Advances in Nutrition 15 (2024) 100130

American Society for Nutrition
Excellence in Nutrition Research and Practice

Advances in Nutrition

AN INTERNATIONAL REVIEW JOURNAL

journal homepage: https://advances.nutrition.org/

Review

Effects of Intermittent Energy Restriction Compared with Those of Continuous Energy Restriction on Body Composition and Cardiometabolic Risk Markers – A Systematic Review and Meta-Analysis of Randomized Controlled Trials in Adults

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ABSTRACT

The interest in intermittent energy restriction (IER) diets as a weight-loss approach is increasing. Different IER protocols exist, including time-restricted eating (TRE), alternate-day fasting (ADF), and the 5:2 diet. This meta-analysis compared the effects of these IER diets with continuous energy restriction (CER) on anthropometrics and cardiometabolic risk markers in healthy adults. Twenty-eight trials were identified that studied TRE (k = 7), ADF (k = 10), or the 5:2 diet (k = 11) for 2–52 wk. Energy intakes between intervention groups within a study were comparable (17 trials), lower in IER (5 trials), or not reported (6 trials). Weighted mean differences (WMDs) were calculated using fixed- or random-effects models. Changes in body weight [WMD: –0.42 kg; 95% confidence interval (CI): –0.96 to 0.13; P = 0.132] and fat mass (FM) (WMD: –0.31 kg; 95% CI: –0.98 to 0.36; P = 0.362) were comparable when results of the 3 IER diets were combined and compared with those of CER. All IER diets combined reduced fat-free mass (WMD: –0.20 kg; 95% CI: –0.39 to –0.01; P = 0.044) and waist circumference (WMD: –0.91 cm; 95% CI: –1.76 to –0.06; P = 0.036) more than CER. Effects on body mass index [BMI (kg/m^2)], glucose, insulin, homeostatic model assessment for insulin resistance (HOMA-IR), serum lipid and lipoprotein concentrations, and blood pressure did not differ. Further, TRE reduced body weight, FM, and fat-free mass more than CER, whereas ADF improved HOMA-IR more. BMI was reduced less in the 5:2 diet compared with CER. In conclusion, the 3 IER diets combined did not lead to superior improvements in anthropometrics and cardiometabolic risk markers compared with CER diets. Slightly greater reductions were, however, observed in fat-free mass and waist circumference. To what extent differences in energy intakes between groups within studies may have influenced these outcomes should be addressed in future studies.

Keywords: healthy adults, meal timing, intermittent fasting, alternate-day fasting, time-restricted eating, 5:2 diet, daily calorie restriction

Statements of significance

This meta-analysis provides an up-to-date overview of the effects of 3 intermittent energy restriction diets – time-restricted eating, alternate-day fasting, and the 5:2 diet – compared with continuous energy restriction on body composition and different cardiometabolic risk markers. The results suggest that intermittent energy restriction diets are not superior to continuous energy restriction diets, except for small but significant additional decreases in waist circumference and fat-free mass.

Abbreviations: ADF, alternate-day fasting; CER, continuous energy restriction; DBP, diastolic blood pressure; FM, fat mass; IER, intermittent energy restriction; RCT, randomized controlled trial; SBP, systolic blood pressure; WC, waist circumference; WMD, weighted mean difference.

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https://doi.org/10.1016/j.advnut.2023.10.003
Received 24 May 2023; Received in revised form 21 September 2023; Accepted 6 October 2023; Available online 10 October 2023

Introduction

Intermittent energy restriction (IER) diets are becoming increasingly popular in managing overweight and obesity and are frequently favored as an alternative to continuous energy restriction (CER). The overall principle of IER diets is to abstain from energy intake for a specific period of time every day or week, alternating with ad libitum energy intake during the remaining period [1]. IER can be considered an umbrella term for various dietary protocols, of which time-restricted eating (TRE), alternate-day fasting (ADF), and the 5:2 diet are the most well-known. TRE is a type of diet in which energy intake is only allowed during a prespecified time window of <12 h each day [2]. In ADF, individuals alternate between days of energy restriction and days of ad libitum food consumption [1,3]. The energy restriction can either be a complete fast (i.e., no energy intake on fasting days) or modified (~25% of daily energetic needs within a certain window of time). The 5:2 diet involves 2 consecutive or nonconsecutive energy-restricted days each week alternated with 5 d of habitual energy intake [3]. Restrictions on dietary intake on fasting days differ between protocols, and intakes range from a complete caloric fast to a maximum intake of ~25% of total daily energy needs [1].

Both rodent studies and human randomized controlled trials (RCTs) have suggested that IER diets improve body composition and cardiometabolic risk markers. For example, studies in rats and mice reported beneficial effects on body fat distribution, the serum lipid profile, fasting glucose and insulin concentrations, insulin sensitivity, blood pressure, and heart rate [4–6]. In humans, IER diets improve body composition, the serum lipid profile, glucose and insulin metabolism, blood pressure, and oxidative stress [1,3,7,8]. Moreover, adhering to an IER diet for 4–24 wk lowered body weight by 4%–10% [4]. Nonetheless, extensive research has already shown that CER also results in significant body weight loss and subsequent improvements in body composition and cardiometabolic risk markers [9–13]. Whether the health effects of IER are superior to those of CER has been studied less extensively. It may be that the prolonged fasting period that is typical for IER diets has additional health effects, which may vary between the different IER protocols and may be related to a metabolic switch. This means the body switches from using liver-derived glucose for energy production to oxidizing fatty acids and ketones [14–16]. Moreover, although evidence for IER diets is limited, prolonged fasting has been linked to autophagy, which results in the elimination of damaged proteins and mitochondria from cells and the recycling of their undamaged components [7,14]. This will ultimately protect cells against oxidative and metabolic stress, preserving normal cell function and protection against various noncommunicable diseases, including cardiovascular diseases, neurodegenerative diseases, and cancers [17]. This systematic review and meta-analysis of RCTs, therefore, compared the effects of 3 types of IER diets – TRE, ADF, and the 5:2 diet – with the CER diet on anthropometrics and cardiometabolic risk markers in apparently healthy adults.

Methods

The protocol was registered in the PROSPERO (registration no CRD42022350008) on 13 August 2022.

Search strategy

The Cochrane Central Register of Controlled Trials, PubMed, and Embase were searched to identify potentially relevant studies. Articles published up to 6 February 2023, were retrieved. The search included keywords and MeSH terms related to the intervention, e.g., "intermittent fasting" or "alternate-day fasting," and outcomes, e.g., "waist circumference" or "cholesterol." The full search string can be found in Supplementary Table 1. Only original RCTs published in English that compared TRE, ADF, or the 5:2 diet with the CER diet were considered for inclusion, and no restriction was applied on the publication date. Additional studies were identified by searching the reference lists of the studies that were obtained by our systematic search.

