



Intermittent Fasting for the Prevention of Cardiovascular Disease Risks: Systematic Review and Network Meta-Analysis

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Abstract

Context While several studies have assessed the potential effect of intermittent fasting on reducing cardiovascular risks, the findings are inconclusive.

Objective To compare the relative effectiveness of intermittent fasting methods in reducing key cardiovascular risks.

Methods Studies were searched from Medline, Embase, Cochrane Library Central and Global Health to identify studies that enrolled adults (≥ 18 years) to intermittent fasting methods and reported effects on one of the six specified cardiovascular risk factors. We performed a random-effects network meta-analysis using a frequentist framework. Outcomes were reported as mean differences (MD) with their corresponding 95% confidence intervals (CI).

Results Fifty-six studies were included in the analysis. With high certainty of evidence, modified alternate-day fasting was found to be the most effective intervention compared to a usual diet in reducing body weight (MD= -5.18 kg; 95% CI: -7.04, -3.32), waist circumference (-3.55 cm; -5.66, -1.45), systolic blood pressure (-7.24 mmHg; -11.90, -2.58), diastolic blood pressure (-4.70 mmHg; -8.46, -0.95). With high certainty, time-restricted eating was the most effective intervention compared to usual diet in reducing fat-free mass (-0.82 kg; -1.46, -0.17), waist circumference (-3.00 cm; -4.50, -1.51), diastolic blood pressure (-3.24 mmHg; -4.69, -1.79) and fasting plasma glucose (-3.74 mg/dL; -6.01, -1.46).

Conclusions Modified alternate-day fasting, and time-restricted eating appear to be promising approaches for reducing most cardiovascular risk factors. These intermittent fasting methods may be considered as potential components of lifestyle interventions aimed at managing cardiovascular disease risk factors. However, further long-term randomised controlled trials comparing intermittent fasting methods are needed to confirm their efficacy and assess their safety over time.

Keywords Intermittent fasting · Cardiometabolic risk factors · Network meta-analysis

Introduction

Cardiovascular diseases (CVD) are a leading cause of morbidity and mortality worldwide, affecting individuals in high-income as well as low-and middle-income countries [1]. The main contributors to the major cardiovascular diseases (ischemic heart disease and stroke) include overweight or obesity, high blood pressure, high blood glucose, and dyslipidaemia [1, 2]. Behavioural modification including dietary intake and physical activity is an important approach to mitigate cardiometabolic risk factors such as overweight or obesity, high blood pressure, elevated cholesterol levels and blood glucose [3, 4]. Weight control through energy restriction has been shown to improve cardiovascular risks including insulin resistance, blood glucose, and blood pressure [5].

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Intermittent fasting, which includes a range of approaches to achieve overall energy restriction, has emerged as an appealing alternative to continuous energy restriction (CER) for managing obesity and its related comorbidities due to its relative ease of maintaining long-term adherence [6, 7]. Intermittent fasting refers to dietary patterns that involve cycling between periods of eating and periods of fasting [8]. This creates periods of energy deficit, and metabolic change which can potentially leading to health benefits, including weight loss, improved insulin sensitivity, and better overall metabolic health [6, 9].

Among the many methods of intermittent fasting, some of the most adopted include alternate-day fasting (ADF), modified alternate day fasting (mADF), periodic fasting (PF), and time-restricted eating (TRE) [6, 10]. ADF is cyclic eating approach involves a 24-hour period of complete fasting (no calorie intake) followed by a 24-hour period of normal eating [8, 11]. The mADF is like ADF but allows for some calorie intake on fasting days (25% or less intake of energy) [8, 11]. PF is a cyclical weekly eating pattern with fasting for one or two days per week (consumption of 25% or less of required calories or restricting calorie intake to around 500–600 kcal/day) and then eating normally for the remaining five or six days a week. The 5:2 diet is a popular form of PF [8, 12]. TRE involves complete fasting (no calorie intake) for at least 12 h per day and eating freely the rest of the time [8, 12]. TRE involves limiting the daily eating window to a specific period, for example, an individual might eat all meals within an 8-hour window (e.g., 12:00 pm to 8:00 pm) and fast for the remaining 16 h each day (16/8 method). The most common TRE methods are the 16/8 and 14/10 method [8, 12].

Previous pairwise meta-analysis studies have shown some promise for intermittent fasting in reducing risk factors for cardiovascular disease. However, the results are not consistent [8, 11, 13]. Some meta-analyses suggest that intermittent fasting is more effective than usual eating pattern in reducing weight and waist circumference [11–14]. However, others showed no significant difference between intermittent fasting and CER for these measures [15, 16]. Regarding fat-free mass, there is no clear conclusion on whether intermittent fasting leads to undesirable loss of muscle mass. Some studies found no effect [13, 16], while others showed an increase [17] or decrease [15] compared to usual diet. Findings on blood pressure are also inconsistent. Some meta-analyses suggest intermittent fasting reduces systolic blood pressure (SBP) and diastolic blood pressure (DBP) compared to usual eating [11, 12], while others found no significant difference [13, 14]. Similarly, some studies showed intermittent fasting reduced fasting blood sugar [11, 14] and low-density lipoprotein (LDL) cholesterol [18], but others found no significant difference

compared to usual eating on fasting plasma glucose (FPG) [13] and LDL reduction [11, 12, 14]. The inconsistencies of results across the previous meta-analyses could be due to differences in terms of the population, the intervention duration (some included short duration studies) [12–14] and number of studies included [12–14]. Further, some conducted the analyses by combining all intermittent fasting methods together [11, 12, 16].

Since conventional pairwise meta-analysis is often limited by comparing two intervention at a time and cannot incorporate indirect evidence, there remains considerable uncertainty about which intermittent fasting methods are the most effective for improving cardiovascular health [19]. An alternative approach is network meta-analysis (NMA) which allows statistical comparison of three or more interventions that have not been directly compared in randomised controlled trials (RCTs) (19). Furthermore, NMA has the potential to enhance the precision of effect estimates derived from RCTs and traditional pairwise meta-analyses by integrating both direct and indirect evidence (19). This method offers a more thorough understanding of relative effectiveness and allows for the ranking of intermittent fasting methods, which is not possible with conventional pairwise meta-analysis. The aim of this systematic review and network meta-analysis was to assess the relative effectiveness of different intermittent fasting methods in improving key cardiovascular risk factors, including body weight, waist circumference, fat free mass, elevated blood pressure, FPG, low density lipoprotein cholesterol.

Methods

The protocol was registered at PROSPERO (CRD42023475279), and the NMA was reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis for Network Meta-Analyses (PRISMA-NMA) guidelines [20] (see supplementary material (S1).

Search Strategy

We searched four databases: Medline, Embase, Cochrane Library, and Global Health—from inception to November 09, 2023, and the search was updated up to December 11, 2024. We also performed manual searches of references from relevant reviews and eligible studies. The key search terms include a combination of “intermittent fasting” or “alternate day fasting” or “periodic fasting” or “time restricted eating /feeding” or “intermittent energy restriction” and body weight or waist circumference or fat-free mass or blood pressure or SBP or DBP or LDL or fasting

plasma/blood glucose. The full search strategy is presented in the supplementary material (S2). The search was limited to RCTs, published in English. There was no limitation on publication date or location. Search results were exported to Covidence for duplicate removal, screening and data extraction.

Eligibility Criteria

We developed the eligibility criteria based on the PICOS framework (Participants, Interventions, Comparisons, Outcomes, and Study design). All inclusion and exclusion criteria are summarised in Table 1. This systematic review and network meta-analysis included only RCTs.

Screening and Data Extraction

Three independent reviewers conducted the title and abstract screening: KTK screened all, TKT screened 69%, and YMM screened 31%. KTK performed the full-text review, with TKT double-checking 20%, applying the inclusion and exclusion criteria. Any discrepancies between the reviewers were resolved through discussion and consensus. The step-by-step procedure of identifying, screening, and incorporating or excluding studies presented using the PRISMA 2020 flow diagram (Fig. 1). Data were extracted using a pre-tested data abstraction form. The following information was extracted from each eligible study: first author, publication year, country, the intervention duration, sample size, participant characteristics (sex, age, BMI) and outcomes measured, intervention or intermittent fasting type (s), control group diet, number of participants in each group (treatment and control group). If intermittent fasting outcomes were

reported at multiple time points, we extracted data from the last reported time point or the end of the intervention.

For studies reporting pre- and post-intervention measures, we calculated mean differences and standard deviations using Cochrane Handbook methods [21]. Missing standard deviations were estimated from standard errors or confidence intervals. For studies that reported only medians and interquartile ranges, means were estimated using the Wan method [22]. In cases the data were only available in figures, numerical data was obtained using Plot Digitiser (<https://plotdigitizer.com/app>).

