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SUPPLEMENT ARTICLE

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A meta-analysis comparing the effectiveness of alternate day fasting, the 5:2 diet, and time-restricted eating for weight loss

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Abstract

Objective: The objective of this meta-analysis was to compare the effectiveness of different intermittent fasting (IF) regimens on weight loss, in the general population, and compare these to traditional caloric energy restriction (CER).

Methods: Three databases were searched from 2011 to June 2021 for randomized controlled trials (RCTs) that assessed weight loss and IF, including alternate day fasting (ADF), the 5:2 diet, and time-restricted eating (TRE). A random effect network analysis was used to compare the effectiveness between the three regimens. Meta-regression analysis was presented as weighted mean differences of body weight loss.

Results: The exploratory random effects network analysis of 24 RCTs ($n = 1768$) ranked ADF as the most effective, followed by CER and TRE. The meta-analysis showed that IF regimens resulted in similar weight loss to CER (mean difference 0.26 kg, 95% CI: −0.31 to 0.84; $p = 0.37$). Compliance was generally high (>80%) in trials shorter than 3 months.

Conclusions: The present meta-analysis concludes that IF is comparable to CER and a promising alternative for weight loss. Among the three regimens, ADF showed the highest effectiveness for weight loss, followed by CER and TRE. Further well-powered RCTs with longer durations of intervention are required to draw solid conclusions.

INTRODUCTION

The rise in prevalence of obesity and related metabolic diseases has led to an increase in dietary interventions to restrict energy intakes to promote weight loss [1,2]. Caloric energy restriction (CER), which involves a daily energy deficit of 500 to 750 kcal, is traditionally recommended in weight-loss or weight-management strategies [2,3]. Over the past decade, intermittent fasting (IF), also called intermittent energy restriction, has increased in popularity as an alternative to conventional weight-loss strategies [1]. IF alternates periods of eating with periods of complete fasting or very limited caloric intake [4–6], and it is thought to have health promoting effects, dependent and independent of the weight-loss benefits [6].

IF is an umbrella term for different variations of fasting regimens, but the three most mentioned variations are the following: alternate day fasting (ADF), the 5:2 diet, and time-restricted eating (TRE; also called time-restricted feeding) [2]. The ADF regimen consists of a fasting day, alternated with a day when participants can eat as desired, called ad libitum eating day. There are two main variations of ADF: zero-calorie ADF and modified alternate day fasting (MADF) [7]. In the zero-calorie ADF regimen, no foods or caloric beverages are

consumed on fasting days whereas in the MADF regimen the caloric intake during the fasting days accounts for 20% to 30% of that of a normal dietary intake [8]. The 5:2 diet is characterized by individuals eating normally on 5 d/wk and fasting (or reduced caloric intake) on two consecutive or nonconsecutive days [1]. A third popular regimen is TRE, in which individuals typically fast for 14 to 16 h/d and consume food ad libitum for 4- to 12-hour feeding windows [9]. The TRE regimen has the most variable design compared with other regimens, as the fasting window can extend from 12 to 21 h/d [10]. TRE differs from the 5:2 diet and ADF, as TRE focuses on a consistent daily eating window rather than energy restriction per se [11], seeking to trigger other potential health benefits [10].

Results on the efficacy of IF regimens for weight loss differ widely, and it remains unknown how their effectiveness compares between each regimen. Providing better understanding of the most effective IF strategy may help to guide clinical practice and understand the physiological mechanisms involved in weight loss. Therefore, the objectives of this meta-analysis are the following: 1) compare the effectiveness of different IF regimens on weight loss in the general population; 2) compare the effectiveness of different IF regimens versus the traditional CER diet for weight loss; and 3) evaluate compliance to different types of IF regimens and, when reported, to CER.

Study Importance

What is already known?

- The three main forms of intermittent fasting (alternate day fasting [ADF], the 5:2 diet, and time-restricted eating) are effective weight-loss interventions, producing body weight reductions ranging from 1% to 13% over 2 to 52 weeks.
- When intermittent fasting is compared with caloric energy restriction (CER), some studies report improvements in short-term studies but not in longer-term trials, and others show no differences.

What does this study add?

- Networking analysis of a pooled data set predicted that alternate day fasting/modified ADF ranked the highest on efficacy for weight loss, followed by CER and time-restricted feeding. It is the first time that such a comparison has been performed in a meta-analysis.

How might these results change the direction of research or the focus of clinical practice

- Intermittent fasting may be implemented as an alternative strategy to CER for weight management tailored to the specific needs and acceptance of the individual.
- Our results ranked alternate day fasting/modified ADF as the regimen with the highest efficacy for weight loss compared with the 5:2 diet and time-restricted eating.
- More research on the physiological mechanism of action for such superiority remains to be investigated.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used for this study [12].

Search strategy and selection process

A systematic literature search was conducted using PubMed, Cochrane Library, and Scopus databases, including publications from 2011 to June 7, 2021 (previous 10 years). Keywords related to intermittent fasting, including "intermittent fasting," "time restricted feeding," "time restricted eating," and "alternate day fasting," were used among others. A complete list of search terms is available in Supporting Information Table S1.

We defined inclusion criteria according to the PICO (population, intervention, comparison, outcome) framework for Cochrane reviews [13]. Two authors (Paloma Elortegui Pascual, Maryann R. Rolands), working together, completed the initial screening of records according to defined criteria. Once the titles and abstracts were screened, two authors reviewed the full texts independently and discussed discrepancies. Randomized controlled trials (RCTs) were included based on the following PICO criteria: 1) population (P): adults over 18 years of age with normal weight, participants with overweight and participants with obesity excluding those diagnosed with metabolic syndrome, prediabetes, or type 2 diabetes and bariatric surgery patients; 2) intervention (I): ADF/MADF, the 5:2 diet, TRE; 3) comparator diets (C): CER, calorie restriction; 4) outcome (O): body weight loss measured as primary or secondary outcome during the intervention period. Studies were also included when the mean value of changes from baseline with standard deviation (SD) or appropriate data to determine the data required such as standard error or 95% confidence interval (CI). Case reports, nonrandomized trials, studies with no control group, animal studies, systematic reviews, and meta-analyses were excluded, as were fasting protocols that were administered together with other dietary interventions (beyond general recommendations to adhere to a balanced nutritional intake) that could have an impact on body weight (e.g., ketogenic diet). Studies in children, studies involving participants with diagnosed diseases, studies of resistance training, endurance training, and high intensity interval training, and those of religious fasting such as in the context of Ramadan were also excluded.

