Effect of Epidemic Intermittent Fasting on Metabolic Syndrome: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Original Investigation

Keywords: Meta-analysis, Intermittent fasting, Metabolic syndrome, Weight loss, Blood pressure, Fasting blood glucose, Blood lipid

DOI: https://doi.org/10.21203/rs.3.rs-214009/v1

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Abstract

Background and aims: Intermittent fasting (IF) has gained attention as a promising diet for weight loss and dysmetabolic diseases management. This systematic review aimed to investigate the effects of IF on metabolic syndrome (MetS).

Methods: A systematic literature search was carried out using three electronic databases, namely PubMed, Embase, and the Cochrane Library, until October 2020. Randomized controlled trials that compared the IF intervention with a control group diet were included. Effect sizes were expressed as weighted mean difference (WMD) using a fixed-effects model and 95% confidence intervals (CI).

Results: Forty-six studies were included. Compared to the ones within control groups, participants exposed to the IF intervention reduced their body weight (WMD, -1.78 kg; 95% CI, -2.21 to -1.35; p < 0.05), waist circumference (WMD, -1.19 cm; 95% CI, -1.8 to -0.57; p < 0.05), fat mass (WMD, -1.26 kg; 95% CI, -1.57 to -0.95; p < 0.05), body mass index (WMD, -0.58 kg/m²; 95% CI, -0.8 to -0.37; p < 0.05), systolic blood pressure (WMD, -2.14 mmHg; 95% CI, -3.54 to -0.73; p < 0.05), diastolic blood pressure (WMD: -1.38 mmHg; 95% CI, -2.35 to -0.41; p < 0.05), fasting blood glucose (WMD, -0.96 mg/dL; 95% CI, -1.89 to -0.03; p < 0.05), fasting insulin (WMD, -0.8 μU/mL; 95% CI, -1.15 to -0.44; p < 0.05), insulin resistance (WMD, -0.21; 95% CI, -0.36 to -0.05; p < 0.05), total cholesterol (WMD, -3.75 mg/dL; 95% CI, -6.64 to -0.85; p < 0.05), triglycerides (WMD, -7.54 mg/dL; 95% CI, -11.45 to -3.63; p < 0.05). No effects were observed for low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or glycosylated hemoglobin.

Conclusions: This meta-analysis supports IF’s role in the improvement of MetS, compared to a control group diet. Further research on IF interventions should take into account long-term and well-designed administration to draw definitive conclusions.

Introduction

Metabolic syndrome (MetS) is an emerging health issue throughout the world. Clinical diagnostic criteria for MetS [1] include increased waist circumference (WC) [2], increased triglycerides (TG), changes in lipoprotein, increased blood pressure (BP) [3], and increased fasting blood glucose (FBG) levels [4, 5]. Moreover, studies have demonstrated that MetS doubled the risk for atherosclerotic cardiovascular diseases (CVDs) [6] and increased the risk for type 2 diabetes five-fold [7]. Considering that calorie restriction and exercise are effective management strategies for MetS, intermittent fasting (IF) can also be used as an important treatment [7].

IF has gradually come into focus in our daily lives [8]. At present, a large number of studies have shown that IF is beneficial in the treatment of metabolic diseases, and because of its simple use, it is easy to accept. Dietary restrictions [9] through IF have been shown to improve metabolic disease risk indicators. Further, IF reportedly plays a considerable role in regulating cardiovascular risk indicators [10], insulin resistance (HOMA-IR), and circulating blood glucose levels [11, 12]. There are different types of IF that act as an energy-limiting diet for a specific period, including alternate-day fasting (ADF), alternate-modified-day fasting (AMDF), periodic fasting (PF), time-restricted feeding (TRF), and religious fasting (Table 1). Intermittent energy restriction (IER) is an alternative of IF in this study, and the control group is often a continuous energy restriction (CER).

Table 1

| Type of Fast | Description |
|-------------|-------------|
| Alternate-day fasting (ADF) | A circular diet that requires fasting for a day (consumption of no calories) and then eating freely for a day [73]. |
| Alternate-modified-day fasting (AMDF) | A circular feeding pattern that requires fasting (consumption of 20-25% of energy needs) for a day, and then eating freely for a day; the popular 5:2 diet includes a discontinuous strict energy limit of 2 days a week and 5 other days of random eating [14, 73]. |
| Time-restricted feeding (TRF) | Complete fast (no calories) for at least 12 hours a day, and eating freely the rest of the time; the 16:8 fasting pattern currently prevails [14, 106, 107]. |
| Periodic fasting (PF) | A circular weekly eating pattern that consists of fasting 1 to 2 days a week (burning 25% or less of the calories required) and eating freely the rest of the week on a 6:1 or 5:2 scale [106]. |

Common religious fasts: These include:
1. The Islamic Ramadan fast: during the 30-day fasting holy month of Ramadan, worshippers fast from sunrise to sunset and eat freely after sunset [108].
2. Greek Orthodox fasts: During fasting, people fast dairy products, eggs, and meat for 40 days [109].
3. Daniel fast: This is a biblical fast, usually for 10 to 40 days [109].
4. Jewish fast: one of the major fasts in the Jewish calendar is the Yom Kippur fast [108].

