Intermittent fasting strategies and their effects on body weight and other cardiometabolic risk factors: systematic review and network meta-analysis of randomised clinical trials

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ABSTRACT

OBJECTIVE

To assess the effect of intermittent fasting diets, with continuous energy restriction or unrestricted (ad-libitum) diets on intermediate cardiometabolic outcomes from randomised clinical trials.

DESIGN

Systematic review and network meta-analysis.

DATA SOURCES

Medline, Embase, and central databases from inception to 14 November 2024.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Randomised clinical trials comparing the association of intermittent fasting diets (alternate day fasting, time restricted eating, and whole day fasting), continuous energy restriction, and ad-libitum diets were included.

MAIN OUTCOMES

Outcomes included body weight (primary) and measures of anthropometry, glucose metabolism, lipid profiles, blood pressure, C-reactive protein, and markers of liver disease.

DATA SYNTHESIS

A network meta-analysis based on a frequentist framework was performed with data expressed as mean difference with 95% confidence intervals (CIs). The certainty of the evidence was assessed using grading of recommendations assessment, development, and evaluation (GRADE).

RESULTS

99 randomised clinical trials involving 6582 adults of varying health conditions (720 healthy, 5862 existing health conditions) were identified. All intermittent fasting and continuous energy restriction diet strategies reduced body weight when compared with ad-libitum diet. Compared with continuous energy restriction, alternate day fasting was the only form of intermittent fasting diet strategy to show benefit in body weight reduction (mean difference −1.29 kg (95% CI −1.99 to −0.59), moderate certainty of evidence). Additionally, alternate day fasting showed a trivial reduction in body weight compared with both time restricted eating and whole day fasting (mean difference −1.69 kg (−2.49 to −0.88) and −1.05 kg (−1.90 to −0.19), respectively, both with moderate certainty of evidence). Estimates were similar among trials with less than 24 weeks follow-up (n=76); however, moderate-to-long-term trials (≥24 weeks, n=17) only showed benefits in weight reduction in diet strategies compared with ad-libitum. Furthermore, in comparisons between intermittent fasting strategies, alternate day fasting lowered total cholesterol, triglycerides, and non-high density lipoprotein compared with time restricted eating. Compared with whole day fasting, however, time restricted eating resulted in a small increase in total cholesterol, low density lipoprotein cholesterol, and non-high density lipoprotein cholesterol. No differences were noted between intermittent fasting, continuous energy restriction, and ad-libitum diets for HbA_{1c} and high density lipoprotein.

CONCLUSIONS

Minor differences were noted between some intermittent fasting diets and continuous energy restriction, with some benefit of weight loss with alternate day fasting in shorter duration trials. The current evidence provides some indication that intermittent fasting diets have similar benefits to continuous energy restriction for weight loss and cardiometabolic risk factors. Longer duration trials are needed to further substantiate these findings.

TRIAL REGISTRATION

ClinicalTrials.gov NCT05309057.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Weight loss can reduce these risk factors and consequently decrease the burden of serious chronic conditions like type 2 diabetes and cardiovascular disease

Intermittent fasting features periods of fasting or restricted energy intake alternating with periods of normal or ad-libitum energy consumption

While intermittent fasting is a popular weight loss strategy, the health effects of intermittent fasting compared with a usual caloric restriction or ad-libitum diet in humans remain unclear

WHAT THIS STUDY ADDS

99 randomised controlled trials that evaluated intermittent fasting diets, with continuous energy restriction, or ad-libitum diets on intermediate cardiometabolic outcomes were evaluated in this systematic review and network meta-analysis

All intermittent fasting strategies and continuous energy restriction diets showed a reduction in body weight when compared with an ad-libitum diet

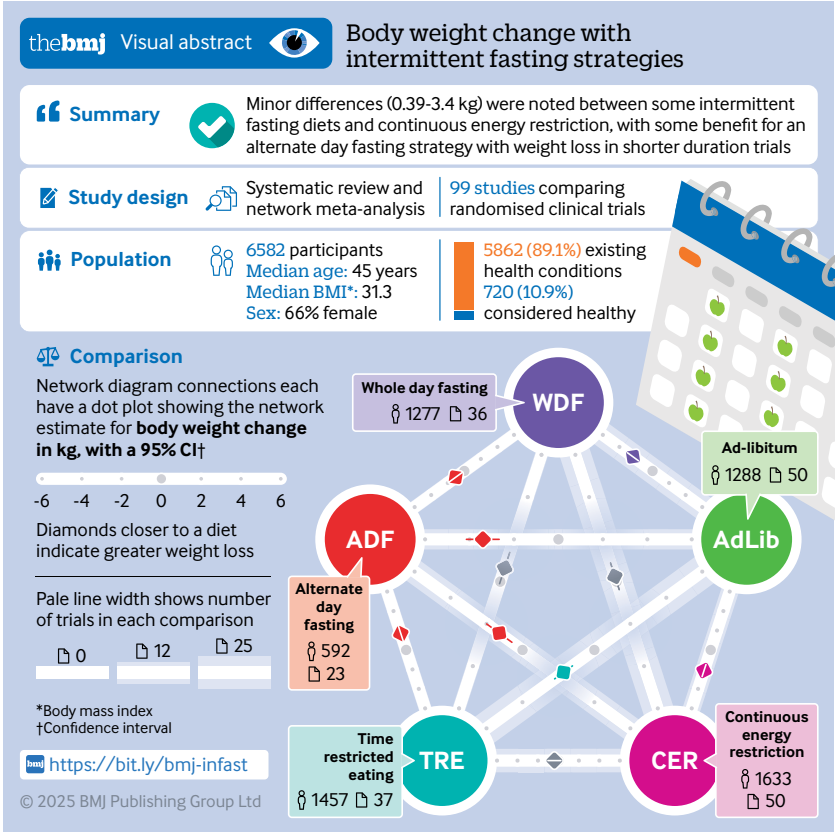
Of three intermittent fasting diets (ie, alternate day fasting, time restricted eating, and whole day fasting), alternate day fasting showed benefit in body weight reduction compared with continuous energy restriction

Introduction

Obesity, hyperglycaemia, and hypertension are among the major cardiometabolic risk factors prevalent in adults.[1] A reduction in these risk factors, all achievable by weight loss, can mitigate the burden of major chronic disease outcomes including type 2 diabetes and cardiovascular disease.[2] As the prevalence of these risk factors increases worldwide, focus has shifted towards behavioural interventions to achieve a more sustainable and wide ranging risk reduction. One common intervention is for weight loss with a continuous energy restriction (CER) diet; although, this strategy is often unsustainable in the long term.[3] An alternative dietary behavioural approach that has gained popularity is intermittent fasting, which encompasses a dietary pattern involving periods of fasting, or restrictive energy intake, interspersed by non-fasting periods of ad-libitum (ie, unrestricted) energy intake.[4 5] The fasting period may vary from several hours during the day to a complete 24 hour period. While no clear definition exists for intermittent fasting, its various methods can fall under three broad categories: time restricted eating (TRE), alternate day fasting (ADF), and whole day fasting (WDF). Briefly, TRE involves a 24 hour pattern consisting of a certain number of hours of non-fasting period, followed by fasting for the remainder of the time. An example is the 16:8 diet involving a 16 hour fasting period followed by an 8 hour eating window. ADF involves a 24 hour fast on alternate days; while WDF involves a cyclical pattern of 24 hour fasting periods followed by ad-libitum periods; for example, a 5:2 diet involving five days of ad-libitum diet and two days of fasting periods.