Data extraction and synthesis

In preparation for the meta-analysis, two reviewers (Paloma Elortegui Pascual, Maryann R. Rolands), working independently, extracted the following data from each study: authors and year of publication, type of

IF regimen (ADF/MADF, 5:2, TRE), comparator diet (CER, ad libitum), duration of intervention, baseline participant characteristics (age range, mean and SD or standard error of mean [SEM] of participants' weights), and intervention effects (mean body weight loss and SD or SEM and CI between pre- and postintervention). If the SD was not published, it was calculated using the standard error, SEM, or CI reported in the study at postintervention [14]. In Varady et al. [15] and Trepanowski et al. [16], data on mean body weight loss were obtained by directly contacting the authors. Several other authors of relevant trials were contacted for additional information, but no suitable data were obtained, which led to the exclusion of these studies. The meta-analysis was based on differences in mean body weight loss at pre- and postintervention for the different IF regimens and type of comparator diet.

Risk-of-bias assessment

Risk of bias of each study was evaluated using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0) [17]. Individual worksheets were completed for each study to evaluate the six domains of potential risk of bias: 1) the randomization process; 2) deviations from the intended interventions (effect of assignment to intervention); 3) missing outcome data; 4) measurement of the outcome; 5) selection of the reported results; and 6) overall risk of bias (Supporting Information Figures S1, S2). Additional supporting materials provided from clinical trial registration (e.g., ClinicalTrials.gov or similar) and publications on the same study were also assessed as needed to complete scoring details for each study.

Compliance

Compliance is a determining factor in the success of weight-loss strategies [18]. Although not consistently reported in the IF literature, compliance data were recorded when available and evaluated as part of this analysis in order to assess adherence to different types of IF regimens and, when reported, to CER. Studies that included compliance based on the use of daily dietary and eating time window logs, self-rating or reported based on follow-ups with study dietitians to discuss and promote dietary adherence were included. Percentage of adherence was calculated as adherent days divided by total days on the diet (ADF/MADF and 5:2) or consumption within the prescribed eating time window (TRE). Data are presented as percentage adherence to the prescribed diet at the end of the intervention period, corresponding to the duration assessed for the meta-analysis. In addition, retention rates were calculated by dividing the number of participants who completed the study by the number enrolled. This was done for all studies that were included in the meta-analysis as a gross indicator of compliance.

Statistical analysis

An exploratory random effects network meta-analysis was performed to consider indirect comparisons between intervention

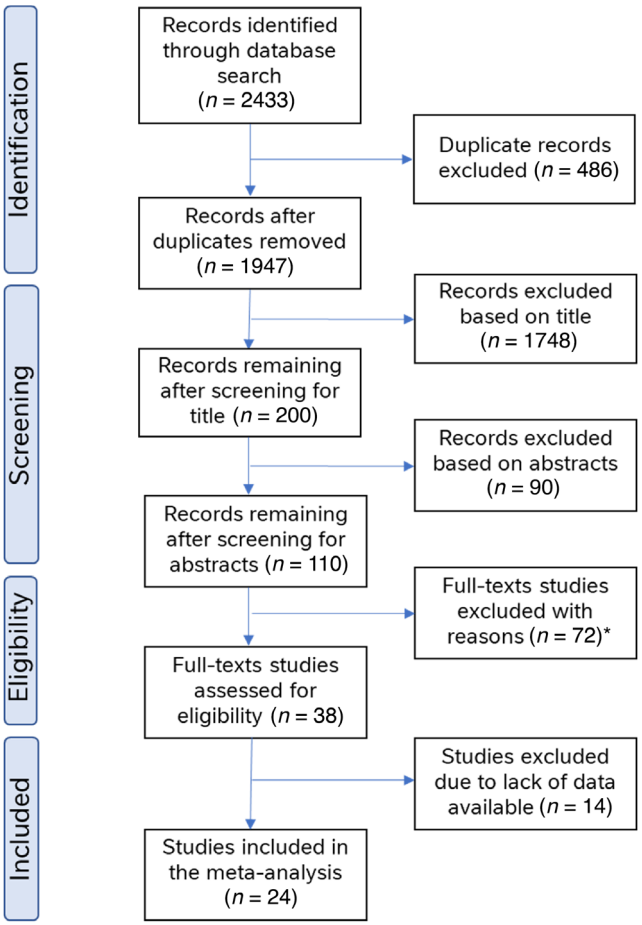


FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart for RCTs selected for inclusion in the meta-analysis. Full text studies were excluded for the following reasons: metabolic diseases other than obesity ($n = 7$), non-RCTs ($n = 7$), non-intermittent fasting regimen ($n = 6$), religious fasting ($n = 2$), no body weight ($n = 3$), no control ($n = 8$), review ($n = 1$), abstract only ($n = 33$), secondary analysis ($n = 4$), duration less than 1 week ($n = 1$). RCT, randomized controlled trial

studies [19]. The five diets (zero-calorie ADF, MADF, 5:2, TRE, CER, and ad libitum diet) assessed in this study were compared against each other and ranked for effectiveness of weight loss. The diets had ranking probability ranges from 0 (low) to 1.0 (high). The inconsistencies in the network were assessed using the node splitting method, which identifies disagreements between the direct and indirect comparisons [20].

