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Evaluating the efficacy of intermittent fasting and exercise combinations for weight loss: A network meta-analysis

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Summary

Objective: The purpose of this study is to utilize network meta-analysis (NMA) to synthesize relevant randomized controlled trials (RCTs) and evaluate the most effective intermittent fasting (IF) combined with exercise interventions for weight loss.

Methods: This study searched five databases up until April 2024, obtaining RCTs that investigated the effects of intermittent fasting (IF) combined with exercise. The quality of the literature was assessed using the Cochrane tool, followed by a random-effects statistical analysis of each intervention. Eventually, a NMA was conducted to compare the effectiveness of each intervention on weight loss, thereby determining their combined effectiveness on reducing weight.

Results: A total of nine trials, comparing 12 interventions involving 570 participants, were included. All interventions significantly reduced body weight (BW) and fat mass (FM) compared to the control (CON) group. In terms of BW reduction, the alternate-day fasting + moderate-intensity continuous training (ADF + MICT) intervention had the highest surface under the cumulative ranking curve average (SUCRA) score 88.1 (MD: −4.44, 95% CI −5.95, −2.92). Furthermore, for improving FM, the ADF + MICT intervention also had the highest SUCRA score 92.7 (MD: −3.65, 95% CI −5.05, −2.25), making it the optimal intervention for improving FM.

Conclusion: The NMA results indicate that all interventions are effective in reducing weight. Among them, ADF + MICT is the most effective strategy for reducing BW, and it is also the best approach for improving FM.

KEYWORDS

intermittent fasting combined with exercise, network meta-analysis, weight loss

Abbreviations: ADF, alternate-day fasting; ADF + EX, alternate-day fasting + resistance and aerobic exercise; ADF + MICT, alternate-day fasting + moderate-intensity continuous training; BW, body weight; CNKI, China National Knowledge Infrastructure; CON, control; EX, resistance and aerobic exercise; FM, fat mass; HIIT, high-intensity interval training; 5:2 + EX, 5:2 diet + resistance and aerobic exercise; 5:2, 5:2 diet; IF, intermittent fasting; MICT, moderate-intensity continuous training; NMA, network meta-analysis; RCT, randomized controlled trial; SUCRA, surface under the cumulative ranking curve average; TRE + HIIT, time-restricted eating + high-intensity interval training; TRE + MICT, time-restricted eating + moderate-intensity continuous training; TRE, time-restricted eating.

1 | INTRODUCTION

Obesity is a leading risk factor for global disease burden.¹ As obesity rates rise annually,² associated health issues including type 2 diabetes, cancer, and cardiovascular diseases increase correspondingly.¹ These diseases pose significant threats to human health and can lead to fatalities.^{3,4} Currently, diet and exercise are the primary strategies for weight loss and preventing obesity,⁵

although, prescription medications, used in conjunction with these strategies, or weight loss surgeries are also used effectively to induce significant weight loss in individuals with overweight or obesity.

Numerous studies have demonstrated the efficacy of various diets for weight loss, including low-fat diets,⁶ extremely low-calorie ketogenic diets,⁷ Mediterranean diets,⁸ and plant-based diets.⁹ Among these, IF has gained popularity.¹⁰ This approach is practical as it does not require specific dietary or strict recipe restrictions but instead adheres to certain eating windows.¹¹ Compared to other diets, IF has better compliance, no significant energy restrictions, and research indicates its total energy intake is reduced, thus providing certain advantages in maintaining long-term weight loss.¹² Despite its benefits, IF has some drawbacks, such as potential loss of lean body weight (BW) and a decline in physical function.¹³ To counteract these, combining IF with exercise has shown to provide better results and a positive impact on physical function.¹⁴ Exercise methods for weight loss include high-intensity interval training (HIIT),¹⁵ moderate-intensity continuous training (MICT),¹⁶ and resistance and aerobic exercise (EX).¹⁷ The combined effect of IF and exercise on weight loss is superior.^{18,19}

Research has demonstrated varying results concerning the efficacy of combining IF with exercise for weight loss. Recent studies reveal that 5:2 diet (5:2) paired with physical activity markedly enhances body fat reduction and muscle strength relative to control (CON) groups. Additionally, alternate-day fasting (ADF) combined with exercise notably diminishes BW, fat mass (FM), and waist circumference. Moreover, time-restricted eating (TRE) when integrated with exercise significantly lowers weight, BMI, overall FM, and visceral fat, though these reductions are not significantly distinct from those observed in diet-only or exercise-only groups.^{17,20-27} Despite the diversity of methods integrating IF with exercise, research has yet to determine the optimal intervention for maximizing weight loss effects through IF.