Despite its popularity as a weight loss strategy in the public, the health effects of intermittent fasting compared with a usual caloric restriction or ad-libitum diet in humans remain unclear. Emerging evidence suggests that intermittent fasting may improve risk markers such as weight,[6] glucose control,[7] and blood pressure[4] more than CER; however, no comprehensive evidence has evaluated the effects of intermittent fasting diets, CER, and ad-libitum diets on cardiometabolic risk factors, or compared the efficacy between the different intermittent fasting methods. Several meta-analyses have been conducted on randomised clinical trials of intermittent fasting in recent years.[8-11] However, these studies have notable limitations, such as focusing solely on the effects of intermittent fasting diets on weight loss. Importantly, these meta-analyses were unable to compare different intermittent fasting strategies because most randomised clinical trials typically compared one intermittent fasting regimen to either CER or ad-libitum diets.

To address these major limitations, and to update the recommendations of the European Association for the Study of Diabetes (EASD), the Diabetes and Nutrition Study Group (DNSG) commissioned this systematic review and meta-analysis. Our aim was to summarise the evidence related to the association of intermittent fasting and CER strategies on body weight and cardiometabolic risk factors in adults from randomised clinical trials that used grading of recommendations assessment, development, and evaluation (GRADE).[12] As few randomised clinical trials comparing intermittent fasting strategies have been published, we conducted network meta-analyses rather than the traditional pairwise meta-analyses to evaluate the association of intermittent fasting strategies on cardiometabolic outcomes.



Methods

This systematic review and network meta-analysis was conducted according to the Cochrane handbook for systematic reviews of interventions[13] and reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA)[14] and the PRISMA extension statement for conducting network meta-analyses.[15] This protocol is registered at Clinicaltrials.gov, NCT05309057.

Data sources, searches, and study selection

We searched Medline, Embase, and the Cochrane central register of controlled trials (Clinical Trials; Central) from database inception to 14 November 2024. Manual searches of the reference lists of included studies and reviews supplemented the electronic search strategy. The search included variations of several key terms for fasting, including "intermittent fasting", "time-restricted eating", "alternate fasting", "whole day fasting", etc; and combined with specific terms for outcomes and study design. We applied validated filters from McMaster University's Health

Information Research Unit to restrict our database search to controlled studies only.[16] See supplemental table 1 for the detailed search strategy.

Supplemental table 2 outlines the PICOTS (population, intervention, comparator, outcome, time, and study) framework used for this network meta-analysis. We included randomised clinical trials in humans, of all health conditions, with a follow-up duration of at least three weeks investigating the association of intermittent fasting, CER, or ad-libitum, or a combination of diets on body measurements, glucose metabolism, lipid profiles, blood pressure, C-reactive protein, and markers of liver disease. Outcomes with fewer than three eligible studies were omitted due to feasibility constraints for the network meta-analysis. We excluded studies of children or pregnant women, had a short follow-up duration (<3 weeks), did not have a suitable control, had a combined intervention where the main association of intermittent fasting strategies could not be separated, or did not report viable endpoint data. Religious fasting were also methods excluded due to wide variability in fasting practices.

Data extraction, risk of bias assessments, and outcomes

Titles and abstracts retrieved were screened to identify studies that met the inclusion criteria by two independent reviewers (ZS-A and TAK). Disagreements were resolved by consensus or a third reviewer (JLS). Study characteristics and relevant data were extracted from each eligible study by independent reviewers (VC, HAB, AC, NC, and JO) and checked by a third reviewer (LC and ZS-A). Mean differences and standard errors (SEs) of the between the treatment group and comparator group were extracted as the main endpoints for each outcome. Between treatment change-from-baseline differences were preferred over end differences. For trials that did not report these values, we used the available data to calculate the appropriate statistics or imputed them using standard formulas and recommended methods.[13 17] We used WebPlotDigitizer to extract data from charts or figures when numerical results were not provided.[18] To prevent unit-of-analysis errors in the network meta-analysis, we adhered to Cochrane guidance by proportionally dividing sample sizes and event counts of shared control groups in multi-arm trials and applied the inverse-variance method for synthesis of multi-arms to avoid over-inflation of their weights.[13] Additionally, data will be available on reasonable request.

When available, information about adverse events and adherence were extracted from each study. Adherence, also referred to as compliance, plays a crucial role in the effectiveness of weight loss strategies.[19] Studies included in this meta-analysis assessed compliance through various methods, such as daily logs of dietary intake and eating time windows, self-assessment, or follow-ups with dietitians. Adherence was calculated as the percentage of days participants adhered to the prescribed diet or eating schedule. The data presented reflect the percentage of adherence to the diet regimen by the end of the intervention period. Furthermore, retention rates were calculated as the ratio of people who completed the study to those initially enrolled. Risk of bias was assessed for each included study using the Cochrane Collaboration Risk of Bias Tool (supplementary methods).[20 21] Additionally, consideration was given to crossover trials, with data analysed using mean differences and an assumed correlation coefficient of 0.5 to estimate standard errors, and risk of bias assessed using the Risk of Bias tool, accounting for period and carryover effects.[13]

The primary outcome of interest was body weight. Secondary outcomes included other important cardiometabolic risk factors including other measures of body measurements (body mass index (BMI), body fat, and waist circumference), glucose metabolism (HbA_{1c}, homeostatic model assessment for insulin resistance (HOMA-IR), fasting glucose, and fasting insulin), blood pressure (systolic and diastolic blood pressure), lipids (total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, non-high density lipoprotein cholesterol, and triglycerides), liver function (alanine transaminase (ALT)), and C-reactive protein.

Statistical analysis and grading the evidence

Our network meta-analysis was based on the frequentist framework and was performed using R 4.4.1 statistical computing environment using the R package netmeta.[22] We performed a random-effects network meta-analysis to compare all the interventions simultaneously (direct and indirect), specifically ADF, WDF, TRE, CER, and ad-libitum diet, in a single analysis using mean differences determined from the included studies. We conducted separate network meta-analyses for each cardiometabolic risk factor. For our primary outcome (body weight), we compared diet strategies in an a-priori stratified analysis by trial duration: acute (<24 weeks) and moderate-to-long term (≥24 weeks). For outcomes with at least 10 trials available, we assessed publication bias using comparison adjusted funnel plots to evaluate funnel plot asymmetry.[22] Additional sensitivity analysis was conducted on studies of participants with diabetes. If at least 10 trials per diet comparisons were available, we conducted a-priori subgroup analyses for body weight and all other outcomes age, sex, study duration, type of design, disease status, risk of bias, and funding source.