In addition, a meta-analysis was conducted using RStudio software version 1.3.1056 and the Meta-Analysis Package for R (metafor package, version 3.0-2). The data are presented as weighted mean differences of body weight loss between the interventions (ADF/MADF, 5:2, and TRE) and comparator groups (CER and ad libitum). To examine heterogeneity, the weighted mean differences with 95% CI were analyzed using the DerSimonian and Laird random effects model [21]. Heterogeneity considers to what extent studies were consistent [22]. The heterogeneity among studies was tested using the I^2 value, where values above 50% may represent substantial heterogeneity across studies [22]. The results were presented as forest plots with effect

TABLE 1 Characteristics of studies selected and included in the meta-analysis

Reference	Number randomized, (sex: F, M) and study population	Number completed (sex: F, M)	Age (y), mean ± SD	BMI (kg/m^2), mean ± SD	Intervention duration	Intervention	Comparator group	Weight reduction for IF intervention from baseline (%)	Weight reduction for comparator diet from baseline (%)
ADF/MADF									
Trepanowski et al., 2017 [16]	100 adults (86 F, 14 M), 18-64 y, with overweight and obesity	69 (57 F, 12 M)	44 ± 11	35 ± 4	26 wk	25% of energy need on fast days	CER: 75% of EER	−5.81%	−4.83%
Bowen et al., 2018 [27]	162 adults (132 F, 31 M), 25-60 y, with overweight and obesity	135	40 ± 8	36 ± 6	16 wk	3 d/wk 600 kcal, 3 d/wk 1200 kcal, 1 d/wk ad libitum	CER: 1200 kcal/d	−10.64%	−11.24%
Beaulieu et al., 2021 [24]	54 adults, 18-55 y, with overweight and obesity	46 (F)	35 ± 10	29.1 ± 2.3	12 wk	75% of baseline energy needs on fast days (24 h), ad libitum on feast days	CER: 25% energy restriction	−6.03%	−5.60%
Bhutani et al., 2013 [25]	83 adults (80 F, 3 M), 25-65 y, with obesity	64	42 ± 3	35 ± 1	12 wk	25% of baseline energy needs on fast days (24 h), ad libitum on feast days, 12 p.m. to 2 p.m. meals, 3 d/wk	*Ad libitum*	−3.19%	0.00%
Coutinho et al., 2018 [47]	35 adults, 18-65 y, with obesity	28 (22 F, 6 M)	39 ± 9	36 ± 4	12 wk	550 to 660 kcal/d, on fast days and ad libitum based on EER on feed days	CER: 33% energy restriction based on EER	−12.97%	−12.10%
Steger et al., 2021 [26]	35 adults (27 F, 8 M), 21-65 y, with overweight and obesity	30	45.6 ± 10.7	31.2 ± 2.4	12 wk	550 to 800 kcal/d 3 d/wk + ad libitum 4 d/wk	CER: 1200-1600 kcal/d	−9.98%	−11.86%
Catenacci et al., 2016 [46]	29 adults, 18-55 y, with obesity	25 (19 F, 6 M)	42.7 ± 7.9 (CR); 42.7 ± 7.9 (ADF)	39.5 ± 6.0 (CR); 35.8 ± 3.7 (ADF)	8 wk	Zero-calorie on fast days and ad libitum on feed days	CER: −400 kcal/d from EER	−8.65%	−6.23%
Hutchison et al., 2019 [48]	88 (F), 35-70 y, with overweight and obesity	79	50 ± 1	32.3 ± 0.5	8 wk	70% of baseline energy requirements, with ∼32% of energy requirements at breakfast on fast days in IF70 and ∼37% in IF100	CER: 70% of EER and ad libitum	−6.04%	−4.41%
Oh et al., 2018 [49]	45 adults (26 F, 19 M), 18-64 y, with normal weight, overweight, and obesity	35	32.9 ± 7.3	27.6 ± 2.8	8 wk	25% of DRI in 3 d alternately on fast days (400-500 kcal), between 12 p.m. and 2 p.m., and ad libitum on feed days	*Ad libitum*	−3.24%	−0.85%
Varady et al., 2013 [15]		30 (22 F, 8 M)	47 ± 3	26 ± 1	8 wk	25% of baseline energy needs on fast days (24 h)	*Ad libitum*	−6.75%	−0.78%

(Continues)

TABLE 1 (Continued)