Risk of Bias Assessment

We assessed the risk of bias using the Cochrane Collaboration's Risk of Bias 2 (Rob 2) tool for RCTs [23]. This tool comprises five bias components: bias in the randomization process, bias resulting from deviations in intended interventions, bias due to missing outcome data, bias in the measurement of outcomes, and bias in the selection of reported results. Each study was assessed and categorised according to its risk of bias into three levels (low risk of bias, some concerns, or high risk of bias), for each domain evaluated. A study was deemed to have a low overall risk of bias if all domains were rated as having a low risk of bias. Conversely, a study was considered to have a high risk of bias if at least one domain is rated as high risk, or if three and more domains were categorised as having 'some concerns'. A study would fall into the 'some concerns' category overall if one or two of the domains are rated as having some concerns, but none were classified as high risk of bias [23].

Table 1 PICOS criteria for inclusion and exclusion of studies

Parameter	Inclusion Criteria	Exclusion criteria
Participant/ Population	Adults aged ≥ 18 years with or without cardiometabolic risk factors but without other chronic diseases such as cancer, non-alcoholic fatty liver disease	studies conducted on children, pregnant women, or animals;
Interventions	One or more types of intermittent fasting (ADF, mADF, PF, TRE) lasting at least for two weeks	studies that combined intermittent fasting with other interventions, such as intermittent fasting plus Mediterranean diets or exercise
Comparators	At least one comparator arm, which could be either control group without intervention (unchanged eating habit or on usual diet) or another intermittent fasting type.	If comparison is one intermittent fasting based on time (e.g. early TRE vs. late TRE)
Outcomes	RCTs reporting effect sizes or changes in data before and after the intervention were included if they assessed at least one of the following cardiometabolic risks: body weight, waist circumference, fat-free mass, blood pressure (SBP and DBP), fasting blood glucose, or LDL cholesterol	studies that did not include any of the outcomes of interest or did not present sufficient information
Study designs	RCTs conducted in developed or developing countries	Religious fasting studies, pre-post studies, studies with small sample size ($n < 10$); non-randomised controlled trials, including cohort studies, case-control studies, cross-sectional studies, reviews, case reports, and conference abstracts.

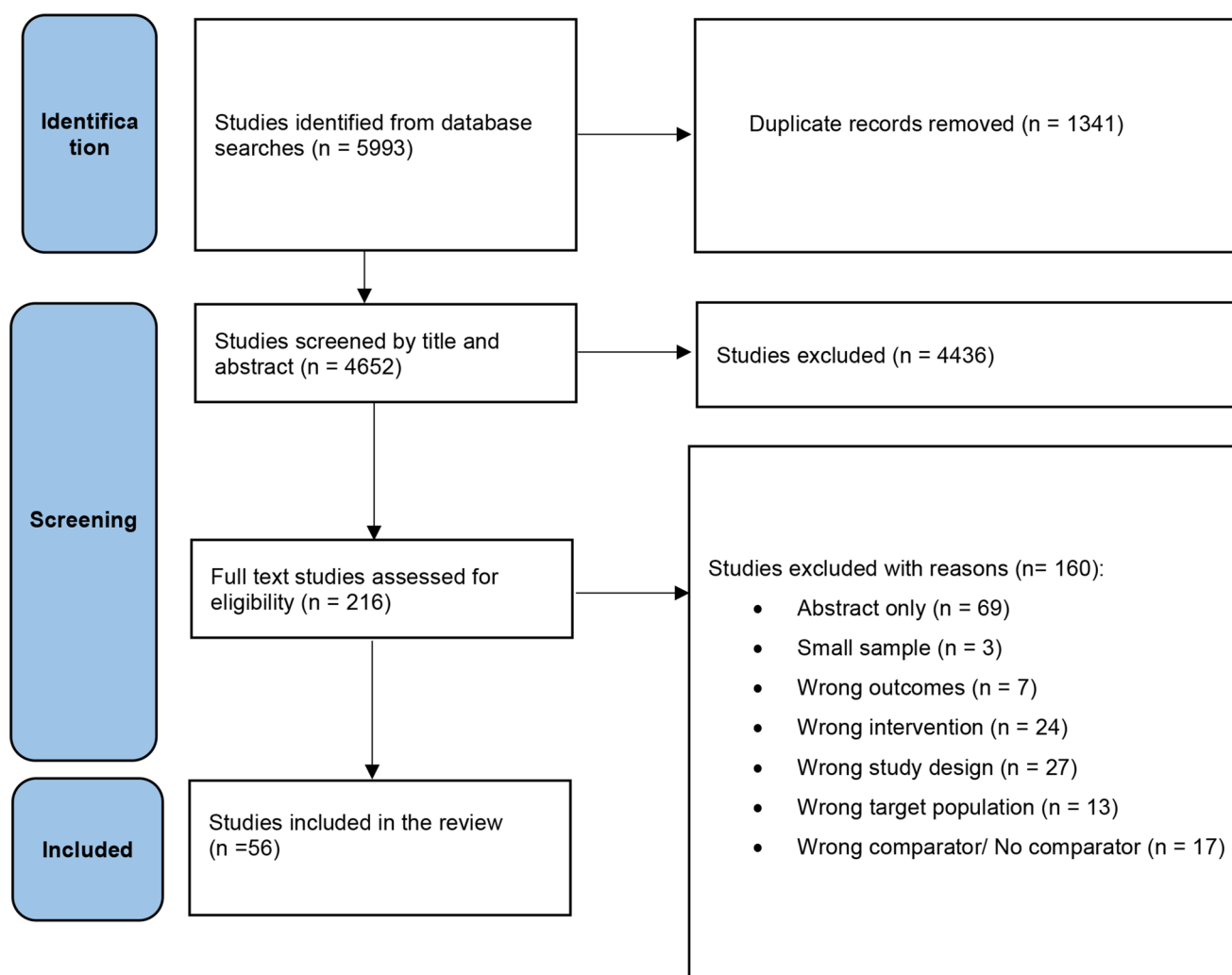


Fig. 1 The PRISMA study selection flow diagram

Grading the Certainty of Evidence

We assessed the certainty of the evidence using Grading of Recommendation Assessment, Development, and Evaluation (GRADE) approach [24]. We classified the certainty of evidence as high, moderate, low, or very low. RCTs initially receive a high grade; however, this grade may be downgraded due to the following specific criteria: the presence of risk of bias (weight assigned to study as assessed by the RoB2 tool); inconsistency (significant unexplained variation among study results, indicated by I^2), indirectness (limitations in the generalizability of the results); imprecision (wide 95% confidence intervals for effect estimates or crossing a null value); incoherence (differences between direct and indirect estimates that contribute to a network estimate); and publication bias (significant evidence of small-study effects) [24–26].

Statistical Analysis

We performed a random-effects network meta-analysis using a frequentist framework to compare the effectiveness of different intermittent fasting methods on cardiovascular disease risks. We chose the frequentist approach over a Bayesian framework for its computational efficiency and straightforward implementation using standard statistical software. Additionally, the frequentist method provides robust and interpretable estimates without requiring prior distributions, which were not available for all comparisons in our network. We reported outcomes as mean differences (MD) with their 95% confidence intervals (CI). We created the network geometry diagrams to explore networks of intervention comparisons. The size of the nodes, representing each intervention, reflects total number of participants while the thickness of the lines connecting any two nodes illustrates the number of intervention comparisons. The incoherence assumption was checked by using a statistical

test (network node-splitting method). In a closed-loop network, the node-splitting method was used to test incoherence between direct and indirect intervention comparisons [27]. We assessed incoherence by comparing the similarity of point estimates, checking for overlapping 95% confidence intervals, and ensuring non-significant p-values.

Transitivity was ensured by including only RCTs with comparable populations, interventions, and outcomes, and verifying that all included studies could be meaningfully compared based on shared treatment nodes. Multilevel meta-analysis was not conducted due to the primary focus on treatment comparisons across studies rather than variability within individual trials.

The relative rankings of all intermittent fasting methods for each outcome were determined by estimating ranking probabilities using ranking plots and the surface under the cumulative ranking curve (SUCRA) [28, 29].

Classification of Intermittent Fasting Methods as More and Less Effective Intervention

Using a new GRADE approach, we analysed NMA results by classifying intermittent fasting interventions from the most to least effective [30] for each outcome. The new GRADE approach considers three factors: effect size from the NMA, evidence certainty, and SUCRA (ranking) values [30]. We first categorised evidence quality into high (moderate-to-high) and low (low-to-very-low) certainty. Within each category, intermittent fasting method were divided based on their effect on outcomes: (1) **Most Effective**: intermittent fasting method with the largest reduction in outcomes compared to the usual diet and superior to at least one moderately effective method; (2) **Moderately Effective**: intermittent fasting method better than the usual diet but not as effective as the most effective method; (3) **Least Effective**: intermittent fasting method similar to the usual diet, with confidence intervals crossing zero.

Sensitivity Analysis

We conducted sensitivity analysis to assess the stability or robustness of the pooled effect size by restricting the analysis to studies with medium to long-term intervention durations, some concern or low risk of bias, and studies that did not include participants with diabetes.

Data analysis was conducted using Stata version 18.0 (StataCorp, College Station, TX) [31], and all graphical displays were generated using the tools developed by Chaimani et al. and White [31, 32].

