Original Article
OBESITY BIOLOGY AND INTEGRATED PHYSIOLOGY

Obesity

Intermittent Versus Continuous Energy Restriction for Weight Loss and Metabolic Improvement: A Meta-Analysis and Systematic Review

Shasha He, Jiao Wang, Jie Zhang, and Jixiong Xu

Objective: This study aimed to evaluate the effects of intermittent energy restriction (IER; only for 2-3 d/wk) versus continuous energy restriction (CER) on weight loss and metabolic outcomes in adults with overweight or obesity.

Methods: Methods included searching databases from the last decade to December 18, 2019, for randomized controlled trials (RCTs) that assessed weight loss and metabolic outcomes in IER and CER. RevMan version 5.3 software was used for statistical analysis of the data. The effect sizes were expressed as weight mean differences and 95% CI.

Results: This review included 11 RCTs (n = 850). Meta-analysis showed that IER had greater effects on absolute weight loss, the percentage of weight loss, and improving insulin sensitivity than CER. In the subgroup analysis, short-term (2-3 months) intervention ($P < 0.0001$) was associated with weight loss.

Conclusions: This systematic review shows that IER (2-3 d/wk) had greater effects on short-term weight loss than CER and that IER results in comparative metabolic improvements. Furthermore, longer RCTs are needed to validate these findings.

Obesity (2021) **29**, 108-115.

Study Importance

What is already known ?

- Related meta-analyses and narrative reviews have shown that intermittent energy restriction (IER) results in greater weight loss and metabolic improvement than continuous energy restriction (CER).

What does this study add?

- We only included studies with 2-3 d/wk of IER, with similar overall energy restriction compared with the CER group.
- Our study found that absolute weight loss and the percentage of weight loss were greater for IER than for CER in the short term, and there is no evidence to suggest that IER is easier to maintain over the long term.

Introduction

In 2015, the overall prevalence of obesity (BMI ≥ 30 kg/m^2) worldwide was 5.0% (107.7 million) among children and 12.0% (603.7 million) among adults, as reported by the Global Burden of Disease study (1). Weight gain is associated with an increased risk of chronic diseases, such as diabetes mellitus (2), cardiovascular disease (2), chronic kidney disease (3), metabolic syndrome (4), cancer (5), and musculoskeletal disorders (6), which not only have negative physical effects but also increase the financial burden on society. In 2014, it was estimated that the impact of obesity on the global economy was about $2 trillion (US dollars), accounting for 2.8% of the global gross domestic product (7). Weight loss has been shown to improve lipids, blood pressure, and glucose and to decrease the risk of cardiovascular disease and all-cause mortality (8). It has been suggested that patients with overweight or obesity should achieve and maintain >5% weight loss to improve obesity-related conditions (9). Lifestyle interventions, including diet, physical activity, and behavioral therapy, are the foundation for weight loss (10). Pharmacotherapy, medical devices, or bariatric surgery is suitable for patients who do not respond to lifestyle intervention (10). Continuous energy restriction (CER) involving a daily energy deficit of 500 to 750 kcal is recommended as a traditional weight management strategy (11). However, many individuals find it difficult to adhere to CER (12) because energy must be limited every day. Intermittent energy restriction (IER), also called intermittent fasting, has gradually attracted attention and popularity in the past few decades (13). IER typically involves periods of energy restriction (a very low-energy diet, approximately 500-600 kcal/d) alternating with periods of unrestricted food intake (14). The main forms of IER include the 5:2 diet and alternate-day fasting (ADF). The 5:2 diet consists of two consecutive or nonconsecutive fasting days and five ad libitum eating days. ADF is characterized by a fasting day alternating with an ad libitum eating day. Time-restricted feeding (13), which allows individuals to eat within a specific range of time, has also been included in previous systematic reviews and meta-analyses on IER.

To the best of our knowledge, previous reviews of randomized controlled trials (RCTs) (13-17) that included weekly IER, that is, from

Department of Endocrine and Metabolism, First Affiliated Hospital of Nanchang University, Nanchang, People's Republic of China. Correspondence: Jixiong Xu (xujixiong@163.com)

 Received: 22 December 2019; **Accepted:** 13 August 2020; **Published online 21 December 2019. doi:10.1002/oby.23023**

one up to six fasting days per week or time-restricted feeding, have concluded that IER and CER achieved alternative and comparative effects in promoting weight loss and metabolic improvement. Additionally, narrative reviews have assessed both weight loss (18) and metabolic markers (19). However, previous meta-analyses did not consider whether the total energy restriction was similar between the IER and CER diets. Moreover, an overall evaluation of the impact of IER (the 5:2 diet and ADF) versus CER regimens on weight loss, multiple metabolic variables, percentage of weight loss consisting of fat mass (FM), and percentage of weight loss consisting of fat-free mass (FFM), as well as inflammation factors, is at present lacking.

The aim of this systematic review and meta-analysis is to compare IER with CER in terms of their impact on weight loss and metabolic outcomes in patients with overweight or obesity.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses(PRISMA) guidelines in the reporting of this study (20).

Search strategy and selection criteria

PubMed, Web of Science, and the Cochrane Library were searched for RCTs that evaluated the effects of IER (2-3 d/wk) versus CER on weight loss and metabolic outcomes in individuals with overweight or obesity. The search was performed on December 18, 2019, and it included papers published in the previous 10 years. The language was English. The search strategy is available in Supporting Information Table S1.