We determined confidence of the network estimates using the confidence in network meta-analysis (CINeMA)[23] framework, which applies the grade system.[24 25] The CINeMA framework estimates confidence based on six domains: within study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence.[23 26] Briefly, within study bias evaluates the potential flaws in the study design or execution that can lead to a systematic difference between the estimated relative treatment

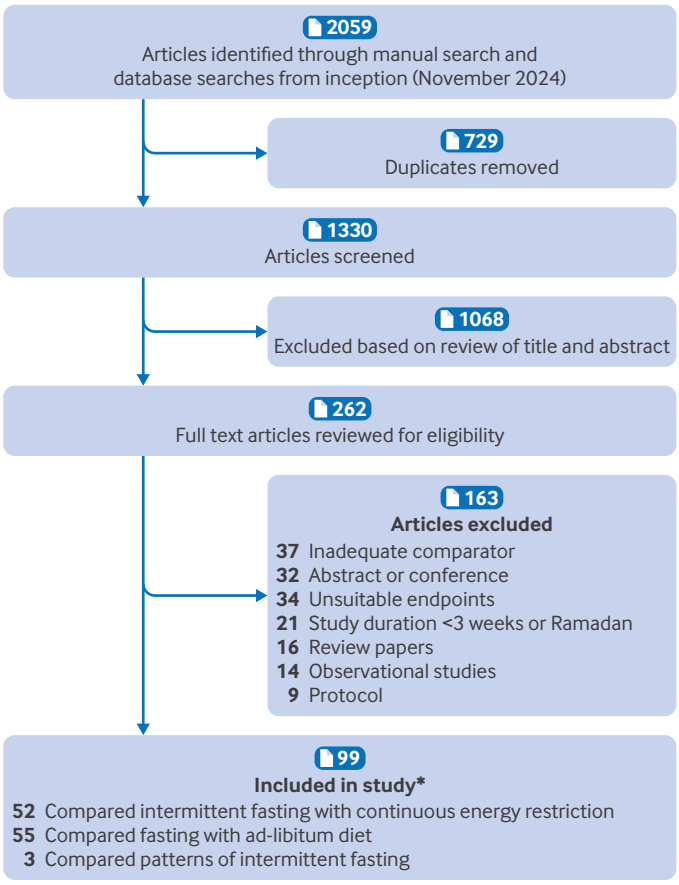


Fig 1 | Flow diagram of study identification and review for randomised clinical trials of intermittent fasting, continuous energy restriction, and ad-libitum diet strategies. *Some studies included comparisons of intermittent fasting with both continuous energy restriction and ad-libitum diets

effect and the true effect, as evaluated using the risk of bias tool. Reporting bias refers to when the results in a systematic review do not accurately represent all the findings from the studies conducted. This bias can occur when non-significant findings or unfavourable results are not reported (publication bias or outcome reporting bias). Indirectness assesses the issue of transitivity, referring to the assumption that trials comparing different interventions are similar in terms of important characteristics that might influence the effect estimate, including age, sex, sample size, and study duration.[27 28] Imprecision, heterogeneity, and incoherence evaluates the reliability and validity of the results. The minimally important difference thresholds used in assessing imprecision, heterogeneity, and incoherence, were predetermined for each outcome based on current clinical evidence. A minimally important difference of 2.0 kg was used to interpret the significance of body weight changes, based on evidence of meaningful weight loss in populations who are obese,[29] while a threshold of 1.0 kg was retained for assessing imprecision in CINeMA GRADE evaluations. Effect sizes were classified as trivial (<1* minimally important difference), small (≥1* minimally important difference), moderate (≥2* minimally important difference), large (≥5* minimally important difference) or very large (≥10* minimally important difference). For body weight, the threshold classifications were trivial (<2.0 kg), small (≥2.0 to <4.0 kg), moderate (≥4.0 to <10.0 kg), large (≥10.0 to <20.0 kg), and very large (≥20.0 kg).

Heterogeneity was assessed based on the confidence and the calculated prediction intervals determined from the network meta-estimates, while incoherence was evaluated using both a global test (random-effects design-by-treatment interaction model approach[30]) and a local test (separating indirect from direct evidence (SIDE)[31]). In the summarised evaluation, the reporting bias domain for each comparison ranged from very low to high risk; while for the other domains, comparisons were assessed as having no concerns, some concerns, or major concerns.

Patient and public involvement

This study evaluated existing data from randomised clinical trials. Due to the limited resources and time and funding constraints, patients and the public were not involved in setting the research question, outcome measures, study design, or data interpretation. To address this gap, we will implement a comprehensive knowledge translation strategy following study dissemination. Our approach includes creating accessible infographics and delivering presentations to diverse community groups to share our findings. We will also develop plain language summaries for distribution across various platforms, including social media feeds. Through these post-study engagement efforts, we aim to gather valuable feedback from individuals with lived experiences of cardiometabolic conditions, which will inform our future research priorities and methodological approaches. This collaboration will ultimately help to ensure subsequent studies better incorporate patient perspectives despite the constraints encountered in our current systematic review and network meta-analysis.

Results

Figure 1 shows the flow of the literature search and selection, of which 99 articles met our inclusion criteria (see supplementary appendix A for the list of excluded studies from the full text review). Table 1 and supplementary table 3 present the key characteristics of the included studies.[6 7 32-128] Overall, included participants had a median age of 45 years (interquartile range 36-50), had overweight or obesity (median BMI of 31.3 (interquartile range 28.4-33.3)), and were mostly female (66% female, 34% male) (total n=6582). The participants had varying health conditions, including having overweight or obesity (54 studies), type 1 diabetes or type 2 diabetes (12 studies), metabolic syndrome (8 studies), or metabolic dysfunction-associated fatty liver disease (also known as non-alcoholic fatty liver disease; 8 studies); overall, 720 individuals were healthy and 5862 had existing health conditions.

Table 1 | Summary of study characteristics (n=99 studies; 6582 adults)

Characteristics	Study Details**
Median no. of participants (IQR)	46 (32-77)
Median age, years (IQR)	45 (36-50)
Female, no. (%)	4336 (66)
Male, no. (%)	2246 (34)
Median baseline body weight, kg (IQR)†	85 (77-94)
Median baseline body mass index (IQR)†	31 (28-33)
Underlying disease status (no. of studies)	Healthy (n=5), hypertension (n=1), metabolic syndrome (n=8), multiple sclerosis (n=2), NAFLD/MAFLD (n=8), normal weight (n=8), overweight/obese (n=54), PCOS (n=1), prediabetic (n=1), type 1 diabetes (n=1), type 2 diabetes (n=11)
Country (no. of comparisons)	Australia (n=9), Austria (n=1), Brazil (n=4), Canada (n=1), China (n=13), Czech Republic (n=2), Germany (n=3), Indonesia (n=1), Iran (n=8), Italy (n=1), Malaysia (n=2), Mexico (n=1), Netherlands (n=1), Norway (n=3), Poland (n=1), Portugal (n=1), South Korea (n=3), Spain (n=1), Sweden (n=1), Taiwan (n=1), Thailand (n=3), Turkey (n=4), UK (n=10), USA (n=24)
Study design (%)	Parallel (92%) Crossover (8%)
Feeding control (%)‡	Dietary advice (75%) Metabolic (10%) Supplemented (15%)
Diet arms (no. of studies)	Ad-libitum (n=54) Continuous energy restriction (n=53) Alternate day fasting (n=25) Time restricted eating (n=40) Whole day fasting (n=38)
Median follow-up, weeks (range)	12 (3-52)
Trial designed for weight loss (%)	Yes (81%) No (19%)
Energy balance (no. of comparisons)	Neutral (n=26) Negative (n=73)
Funding sources (%)	Agency§ (81%) Agency plus industry (5%) Industry (5%) No funding (1%) Not reported (2%)

Detailed characteristics from each identified study is outlined in supplementary table 3. IQR=interquartile range; PCOS=polycystic ovary syndrome; NAFLD=non-alcoholic fatty liver disease; MAFLD=metabolic dysfunction-associated fatty liver disease.
*Values rounded to the nearest whole number.
†Based on studies that reported data.
‡Metabolic feeding control included provision of all study foods, supplement feeding control included provision of study supplements only, and dietary advice included dietary counselling without the provision of any dietary foods or supplements.
§Agency funding included government, not-for profit health agencies or University sources.

