

Is Intermittent Fasting Better Than Continuous Energy Restriction for Adults with Overweight and Obesity?

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Abstract: As a popular weight management intervention, intermittent fasting (IF) has been widely applied to the treatment of overweight and obesity in adults. This review describes the different forms and implementation protocols of IF and their effects on body weight, body composition, cardiometabolic risk factors and other diseases. The existing evidence suggests that IF is as effective as continuous energy restriction and may be a feasible and effective approach to weight loss.

Keywords: overweight, obesity, intermittent fasting, continuous energy restriction, weight management

Introduction

Overweight and obesity have become global health issues. In 2016, China had the highest number of adults with overweight and obesity at 600 million, with rates of 34.3% and 16.4%, respectively.^{1,2} Overweight and obesity are major risk factors for and increase the risk of all-cause mortality from chronic diseases such as cardiovascular disease, diabetes, and cancer, reducing life expectancy by five to twenty years.³ Weight loss can significantly diminish the risk of developing overweight and obesity. Two popular weight management strategies are Continuous Energy Restriction (CER)⁴ and Intermittent Fasting (IF).⁵ The former achieves weight loss through continuous restriction of daily energy intake, but the resultant hunger reduces adherence to the regimen, which can lead to greater weight regain once the restriction on intake is removed.⁶ As a new method to prevent and treat obesity, IF restricts calorie intake through alternate fasting and free eating, which can also achieve weight loss, improve metabolic status, and enhance the immune system and cognitive function in a relatively short period of time in a manner similar to CER.⁷ However, the beneficial effects of IF on weight loss, body composition, and cardiovascular health in adults with overweight and obesity with diverse characteristics are controversial, and may be influenced by factors such as comorbidities and the duration of fasting. This review examines the different strategies and protocols used for IF, through the comparison between the effects of IF and CER on weight loss, with the aim of providing a reference for its broader clinical application for weight loss in adults with overweight and obesity.

Common Forms of IF

Alternate-Day Fasting (ADF)

ADF alternates between fasting and free-eating days to achieve weight loss. On fasting days, individuals consume only 25% of their basal calories (approximately 500 kcal), whereas on eating days, there is no restriction on calorie intake.⁸ Individuals with overweight and obesity can lose 3%–7% of their body weight after two to three months of ADF, which

is accompanied by improvements in blood lipids, blood pressure, and insulin sensitivity.⁹ However, a Randomized Controlled Trial (RCT) showed that ADF had no advantages over CER in terms of compliance, weight loss or maintenance, and cardioprotection in adults with obesity and normal metabolism.¹⁰ A systematic review found that ADF was effective for short-term (two to three months) weight loss in individuals with normal weight, overweight, and obesity, although there are no long-term follow-up data. Additionally, ADF is not suitable for individuals who require regular feeding or medication such as pregnant and lactating women, elderly people, or patients with type 1 diabetes or eating disorders.¹¹ Despite its widespread adoption, compared with CER, ADF may be less sustainable in the long term for most individuals with overweight and obesity because of the intense feeling of hunger elicited by low-calorie intake on fasting days.¹⁰

5:2 Fasting

The best-selling book “The Fast Diet” published by Mosley et al in 2013 touted the benefits of severely restricting energy intake for two days a week but eating normally during the rest of the week.¹² Since then, the 5:2 fasting has become more and more popular, which involved restricting energy intake to 25%–30% of the usual level on two nonconsecutive days within a week with no restriction on the remaining five days.¹³ Some researchers have concluded that the 5:2 fasting method is as effective as CER in reducing weight and improving glucose and lipid metabolism, waist-to-hip ratio, and insulin sensitivity.¹⁴ Compared with ADF, 5:2 fasting can lessen the feeling of hunger and is associated with fewer undesirable reactions such as dizziness, constipation, nausea, and vomiting during the weight loss process,^{15,16} which encourages adherence for people with overweight and obesity. Additionally, 5:2 fasting has been shown to reduce basal metabolic rate and skeletal muscle mass.¹⁷ The effect of 5:2 fasting on weight maintenance warrants further investigation.