We included trials with the following characteristics: (a) RCTs, (b) 0% to 30% of energy intake on the fasting day, with a maximum of 800 kcal/d; (c) intermittent regimens including the 5:2 diet or ADF; (d) CER group inclusion; (e) RCT duration ≥ 2 months; (f) participants with overweight or obesity (BMI ≥ 25 kg/m^2) who were ≥18 years of age; (g) inclusion of weight loss or percentage of weight loss as one of the study outcomes, and (h) similarity between IER and CER regarding the overall prescribed energy restriction. We excluded case reports, meta-analyses, reviews, animal trials, and trials that did not advise equivalent calorie restriction within IER and CER. The ADF group achieved a 376-kcal/d greater energy deficit in the study by Catenacci et al. (21), so it was excluded.

Data collection and risk-of-bias assessment

Two authors separately searched and reviewed the abstracts according to their inclusion and exclusion criteria. Any disagreements were resolved by consulting the senior investigator. The following information was extracted: (a) first author name and year of publication, (b) inclusion criteria of participants, (c) RCT duration, (d) number of subjects enrolled in each group, (e) type of dietary intervention, (f) primary and secondary outcomes, (g) side effects, and (h) attrition rate.

Two authors independently assessed the risk of bias using the Cochrane Collaboration tool (22). Six domains of potential risk of bias were assessed; these included selection bias (assessment of random sequence generation and allocation concealment), performance bias (blinding of participants and researchers), detection bias (blinding of outcome assessment), attrition bias (reporting of incomplete outcomes), reporting bias (selective reporting of outcomes), and other risks of bias, such as confounding factors. All RCTs were assessed as having low, high, or unclear risk of bias. Any disagreements were resolved by consulting the senior investigator.

Data synthesis and statistical analysis

The effects of the RCTs were expressed as weight mean differences (WMDs), and the CI was 95%. The random-effects model with inverse-variance methods was performed for meta-analyses. Heterogeneity was identified by using the I^2 test (23), and when P was greater than 0.1 and I^2 was less than 50%, low heterogeneity was considered to exist between RCTs. Sensitivity analysis was conducted by removing each study one by one, and then the effect size was merged again to evaluate the stability and reliability of the meta-analysis results. The intervention duration (short-term, <6 months vs. long-term, ≥6 months) and diabetes status (diabetes vs. nondiabetes vs. prediabetes) were analyzed by subgroup. All analyses were performed with RevMan version 5.3 (Cochrane, London, United Kingdom).

Results

Literature search and study characteristics

The total published literature search identified 3,754 records, and a total of 11 RCTs (24-34) were included (n = 850) for the systematic review and meta-analysis. The flow diagram is shown in Figure 1.

The main characteristics of this meta-analysis are summarized in Table 1. Eight RCTs (24-31) compared the 5:2 diet with CER (n = 707), and three RCTs (32-34) compared ADF with CER (n = 143). Three RCTs (26,31,32) included individuals with obesity, and others included individuals with overweight or obesity. Two RCTs (24,25) included patients with type 2 diabetes mellitus (T2DM), and one RCT (30) included participants with more than one additional metabolic-syndrome component besides waist circumference (WC) ≥ 90/80 cm (male/female). A large number of included participants were women, with three of the trials having participants who were all women (27,28,34) and one trial having participants who were all men (26). Interventions ranged from 2 months (34) to 12 months (25,29) in duration across studies, among which there were five RCTs (24,28,30,32,34) with short-term interventions and six RCTs (25-27,29,31,33) with long-term interventions. There were five RCTs (24,26,27,32,34) that only conducted an intervention phase. The timing of the weight maintenance or follow-up phase ranged from 1 month (28) to 12 months (35) after the intervention phase. The publication date ranged from 2011 (27) to 2019 (29,34). The RCTs were performed in the United Kingdom (27,28), Germany (30), Australia (24-26,29,34), the United States (33), and Norway (31,32), respectively.

Dietary intervention

Participants received dietary education before the experiment was conducted and provided their electronic scales to ensure the accuracy of energy intake. The IER groups restricted energy intake by 400 to 600 kcal or by 25% to 30% on fasting days and were allowed ad libitum intake or energy according to needs on feeding days. Participants in the intermittent energy and carbohydrate restriction group were asked not only to restrict energy intake but also restrict their intake of carbohydrates to 40 g on fasting days (28). The ADF group (33) required 125% of energy needs on feeding days. All studies advised following healthy eating practices on feeding days. The CER groups were prescribed to

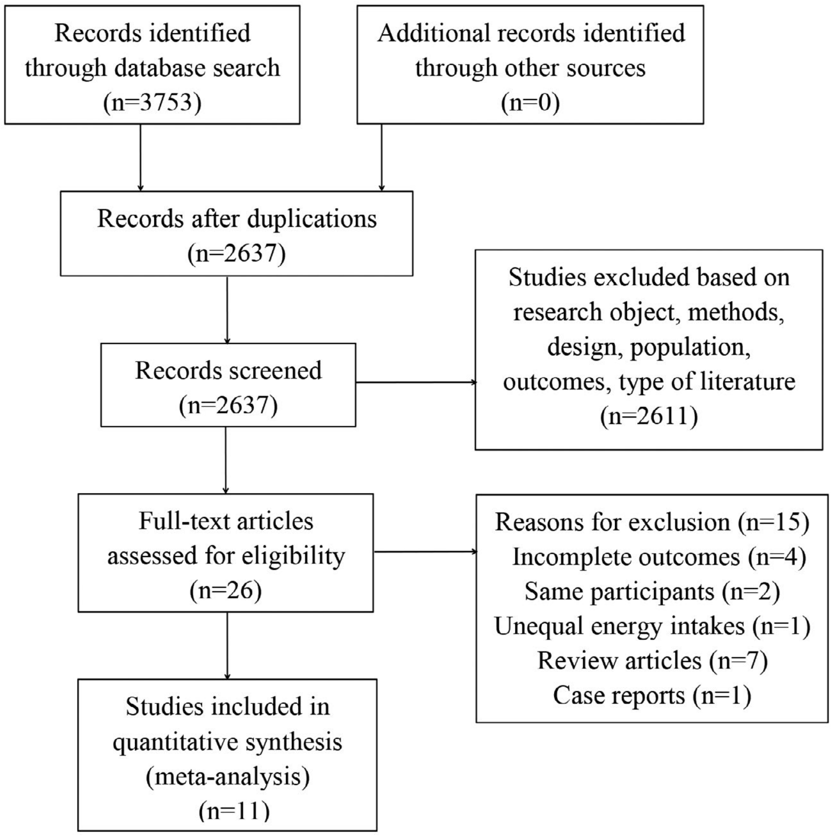

Figure 1 Flow diagram of study selection.