Of the identified randomised clinical trials, almost all (92%) were parallel in study design, with a median follow-up time of 12 weeks (range 3-52 weeks), a median sample size of 46 participants,[32-77] and most trials (81%) were designed for weight loss. A small subset of trials had a duration of three weeks, the minimum threshold, typically reporting modest weight reductions (eg, 0.5-2 kg), consistent with early phase feasibility studies. Conversely, only five trials extended to 52 weeks or more, limiting the feasibility of undertaking a robust analysis for very long term outcomes. Of the intermittent fasting diet groups, we identified 38 studies that evaluated WDF, 40 studies that evaluated TRE, and 25 studies that evaluated ADF. In some studies, the diet composition for different strategies was reported, which showed variability. Many of these diets were designed or recommended to include a higher proportion of carbohydrates compared with protein and fat. Most included studies were conducted in the USA (n=24) and the UK (n=10). Additionally, most of the randomised clinical trials (81%) received funding solely from agencies (ie, government, not-for profit health agencies, or universities).

Supplementary figures 1 and 2 show the individual assessments using the Cochrane risk-of-bias tool for each of the included trials. Taken together with the evidence of the present literature, a serious risk of bias was not indicated because more than 80% of studies were considered to have low risk of bias.

GRADE assessment

The GRADE certainty of evidence for all diet group comparisons are presented in supplementary tables 5-21. For body weight, confidence rating ranged from moderate to high (supplementary table 5). Downgrades from high for comparisons rated as moderate were due to concerns in indirectness, imprecision, or heterogeneity. The remaining comparisons were all rated moderate with downgrades from high for either major concerns in heterogeneity or some concerns for imprecision, heterogeneity or incoherence. Similarly, the certainty of the evidence for other body properties and cardiometabolic outcome measures was on average moderate but ranged from very low to high for each comparison.

Figure 2 and figure 3 display the network analysis of all trials that reported body weight (93 studies;

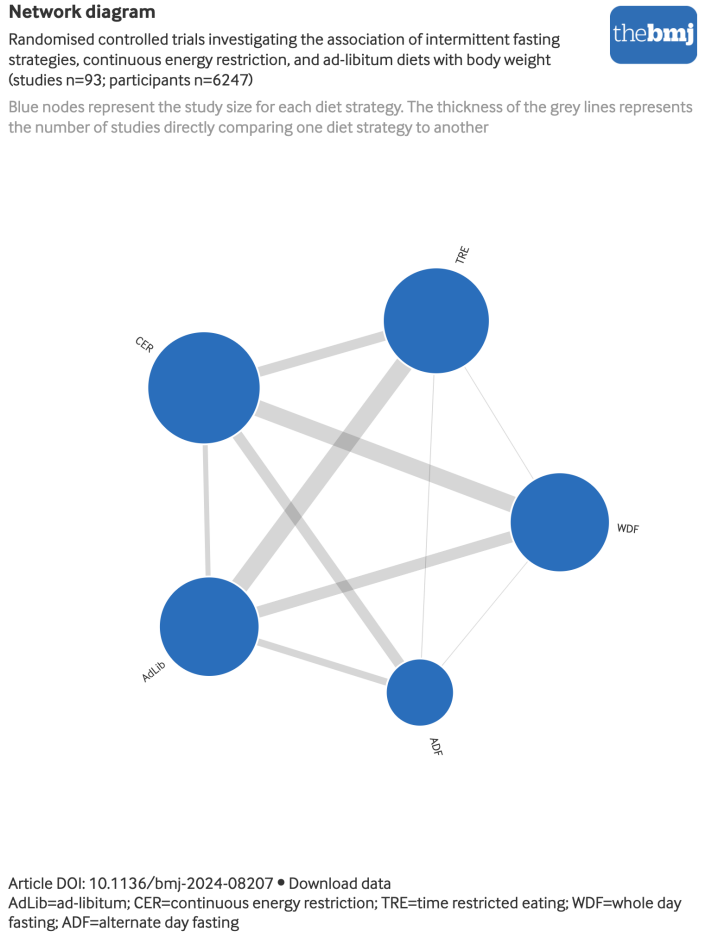


Fig 2 | Network diagram for randomised controlled trials investigating the association of intermittent fasting strategies, continuous energy restriction, and ad-libitum diets with body weight. An interactive version of this graphic is available at https://public.flourish.studio/visualisation/23222926/

6247 participants). The highest number of dietary comparisons were between TRE and ad-libitum (n=25), followed by CER and WDF (n=23), and WDF and ad-libitum comparisons (n=16, fig 2). When compared with the ad-libitum diet, the network analysis showed a small reduction in body weight for ADF (mean difference −3.40 kg (95% CI −4.14 to −2.67), high certainty of evidence), WDF (−2.36 kg (−3. 02 to −1.70), high certainty of evidence), and CER (−2.11 kg (−2.73 to −1.50), moderate certainty of evidence); while TRE showed a trivial reduction (−1.72 kg (−2.21 to −1.22), moderate certainty of evidence) (fig 3). Furthermore, the ADF diet resulted in a trivial additional weight loss when compared with CER (−1.29 kg (−1.99 to −0.59), moderate certainty of evidence). Comparisons between intermittent fasting diet strategies showed a trivial reduction in body weight for ADF versus both TRE (−1.69 kg (−2.49 to −0.88) and WDF −1.05 kg (−1.90 to −0.19), both moderate certainty of evidence); however, no difference was noted between the TRE and WDF diet comparison (fig 3).

The network analysis by trial duration for body weight is shown in fig 4. In trials with less than 24 weeks of follow-up (n=76), ADF showed a small body weight reduction compared with ad-libitum (mean difference −3.37 kg (95% CI −4.16 to −2.59)), and a trivial reduction in weight compared with CER (−1.29 kg (−2.05 to −0.53)), and TRE (−1.72 kg (−2.58 to −0.87)). Compared with ad-libitum, both WDF and CER showed a small reduction in body weight and TRE showed a trivial reduction in weight. Additionally, WDF showed a trivial reduction in body weight when compared with TRE (−0.88 kg (−1.71 to −0.06)). In trials of 24 weeks or more (n=17), the most restrictive strategies (ADF, TRE, and CER) showed small body weight reductions versus ad-libitum (mean difference range −1.88 to −3.63 kg), with no differences between intermittent fasting strategies and CER in these moderate-to-long term studies. WDF, however, showed a trivial reduction in weight loss when compared with ad-libitum.

Figure 5 displays the summary of the network estimates and certainty of the evidence for all diet group comparisons for each outcome of interest. Details on the network analysis and network diagram for the secondary outcomes are presented in supplementary figures 3-34. Similar beneficial results in body weight were observed for intermittent fasting strategies with ad-libitum diets for other body measurements including BMI, body fat, and waist circumference. Among these measurements, ADF showed a large reduction in BMI when compared with ad-libitum (mean difference −1.22 (95% CI −1.55 to −0.89), high certainty of evidence); however, reductions in waist circumference were small (high certainty of evidence) and in body fat were trivial (moderate certainty of evidence). Additionally, moderate reductions in BMI were observed in ADF with WDF (−0.53 (−0.94 to −0.13)) and TRE (−0.60 (−0.97 to −0.24)), with moderate certainty of evidence (fig 5, supplementary figure 4). Furthermore, ADF showed reductions in both BMI (−0.52 (−0.85 to −0.19)) and waist circumference (−1.19 cm (−2.13 to −0.24)), when compared with CER, both with moderate certainty of evidence.