This paper employs NMA to compare the differential effects of various interventions on weight loss, enabling direct and indirect evidence comparisons.²⁸ The transitivity assumption of NMA postulates that trials comparing different interventions share similar characteristics that could influence outcome indicators.²⁹ Thus, this study hypothesizes that interventions of IF combined with exercise will be more effective for weight loss than diet or exercise alone, and it aims to identify the most effective intervention for weight loss.

2 | MATERIALS AND METHODS

This study adheres to the PRISMA guidelines for NMA of different interventions of IF combined with exercise.^{30,31} The protocol is registered in PROSPERO, under the registration number: CRD42023405620, and the related protocol and predefined definitions have been published.

2.1 | Search strategy

A systematic literature search was conducted using the PubMed, Web of Science, Embase, Google scholar, and China National Knowledge Infrastructure (CNKI) databases for articles published up until April 2024. The search strategy aligns with the RCT search strategy delineated in the Cochrane Systematic Review Manual 5.1.0 (www.cochranehandbook.org), utilizing a combination of subject and free words, unrestricted by language or date, and adjusted per the specific database. The search concluded after multiple attempts. Search terms comprised: (1) forms of IF: “intermittent fasting,” “IF,” “time restricted eating,” “time restricted feeding,” “TRF,” “TRE,” “alternate day fasting,” “ADF,” “modified alternate day fasting,” “MADF,” and “5:2 diet”; (2) exercise: “exercise,” “training,” “sports,” “motion,” and “movement”; (3) outcome indicators: “body weight” and “fat mass.” In the CNKI, “intermittent diet” and “exercise” were used as subject words for the search. Additionally, to avoid overlooking potential related studies, the reference lists of systematic reviews and relevant literature were examined.

2.2 | Inclusion and exclusion criteria

The study adheres to the PICOS principle of medicine.³² Inclusion criteria: (1) participants, adults aged ≥ 18 years; (2) interventions, IF combined with exercise; (3) control group, blank control; (4) outcomes, BW, FM; (5) study design, RCT.

Exclusion criteria: (1) non-IF combined with exercise; (2) fasting; (3) non-RCT study; (4) basic disease study; (5) literature lacking data; (6) nonhuman studies; (7) intervention studies using supplements as a placebo.

2.3 | Information extraction

After determining the study selection, two researchers independently screened the literature according to the inclusion and exclusion criteria, excluded obviously irrelevant literature and read the full text of potentially relevant literature. If they disagreed, they resolved it by discussion or consulting a third researcher. We extracted the literature according to a predefined information extraction table, mainly including the following features: first author's name, year of publication, study design, sample size, average baseline age, average baseline BMI, trial period, gender, intervention measures, control group, and outcome indicators.

2.4 | Risk of bias

The risk of bias in the incorporated studies was independently evaluated by two researchers using the Cochrane ROB 2.0 tool.³³ This tool assesses bias from several aspects: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants, personnel, and

outcome assessors; (4) incomplete outcome data; (5) selective outcome reporting; and (6) other bias sources.³⁴ Based on this tool, studies were categorized as having a low risk of bias (if at least three out of five items were deemed low risk), high risk of bias (if at least two out of five items were deemed high risk), or unclear risk of bias (for all remaining studies). Any discrepancies were resolved via discussion or third-party researcher consultation.

2.5 | Statistical analysis

This study used RevMan5.4 statistical software to make literature quality assessment, and used CINeMA (<https://cinema.ispm.unibe.ch>) to make credibility inference, and used STATA 18.0 (<http://www.stata.com/>) to perform NMA. If standard errors (Standard Error of Mean, SE), confidence intervals (CI), or quartiles were reported in the included studies, they were converted to standard deviations (SD) for analysis. The net effect size was calculated as the difference between the baseline and post-intervention measurements, that is, $\text{Meanchange} = \text{Meanpost} - \text{Meanpre}$ and $\text{SDchange} = \text{SQRT}[(\text{SDpre}^2 + \text{SDpos}^2) - (2 \times \text{Corr} \times \text{SDpre} \times \text{SDpost})]$, where the correlation coefficient was assigned as 0.5. The net effect size was calculated as the difference between the baseline and post-intervention measurements. A $p < 0.05$ and a 95% CI were used as the criteria for statistical significance. The extracted data were transformed into a format suitable for NMA using commands, and prior evaluation and processing of the study data were

performed. A random-effects model was used to perform pairwise meta-analysis of the included RCTs. The results showed that when $p < 0.05$, there was a statistical difference. Stata was used to analyze the effects of direct and indirect intervention measures comparison. Finally, ranking probability distribution and cumulative ranking curve average (SUCRA) were used to rank the intervention measures according to the results.³⁵ The higher the SUCRA value ranked in front, the more effective the intervention was. For each ranking result of each intervention measure, we assumed a common network-specific heterogeneity parameter to assess how much this heterogeneity affected the expected additional uncertainty in future studies. We used STATA NMA to generate all analyses described in the frequentist framework.^{29,36}