Reference	Number randomized, (sex: F, M) and study population	Number completed (sex: F, M)	Age (y), mean ± SD	BMI (kg/m^2), mean ± SD	Intervention duration	Intervention	Comparator group	Weight reduction for IF intervention from baseline (%)	Weight reduction for comparator diet from baseline (%)
	32 adults, 35-65 y, with normal weight and overweight					and ad libitum on feed days (24 h)			
Stekovic et al., 2019 [50]	90 adults (52 F, 38 M), 35-65 y, with normal weight, overweight, and obesity	57	50.5 (44.5-56.75)[a] (ad libitum); 48 (42.5-55) (ADF)	25.21 (23.57-27.34) (ad libitum); 25.48 (24.21-27.06) (ADF)	4 wk	0% of energy needs on fast days (only water, flavored carbonated water, unsweetened black or green tea, or coffee) and ad libitum on feed days	Ad libitum	−4.53%	−0.26%
Templeman et al., 2021 [51]	36 adults (21 F, 15 M), 18-65 y, with normal weight	36	45 ± 6 (CER); 41 ± 14 (ADF)	24.0 ± 1.9 (CER); 23.7 ± 2.1 (ADF)	3 wk	0% of energy needs on fast days (only water, herbal tea, black tea/coffee) and 150% or 200% of energy needs on feed days	CER: 75% of EER	−0.77%	−2.65%
5:2 diet									
Conley et al., 2018 [30]	24 adults (M), 55-75 y, with obesity	23	67.1 ± 3.9 (CER); 68 ± 2.7 (5:2 diet)	36.2 ± 4.3 (CER); 33.4 ± 1.8 (5:2 diet)	26 wk	"Fast" for 2 nonconsecutive days per week (600 calories) and ad libitum on remaining 5 days	CER: −500 kcal daily reduction	−5.35%	−5.13%
Harvie et al., 2011 [31]	107 adults (F), 30-45 y, with overweight and obesity	89	40.0 ± 3.9 (CER); 40.1 ± 4.1 (5:2 diet)	30.5 ± 5.2 (CER); 30.7 ± 5.0 (5:2 diet)	26 wk	2 d/wk 25% restriction, 5 d/wk ad libitum	CER: 25% restriction	−7.97%	−6.75%
Schübel et al., 2018 [29]	150 adults (75 F,75 M), 35-50 y, with overweight and obesity	144	50.7 ± 7.1 (ad libitum); 50.5 ± 8.0 (CER); 49.4 ± 9.0 (5:2 diet)	31.1 ± 3.6 (ad libitum); 31.2 ± 4.0 (CER); 32.0 ± 3.8 (5:2 diet)	12 wk	2 d/wk 25% of energy needs on fast days	CER: 80% of EER and ad libitum	−7.10%	−5.20%
Antoni et al., 2018 [46]	48 adults, 18-65 y, with overweight and obesity	27	48 ± 3 (CER); 42 ± 4 (5:2 diet)	30.8 ± 1.1 (CER); 29.8 ± 0.9 (5:2 diet)	8-10 wk	2 d/wk 25% of caloric needs on fast days	CER: 2510 kJ below EER	−5.30%	−5.01%
Headland et al., 2019 [52]	332 adults, (276 F, 56 M), 18-72 y, with overweight and obesity	244	49.3 ± 13.7	33.5 ± 5.2	8 wk	2 d/wk 500/600 kcal on fast day	CER: 1000-1200 kcal/d	−4.12%	−5.53%
Hirsh et al., 2019 [28]	23 adults (14 F, 9 M), 21-65 y, with overweight	22	41.0 ± 11.7	27.3 ± 2.6	7.4 wk	2 d/wk decreased energy intake (730 kcal/d; 3050 kJ/d) by consuming a commercially available shake four times a day, 5 d/wk ad libitum	*Ad libitum* + one multivitamin tablet daily	−1.70%	−0.50%

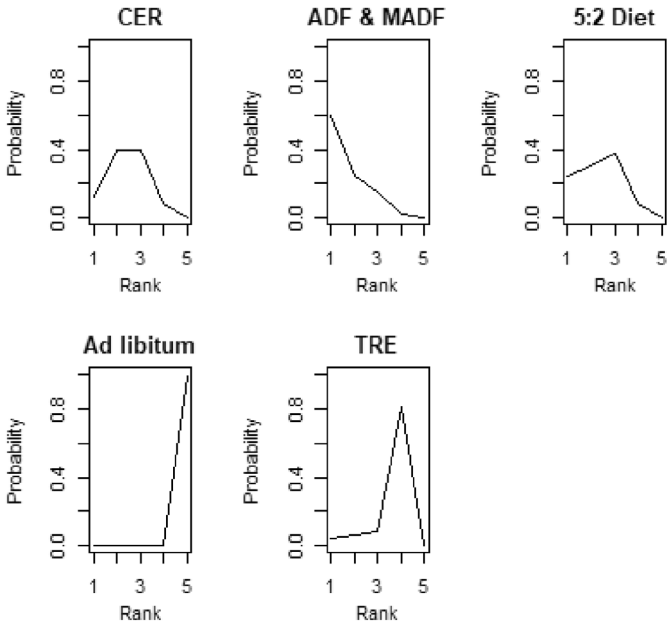
(Continues)

TABLE 1 (Continued)

Reference	Number randomized, (sex: F, M) and study population	Number completed (sex: F, M)	Age (y), mean ± SD	BMI (kg/m^2), mean ± SD	Intervention duration	Intervention	Comparator group	Weight reduction for IF intervention from baseline (%)	Weight reduction for comparator diet from baseline (%)
Pinto et al., 2020 [53]	43 adults, 35-75 y, with central obesity	43 (31 F, 12 M)	56 ± 8 (CER); 50 ± 12 (5:2)	31.1 ± 5.7 (CER); 31.8 ± 4.5 (5:2)	4 wk	2 consecutive days per week: 600 kcal/d	CER: reduce weekly energy intake by 3500 kcal	−2.05%	−3.36%
Gao et al., 2021 [54]	16 adults, 20-35 y, with normal weight	16 (8 F, 8 M)	23 ± 1 (5:2); 26 ± 2 (CER)	21.7 ± 0.8 (5:2); 22.7 ± 0.6 (CER)	2 wk	70% below EER on 2 nonconsecutive days, 5 days ad libitum	CER: 20% below EER	−3.94%	−3.33%
TRE									
Chow et al., 2020 [33]	22 adults, 18-65 y, with overweight and obesity	20 (17 F, 3 M)	45.5 ± 12.1	33.8 ± 7.6 (TRE); 34.4 ± 7.8 (non -TRE)	12 wk	16-h fasting, 8-h eating window	*Ad libitum*	−3.18%	−0.79%
Lowe et al., 2020 [55]	116 adults, 18-64 y, with overweight and obesity	116 (46 F, 70 M)	46.5 ± 10.5	32.7 ± 4.2	12 wk	12-h fasting, 12-h eating window	*Ad libitum*, with 3 structured meals per day; snacks allowed	−0.95%	−0.69%
Cienfuegos et al., 2020 [32]	58 adults, 18-65 y, with obesity	49	47 ± 3 (TRE); 45 ± 2 (control)	37 ± 1 (TRE); 36 ± 1 (control)	8 wk	18-h fasting, 6-h eating window	*Ad libitum*	−3.20%	−0.10%
Peeke et al., 2021 [23]	60 adults, 18-65 y, with obesity	60	44 ± 11	33.5 ± 5.2	8 wk	14-h fasting and fasting snack of 200 kcal, 10-h eating window	CER: 500-1000 kcal deficit	−8.60%	−7.34%

Abbreviations: ADF, alternate day fasting; CER, caloric energy restriction; CR, calorie restriction; DRI, dietary reference intake; EER, estimated energy requirements; F, female; M, male; TRE, time-restricted eating.