Time-Restricted Eating (TRE)

TRE is an IF method that requires subjects to eat within a fixed period of 8–10 h or less per day and fast at other times¹⁸ to maintain a stable circadian rhythm in their calorie intake. Compared with ADF and 5:2 fasting, TRE only limits daily meal times and not the types or quantity of food, making it more acceptable to patients and facilitating adherence. The effect of TRE on weight loss was significantly correlated with the time of carbohydrate and protein intake;¹⁹ people who ate earlier in the day lost more weight than those who ate later.²⁰ Meanwhile, eating more staple foods in the evening was not beneficial for weight loss. In a 12-week RCT, women with overweight or obesity who consumed a high-calorie breakfast had better fasting glucose, insulin sensitivity, and blood lipids than those who consumed a high-calorie dinner.²¹ This result is consistent with the latest findings from healthy non-obese volunteers showing that 16:8 IF was more beneficial when food was consumed between 06:00 and 15:00 (ie, early eating) vs 11:00 and 20:00 (midday eating).²² Another study found that 12 weeks of TRE with a mealtime between 12:00 and 08:00 did not lead to weight loss in adults with overweight and obesity without controlling food intake but resulted in loss of muscle mass.²³ However, in an RCT of TRE (08:00–16:00) for 12 months, there was no significant loss of muscle mass, and regardless of the time of calorie intake, TRE had a significant impact on weight loss when total calories were restricted and was found to be a safe and effective strategy for weight management.²⁴ As there is no restriction on calorie intake and uniform regulation of allowed eating times in TRE, different studies have reported variable results. Nonetheless, the data suggest that reducing total calorie intake by limiting eating time, especially to earlier times of the day, is a beneficial weight management strategy. Given these findings, people with overweight and obesity should consider changing their traditional concept of dinner as a social meal in order to maximize weight loss.

Irrespective of the duration of the intervention (short term [4–12 weeks] or long term [24–102 weeks]), weight loss with ADF and 5:2 fasting was comparable to that achieved by calorie restriction (CR).^{10,14,15,25–34} Meanwhile, weight loss with TRE alone (1%–5% decrease from baseline over 8–12 weeks)^{23,35,36} was not superior to that achieved with CR and was less than that observed with ADF or 5:2 fasting unless total calorie intake was restricted along with TRE. Thus, long-term TRE combined with an appropriate energy-restricted diet can enhance weight loss, but this is mainly attributed to CR.^{24,37}

Summarizing the effects of three forms of IF on clinical outcomes reported in the literature (Table 1), it shows that there have been no trials directly comparing the effects of the three different fasting methods; further research is needed to determine which methods are more effective for achieving weight loss.

Table I Randomized Controlled Trials of IF and CR in Adults with Overweight and Obesity

Study, Y	Country	Participants	Duration	Intervention	Body Weight, % of Baseline Weight	VAT, % of Baseline	SAT, % of Baseline	Total Fat Mass, % of Baseline	Key result
ADF									
Trepanowski et al, ¹⁰ 2017	USA	N = 100 (m = 14, f = 86), age 18–64 years; mean BMI 34 kg/m ²	12 months (6 months of weight-loss phase and 6 months of weight-maintenance phase)	ADF (fast day 25% intake and feed day 125% intake)	↓7.0% at 6 months; ↓5.0% at 12 months	NA	NA	NA	ADF did not produce superior adherence, weight loss, weight maintenance, or cardioprotection to CR
				CR (75% intake)	↓7.3% at 6 months; ↓4.5% at 12 months	NA	NA	NA	
				Control (no-intervention)	↓0.7% at 6 months; ↑0.4% at 12 months	NA	NA	NA	
Catenacci et al, ²⁵ 2016	USA	N = 26 (m = 6, f = 20), age 18–55 years, BMI ≥30 kg/m ²	32 weeks (8 weeks of intervention + 24 weeks of unsupervised follow-up)	ADF (0-kcal fast day)	↓8.8% at 8 weeks; ↓5.9% at 32 weeks	NA	NA	↓1.1% at 8 weeks; ↓2.4% at 32 weeks	Similar decrease in weight loss, but IF better than CR to prevent weight regain
				CR (1500 kcal/d)	↓6.2% at 8 weeks; ↓4.4% at 32 weeks	NA	NA	↓1.0% at 8 weeks; ↓0.7% at 32 weeks	
Trepanowski et al, ²⁶ 2018	USA	N = 100 (m = 14, f = 86), age 18–64 years; mean BMI, 34 kg/m ²	12 months (6 months of weight-loss phase and 6 months of weight-maintenance phase)	ADF (fast day 25% intake and feed day 125%)	↓7.0% at 6 months; ↓5.0% at 12 months	↓15.8% at 6 months; NA at 12 months	↑3.7% at 6 months; NA at 12 months	↓7.1% at 6 months; NA at 12 months	ADF and CR similarly increased the FFM: total mass ratio and decreased circulating leptin, without affecting the VAT:SAT ratio or other measured adipokines
				CR (75% intake)	↓7.3% at 6 months; ↓4.5% at 12 months	↓13.0% at 6 months; NA at 12 months	↑3.9% at 6 months; NA at 12 months	↓7.1% at 6 months; NA at 12 months	
				Control (no-intervention)	↓0.7% at 6 months; ↑0.4% at 12 months	↓9.1% at 6 months; NA at 12 months	↑2.6% at 6 months; NA at 12 months	↓2.6% at 6 months; NA at 12 months	

(Continued)

Table 1 (Continued).

