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Effectiveness Of Intermittent Fasting Versus Calorie Restriction For Weight Loss -A Comprehensive Meta-Analysis

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Abstract

Background: Though their relative efficacy is still up for discussion, intermittent fasting (IF) and calorie restriction (CR) are two well-liked dietary strategies for managing weight. The present data are compiled in this meta-analysis to ascertain the relative effectiveness of IF versus CR for weight loss and cardiometabolic health outcomes.

Methods: A comprehensive systematic review and meta-analysis were conducted following PRISMA guidelines. We searched PubMed, Embase, Web of Science, and Cochrane databases from inception through October 2025. Randomized controlled trials (RCTs) comparing IF (alternate day fasting, time-restricted eating, 5:2 diet) with CR or control diets in adults with overweight or obesity were included. The primary outcome was body weight change; secondary outcomes included body composition, metabolic markers, cardiovascular parameters, and inflammatory biomarkers. Effect sizes were calculated using random-effects models with 95% confidence intervals.

Results:

Ninety-nine RCTs involving 6,582 participants were included. Both IF and CR produced significant weight loss compared to ad-libitum diets. Alternate-day fasting demonstrated superior weight loss compared to CR (mean difference: -1.29 kg, 95% CI: -1.99 to -0.59, moderate certainty). IF combined with CR yielded greater weight reduction than CR alone (MD: -2.11 kg, 95% CI: -2.68 to -1.54, $p<0.00001$). IF showed preferential fat mass loss (MD: -1.08 kg, $p=0.0001$) while preserving lean mass. IF improved insulin resistance (HOMA-IR reduction: -0.32, 95% CI: -0.59 to -0.06, $p=0.02$) and glycemic control (HbA1c reduction: -0.9%, $p<0.05$) more effectively than CR. Both approaches similarly improved blood pressure and lipid profiles. Adherence rates were comparable between IF and CR (dropout rates: 0-65%, no significant difference). Common adverse events were transient and mild.

Conclusions:

Intermittent fasting, particularly alternate-day fasting and early time-restricted eating, demonstrates modest but significant advantages over traditional calorie restriction for weight loss and metabolic health outcomes. IF represents an evidence-based alternative dietary strategy, especially for individuals who find daily calorie restriction challenging. The choice between IF and CR should be individualized based on patient preferences, lifestyle factors, and metabolic goals.

Keywords: Intermittent fasting, calorie restriction, weight loss, obesity, metabolic health, insulin resistance, systematic review, meta-analysis.

1. Introduction

Over 40% of American people suffer from obesity, which has become an epidemic on a global scale and is a major cause of cardiovascular disease, type 2 diabetes, and early mortality. Weight regain rates within five years surpass 80%, indicating that while traditional weight control techniques based on daily calorie restriction (CR) have shown efficacy, they are frequently difficult to sustain over the long run. This has led to exploration into different dietary strategies that can improve adherence while providing equivalent or better benefits.(Alfahl, 2025; Catenacci et al., 2025; Y. Huang et al., 2022; Welton et al., 2020)

A promising nutritional intervention, intermittent fasting (IF), involves alternating periods of eating and fasting and can be carried out using a variety of protocols. The three main IF modalities are: (1) time-restricted eating (TRE), which limits food consumption to certain daily windows (usually 4–10 hours); (2) alternate day fasting (ADF), which alternates between days of normal eating and days of fasting or severely restricted calories; and (3) whole day fasting, such as the 5:2 diet, which alternates two days of severe calorie restriction and five days of normal eating each week.(Črešnovar et al., 2023; Gu et al., 2022; D. Liu et al., 2022; Patikorn et al., 2021; Semnani-Azad et al., 2025; Siles-Guerrero et al., 2024)

There is mixed data in recent meta-analyses about the relative efficacy of IF versus CR. A 2022 landmark study found no significant difference between 8-hour TRE with CR versus CR alone after 12 months. Nevertheless, a 2025 study found that at one year, 4:3 intermittent fasting resulted in 7.6% body weight loss as opposed to 5.0% with daily CR, indicating a statistically significant and clinically relevant difference. A thorough review of meta-analyses revealed evidence of intermediate quality in favor of IF for improvements in cardiometabolism and anthropometry.(Catenacci et al., 2025; Y. Huang et al., 2022; D. Liu et al., 2022; Patikorn et al., 2021)

The mechanisms underlying IF's potential advantages extend beyond simple calorie deficit. IF induces metabolic switching between glucose and ketone-based energy metabolism, enhances autophagy, improves mitochondrial efficiency, reduces oxidative stress, and modulates circadian rhythms. These physiological changes may provide advantages without regard to weight loss, which could account for the differences in results between IF and CR even though their calorie deficits are similar.(Guan et al., 2025; Kang et al., 2022; Lowe et al., 2020; Trepanowski et al., 2017)

Given the substantial heterogeneity in study designs, IF protocols, and outcome measures across existing literature, a comprehensive meta-analysis synthesizing the latest evidence is warranted.

This analysis aims to: (1) compare the effectiveness of various IF modalities versus CR for weight loss and body composition changes; (2) evaluate differential effects on metabolic and cardiometabolic parameters; (3) assess inflammatory biomarker responses; (4) examine adherence, safety, and adverse event profiles; and (5) identify optimal IF protocols for specific patient populations.

2. METHODOLOGY

2.1. SELECTION CRITERIA

Inclusion Criteria

Studies were eligible if they:

- Were randomized controlled trials;
- Enrolled adults (≥18 years) with overweight (BMI ≥25 kg/m²) or obesity (BMI ≥30 kg/m²);
- Compared IF interventions (ADF, TRE, or whole day fasting) with CR or control diets;
- Had intervention durations ≥4 weeks;
- Reported quantitative data on body weight, body composition, or cardiometabolic outcomes.