[a]Information extracted from the paper as median (interquartile range).



	Probabilities of Ranking 1	Probabilities of Ranking 2	Probabilities of Ranking 3	Probabilities of Ranking 4	Probabilities of Ranking 5
CER	0.121	**0.381**	**0.401**	0.094	0.000
ADF & MADF	**0.570**	0.253	0.157	0.017	0.000
5:2 Diet	0.258	0.296	0.354	0.090	0.000
Ad libitum	0.000	0.000	0.000	0.004	**0.995**
TRE	0.048	0.067	0.086	**0.793**	0.004

FIGURE 2 Exploratory network analysis on the probability of ranking on the effectiveness of weight loss between the intermittent fasting regimens: MADF, ADF, 5:2, TRE, and comparator diets: CER and control. The table provides support to the interpretation of the network plot for the probabilities of each regimen's rankings. The highest probability for each rank is highlighted in bold. ADF, alternate day fasting; CER, caloric energy restriction; MADF, modified alternate day fasting; TRE, time-restricted eating

size, 95% CI, I^2 value, and $p < 0.05$ for significance. A model was constructed to determine the effect of duration on weight loss to account for biases that could occur from extended trial durations. Meta-regression analyses were conducted to examine differences between IF diet types (ADF/MADF, 5:2, and TRE) and comparator diets (either CER or ad libitum) [22]. Publication bias was examined by assessing the symmetry of the funnel plot and carrying out the Egger's weighted regression test.

RESULTS

Literature search and identification of studies

The literature search identified 2433 records, including a total of 1947 unique titles. These were screened using PICO criteria defined for this study by assessing first the titles and then the abstracts. Among the articles included after screening for titles ($n = 200$) and for abstracts ($n = 110$), 38 full text articles were identified through an eligibility assessment. Fourteen of these did not present body weight end points that were suitable for analysis, resulting in 24 studies ($n = 1768$) included in our meta-analysis (Figure 1).

Risk-of-bias assessments

Risk-of-bias assessments were performed for all included RCTs (Supporting Information Figures S1, S2). Overall, risk-of-bias assessments showed moderate to high risk of bias in at least one attribute. Because the interventions involved diet, all participants were aware of their assigned eating pattern, leading to a potential for performance bias in all studies. Two other sources of bias were present in some studies included in these analyses: incomplete outcome data as a result of missing outcome measures related to dropouts (nine studies) and selective reporting of results (four studies).

Study characteristics

Table 1 summarizes the general characteristics of the 24 RCTs included in this meta-analysis. The studies included a range of 16 to 332 participants ($n = 1768$). Intervention periods ranged from 2 to 26 weeks. Age of participants ranged from 23 ± 1 to 68 ± 2.7 years old. The body mass index (BMI) of the participants ranged between 21.7 ± 0.8 kg/m^2 and 39.5 ± 6.0. The selected studies included both females and males, although the majority were females. The studies included participants