Results

Study Selection and Characteristics

A total of 5993 articles were identified, resulting in the inclusion of 56 studies [33–88] (Fig. 1). These 56 studies were conducted between 2013 and 2024 with a sample size ranging from 18 to 222 and totalling 3,965 participants. The studies were carried out in 16 different countries, including the USA ($n=17$), Australia ($n=8$), China ($n=6$), and Norway ($n=4$). The duration of interventions varied from 4 weeks to 104 weeks. Of the 56 studies, seven were three-arm while the rest were two-arm studies. The mean age of participants was 45.0 (SD 10.1) years (see details in Table 2).

Risk of Bias

Out of the 56 RCTs, 21 (37.5%) studies were determined to have an overall high risk of bias while 12 (21.4%) studies were rated as overall low risk of bias (Fig. 2). The most common source of bias was related to the randomisation process (high risk, $n=13$; some concern, $n=21$) followed by bias due to missing outcome data (high risk, $n=5$; some concern, $n=13$). Detailed risk of bias assessment results is presented in Supplementary Fig. S1.

Certainty of Evidence and Intervention Classifications

The GRADE assessment details for all outcomes are presented in supplementary Tables S1 A-G. Figure 3 and supplementary Table S2 presents the classification of all interventions for each outcome based on the new GRADE certainty of evidence framework.

Comparative Effectiveness of Intermittent Fasting

Body Composition

Body Weight A total of 52 studies reported weight change after intermittent fasting intervention with a total of 3241 participants. Most of the 52 comparisons were between CER vs. PF ($n=14$) followed by TRE vs. usual diet ($n=14$) (Fig. 4A and Supplementary Table S3). The inconsistency analysis revealed the absence of global inconsistency (Supplementary Fig. S2A) and local inconsistency (Supplementary Table S4). Compared to TRE, mADF (MD= -3.24 kg, 95% CI -5.29 to -1.20, high certainty evidence) effective intervention in reducing weight.

When compared to usual diet mADF (MD=-5.18 kg; 95% CI: -7.04 to -3.22, high certainty evidence), ADF (-4.27 kg;

Table 2 Characteristics of included studies

Study ID	Country	Total participants	Study population description	Interventions groups	Sample size	Mean age	Male	Female	BMI	Intervention detail	Intervention duration (wks)
He et al. (2021)	China	205	age 18–70 years, hypertension but not \geq 180/120, BMI, 24–40 kg/m ² , non-diabetic	CER	103	50.7	43	60	28.7	1000/1200 kcal/day (f/m)	26
Pavlou et al. (2023)	USA	75	aged 18 to 80 years with obesity 30–50 kg/m ² and T2DM	CER	25	55	8	17	38	500/600 kcal/day (f/m) on 2 fast days, and usual diet on 5 days per week reduced their energy intake by 25% of their energy needs every day	26
Lin et al. (2023)	USA	90	age 18–65 years, BMI 30–50 kg/m ² , stable weight, no diabetes, non-smoker	TRE Usual CER	25 25 30	56 54 44	7 7 6	18 18 24	39 39 NA	16-hour fasting and 8 h eating usual eating 25% energy restriction daily 16 h fasting and 8-hour eating between noon and 8:00p.m.	52
Haganes et al. (2022)	Norway	66	women (36.2 \pm 6.2 years with overweight/obesity)	Usual TRE	30 33	44 36.2	5 0	25 33	NA 31.8	Eating over period of 10 or more hours per day energy intake limited to a <10-hours eating window every day	7
Akashah et al. (2020)	USA	54	age: 18–65 years, BMI 25–40 kg/m ² , non-diabetic, no history of cardiovascular disease, and nonsmoker	Usual ADF	33 11	36.4 NA	0 NA	33 NA	33.1 NA	Usual diet Consume 25% of energy needs on the fast day (500 kcal) and 125% of energy needs on feast days	26
Arciero et al. (2022)	USA	41	aged (30–65 years), healthy non-smoking men and women, no history or current cardiovascular or metabolic disease, BMI > 27.5 kg/m ²	CER	15	NA	NA	NA	NA	Consume 75% of energy needs (1500 kcal) every day	8
Miranda et al. (2018)	USA	42	18–65 years, BMI 25.5–39.9 kg/m ² , no cardiovascular disease, no diabetes	Usual CER PF	17 19 20	NA 50.7 49.7	NA 33 32.4	NA 12 14	NA 7 6	Usual diet 1200/1500 kcal/d (f/m) 500 kcal/day for the two consecutive fasting days	24
Obermayer et al. (2023)	Australia	46	18 to 75 years and had diabetes	Usual PF	20 22	44 65	3 10	17 12	33 33.5	Consume 25% of energy needs on fast days Usual diet Fasting 3 days a week, reducing their calories on these days by 75%	12
Razavi et al. (2021)	Iran	75	80 individuals with MetS, age 25–60 years, and BMI 25–40 kg/m ²	Usual CER	24 37	61 43.1	14 20	10 14	35 31.2	Usual diet Consumed 75% energy needs each day	17
Sundfor et al. (2018)	Norway	112	men and women aged 21 to 70 years with BMI 30 to 45 kg/m ²	mADF CER	38 58	41.3 47.5	21 28	14 30	31.3 35.3	75% energy restriction during the 3 fast days Reduce their energy intake every day (25%)	26
Cienfuegos et al. (2022)	USA	33	BMI 30.0–49.9 kg/m ² ; age 18–65 years; sedentary non-smoker, non-diabetic	PF TRE Usual	54 19 14	49.9 46 45	28 1 2	26 18 12	35.1 NA	400/600 kcal/day (f/m) on two non-consecutive days and usual diet 5 days a week Eat ad libitum from 1 to 7 p.m. daily, and fast from 7 to 1 p.m. (18-h fast) Usual diet	10

Table 2 (continued)

Study ID	Country	Total participants	Study population description	Interventions groups	Sample size	Mean age	Male	Female	BMI	Intervention detail	Intervention duration (wks)
He et al. (2022)	China	113	Individuals met three or more metabolic syndrome- MetS criteria	CER	55	41.3	35	20	29.3	restricts to <26% of energy intake	13
Varady et al. (2013)	USA	32	BMI 20–29.9 kg/m ² ; age 35–65 years	TRE Usual mADF	55 15 15	43 48 47	30 3 5	25 12 10	29.6 26 26	16:8 diet (8 h eating and 16 h fasting each day) Eat ad libitum every day Consumed 25% of energy needs on the fast day, and ate ad libitum on each alternating feed day	12
Oh et al. (2018)	South Korea	23	overweight or obese but healthy adults, 32 to 40 years	Usual mADF	10 13	40.6 32.9	4 3	6 10	26.3 27.6	Usual diet Consumed 25% (400–500 kcal) of energy need in 3 days alternately on fast days	8
Maroofi et al. (2020)	Iran	88	men and women with a BMI > 25 kg/m ² , fasting plasma TG 150–400 mg/dL	CER PF	44 44	45.2 44	15 10	29 30	32.4 31.6	Consume 70% of the estimated total energy needs 30% of daily calories requirement) for 3 days per week	8
Kunduraci et al. (2020)	Turkey	70	metabolic syndrome patients, aged 18–65 years, BMI > 27 kg/m ²	CER TRE	33 32	48.76 47.44	15 16	18 16	32.8 36.58	reduction of 25% from habitual energy intake 16 h fasting and 8 h feast	12
Guo et al. (2021)	China	46	aged 30 to 50 years, with metabolic syndrome, no CVD, no chronic diseases	PF	21	40.2	10	11	28	a 75% of energy restriction for 2 non consecutive days a week and an ad libitum diet on 5 days	8
Domaszewski et al. (2022)	Poland	46	Men, age 65–74 years old, Nonsmoking, BMI: 25–29.9 kg/m ²	Usual TRE Usual	18 23 23	42.7 69.3 69.6	11 23 23	7 0 0	27.7 28 28.38	routine diet entirely abstaining from food for 16 h a day Usual diet	6
Manooogian et al. (2022)	USA	137	21–65 years old, firefighters, had at least one cardiometabolic risk factor	TRE Usual	70 67	41.07 39.6	60 65	10 2	27.77 27.65	10-hours TRE Standard eating	12
Fagundes et al. (2023)	Brazil	36	Women age 18–59y with a body mass index \geq 25 kg/m ² , no chronic disease (e.g., diabetes, hypertension, chronic renal failure)	CER TRE	12 24	31.1 36.2	0 0	12 24	30.1 30.5	Caloric restriction ranged from 513 to 770 kcal/d 8–h eating window and 16 h of fasting every day caloric restriction ranged from 513 to 770 kcal/d	8
Liu et al. (2023)	China	38	aged 18–22 years, BMI 18.5–23.9 kg/m ² , no underlying diseases	TRE	19	20.3	0	19	21.6	Eating for 8 h and fasting for the remainder of the day	8
Teong et al. (2023)	Australia	209	aged 35–75 years, score > 12 on the Australian Type 2 Diabetes Risk Assessment Tool	Usual CER PF	19 83 85	20.1 58 57	0 34 36	19 49 49	20.32 35 34.7	maintain their usual lifestyle 30% reduction of energy requirements daily Fasting on three non-consecutive days per week, and ad libitum eating on other days	26
Suthutvoravut et al. (2023)	Thailand	46	aged 18 to 65 years, diagnosed with IFG (i.e., FPG of 100–125 mg/dL, BMI > 25 kg/m ²)	Usual TRE Usual	41 24 22	59 55.5 55.2	19 8 6	22 16 16	33.8 29.2 30.3	standard care 15 h fasting usual eating	12