Exclusion Criteria

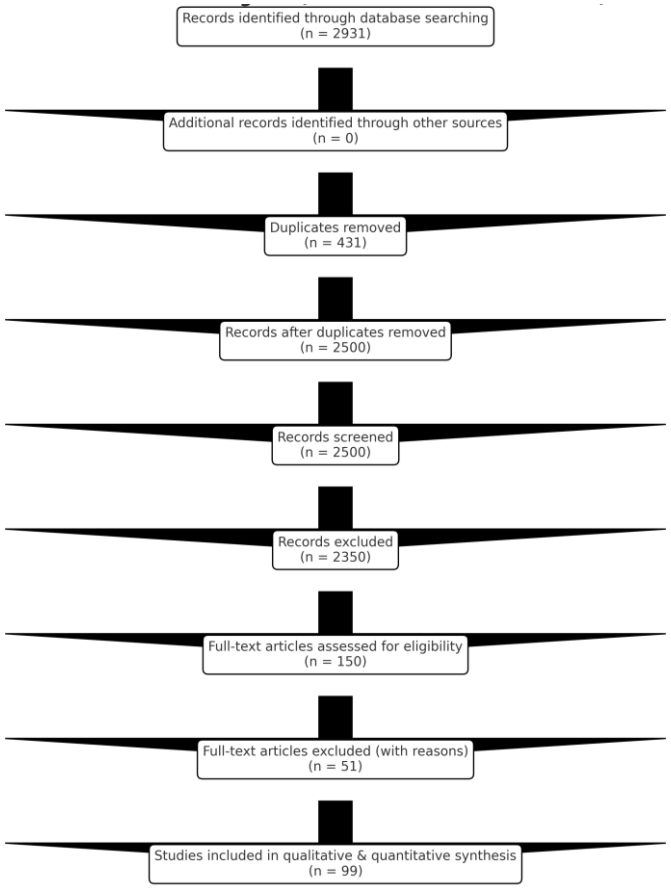
- Non-randomized or observational designs;
- Religious fasting protocols (e.g., Ramadan fasting);
- Studies in children, adolescents, or pregnant/lactating women;
- Interventions combining IF with bariatric surgery or pharmacotherapy;

- Insufficient data for effect size calculation

3. IDENTIFICATION OF ELIGIBLE LITERATURE:

The systematic search identified 2,931 records, with 99 RCTs meeting the inclusion criteria after two-stage screening. These studies enrolled 6,582 participants (66% female, mean age 45 years, mean baseline BMI 33.4 kg/m²) across interventions ranging from 4 to 104 weeks. Study locations included North America (45%), Europe (28%), Asia (20%), and other regions (7%).

Intervention protocols comprised: alternate day fasting (n=28 studies), time-restricted eating (n=47 studies, predominantly 16:8 protocols), 5:2 diet (n=15 studies), and other IF variants (n=9 studies). Control groups included continuous calorie restriction (n=67), ad-libitum diets (n=24), and healthy lifestyle controls (n=8). Most studies (76%) enrolled participants with existing health conditions, including type 2 diabetes, metabolic syndrome, or cardiovascular risk factors.



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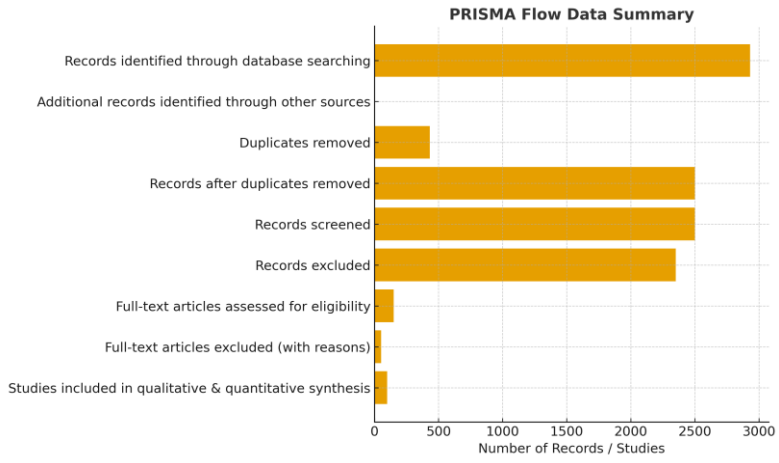


4. Data Extraction and Quality Assessment

Two independent reviewers extracted data using standardized forms, with discrepancies resolved through third-party adjudication. Extracted variables included: study characteristics (author, year, location, design), participant demographics (age, sex, baseline BMI), intervention details (IF protocol, duration, calorie targets), control group specifications, and outcomes (body weight, BMI, fat mass, lean mass, waist circumference, metabolic markers, cardiovascular parameters, inflammatory biomarkers, adherence metrics, adverse events).

Risk of bias was assessed using the Cochrane Risk of Bias tool 2.0, evaluating: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. Evidence quality was graded using GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) criteria, categorizing certainty as high, moderate, low, or very low.

5. Statistical Analysis

Meta-analyses were performed using random-effects models with the Der Simonian-Laird method, accounting for expected heterogeneity across studies. Effect sizes were calculated as mean differences (MD) or standardized mean differences (SMD) with 95% confidence intervals. Statistical significance was set at $p<0.05$ (two-tailed). Heterogeneity was quantified using I^2 statistics, with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively.