Selection procedure

Search results that were retrieved by the search strategy were imported into Endnote X9 (Clarivate Analytics) and screened in a 2-stage approach after duplicates were removed. Two review authors (RPM and MMS) first independently read the titles and abstracts of the identified studies to select studies of potential relevance. Then, the full texts of these potentially relevant articles were read independently by the 2 review authors and assessed for eligibility. The articles were included if they met all the inclusion criteria, and any disagreement between the 2 review authors was resolved through discussion until a consensus was reached.

Eligibility criteria

The following inclusion criteria based on the population, intervention, comparison, and outcome approach were used to select studies eligible for this systematic review and meta-analysis: *1*) a population of apparently healthy individuals aged ≥18 y with a normal weight, overweight, or obese, *2*) parallel or cross-over RCTs with IER protocols, i.e., TRE, ADF, or the 5:2 diet, as the intervention group, and *3*) CER as the control group, and *4*) outcome measures included anthropometrics [body weight, BMI, fat mass (FM), fat-free mass (FFM), and waist circumference (WC)], and parameters related to fasting lipids and lipoproteins [total cholesterol (TC), LDL cholesterol, HDL cholesterol, and triacylglycerol (TG)], fasting glucose and insulin concentrations, HOMA-IR, and blood pressure [systolic blood pressure (SBP) and diastolic blood pressure (DBP)]. Only studies in which body weight and ≥2 of these aforementioned outcome measures were reported were considered for inclusion in this systematic review. We excluded studies in individuals with specific diseases or health conditions, such as cancer, diabetes, and nonalcoholic fatty liver disease. RCTs that contained multiple intervention arms were considered, but we excluded intervention groups that received a cointervention that was not provided to the other intervention arms, such as added physical activity, support sessions, or a specific nutrient-rich diet. Studies that only presented median values for the outcomes of interest were also excluded from meta-analyses for those specific outcomes.

Data extraction

Data from the studies that were selected after the second study selection round were extracted and collected into an Excel spreadsheet (Microsoft Excel, version 16.60). The following data were extracted: study information (first author, year of publication, study design, subgroups, health status, dietary instructions, medication use, study duration, data adjustment, and funding received), study population at baseline (sample size of each subgroup, sex, mean age, and mean BMI), data collection and study outcomes (anthropometrics, lipids and lipoproteins, glucose and insulin, blood pressure, energy intakes, timepoints of measurements, and methodology of measurements). Quantitative baseline and outcome measures, such as means, medians, SD, SEM, and 95% confidence intervals (95% CIs), were extracted. In case outcome parameters were reported in figures alone, a pixel ruler was used to estimate the corresponding mean value for each subgroup [18].

Risk of bias assessment

The Risk of Bias 2 (RoB 2) tool for parallel studies [19] was used to assess the RoB of each study that was included in this systematic review and meta-analysis. The RoB 2 tool assessed the following 5 domains: *1*) randomization process, *2*) deviations from the intended interventions, *3*) missing outcome data, *4*) measurement of the outcomes, and *5*) selection of the reported result. These domains were judged as having a low RoB, some concerns, or a high RoB, which was then used to determine the overall RoB score for each study. The overall RoB score was based on RoB 2 recommendations. A study was scored as "low risk of bias" in case all 5 domains were judged as low risk. It was scored as "some concerns" if ≥1 out of 5 domains was judged as "some concerns," but none of the domains was scored as "high-risk." An overall "high-risk" score was given when ≥1 domain was scored as high-risk.

Statistical analysis

A meta-analysis was performed when ≥2 different IER diets (i.e., TRE, ADF, or the 5:2 diet) included a minimum of 2 studies that provided data for that specific outcome variable. For all outcome parameters, mean changes between baseline and postintervention in the comparison group were subtracted from mean changes in the intervention group, and in case studies reported multiple time points, the values measured at baseline and at the end of the weight-loss intervention period or at the end of the supervised intervention period were used to calculate mean changes. Fixed-effect models were used to calculate summary estimates of weighted mean differences (WMDs) and 95% CIs. These were then visualized using forest plots, including specific subgroup analyses for TRE, ADF, and the 5:2 diet. The inverse of the $1/SE^2$ (within-subject variant) was used as a weighting factor. The correlation coefficients, which represent the within-subject correlation between repeated measurements that were used in the meta-analysis calculations can be found in Supplementary Table 2.

Heterogeneity between studies was assessed using the I^2 value, which estimates the proportion of variation in point estimates that is because of heterogeneity rather than chance [20]. In case of relevant heterogeneity among studies, as indicated by I^2 >50%, a random-effects model was selected to calculate WMDs and 95% CIs. Potential sources of heterogeneity were explored with further subgroup analyses. The following subgroups were explored: differences in reported energy intakes between IER and CER groups within studies (statistically significant difference compared with no statistically significant difference compared with an unknown difference in energy intake), mean BMI (<33 compared with ≥33 kg/m^2), sex (male compared with female compared with both), study duration (<13 compared with >13 wk), and mean age (≤43 compared with >43 y). Subgroups for BMI, study duration, and age were based on median baseline values to have a comparable number of studies in each subgroup.

Publication bias was assessed by visual inspection of funnel plots and evaluation of funnel plot asymmetry using Egger's weighted regression test [21]. An intercept that did not significantly differ from 0 indicated the absence of publication bias. Meta-analyses were performed using Stata version 14.0 (Stata Corporation), and Egger's weighted regression tests were performed in SPSS for Mac version 28.0 (IBM Corporation). Results were considered to be significant if *P* value of <0.05.

Results

Study selection

Figure 1 [22] shows the selection process. Initially, 5982 articles were identified, and an additional 12 articles were selected from reference lists. After removing duplicates (k = 964), the titles and abstracts of the remaining 5018 articles were screened, and 4948 articles were excluded. The full texts of the remaining 70 articles were read. Finally, 28 articles met the inclusion criteria, of which 27 were retrieved from the database search and 1 from the reference lists. Of these, 28 included studies, 26 were original studies, and 2 of those studies published an additional paper in which different outcome measures were reported.