Study, Y	Country	Participants	Duration	Intervention	Body Weight, % of Baseline Weight	VAT, % of Baseline	SAT, % of Baseline	Total Fat Mass, % of Baseline	Key result
Coutinho et al, ²⁷ 2018	Norway	N = 35, age 39 ± 9 years, BMI 36 ± 4 kg/m ²	12 weeks	ADF (3-day fasting 550 and 660 kcal; 4-day full caloric needs)	↓13% at 12 weeks	NA	NA	↓5.4% at 12 weeks	IF as effective as CR, similar in weight loss, body composition and compensatory responses activated with weight reduction.
				CR (33% reduction of the estimated energy needs)	↓12.1% at 12 weeks	NA	NA	↓5.2% at 12 weeks	
Steger et al, ²⁸ 2021	USA	N = 35, ages 21–65 years, BMI 31.2 ± 2.4 kg/m ²	24 weeks (12-week weight loss and 12-week weight loss maintenance)	ADF (3-day fasting 550 and 800 kcal; 4-day healthy eating)	↓8.9% at 12 weeks; ↓10% at 24 weeks	NA	NA	↓4.1% at 12 weeks; ↓5.7% at 24 weeks	IF and CR result in similar weight loss, maintenance, and body composition changes.
				CR (1200–1600kcal)	↓10.4% at 12 weeks; ↓11.9% at 24 weeks	NA	NA	↓3.6% at 12 weeks; ↓5.3% at 24 weeks	
The 5:2 diet									
Carter et al, ¹⁴ 2018	Australia	N = 137 (m = 60, f = 77), with T2DM, age 61.0 ± 9.1 years; BMI, 36.0 ± 5.8 kg/m ²	12 months	5:2 fast day (500–600kcal)	↓6.8% at 12 months	↓9.1% at 12months	NA	↓11.8% at 12 months	Similar decrease in HbA _{1c} level and weight with IF or CR
				CR (1200–1500kcal)	↓4.9% at 12 months	↓8% at 12 months	NA	↓8.1% at 12 months	
Sundfør et al, ¹⁵ 2018	Norway	N = 112,(m =56, f = 56), age 21–70 years, BMI 30–45 kg/m ²	12 months (6 months of weight-loss phase and 6 months of weight-maintenance phase)	5:2 fast day (400/600 kcal for female/male)	↓8.4% at 6 months; ↓7.4% at 12months	NA	NA	NA	Weight loss and maintenance are similar in IF and CR,; IF has more pronounced hunger
				CR (1500kcal)	↓8.7% at 6 months; ↓8.4% at 12 months	NA	NA	NA	