Table 2 (continued)

Study ID	Country	Total participants	Study population description	Interventions groups	Sample size	Mean age	Male	Female	BMI	Intervention detail	Intervention duration (wks)
Lowe et al. (2020)	USA	50	ages 18–64 BMI 30 kg/m ² –40 kg/m ² , non diabetic	TRE	25	43.3	13	12	31.5	16 h fasting and 8-hours eating	12
Carter et al. (2016)	Australia	63	>=18years) with T2DM, BMI > 27 kg/m ²)	Usual CER PF	25 32 31	44.4 16 14	15 16 17	10 62 62	31.3 36 35	3 structured meal per day 1200–1500 kcal/day 400–600 kcal/day on 2 fast days and regular diet on 5 feed days	12
Pinto et al. (2020)	UK	45	non-smoker aged 35–75 years, with a high waist circumference (a high risk of cardiometabolic disease), no diabetes, no cardiovascular disease	CER PF	22 21	56 50	6 5	16 15	31.1 31.8	daily 500 kcal deficit consume 600 kcal on 2 consecutive days per week	4
Stekovic et al. (2019)	Austria	60	35–65 Years, BMI 22.0–27.0 kg/m ²	ADF	28	48	12	17	25.51	eat every second-day ad libitum, but to completely exclude foods on the fast days	4
Schabel et al. (2018)	Germany	150	women and men, BMI > 25 and < 40 kg/m ² , age 35–65y, nonsmokers	Usual CER PF	29 49 49	50.5 50.5 49.4	11 31.2 32	17 24 24	25.37 25 25	usual diet 5:2 diet: consume 80% of the individual energy requirement daily restrict to 25% on 2 non-consecutive days per week	12
Gray et al. (2021)	Australia	121	females aged > 18y with a previous diagnosis of GDM during pregnancy and a current BMI > 25 kg/m ² , no diabetes, or other illness or disease	Usual CER PF	52 60 61	50.7 40.2 39.3	31.1 0 0	27 60 61	25 32.6 34.8	usual diet follow a diet of 1500 kcal per day for 7 days a week follow 500 kcal per day for 2 non-consecutive days each week	52
Bhutani et al. (2013)	USA	41	age 25–65 years, BMI 30–39.9 kg/m ² , non-smoker non-diabetic; no history of cardiovascular disease	ADF	25	42	1	24	35	Consumed 25% of their energy needs on the fast days	12
Cho et al. (2019)	South Korea	31	Age 20–65 years; BMI > = 23.0 kg/m ² , stable weight, non-diabetic, no chronic disease	Usual Usual mADF	16 5 8	49 42.6 33.5	1 3 2	15 2 5	35 25.8 27.8	Regular diet Usual diet Consumed 25% of their daily energy needs (500 kcal) on fast days	8
Carter et al. (2019)	Australia	137	aged > 18, with Type 2 diabetes, BMI > 27 kg/m ²	CER PF	67 70	61 61	29 31	38 39	37 35	Followed a diet of 5000 to 1200–1500 kcal/day followed a diet of 500–600 kcal/day for 2 days per week and usual diet for the other 5 days	104
Headland et al. (2019)	Australia	222	overweight and obese adults, ages 18–72 years	CER PF	104 118	51.7 47.5	19 21	85 97	33.4 32.9	4200 kJ/day for women and 5040 kJ/day for men energy restriction (2100 kJ/day for women and 2520 kJ/day for men energy restriction of 2 day /week and usual diet for 5 days)	52
Coutinho et al. (2018)	Norway	35	Adults (18–65 years of age, with obesity (30 < BMI < 40 kg/m ²), non-diabetes	CER PF	14 14	39.1 39.4	2 4	12 10	35.1 35.6	energy restriction (33% reduction of the estimated energy needs; 3 non-consecutive days of partial fasting per week (550 and 660 kcal/day for women and men, respectively)	12

Table 2 (continued)

Study ID	Country	Total participants	Study population description	Intervention groups	Sample size	Mean age	Male	Female	BMI	Intervention detail	Intervention duration (wks)
Byrne et al. (2018)	Australia	41	males aged 25–54 years, with a body mass index classified as obese (30–45 kg/m ²)	CER mADF	23 24	39.4 39.8	23 24	0 0	34.3 34.5	33% reduction in energy intake	16
Harvie et al. (2013)	USA	77	Overweight women aged 20–69 years, BMI 24–45 kg/m ² , no diabetes, no CVD	CER PF	40 37	47.9 45.6	0 0	37 40	32.2 29.6	a 25% (6000 kJ/d) energy restriction for 7d/week 25% energy restriction for consecutive 2 days and al libitum in for 5 days per week	12
Parvaresh et al. (2019)	Iran	70	adults with MeS, aged 25–60 and overweight (BMI 25–40 kg/m ²)	CER mADF	34 35	46.4 44.6	20 21	14 14	31.6 31.1	consumed 75% of their energy need each day consume a very low-calorie diet (75% energy restriction) during the 3 fast days	8
Trepalowski et al. (2018)	USA	79	aged 18–65y, BMI 25–40 kg/m ² , nonsmoker, non-diabetes or CVD	CER Usual mADF	29 25 25	44 44 46	6 4 3	23 21 22	35 34 34	consumed 75% of energy needs everyday Usual diet Consuming 25% of energy needs fast day and 125% on eat day	24
Lin et al. (2022)	Taiwan	63	women ages 40–65 y, BMI >= 24 kg/m ² or waist circumference > 80 cm	TRE Usual	30 33	50.1 54.2	0 0	30 33	25.9 25.7	8 h of eating time and fasting for 16 h) unrestricted eating time)	8
Gabel et al. (2019)	USA	43	age 18 to 65 years old, had a BMI of 25.0 to 39.9 kg/m ² , insulin-resistant, no type 2 diabetes or cardiovascular disease	CER Usual mADF	17 15 11	42 41 43	4 4 2	13 11 9	36 35 34	every day 75% intake energy need every day usual diet intake Fast day: 125% intake, Fast day: 25% intake energy need	52
Che et al. (2021)	China	120	age 18–70 with type 2 diabetes, BMI >= 25 kg/m ²	TRE	60	48.2	31	29	26.42	The 10-h TRF group fed freely from 8:00 to 18:00 and fasted from 18:00 to 8:00 daily (a 14-h fast)	12
Chow et al. (2020)	USA	22	overweight or obese (18–65 years, BMI >= 25 kg/m ²), non-diabetic	Usual TRE	60 13	48.8 46.5	34 2	26 9	26.08 33.8	maintain their normal diet 16 h fasting and 8-hour eating window for ad libitum intake	12
Harvie et al. (2011)	UK	107	premenopausal women aged 30–45 years, BMI 24–40 kg/m ² , non smoker, no diabetes or other chronic diseases	Usual CER PF	9 54 53	44.2 40 40.1	1 0 0	8 54 53	34.4 30.5 30.7	eat ad libitum per their usual habits 25% energy restriction for 7 days per week 25% energy restriction for 2 day and no restriction for 5 days per week	24
Catenacci et al. (2016)	USA	29	Adults with obesity BMI >= 30 kg/m ² , age 18–55, nonsmoker, 4.5 kg weight change over past 6 months	ADF CER	13 12	39.6 42.7	3 3	10 9	39.5 35.8	zero calorie alternate day fasting a 400 kcal/day deficit from estimated energy requirements	8
Liu et al. (2022)	China	139	18 to 75 years of age, BMI 28–45 kg/m ² , no diabetes, no chronic disease	CER	70	32.2	35	35	31.3	follow a diet of 1500 to 1800 kcal per day and the women to follow a diet of 1200 to 1500 kcal per day	52
				TRE	69	31.6	35	34	31.8	consume the prescribed calories within an 8-hour period (from 8:00 a.m. to 4:00 p.m.) each day	

Table 2 (continued)