Study characteristics

Table 1 presents the characteristics of the 28 included RCTs. All studies had a parallel design. Seven studies involved a TRE intervention group [23–29], 10 studies an ADF intervention group [30–39], and 11 studies a 5:2 diet intervention group [40–50]. In total, 2043 participants were included in the studies, ranging from $N = 8$ to $N = 118$ participants per study arm. The mean age of the participants varied from 27 to 68 y, and their mean BMI from 22 to 40 kg/m^2. Most studies included both men and women [26–31,33–36,38,39,42,44–47,49,50]. In 1 study, only men participated [43], and in 8 studies, only women [23–25,32,37,40,41,48]. The intervention periods ranged from 2 to 52 wk. In 1 study, however, postintervention measurements were performed as soon as participants had lost ≥5% of their baseline body weight. The median intervention period had a duration of 59 d in the IER group and 73 d in the CER group [42]. We excluded intervention or control arms from multiple studies because they did not fulfill the inclusion criteria [31,33,37,38,41,44,47,49]. Pureza et al. [23,25] reported the effects of TRE compared to CER on BMI, WC, and blood pressure after both 3 wk and 12 mo, but only data collected after 12 mo were included. Finally, Thomas et al. [29] only reported median changes for TC, HDL cholesterol, LDL cholesterol, and TG concentrations, and these outcomes could not be used in the meta-analyses. Funding information for the included studies can be found in Supplementary Table 3.

Data on daily energy intakes were reported in 23 of the included studies [24,26–35,37–46,48]. In 13 of these studies, energy intakes at baseline and at the end of the intervention periods were provided [24,29,31,32,34,38,40–46]. In the 10 other articles, the change in energy intakes from baseline [27,28,33,

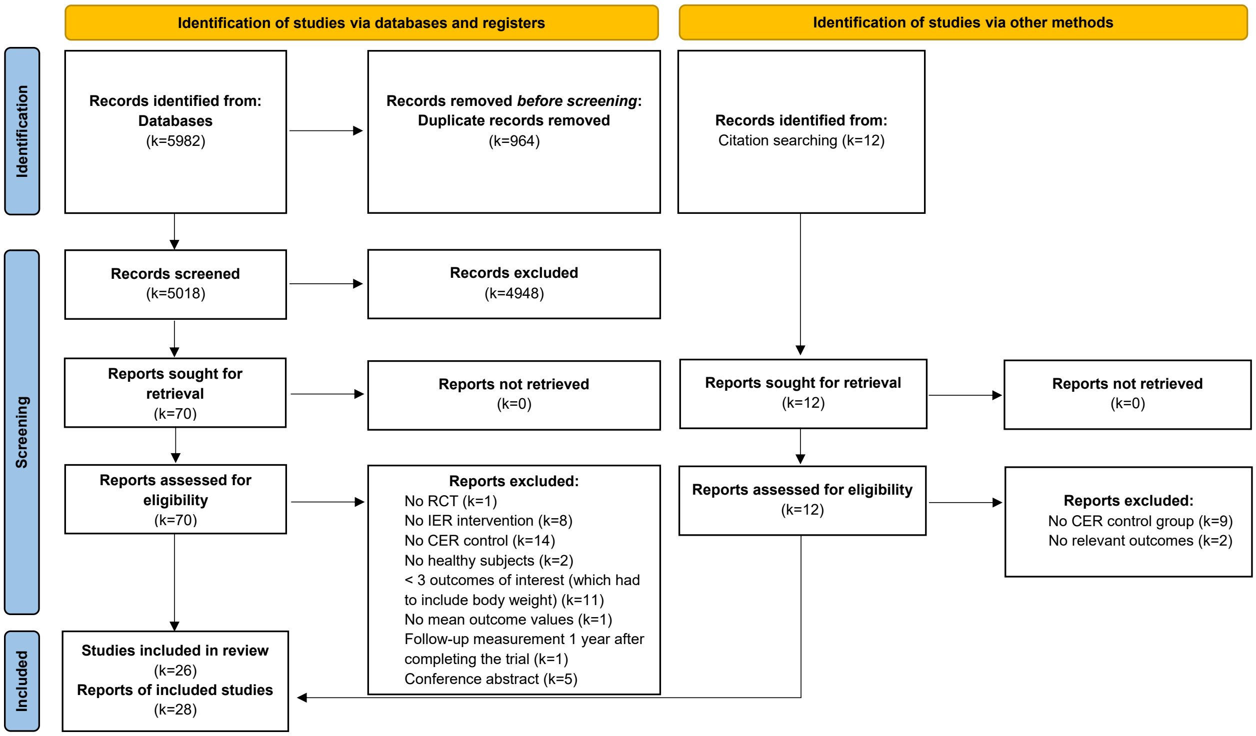

FIGURE 1. PRISMA flow diagram for the selection process and inclusion of the human randomized controlled trials [22]. CER, continuous energy restriction; IER, intermittent energy restriction; PRISMA, preferred reporting items for systematic reviews and meta-analyses; RCT, randomized controlled trial.

37], only the postintervention energy intakes [26], the energy intakes at various time points during and at the end of the intervention period [35,39,48], or the mean energy intakes during the intervention period [30] were given. Of the articles that reported data on energy intake, 17 articles found that the difference in changes in energy intakes [28,33], postintervention energy intakes [26], or energy intakes during the intervention periods [24, 27,29,31,32,35,38,39,41,43–46,48] did not significantly differ between the IER and CER group. In 5 articles, a lower dietary energy intake in the IER than in the CER group was observed [30, 34,37,40,42]. No results on energy intakes during the intervention periods were published in the 6 other papers [23,25,36,47, 49,50]. The methods used to estimate the energy intakes of the participants can be found in Supplementary Table 4.

Effects on anthropometrics

No significant differences were found between the IER and CER diet for changes in body weight (WMD: –0.42 kg; 95% CI: –0.96 to 0.13; k = 25; $P = 0.132$; Supplementary Figure 1A) and BMI (WMD: −0.03; 95% CI: –0.30 to 0.24; k = 13; $P = 0.814$; Supplementary Figure 1B). The TRE diet showed a greater weight loss than CER diet (WMD: –0.93 kg; 95% CI: –1.69 to –0.17; k = 6; $P = 0.016$), whereas ADF and the 5:2 diet achieved a comparable weight loss as the CER diet. BMI was reduced less in the 5:2 diet group compared with the CER diet group (WMD: 0.34; 95% CI: 0.04–0.64; k = 4; $P = 0.025$). The IER regimen resulted in a significantly greater WC reduction than the CER regimen (WMD: –0.91 cm; 95% CI: –1.76 to –0.06; k = 17; $P = 0.036$; Supplementary Figure 1C). No significant effects on WC were found for the 3 IER diets separately ($P > 0.05$). Relevant heterogeneity between studies was found for body weight, BMI, and WC ($I^2 > 50\%$).

FFM decreased more in the IER diet groups than in the CER diet group (WMD: –0.20 kg; 95% CI: –0.39 to –0.01; k = 16; $P = 0.044$, Supplementary Figure 1D) and no relevant heterogeneity was observed ($I^2 = 39.7\%$). No overall effect was found for FM (WMD: –0.31 kg; 95% CI: –0.98 to 0.36; k = 15; $P = 0.362$; Supplementary Figure 1E), and heterogeneity was relevant ($I^2 = 74.9\%$). The changes in FFM and FM were significantly greater for TRE than that for CER (FFM: WMD: –0.34 kg; 95% CI: –0.67 to –0.01; k = 5; $P = 0.042$ | FM: WMD: –0.91 kg; 95% CI: –1.63 to –0.18; k = 4; $P = 0.014$). These significant subgroup effects were not observed for ADF and the 5:2 diet.