Schübel et al, ²⁹ 2018	Germany	N = 150, (m = 75, f = 75), 25 ≤ BMI < 40, age 35–65 years	50 weeks (12-week intervention phase, 12-week maintenance phase, and 26-week follow-up phase)	5:2 fast day (75% reduction in energy needs)	↓7.1% at 12 weeks; ↓7.1% at 24 weeks; ↓5.2% at 50 weeks	↓22% at 12 weeks; NA at 24 weeks; ↓23% at 50 weeks	↓17% at 12 weeks; NA at 24 weeks; ↓12% at 50 weeks	NA	IF may be equivalent but not superior to CR for weight reduction and prevention of metabolic diseases
				CR (daily energy deficit ~20%)	↓5.2% at 12 weeks; ↓5.5% at 24 weeks; ↓4.9% at 50 weeks	↓16% at 12 weeks; NA at 24 weeks; ↓19% at 50 weeks	↓12% at 12 weeks; NA at 24 weeks; ↓12% at 50 weeks	NA	
				Control (no advice to restrict energy)	↓3.3% at 12 weeks; ↓3.3% at 24 weeks; ↓1.7% at 50 weeks	↓9% at 12 weeks; NA at 24 weeks; ↓6% at 50 weeks	↓8% at 12 weeks; NA at 24 weeks; ↓4% at 50 weeks	NA	
Headland et al, ³⁰ 2019	Australia	N = 244, ages 18–72 years, BMI ≥27 kg/m ²	52 weeks	5:2 fast day (500/600 kcal for female/male)	↓6.0% at 8 weeks; ↓5.7% at 52 weeks	NA	NA	↓9.6% at 8 weeks; ↓10.1% at 52 weeks	IF and CR have similar weight loss results at one year
				CR (1000/1200 kcal for female/male)	↓6.9% at 8 weeks; ↓7.4% at 52 weeks	NA	NA	↓11.2% at 8 weeks; ↓13.4% at 52 weeks	
				WOWO (one-week restriction and one-week habitual diet)	↓6.4% at 16 weeks; ↓5.6% at 52 weeks	NA	NA	↓10% at 16 weeks; ↓10% at 52 weeks	
Pinto et al, ³¹ 2020	England	N = 45, central obesity men and women, ages 35–75 years, with waist circumference >102 cm and >88 cm for men and women	4 weeks	5:2 fast day (48 h 600 kcal/d)	↓2.1% at 4 weeks	NA	NA	↓4.8% at 4 weeks	Similar decrease in weight loss and markers of cardiometabolic health
				CR (500 kcal/d reduction)	↓3.6% at 4 weeks	NA	NA	↓4.4% at 4 weeks	
Opstad et al, ³² 2021	Norway	N = 112, abdominally obese subjects, aged 21–70 years, BMI 30–45 kg/m ²	12 months	5:2 fast day (400/600 kcal for female/male)	↓7.3% at 12 months	NA	NA	NA	Similar decrease in weight loss with 5:2 diet and CR.
				CR	↓8.3% at 12 months	NA	NA	NA	

(Continued)

Table I (Continued).

Study, Y	Country	Participants	Duration	Intervention	Body Weight, % of Baseline Weight	VAT, % of Baseline	SAT, % of Baseline	Total Fat Mass, % of Baseline	Key result
Conley et al, ³³ 2018	Australia	N = 24: males aged 55–75 years, BMI ≥30 kg/m ²	6 months	5:2 fast day (600 kcal)	↓5.5% at 6 months	NA	NA	NA	The 5:2 diet was similar to CR for weight loss in the older male population and was well tolerated and effective.
				CR (500 kcal/d reduction)	↓5.4% at 6 months	NA	NA	NA	
Pannen et al, ³⁴ 2021	Germany	N = 98 (m = 50, f = 48), ages 35–65 years, BMI 25–39.9kg/m ²	102 weeks (12-wk intervention phase, 12-wk maintenance phase, and 26-wk follow-up phase, 52-wk follow-up phase)	5:2 fast day (25% of the isoenergetic energy requirement)	↓7.1% at 12 weeks; ↓7.1% at 24 weeks; ↓5.2%at 50 weeks; ↓4.3% at 102 weeks	NA	NA	NA	IF and CR were equivalent in achieving modest weight loss over two years. In the long term, more people seem to have difficulty following IF than CR.
				CR (80% of the individual energy requirement)	↓5.1% at 12 weeks; ↓5.6% at 24 weeks; ↓4.9% at 50 weeks; ↓5.0% at 102 weeks;	NA	NA	NA	
				Control (no calorie restriction)	NA	NA	NA	NA	
TRE									
Lowe et al, ²³ 2020	USA	N = 116 (m = 70, f = 46), ages 18–64 years, BMI 27 ~43kg/m ²	12 weeks	8-h TRE (12:00–20:00)	↓0.95% at 12 weeks	NA	NA	NA	No significant differences in weight loss, fat mass, fasting insulin, glucose, HbA1C, or blood lipids between two groups
				Control (no meal timing restrictions)	↓0.69% at 12 weeks	NA	NA	NA	
Liu et al, ²⁴ 2022	China	N = 118, ages 31.9 ± 9.1 years, BMI 28~45kg/m ²	12 months	8-h TRE (8:00–16:00)	↓10.6% at 6 months; ↓9.0% at 12 months	↓26.9% at 6 months; ↓21.3% at 12 months	↓22.4% at 6 months; ↓17.0% at 12 months	↓20.9% at 6 months; ↓17.9% at 12 months	Similar reduction in body weight, body fat, or metabolic risk factors with IF and CR, TRE can lead to weight loss, mainly attributed to CR
				CR (man 1500~1800 kcal, women 1200~1500kcal)	↓10.1% at 6 months; ↓7.2% at 12 months	↓25.1% at 6 months; ↓16.9% at 12 months	↓16.2% at 6 months; ↓12.2% at 12 months	↓19.3% at 6 months; ↓13.6% at 12 months	