2.6 | Grading of evidence quality

The CINeMA framework³⁷ was applied to infer the credibility of NMA evidence and assess the quality of effect estimates for all intervention comparisons. CINeMA's evidence quality grading aligns with the GRADE method suggested by Salanti et al.,³⁸ comprising four levels: high, moderate, low, and very low. Evidence quality was evaluated considering study bias, reporting bias, indirectness, imprecision, heterogeneity, and inconsistency. In alignment with the NMA objectives, we synthesized the evidence quality for each intervention comparison.

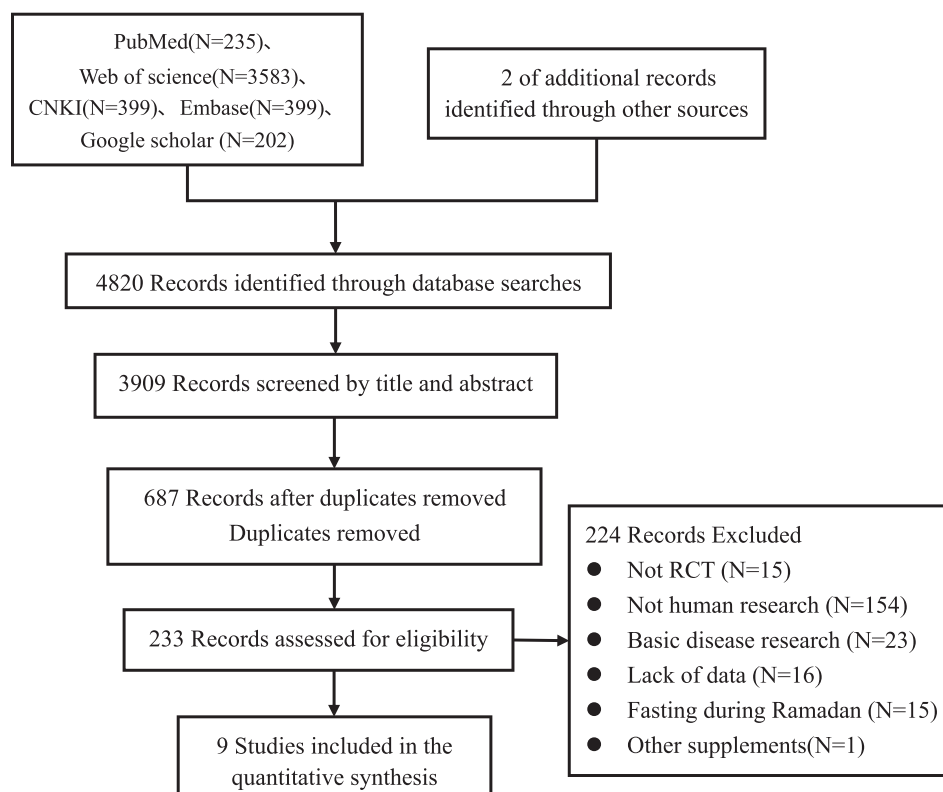


FIGURE 1 Literature screening flowchart.

3 | RESULTS AND ANALYSIS

3.1 | Literature search and selection

Our search across various databases yielded 4820 relevant articles. Upon applying the inclusion and exclusion criteria, we eliminated 4811 articles, leaving 9 articles for our study.^{17,20–27} Figure 1 illustrates the literature selection process.

3.2 | Characteristics of included studies

This research comprises 9 literature reviews with a total of 570 participants. Intervention categories include CON; dietary approaches such

as the 5:2, ADF, and TRE; exercise regimens encompassing HIIT, MICT, and EX; along with interventions that integrate IF with exercise (Table 1).

3.3 | Literature quality assessment

This article employs the Cochrane ROB 2.0 tool for risk-of-bias assessment to evaluate study quality, with findings summarized as follows: (1) Selection bias: Among nine studies, six used specific random allocation methods, two referenced random allocation generally, and one employed a distinct allocation approach; three studies mentioned allocation concealment, two of which had a high risk of bias in this regard; (2) performance bias: five studies implemented blinding

TABLE 1 Basic characteristics of included studies.