Study ID	Country	Total participants	Study population description	Interventions groups	Sample size	Mean age	Male	Female	BMI	Intervention detail	Intervention duration (wks)
Conley et al. (2018)	Australia	24	males aged 55–75, BMI >= 30 kg/m ² and stable weight, non-diabetic	CER	12	67.1	12	0	36.2	follow a continuous daily energy-restricted diet (500 calorie daily reduction from average requirement)	24
Domaszewski et al. (2020)	Poland	45	non-smoking women over 60 years of age, average BMI 25 kg/m ²	PF	11	68	11	0	33.4	fasting for two non-consecutive days (restrict calorie intake to 600 calories)	6
Beaulieu et al. (2020)	UK	46	Women aged between 18 and 55y, BMI between 25.0 and 34.9 kg/m ²	TRE Usual ADF CER	25 20 24 22	65 66 35 34	0 0 2 2	25 20 20 20	28.99 26.99 29.4 28.9	completely abstaining from food for 16 h a day, from 20:00p.m. to 12:00a.m. (the next day) usual diet on fast days, volunteers consumed 25% of their daily energy requirements participants consumed 75% of their daily energy requirement each day	12
Cienfuegos et al. (2020)	USA	58	m/f age 18–65, BMI 30–49.9 kg/m ² , sedentary, non-diabetic,	TRE	20	47	19	1	37	eat ad libitum from 1 to 7 pm daily, and fast from 7 to 1 pm (18-hfast)	8
Castela et al. (2022)	Norway	28	adults (20–55 years), with obesity	Usual CER	19 14	45 39.1	17 2	2 12	36 35.1	usual diet every day 33% reduction of the energy needs	12
Steger et al. (2021)	USA	35	21–65years, BMI 25–35 kg/m ² , weight stable	PF CER	14 17	39.4 48	4 3	10 14	35.6 31.4	3 non consecutive days of partial fasting per week, (consume 550 / 660 kcal/day (f/m) continuous/daily energy restriction consisted of 1200 to 1600kcal	12
Mena-Hernandez et al. (2024)	Mexico	28	men and women between 18 and 50 years old; BMI > 25 kg/m ² ; stable body weight for three months before the study	PF Usual	18 8	43.4 26	5 5	13 12	31.1 32	IER with 3 days of a very-low energy diet (550 to 800 kcal/d 3 days per week) and 4 days of normal eating 16/8 protocol Usual diet	4
Sukkrirang et al. (2024)	Thailand	66	BMI >= 25 kg/m ² , age 30–60 years old, with type 2 diabetes mellitus	TRE Usual	33 33	46 44	13 15	20 18	32 32	16/8 protocol usual diet	12
Hooshar et al. (2024)	Iran	49	women aged 18–50years, with a BMI 25–40, and normal menstrual cycles of 21–35days	CER mADF	24 25	32 32	0 0	24 25	32 32	daily energy restrictions During fasting days, participants only consuming quarter of their needs	8
Herz et al. (2024)	Germany	18	Healthy aged 18–65 years with a BMI >= 20 kg/m ² and no cardiac problem	ADF TRE	8 11	25 26			25 25	fasting periods occurring on alternate days, the participants abstained from food and beverages for 24 h 16/8 protocol, fasted for 16 h and remaining 8 h eating	8

Table 2 (continued)

Study ID	Country	Total participants	Study population description	Interventions groups	Sample size	Mean age	Male	Female	BMI	Intervention detail	Intervention duration (wks)
Quist et al. (2024)	Denmark	100	age 30–70 years with either overweight (BMI >= 25 and concomitant prediabetes (i.e., glycated haemoglobin) 39–47 mmol/mol) or obesity (i.e., BMI >= 30) [HbA1c with or without prediabetes]	TRE Usual	46 46	46 59	18 16	32 34	34 34	10-h per-day eating window usual eating	13 13

ADF- alternate fasting, CER- Continuous energy restrictions, mADF- modified alternate day fasting, PF- Periodic fasting, TRE- Time restricted eating, BMI- body mass index

-6.12 to -2.42, high certainty evidence), PF (-3.82 kg; -5.44, -2.21, high certainty evidence), CER (-3.42 kg; -4.73 to -2.11, high certainty evidence), and TRE (-1.93 kg; -3.06, -0.81, moderate certainty evidence) significantly reduced body weight (Fig. 5A, Supplementary Table S1).

Among the intermittent fasting methods with high or moderate certainty of evidence, compared to a usual diet, mADF was the most effective, whereas CER, TRE, ADF and PF were among the interventions with intermediate effectiveness in reducing body weight compared to usual diet (Fig. 3 and Supplementary Table S2, Supplementary Fig. S3A).

Fat Free Mass Change in fat-free mass was reported in 32 studies with a total of 2045 participants. Most comparison were between PF vs. CER (*n*=10), followed by TRE vs. usual diet (*n*=6) (Fig. 4 and Supplementary Table S3). Both the global inconsistency test (Supplementary Fig. S2B) and the local inconsistency test supported the consistency of the direct and indirect estimates (Supplementary Table S4).

Compared to usual diet, TRE (MD= -0.82 kg; 95% CI: -1.46 to -0.17, moderate certainty evidence), PF (-0.80 kg; -1.58 to -0.02, high certainty of evidence) significantly reducing fat-free mass (Fig. 5B and Supplementary Table S1). Among intermittent fasting methods with high or moderate certainty of evidence, compared to a usual diet, TRE, and PF were the most effective for fat free mass reduction, whereas mADF and ADF was not better than usual diet (Fig. 3, Supplementary Table S2, Supplementary Fig. 3B).

Waist Circumference Most of the 22 comparisons were between CER vs. PF (*n*=7), CER vs. mADF(*n*=3) and TRE vs. usual diet (*n*=3) (Fig. 4C and Supplementary Table S3). The global and local inconsistency test indicated no violation of the consistency assumption for direct and indirect estimates (Supplementary Fig. 2C and Supplementary Table S3).

Compared to usual diet with high certainty of evidence, mADF (MD= -3.55 cm; 95% CI: -5.66 to -1.45), CER (-1.78 cm; -3.23, -0.34), PF (-2.77 cm; -4.47, -1.07) and TRE (-3.00 cm; -4.50, -1.51) significantly reduced waist circumference (Fig. 5C and Supplementary Table S1). However, there were no statistically significant differences among the other comparisons (Fig. 5C). Among the intermittent fasting methods with high or moderate certainty of evidence, compared to a usual diet, mADF, CER, TRE, and PF were the most effective for fat free mass reduction, whereas ADF was probably among least effective (not better than usual diet) (Fig. 3, Supplementary Table S2, Supplementary Fig. S3C).

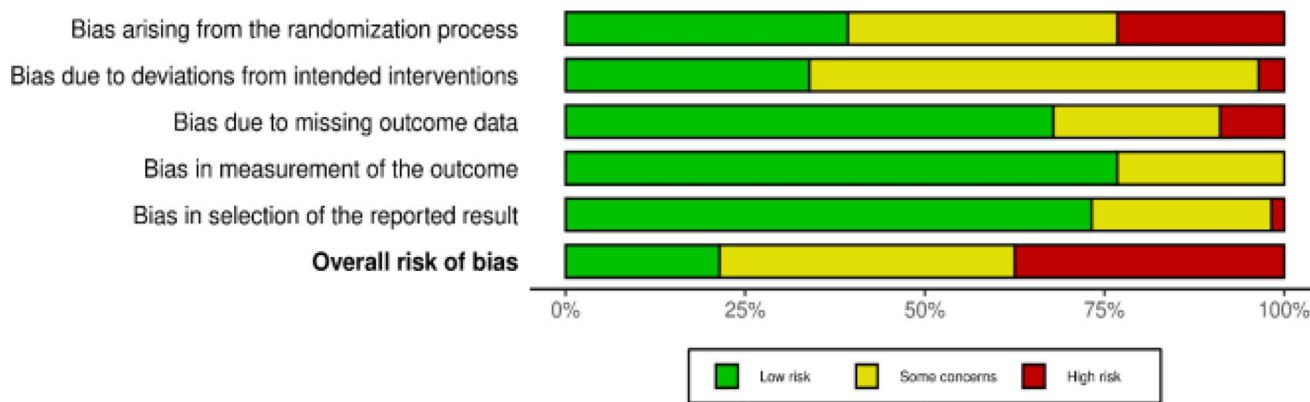


Fig. 2 Risk of bias (Summary)

IF vs Usual diet	Weight reduction	Fat free mass reduction	Waist circumference reduction	Low density lipoprotein reduction	Systolic blood pressure reduction	Diastolic blood pressure reduction	Fasting plasma glucose reduction
mADF	-5.18 (-7.04,-3.32)	-1.08 (-2.16,0.01)	-3.55 (-5.66,-1.45)	-2.96 (-12.13,6.21)	-7.24 (-11.90,-2.58)	-4.70 (-8.46,-0.95)	-4.14 (-8.46,0.18)
TRE	-1.93 (-3.06,-0.81)	-0.82 (-1.46,-0.17)	-3.00 (-4.50,-1.51)	-3.30 (-7.44,0.85)	-3.18 (-5.22,-1.13)	-3.24 (-4.69,-1.79)	-3.74 (-6.01,-1.46)
PF	-3.82 (-5.44,-2.21)	-0.80 (-1.58,-0.02)	-2.77 (-4.47,-1.07)	-6.80 (-12.59,-1.00)	-3.17 (-6.01,-0.32)	-2.90 (-4.79,-1.02)	-0.12 (-3.17,2.93)
CER	-3.42 (-4.73,-2.11)	-0.63 (-1.30,0.04)	-1.78 (-3.23,-0.34)	-3.92 (-8.67,0.84)	-4.55 (-6.82,-2.27)	-2.66 (-4.11,-1.22)	-0.28 (-2.87,2.31)
ADF	-4.27 (-6.12,-2.42)	-1.01 (-2.07,0.06)	-2.86 (-5.88,0.16)	0.37 (-8.10,8.83)	-1.17 (-4.61,2.28)	0.49 (-1.95,2.93)	-2.74 (-7.37,1.88)