follow a 400- to 600-kcal daily reduction or a 20% (30) to 33% (32) energy restriction. The principle of energy composition was in accordance with the Mediterranean-type diet.

Risk-of-bias assessment for included RCTs

All RCTs had a high risk of bias because of performance bias. The dropout rates were similar in both groups. Intention-to-treat analyses were performed in 9 of 11 studies (24-28,30-32,34). For selection, reporting, attrition, and other biases, all RCTs had either low or unclear risk (Figure 2). The grades of recommendations assessment, development and evaluation assessment is presented in Supporting Information Table S2. Overall, the evidence comparing IER with CER was of low quality.

Meta-analysis

Weight loss. Eleven RCTs (24-34) reported weight loss, and mean weight loss in almost studies was >5%. Absolute weight loss (WMD: −0.95 kg; 95% CI: −1.63 to −0.27; *P*=0.01) (Figure 3) and percentage of weight loss (WMD: −1%; 95% CI: −2 to 0; *P*= 0.02) were greater for IER than for CER. Subgroup analyses showed that short-term interventions with IER were associated with increased weight loss (Figure 3). Subgroup analyses of the percentage of weight loss showed results similar to those of the absolute values. Pooled data from four RCTs (28,30,33,35) showed no significant effect of IER on weight loss from baseline to the weight maintenance or follow-up phase (Supporting Information Figure S1). The result was the same in the sensitivity analysis.

Other anthropometric measures. Eight RCTs (24,25,27-29,32-34) reported changes in FM and FFM, and four RCTs (26-28,31) reported changes in WC. The percentage lost as FFM ranged from between 14% (29) and 37% (25) to between 17% (33) and 31% (25) in the IER and CER groups in our review, respectively. FM and FFM were assessed in different ways, such as body independence analysis (27,28), dual x-ray absorptiometry (24,25,29,33,34), and air-displacement plethysmography (32). This meta-analysis showed no significant reduction in FM, FFM, and WC (Supporting Information Figures S2A-S2B and Supporting Information Figure S3). Subgroup analysis showed that short-term interventions with IER were associated with a reduction in FM and FFM (Supporting Information Figure S2B). However, this reduction did not differ between groups when expressed as the percentage of weight lost rather than as the absolute reduction.

Changes in insulin sensitivity and associated markers. For the population without diabetes, five RCTs (27,28,30,33,34) reported changes in the homeostatic model assessment of insulin resistance (HOMA-IR) and fasting insulin, and six RCTs (26-28,30,33,34) reported changes in fasting glucose. Four RCTs (24,25,27,30) analyzed the changes of glycated hemoglobin, two of which (24,25) were studies of people with diabetes. Fasting glucose and glycated hemoglobin did