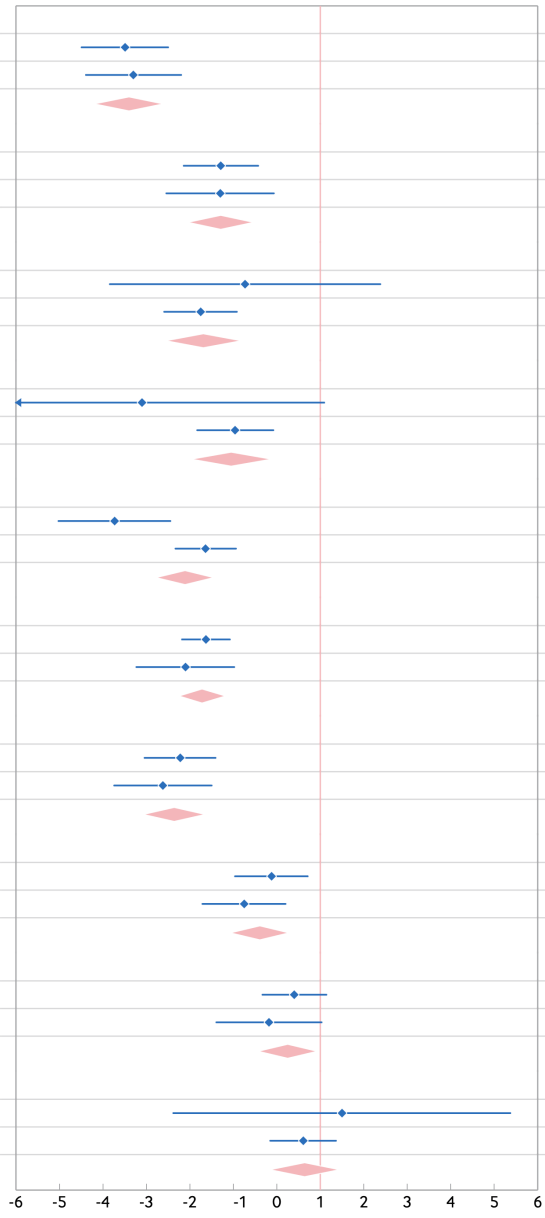
In comparison with intermittent fasting strategies, ADF, compared with TRE, showed small reductions in concentrations of triglycerides and in systolic blood pressure, but showed moderate reductions in non-high density lipoprotein cholesterol and total cholesterol, with certainty of evidence ranging from low to moderate (supplementary figures). ADF compared with WDF, however, only showed small reductions in both non-high density lipoprotein cholesterol and triglycerides (supplementary figures). For comparisons between TRE and WDF, WDF showed small increases in low density lipoprotein cholesterol (mean difference 0.11 mmol/L (95% CI 0.01 to 0.21)), non-high density lipoprotein cholesterol (0.15 mmol/L (0.03 to 0.27)), and total cholesterol (0.17 mmol/L (0.05 to 0.29)), all with low certainty of evidence (supplementary figures 11, 12, and 16).

The assessment of all diet strategy comparisons showed no association with HbA_{1c} or high density lipoprotein cholesterol; certainty of evidence ranged

Network analysis comparing intermittent fasting strategies, continuous energy restriction, and ad-libitum diets on body weight (kg)

Each comparison evaluates the assessment of diet arm one compared with diet arm two. The blue diamond represents the mean difference (MD) and the line represents the 95% confidence interval (CI). This is presented for direct estimates and indirect estimates. The red diamond represents the overall network estimate for that comparison, which integrates both direct and indirect estimates. For example, ADF:AdLib comparison shows the MD of ADF compared to ad-libitum. A negative MD suggests diet 1 had greater reduction compared with diet 2; whereas a positive MD suggests diet 2 had a greater reduction compared with diet 1. Number of studies refers to the total number of direct evidence published for the specific comparison. Direct evidence refers to the proportion of the evidence available from direct assessments through published literature. I^2 refers to the percentage of the total variability in a set of effect sizes due to true heterogeneity

Outcome	No of studies	I^2 (%)	Direct evidence	Mean difference (95% CI)
ADF:AdLib				
Direct estimate	10	21	0.55	-3.49 (-4.49 to -2.50)
Indirect estimate				-3.30 (-4.39 to -2.20)
Network estimate				-3.40 (-4.14 to -2.67)
ADF:CER				
Direct estimate	15	53	0.68	-1.29 (-2.14 to -0.43)
Indirect estimate				-1.30 (-2.54 to -0.07)
Network estimate				-1.29 (-1.99 to -0.59)
ADF:TRE				
Direct estimate	1		0.07	-0.73 (-3.84 to 2.38)
Indirect estimate				-1.75 (-2.59 to -0.92)
Network estimate				-1.69 (-2.49 to -0.88)
ADF:WDF				
Direct estimate	1		0.04	-3.10 (-7.29 to 1.09)
Indirect estimate				-0.96 (-1.83 to -0.08)
Network estimate				-1.05 (-1.90 to -0.19)
CER:AdLib				
Direct estimate	7	46	0.23	-3.73 (-5.02 to -2.45)
Indirect estimate				-1.64 (-2.33 to -0.94)
Network estimate				-2.11 (-2.73 to -1.50)
TRE:AdLib				
Direct estimate	25	90	0.81	-1.63 (-2.18 to -1.08)
Indirect estimate				-2.10 (-3.23 to -0.98)
Network estimate				-1.72 (-2.21 to -1.22)
WDF:AdLib				
Direct estimate	16	78	0.65	-2.22 (-3.04 to -1.41)
Indirect estimate				-2.62 (-3.74 to -1.50)
Network estimate				-2.36 (-3.02 to -1.70)
CER:TRE				
Direct estimate	14	88	0.57	-0.12 (-0.96 to 0.71)
Indirect estimate				-0.75 (-1.71 to 0.20)
Network estimate				-0.39 (-1.02 to 0.23)
CER:WDF				
Direct estimate	23	65	0.73	0.40 (-0.33 to 1.14)
Indirect estimate				-0.18 (-1.39 to 1.03)
Network estimate				0.25 (-0.38 to 0.88)
TRE:WDF				
Direct estimate	1		0.04	1.50 (-2.38 to 5.37)
Indirect estimate				0.61 (-0.15 to 1.36)
Network estimate				0.64 (-0.10 to 1.38)



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ADF=alternate day fasting; AdLib=ad-libitum; CER=continuous energy restriction; TRE=time restricted eating; WDF=whole day fasting

Fig 3 | Network analysis comparing intermittent fasting strategies, continuous energy restriction, and ad-libitum diets on body weight (kg). An interactive version of this graphic is available at https://public.flourish.studio/visualisation/23092314/