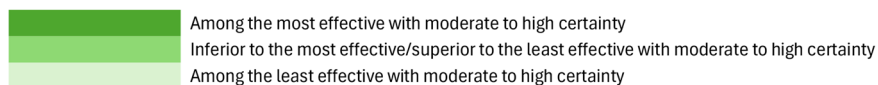


Fig. 3 The summary of results network meta-analysis of intermittent fasting regimes (mean difference with 95% CI) in comparison with usual diet for all outcomes along with ranking by new GRADE cer-

tainty of evidence framework. Note: mADF=modified alternate day fasting; ADF=alternate day fasting; CER=continuous energy restriction; PF=periodic fasting; TRE time restricted eating

LDL Cholesterol

Change in LDL cholesterol levels were reported in 35 articles with a total of 2488 participants, and most comparisons were TRE vs. usual diet ($n=10$) and CER vs. usual diet ($n=9$) (Fig. 4D and Supplementary Table S3). With high certainty of the evidence, PF (MD= -6.80 mg/dL; 95% CI: -12.59, -1.00) was associated with a significant reduction in LDL level compared to usual diet; however, there were no significant differences among the other comparisons (Fig. 5D and Supplementary Table S1). Among the intermittent fasting methods with high or moderate certainty of evidence, compared to a usual diet, PF was among the most effective, while mADF, CER, TRE and ADF were not better than usual diet for LDL reduction (Fig. 3 and Supplementary Table S2, Supplementary Fig. S3D).

Blood Pressure

Systolic Blood Pressure (SBP) SBP was reported in 27 studies, with a total of 1852 participants. Most of the 27

comparisons were CER vs. usual diet ($n=7$) and TRE vs. usual diet ($n=6$). With high certainty, mADF (-6.08 mmHg; -11.83 to -0.32) was more effective in reducing SBP compared to ADF. Compared to usual diet with high certainty of evidence, mADF (MD= -7.24 mmHg; 95%CI: -11.90 to -2.58), CER (-4.55 mmHg; -6.82 to -2.27), PF (-3.17 mmHg; -6.01 to -0.32) and TRE (-3.18 mmHg; -5.22 to -1.13) significantly reduced SBP (Fig. 5E and Supplementary Table S1). Among the intermittent fasting methods with high or moderate certainty of evidence, compared to a usual diet, mADF, CER, TRE, and PF were the most effective for SBP reduction, whereas ADF was not better than usual diet (Fig. 3, Supplementary Table S2, Supplementary Fig. S3E).

Diastolic Blood Pressure (DBP) DBP was reported in 27 studies, with a total of 1861 participants, and most compared CER vs. usual diet ($n=7$) and TRE vs. usual ($n=6$). Compared to ADF, mADF (-5.19 mmHg; -9.61 to -0.78, high certainty evidence), TRE (-3.73 mmHg; -6.49 to -0.98, high certainty evidence), PF (-3.40 mmHg; -6.34

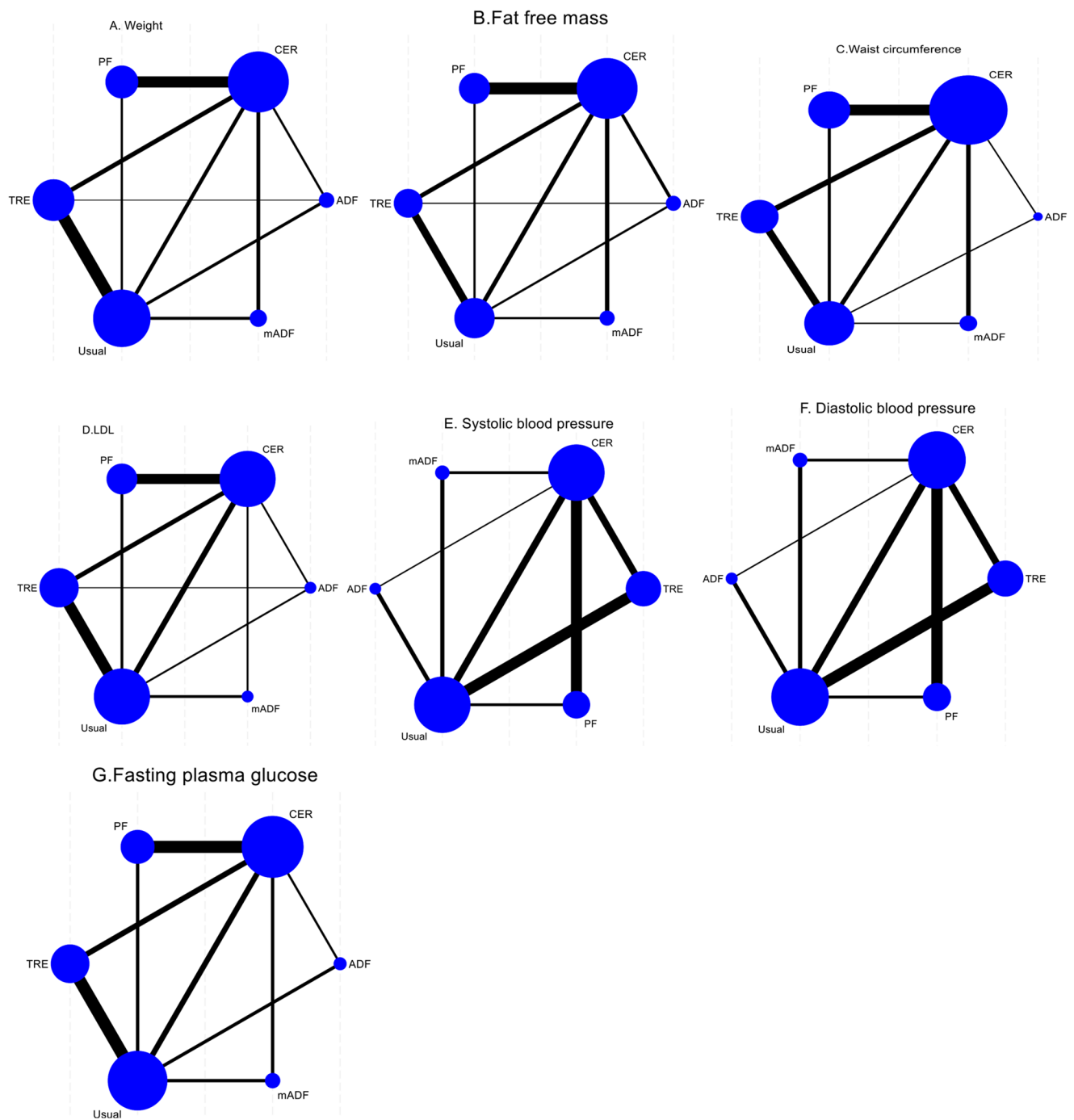


Fig. 4 Network plots of the direct comparisons between intermittent fasting interventions from head-to-head trials for the outcomes: (A) Weight; (B) Fat free mass; (C) Waist circumference; (D) LDL-cholesterol; (E) Systolic blood pressure; (F) Diastolic blood pressure; (G) Fasting plasma glucose. The sizes of nodes correspond to the

number of participants randomized to the intermittent fasting methods and the width of line corresponds to the number of studies. Note: mADF=modified alternate day fasting; ADF=alternate day fasting; CER=continuous energy restriction; PF=periodic fasting; TRE time restricted eating

to -0.45, high certainty evidence) are more effective in reducing DBP. Compared to usual diet with high certainty of evidence, mADF (MD= -4.70 mmHg; 95%CI: -8.46 to -0.95), CER (2.66 mmHg; -4.11 to -1.22), PF (-2.90 mmHg; -4.79 to -1.02) and TRE (-3.24 mmHg; -4.69 to -1.79) sig-

nificantly reduced DBP (Fig. 4F and Supplementary Table S1). Among the intermittent fasting methods with high or moderate certainty of evidence, compared to a usual diet, mADF, CER, TRE, and PF were the most effective for DBP

		Treatment					
		Usual	mADF	TRE	PF	CER	ADF
Comparator	Usual diet		-5.18 (-7.04,-3.32)	-1.93 (-3.06,-0.81)	-3.82 (-5.44,-2.21)	-3.42 (-4.73,-2.11)	-4.27 (-6.12,-2.42)
	5.18 (3.32,7.04)	mADF		3.24 (1.20,5.29)	1.35 (-0.79,3.50)	1.76 (-0.07,3.58)	0.91 (-1.61,3.43)
	1.93 (0.81,3.06)	-3.24 (-5.29,-1.20)	TRE		-1.89 (-3.65,-0.13)	-1.49 (-2.91,-0.07)	-2.34 (-4.34,-0.33)
	3.82 (2.21,5.44)	-1.35 (-3.50,0.79)	1.89 (0.13,3.65)	PF		0.40 (-0.88,1.68)	-0.44 (-2.74,1.85)
	3.42 (2.11,4.73)	-1.76 (-3.58,0.07)	1.49 (0.07,2.91)	-0.40 (-1.68,0.88)	CER		-0.85 (-2.90,1.20)
	4.27 (2.42,6.12)	-0.91 (-3.43,1.61)	2.34 (0.33,4.34)	0.44 (-1.85,2.74)	0.85 (-1.20,2.90)	ADF	