Study	Age	Duration	BMI (kg/m ²)	Sex (M/F)	Study design	Intervention class	Outcome
Bhutani, S. (2013)	45 ± 5	12w	35 ± 1	/	4arms	ADF + MICT	①②
	42 ± 2		35 ± 1	/		ADF	
	42 ± 2		35 ± 1	/		MICT	
	49 ± 2		35 ± 1	/		CON	
Oh, M. (2018)	37.3 ± 7.3	8w	27.5 ± 2.6	5/7	4arms	ADF + EX	①②
	32.9 ± 7.3		27.6 ± 2.8	3/10		ADF	
	35.7 ± 7.9		28.3 ± 4.1	7/3		EX	
	40.6 ± 10.0		26.3 ± 3.0	4/6		CON	
Cho, A-Ra. (2019)	34.5 ± 5.7	12w	28.0 ± 2.6	5/4	4arms	ADF + EX	①②
	33.5 ± 5.0		27.8 ± 3.4	2/6		ADF	
	38.6 ± 8.2		26.9 ± 3.9	5/4		EX	
	42.6 ± 10.6		25.8 ± 3.4	3/2		CON	
Haganes, K.L. (2022)	37.3 ± 5.7	7w	31.4 ± 4.0	0/22	4arms	TRE + HIIT	①②
	36.2 ± 5.9		31.8 ± 3.3	0/21		TRE	
	34.9 ± 7.0		32.5 ± 4.5	0/27		HIIT	
	36.4 ± 6.2		33.1 ± 4.2	0/29		CON	
Zhao XY (2022)	20.87 ± 2.91	8w	26.27 ± 1.06	8/0	4arms	TRF + HIIT	①
	19.67 ± 3.01		26.91 ± 0.94	8/0		TRF	
	21.04 ± 1.77		25.77 ± 0.88	10/0		HIIT	
	20.32 ± 2.17		26.89 ± 1.21	10/0		CON	
Ezpeleta, PhD, M. (2023)	44 ± 13	12w	37 ± 5	3/17	4arms	ADF + MICT	①②
	44 ± 16		36 ± 8	4/16		ADF	
	44 ± 13		37 ± 6	4/16		MICT	
	44 ± 12		37 ± 5	4/16		CON	
Ezpeleta, M. (2023)	44 ± 3	12w	37 ± 5	3/17	4arms	ADF + MICT	①②
	44 ± 3		36 ± 8	4/16		ADF	
	44 ± 3		37 ± 6	4/16		MICT	
	44 ± 3		37 ± 5	4/16		CON	
Haitao, Liu. (2023)	19.93 ± 0.61	8w	21.86 ± 1.48	/	4arms	TRF + MICT	①
	20.29 ± 1.79		21.63 ± 1.24	/		TRF	
	20.09 ± 1.35		21.35 ± 1.56	/		MICT	

TABLE 1 (Continued)

Study	Age	Duration	BMI (kg/m ²)	Sex (M/F)	Study design	Intervention class	Outcome
	20.08 ± 1.76		20.32 ± 1.06	/		CON	
Keawtep, P. (2024)	52.17 ± 3.35	12w	29.73 ± 4.57	/	4arms	5:2 + EX	①②
	52.87 ± 3.88		28.28 ± 2.78	/		5:2	
	52.70 ± 3.60		29.06 ± 2.90	/		EX	
	53.61 ± 2.81		29.18 ± 2.85	/		CON	

Note: w, week; ①, Body weight; ②, Fat mass.

Abbreviations: ADF, alternate-day fasting; ADF + MICT, alternate-day fasting + moderate-intensity continuous training; CON, control; EX, resistance and aerobic exercise; HIIT, high-intensity interval training; MICT, moderate-intensity continuous training; TRE, time-restricted eating; TRE + HIIT, time-restricted eating + high-intensity interval training.

methods considered to have a low risk of bias, while one study demonstrated a high risk of performance bias; (3) detection bias: all seven studies furnished explanations for this bias; (4) attrition bias: all studies reported no missing data; (5) reporting bias: none of the studies exhibited instances of selective reporting; (6) other biases: eight studies did not report other biases, and one displayed unclear risks concerning additional biases (Figure 2).