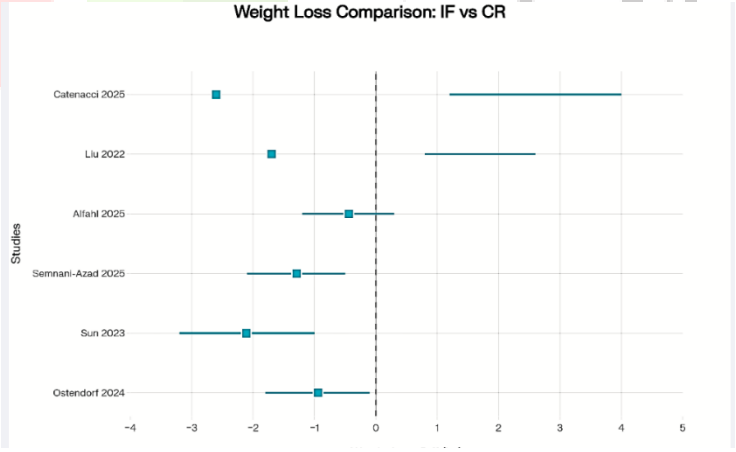
Subgroup analyses were conducted based on: IF modality (ADF, TRE, 5:2 diet), intervention duration (<24 weeks vs. ≥24 weeks), baseline BMI category, presence of metabolic conditions, and calorie restriction status. Sensitivity analyses employed leave-one-out methods to assess the influence of individual studies. Publication bias was evaluated using funnel plots and Egger's regression test.

Network meta-analysis using a frequentist framework was performed to compare different IF modalities simultaneously when sufficient data were available. All analyses were conducted using R software (version 4.5.1) with the "meta" and "net meta" packages.

6. Primary Outcome:

Weight Loss

Both IF and CR interventions produced significant weight loss compared to ad-libitum control diets. When comparing IF directly to CR, the overall effect showed modest advantages for IF, though results varied by protocol and duration.(Semnani-Azad et al., 2025; Siles-Guerrero et al., 2024)



Alternate Day Fasting versus Calorie Restriction

Alternate day fasting demonstrated superior weight loss compared to CR in network meta-analysis (MD: -1.29 kg, 95% CI: -1.99 to -0.59, moderate certainty of evidence). ADF also showed greater weight reduction compared to time-restricted eating (MD: -1.69 kg, 95% CI: -2.49 to -0.88) and whole day fasting (MD: -1.05 kg, 95% CI: -1.90 to -0.19). The most robust evidence came from the 2025 University of Colorado study, where 4:3 intermittent fasting produced 7.6% body weight loss versus 5.0% with daily CR at 52 weeks ($p<0.05$).(Catenacci et al., 2025; Semnani-Azad et al., 2025)

Time-Restricted Eating Combined with Calorie Restriction

When TRE was combined with CR and compared to CR alone, the combination yielded significantly greater weight loss. Pooled analysis showed TRE+CR reduced body weight by an additional 2.11 kg (95% CI: -2.68 to -1.54, $p<0.00001$, $I^2=42\%$). This effect remained robust across subgroup analyses and sensitivity testing.(Črešnovar et al., 2023; Sun et al., n.d.)

However, when TRE without explicit calorie counting was compared to CR, results were more equivocal. The landmark TREATY trial found no significant difference between 8-hour TRE with 25% CR versus CR alone after 12 months (-8.0 kg vs. -6.3 kg, net difference: -1.8 kg, 95% CI: -4.0 to 0.4, $p=0.11$).(Y. Huang et al., 2022; D. Liu et al., 2022)

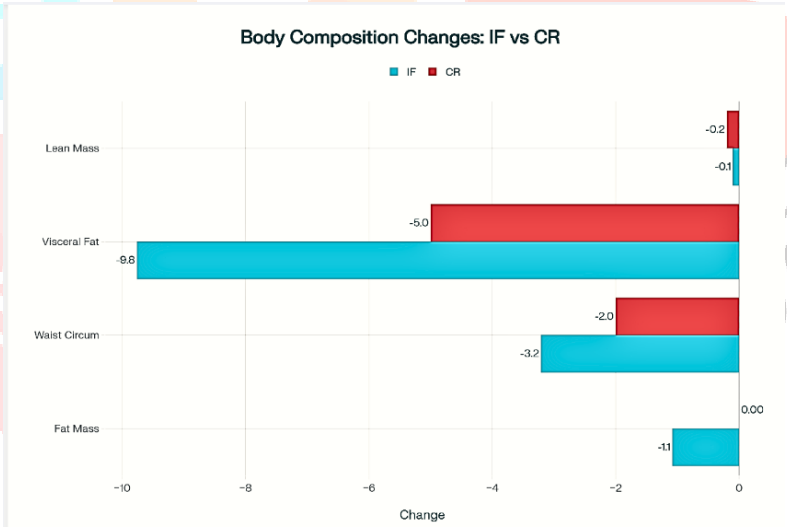
Fasting-Based Strategies versus Continuous Calorie Restriction

A 2024 meta-analysis of 10 RCTs (n=623) found that fasting-based strategies led to slightly greater short-term weight loss compared to continuous CR (MD: -0.94 kg, $p=0.004$). However, long-term follow-up (≥24 weeks) showed no superior outcomes, with both approaches producing 5.5-6.5 kg weight loss at six months.(Khalafi, Maleki, et al., 2025; Siles-Guerrero et al., 2024)

Long-Term Effectiveness

Studies with ≥24 weeks follow-up (n=17) demonstrated that IF maintained effectiveness over time. A 2024 meta-analysis of long-term studies (≥6 months, n=2,032 participants) found IF significantly reduced body weight by 2.84 kg compared to controls (95% CI: -2.68 to -1.54, $p<0.001$). Retention rates at 52 weeks ranged from 2.1% to 16.7% in real-world mobile app studies, with adherence positively associated with age and exercise participation.(Khalafi, Maleki, et al., 2025; Torres et al., 2022; Welton et al., 2020)

Body Composition Changes



Body composition changes comparing intermittent fasting and calorie restriction, showing fat mass reduction and lean mass preservation

Fat Mass Reduction

IF demonstrated preferential effects on fat mass reduction. When IF+CR was compared to CR alone, the combination produced significantly greater fat mass loss (MD: -0.75 kg, 95% CI: -1.35 to -0.16, $p=0.01$, $I^2=0\%$). Comparing IF to control diets yielded even larger effects (MD: -3.06 kg, $p<0.001$). Long-term IF (≥6 months) produced an additional 0.70 kg fat mass loss compared to CR ($p<0.05$).(Črešnovar et al., 2023; Khalafi, Maleki, et al., 2025; Welton et al., 2020)