TABLE 1 Characteristics of the included studies

Author, year (reference)	Duration	Study group	Samples (F/M)	BMI (kg/m²)	Age (y)	Weight (kg)	FM; FFM (kg)	Fasting glucose (mmol/L); HbA_{1c} (%)	Fasting insulin (μU/mL); HOMA-IR (mmol/L × μU/mL)	Total cholesterol (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)	TG (mg/dL)
Carter, 2016 (24)	3 mo	5:2 (2 d/wk): 400-600 kcal on fasting days	17/14	35 ± 5	61 ± 8	99 ± 16	38 ± 9; 55 ± 11	ND; 7.2 ± 1.3	ND	ND	ND	ND	ND
		CER: 1200-1500 kcal/d	16/16	36 ± 5	62 ± 9	99 ± 15	40 ± 11; 54 ± 9	ND; 7.5 ± 1.4	ND	ND	ND	ND	ND
Carter, 2018 (25)	12 mo	5:2 (2 d/wk): 500-600 kcal on fasting days	39/31	35 ± 6	61 ± 9	100 ± 19	40 ± 9; 54 ± 10	ND; 7.2 ± 1.2	ND	179 ± 48	47 ± 14	107 ± 43	129 ± 62
		CER: 1200-1500 kcal/d	38/29	37 ± 6	61 ± 9	102 ± 17	42 ± 9; 54 ± 10	ND; 7.5 ± 1.4	ND	195 ± 64	46 ± 17	116 ± 50	168 ± 127
Conley, 2018 (26)	6 mo	5:2 (2 d/wk): 600 kcal on fasting days	0/11	33 ± 2	68 ± 3	99 ± 8	ND	6.0 ± 1.5; ND	ND	151 ± 35	45 ± 12	77 ± 31	168 ± 53
		CER: 600 kcal/d less than needs	0/12	36 ± 4	67 ± 4	107 ± 17	ND	6.1 ± 1.7; ND	ND	166 ± 39	46 ± 12	98 ± 35	212 ± 150
Harvie, 2011 (27)	6 mo	5:2 (2 d/wk): 25% energy intake on fasting days	53/0	31 ± 5	40 ± 4	82 (78-85)	34 (31-36); 48 (46-49)	4.8 (4.7-4.9); ND	7 (6-8); 1.5 (1.3-1.8)	197 (189-197)	58 (54-58)	119 (112-127)	106 (88-124)
		CER: 25% energy restriction every day	54/0	31 ± 5	40 ± 4	84 (80-89)	35 (32-39)	4.8 (4.6-4.9)	7 (6-9)	200 (193-208)	62 (54-66)	119 (108-127)	115 (97-124)
Harvie, 2013 (28)	3 mo	5:2 (2 d/wk): 30% energy intake on fasting days	37/0	30 ± 4	46 ± 8	79 (75-84)	31 (28-34); 49 (46-51)	4.9 (4.7-5.0); 5.3 (5.2-5.4)	6 (5-8); 1.6 (1.3-1.9)	204 (191-229)	50 (49-59)	128 (116-139)	88 (75-102)
		CER: 25% energy restriction every day	40/0	32 ± 6	48 ± 8	86 (81-91)	36 (32-39); 50 (48-52)	5.0 (4.8-5.1)	7 (6-9)	205 (193-218)	51 (48-55)	129 (118-139)	97 (83-111)
Headland, 2019 (29)	12 mo	5:2 (2 d/wk): 500/600 kcal (F/M) on fasting days	97/21	33 ± 5	48 ± 15	90 ± 17	42 ± 11; 48 ± 9	5.6 ± 0.6; ND	ND	224 ± 43	58 ± 19	155 ± 39	115 ± 80
		CER: 1000-1200 kcal/d (F/M)	85/19	33 ± 5	52 ± 13	92 ± 17	43 ± 11; 50 ± 10	5.5 ± 0.6; ND	ND	213 ± 43	54 ± 15	151 ± 43	115 ± 71
Schübel, 2019 (30)	3 mo	5:2 (2 d/wk) : 25% energy intake on fasting days	24/25	32 ± 4	49 ± 9	96 ± 16	ND	5.2 ± 0.4; ND	12 ± 5 2.7 ± 1.3	205 ± 31	54 ± 14	125 ± 22	130 ± 84
		CER: 20% energy restriction every day	24/25	31 ± 4	51 ± 8	93 ± 16	ND	5.2 ± 0.4; ND	13 ± 7; 3.0 ± 1.7	203 ± 39	56 ± 16	123 ± 32	121 ± 66
Sundfør, 2018 (31)	6 mo	5:2 (2 d/wk): 400/600 kcal (F/M) energy intake on fasting days	26/28	35 ± 4	50 ± 10	109 ± 16	ND	5.8 ± 1.2; 5.6 ± 0.7	ND	192 ± 35	47 ± 13	126 ± 32	162 ± 73
		CER: 400/600 kcal/d (F/M) less than needs	30/28	35 ± 4	48 ± 12	108 ± 16	ND	5.7 ± 0.7; 5.5 ± 0.5	ND	197 ± 34	45 ± 10	133 ± 32	137 ± 60
Coutinho, 2017 (32)	3 mo	ADF (3 d/wk): 550-660 kcal on fasting days	10/4	36 ± 3	39 ± 11	107 ± 14	47 ± 8; 60 ± 12	ND	ND	ND	ND	ND	ND
		CER: 33% energy restriction every day	12/2	35 ± 4	39 ± 9	98 ± 13	43 ± 8 55 ± 9	ND	ND	ND	ND	ND	ND
Hutchison, 2019 (33)	2 mo	ADF (3 d/wk): 30% of baseline energy restriction per week	25/0	32 ± 1	49 ± 2	89 ± 3	ND	4.9 ± 0.1; ND	19.5 ± 1.5; ND	186 ± 4	54 ± 4	112 ± 4	106 ± 9
		CER: 30% energy restriction every day	26/0	33 ± 1	51 ± 2	88 ± 3	ND	4.9 ± 0.1; ND	15.5 ± 1.3; ND	189 ± 4	54 ± 4	116 ± 4	115 ± 9

TABLE 1 (continued).

Author, year (reference)	Duration	Study group	Samples (F/M)	BMI (kg/m^2)	Age (y)	Weight (kg)	FM; FFM (kg)	Fasting glucose (mmol/L); HbA_{1c} (%)	Fasting insulin (μU/mL); HOMA-IR (mmol/L × μU/mL)	Total cholesterol (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)	TG (mg/dL)
Trepanowski, 2017 (34)	6 mo	ADF (3 d/wk): 25% energy intake on fasting days	30/4	34 ± 4	40 ± 10	95 ± 13	38 ± 7 55 ± 9	5.1 ± 0.7; ND	16 ± 14; 3.7 ± 3.6	188 ± 35	57 ± 14	111 ± 13	101 ± 59
		CER: 25% energy restriction every day	29/6	35 ± 4	43 ± 12	101 ± 16	40 ± 7; 58 ± 12	5.1 ± 1; ND	20 ± 18; 5.1 ± 5.9	184 ± 35	53 ± 11	112 ± 31	97 ± 27

Participants in the IER groups attended final appointments after at least one habitual eating day in an attempt to avoid any potential acute effects.
ADF, alternate-day fasting; CER, continuous energy restriction; F, female; FM, fat mass; FFM, fat-free mass; HbA_{1c}, glycated hemoglobin; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; M, male; NA, no data; TG, triglycerides.