	Ad-libitum	Continuous energy restriction	Alternate day fasting	Time restricted eating	Whole day fasting	Versus
Ad-libitum		**-2.21† (-3.72 to -0.70) (n=3)**	**-3.63† (-5.91 to -1.35) (n=2)**	**-2.46† (-4.19 to -0.72) (n=2)**	**-1.88* (-3.37 to -0.39) (n=2)**	Ad-libitum
Continuous energy restriction	**-2.09† (-2.77 to -1.41) (n=4)**		-1.42 (-3.44 to 0.61) (n=4)	-0.24 (-2.06 to 1.58) (n=3)	0.34 (-0.91 to 1.58) (n=7)	Continuous energy restriction
Alternate day fasting	**-3.37† (-4.16 to -2.59) (n=8)**	**-1.29* (-2.05 to -0.53) (n=11)**		1.17 (-1.42 to 3.77) (n=0)	1.75 (-0.53 to 4.04) (n=0)	Alternate day fasting
Time restricted eating	**-1.65* (-2.17 to -1.13) (n=23)**	0.44 (-0.25 to 1.12) (n=11)	**1.72* (0.87 to 2.58) (n=1)**		0.58 (-1.41 to 2.56) (n=0)	Time restricted eating
Whole day fasting	**-2.53† (-3.28 to -1.79) (n=14)**	-0.45 (-1.19 to 0.29) (n=16)	0.84 (-0.11 to 1.79) (n=1)	**-0.88* (-1.71 to -0.06) (n=1)**		Whole day fasting
Versus	Ad-libitum	Continuous energy restriction	Alternate day fasting	Time restricted eating	Whole day fasting	

Fig 4 | Network meta-analysis of body weight outcome from 93 randomised clinical trials by follow-up duration: ≥24 weeks (n=17) and <24 weeks (n=76). Results are presented as mean differences and 95% confidence intervals (CIs) based on results from the 93 studies that reported on body weight (kg). Total number of direct comparison studies are noted in the brackets below the confidence intervals. Statistically significant results are in bold. The minimally important difference for body weight was 2.0 kg. Of the minimally important differences that were significant, effect sizes were classified as *trivial (<2.0 kg) and †small (≥2.0 to <4.0 kg); moderate (≥4.0 to <10.0 kg), large (≥10.0 to <20.0 kg), and very large (≥20.0) effect sizes were not noted. Green boxes show studies with <24 weeks duration (n=76). These results compare diets listed on the left column versus bottom row. For example, continuous energy restriction compared with ad-libitum diet shows −2.09 kg (95% CI −2.77 to −1.41), in which continuous energy restriction diets resulted in a 2.09 kg weight loss compared with ad-libitum diets in studies with <24 weeks duration. Blue boxes show studies with ≥24 weeks (n=17). These results compare diets listed on the top row versus right column. For example, continuous energy restriction compared with ad-libitum diet shows −2.21 kg (95% CI −3.72 to −0.70), in which continuous energy restriction diets resulted in a 2.21 kg weight loss compared with an ad-libitum diet in studies with ≥24 weeks duration

from low to high (supplementary figures 10 and 11). Conversely, all diet strategies showed a trivial decline in fasting glucose and HOMA-IR when compared with ad-libitum diet; evidence was of moderate certainty (supplementary figures 8 and 12). Additionally, ADF compared with an ad-libitum diet showed the greatest number of changes across the cardiometabolic risk factors.

Adverse events and adherence

Supplementary table 4 outlines the adverse events and adherence reported in the identified studies. Assessment of adverse events were reported in 56 trials, of which 27 trials reported no harmful events in the intermittent fasting groups. Of the 29 studies that described some adverse events, all but one was considered severe. Most trials reported mild side effects including constipation, nausea, hunger, diarrhoea, and dizziness. Holmer and colleagues reported a severe event of one participant with hypoglycaemia having a fall[66]; however, the participant remained in the study. A separate study reported one case of high bilirubin and low sodium concentrations in the midstudy follow-up, and one person with low potassium concentrations at the end of the 26 week trial.[35]

Of the 99 identified studies, 74 studies included description of adherence or sufficient information to determine adherence. Most trials reported high adherence (>80%) throughout the duration of the study. Among the trials that had a 52 week follow-up,[50 57 59 64 79] most stated poor adherence in the intervention groups. In one study,[59] adherence to the WDF declined from 74% at six weeks to 22% at 52 weeks. By contrast, however, another 52 week study reported high adherence in the TRE and CRE diet groups (both approximately 84%).[79]

Sensitivity analysis and publication bias

We conducted a sensitivity network meta-analyses for studies with people with type 2 diabetes (n=11) (supplementary figure 35). Briefly, TRF compared with ad-libitum only showed a trivial improvement for body weight (mean difference −1.93 kg (95% CI −2.44 to −1.43)), while WDF (−2.74 kg (−4.30 to −1.18)) and CER (−2.87 kg (−4.63 to −1.11)) diets showed small reductions in body weight compared with ad-libitum. ADF, however, showed a moderate reduction in body weight compared with ad-libitum (−4.42 kg (−5.91 to −2.94)). Additionally, TRE showed a moderate reduction for BMI, small reductions for fasting blood