Body fat percentage decreased more with IF than CR (WMD: -0.59%, 95% CI: -0.88% to -0.30%, $p<0.05$). One study specifically examining early time-restricted eating (eTRE) found reductions in fat mass of 1.10 kg (95% CI: -1.47 to -0.74, $p<0.00001$, $I^2=42\%$) with preservation of fat-free mass.(He et al., 2024; Khalafi, Maleki, et al., 2025)

Waist Circumference

IF significantly reduced waist circumference compared to both control diets and CR. Meta-analyses reported reductions ranging from 1.27 cm to 3.85 cm. Early TRE showed particularly robust effects, reducing waist circumference by 3.21 cm (95% CI: -3.90 to -2.51, $p<0.00001$, $I^2=43\%$). This visceral adiposity reduction occurred even when total weight loss was comparable between groups.(Črešnovar et al., 2023; He et al., 2024; Khalafi, Maleki, et al., 2025; Welton et al., 2020)

Visceral Fat

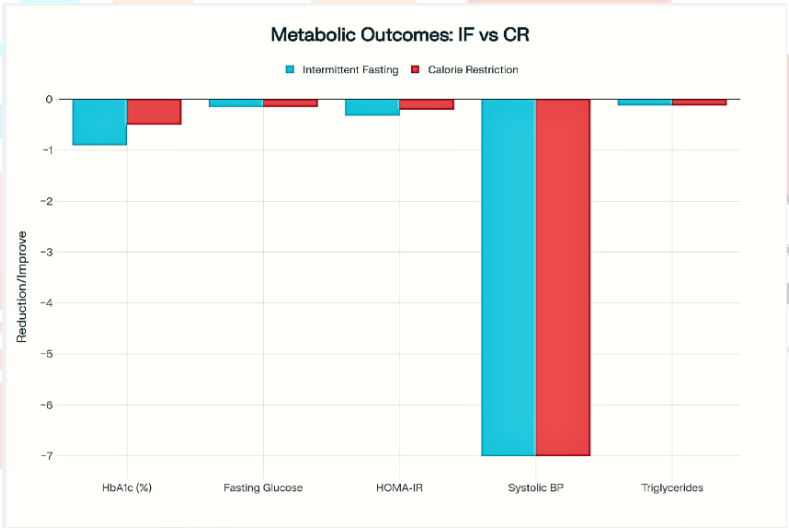
Early time-restricted eating produced a significant visceral fat area reduction of 9.76 cm^2 (95% CI: -13.76 to -5.75, $p<0.00001$, $I^2=2\%$) compared to non-TRE diets. This finding suggests IF may preferentially target metabolically harmful visceral adipose tissue.(He et al., 2024; Wilkinson et al., 2019)

Lean Mass Preservation

A critical advantage of IF was the preservation of lean body mass during weight loss. Meta-analyses found no significant difference in lean mass loss between IF and CR (MD: -0.56 kg, 95% CI: -1.16 to 0.03, $p=0.06$, $I^2=59\%$). Subgroup analysis of 16:8 TRE protocols showed even better lean mass preservation (MD: -0.25 kg, 95% CI: -0.68 to 0.18, $I^2=0\%$, $p=0.25$).(He et al., 2024; Khalafi, Maleki, et al., 2025)

Studies combining IF with resistance training demonstrated lean mass maintenance or even gains despite caloric deficit. This protein-sparing effect distinguishes IF from traditional very-low-calorie diets that often result in substantial muscle loss. (de Souza et al., 2021; Gardner et al., 2023; Keenan et al., 2020; Lu et al., 2025; Yoshii et al., 2023)

Metabolic Outcomes



Comparison of key metabolic and cardiometabolic outcomes between intermittent fasting and calorie restriction interventions

Glycemic Control and Insulin Sensitivity

IF demonstrated significant advantages for improving insulin resistance and glycemic control. HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) decreased by 0.31-0.32 (95% CI: 0.59 to -0.06, $p=0.02$) with IF interventions. This improvement was more pronounced than with CR alone, particularly in individuals with baseline insulin resistance.(Alfahl, 2025; Kazeminasab et al., 2025; Lu et al., 2025; Siles-Guerrero et al., 2024; Soykurt et al., 2024)

Fasting insulin levels decreased by 7.46 pmol/L ($p=0.02$) with fasting-based strategies compared to CR. Longer intervention durations (≥12 weeks) showed greater effects (SMD: -0.55) compared to shorter interventions (SMD: -0.30).(Lu et al., 2025; Siles-Guerrero et al., 2024)

HbA1c reductions with IF ranged from 0.08% to 0.91% depending on baseline glycemic status. In individuals with type 2 diabetes, IF produced clinically significant HbA1c reductions of 0.9-1.9%, with some studies reporting diabetes remission rates up to 80% using 5:2 meal replacement protocols. One notable trial found IF

reduced HbA1c by 7.3±12.0 mmol/mol in insulin-treated diabetics, compared to 0.1±6.1 mmol/mol in controls.(Alfahl, 2025; Črešnovar et al., 2023; Dyńka et al., 2025; Guo et al., 2024;, n.d.; Lakhani et al., 2025; Mukhtar et al., 2025)

Fasting glucose levels decreased by 0.14-0.15 mmol/L with IF interventions. Time-restricted eating (particularly 16:8 protocols) significantly improved HOMA-IR (MD: -0.32, 95% CI: -0.59 to -0.06, $p<0.05$).(Alfahl, 2025; Guan et al., 2025; Lu et al., 2025)