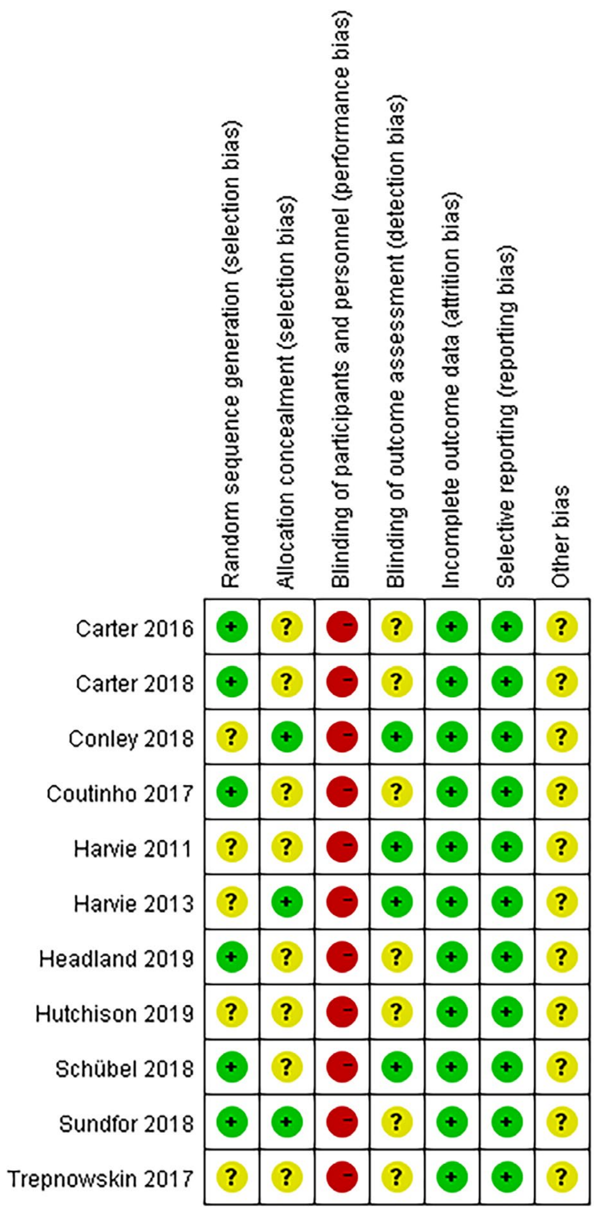

Figure 2 Risk-of-bias graph. [Color figure can be viewed at wileyonlinelibrary.com]

not change significantly over the course of the studies in either group (Supporting Information Figures S4A and S4D)

The heterogeneity of HOMA-IR and fasting insulin was high, and it decreased significantly after excluding one RCT (30). The sensitivity analysis showed a significant reduction in fasting insulin (WMD: −1.14 μU/mL; 95% CI: −1.81 to −0.47; $P = 0.0008$) and HOMA-IR (WMD: −0.22 mmol/L × μU/mL; 95% CI: −0.40 to −0.04; $P = 0.02$) with IER (Supporting Information Figures S4B-S4C). Two RCTs (27,28), which included only women with overweight or obesity, suggested that fasting insulin and HOMA-IR in the IER groups were significantly lower than those in CER groups. However, when Schübel et al. (30) conducted subgroup analysis by sex, it was not found that there was a significant

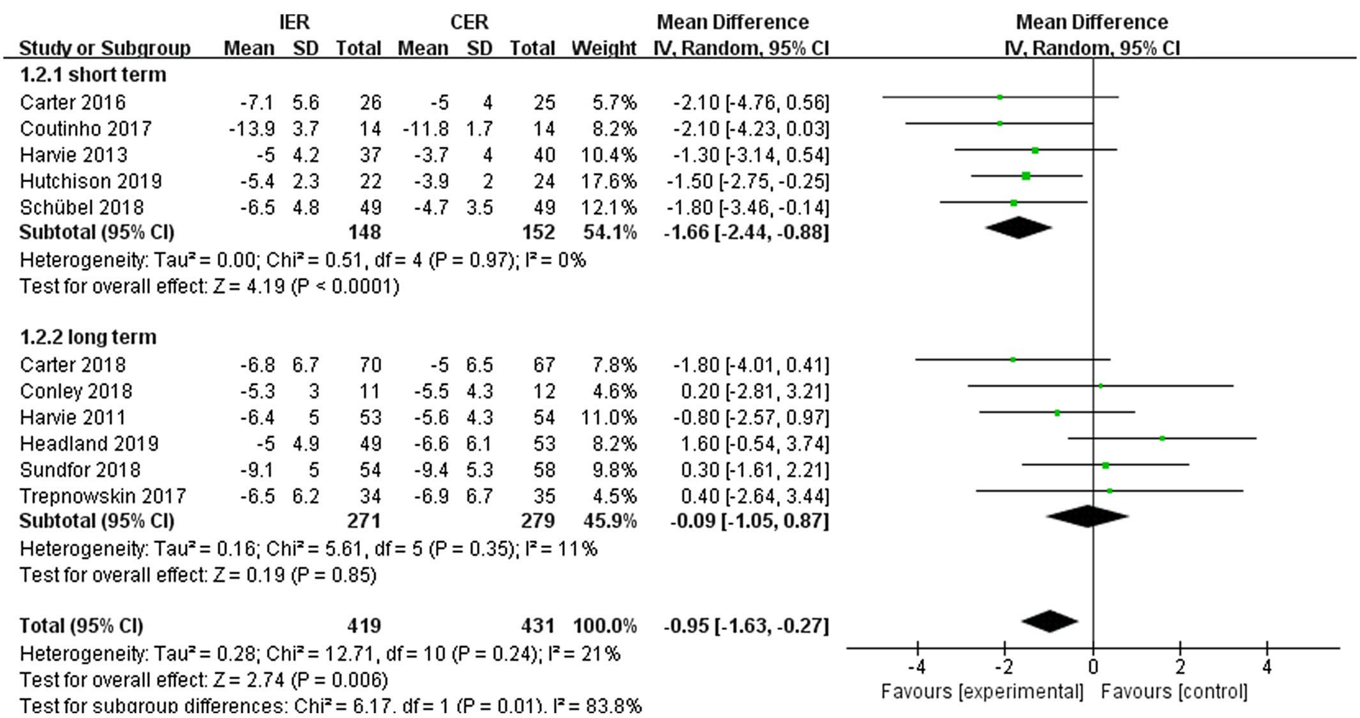

Figure 3 Meta-analysis of the effect of intermittent energy restriction (IER) versus continuous energy restriction (CER) on weight loss (subgroups by intervention). [Color figure can be viewed at wileyonlinelibrary.com]

decrease in fasting insulin and HOMA-IR in female participants in the IER group.