Isenmann et al, ³⁵ 2021	Germany	N = 35, physically active individuals (m = 14, f = 21), ages 20~40 years, BMI 26~33kg/m ²	14weeks (8-week intervention phase and 6-week independent phase)	8-h TRE (12:00~20:00)	↓4.75% at 8 weeks; ↓4.75% at 14 weeks	NA	NA	↓14.99% at 8 weeks; ↓14.99% at 14 weeks	IF and CR have similar weight loss, fat mass and maintained LBM
				Control (healthy and balanced diet)	↓5.37% at 8 weeks; ↓5.37% at 14weeks	NA	NA	↓16.13% at 8 weeks; ↓16.13% at 14 weeks	
Chow et al, ³⁶ 2020	USA	N = 20 (m = 3, f = 17), ages 45.5 ± 12.1 years, BMI 34.1 ± 7.5kg/m ²	12 weeks	8-h TRE (self-selected)	↓3.8% at 12 weeks	↓17.6% at 12 weeks	NA	↓4.1% at 12 weeks	Compared to non-TRE, TRE decreased the weight, lean mass and visceral fat.
				Control (no meal timing restrictions)	↓1.5% at 12 weeks	0% at 12 weeks	NA	↓2.0% at 12 weeks	
Thomas et al ³⁷ 2022	USA	N = 81 (m = 12, f = 69), ages 38.0 ± 7.8 years, BMI 34.1 ± 5.7 kg/m ²	39 weeks (12W intervention, 27W follow-up)	10-h TRE +CR (self-selected starting within 3 hours of waking and 35% caloric restriction)	↓4.6% at 12 weeks; ↓5.2% at 39weeks	NA	NA	NA	Similar weight loss in the CR and TRE+CR.
				CR (35% caloric restriction)	↓4.0% at 12 weeks; ↓4.7% at 39 weeks	NA	NA	NA	

Abbreviations: ADF, alternate day fasting; TRE, time restricted eating; CR, calorie restriction; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; T2DM, type 2 diabetes mellitus; ↓, decrease in the indicated parameter; ↑, increase in the indicated parameter; NA, not applicable (parameter not measured).

IF Combined with Other Interventions

IF Combined with Exercise

Many studies on IF have controlled only dietary factors and neglected the long-term effects of exercise on weight. In a study of 64 patients with obesity, IF combined with endurance exercise of moderate intensity three times a week resulted in greater reductions in body weight, body fat mass (FM), and lipid-related indicators after 12 weeks than IF or exercise alone, although there were no significant differences in lean body mass (LBM) between groups.³⁸ Another study showed that the combination of resistance and aerobic exercise three times a week combined with IF led to larger reductions in body weight and FM than exercise alone although these parameters did not differ with respect to the IF group; on the other hand, exercise had a greater effect on cholesterol metabolism than IF or CR.³⁹ Adults with overweight or obesity are more prone to knee joint damage in activities like running, climbing, and basketball,⁴⁰ which negatively impacts their persistence with an exercise-based intervention. Effective muscle mass can be maintained by increasing protein intake and engaging in a reasonable exercise regimen. One study found that young people who fasted for 16 h a day over a 2-month period with resistance training had a reduction in body fat percentage while maintaining muscle mass;⁴¹ and a systematic review of 332 subjects showed that postprandial exercise was more effective in preventing hyperglycemia and enhancing insulin sensitivity than preprandial exercise.⁴² Thus, IF combined with exercise can improve the aerobic capacity of skeletal muscle, resulting in greater weight loss and providing more health benefits than IF²⁴ or exercise alone.³⁸

IF Combined with Meal Replacement

IF combined with meal replacement is a common weight loss intervention that has the advantage of not only allowing quantification of calorie intake on fasting days but also reducing malnutrition. In a single-blind randomized cross-over trial of eight healthy young women, processed meal replacements with a precisely calculated scientific nutrition ratio increased postprandial caloric expenditure and promoted carbohydrate oxidation to a greater extent than whole-food meals with the same total calories. Moreover, there were no differences among subjects in postprandial blood glucose response, satiety, feeling of hunger, and desire to eat, demonstrating that the processed meal replacements were an effective strategy for preventing and treating obesity.⁴³