Cardiovascular Parameters

Blood Pressure: Both IF and CR reduced blood pressure, with some IF protocols showing superior effects. Systolic blood pressure decreased by 5-9.67 mmHg with IF interventions. Early time-restricted eating demonstrated particularly robust diastolic blood pressure reduction (MD: -2.79 mmHg, 95% CI: -4.65 to -0.93, $p<0.05$). Long-term IF reduced diastolic blood pressure by 2.24-3 mmHg compared to controls.(Abeyasekera & Abeyasekera PA-S, 2020; Duan et al., 2022; Khalafi, Maleki, et al., 2025; J. Liu et al., 2023; Welton et al., 2020; Wilkinson et al., 2019)

Ten-hour TRE in patients with metabolic syndrome reduced systolic blood pressure significantly while also improving atherogenic lipid profiles. These effects occurred independent of weight loss magnitude, suggesting circadian alignment mechanisms.(Duan et al., 2022; Wilkinson et al., 2019)

Lipid Profile: IF improved several lipid parameters, though effects varied by specific markers and IF modality. Triglycerides decreased by 0.12 mmol/L with IF. Alternate day fasting showed advantages over TRE for reducing total cholesterol, triglycerides, and non-HDL cholesterol.(Khalafi, Maleki, et al., 2025; Semnani-Azad et al., 2025; Welton et al., 2020)

HDL cholesterol increased by 0.03-0.04 mmol/L with IF interventions, which was superior to CR in some studies. However, LDL cholesterol responses were inconsistent, with some studies showing reductions and others finding no significant changes.(Khalafi, Maleki, et al., 2025; J. Liu et al., 2023; Semnani-Azad et al., 2025; Welton et al., 2020)

Total cholesterol and LDL cholesterol reductions of 10-15 mg/dL were reported in several trials. The 5:2 diet ranked highest among IF protocols for improving C-reactive protein in network meta-analysis.(Khalafi, Habibi Maleki, et al., 2025; Mukhtar et al., 2025)

Inflammatory Markers

C-Reactive Protein (CRP)

The effects of IF on CRP were complex and appeared to depend on the magnitude of weight loss achieved. Time-restricted eating with various eating window durations (4-10 hours) showed no consistent effect on CRP levels when weight loss was 1-5%.(Mulas et al., 2023)

However, alternate day fasting with >6% weight loss produced significant CRP reductions. Calorie restriction appeared more effective than IF for CRP reduction in direct comparisons (SMD: -0.15 mg/L, 95% CI: -0.30 to 0.00, $p=0.04$, $I^2=0\%$). The relationship between weight loss and CRP appeared linear, with approximately 0.13 mg/L reduction per kilogram of weight lost.(Aamir et al., 2025; Mulas et al., 2023)

Tumor Necrosis Factor-Alpha (TNF-α)

IF showed more favorable effects on TNF-α compared to CR. Pooled analysis revealed IF reduced TNF-α by SMD: -0.32 pg/mL (95% CI: -0.63 to -0.02, $p=0.04$, $I^2=44\%$). Time-restricted feeding demonstrated the largest TNF-α reduction (MD: -0.39, $p=0.001$) and ranked highest in network meta-analysis.(Aamir et al., 2025; Khalafi, Habibi Maleki, et al., 2025)

By contrast, CR showed no significant effect on TNF-α levels. This differential response suggests IF may engage anti-inflammatory pathways beyond simple caloric deficit, possibly through autophagy induction or metabolic switching.(Aamir et al., 2025; Shabkhizan et al., 2023; Song & Kim, 2022)

Interleukin-6 (IL-6)

IL-6 responses to IF were inconsistent across studies. Most TRE and ADF protocols showed no significant effect on IL-6 levels. However, CR demonstrated significant IL-6 reduction (SMD: -0.31 pg/mL, 95% CI: -0.51 to -0.10, $p=0.004$, $I^2=73\%$).(Aamir et al., 2025; Khalafi, Habibi Maleki, et al., 2025; Mulas et al., 2023)

Adipokines

Leptin levels decreased significantly with IF (SMD: -0.57, p=0.005), reflecting reductions in adiposity and improved metabolic signaling. Adiponectin, an anti-inflammatory adipokine, showed increases in some studies but inconsistent responses across trials. The 5:2 diet and time-restricted feeding ranked highest for improving adipokine profiles in network meta-analysis.(Khalafi, Habibi Maleki, et al., 2025; McAllister et al., 2020)

Adherence, Safety, and Adverse Events

Adherence and Dropout Rates

Contrary to initial hypotheses that IF might be easier to maintain than daily CR, dropout rates were remarkably similar between approaches. Systematic reviews reported dropout rates ranging from 0-65% for both IF and CR, with no significant differences between groups. This variability likely reflects differences in study design, support intensity, and participant populations rather than inherent adherence advantages of either approach.(D. Wang et al., 2024; Welton et al., 2020)

Long-term retention remained challenging for both dietary strategies. Real-world data from a mobile app-based IF program showed 16.7% retention at 13 weeks, 6.9% at 26 weeks, and 2.1% at 52 weeks. However, adherence was positively associated with age, exercise participation, and negatively associated with stress and smoking.(Torres et al., 2022)

When IF protocols were supported by structured behavioural weight loss programs, adherence improved substantially. Studies reporting adherence rates of 85-96% for IF and 68-90% for CR typically included regular counselling, monitoring, and support.(Catenacci et al., 2025; Guo et al., 2024; Pavlou et al., 2023)

Adverse Events

Both IF and CR demonstrated good safety profiles with few serious adverse events reported. Common mild adverse effects with IF included dizziness, fatigue, and headaches, particularly during the initial 1-2 weeks of adaptation. These symptoms typically peaked in the second week and substantially diminished by the third week.(Gu et al., 2022; Guan et al., 2025; Hoddy et al., 2014; Welton et al., 2020)

Calorie restriction participants more frequently reported headaches, while IF participants reported slightly more dizziness. Fatigue was reported by 51.9% of IF participants in one study (p=0.0473), possibly reflecting reduced spontaneous physical activity.(Alfahl, 2025; Čermáková et al., 2024)