Effects on fasting lipids and lipoproteins

Changes in fasting TG (WMD: –0.01 mmol/L; 95% CI: –0.07 to 0.04; k = 17; $P = 0.673$; Supplementary Figure 2A), TC (WMD: –0.03 mmol/L; 95% CI: –0.11 to 0.05; k = 16; $P = 0.604$; Supplementary Figure 2B), HDL cholesterol (WMD: –0.001 mmol/L; 95% CI: –0.03 to 0.02; k = 16; $P = 0.934$; Supplementary Figure 2C), and LDL cholesterol concentrations (WMD: –0.04 mmol/L; 95% CI: –0.10 to 0.02; k = 16; $P = 0.162$, Supplementary Figure 2D) were not significantly different between IER and CER. Relevant heterogeneity was not observed for TG, TC, HDL cholesterol, and LDL cholesterol ($I^2 < 50\%$). Effects on fasting TG, TC, HDL cholesterol, and LDL cholesterol concentrations did not differ between the TRE, ADF, and 5:2 subgroups compared with CER ($P > 0.05$).

Effects on fasting glucose and insulin concentrations and insulin sensitivity

Comparable changes were observed between IER and CER for fasting glucose concentrations (WMD: –0.01 mmol/L; 95% CI: –0.08 to 0.05; k = 19; $P = 0.681$; Supplementary Figure 3A),

TABLE 1
Characteristics of the studies included in this systematic review and meta-analysis

Reference	Population	Intervention		Duration	Sample size		Age (y)[1]		BMI (kg/m^2)[1]		Outcomes
		IER	CER		IER	CER	IER	CER	IER	CER	
The 5:2-diet:											
Antoni et al. [42]	Overweight and obese individuals	• ER days: ~630 kcal/d • Feast days: eu-energetic healthy diet	~23% ER daily	After 5% body weight loss was achieved (median days: 59 for IER and 73 for CER)	N = 24 started N = 15 met weight loss target (53% women)	N = 17 started N = 12 met weight loss target (50% women)	42 ± 15	48 ± 12	30 ± 3	31 ± 5	Body composition, blood pressure, lipid- and glucose metabolism
Conley et al. [43]	Obese males	• ER days: 600 kcal/d • Feast days: ad libitum intake	500 kcal/d energy deficit	6 mo	N = 12 started N = 11 finished	N = 12 started and finished	68 ± 3	67 ± 4	33 ± 2	36 ± 4	Body composition, blood pressure, lipid- and glucose metabolism
Gao et al. [50]	Healthy, normal-weight adults	• ER days: 70% ER • Feast days: estimated energy requirements	20% ER daily	2 wk	N = 8 (50% women)	N = 8 (50% women)	23 (1)	26 (2)	22 (1)	23 (1)	Body composition, blood pressure, lipid- and glucose metabolism
Gray et al. [48]	Overweight women with previous but no current gestational diabetes	• ER days: 500 kcal/d • Feast days: habitual eating pattern	1500 kcal/d intake (~25% ER)	12 mo	N = 61 started N = 32 finished	N = 60 started N = 30 finished	39 (9)	40 (9)	35 (10)	33 (8)	Body composition, lipid- and glucose metabolism
Hajek et al. [47]	Obese individuals	• ER days: women 500 and men 600 kcal/ d • Feast days: unknown	Information and advice on healthy lifestyle	12 mo	N = 100 started (68% women) N = 99 finished	N = 100 started and finished (64% women)	51 ± 13	47 ± 13	33 (32–38)	34 (31–38)	Body composition and blood pressure
Harvie et al. [40]	Overweight and obese premenopausal women	• ER days: 75% ER with 50 g protein • Feast days: estimated energy requirements	25% ER daily	6 mo	N = 53 started N = 42 finished	N = 51 started N = 47 finished	40 ± 4	40 ± 4	31 ± 5	31 ± 5	Body composition, blood pressure, lipid- and glucose metabolism
Harvie et al. [41]	Overweight women	• ER days: 70% ER and ≤40 g cho • Feast days: estimated energy requirements	25% ER daily	3 mo + a 1-mo weight maintenance period	N = 37 started N = 33 finished	N = 40 started N = 27 finished	46 ± 8	48 ± 8	30 ± 4	32 ± 6	Body composition, blood pressure, lipid- and glucose metabolism
Headland et al. [49]	Overweight and obese individuals	• ER days: women 2100 and men 2520 kJ/d • Feast days: habitual diet	Women 4200 kJ/d and men 5040 kJ/d	12 mo	N = 118 started (82% women) N = 49 finished	N = 104 started (82% women) N = 53 finished	48 ± 15	52 ± 13	33 ± 5	33 ± 5	Body composition, lipid- and glucose metabolism
Pinto et al. [46]	Individuals with central obesity	• ER days: 600 kcal/d • Feast days: healthy eating advice	500 kcal/d energy deficit	4 wk	N = 23 started N = 21 finished (71% women)	N = 22 started and finished (73% women)	50 ± 12	56 ± 8	32 ± 5	31 ± 6	Body composition, blood pressure, lipid- and glucose metabolism
Schübel et al. [44]	Overweight and obese individuals	• ER days: daily 25% of energy requirements • Feast days: eu-caloric balanced diet	20% ER daily	12-wk intervention + a 12-wk weight maintenance + 26-wk follow-up	N = 49 started (49% women) N = 45 finished	N = 49 started (49% women) N = 41 finished	49 ± 9	51 ± 8	32 ± 4	31 ± 4	Body composition, blood pressure, lipid- and glucose metabolism
Sundfør et al. [45]	Adults with abdominal obesity and ≥1 other trait of MS	• ER days: women 400 and men 600 kcal/d • Feast days: habitual energy intake	Evenly reduced EI daily	6-mo weight loss period + a 6-mo weight maintenance phase	N = 54 started (48% women) N = 50 finished	N = 58 started (52% women) N = 55 finished	50 ± 10	48 ± 12	35 ± 4	35 ± 4	Body composition, blood pressure, lipid- and glucose metabolism
Alternate-day fasting:											
Beaulieu et al. [32]	Overweight and obese women	• ER days: 75% ER • Feast days: ad libitum intake	25% ER daily	Once 5% body weight loss was achieved within 12 wk	N = 24 started N = 12 met weight loss target	N = 22 started N = 18 met weight loss target	34 ± 9	35 ± 11	29 ± 3	29 ± 2	Body composition
Bowen et al. [36]	Overweight and obese individuals	• ER days: 5000 kJ/d • Modified fast days: 2400 kJ/d • Feast days: ad libitum intake	5000 kJ intake daily	16-wk weight loss + 8-wk weight maintenance period	N = 82 started (82% women) N = 67 finished	N = 81 started (80% women) N = 68 finished	40 ± 8	41 ± 9	36 ± 6	35 ± 6	Body composition, blood pressure, and lipid- and glucose metabolism
Catenacci et al. [30]	Obese individuals	• ER days: 0 kcal/d • Feast days: estimated energy requirements	400 kcal/d energy deficit	8 wk + a 24-wk follow-up period	N = 15 started (77% women) N = 14 week 8 N = 11 finished	N = 14 started (75% women) N = 12 week 8 N = 10 week 24	40 ± 10	43 ± 8	36 ± 4	40 ± 6	Body composition and lipid- and glucose metabolism
Coutinho et al. [35]/Castela et al. [39]	Obese individuals	• ER days: women 550 and men 660 kcal/d	33% ER daily	12 wk	N = 18 started N = 14	N = 17 started N = 14	39 ± 11	39 ± 9	36 ± 3	35 ± 4	