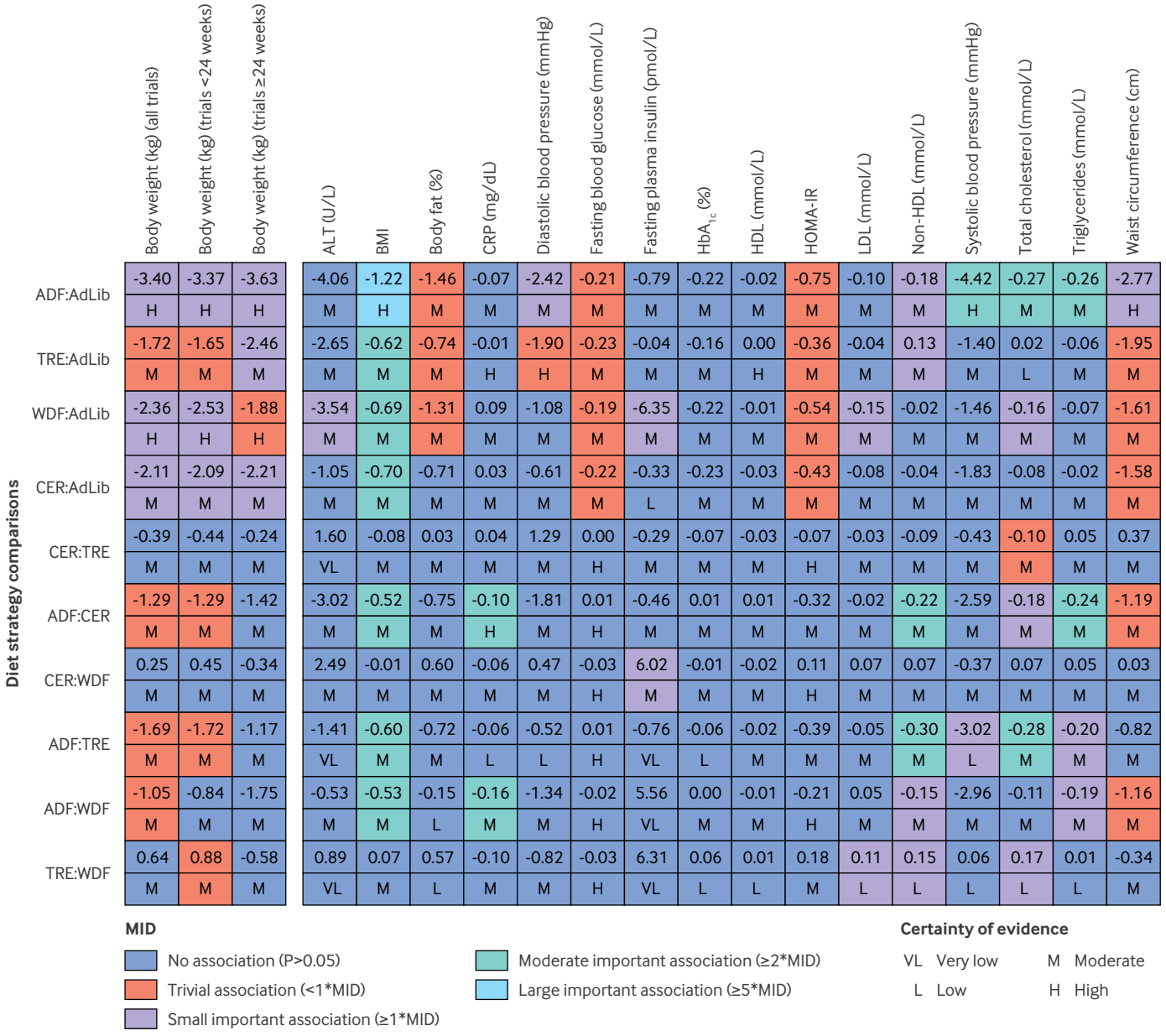

Fig 5 | Summary heatmap of the network effect size estimates (mean differences) and CINeMA certainty of the evidence, which applied the GRADE system, for all comparisons with each outcome of interest (n=17). Results are given as diet strategy 1 compared with diet strategy 2 with reductions favouring diet strategy 1 and increases favouring diet strategy 2 (opposite for high density lipoprotein cholesterol). The colours represent the level of effect based on MID for each outcome (supplementary table 22 for the MIDs). Very large effects (≥10 kg) are not shown as no effect size reached this. The blue boxes represent non-significant network effect estimates (P>0.05) and no important effect; the letters represent certainty of evidence, as per GRADE. ADF=alternate day fasting; AdLib=Ad-libitum; CER=continuous energy restriction; CINeMA=confidence in network meta-analysis; GRADE=grading of recommendations assessment, development, and evaluation; HDL=high density lipoprotein; HOMA-IR=homeostatic model assessment for insulin resistance; LDL=low density lipoprotein; MID=minimally important difference; TRE=time restricted eating; WDF=whole day fasting

glucose and waist circumference, and trivial reductions for both fasting plasma insulin and HOMA-IR. WDF, however, only showed a moderate improvement for fasting plasma insulin when compared with ad-libitum. Among intermittent fasting strategies, ADF moderately improved body weight reduction compared with both TRE, while TRE resulted in a moderate increase in fasting plasma insulin compared with WDF. Since no other study outcome had at least 10 trials in all diet group comparisons, we did not conduct additional subgroup analyses.

Supplementary figures 36-51 show the comparison adjusted funnel plots for all outcomes with 10 or more trials, including body weight, alanine transaminase, body fat percentage, BMI, C-reactive protein, fasting glucose, fasting insulin, HbA_{1c}, high density lipoprotein cholesterol, HOMA-IR, low density lipoprotein cholesterol, non-high density lipoprotein

cholesterol, systolic blood pressure, total cholesterol, triglycerides, and waist circumference. Funnel plot asymmetry was not observed for any of the outcomes.

Discussion

This meta-analysis concurrently and comprehensively evaluates the association of intermittent fasting, CER, and ad-libitum diets on cardiometabolic risk factors. Our findings showed a trivial to small reduction in body weight for all diet strategies compared with ad-libitum, and trivial reductions for ADF compared with CER, TRE, and WDF. These associations, however, were only significant among comparisons with ad-libitum diet in moderate-to-long term follow-up durations of at least 24 weeks. ADF when compared with TRE or WDF was associated with a reduction in BMI, non-high density lipoprotein cholesterol, and triglycerides. WDF only showed an improvement in total cholesterol over TRE. Additionally, all diet strategies presented similar benefits in cardiometabolic risk over an ad-libitum diet. ADF was the only intermittent fasting strategy to show an improvement in anthropometric and lipid measures when compared to CER. No benefit was observed for HbA_{1c} or high density lipoprotein cholesterol in any diet strategy comparison.

Comparison with other studies

While several systematic reviews and meta-analysis have been performed on intermittent fasting over the years, there are numerous limitations which restrict their overall interpretation or applicability. Previous meta-analyses either focused solely on weight loss, focused on a specific method of fasting, excluded studies with people who have comorbidities, even though this population stands to benefit the most from intermittent fasting, lacked assessment of heterogeneity, or did not assess the certainty of evidence.[8-10 129-131] Our network meta-analysis addresses these important limitations through our comprehensive evaluation of intermittent fasting diet strategies, CER, and ad-libitum diet, on body weight and other cardiometabolic risk factors.

In our analysis, intermittent fasting strategies showed trivial to small improvements in body weight reduction, with similar improvements in other anthropometric measurements including BMI and waist circumference compared to an ad-libitum diet and little additional benefit against CER. These findings are in accordance with previously published meta-analyses.[9 10] Cioffi and colleagues evaluated intermittent fasting, which grouped together WDF and ADF, against CER, in 11 identified trials of adults with overweight or obesity and observed no significant improvement for weight loss.[9] In our network meta-analysis, ADF was the only intermittent fasting strategy to show a reduction in weight when compared with CER, perhaps due to easier adherence to ADF compared with a continuous diet strategy.[11] To date, however, only three studies have directly compared intermittent fasting diets with cardiometabolic outcomes.[39 52 102] Among patients with non-alcoholic fatty liver disease, Cai and colleagues showed that both intermittent fasting strategies were effective in weight loss and other anthropometric measures over an ad-libitum diet; however, no significant differences were observed between intermittent fasting strategies.[39] Similarly, Erdem and colleagues compared anthropometric changes across a 12 week period and observed no significant difference in body weight between intermittent fasting groups (TRF and WDF).[52] Among people with type 2 diabetes and obesity, Umphonsathien and colleagues' study results showed similar improvements for glycaemic control between WDF and ADF.[102] For the first time, using the network meta-analysis approach, we were able to comprehensively examine the associations between intermittent fasting strategies, accounting for both direct and indirect estimates, and observed an improvement in body weight for ADF over TRE. ADF's greater weight loss and cardiometabolic benefits, such as reduced HOMA-IR, may reflect enhanced fat oxidation and insulin sensitivity from prolonged fasting periods; although, short trial durations probably limited larger differences compared with TRE, WDF, or CER.

While our analysis by trial duration for body weight showed similar changes in trials with less than 24 weeks duration to the network analysis of all trials, assessment of longer trial studies showed a reduction in body weight for diet interventions when compared with ad-libitum. The loss of association in the network assessment of moderate to longer term trials (≥24 weeks) may be due to an insufficient number of studies available. Additionally, while our analysis included randomised clinical trials, adherence to dietary interventions may decline over time,[11] and metabolic adaptation could limit sustained weight loss in longer term trials.[132] Notably, the results show that intermittent fasting may offer unique benefits primarily in the short term, whereas both intermittent fasting and CER appear to provide similar moderate-to-long term improvements over ad-libitum diets. This equivalence in sustained outcomes in the moderate-to-long term is a critical take-away for clinicians managing chronic metabolic conditions. The inclusion of three week trials, while showing early weight loss (eg, 0.5-2 kg), reflects short term feasibility rather than sustained effects, which potentially may have inflated short term benefits in the less than 24 week stratum. Additionally, the scarcity of trials of 52 weeks or longer (only five identified) precluded a separate network meta-analysis for very long term effects, limiting relevance to related to sustained long term weight loss. Future randomised clinical trials with extended follow-up are needed to assess the durability of these dietary strategies.