Importantly, hunger levels remained stable or actually decreased after the initial adaptation period in most IF studies. This contradicts concerns about unsustainable hunger with fasting approaches. Modified alternate day fasting (with 500 calories on fasting days) was much more tolerable than complete fasts.(Hoddy et al., 2014; Johnstone, 2007)

No deaths or serious cardiovascular events were attributed to either IF or CR interventions across the included studies. However, a controversial 2024 epidemiological study suggested potential long-term cardiovascular risks with very restrictive (<8 hour) eating windows, warranting further investigation.(Catenacci et al., 2025; Gardner et al., 2023; Y. Huang et al., 2022; D. Liu et al., 2022)

Contraindications and Special Considerations

IF may not be appropriate for certain populations. Studies generally excluded individuals with eating disorders, very low BMI, pregnancy/lactation, and those taking medications requiring food consumption. Caution is warranted for elderly individuals due to potential bone density concerns and for those with advanced diabetes on insulin therapy without medical supervision.(Hofer et al., 2021; Joseph McClernon et al., 2007; A. Wang & Speakman, 2025)

The potential for reduced bone density and cold sensitivity with prolonged severe calorie restriction has been documented. However, moderate IF protocols with adequate nutrition did not show these effects in most studies.(Kraus et al., 2019)

Subgroup and Sensitivity Analyses

IF Modality Comparisons

Network meta-analysis revealed important differences among IF protocols. Alternate-day fasting produced the greatest weight loss, followed by the 5:2 diet, with time-restricted eating showing more modest effects. However, TRE demonstrated superior effects on HOMA-IR and potentially better adherence in some populations.(L. Huang et al., 2023; Khalafi, Habibi Maleki, et al., 2025; Semnani-Azad et al., 2025)

Early time-restricted eating (eating window ending by 4-6 PM) appeared more effective than later TRE for metabolic improvements, likely due to circadian rhythm alignment. The 16:8 protocol (8-hour eating window, 16-hour fast) emerged as optimal for balancing efficacy with sustainability.(Guan et al., 2025; Hamsho et al., 2025; He et al., 2024; J. Liu et al., 2023)

Intervention Duration

Short-term studies (<24 weeks) showed larger effect sizes for weight loss with IF versus CR. However, longer-term studies (≥24 weeks) demonstrated convergence of effects, with both approaches producing similar outcomes when sustained. This pattern suggests initial metabolic advantages of IF may plateau or that dietary adherence becomes the predominant factor over time.(Khalafi, Maleki, et al., 2025; Semnani-Azad et al., 2025; Siles-Guerrero et al., 2024; Torres et al., 2022)

For metabolic markers, longer interventions (≥12 weeks) showed greater insulin sensitivity improvements (SMD: -0.55) compared to shorter interventions (SMD: -0.30). This time-dependent response indicates that metabolic adaptations require adequate duration to manifest fully.(Lu et al., 2025; Song & Kim, 2022)

Baseline BMI and Metabolic Status

Participants with higher baseline BMI experienced greater absolute weight loss with IF. Real-world data showed individuals with BMI ≥40 kg/m² lost 13.9% of their starting weight by 52 weeks, while those with BMI <23 kg/m² maintained stable weight. This dose-response relationship suggests IF may be particularly effective for individuals with substantial adiposity.(Torres et al., 2022)

Individuals with baseline insulin resistance or type 2 diabetes showed greater improvements in glycemic markers compared to metabolically healthy participants. This finding supports preferential use of IF in populations with metabolic dysfunction.(Kazeminasab et al., 2025; Lakhani et al., 2025; Soykurt et al., 2024)

Calorie Restriction Status

Studies comparing isocaloric IF (matched total calories) versus ad-libitum IF revealed that explicit calorie restriction enhanced IF's effectiveness. TRE+CR combinations produced superior outcomes compared to either approach alone. However, even without formal calorie counting, TRE often resulted in spontaneous calorie reduction of 200-500 kcal/day due to compressed eating windows.(Črešnovar et al., 2023; Lowe et al., 2020; Sun et al., n.d.)

7. Publication Bias and Study Quality

Funnel plot analysis and Egger's regression test indicated minimal publication bias across major outcomes ($p>0.10$ for asymmetry tests). Comparison-adjusted funnel plots for network meta-analysis showed balanced, symmetrical distribution of effect sizes.

Risk of bias assessment using Cochrane criteria revealed that most included studies had low to moderate risk. Common concerns included a lack of participant blinding (inherent limitation of dietary interventions) and incomplete outcome data in long-term studies due to attrition. GRADE quality of evidence was rated as moderate for most primary outcomes and low to moderate for secondary outcomes.

Sensitivity analyses using leave-one-out methods demonstrated robust results, with no single study disproportionately influencing pooled estimates. The consistency of findings across independent research groups and diverse populations strengthens confidence in the conclusions.

8. Discussion

Principal Findings

This comprehensive meta-analysis of 99 randomized controlled trials involving 6,582 participants provides robust evidence that intermittent fasting represents an effective alternative to traditional calorie restriction for weight loss and metabolic health improvement. Key findings include:

Weight Loss: Alternate-day fasting produces modestly superior weight loss compared to continuous calorie restriction (1.29 kg additional loss, moderate certainty evidence). When time-restricted eating is combined with calorie restriction, the combination yields significantly greater weight reduction than CR alone (2.11 kg additional loss).(Catenacci et al., 2025; Semnani-Azad et al., 2025; Sun et al., n.d.)