Cardiovascular risk markers. Most studies did not show significant effects of IER on lipids (25-31,33,34), systolic blood pressure (26-28,31,33,34), diastolic blood pressure (26,27,31,33,34), or C-reactive protein (CRP) (27,30,31,33,34). Trepanowski et al. (33) found that the level of high-density lipoprotein cholesterol increased significantly in the ADF group after 6 months of intervention, and there was no statistical difference between the two groups after 12 months of intervention. Hutchison et al. (34) revealed that lipids in the ADF group were significantly lower than those in the CER group after 8 weeks of intervention. Moreover, Conley et al. (26) showed that the two interventions can significantly reduce systolic blood pressure, whereas the reduction in diastolic blood pressure was not significant.

Safety. No major adverse events were reported in either group (Supporting Information Table S3). We found that the probability of side effects was small, but they were more likely to occur in the IER groups. In the CER groups (24,25,27,28,30,31), 2% to 7% reported mild nausea, dizziness, feeling cold, constipation, lack of concentration, being preoccupied with food, mood swings or bad temper, mild headache, and decreased energy levels. Of participants in the 5:2 diet, 27.3% reported constipation (26), 11% reported dizziness (28), 54.5% reported hunger (27), 20% reported mild headache (28), 2% reported temporary sleep disturbance (28), and 5% reported bad breath on energy-restricted days (25). The hunger could be improved over time for most participants, but two participants from the IER group withdrew from the study because of headache brought on by hunger (22). Hypoglycemia (<4 mmol/L) and hyperglycemia (>8 mmol/L) occurred in 12% to 17% and 6% to 22%, respectively, because of diet and medication adjustment in patients with diabetes, with no differences between groups (24,25). When participants, especially those with T2DM, begin their clinical trials, specific attention should be paid to medication adjustment, frequency of glucose monitoring, and fluid intake to prevent hypoglycemic events and hypotension (36). Hoddy et al. (37) found that depression and binge eating decreased after 8 weeks of ADF, with no exacerbating disordered eating.

Discussion

Summary of main findings

There is a marginally greater loss of weight but a higher loss of FFM and no difference in the percentage lost as FFM with short-term IER (2-3 d/wk). Weight loss has been shown to reduce all-cause, cardiovascular, and cancer mortality in clinical studies. Sensitivity analysis showed a significant reduction in fasting insulin with IER.

Effects of IER on weight loss

Our included studies attempted to match for calorie restriction with IER and CER, not including time-restricted feeding. The long-term effects on weight loss with IER versus CER were consistent with findings of previous reviews (11-16). The short-term effects of IER were superior to those of CER. A median of 59 days was required in IER, compared with 73 days in CER, to achieve 5% weight loss in the Antoni et al. trial (38). However, the mechanistic reason for this remains unclear. A greater adherence and spontaneous energy restriction on feeding days with IER during the short term may play a role. Patients with overweight or obesity lose more than 5% of weight, which can significantly reduce blood lipids, blood sugar, and blood pressure.

Other anthropometric measures

Our results showed a significant reduction in FFM in the short term, but this reduction did not differ significantly between groups when expressed as the percentage of weight lost. Harris et al. (14) reported a significant reduction in FM for IER in comparison with CER, but Cioffi et al. (13) and Roman et al. (16) found no significant difference between groups. Roman et al. (16) found that FFM was significantly lower with IER, yet there was no significant difference in the studies by Cioffi et al. (13) and Harris et al. (14). Although body independence analysis is relatively simple, quick, relatively inexpensive, and noninvasive, this method is prone to error when there are fluctuations in body water content (39). Furthermore, it is likely to overestimate reductions in FFM in comparison with dual x-ray absorptiometry because of dehydration caused by ketone production during fasting (40), so participants were asked to drink water and empty their bladder before the weight and impedance measurements (28). Bhutani et al. (41) stated that FFM can be retained in the combination of ADF plus moderate-intensity exercise. Further research is needed to verify whether resistance training can effectively slow or stop the loss of FFM typically seen in individuals following energy restriction (42).

Effects of IER on fasting insulin and related values

Sensitivity analysis showed a significant reduction in fasting insulin and HOMA-IR with IER in the population without diabetes, and the statistical heterogeneity of effects across RCTs in fasting insulin and HOMA-IR were high. One possible explanation may be that the two energy-restricted days were consecutive in the Harvie et al. trials (27,28) but were nonconsecutive in the Schübel et al. trial (30). The result was in line with those of the previous meta-analyses (13,14). Although there was a significant increase in insulin sensitivity, blood glucose, blood pressure, and blood lipids between the two groups did not improve significantly. Therefore, it was considered that the metabolic improvement between the two diets was similar, and it is necessary to further expand the sample size and intervention duration in order to obtain more abundant results. Studies have shown that reducing fasting insulin in the circulatory system by 25% to 34% can significantly increase insulin sensitivity, reduce fasting blood glucose, and prolong the life of mice (43). The increase in insulin sensitivity is thought to be related to the increase of adenosine monophosphate kinase during fasting (44). Moreover, it was found that beta islet cells can regenerate during fasting (45). On the basis of these data, we guess that it may be able to prevent or slow diabetic disease (46).