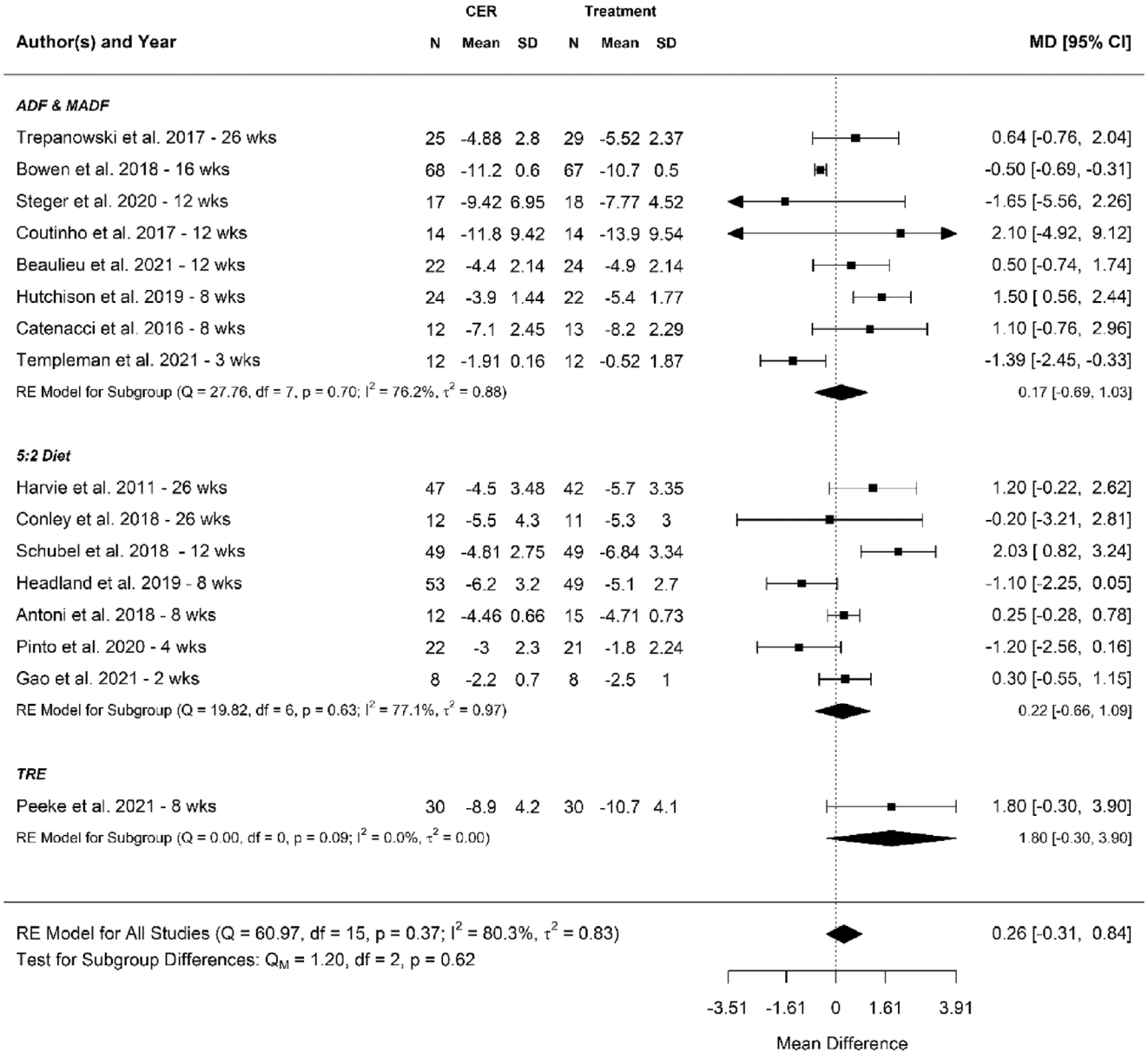


FIGURE 3 Forest plot on the effect of weight loss between CER and the intermittent fasting regimens (ADF/MADF, 5:2, and TRE). The arrows in the forest plot imply the CI going beyond the numbers showed in the plot. ADF, alternate day fasting; CER, caloric energy restriction; MADF, modified alternate day fasting; MD, mean difference in body weight loss; RE, random effects; TRE, time-restricted eating

with a range of body weights, with most of these restricted to participants with overweight and obesity or only obesity, whereas five studies included normal weight participants. We identified 12 RCTs on ADF/MADF, 8 on the 5:2 diet, and 4 on TRE. Fourteen studies compared IF with CER, eight studies compared IF with an ad libitum diet, and two studies used both ad libitum and CER as comparator diets.

Networking analysis

Figure 2 shows, for each regimen, the probability that it is ranked in any given position for the effectiveness of intervention for weight loss. The horizontal axis shows the possible ranks and the vertical axis the ranking probabilities. Each line connects the estimated probabilities of being at a particular rank for every intervention. ADF/MADF diets had the highest probability of 0.570 of ranking first for being the most effective for weight loss. The CER diet ranked after (0.381) followed by TRE (0.793) for weight-loss effectiveness. Not surprisingly, the ad libitum diet had the highest probability of 0.995 for ranking last as an effective weight loss strategy (Figure 2). The 5:2 diet had no clear ranking when compared with the other IF regimens. There were no observed inconsistencies found between direct and indirect comparison of studies in the network analysis using the node splitting method (Supporting Information Figure S3).

TABLE 2 Reported adherence of studies included in the meta-analysis

		Adherence					
Duration of weight loss	***Study***	**ADF**	**CER**	**5:2 diet**	**CER**	**TRE**	***Ad libitum***
Short term (≤3 mo)	Beaulieu et al., 2021 [24]	81% ± 16%[b]	90 ± 9%				
	Bhutani et al., 2013 [25]	80% ± 9%	Not reported				
	Steger et al., 2021 [26]	80%	80%				
	Varady et al., 2013 [15]	98% ± 5%	Not reported				
	Hirsh et al., 2019 [28]			98.0 ± 7.3%	Not reported		
	Schübel et al., 2018[a] [29]			73.5%	Not reported		
	Chow et al., 2020 [33]					60%[c]	NA[c]
	Cienfuegos et al., 2020 [32]					88.6%	Not reported
Long term (>3 mo)	Bowen et al., 2018 [27]	71.7%[a]	69.6%				
	Trepanowski et al., 2017 [16]	8%[b]	31%				
	Conley et al., 2018 [30]			73%	75%		
	Harvie et al., 2011 [31]			44%	32%		

Abbreviations: ADF, alternate day fasting; CER, caloric energy restriction; TRE, time-restricted eating.
[a]Estimated from figures presented in the publication.
[b]Significantly different from CER.
[c]The TRE group was adherent on 55.5% ± 22.4% of days to eating within ±15 minutes of the 8-hour eating time window, on 60% ± 23% of days to within ±30 minutes, and on 66.3% ± 20.7% of days to within ±60 minutes of the 8-hour time window. The average adherence to the intervention was therefore 60%.

Meta-analysis of IF regimens for weight loss

ADF/MADF versus 5:2 versus TRE

ADF/MADF interventions induce a body weight loss ranging from 0.77% to 12.97%, whereas the 5:2 diet resulted in weight loss ranging from 1.70% to 7.97%. The range of body weight loss from TRE was between 0.95% a 8.60% (Table 1). The degree of weight loss achieved by ADF/MADF, the 5:2 diet, and TRE were not statistically different from one another (Figure 3).

IF versus CER

Meta-regression analyses have shown that weight loss was similar when IF regimens were compared with CER (mean difference: 0.26 kg, 95% CI: −0.31 to 0.84; $p = 0.37$; Figure 3). The moderate mean differences of loss of body weight observed were similar when comparing the ADF/MADF regimen with CER diets and were not statistically significant (0.17 kg, 95% CI: −0.69 to 1.03; $p = 0.70$) or the 5:2 diet to CER (0.22 kg, 95% CI: −0.66 to 1.09; $p = 0.63$). Only one study compared TRE with CER, and this study also reported nonsignificant differences (1.80 kg, 95% CI: −0.30 to 3.90; $p = 0.09$) in body weight between the two diet groups [23]. The results of the meta-regression are ranked by study duration (Figure 3 and Supporting Information Figure S4). We tested study duration in the meta-regression because of its potential confounding effect on weight loss, but there were no significant differences between ADF/MADF versus CER ($p = 0.6858$) and 5:2 versus CER ($p = 0.2797$; Figure 3) [22]; therefore, the figures presented did not include duration as a confounding factor. High heterogeneity was observed in studies assessing IF regimens versus CER diets and ad libitum food consumption ($I^2 > 70\%$) [22].