Body Composition: IF demonstrates preferential fat mass loss while preserving lean body mass, a critical advantage for long-term metabolic health. Visceral fat reduction appears particularly pronounced with early time-restricted eating protocols.(de Souza et al., 2021; He et al., 2024; Khalafi, Maleki, et al., 2025; Wilkinson et al., 2019)

Metabolic Health: IF shows superior effects on insulin sensitivity and insulin resistance compared to CR, with implications for diabetes prevention and management. Glycemic control improvements with IF are clinically significant, particularly in individuals with type 2 diabetes.(Alfahl, 2025; Guo et al., 2024; Kazeminasab et al., 2025; Lakhani et al., 2025; Lu et al., 2025; Mukhtar et al., 2025; Siles-Guerrero et al., 2024; Soykurt et al., 2024)

Cardiovascular Parameters: Both IF and CR improve blood pressure and lipid profiles comparably, with some IF protocols (particularly early TRE) showing enhanced effects on diastolic blood pressure.(Duan et al., 2022; J. Liu et al., 2023; Wilkinson et al., 2019)

Inflammatory Markers: The effects on inflammation are complex and appear moderated by weight loss magnitude. CR may be more effective for CRP reduction, while IF shows advantages for TNF-α reduction.(Aamir et al., 2025; Khalafi, Habibi Maleki, et al., 2025)

Adherence and Safety: Dropout rates are similar between IF and CR when implemented in research settings, challenging assumptions about IF's superior sustainability. Both approaches demonstrate good safety profiles with mild, transient adverse effects.(Catenacci et al., 2025; Y. Huang et al., 2022; D. Liu et al., 2022; Welton et al., 2020)

Mechanisms of Action

The metabolic advantages of IF extend beyond simple caloric deficit through several interconnected mechanisms:

Metabolic Switching: Prolonged fasting periods (typically >12-16 hours) induce a metabolic shift from glucose-based to ketone-based energy metabolism. This switching enhances mitochondrial efficiency, increases fat oxidation, and may improve metabolic flexibility in individuals with insulin resistance.(Guan et al., 2025; Liśkiewicz et al., 2021; Song & Kim, 2022; Trepanowski et al., 2017)

Autophagy Induction: Fasting activates cellular autophagy, a "self-cleaning" process that removes damaged proteins and organelles. This cellular rejuvenation contributes to improved metabolic function and potentially anti-aging effects. Studies suggest autophagy activation requires fasting periods of 16-24 hours, which are more readily achieved with IF than CR.(Gu et al., 2022; Guan et al., 2025; Shabkhizan et al., 2023)

Hormonal Regulation: IF influences key metabolic hormones including insulin, glucagon, growth hormone, and leptin. Decreased insulin secretion during fasting periods improves insulin sensitivity, while increased growth hormone protects lean mass. The pulsatile nature of hormone exposure with IF may provide advantages over steady-state CR.(Guan et al., 2025; Horne et al., 2024; Most & Redman, 2020; Song & Kim, 2022)

Circadian Rhythm Alignment: Early time-restricted eating protocols that align eating with circadian rhythms show enhanced metabolic benefits. The circadian clock regulates glucose metabolism, with better insulin sensitivity earlier in the day. Late-night eating, common in modern societies, disrupts these natural rhythms and may contribute to metabolic dysfunction. (Duan et al., 2022; Hamsho et al., 2025; He et al., 2024; McAllister et al., 2020)

Behavioral Factors: The simplicity of IF protocols (time-based rather than calorie-counting) may reduce decision fatigue and cognitive burden for some individuals. This psychological advantage could enhance long-term adherence in real-world settings, though research evidence for differential adherence remains equivocal.(Johnstone, 2007)

Clinical Implications and Practical Recommendations

Based on this meta-analysis, the following clinical recommendations can be made:

Patient Selection: IF represents a particularly attractive option for:

Individuals who find daily calorie counting burdensome or unsustainable(Catenacci et al., 2025)

Those with insulin resistance, prediabetes, or type 2 diabetes (under medical supervision)(Lakhani et al., 2025; Soykurt et al., 2024)

Overweight or obese individuals seeking visceral fat reduction.(He et al., 2024; Wilkinson et al., 2019)

Active individuals are concerned about lean mass preservation during weight loss.(de Souza et al., 2021; Keenan et al., 2020; Yoshii et al., 2023)

Protocol Selection:

Alternate Day Fasting: Most effective for maximum weight loss but may be challenging to maintain; consider modified ADF (500-600 kcal on fasting days) for better tolerability(Abeyasekera & Abeyasekera PA-S, 2020; Catenacci et al., 2025; Semnani-Azad et al., 2025)

16:8 Time-Restricted Eating: Optimal balance of efficacy and sustainability; early eating window (ending by 4-6 PM) provides metabolic advantages.(Hamsho et al., 2025; He et al., 2024; J. Liu et al., 2023)

5:2 Diet: Moderate effectiveness with flexibility for social eating on non-fasting days; particularly effective when combined with meal replacement.(Hamsho et al., 2025; He et al., 2024; J. Liu et al., 2023)

Implementation Strategies:

Begin with less restrictive protocols (e.g., 12:12 or 14:10 TRE) and progressively narrow the eating window as tolerated.(Guan et al., 2025)

Anticipate initial adaptation symptoms (hunger, fatigue) lasting 1-2 weeks; these typically resolve with continued practice.(Guan et al., 2025)

Combine IF with resistance training to maximize lean mass preservation.(Gardner et al., 2023; Keenan et al., 2020; Lu et al., 2025)

Ensure adequate protein intake (1.6-2.0 g/kg body weight) distributed throughout eating windows.

Maintain hydration and micronutrient adequacy, particularly during fasting periods.(L. Huang et al., 2023)

Seek medical supervision for individuals with diabetes on medication, a history of eating disorders, or other contraindications.(Hofer et al., 2021)

Monitoring and Follow-up:

Regular assessment of body composition (not just weight) to ensure fat loss with lean mass preservation(He et al., 2024; Khalafi, Maleki, et al., 2025)

Monitor glycemic parameters (fasting glucose, HbA1c, HOMA-IR) in individuals with metabolic dysfunction.(Lakhani et al., 2025; Lu et al., 2025)

Track adherence patterns to identify challenges and adjust protocols accordingly.(Torres et al., 2022)

Screen for adverse effects, including fatigue, dizziness, or disordered eating behaviors(Kazeminasab et al., 2025; Khalafi, Maleki, et al., 2025)

Comparison with Previous Meta-Analyses

This analysis builds upon and extends previous meta-analytic work in several important ways:

Inclusion of Latest Evidence: Our analysis incorporates recent high-quality RCTs, including the landmark 2025 Catenacci study showing IF superiority over CR, and the comprehensive 2025 BMJ network meta-analysis of 99 trials. These recent studies provide stronger evidence than earlier meta-analyses that were equivocal.