In a study of 164 adults with overweight or obesity that were divided into two groups using IF combined with a high protein meal replacement or the protein meal replacement alone, both groups showed significant reductions in weight, body fat, visceral fat, and LBM at week 16 with no significant differences between them. However, the combined intervention reduced participants' cravings for food, thus improving their compliance and more effectively preventing weight regain within six months.⁴⁴ In a multicenter clinical study of 300 individuals with overweight or obesity in China, a dietary program consisting of 500–600 kcal solid drinks as meal replacement on IF days not only led to body weight reduction and maintenance of weight loss but also decreased the incidence of clinical symptoms such as mouth ulcers, constipation, hair loss, and insomnia experienced by the subjects during the weight loss process.⁴⁵ Another study conducted in China on patients with type 2 diabetes with comorbid obesity found that combined use of food substitutes during fasting periods safely and effectively improved metabolic indices such as blood glucose, blood pressure, and lipids; reduced body weight; improved patient compliance; and achieved stable and lasting glycemic control.⁴⁶ However, whether this method is effective in improving metabolic indices in type 2 diabetes patients with normal weight remains to be determined. In a study of healthy adults with overweight and obesity using meal replacements on fasting days, short-term fasting (4 weeks) resulted in greater weight loss and improved body composition and cardiometabolic health without exacerbating the feeling of hunger or adversely affecting appetite.⁴⁷ The investigators also found that two days of fasting per week was more beneficial than one day. Higher protein intake and more frequent eating were shown to reduce the amount of total and abdominal fat and improved LBM and postprandial thermogenesis; both were effective for long-term weight maintenance and are feasible for patients with overweight or obesity.^{48,49}

IF Combined with Psychological Intervention

Obesity may be associated with psychological problems such as depression, body image disorders, stress, and low self-esteem.⁵⁰ Furthermore, self-stigma in individuals with overweight and obesity can not only lead to psychological problems such as depression, anxiety, and low self-esteem but may also increase the risk of cardiovascular disease, metabolic abnormalities, and even death.⁵¹ These psychological problems can lead to a vicious cycle of unhealthy eating or overeating and reduced exercise or activity. Therefore, guidelines for weight reduction in Europe, Canada, and other countries have incorporated psychotherapy into routine weight loss approaches. Psychotherapy can increase patients' confidence in weight reduction interventions and help them to better implement IF programs and behavioral training by addressing the psychological factors that contribute to unhealthy eating habits of individuals with overweight and obesity through psychological assessment, respect, listening, guidance, and cognitive-behavioral therapy; this can have multiplicative effects on weight reduction and maintenance.⁵² A 5-year prospective study showed that fasting increased the risk of binge eating and bulimic pathology.⁵³ Disordered eating—ie, overeating—requiring psychological treatment has been suggested as a root cause of obesity. Psychologists in the United States and other countries believe that cognitive and behavioral therapies combined with dietary strategies and physical activity can improve both short- and long-term outcomes in the treatment of obesity.^{54,55} A scoping review shows that psychological interventions can increase patients' awareness and compliance with their eating behaviors and enhance self-behavior management to ensure weight loss maintenance in non-surgical interventions for hospitalized adults with class II or class III obesity.⁵⁶ IF in combination with supportive psychodynamic psychotherapy and physical activity is an effective strategy for long-term weight loss and body mass index (BMI), waist-to-hip ratio, and body fat reduction.⁵⁷

Evaluation of the Effect of IF

Effects on Body Weight, Body Fat, and LBM

Most of the weight loss associated with IF is due to a reduction in body FM;⁵⁸ one study calculated that 79% of the weight loss was attributable to a reduction in fat (level I evidence).⁵⁹ However, some studies have found that IF can result in the loss of LBM concurrent with weight loss, typically accounting for 20%–30% of total weight loss.⁶⁰ Short-term (4 weeks) IF decreased body weight and improved body composition and cardiometabolic health while having no adverse effects on the feeling of hunger or appetite, whereas long-term (52 weeks) IF reduced the amount of total and abdominal fat and increased LBM, thereby promoting weight maintenance.^{47,49} A lower LBM is associated with a lower metabolic rate and neuromuscular function, fatigue, and increased risk of injury, with the degree of LBM reduction positively correlated with weight regain.⁶¹ Thus, a reasonable weight loss goal is to reduce body fat while avoiding loss of muscle mass. Although both IF and CER led to varying degrees of weight regain after six months, CER increased FM and LBM, whereas IF decreased FM while increasing LBM.²⁵ Exercise has been shown to preserve or prevent a decline in basal metabolism and prevent the loss of muscle mass in people under the age of 60, and IF combined with resistance training programs are commonly used to promote fat loss and improve glucose and insulin levels in this population.^{62,63} However, whether this is related to adequate protein intake and energy balance is unclear and requires examination in a larger sample size of patients who are elderly or have chronic diseases. It was also reported that IF combined with a high-protein diet reduced BMI and lipids in people with obesity and limited weight regain while increasing arterial compliance.⁶⁴