(continued on next page)

TABLE 1 (*continued*)

Reference	Population	Intervention		Duration	Sample size		Age (y)[1]		BMI (kg/m^2)[1]		Outcomes
		IER	CER		IER	CER	IER	CER	IER	CER	
		• Feast days: estimated energy requirements			finished (71% women)	finished (86% women)					Body composition and lipid- and glucose metabolism
Hutchison et al. [37]	Overweight and obese women	• ER days: 24-h fast • Feast days: 100% of energy requirements	30% ER daily	8 wk	*N* = 25 started *N* = 22 finished	*N* = 26 started *N* = 24 finished	49 (2)	51 (2)	32 (1)	33 (1)	Body composition, blood pressure, and lipid- and glucose metabolism
Steger et al. [34]	Overweight and obese individuals	• ER days: 550–800 kcal/d • Feast days: healthy eating, no requirements on energy intake	1200–1600 kcal intake daily	12-wk weight loss period + 12-wk weight maintenance period	*N* = 18 started (72% women) *N* = 14 week 12 *N* = 13 finished	*N* = 17 started (82% women) *N* = 14 week 12 *N* = 14 finished	43 ± 11	48 ± 10	31 ± 2	31 ± 3	Body composition and blood pressure
Templeman et al. [38]	Healthy, lean adults	• ER days: 24-h fast • Feast days: 150% of energy requirements	25% ER daily	3 wk	*N* = 12 (42% women)	*N* = 12 (58% women)	42 ± 11	45 ± 6	24 ± 2	24 ± 2	Body composition and lipid- and glucose metabolism
Trepanowski et al. [31]/Trepanowski et al. [33]	Overweight and obese individuals	• ER days: 25% of energy needs daily (month 0–6) • Feasts days: 125% of energy needs daily (month 0–6)	25% ER daily (month 0–6)	6-mo weight loss period + a 6-mo weight maintenance phase	*N* = 34 started (88% women) *N* = 25 month 6 (88% women) *N* = 21 finished	*N* = 35 started (83% women) *N* = 29 month 6 (79% women) *N* = 25 finished	46 (2)	44 (2)	34 (1)	35 (1)	Body composition, blood pressure, and lipid- and glucose metabolism
<u>Time-restricted eating:</u>											
Isenmann et al. [26]	Overweight and obese individuals	• Food intake (8 h): ad libitum intake • Fasting period (16 h): 0 kcal	500 kcal/d energy deficit	2-wk familiarization + 14-wk intervention period	*N* = 21 started *N* = 18 finished (56% women	*N* = 21 started *N* = 17 finished (65% women)	28 ± 5	27 ± 6	26 ± 3	26 ± 3	Body composition
Jamshed et al. [28]	Obese adults	• Food intake (8 h): 500 kcal/d energy deficit • Fasting period (16 h): 0 kcal	500 kcal/d energy deficit	14 wk	*N* = 45 (78% women)	*N* = 45 (82% women)	43 ± 10	43 ± 11	40 ± 7	39 ± 7	Body composition, blood pressure, and lipid- and glucose metabolism
Lin et al. [24]	Postmenopausal overweight women	• Food intake (8 h): 1400 kcal • Fasting period (16 h): 0 kcal	1400 kcal intake daily	8 wk	*N* = 30 (100 % women)	*N* = 33 (100% women)	50 ± 8	54 ± 8	26 ± 4	26 ± 4	Body composition, blood pressure, and lipid- and glucose metabolism
Liu et al. [27]	Obese adults	• Food intake (8 h): women 1200-1500 kcal/d and men 1500-1800 kcal/d • Fasting period (16 h) 0 kcal	Women 1200-1500 kcal/d men and 1500-1800 kcal/d	12 mo	*N* = 69 (48% women)	*N* = 70 (50% women)	32 ± 9	32 ± 9	32 ± 3	31 ± 3	Body composition, blood pressure, and lipid- and glucose metabolism
Pureza et al. [23]	Obese women	• Food intake (12 h): ~500–1000 kcal/d energy deficit • Fasting period (12 h): 0 kcal	~500–1000 kcal/d energy deficit	3 wk	*N* = 31 started *N* = 31 finished	*N* = 27 started *N* = 24 finished	32 (29–34)	31 (28–34)	34 (32–36)	33 (32–35)	Body composition, blood pressure, and glucose metabolism
Pureza et al. [25]	Obese women	• Food intake (12 h): ~500–1000 kcal/d energy deficit • Fasting period (12 h): 0 kcal	~500–1000 kcal/d energy deficit	12 mo	*N*=31 started *N*=13 finished	*N* = 27 started *N* = 14 finished	32 ± 7	31 ± 7	34 ± 5	33 ± 4	Body composition and blood pressure
Thomas et al. [29]	Overweight and obese individuals	• Food intake (10 h): 35% ER • Fasting period (14 h): 0 kcal	35% ER	39 wk	*N* = 41 started (83% women) *N* = 36 week 12 *N* = 32 finished	*N* = 40 started (88% women) *N* = 34 week 12 *N* = 31 finished	38 ± 8	38 ± 8	35 ± 6	34 ± 6	Body composition

Abbreviations: BMI, body mass index; CER, continuous energy restriction; CHO, carbohydrates; CI, confidence interval; EI, energy intake; ER, energy restriction; IER, intermittent energy restriction; IQR, interquartile range; MS, metabolic syndrome; SD, standard deviation; SEM, standard error of the mean.