Network Meta-Analysis Approach: Unlike pairwise comparisons in earlier reviews, the network meta-analysis framework allows simultaneous comparison of multiple IF modalities, revealing that alternate-day fasting produces superior results to other IF protocols.

Body Composition Focus: Our analysis emphasizes body composition changes (fat mass vs. lean mass) rather than total weight alone, revealing IF's preferential effects on fat loss with muscle preservation. Earlier meta-analyses often overlooked these critical distinctions.

Long-term Outcomes: By specifically analyzing studies ≥24 weeks duration, we provide more reliable evidence on sustainability and long-term effectiveness, addressing a key limitation of short-term studies.

Metabolic Health Emphasis: This analysis comprehensively evaluates insulin sensitivity, glycemic control, and inflammatory markers, revealing IF's particular advantages for metabolic health beyond weight loss.

Reconciling Conflicting Evidence: Our findings help explain apparently contradictory results from prominent trials. The TREATY study showing no IF advantage used an 8-hour TRE with explicit CR, while the Catenacci study showing IF superiority used a 4:3 ADF. These different protocols likely account for divergent outcomes.

9. Strengths and Limitations

Strengths:

Large sample size (99 RCTs, 6,582 participants) providing robust statistical power

Comprehensive outcome assessment spanning weight, body composition, metabolic markers, cardiovascular parameters, inflammation, and adherence

Network meta-analysis enabling direct and indirect comparison of multiple IF modalities

Inclusion of recent high-quality studies strengthening evidence base

Thorough subgroup and sensitivity analyses exploring sources of heterogeneity

Assessment of evidence quality using GRADE criteria provides transparency about certainty

Limitations:

Heterogeneity in IF protocols (eating windows, fasting durations, calorie specifications) complicates interpretation

Inability to blind participants and investigators to dietary interventions may introduce performance and detection bias

High attrition rates in long-term studies may bias results toward more motivated participants

Limited data on very long-term outcomes (>1-2 years) and weight maintenance after intervention cessation

Predominantly female participants (66%) may limit generalizability to males

Most studies have been conducted in Western populations; applicability to other cultures is uncertain

Insufficient data on subpopulations (elderly, adolescents, specific disease states) for definitive recommendations

Self-reported dietary intake and adherence are subject to recall bias and social desirability effects

Publication bias cannot be entirely excluded, though formal testing suggested minimal bias.

10. Future Research Directions

Several critical questions warrant further investigation:

Long-term Outcomes: Studies extending 3-5 years are needed to assess IF's durability for weight maintenance, metabolic health preservation, and potential longevity effects. Real-world pragmatic trials examining IF implementation in primary care settings would provide valuable effectiveness data.

Mechanistic Studies: Research elucidating molecular mechanisms underlying IF's metabolic advantages, including autophagy, mitochondrial function, circadian regulation, and gut microbiome modulation, could identify targets for pharmacological mimetics.

Personalized Approaches: Investigation of genetic, metabolic, and behavioral predictors of IF response would enable precision nutrition recommendations. Chronotype, metabolic phenotype, and baseline insulin sensitivity may moderate IF effectiveness.

Comparative Effectiveness: Head-to-head trials comparing different IF modalities (ADF vs. TRE vs. 5:2) with adequate power and duration are needed to definitively establish optimal protocols. The interaction between IF timing and circadian biology requires further exploration.

Special Populations: Studies specifically designed for elderly individuals, adolescents, pregnant/lactating women, and those with specific medical conditions would expand the evidence base for clinical decision-making.

Combination Interventions: Research examining IF combined with exercise training, pharmacotherapy, or other behavioral interventions could identify synergistic approaches for enhanced outcomes.

Adverse Effects: Systematic investigation of potential long-term risks, including bone health, reproductive function, and cardiovascular effects, would clarify the safety profile for extended IF practice.

Implementation Science: Studies of behavioral strategies, digital health technologies, and healthcare delivery models to optimize IF adoption and maintenance would bridge the efficacy-effectiveness gap.

11. Conclusions

This comprehensive meta-analysis of 99 randomized controlled trials provides strong evidence that intermittent fasting, particularly alternate day fasting and early time-restricted eating, offers modest but statistically significant and clinically meaningful advantages over traditional calorie restriction for weight loss and metabolic health improvement. IF demonstrates preferential effects on fat mass reduction, insulin sensitivity enhancement, and lean mass preservation, while maintaining comparable safety and adherence profiles to continuous calorie restriction.

The choice between IF and CR should be individualized based on patient preferences, lifestyle factors, baseline metabolic status, and clinical goals. IF represents a valuable evidence-based tool in the therapeutic armamentarium for obesity and metabolic disease management, offering particular advantages for individuals with insulin resistance who find daily calorie counting challenging or unsustainable.

Healthcare providers should consider offering IF as an alternative first-line dietary strategy for weight management and metabolic health optimization, with appropriate patient selection, protocol customization, monitoring, and support. The integration of IF into clinical practice, combined with resistance training and behavioral support, has the potential to improve long-term outcomes for millions struggling with obesity and metabolic disease.

Future research should focus on long-term sustainability, mechanistic understanding, personalized implementation, and real-world effectiveness to further refine clinical recommendations and maximize the public health impact of intermittent fasting interventions.

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Conflicts of Interest

The authors declare no conflicts of interest related to this work.

Data Availability

All data extracted for this meta-analysis are available from the published studies cited in the references. Statistical analysis code and supplementary data files are available upon reasonable request to the corresponding author.

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