Effects on Blood Glucose, Insulin, and Lipids

IF can reduce body weight and improve lipid and glucose abnormalities.⁶⁵ Short-term (12-week) IF with a low-calorie, high-protein diet reduced total adiposity, abdominal and visceral FM, and plasma biomarkers (insulin, glucose, triglycerides, low-density lipoprotein [LDL], and total cholesterol) while improving metabolism (resting metabolic rate and respiratory quotient) in obese men and women.^{49,64} However, although IF was superior to CER in reducing insulin resistance (possibly by decreasing total energy expenditure), it also increased insulin levels and promoted fat storage, without significantly lowering blood glucose and lipids.⁶⁶ On the other hand, in another RCT of centrally obese adults, IF and CER had comparable effects on cardiometabolic health and were not superior to CER in terms of increasing insulin sensitivity.³¹ In

a study of 19 subjects with metabolic syndromes, IF significantly reduced atherogenic lipids: total cholesterol decreased by 7%, LDL cholesterol by 11%, and non-high-density lipoprotein cholesterol by 9%. Additionally, a decreasing trend was observed in the number of total cholesterol and LDL cholesterol particles.⁶⁷ In an RCT of eight prediabetic men with obesity, five weeks of IF increased insulin sensitivity and islet β -cell reactivity and decreased insulin level, blood pressure, and oxidative stress, although there were no significant changes in body weight or fasting and postprandial blood glucose.⁶⁸ Collectively, these findings indicate that although IF has benefits for patients with prediabetes and prehypertension, there is insufficient supporting evidence from large samples of different patient populations.

Effects on Cardiometabolic Health

IF not only alleviates blood pressure and improves lipid and glucose levels and other cardiovascular disease-related risk factors, it also reduces the risk of coronary heart disease and improves the prognosis of cardiac events.⁶⁵ Short-term intervention with a low-calorie, high-protein diet lowered cholesterol and improved BMI as well as cardiovascular variables such as resting heart rate and blood pressure. Compared with a heart-healthy diet, IF with a low-calorie, high-protein diet for one year had certain advantages for cardiometabolic health such as weight reduction, prevention of low-density-lipoprotein rebound, and enhanced arterial compliance.^{47,64} Meal timing also influences cardiometabolic health; according to the American Heart Association, nighttime fasting can reduce the risk of cardiovascular disease.⁸ A study of lean and healthy adults showed that although IF yielded comparable overall weight loss to energy restriction and balanced diets, subjects in the IF group showed less weight loss due to fat reduction and there were no specific benefits in terms of metabolic regulation or cardiovascular health.⁶⁹ This is supported by the finding from a study of 139 obese adults that IF was not more effective than daily CR in reducing body weight, body fat, and cardiovascular metabolic risk factors.²⁴ More clinical studies are needed to determine whether IF has benefits for the prevention and treatment of cardiovascular diseases.

Effects of IF on Other Diseases

Apart from body weight, IF can be applied to the management of metabolic disorders such as diabetes and Non-alcoholic Fatty Liver Disease (NAFLD).⁷⁰ In a randomized trial of 137 adults with type 2 diabetes, IF had similar effects to CER in reducing hemoglobin A1c level and improving blood glucose. On the other hand, IF showed superior performance for lowering body weight and in increasing insulin sensitivity.¹⁴ In patients with NAFLD, IF for eight weeks decreased BMI, alanine aminotransferase level, and steatosis and fibrosis rates compared with a normal diet, with good compliance among patients in the IF group.⁷¹ ADF also resulted in greater weight loss and improvement in blood lipid levels in a shorter period (4–12 weeks) than TRE.⁷²