Publication bias was assessed using funnel plots for IF regimens compared with both CER and ad libitum diets (Supporting Information Figures S5, S6). The funnel plots were both symmetrical, and there was no publication bias observed using Egger's test ($p = 0.8251$ and $p = 0.5110$, respectively).

Compliance assessment

Twelve studies reported percentage adherence to the prescribed diet and were included in the compliance evaluation: six ADF/MADF [15,16,24–27], four for the 5:2 diet [28–31], and two for TRE [32,33] (Table 2). For the short-term studies, percentage adherence ranged from 71.7% to 98% for ADF/MADF, 73.5% to 98% for the 5:2 diet, and 83% to 89% for TRE. In the longer-term studies (>3 months), adherence was generally lower than for the short-term studies, ranging from 8% [16] to 73% [28]. Beaulieu et al. [24] and Trepanowski et al. [16] reported a significantly lower dietary adherence to MADF versus CER, whereas Bowen et al. [27] and Steger et al. [26] found no difference between the two groups. As for the 5:2 diets, no significant differences in adherence were noted when 5:2 was compared with CER [30,31]. When average retention rates (enrolled/completed) were used as a gross indicator of compliance for all included studies, TRE ranked the highest (94%), followed by the 5:2 diet (88%) and ADF/MADF (85%).

DISCUSSION

Recent systematic reviews have compared the efficacy of IF regimens with ad libitum eating and CER on microbiota [34], cardiometabolic risk factors [5,35], and weight loss [2,5,36]. Our present study showed that there was no statistical difference in the percentage of weight loss of either of the IF regimens when compared with CER and confirms results of previous meta-analyses by showing that IF regimens lead to successful weight loss relative to an ad libitum diet. IF regimens have the potential to be recommended as an alternative dietary intervention to CER for weight loss, but which ones may be most effective remains an open question, with potentially important implications for future studies and ultimately clinical practice. In the absence of direct comparisons, we applied a statistical approach to predict the most effective dietary weight-loss strategy. This indirect comparison is made possible by pooling data from the five regimens investigated in this study into a single network model. Such a method allows us to statistically rank the weight-loss efficacy of the three types of IF regimens (ADF/MADF, 5:2, and TRE). An important limitation is that the studies must be similar enough to be correctly interpreted by the statistical model. Despite the differences noted on meal timings and duration of fasting, consistency of the model was checked by the split node method and found to be adequate. The network analysis revealed that the ADF/MADF regimen had the highest probability of ranking first in effectiveness of weight loss as compared with the other regimens, including CER. This can be of practical relevance as CER is today considered the first choice among dietary interventions recommended for people with obesity [3,37]. We therefore suggest investigating the advantages of ADF/MADF for sustained weight loss, including their potential advantages over CER.

ADF/MADF showed the highest range of weight loss from 0.77% to 12.97% over 3 to 26 weeks as compared with the other regimens. The 5:2 diet produced weight loss ranging from 1.7% to 7.97%, whereas TRE ranged from 0.95% to 8.60% body weight loss. The high heterogeneity $I^2 > 70\%$ between the studies used in this meta-analysis could be attributed to various reasons such as the differences in study population, study design and study duration. The effect size for duration was taken into account in the model, with no statistical relevance, although the short time frames of the studies ranging from a few weeks to a maximum of 26 weeks limits a conclusive interpretation. Baseline BMI of study participants could also explain the variability in outcomes of the interventions. Most studies reported weight loss above 5% indicating a priori successful lowering of body weight within time frames between 8 and 26 weeks. Of note, most of the studies included in our analysis concluded that IF, independent of the type, led to similar weight loss compared with CER. These results are consistent with previous meta-analyses, which examined body weight outcomes in response to IF regimens compared with CER [1,2,9,38,39]. Collectively, IF diets, and in particular ADF/MADF, show promise to achieve weight loss in the ranges that associate with meaningful clinical benefits while potentially providing greater dietary flexibility.

The physiological effects of IF regimens have mechanistic similarities: alternating periods of food intake with periods of limited or null nutrient availability causes changes in metabolic flux within organs switching between storage and use of energy substrates. In response to food ingestion, carbohydrates and lipids are stored primarily in the liver, skeletal muscle and adipose tissue. In contrast, fasting promotes depletion of glycogen and mobilization of triglycerides to provide energy substrates for oxidative metabolism [40,41]. The more pronounced cycling between macronutrient storage and oxidation compared with the more constant nutrient fluxes associated with ad libitum eating are thought to promote metabolic flexibility with a range of whole-body metabolic benefits, including improved insulin sensitivity, fat turnover, and weight loss [6]. Importantly, reduced triglyceride removal rates and a lower turnover are considered a main determinant of weight gain in participants with obesity [40,41]. Therefore, ADF/MADF, which combines extreme day-to-day cycling of macronutrient anabolism and catabolism with overall reduced energy intake, may support metabolic flexibility while also preventing a decline of whole-body energy expenditure when calories are chronically restricted. However, the extent by which ADF/MADF and other IF patterns contribute to the mobilization and turnover of adipose tissue and how they impact whole-body energy expenditure during weight loss are not well understood, despite the central role of these two mechanisms on body weight control [6]. Therefore, further investigating how IF regimens compare in effectiveness and through which underlying mechanisms they promote weight loss would be important to provide optimal dietary guidance.