A. Weight

		Treatment					
		Usual	mADF	TRE	PF	CER	ADF
Comparator	Usual diet		-1.08 (-2.16,0.01)	-0.82 (-1.46,-0.17)	-0.80 (-1.58,-0.02)	-0.63 (-1.30,0.04)	-1.01 (-2.07,0.06)
	1.08 (-0.01,2.16)	mADF		0.26 (-0.89,1.41)	0.28 (-0.86,1.41)	0.45 (-0.56,1.45)	0.07 (-1.36,1.50)
	0.82 (0.17,1.46)	-0.26 (-1.41,0.89)	TRE		0.02 (-0.83,0.86)	0.19 (-0.51,0.88)	-0.19 (-1.30,0.91)
	0.80 (0.02,1.58)	-0.28 (-1.41,0.86)	-0.02 (-0.86,0.83)	PF		0.17 (-0.41,0.75)	-0.21 (-1.41,0.99)
	0.63 (-0.04,1.30)	-0.45 (-1.45,0.56)	-0.19 (-0.88,0.51)	-0.17 (-0.75,0.41)	CER		-0.38 (-1.48,0.73)
	1.01 (-0.06,2.07)	-0.07 (-1.50,1.36)	0.19 (-0.91,1.30)	0.21 (-0.99,1.41)	0.38 (-0.73,1.48)	ADF	

B. Fat free mass

		Treatment					
		Usual	mADF	TRE	PF	CER	ADF
Comparator	Usual diet		-3.55 (-5.66,-1.45)	-3.00 (-4.50,-1.51)	-2.77 (-4.47,-1.07)	-1.78 (-3.23,-0.34)	-2.86 (-5.88,0.16)
	3.55 (1.45,5.66)	mADF		0.55 (-1.72,2.82)	0.78 (-1.43,2.99)	1.77 (-0.12,3.65)	0.69 (-2.83,4.22)
	3.00 (1.51,4.50)	-0.55 (-2.82,1.72)	TRE		0.23 (-1.61,2.07)	1.22 (-0.27,2.71)	0.14 (-3.10,3.38)
	2.77 (1.07,4.47)	-0.78 (-2.99,1.43)	-0.23 (-2.07,1.61)	PF		0.99 (-0.26,2.24)	-0.09 (-3.36,3.19)
	1.78 (0.34,3.23)	-1.77 (-3.65,0.12)	-1.22 (-2.71,0.27)	-0.99 (-2.24,0.26)	CER		-1.08 (-4.18,2.03)
	2.86 (-0.16,5.88)	-0.69 (-4.22,2.83)	-0.14 (-3.38,3.10)	0.09 (-3.19,3.36)	1.08 (-2.03,4.18)	ADF	

C. Waist circumference

		Treatment					
		Usual diet	mADF	TRE	PF	CER	ADF
Comparator	Usual diet		-2.96 (-12.13,6.21)	-3.30 (-7.44,0.85)	-6.80 (-12.59,-1.00)	-3.92 (-8.67,0.84)	0.37 (-8.10,8.83)
	2.96 (-6.21,12.13)	mADF		-0.33 (-10.04,9.37)	-3.83 (-13.75,6.08)	-0.96 (-10.08,8.17)	3.33 (-8.73,15.38)
	3.30 (-0.85,7.44)	0.33 (-9.37,10.04)	TRE		-3.50 (-9.76,2.76)	-0.62 (-5.71,4.47)	3.66 (-5.16,12.49)
	6.80 (1.00,12.59)	3.83 (-6.08,13.75)	3.50 (-2.76,9.76)	PF		2.88 (-1.41,7.17)	7.16 (-2.26,16.58)
	3.92 (-0.84,8.67)	0.96 (-8.17,10.08)	0.62 (-4.47,5.71)	-2.88 (-7.17,1.41)	CER		4.28 (-4.34,12.91)
	-0.37 (-8.83,8.10)	-3.33 (-15.38,8.73)	-3.66 (-12.49,5.16)	-7.16 (-16.58,2.26)	-4.28 (-12.91,4.34)	ADF	

D. LDL

E.

		Treatment					
		Usual diet	mADF	TRE	PF	CER	ADF
Comparator	Usual diet		-7.24 (-11.90,-2.58)	-3.18 (-5.22,-1.13)	-3.17 (-6.01,-0.32)	-4.55 (-6.82,-2.27)	-1.17 (-4.61,2.28)
	7.24 (2.58,11.90)	mADF		4.06 (-0.94,9.07)	4.08 (-1.19,9.34)	2.70 (-2.26,7.65)	6.08 (0.32,11.83)
	3.18 (1.13,5.22)	-4.06 (-9.07,0.94)	TRE		0.01 (-2.91,2.93)	-1.37 (-3.61,0.88)	2.01 (-1.89,5.91)
	3.17 (0.32,6.01)	-4.08 (-9.34,1.19)	-0.01 (-2.93,2.91)	PF		-1.38 (-3.43,0.67)	2.00 (-2.26,6.26)
	4.55 (2.27,6.82)	-2.70 (-7.65,2.26)	1.37 (-0.88,3.61)	1.38 (-0.67,3.43)	CER		3.38 (-0.49,7.25)
	1.17 (-2.28,4.61)	-6.08 (-11.83,-0.32)	-2.01 (-5.91,1.89)	-2.00 (-6.26,2.26)	-3.38 (-7.25,0.49)	ADF	

Fig. 5 Intermittent fasting network meta-analysis results (mean difference with 95% CI) with corresponding GRADE certainty of evidence for: Weight in kg (A); Fat-free mass in kg (B); Waist circumference in cm (C); Low density lipoprotein-LDL in mg/dL (D); Systolic blood pressure -SBP in mmHg (E); Diastolic blood pressure - DBP in mmHg (F); Fasting plasma glucose– FPG in mg/dL (G). Values in bold

indicate a statistically significant effect. Colour coding indicates the GRADE certainty of evidence: green=high certainty, blue=moderate certainty. Note: mADF=modified alternate day fasting; ADF=alternate day fasting; CER=continuous energy restriction; PF=periodic fasting; TRE time restricted eating

F. SBP

		Treatment					
		Usual diet	mADF	TRE	PF	CER	ADF
Comparator	Usual diet		-4.70 (-8.46,-0.95)	-3.24 (-4.69,-1.79)	-2.90 (-4.79,-1.02)	-2.66 (-4.11,-1.22)	0.49 (-1.95,2.93)
	4.70 (0.95,8.46)	mADF		1.46 (-2.43,5.36)	1.80 (-2.18,5.78)	2.04 (-1.73,5.80)	5.19 (0.78,9.61)
	3.24 (1.79,4.69)	-1.46 (-5.36,2.43)	TRE		0.33 (-1.57,2.24)	0.57 (-0.87,2.02)	3.73 (0.98,6.49)
	2.90 (1.02,4.79)	-1.80 (-5.78,2.18)	-0.33 (-2.24,1.57)	PF		0.24 (-1.12,1.60)	3.40 (0.45,6.34)
	2.66 (1.22,4.11)	-2.04 (-5.80,1.73)	-0.57 (-2.02,0.87)	-0.24 (-1.60,1.12)	CER		3.16 (0.53,5.79)
	-0.49 (-2.93,1.95)	-5.19 (-9.61,-0.78)	-3.73 (-6.49,-0.98)	-3.40 (-6.34,-0.45)	-3.16 (-5.79,-0.53)	ADF	

F. DBP

		Treatment					
		Usual diet	mADF	TRE	PF	CER	ADF
Comparator	Usual diet		-4.14 (-8.46,0.18)	-3.74 (-6.01,-1.46)	-0.12 (-3.17,2.93)	-0.28 (-2.87,2.31)	-2.74 (-7.37,1.88)
	4.14 (-0.18,8.46)	mADF		0.40 (-4.22,5.03)	4.02 (-0.55,8.58)	3.86 (-0.16,7.88)	1.40 (-4.56,7.35)
	3.74 (1.46,6.01)	-0.40 (-5.03,4.22)	TRE		3.61 (0.19,7.04)	3.46 (0.57,6.34)	0.99 (-3.99,5.97)
	0.12 (-2.93,3.17)	-4.02 (-8.58,0.55)	-3.61 (-7.04,-0.19)	PF		-0.16 (-2.53,2.21)	-2.62 (-7.67,2.42)
	0.28 (-2.31,2.87)	-3.86 (-7.88,0.16)	-3.46 (-6.34,-0.57)	0.16 (-2.21,2.53)	CER		-2.46 (-7.09,2.16)
	2.74 (-1.88,7.37)	-1.40 (-7.35,4.56)	-0.99 (-5.97,3.99)	2.62 (-2.42,7.67)	2.46 (-2.16,7.09)	ADF	

G. FPG

Fig. 5 (continued)

reduction (Fig. 3, Supplementary Table S2, Supplementary Fig. S3F).