[1] Age and BMI are presented as mean ± SD, except for Gao et al. [50] [mean (SEM)], Gray et al. [48] [median (IQR)], Hajek et al. [47] [median (IQR) for BMI], Hutchinson et al. [37] [mean (SEM)], Trepanowski et al. [31,33] [mean (SEM)], and Pureza et al. [23] [mean (95% CI)]. Data are presented for completers only for [26,29,31–33,35,38,39,42,43,46,47,50] and for the whole population for [23–25,27,28,30,34,36,37,40,41,44,45,48,49]. All studies, except for Isenmann et al. [26], received funding. Sundfør et al. [45] did not report funding. For funding details, see Supplementary Table 3.

fasting insulin concentrations (WMD: –0.17 μIU/mL; 95% CI: –0.82 to 0.47; k = 14; P = 0.604; Supplementary Figure 3B) and HOMA-IR (WMD: –0.07; 95% CI: –0.22 to 0.08; k = 13; P = 0.338; Supplementary Figure 3C). No heterogeneity was present for these outcomes ($I^2 < 50\%$). When analyzed separately, TRE, ADF, and the 5:2 diet did not show significantly different changes in glucose and insulin concentrations compared with the CER diet, whereas HOMA-IR decreased more in ADF than in CER (WMD: –0.73; 95% CI: –1.43 to –0.03; k = 4; P = 0.042).

Effects on blood pressure

Changes in SBP and DBP did not significantly differ between IER and CER (SBP: WMD: –0.48 mm Hg; 95% CI: –1.64 to 0.69; k = 15; P = 0.423 | DBP: WMD: –0.67 mm Hg; 95% CI: –2.05 to 0.71; k = 14; P = 0.342; Supplementary Figure 4). Relevant heterogeneity was found for DBP (I^2 = 59.2%) and not for SBP. In agreement with the overall effects of SBP and DBP, none of the separate IER diets differed significantly from the CER diet (P > 0.05).

Overview of the main findings

The main findings of the meta-analysis are summarized in Table 2. This table includes WMDs with the corresponding 95% CIs for all IER groups together and for the TRE, ADF, and 5:2 diet separately.

Subgroup analyses based on the influence of differences in energy intake

As previously mentioned, 17 articles reported no significant difference in daily energy intakes between the IER and CER group [24,26–29,31–33,35,38,39,41,43–46,48], whereas 5 articles found significantly greater decreases in daily energy intake in the IER group than in the CER group [30,34,37,40,42]. For the studies that reported either the energy intake at baseline and at the end of the intervention period or the percentage change from baseline, we have estimated the energy deficit over the complete intervention period (i.e., the energy deficit per day × the number of days of the intervention period) for the IER and CER groups. When a significant difference in energy intakes between the IER and CER regimens was reported, the mean difference (IER–CER) in total energy intakes during the intervention period was –19, 085 kcal [median (IER–CER): –20,705 kcal] compared to –4225 kcal [median (IER–CER): –2529 kcal] for studies that reported no significant difference in daily energy intakes between the IER and CER regimens.

Three subgroups were made: studies that reported a significantly lower energy intake during IER than CER, studies that reported no significant difference in energy intake between IER and CER, and studies that did not report data on energy intake. In none of the included studies, decreases in energy intakes were more pronounced in the CER than in the IER diet. The decreases in body weight were greater for IER than for CER within the subgroup in which differences in energy intake were significantly lower during IER than CER (WMD: –1.07 kg; 95% CI: –1.89 to –0.26; k = 5; P = 0.009) and in the subgroup with studies in which energy intakes did not significantly differ (WMD: –0.77 kg; 95% CI: –1.26 to –0.28; k = 15; P = 0.002) (Supplementary Table 5).

For the subgroup that included studies that reported a significantly lower energy intake in IER than CER, FFM was more

TABLE 2
An overview of the main findings of the meta-analysis

	IER combined				Time-restricted eating				Alternate-day fasting				5:2-diet			
Anthropometrics:																
Body weight (kg)	–0.42	(–0.96	to	0.13)	–0.93	(–1.69	to	–0.17)	–0.12	(–1.35	to	1.10)	–0.31	(–1.03	to	0.41)
BMI (kg/m^2)	–0.03	(–0.30	to	0.24)	–0.32	(–0.81	to	0.16)	0.04	(–0.35	to	0.42)	0.34	(0.04	to	0.64)
Waist circumference (cm)	–0.91	(–1.76	to	–0.06)	–1.17	(–2.54	to	0.20)	0.49	(–0.56	to	1.54)	–1.23	(–2.66	to	0.21)
Fat mass (kg)	–0.31	(–0.98	to	0.36)	–0.91	(–1.63	to	–0.18)	0.07	(–0.98	to	1.12)	–0.33	(–1.72	to	1.06)
Fat-free mass (kg)	–0.20	(–0.39	to	–0.01)	–0.34	(–0.67	to	–0.01)	–0.15	(–0.50	to	0.21)	–0.10	(–0.43	to	0.22)
Fasting cardiometabolic risk markers:																
Triacylglycerol (mmol/L)	–0.01	(–0.07	to	0.04)	0.02	(–0.12	to	0.15)	–0.05	(–0.16	to	0.06)	–0.00	(–0.08	to	0.07)
Total cholesterol (mmol/L)	–0.03	(–0.11	to	0.05)	0.07	(–0.13	to	0.28)	–0.07	(–0.23	to	0.08)	–0.03	(–0.14	to	0.07)
LDL cholesterol (mmol/L)	–0.04	(–0.10	to	0.02)	0.00	(–0.13	to	0.14)	–0.04	(–0.14	to	0.07)	–0.06	(–0.14	to	0.02)
HDL cholesterol (mmol/L)	–0.00	(–0.03	to	0.02)	0.02	(–0.02	to	0.06)	–0.04	(–0.08	to	0.01)	0.00	(–0.04	to	0.05)
Glucose (mmol/L)	–0.01	(–0.08	to	0.05)	–0.00	(–0.15	to	0.14)	–0.11	(–0.26	to	0.04)	0.01	(–0.07	to	0.10)
Insulin (μIU/mL)	–0.17	(–0.82	to	0.47)	–1.69	(–4.07	to	0.69)	0.27	(–0.62	to	1.17)	–0.47	(–1.49	to	0.55)
HOMA-IR	–0.07	(–0.22	to	0.08)	0.06	(–0.31	to	0.43)	–0.73	(–1.43	to	–0.03)	–0.06	(–0.23	to	0.10)
Blood pressure																
Systolic blood pressure (mm Hg)	–0.48	(–1.64	to	0.69)	–1.35	(–3.55	to	0.84)	1.26	(–0.84	to	3.37)	–1.16	(–2.97	to	0.65)
Diastolic blood pressure (mm Hg)	–0.67	(–2.05	to	0.71)	–2.91	(–6.62	to	0.81)	–0.29	(–1.76	to	1.18)	0.52	(–0.75	to	1.80)