Over the past three decades, original studies [13, 14] have investigated the impact of IF on a variety of health outcomes, including metabolic disease risk factors, such as weight, BP, WC, body fat, lipid distribution, and blood glucose. However, a recent study by [15] demonstrated that in the absence of controlled food intake, IF will not play a significant role in weight loss. In turn, it will lead to a reduction in muscle mass. In some randomized crossover trials, IF had no effect on glucose and lipid metabolism [16, 17]. These results indicate that the effects of IF on various metabolic factors are contradictory. While systematic reviews and meta-analyses have reported that religious fasting and time-restricted fasting have regulatory effects on MetS [18, 19], they have failed to include various IF types. Therefore, we need a comprehensive and systematic meta-analysis representing all included randomized controlled trials (RCTs), a large
sample size, a variety of IF types, and multiple effect indicators to determine the effectiveness of IF interventions in improving health outcomes and modifiable risk factors for people with MetS.

**Methods**

This study used a systematic review and a meta-analysis of PRISMA's preferred reporting items as a guide for reporting research results [20, 21].

**Data source and search strategy**

Articles were identified by searching through three electronic databases, i.e., PubMed, Embase, and the Cochrane Library until October 2020. Two reviewers (C.L. and X.L.) independently evaluated articles’ eligibility, and the inconsistencies shall be made by the corresponding author (F.Y.). Solve it. The search strategy is described in detail in Supplementary Table 1.

**Inclusion and Exclusion Criteria**

The articles had the following characteristics: (1) Type study: RCTs; (2) Participants: participants >18 years; (3) Intervention: different types of IF including PF, ADF, AMDF, TRF, and part of IER; and (4) Outcomes: data on at least one MetS component: body composition (weight, WC, fat mass [FM], and body mass index [BMI]), BP (systolic blood pressure [SBP], diastolic blood pressure [DBP]), lipid panel (total cholesterol [TC], TG, low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]), glycemic control (FBG, fasting insulin [Fins], glycosylated hemoglobin [HbA1c], and HOMA-IR).

The exclusion criteria were as follows: (1) uncontrolled trials or other study designs; (2) studies lacking a control group; (3) studies without MetS component as an outcome and/or lacking sufficient information; (4) non-human samples, reviews, case studies, as well as unpublished abstracts; (5) studies with animal models; (6) pregnant or lactating women; (7) studies in languages other than English; (8) absence of time limits in IER and fasting, including Ramadan fasting.

**Data extraction and study quality assessment**

Two investigators independently extracted the relevant data from the eligible studies using predesigned forms. Data included study, publication year, country, study design, inclusion and exclusion criteria, total number of participants, participant details, study duration, intervention details and control groups, baseline patient characteristics (mean age, sex), body composition, BP, glycemic control, and lipid panel. Disagreements were resolved by consensus. When necessary, we emailed the corresponding author to acquire study details.

**Quality assessment and publication bias**

The researchers used Cochrane Collaboration's bias risk tool to evaluate the quality of the methodology included in the studies. According to the criteria of the Cochrane handbook for systematic reviews, the bias risk of each item is classified as low, high, or unclear [22].

**Data statistical and analysis**

Effect estimates were expressed as weighted mean differences (WMD) with a 95% confidence interval (CI). Inter-study heterogeneity was tested using the Higgins $I^2$ statistic, and $I^2 >50\%$ indicated significant statistical heterogeneity. The heterogeneity of the study and measurement of effect estimates were determined using the mean and standard deviation (SD) of the differences before and after IF intervention. Publication bias was evaluated using funnel plots; formal testing was conducted with Egger's test [23], and a sensitivity analysis was also performed. We used STATA 16 (StataCorp LLC, College Station, TX, USA) for the statistical analyses.

In order to determine the influence of IF on various effect indicators, it is necessary to change the mean value before and after intervention as well as the SD of the changes. Therefore, we used a method outlined in the Cochrane handbook [22, 24] to determine the SD of changes between time points.

$SD_{\text{change}} = \sqrt{SD_{\text{baseline}}^2 + SD_{\text{final}}^2 - (2 \times R \times SD_{\text{baseline}} \times SD_{\text{final}})}$. In addition, we performed some conversion of data units through international calculation formulas to ensure that results are clinically significant.