Cardiovascular risk markers

Our study found that IER and CER had similar effects on improving blood lipids, blood pressure, and WC, as was found in previous studies (13-16). Because many participants had normal blood lipids and blood pressure at baseline, it was not surprising that most metabolic risk indicators were unchanged. The CRP level was considered as a marker of inflammation and a predictor of cardiovascular risk (47). There were no data on CRP changes in previous meta-analyses or reviews, and our meta-analysis showed no significant difference between groups.

Strengths and limitations

This study is unique in that it focused on 5:2 and ADF diets, and not on time-restricted feeding, and compared these with matched CER. In addition, the various sensitivity analyses we have carried out included short- and long-term studies. Moreover, we assessed the reduction of weight, FM, and FFM not only in terms of absolute values but also in terms of relative values. The limited follow-up, small sample sizes, high dropout rates, high risk of performance bias, enrollment of metabolically healthy individuals or well-controlled patients with T2DM and overweight or obesity, different methods of measuring FM and FFM, and other methodological problems limit the generalizability of these results. Furthermore, that many of the serum markers were measured immediately after restricted days may be linked to the potential acute effects.

Conclusion

This systematic review shows that IER is a viable alternative to CER for many patients. Further RCTs with longer follow-up are required to draw solid conclusions.O

Funding agencies: This study was supported by grants from the National Natural Science Funds of China (81760168) and the Jiangxi Provincial Graduate Innovation Foundation of China (YC2018-S101).

Disclosure: The authors declared no conflict of interest.

Author contributions: JX participated in the conception and design of the study, manuscript writing, and revision. SH participated in the data collection, data analysis, interpretation of the findings of the study, manuscript writing, and revision. JW and JZ designed the study and contributed to the introduction and the discussion. All authors read and approved the final manuscript.

Supporting information: Additional Supporting Information may be found in the online version of this article.

References

1. Afshin A, Forouzanfar MH, Reitsma MB, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med* 2017;377:13-27.
2. Singh GM, Danaei G, Farzadfar F, et al. The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. *PLoS One* 2013;8:e65174. doi:10.1371/journal.pone.0065174
3. Michishita R, Matsuda T, Kawakami S, et al. Long-term body weight gain after maturity is associated with the incidence of chronic kidney disease (CKD), independent of current body weight, in middle-aged and older men. *J Epidemiol* 2019;29:213-219.
4. Hashimoto Y, Hamaguchi M, Fukuda T, Obora A, Kojima T, Fukui M. Weight gain since age of 20 as risk of metabolic syndrome even in non-overweight individuals. *Endocrine* 2017;58:253-261.
5. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body fatness and cancer-viewpoint of the IARC working group. *N Engl J Med* 2016;375:794-798.
6. Messier SP. Weight gain and incident knee osteoarthritis in asymptomatic at risk patients: a step closer to primary prevention trials. *Osteoarthritis Cartilage* 2015;23:501-502.
7. Tremmel M, Gerdtham UG, Nilsson PM, Saha S. Economic burden of obesity: a systematic literature review. *Int J Environ Res Public Health* 2017;14:435. doi:10.3390/ijerph14040435
8. Ma C, Avenell A, Bolland M, et al. Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis. *BMJ* 2017;359:j4849. doi:10.1136/bmj.j4849
9. Ramage S, Farmer A, Eccles KA, McCargar L. Healthy strategies for successful weight loss and weight maintenance: a systematic review. *Appl Physiol Nutr Metab* 2014;39:1-20.
10. Kahan S. Overweight and obesity management strategies. *Am J Manag Care* 2016;22 (7 suppl):s186-s196.
11. Ryan D, Heaner M. Guidelines (2013) for managing overweight and obesity in adults. Preface to the full report. *Obesity (Silver Spring)* 2014;22(suppl 2):S1-S3.