Fasting Plasma Glucose (FPG)

A total of 36 studies reported FPG change after intermittent fasting intervention involving a total of 2428 participants. Most comparison were TRE vs. usual diet (10) and PF vs. CER ($n=9$) (Fig. 4 and Supplementary Table S3). The inconsistency examination revealed the absence of global inconsistency and local inconsistency (Supplementary Fig. S2G and Supplementary Table S4). With high certainty, TRE (-3.46 mg/dL; -6.34, -0.57) are more effective than CER in reducing FPG. Similarly, TRE (-3.61 mg/dL; -7.04, -0.19) with high certainty is effective in reducing FPG compared to PF. Relative to usual diet with high certainty of evidence, TRE (-3.74 mg/dL; -6.01, -1.46) significantly reduced FPG (Fig. 5G and Supplementary Table S1). Among the intermittent fasting methods with high or moderate certainty of evidence, compared to a usual diet, TRE was probably the most effective; mADF, PF, and ADF probably among least effective intermittent fasting methods (not better than usual diet) for FPG reduction (Fig. 3 and Supplementary Table S2, Supplementary Fig. S3G).

Sensitivity Analysis

Excluding Studies with Participants with Diabetes

Compared to the main analysis, the effects of intermittent fasting on body weight, FPG, SBP, and DBP remained similar in magnitude and direction. However, the previously significant effects of mADF and CER on waist circumference was no longer observed. Additionally, the positive effects of PF on waist circumference and fat-free mass were no longer statistically significant (Supplementary Fig. S4).

Excluding Studies with High-Risk of Bias

The size and direction of the network estimates for weight, FPG and SBP were consistent with the full analysis in this sensitivity analysis. However, the previously significant effects of PF on waist circumference and LDL, and the effect of mADF on DBP and TRE on fat free mass were no longer significant. Conversely, the effect of CER on fat free mass was statistically significant among this sub-set of higher quality studies (Supplementary Fig. S5).

Excluding Studies with Short Intervention Durations

The size and direction of the network estimates for weight, waist circumference and LDL cholesterol were in line with the full analysis. But the effects of mADF on SBP and DBP, and the effect of TRE on FPG and fat free mass were no longer significant. Conversely, the effect of CER on fat free

mass and the effect of mADF on FPG were statistically significant (Supplementary Fig. S6).

Discussion

This systematic review and network meta-analysis synthesised the evidence on the effect of various intermittent fasting methods on cardiovascular disease risk factors using 56 randomised controlled trials conducted between 2013 and 2024. The findings indicated that different intermittent fasting modalities, when compared to a usual diet, significantly reduced body weight, fat-free mass, waist circumference, LDL levels, blood pressure, and FPG. The mADF was found to be the most effective intervention, with high or moderate certainty of the evidence, for the reduction of cardiovascular risk factors including SBP, DBP, weight, and waist circumference. Compared to a usual diet, time-restricted eating was the most effective intermittent fasting regimen for the reduction of fat-free mass and FPG. Moreover, PF was superior to a usual diet in reducing LDL levels. ADF did not show convincing evidence of superiority to a usual diet to reduce cardiovascular risks except for weight. When comparing each other, mADF is more effective than ADF in reducing SBP and DBP. Similarly, TRE and PF are more effective than ADF in reducing DBP. Additionally, TRE is more effective in reducing FPG compared to PF and CER.

The results of this network meta-analysis revealed a significant reduction in body weight across intermittent fasting methods compared to the usual diet, with ADF, mADF, PF, and TRE demonstrating notable effects compared to a usual diet. Likewise, compared to the usual diet, three intermittent fasting methods - mADF, PF, and TRE - significantly reduced waist circumference, a crucial marker of central adiposity. These results align with previous research [11–14] highlighting the weight management potential of intermittent fasting method. These findings reinforce the potential of intermittent fasting as a viable intervention for weight or waist circumference reduction.

One of the concerns surrounding intermittent fasting is its potential undesirable effect on fat-free mass loss which can impair physical function and cardiometabolic health [15, 89]. However, the evidence regarding this effect was not conclusive. Some studies reported no impact on fat free mass [13, 16], while others indicated an increase in fat-free mass [17], and yet other showed intermittent fasting significantly reduced fat-free mass [15]. Our study revealed a significant reduction in fat-free mass in two intermittent fasting methods (TRE and PF), but no significant reduction in other two intermittent fasting methods (mADF, and ADF). But compared to CER, there is no significant difference in fat-free mass reduction in most intermittent fasting methods.

It is important to note that reductions in fat free mass are common across various weight loss strategies [90]. This underscores the necessity for a nuanced understanding of the physiological changes associated with different intermittent fasting strategies.

LDL-cholesterol, as a component of lipid profiles, is another important cardiovascular disease risk factor. Our study found variations in effects on LDL-cholesterol among the different intermittent fasting method. Notably, the PF regimen showed a significant reduction in LDL levels. This aligns with a previous study [18]. However, other studies have not found a consistent effect of intermittent fasting on LDL reduction compared to a usual diet [11, 12, 14].

Our study found significant reductions in both SBP and DBP across multiple intermittent fasting methods, including mADF, PF, and TRE. These findings are partially consistent with previous meta-analyses. Some reported a significant decrease in DBP with intermittent fasting [11, 12], while others did not [13]. Similarly, one meta-analysis found a decrease in DBP with intermittent fasting [11], whereas others showed no effect [13, 14]. These variations highlight the need for further research and potentially personalised approaches to intermittent fasting, considering individual health conditions and risk factors. Another potential benefits of intermittent fasting could be for glycemic control (reduction of blood glucose level). Our study found that TRE method significantly reduced FPG levels. However, these findings are not entirely consistent with previous research. While some meta-analyses reported significant FPG reductions with intermittent fasting [11, 14], others did not observe a significant difference compared to usual eating [13]. The discrepancy could potentially be explained by differences in the duration of the intervention (with some having shorter duration studies) [12–14] and number of studies (with some having fewer studies) [12–14], as well as some analyse lumped different intermittent fasting method together [11, 12].

The underlying mechanisms of the effect of fasting on cardiovascular risk factors are thought to be mediated, at least in part, by the metabolic switch from carbohydrate utilization to fat and ketones oxidation that happens during fasting [9]. Intermittent fasting causes organs to switch between storing and using energy sources [9]. In conventional eating, carbohydrates and fats get stored in the liver, muscles, and fat tissue. But during fasting, the body burns stored glycogen and fat for energy, resulting in more frequent cycling between storing and burning nutrients compared to constant eating and creates metabolic adaptability and weight reduction [91, 92]. This helps the body become more flexible in using energy, leading to various health benefits, including better insulin sensitivity, increased fat burning, and weight loss [93]. However, more research is needed

to understand exactly how specific intermittent fasting patterns affect fat breakdown and turnover and how they influence overall calorie burning.

Strengths and Limitations

This comprehensive systematic review and network meta-analysis employed stringent inclusion and exclusion criteria and included only RCTs. A strength of this review is the ability to compare the relative effectiveness of five commonly used intermittent fasting modalities on a range of cardiovascular disease risk factors, and the certainty of evidence was assessed using the revised version of Cochrane risk of bias assessment tool. This provides valid evidence for decision making and the development of guidance on intermittent fasting. This study incorporated both short-term and long-term studies, and sensitivity analysis was done to assess the robustness of the results. Moreover, in this study, the evidence of certainty has been assessed using the newly validated GRADE framework, which helped to grade the intermittent fasting modalities in a more stringent manner based on a combination of criteria, including effect size, certainty of evidence and SUCRA rankings. Our use of randomized trials strengthens the study's internal validity but may limit generalizability to real-world settings.

It is essential to note that the lack of direct comparisons between specific intermittent fasting modalities, such as ADF, mADF, TRE, and PF, in our study points towards a gap in the existing literature. The observed risk of bias in 37% of the studies included in our analysis is consistent with the challenges faced by many meta-analyses where the quality of individual studies varies, even though the result remains consistent in the sensitivity analysis. Similarly, the short duration of the included studies might limit the findings, even though the results remain consistent in the sensitivity analysis, except for the effects of mADF on SBP and DBP and the effect of TRE on fat-free mass and FPG, which were no longer significant when excluding studies with short intervention durations. This underscores the importance of interpreting the findings with caution and emphasizes the need for further studies. Future studies should aim to directly compare different intermittent fasting modalities, consider longer-term outcomes, and adhere to rigorous methodologies, including randomization and blinding, to enhance the reliability of results.

Conclusions

This network meta-analysis compared various intermittent fasting methods and found that mADF and TRE were associated with greater reductions in SBP and DBP compared to

ADF, and TRE showed greater effects on FPG compared to PF and CER. PF was more effective than usual diets in lowering LDL cholesterol. Both mADF and ADF were more effective than usual diets in reducing body weight, while TRE was associated with reductions in waist circumference, DBP, FPG, and fat-free mass. Among the methods assessed, mADF showed relatively greater effects across several cardiovascular risk factors. These findings suggest that certain intermittent fasting approaches may hold promise as part of lifestyle strategies to improve cardiovascular risk profiles. However, the results should be interpreted with caution due to high risk of bias as per reviewer, and other limitations such as short intervention duration in many studies. Further high-quality, long-term randomized controlled trials are needed to establish the sustained efficacy and safety of different intermittent fasting methods.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

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