Data are presented as weighted mean differences (95% confidence intervals) for IER diets compared to CER diets.
BMI, body mass index; CER, continuous energy restriction; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; IER, intermittent energy restriction; LDL, low-density lipoprotein.

reduced in the IER diet than in the CER diet (WMD: –0.43 kg; 95% CI: –0.81 to –0.06; k = 5; $P = 0.025$). For the subgroup that included studies that reported no difference in energy intake, the decrease in FFM was also greater within the IER diet than CER diet (WMD: –0.38 kg; 95% CI: –0.64 to –0.12; k = 9; $P = 0.005$). Significant results for both FFM and FM were observed in the subgroup that did not report on energy intake. Both outcomes were reduced less in the IER diet compared with the CER diet (FFM: WMD: 0.68 kg; 95% CI: 0.22–1.13; k = 2; $P = 0.004$ | FM: WMD: 1.58 kg; 95% CI: 0.87–2.30; k = 2; $P < 0.001$). Within all 3 subgroups, heterogeneity between studies was no longer present for FFM ($I^2 < 50\%$), but heterogeneity was not completely removed for the other anthropometric parameters. For the cardiometabolic risk markers, only significant findings were observed in the subgroup that did not report on energy intake. In this subgroup, glucose and HDL cholesterol concentrations were significantly decreased in IER compared with the CER diet (glucose: WMD: –0.21 mmol/L; 95% CI: –0.36 to –0.07; k = 3; $P = 0.005$ | HDL cholesterol: WMD: –0.08 mmol/L; 95% CI: –0.15 to –0.01; k = 3; $P = 0.020$).

Subgroup analyses for BMI, sex, study duration, and age

Subgroup analyses were performed for the outcomes that showed relevant heterogeneity in the main analyses. For that reason, changes in fasting lipids and lipoproteins, glucose and insulin concentrations, and SBP were not included in these analyses. Stratification for median BMI did not remove heterogeneity, except for body weight in the lower BMI subgroup and for DBP in the higher BMI group. In the lower BMI group, a meta-analysis showed a significantly greater reduction in body weight in IER compared with CER (WMD: –0.65 kg; 95% CI: –1.09 to –0.22; k = 13; $P = 0.003$). No other significant BMI subgroup effects were observed (Supplementary Table 6).

After stratification for sex, relevant heterogeneity was no longer present for body weight and FM in the groups that only contained women and for DBP in the group that contained both men and women, but heterogeneity remained for the other outcomes. In women, decreases in body weight (WMD: –1.01 kg; 95% CI: –1.52 to –0.50; k = 7; $P < 0.001$), FM (WMD: –1.08 kg; 95% CI: –1.68 to –0.48; k = 4; $P < 0.001$), and WC (WMD: –1.40 cm; 95% CI: –2.64 to –0.15; k = 6; $P = 0.028$) were significantly greater in the IER diet than in the CER diet (Supplementary Table 7). No significant differences between IER and CER were observed for subgroups that contained only men or both men and women.

Stratification for a shorter compared with longer study duration did not explain much of the heterogeneity among studies. It was no longer relevant for BMI and DBP in the subgroup that contained the studies with a longer study duration and for body weight in the subgroup with a short study duration. The subgroup that only included trials with a duration of <13 wk showed significantly greater decreases in body weight (WMD: –0.75 kg; 95% CI: –1.24 to –0.25; k = 12; $P = 0.003$) in IER compared with CER (Supplementary Table 8). The subgroup that only contained studies with a duration of >13 wk showed that the decrease in WC was significantly larger in IER than in CER (WMD: –1.28 cm; 95% CI: –2.42 to –0.15; k = 7; $P = 0.026$).

The subgroups for age did not remove the relevant heterogeneity. The effects of IER compared with CER on body weight, body composition, and DBP were not significant in both subgroups that were based on the mean age (Supplementary Table 9).

Publication bias

Funnel plots were created for all outcomes and presented in the supplements (Supplementary Figure 5). Visual evaluation of the funnel plots did not indicate the presence of publication bias. Egger's weighted regression tests also did not show funnel plot asymmetry for the included outcomes (all $P > 0.05$).

RoB

Supplementary Table 10 presents the results of the RoB assessment for each included study. In total, 5 studies (17.2%) were classified as having a low RoB, whereas the other studies (82.8%) were classified as having some bias concerns. This was mainly because most of these studies did not report whether outcome assessors were aware of the intervention received by the participants. Furthermore, all studies involved energy-restricted diets, and hence, participants were aware of their assigned intervention arm.

Discussion

The present systematic review and meta-analysis found that IER was not superior to CER for changes in weight loss, body fat, and other fasting cardiometabolic risk markers in adults who were apparently healthy with a healthy weight, overweight, or obese. The results further indicate that IER diets may have more pronounced effects on FFM and WC changes than the CER diet. Analysis of TRE, ADF, and the 5:2 diet separately also suggested limited differences compared with CER for all outcomes. The TRE diet led to significantly greater reductions in anthropometrics (body weight, FM, and FFM) than the CER diet, the ADF diet reduced HOMA-IR more than the CER diet, and BMI decreased less in the 5:2 diet compared with the CER diet.

To date, several systematic reviews and meta-analyses have been conducted that compared the effects of the IER diet with those of the CER diet on various health outcomes [51–57]. The added relevance of the present meta-analysis is the comparison of the TRE, ADF, and the 5:2 dietary protocols to understand better the different health effects of these types of IER. Additionally, a clear, homogenous population and a larger set of outcomes were selected as compared with other meta-analyses. In agreement with our meta-analysis's findings, various systematic reviews and meta-analyses have reported that IER and CER regimens result in comparable changes in body weight [51–54] and FM [51,52]. In contrast, the meta-analysis by Schwingshackl et al. [55] reported a small but significant effect of IER diets on body weight, whereas 2 other meta-analyses have reported that IER diets resulted in a greater reduction in FM compared with CER [53,55]. The present meta-analysis found that all IER diets combined reduced FFM slightly more than CER. If true, the added reduction of –0.20 kg FFM may not be clinically relevant and is unlikely to lead to muscle wasting. Similar to Harris et al. [53], the present study suggests that the IER diet reduced WC more than the CER diet. This effect, however, was not reported by 2 other meta-analyses [52,55]. The number of studies included in these meta-analyses for WC was smaller than the present study, and both meta-analyses did not include TRE diets in their analyses [52,55], whereas we found a significant subgroup effect for TRE. Schwingshackl et al. [55] did not include TRE interventions in their analyses because they only included studies with a duration of ≥12 wk, and all TRE trials obtained from their search had a duration of <12 wk [55]. Guerrero et al. [52] did not mention TRE in their inclusion criteria. The added reduction in WC of 0.91 cm that we report here is relatively small but may still be promising because it is an indicator of abdominal obesity and has been positively associated with the risk of developing cardiovascular diseases [58]. A meta-regression of prospective observational studies found that a 1 cm decrease in WC was associated with a 2.0% lower relative risk of incident cardiovascular disease events in the future [59].