3.4 | Results of NMA

The network evidence map identifies 12 intervention measures for BW, including CON, 5:2, ADF, TRE, HIIT, MICT, EX, 5:2 diet + resistance and aerobic exercise (5:2 + EX), alternate-day fasting + moderate-intensity continuous training (ADF + MICT), alternate-day fasting + resistance and aerobic exercise (ADF + EX), time-restricted eating + high-intensity interval training (TRE + HIIT), and time-restricted eating + moderate-intensity continuous training (TRE + MICT), and 11 for FM: CON, 5:2, ADF, TRE, HIIT, MICT, EX, 5:2 + EX, ADF + MICT, ADF + EX, TRE + HIIT. The map offers a visual comparison of the number of studies involving BW, FM, and the CON, alongside the corresponding number of participants and studies, depicted by the size of each node. Each node, represented by a blue dot, correlates with an intervention measure, the size proportional to the aggregate number of participants in that intervention. The lines between nodes indicate direct comparisons between two interventions, with the line thickness reflecting the volume of studies evaluating each comparison (Figure 3).

Pairwise comparisons were conducted for all intervention measures in both BW and FM studies (Figure S1). Examination of the figure reveals that a value greater than 0 denotes congruent findings across the two studies, indicative of positive outcomes and strong homogeneity between them. Conversely, a value below 0 signifies heterogeneity between the two studies.

The NMA carried out pairwise comparisons of all intervention strategies for BW and FM (Table 2; Table 3), providing estimates of the effect size of each intervention on BW and FM results. Compared with the CON, all interventions significantly reduced BW and enhanced FM outcomes. Specifically, interventions such as

ADF + MICT (MD: −4.44, 95% CI −5.95, −2.92), TRE + HIIT (MD: −4.30, 95% CI −6.29, −2.31), and ADF + EX (MD: −3.51; 95% CI −6.34, −0.68) demonstrated superior efficacy in reducing BW when compared to other methods. Concurrently, ADF + MICT (MD, −3.65, 95% CI −5.05, −2.25), ADF + EX (MD, −2.90, 95% CI −4.47, −1.34), and 5:2 + EX (MD, −2.95, 95% CI −5.31, −0.59) were notably more effective in enhancing FM outcomes in comparison to other interventions.

The comparative effect analysis of IF combined with exercise interventions on BW and FM (Figure 4), with SUCRA values (Table S1). Relative to the CON, all tested interventions demonstrated a significant weight reduction effect. Among them, the ADF + MICT regimen, with a SUCRA of 88.1, noticeably outperformed other methods such as TRE + HIIT (SUCRA: 84.3) and ADF + EX (SUCRA: 69.2), making it the most effective strategy for BW reduction. Concurrently, in terms of improving FM, ADF + MICT (SUCRA: 92.7) significantly exceeded both ADF + EX (SUCRA: 78.5) and 5:2 + EX (SUCRA: 77.6), establishing it as the superior approach. Accordingly, the ADF + MICT method is recognized as the most proficient in reducing BW and enhancing FM outcomes.

The analysis demonstrated consistent results for BW and FM outcome measures ($p > 0.05$), with no significant discrepancies (Figure S2; Figure S3). Consequently, the reviewed literature displays robust consistency. The assessment of evidence quality utilized the CINeMA evidence grading system, accounting for factors including the risk of bias in a limited number of studies and the challenges in evaluating composite hypotheses. The NMA conducts both direct comparisons of interventions within trials and indirect comparisons across trials using shared comparators. The research assessed the reliability of the evidence, considering aspects such as in-study bias, reporting bias, indirectness, imprecision, heterogeneity, and inconsistency, ultimately determining the evidence to be of high credibility (Table S2).

4 | DISCUSSION

Obesity is a critical global health concern, and the integration of IF with exercise constitutes an innovative, time-saving, and efficacious