Moreover, as glucose, lipid, and energy metabolism are all regulated by the circadian system, eating at certain times of the day may provide benefits beyond weight loss through differences in insulin sensitive periods, beta cell responsiveness, and thermic effect of food.[133] In a proof-of-concept study among men with prediabetes, a group using TRE with a morning eating window improved (insulin resistance and blood

pressure) and impaired (triglycerides) cardiometabolic risk factors independent of weight loss when compared with a control group.[134] While our analysis did not examine specific eating time windows, these findings were generally consistent with our results for TRE versus ad-libitum diet showing a benefit in fasting blood glucose, insulin resistance (HOMA-IR), and diastolic blood pressure. Similar benefits were evaluated in the other intermittent fasting diets, ADF and WDF, with additional benefits for total cholesterol. A meta-analysis also showed similar improvements in intermittent fasting compared with a non-intervention diet for insulin and HOMA-IR.[135]

The benefits between intermittent fasting and CER, and among intermittent fasting strategies, for cardiometabolic markers remain unclear. We showed that ADF improved several cardiometabolic risk factors, including non-high density lipoprotein cholesterol, triglycerides, and total cholesterol, while TRE and WDF generally did not result in additional benefits to CER. A few meta-analyses that evaluated intermittent fasting with CER showed no significant benefit for several cardiometabolic risk factors including fasting glucose,[9 10 136 137] HbA_{1c},[9] HOMA-IR,[9] or lipid markers[10 136 137]; however, findings for high density lipoprotein cholesterol are less consistent. In a review of patients with metabolic syndrome, intermittent fasting improved high density lipoprotein cholesterol concentrations,[136] while a separate analysis among individuals with type 2 diabetes and metabolic syndrome found no significant change for high density lipoprotein cholesterol.[137] In our analyses, we found no significant changes in any diet comparison for high density lipoprotein cholesterol. However, comparisons between intermittent fasting showed that ADF was more effective in lowering total cholesterol and triglyceride concentrations. WDF also showed an improvement in reducing total cholesterol levels when compared with TRE. These findings were primarily based on indirect estimates, and thus, direct comparisons are not needed to confirm these associations.

The hypothesised improvement in cardiometabolic health through a fasting diet approach derives primarily from extensive animal model studies.[138-140] Such studies have noted that fasting states can encourage the use of fat stores, with a preferential reduction or browning of adipose tissue mass, improved insulin sensitivity, and reduction in inflammation and oxidative stress.[138] Furthermore, the notion of metabolic switching between the fed and fasted states, particularly through a TRE approach, have also shown benefits in preventing glucose intolerance and dyslipidaemia.[139 140] These metabolic changes, however, have not been substantiated in humans. Moreover, as determined in our network analyses, poor adherence, particularly in longer trials, pose challenges in assessing the true impact of these diet strategies on cardiometabolic health. Additional studies focused on comparing intermittent fasting strategies with focused improvement in participant adherence are needed to elucidate potential differences in dietary approaches and their impact on cardiometabolic risk factors.

The 2.0 kg minimally important difference reflects clinically meaningful weight loss in largely obese populations, aligning with prior evidence.[29] While many observed reductions with intermittent fasting strategies compared to ad-libitum exceeded this threshold, individual strategies of intermittent fasting particularly ADF versus CER (−1.29 kg) fell below this level, suggesting somewhat limited clinical impact in those comparisons. Nevertheless, these intermittent fasting strategies offer a valuable non-pharmacological option for improving cardiometabolic health. By contrast, GLP-1 receptor agonists, such as semaglutide, result in substantial weight reductions of 10-15% body weight (approximately 8-12 kg for an 80 kg individual) alongside significant in improvements HbA_{1c} and cardiovascular risk in adults with overweight or obesity.[141] While GLP-1 treatments provide a powerful tool for transformative outcomes, intermittent fasting strategies remain an effective, accessible approach for those seeking sustainable weight management and cardiometabolic benefits without medication.

Strengths and limitations

This review has several strengths. This systematic review leverages both direct and indirect comparisons of all diet strategies through a network meta-analysis approach. Unlike the traditional pairwise meta-analysis, a network approach allows for more precise estimates, compared with single direct or indirect estimates, and allows for the ability to compare interventions that had not been previously compared. Additionally, we further evaluated the clinical value of these diet strategies on body weight using trial duration stratification. Moreover, we conducted a comprehensive literature search of randomised clinical trials using several databases in conjunction with a manual search. The bias was protection against with a focus on randomised clinical trials, no evidence of serious risk of bias was noted among included trials, and the use of the GRADE approach to assess the certainty of the estimates.

Conversely, important limitations should be considered. Firstly, the GRADE evaluation of the certainty of evidence was downgraded due to considerable heterogeneity and incoherence in the primary outcome of body weight among the various diet strategy comparisons. These downgrades are reflective of unexplained inconsistencies in the treatment effects (heterogeneity) and variations in the direct versus indirect estimates (incoherence). Certainty of evidence was also downgraded for imprecision based on 95% CIs crossing the prespecified minimal important differences for the outcomes of interest. Many randomised clinical trials had small sample sizes, which would have influenced the precision of the effect estimates. Similar downgrades were applied for several secondary cardiometabolic risk factors. Secondly, evidence of serious concern was considered for indirectness in several analyses,

particularly among intermittent fasting strategy comparisons. Only three randomised clinical trials of direct assessment between intermittent fasting diets were available, thereby limiting generalisability and resulting in downgrades for indirectness.[39 52 102] Thirdly, we acknowledge that adjustments for multiple comparisons were not applied, as they are generally not recommended for prespecified outcomes in meta-analyses.[13] Furthermore, we excluded outcomes with fewer than three eligible studies, which may limit the comprehensiveness of our findings. Future studies with more data could address these gaps. Taken together, the assessments of the strengths and limitations led to the certainty of the evidence to range from low to moderate in most of the investigated outcomes.

Conclusions

Our network meta-analysis showed similar benefits for various intermittent fasting strategies and CER in cardiometabolic risk compared with ad-libitum diets. ADF presented additional trivial to moderate improvements to CER in overall weight, anthropometric measurements, lipid, and systolic blood pressure measures; however, this benefit was not observed in other intermittent fasting strategies. In relation to body weight, ADF showed a reduction when compared with CER, and TRE in shorter trials, although benefits of any diet strategies were lost in longer duration studies. The current evidence provides some indication of the benefits for caloric restriction and intermittent fasting diets, with little additional benefit for intermittent fasting, in cardiometabolic risk. Additional high quality randomised clinical trials with extended durations beyond 52 weeks are needed to elucidate the long term effects of these dietary strategies, with greater emphasis between intermittent fasting diets, and their impact on cardiometabolic health and cardiovascular outcomes across diverse populations.

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Ethical approval: This study did not require research ethics committee approval.

Data sharing: All data are freely available within the supplementary file. Additional data is available upon request.

Transparency: The primary guarantor and corresponding author (JLS) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

Dissemination to participants and related patient and public communities: The findings of this systematic review and network meta-analysis will be disseminated through conference presentations, education sessions for healthcare professionals, social media feeds, newsletters, and direct outreach to government and stakeholders such as patient organisations and commonly used public sources of patient information. This work was commissioned by EASD and will inform updated guidelines.

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