. The influence of very-low-calorie diet on serum leptin, soluble leptin receptor, adiponectin and resistin levels in obese women. Physiol Res. 2006; 55(3):277.

2. Bailey BW, Jacobsen DJ, Donnelly JE. Weight loss and maintenance outcomes using moderate and severe caloric restriction in an outpatient setting. Dis Manag. 2008; 11(3):176-80.

3. Garfield G, Duncan MD. Intermittent fasts in the correction and control of intractable obesity. Trans Am Clin Climatol Assoc. 1963; 74:121.

4. Gillen JB, Percival ME, Ludzki A, Tarnopolsky MA, Gibala M. Interval training in the fed or fasted state improves body composition and muscle oxidative capacity in overweight women. Obes. 2013; 21(11):2249-55.

5. Hoddy KK, Kroeger CM, Trepanowski JF, Barnosky AR, Bhutani S, Varady KA. Safety of alternate day fasting and effect on disordered eating behaviors. Nutr J. 2015; 14(1):1.

6. Johnson JB, Laub DR, John S. The effect on health of alternate day calorie restriction: eating less and more than needed on alternate days prolongs life. Med Hypotheses. 2006; 67(2):209-11.

7. Joseph LJ, Prigeon RL, Blumenthal JB, Ryan AS, Goldberg AP. Weight loss and low-intensity exercise for the treatment of metabolic syndrome in obese postmenopausal women. The Journals of Gerontology Series A: Bio Sci Med Sci. 2011; 66(9):1022-9.

8. Klempel MC, Bhutani S, Fitzgibbon M, Freels S, Varady KA. Dietary and physical activity adaptations to alternate day modified fasting: implications for optimal weight loss. Nutr J. 2010; 9(1):1.

9. Stewart WK, Fleming LW, Robertson PC. Massive obesity treated by intermittent fasting: A metabolic and clinical study. Am J Med. 1966;40(6):967-86.

10. Wright G, Dawson B, Jalleh G, Couch MH. A retrospective comparison of two very low energy diets on weight loss and health status in obese women completing a 26-week program. Obes Res Clin Pract. 2007; 1(4):281-8.

Reason for exclusion: Not published in English language (n = 2)

11. Jing RY, Bian HW. Evaluation of the Effectiveness of Losing Weight and Keeping Fit by Controlling Diet and Having Appropriate Physical Activities. Chinese J Clin Nutr. 2006; 3:009.

12. Martinez-Riquelme A, Sajoux I, Fondevila J. [Results of PROMESA I study; efficacy and safety of a very low calorie diet application and following alimentary reeducation with the PronoKal® method in the treatment of excess of weight]. Nutr Hosp. 2013; 29(2):282-91.

Reason for exclusion: IER intervention less than 12 weeks duration (n = 5)

13. Arguin H, Dionne IJ, Sénéchal M, Bouchard DR, Carpentier AC, Ardilouze JL, et al. Short-and long-term effects of continuous versus intermittent restrictive diet approaches on body composition and the metabolic profile in overweight and obese postmenopausal women: a pilot study. Menopause. 2012; 19(8):870-6.

14. Eshghinia S, Mohammadzadeh F. The effects of modified alternate-day fasting diet on weight loss and CAD risk factors in overweight and obese women. J Diabetes Metab Disord. 2013; 12(1):1.

15. Klempel MC, Kroeger CM, Varady KA. Alternate day fasting increases LDL particle size independently of dietary fat content in obese humans. Eur J Clin Nutr. 2013; 67(7):783-5.

16. Klempel MC, Kroeger CM, Varady KA. Alternate day fasting (ADF) with a high-fat diet produces similar weight loss and cardio-protection as ADF with a low-fat diet. Metab. 2013; 62(1):137-43.

17. Wright JL, Plymate S, D'Oria-Cameron A, Bain C, Haugk K, Xiao L, et al. A study of caloric restriction versus standard diet in overweight men with newly diagnosed prostate cancer: a randomized controlled trial. Prostate. 2013; 73(12):1345-51.

Reason for exclusion: Not original article, review article (n = 11)

18. Boling CL, Westman EC, Yancy WS. Comparison of weight loss diets. N Engl J Med. 2009. 26; 360(9): 2247-2248.

19. Brown JE, Mosley M, Aldred S. Intermittent fasting: a dietary intervention for prevention of diabetes and cardiovascular disease? Brit J Diab Vasc Dis. 2013 Mar 1;13(2):68-72.

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21. Champ CE, Simone NL. RE: Calorie or carbohydrate restriction? The ketogenic diet as another option for supportive cancer treatment. Oncologist.2013; 18; 1057.

22. Farsad Naimi A, Nourmohammady M. Effect of Moderate-carbohydrate and Low-calorie Diet on Metabolic Risk Factors, Liver Enzymes and Sonographic Findings in Patients with Non-alcoholic Fatty Liver Disease (NAFLD). Iranian J Endocrinol Metab. 2013; 15(3):262-8.