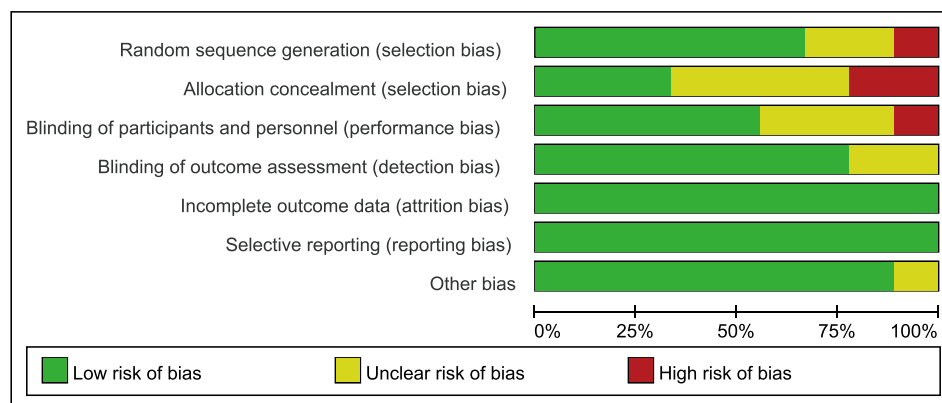
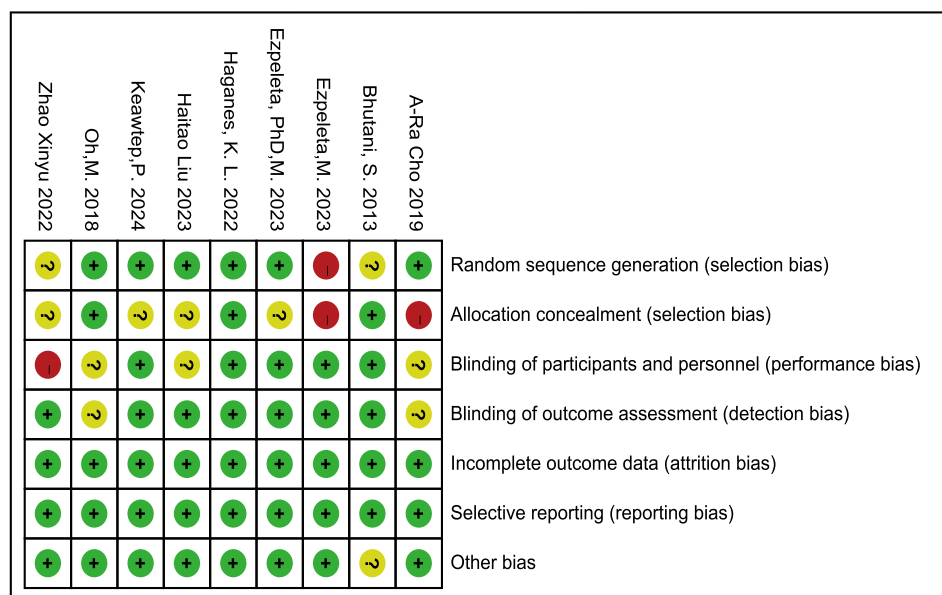


FIGURE 2 Risk-of-bias plot.

Risk of bias graph



Risk of bias summary

approach to weight loss.³⁹ This study employed NMA to evaluate the impact of IF combined with exercise on weight reduction. It analyzed 12 interventions, encompassing 570 participants in total. The findings demonstrate that all interventions significantly reduced weight. Notably, ADF + MICT emerged as the most effective in decreasing BW and excelled in enhancing FM outcomes.

IF can reduce energy intake, while exercise can improve appetite and enhance body functions, thereby mitigating the adverse effects of dietary patterns.⁴⁰ Therefore, IF serves as the foundation for weight loss, with exercise being the crucial promoting factor. Consequently, combined dietary and exercise interventions are more effective for weight loss than diet or exercise alone.⁴¹ Notably, IF combined with various exercise interventions can effectively reduce the risk of obesity,¹³ but no studies have systematically determined which specific combination is most effective for weight loss. This study identified that the ADF + MICT (SUCRA: 88.1) intervention was the most effective in reducing BW, with TRE + HIIT (SUCRA: 84.3) and ADF + EX (SUCRA: 69.2) following in effectiveness. The ADF

method alternates between eating days and fasting days.⁴² A meta-analysis has shown that ADF outperforms other IF methods in achieving weight loss.⁴³ MICT is a prolonged aerobic exercise that promotes fat oxidation and weight reduction. Extensive reviews and meta-analyses indicate that MICT can moderately improve body composition in overweight and individuals with obesity.⁴⁴ The ADF + MICT intervention thus demonstrates substantial efficacy in decreasing BW. However, during weight loss, the reduction in BW may result from a decrease in body water, muscle protein, or other tissues rather than FM. Excessive FM accumulation can lead to obesity and endanger human health.⁴⁵ Therefore, reducing FM remains a crucial focus.