In patients with Multiple Sclerosis (MS), IF was as safe and effective as CER in reducing body weight and improving mood.⁷³ Meanwhile, IF was shown to improve the immune recovery of patients with MS by altering intestinal flora composition and reducing the inflammatory response.⁷⁴ By reducing fat, IF not only improves body shape but also diminishes the risk of obesity-related diseases such as dyslipidemia, type 2 diabetes, hypertension, and NAFLD. In preclinical studies, fasting and CR have been shown to prolong life- and healthspan, induce autophagy, and ameliorate symptoms of various diseases, such as CVDs, type 2 diabetes, neurodegenerative diseases, cancer, or ischemic injuries.⁷⁵ It should be noted that although IF can lead to better clinical outcomes compared with other dietary modifications, the benefits are mainly derived from energy restriction rather than fasting; as such, it should not be considered as the ideal dietary intervention.⁷⁶ Future studies should also prioritize testing the health benefits of these diets in patients with type 1 diabetes, polycystic ovary syndrome and thyroid disorders.⁷⁷ Based on human studies, we outline the overall effects of IF versus CR (Figure 1).

Summary

Preclinical and clinical evidence suggests that IF is an effective nonpharmacologic therapy for weight loss that can decrease body weight and improve body composition (total body fat, abdominal fat, and LBM) as well as physiologic indices such as blood glucose, lipids, insulin sensitivity, and cardiovascular metabolism in adults with overweight and obesity. Most IF-related intervention studies have been conducted over a short period, with some long-term clinical trials lasting more than one year. Moreover, the study subjects have mainly been adults with overweight and obesity with or

Evidence from amounting clinical trials point towards systemic health benefits of CR and IF in humans. Less evidence exists that intermittent fasting superior effects over continuous CR. IF, intermittent fasting; CR, calorie restriction; FM, fat mass; LBM, lean body mass; S, short-term; L, long-term; T2DM, type 2 diabetes; NAFLD, non-alcoholic fatty liver disease; ↓, decreased or reduced; ↑, increased.

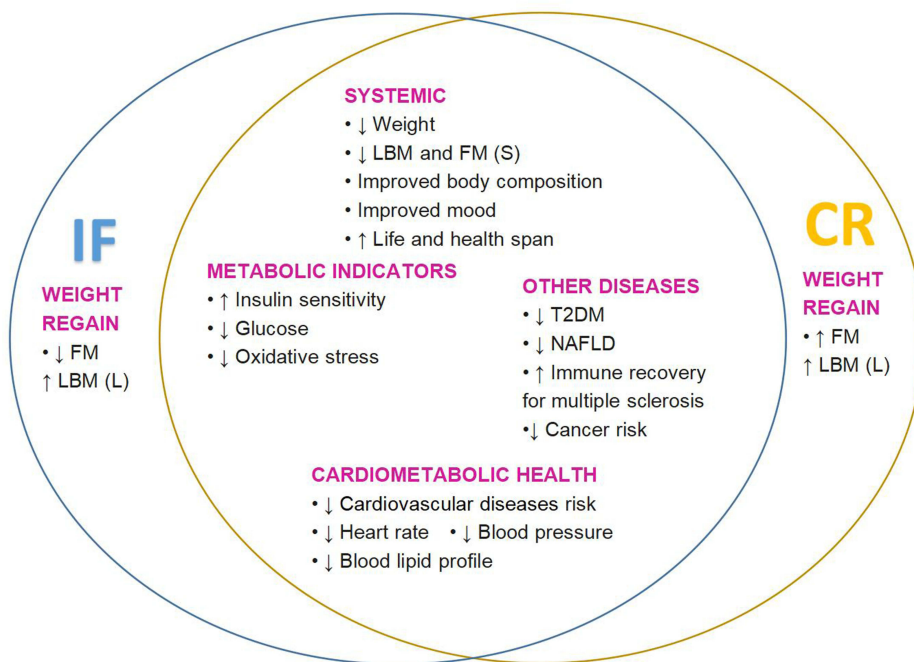


Figure 1 Overall effects of IF versus CR.

without diabetes mellitus, hyperlipidemia, or other comorbidities. Longitudinal population studies with large samples are needed to evaluate the safety and effectiveness of IF. Given the diverse forms of IF and its combination with other interventions such as exercise, meal replacement, and psychotherapy, the effects of IF on weight loss vary considerably across studies. IF is only one dietary strategy, and dietary components also play a key role in the development of obesity. Changing our lifestyle towards healthy eating and more physical activity may help reduce or prevent the development of obesity.⁷⁸ Future studies should address the synergistic effects of IF combined with other interventions in weight management as a means to improve adherence⁷⁹ to weight loss regimens for long-term weight control.

All studies that adopt IF to manage weight are required to undergo ethics review.

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Disclosure

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