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24. Imai SI. SIRT1 and caloric restriction: an insight into possible trade-offs between robustness and frailty. Curr Opin Clin Nutr Metab Care. 2009;12(4):350.

25. Jan MM. Fasting. Med Forum Monthly. 2015. 26, 1.

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27. Langland JT. Efficacy of Commercial Weight-Loss Programs. Ann Intern Med. 2015. 16; 398.

28. Patterson RE, Laughlin GA, LaCroix AZ, Hartman SJ, Natarajan L, Senger CM, et al. Intermittent fasting and human metabolic health. J Acad Nutr Diet. 2015;115(8):1203-12.

Reason for exclusion: Intermittent fasting criteria not met (n = 2)

29. Keogh JB, Pedersen E, Petersen KS, Clifton PM. Effects of intermittent compared to continuous energy restriction on short-term weight loss and long-term weight loss maintenance. Clin Obes. 2014 ;4(3):150-6.

30. Klempel MC, Kroeger CM, Bhutani S, Trepanowski JF, Varady KA. Intermittent fasting combined with calorie restriction is effective for weight loss and cardio-protection in obese women. Nutr J. 2012; 11(1):1.

Reason for exclusion: Control intervention criteria not met (n = 5)

31. Langendonk JG, Kok P, Frölich M, Pijl H, Meinders AE. Decrease in visceral fat following diet-induced weight loss in upper body compared to lower body obese premenopausal women. Eur J Intern Med. 2006; 17(7):465-9.

32. Neovius M, Rössner S. Results from a randomized controlled trial comparing two low-calorie diet formulae. Obes Res Clin Pract. 2007; 1(3):165-71.

33. Tapsell L, Batterham M, Huang XF, Tan SY, Teuss G, Charlton K, et al. Short term effects of energy restriction and dietary fat sub-type on weight loss and disease risk factors. Nutr Metab Cardiovas Dis. 2010; 20(5):317-25.

34. Varady KA, Dam VT, Klempel MC, Horne M, Cruz R, Kroeger CM, et al. Effects of weight loss via high fat vs. low fat alternate day fasting diets on free fatty acid profiles. Sci Report. 2015; 5.

35. Wegman MP, Guo MH, Bennion DM, Shankar MN, Chrzanowski SM, Goldberg LA, et al. Practicality of intermittent fasting in humans and its effect on oxidative stress and genes related to aging and metabolism. Rejuvenation Res. 2015;18(2):162-72.

Reason for exclusion: Incorrect study population (n = 9)

36. Albuerque Filho NB, Bellaguarda ERF, Reboucas GM, Felipe TR, Dantas PMS, Knackfuss et al. Concurrent exercise program plus diet intervention on body adiposity and lipid profile in obese adolescents. Gazzetta Medica Italiana Archivio per le Scienze Mrdiche. 2015. 174; 259-266.

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38. König D, Kookhan S, Schaffner D, Deibert P, Berg A. A meal replacement regimen improves blood glucose levels in prediabetic healthy individuals with impaired fasting glucose. Nutr 2014;30(11):1306-9.

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40. Sands RX. Intermittent modified total-fasting in the treatment of obstetric obesity. Am J Obstet Gynecol. 1964; 90(7):885-90.

41. Soeters MR, Lammers NM, Dubbelhuis PF, Ackermans M, Jonkers-Schuitema CF, Fliers E, et al. Intermittent fasting does not affect whole-body glucose, lipid, or protein metabolism. Am J Clin Nutr. 2009; 90(5):1244-51.

42. Teng NI, Shahar S, Manaf ZA, Haron H, Ngah WZ. Fasting calorie restriction improved the quality of dietary intake among aging men in Klang Valley, Malaysia. Pakistan J Nutr. 2013;12(7):607.

43. Teng NI, Shahar S, Manaf ZA, Das SK, Taha CS, Ngah WZ. Efficacy of fasting calorie restriction on quality of life among aging men. Physiology & behavior. 2011 Oct 24;104(5):1059-64.

44. Teng NI, Shahar S, Rajab NF, Manaf ZA, Johari MH, Ngah WZ. Improvement of metabolic parameters in healthy older adult men following a fasting calorie restriction intervention. The Aging Male. 2013; 16(4):177-83.

Reason for exclusion: Not IER intervention (n = 60)

45. Abete I, Parra D, Crujeiras AB, Goyenechea E, Martinez JA. Specific insulin sensitivity and leptin responses to a nutritional treatment of obesity via a combination of energy restriction and fatty fish intake. J Hum Nutr Diet. 2008; 21(6):591-600.

46. Anton SD, Han H, York E, Martin CK, Ravussin E, Williamson DA. Effect of calorie restriction on subjective ratings of appetite. J Hum Nutr Diet. 2009; 22(2):141-7.

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51. Betts JA, Thompson D, Richardson JD, Chowdhury EA, Jeans M, Holman GD, Tsintzas K. Bath Breakfast Project (BBP)-Examining the role of extended daily fasting in human energy balance and associated health outcomes: Study protocol for a randomised controlled trial [ISRCTN31521726]. Trials. 2011;12(1):1.

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