Compliance and study duration in IF regimens

Compliance is a main determinant of the success of weight-loss regimens, both for IF and CER [9,42]. However, it is challenging to draw conclusions on dietary adherence to IF from the reviewed studies because few studies reported adherence to both IF and CER in the same study. Yet we found that adherence to IF and CER was similar in the reviewed studies that directly compared the two groups [24,25,28,29]. Our observations are in line with the meta-analysis by Cioffi et al. [43], concluding that the two diets appear to have similar adherence rates. Supporting this conclusion, Pannen et al. [44], in a follow-up analysis to Schübel et al. [29], reported equally high adherence to IF, 5:2, and CER after a 12-week active weight-loss intervention. Nevertheless, we agree with other authors who maintain that adherence to IF remains inconclusive owing to methodological inconsistencies, and that further targeted studies should be conducted to assess dietary adherence to IF versus CER [9,45].

Study duration has been raised as a determining factor for compliance to IF as adherence starts declining after 3 months [5]. The reviewed studies here show a tendency for better dietary adherence in studies shorter than 3 months compared with longer-term studies (Table 2). This observation is in line with Pannen et al. [44] who reported declining adherence rates at the end of the maintenance phase (week 24) and the follow-up phase (week 50) compared with CER. Overall, and given that compliance to weight-loss regimens in general and IF in particular was seen to decline after 1 to 4 months [5,9], duration is a factor that should be taken into consideration when evaluating the efficacy of IF weight-loss interventions. Finally, although retention rates are sometimes used to provide a rough estimate of compliance, they generally reflect multiple reasons for dropping out of a study and therefore do not isolate adherence to the IF regimen. In addition, few

studies reported participants who have completed the study per group, making it more difficult to calculate retention rates specific to each regimen. Adherence and retention data from Chow et al. illustrate this discrepancy well, with a 90% retention rate on one hand and an adherence rate of 55% to 65% on the other [33]. For these reasons, we based our conclusions regarding compliance on adherence reporting.

Strengths and limitations

A strength of this review is that it included rigorous inclusion criteria selecting only randomized controlled studies. Furthermore, it used short-term and long-term studies, adjusting the models for study duration. However, our meta-analysis does have some limitations. For instance, the majority of the studies reviewed had small sample sizes, potentially limiting their ability to detect significant differences between intervention groups. In addition, the maximum length of the included studies is 12 months, which limits the applicability to longer-term health outcomes. Moreover, meal timing, duration of fasting, and background diet differed from study to study and were not controlled for in the present analysis. Only one TRE study directly compared outcomes with CER, thus no conclusion on effectiveness of weight loss could be made between these two regimens. In addition, owing to the nature of dietary intervention studies, participants were not blinded, which increases risk of bias.

Implications for future research

IF shows promise as a weight-management strategy for people with normal weight and a weight-loss strategy for people with overweight and obesity, but little is known about long-term sustainability and health effects. Longer-term RCTs (>1 year), will be needed to understand whether IF regimens are indeed sustainable and tolerable weight-management strategies for long-term use. Future research could also investigate the correlation between weight loss and BMI at the start of study, which we could not establish owing to the limited number of publications including normal weight participants. Finally, our results suggest that ADF/MADF may be the most effective IF regimen for weight loss. Additional RCTs designed to specifically compare the different IF regimens would allow validation of such findings and shed light on the mechanism of action underlaying their effectiveness.

In addition, studies with a longer duration and a larger population sample are also needed to understand potential long-term consequences on macro- and micronutrient inadequacies that may arise from intermittent food intake and their subsequent effects on health.

CONCLUSION

In summary, findings from this meta-analysis suggest that the three main forms of IF (ADF/MADF, the 5:2 diet, and TRE) are effective weight-loss interventions. These protocols produce body weight reductions ranging from 1% to 13% over 2 to 52 weeks. No statistically significant differences for weight loss were noted between IF regimens, suggesting that they may be equally effective for reducing body weight. We also compared the weight-loss efficacy of IF with that of CER but found no statistically significant differences. Networking analysis of a pooled data set predicted that ADF/MADF ranked the highest for weight loss, followed by CER, then TRE. No clear conclusions could be drawn on the 5:2 diet. Compliance to these protocols was also assessed. We found that adherence to each of the protocols was moderately high at the onset of treatment (80%), but it diminished over time. Compliance was similar for ADF/MADF, the 5:2 diet, TRE, and CER. Taken together, our results suggest that IF may be implemented as an alternative strategy to CER for weight loss and weight management tailored to the specific needs and acceptance by the individual. Well-powered RCTs that directly compare the weight-loss efficacy of the various IF regimens to one another, and also to that of CER, will be required to confirm these conclusions.

CONFLICT OF INTEREST

Paloma Elortegui Pascual, Maryann R. Rolands, Alison L. Eldridge, Philipp Gut, Kim Anne Lê, and Fabio Mainardi are employees of Société des Produits Nestlé S.A., a funder of the study. Leonidas G. Karagounis is an employee of Nestlé Health Science, Lausanne, Switzerland. Amira Kassis and Krista A. Varady have received financial support for this project from Société des Produits Nestlé S.A.

AUTHOR CONTRIBUTIONS

Paloma Elortegui Pascual, Maryann R. Rolands, Alison L. Eldridge, Kim Anne Lê, Philipp Gut, and Amira Kassis designed the study and defined the search strategy. Paloma Elortegui Pascual and Maryann R. Rolands performed the data extraction. Maryann R. Rolands and Fabio Mainardi did the data analysis. Alison L. Eldridge did the risk-of-bias assessments. All authors were involved in interpretation of findings, contributed to writing the paper, and had final approval of the submitted and published versions.

DATA AVAILABILITY STATEMENT

The R scripts used for analysis are available here: Mrolands123/FAST (github.com).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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