FM, defined as the proportion or weight of fat within human tissues, significantly impacts health, with its increase identified as a primary risk factor for various diseases.⁴⁶ This study determined that the ADF + MICT (SUCRA: 92.7) intervention is the most effective for improving FM, followed by ADF + EX (SUCRA: 78.5) and 5:2 + EX (SUCRA: 77.6). Studies by Razavi et al.⁴⁷ confirm that ADF effectively

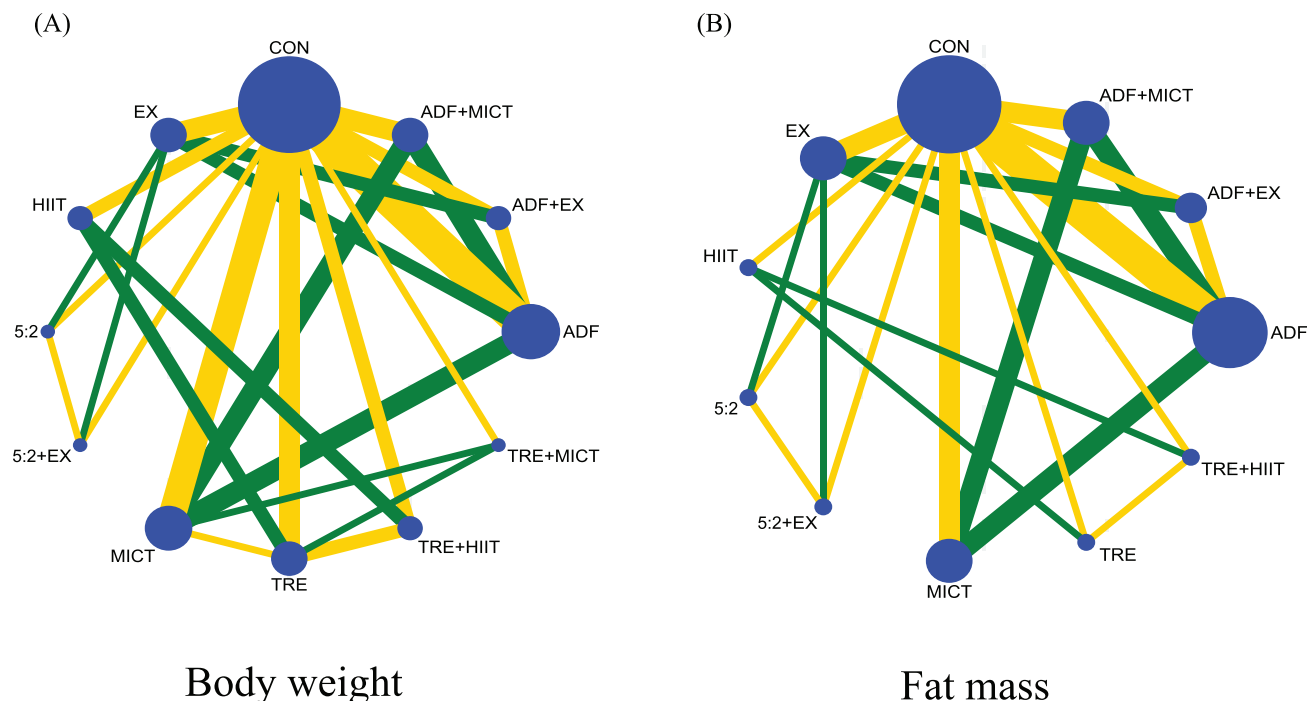


FIGURE 3 Network of treatment comparisons.

reduces FM, particularly visceral fat, and enhances fat metabolism, culminating in notable fat level decrease. MICT contributes to this process by boosting fatty acid availability and improving oxygen delivery within the body, subsequently speeding up fat oxidation and overall metabolism.⁴⁸ Additionally, it fosters heightened insulin sensitivity and diminishes fat storage.⁴⁹ Further investigations by Bhutani et al.²¹ corroborate that ADF lessens visceral fat, MICT hastens fat metabolism, and their synergy sustains an elevated resting metabolic rate, thereby optimizing body composition. Consequently, the ADF + MICT regimen emerges as a robust approach for FM enhancement.

This study's results demonstrate the efficacy of various interventions in weight reduction. Notably, ADF + MICT yields superior outcomes in BW reduction compared to TRE + HIIT, diet-only, and exercise-only interventions. In terms of improving FM, ADF + MICT surpasses 5:2 + EX, as well as diet-only and exercise-only strategies. A meta-analysis of RCTs illustrates that ADF enhances disease risk reduction, facilitates fat loss, and diminishes levels of insulin and inflammation more effectively than the 5:2 diet and TRE.⁵⁰ Despite this, Zhang et al.⁵¹ suggest that while long-duration MICT lacks a numerical superiority over HIIT in abdominal visceral fat reduction, HIIT is favored as a primary obesity control strategy due to its efficiency in time use. Additionally, DeFeo⁵² asserts that there is no definitive proof favoring HIIT over MICT in terms of weight or FM reduction, although MICT exhibits greater adherence, rendering it more advantageous for sustained weight loss. Consequently, ADF effectively reduces fat and regulates metabolism, whereas MICT enhances fat oxidation and mitigates fat accumulation. The high

compliance associated with both ADF and MICT boosts their acceptability and sustainability, thereby augmenting their combined efficacy, making ADF + MICT more effective than other interventions for weight loss.