The current findings suggest that weight loss may be more important than the type of diet for the beneficial effects of IER diets on cardiometabolic risk markers. In fact, no differences were found between the IER and CER diets for changes in fasting TC, LDL cholesterol, HDL cholesterol, TG, glucose, insulin concentrations, insulin resistance, and blood pressure. The no differences between the 2 dietary regimens in fasting TC [51–53], LDL cholesterol [51–53,55], HDL cholesterol [51–53], TG [53,55], and glucose concentrations [51,53,55], HOMA-IR [51], SBP [51,53,55,56], and DBP [51,53] agree with other meta-analyses. In contrast, 3 meta-analyses reported a significantly stronger reduction in fasting insulin concentrations in IER diets than in CER diets [51,53,57]. Of these, Cioffi et al. [51] included people with diabetes. He et al. [57] only included studies with ADF or the 5:2 diet as an intervention and excluded studies that did not report an equivalent energy restriction within IER and CER, whereas Harris et al. [53] only included studies in which individuals in the intervention group consumed ≤800 kcal daily for 1–6 d/wk and with a follow-up period of ≥12 wk. It has been hypothesized that the fasting period in IER diets lowers fasting glucose and insulin concentrations, which may consequently improve insulin resistance. This was confirmed by several human clinical trials [7,8]. In these studies, the IER diets were not compared with a CER diet but to another control regimen, for example, a 6-h TRE eating window that was compared to a 12-h eating window [7,8]. Thus, IER diets have been shown to improve glycemic control, but the present results in adults who were apparently healthy with a healthy weight, overweight, or obese suggest that these health effects are not more pronounced than the CER diet.

Next to the effects of all IER regimens combined, we performed subgroup analyses for TRE, ADF, and the 5:2 diet. Compared with CER, body weight, FM, and FFM were more decreased in TRE. HOMA-IR showed a greater reduction in ADF compared with CER, and BMI was less decreased in the 5:2 diet compared with CER. No evidence was found for differential effects of TRE, ADF, and the 5:2 diet on fasting lipid and lipoprotein concentrations, glucose and insulin concentrations, and blood pressure. The present findings, therefore, do not indicate that 1 of the 3 IER diets is superior compared with the other 2 regarding improvements in cardiometabolic health. However, these analyses should be interpreted with caution given the limited number of studies that were included in these subgroups.

When interpreting the results, it is important to realize that decreases in energy intake during the intervention periods between the IER and CER groups were not comparable in all included studies, which makes it difficult to compare the specific diets without the influence of differences in energy intake. All studies that reported a significant difference in energy intakes between the IER and CER groups found a greater caloric deficit over the intervention period in the IER group. For some studies, this difference in energy deficit between groups was relatively large, and we therefore expected to find a greater effect size for body weight than the meta-analysis found. In addition, subgroup analyses showed that body weight and FFM were more reduced in the IER diet than in the CER diet in the 2 subgroups with and without a comparable decrease in energy intake between the 2 arms. These effects did not differ between subgroups with and without a comparable decrease in energy intake. In contrast, FFM and FM reduced less in IER than in CER in the subgroup of studies that did not report on energy intakes. The finding that body weight decreased more in the 2 subgroups that reported energy intakes can partly be explained by the longer fasting duration in IER compared with CER. It has been suggested that fasting with a minimum duration of 12 h, which is typically observed in IER diets but not necessarily in CER diets, leads to intermittent metabolic switching, which may preserve muscle mass during fasting and have a beneficial effect on body composition [16]. Serum ketone concentrations, such as β-hydroxybutyrate, can be measured as metabolic switch biomarkers [16]. Ketones were, however, only measured and reported by 6 of the included studies [37,40–42,46]. Future IER studies should consider measuring these ketone concentrations to determine whether the metabolic switch may have occurred in participants and could potentially explain part of the findings. Finally, performing subgroup analyses for BMI, sex, study duration, and age did not remove all the heterogeneity between studies. In contrast, part of the heterogeneity was removed within subgroups for differences in energy intake, as indicated by $I^2 < 50\%$. This, thus, suggests that part of the heterogeneity and variation in effect sizes for specific outcomes between studies could be explained by the differences in energy intake. Additionally, the findings of the subgroup analyses could be considered exploratory and should be interpreted cautiously. Future studies are needed to further examine possible sex and age differences after adhering to an IER diet.

The systematic review and meta-analysis had several potential strengths and limitations. The study was registered a priori. A RoB assessment was also performed and suggested that the results were from studies ranging from a low RoB to some concerns. The total number of studies was relatively large, and therefore, various subgroup analyses could be performed, including the comparison of 3 different types of IER to also differentiate between their possible health effects. In addition, subgroups were formed for differences in energy intakes, which separated the effects of the eating schedules from the differences in calories consumed within the IER and CER groups. Unfortunately, subgroup analyses did not completely remove heterogeneity for all study outcomes. Furthermore, no RCTs with a duration of >1 y were included, making it difficult to comment on the long-term health effects of these types of diets. In addition, including anthropometrics and cardiometabolic risk markers alone may not reflect the full impact of IER diets on human health. Finally, some correlation coefficients for calculating the WMDs had to be estimated from previous research. If possible, we estimated these coefficients from studies included in the present meta-analysis, but for HOMA-IR, SBP, and DBP, these values were derived from another weight-loss study [9].

In conclusion, this systematic review and meta-analysis in individuals who were apparently healthy with a normal weight, overweight, or obese found that IER diets are not superior to the CER diet in improving anthropometrics and cardiometabolic risk markers. The potential effect of differences in energy intake between groups should be considered, as this may have influenced the main findings. Overall, the loss in body weight may be more important for improvements in cardiometabolic risk markers than the type of diet used to reach that weight loss. Future IER studies should include other health-related outcomes and should take differences in energy intake between groups into account to clearly differentiate between the effects of weight loss and the eating schedule, including the time of food intake on the results.

Author contributions

The authors' responsibilities were as follows – MMS, RPM: performed the literature searches, performed the screening of titles, abstracts, and full-text records, and data extraction from full-text records; MMS, PJJ: performed the statistical analyses; MMS: performed the risk of bias assessments and drafted the manuscript; all authors: contributed to the interpretation of the data and revised each draft of the manuscript for important intellectual content; and all authors: read and approved the final manuscript.

Conflict of interest

The authors report no conflicts of interest.

Funding

The authors reported no funding received for this study.

Data availability

Data described in the manuscript will be made available upon reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.advnut.2023.10.003.

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