12. Middleton KR, Anton SD, Perri MG. Long-term adherence to health behavior change. *Am J Lifestyle Med* 2013;7:395-404.
13. Cioffi I, Evangelista A, Ponzo V, et al. Intermittent versus continuous energy restriction on weight loss and cardiometabolic outcomes: a systematic review and meta-analysis of randomized controlled RCTs. *J Transl Med* 2018;16:371. doi:10.1186/s12967-018-1748-4
14. Harris L, Hamilton S, Azevedo LB, et al. Intermittent fasting interventions for treatment of overweight and obesity in adults: a systematic review and meta-analysis. *JBI Database System Rev Implement Rep* 2018;16:507-547.
15. Headland M, Clifton PM, Carter S, Keogh JB. Weight-loss outcomes: a systematic review and meta-analysis of intermittent energy restriction RCTs lasting a minimum of 6 months. *Nutrients* 2016;8:354. doi:10.3390/nu8060354
16. Roman YM, Dominguez MC, Easow TM, Pasupuleti V, White CM, Hernandez AV. Effects of intermittent versus continuous dieting on weight and body composition in obese and overweight people: a systematic review and meta-analysis of randomized controlled RCTs. *Int J Obes (Lond)* 2019;43:2017-2027.
17. Harris L, McGarty A, Hutchison L, Ells L, Hankey C. Short-term intermittent energy restriction interventions for weight management: a systematic review and meta-analysis. *Obes Rev* 2018;19:1-13.
18. Antoni R, Johnston KL, Collins AL, Robertson MD. Effects of intermittent fasting on glucose and lipid metabolism. *Proc Nutr Soc* 2017;76:361-368.
19. Harvie MN, Howell T. Could intermittent energy restriction and intermittent fasting reduce rates of cancer in obese, overweight, and normal-weight subjects? A summary of evidence. *Adv Nutr* 2016;7:690-705.
20. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of RCTs that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6:e1000100. doi:10.1371/journal.pmed.1000100
21. Catenacci VA, Pan Z, Ostendorf D, et al. A randomized pilot study comparing zero-calorie alternate-day fasting to daily caloric restriction in adults with obesity. *Obesity (Silver Spring)* 2016;24:1874-1883.
22. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised RCTs. *BMJ* 2011;343:d5928. doi:10.1136/bmj.d5928
23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-560.
24. Carter S, Clifton PM, Keogh JB. The effects of intermittent compared to continuous energy restriction on glycaemic control in type 2 diabetes; a pragmatic pilot trial. *Diabetes Res Clin Pract* 2016;122:106-112.
25. Carter S, Clifton PM, Keogh JB. Effect of intermittent compared with continuous energy restricted diet on glycemic control in patients with type 2 diabetes: a randomized noninferiority trial. *JAMA Netw Open* 2018;1:e180756. doi:10.1001/jamanetworkopen.2018.0756
26. Conley M, Le Fevre L, Haywood C, Proietto J. Is two days of intermittent energy restriction per week a feasible weight loss approach in obese males? A randomised pilot study. *Nutr Diet* 2018;75:65-72.
27. Harvie MN, Pegington M, Mattson MP, et al. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized RCT in young overweight women. *Int J Obes (Lond)* 2011;35:714-727.
28. Harvie M, Wright C, Pegington M, et al. The effect of intermittent energy and carbohydrate restriction v. daily energy restriction on weight loss and metabolic disease risk markers in overweight women. *Br J Nutr* 2013;110:1534-1547.
29. Headland ML, Clifton PM, Keogh JB. Effect of intermittent compared to continuous energy restriction on weight loss and weight maintenance after 12 months in healthy overweight or obese adults. *Int J Obes (Lond)* 2019;43:2028-2036.
30. Schübel R, Nattenmuller J, Sookthai D, et al. Effects of intermittent and continuous calorie restriction on body weight and metabolism over 50 wk: a randomized controlled trial. *Am J Clin Nutr* 2018;108:933-945.
31. Sundfør TM, Svendsen M, Tonstad S. Effect of intermittent versus continuous energy restriction on weight loss, maintenance and cardiometabolic risk: a randomized 1-year trial. *Nutr Metab Cardiovasc Dis* 2018;28:698-706.
32. Coutinho SR, Halset EH, Gasbakk S, et al. Compensatory mechanisms activated with intermittent energy restriction: a randomized control trial. *Clin Nutr* 2018;37:815-823.
33. Trepanowski JF, Kroeger CM, Barnosky A, et al. Effect of alternate-day fasting on weight loss, weight maintenance, and cardioprotection among metabolically healthy obese adults: a randomized clinical trial. *JAMA Intern Med* 2017;177:930-938.
34. Hutchison AT, Liu B, Wood RE, et al. Effects of intermittent versus continuous energy intakes on insulin sensitivity and metabolic risk in women with overweight. *Obesity (Silver Spring)* 2019;27:50-58.
35. Carter S, Clifton PM, Keogh JB. The effect of intermittent compared with continuous energy restriction on glycaemic control in patients with type 2 diabetes: 24-month follow-up of a randomised noninferiority trial. *Diabetes Res Clin Pract* 2019;151:11-19.
36. Grajower MM, Horne BD. Clinical management of intermittent fasting in patients with diabetes mellitus. *Nutrients* 2019;11:873. doi:10.3390/nu11040873
37. 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;14:44. doi:10.1186/s12937-015-0029-9
38. Antoni R, Johnston KL, Collins AL, Robertson MD. Intermittent v. continuous energy restriction: differential effects on postprandial glucose and lipid metabolism following matched weight loss in overweight/obese participants. *Br J Nutr* 2018;119:507-516.
39. Schoenfeld BJ, Nickerson BS, Wilborn CD, et al. Comparison of multifrequency bioelectrical impedance vs. dual-energy x-ray absorptiometry for assessing body composition changes after participation in a 10-week resistance training program. *J Strength Cond Res* 2020;34:678-688.
40. Sadikot S, Jothydev K, Zargar AH, Ahmad J, Arvind SR, Saboo B. Clinical practice points for diabetes management during RAMADAN fast. *Diabetes Metab Syndr* 2017;11(suppl 2):S811-S819.
41. Bhutani S, Klempel MC, Kroeger CM, Trepanowski JF, Varady KA. Alternate day fasting and endurance exercise combine to reduce body weight and favorably alter plasma lipids in obese humans. *Obesity (Silver Spring)* 2013;21:1370-1379.
42. Tinsley GM, Willoughby DS. Fat-free mass changes during ketogenic diets and the potential role of resistance training. *Int J Sport Nutr Exerc Metab* 2016;26:78-92.
43. Templeman NM, Flibotte S, Chik J, et al. Reduced circulating insulin enhances insulin sensitivity in old mice and extends lifespan. *Cell Rep* 2017;20:451-463.
44. Anton SD, Moehl K, Donahoo WT, et al. Flipping the metabolic switch: understanding and applying the health benefits of fasting. *Obesity (Silver Spring)* 2018;26:254-268.
45. Cheng CW, Villani V, Buono R, et al. Fasting-mimicking diet promotes Ngn3-driven beta-cell regeneration to reverse diabetes. *Cell* 2017;168:775-788.
46. Barnosky AR, Hoddy KK, Unterman TG, et al. Intermittent fasting vs daily calorie restriction for type 2 diabetes prevention: a review of human findings. *Transl Res* 2014;164:302-311.
47. Choi J, Joseph L, Pilote L. Obesity and C-reactive protein in various populations: a systematic review and meta-analysis. *Obes Rev* 2013;14:232-244.