To date, no research has definitively determined which method is superior, though evidence suggests a combination of diet and exercise may be beneficial for weight loss.³⁹ Nonetheless, biases within research persist. Individuals should select an appropriate combination of IF and exercise methods based on their personal circumstances and preferences. A multitude of combinations can be chosen for varying effects.

5 | STRENGTHS AND LIMITATIONS

This study is the first to utilize network meta-analysis to compare the effects of IF and exercise combinations, providing comprehensive evidence-based support. It also found that the strategies for reducing BW and FM are identical. However, some limitations need consideration. The studies did not fully account for the specific details of the intervention plans nor did it thoroughly analyze the energy balance between macronutrient intake and expenditure. Additionally, individual differences were not fully considered due to the different intervention methods chosen by each participant, and the various outcome indicators of different interventions may also affect the results of the NMA. Therefore, a more comprehensive and detailed description is required to address this NMA issue.

TABLE 2 Body weight the league table.

[illegible]

Note: The corresponding values of the aforementioned interventions represent the MD and 95% confidence intervals (CI) (%) of BW between rows and columns. The statistical significance of the comparative effect size is generally determined by the 95% CI (%) of the comparative effect size (e.g., the MD of BW between ADF + MICT and TRE + HIIT interventions is -0.14 , 95% CI is -2.61 , 2.33). Statistically significant results are highlighted in bold black font.

MICT, moderate-intensity continuous training; TRE, time-restricted eating + high-intensity interval training.

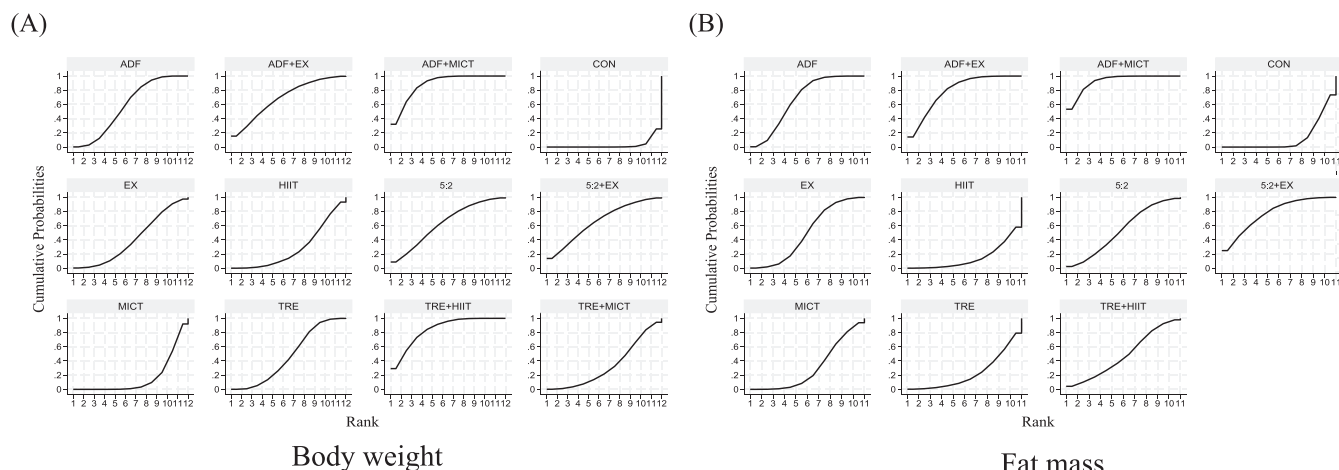


FIGURE 4 Surface under the cumulative ranking curve average.

6 | CONCLUSION

The NMA results reveal that varying combinations of diet and exercise demonstrate differential impacts on weight loss. Relative to the control group, all interventions effectively reduce weight. Notably, the combination of ADF + MICT emerges as the most effective regime for lowering BW, and it additionally provides the greatest enhancement in reducing FM.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

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