**Results**

**Characteristics of included studies**

The PRISMA statement flow diagram is shown in Fig. 1[25]. A total of 9087 studies were part of the initial database search (PubMed: 6128, EMBASE: 40, Cochrane Library: 2919), after the removal of 1540 duplicate studies. After filtering the titles and abstracts to exclude irrelevant articles, we found 106 studies that met the topic of interest. The full texts of the 106 records were reviewed. Of them, 60 records were excluded for the following reasons: data not available ($n=15$), literature review, letter, or case report ($n=34$), unrelated to relevant predictive factors ($n=2$), related to protocol ($n=2$), and meta-analyses ($n=7$). Finally, 46 studies from the database searches were included in the meta-analysis[15, 26-71]. A total of 2681 participants were randomized in the IF
intervention group (n = 1423) and the control group (n = 1258). The characteristics of the eligible trials are summarized in Table 2. All the results calculated using Stata are shown in Table 3.
| Study and publication year | Country       | RCT design (blinding) | Total sample (case: control) | Participants | Intervention and intervention details | Control | Duration | Mean age | Sex (F: M: O) |
|---------------------------|---------------|-----------------------|------------------------------|--------------|--------------------------------------|---------|----------|----------|-------------|
| Chow et al. (2020)[35]    | USA           | A randomized clinical trial | 11:9                         | People with overweight or obesity | TRF: 11:8 hour window, with unrestricted eating within the window | Unrestricted (non-TRE) control | 12w      | 46.5 ±12.4 | 9:2 w D D L H |
| Cienfuegos et al. (a) (2020)[36] | USA          | A randomized controlled trial | 16:14                        | Adults with obesity | 4-hour TRF: eating only between 3 and 7 pm (without having to count calories) | The control group continued their usual diet pattern with no meal timing restrictions | 8w       | 47 ± 8      | 14:2 F D L H F T H H |
| Cienfuegos et al. (b) (2020)[36] | USA          | A randomized controlled trial | 19:14                        | Adults with obesity | 6-hour TRF: eating only between 1 and 7 pm (without having to count calories) | The control group continued their usual diet pattern with no meal timing restrictions | 8w       | 47 ± 13.8   | 18:1 F D L H F T H H |
| de Oliveira Maranhao et al. (2020)[39] | Brasil      | A randomized, parallel, controlled clinical trial | 31:27                        | Obesity people | TRF and a hypoenergetic diet: meals only in a 12-hour feeding window and fasting for the other 12 hours. | Hypoenergetic diet | 12w      | 31.03 ±7.16 | NA w W W SI |
| Domaszewski et al. (2020)[40] | Poland       | A randomized clinical trial | 25:20                        | Overweight women over 60 years of age | Experimental group involved completely abstaining from food for 16 hours a day, from 8 pm to 12 am (the next day) | Followed their previous eating plan | 6w       | 65 ± 4      | 25f w FT |
| Finlayson et al. (2020)[41] | USA          | A parallel-group controlled-feeding randomized controlled trial | 24:22                        | Overweight and obesity Women | IER: alternating ad libitum and 75% energy restriction days | CER | 12w      | 34 ± 10   | 24f W BI |
| Lowe et al. (2020)[15]    | USA          | A randomized clinical trial | 59:57                        | Adults with obesity | TRF: Eat 8 hours a day and fast the rest of the day | Consistent meal timing | 12w      | 46.8 ±10.8 | 24:35 w W |
| Martens et al. (2020)[50] | USA          | A randomized controlled crossover trial | 14:10                        | Healthy middle-aged and older men and postmenopausal women | TRF: Eat 9 hours a day and fast the rest of the day | Chronic calorie restriction | 6w       | 66 ± 6.92   | 7:5 T r L H F T |
| Pinto et al. (2020)[69]   | UK           | A parallel-arm randomized controlled trial | 21:22                        | Non-smoking men and women | Short-term effects of IER: 48 hours, 600 kcal/day, followed by 5-day healthy eating advice | CER: 500 kcal/day, healthy eating advice | 4w       | 50 ± 12     | 15:6 w W W SI T r F T H H |
| Pureza et al. (2020)[54]  | Brazil       | A randomized, parallel, controlled trial | 31:27                        | Women with obesity | Hypoenergetic diet with TRF: women were instructed to eat only | A diet with the same energy restriction but without TRF | 21d      | 31.8 ± 7.25 | 31f W W W SI F T H H |
| Study                                    | Country | Design Type                   | Eating Schedule | Participants                                      | Intervention Details                                                                 | Duration | Baseline | Final  | Effect Size |
|-----------------------------------------|---------|-------------------------------|-----------------|---------------------------------------------------|--------------------------------------------------------------------------------------|----------|----------|--------|-------------|
| Stratton et al. (2020) [57]             | USA     | A randomized controlled trial | 13:13           | Active males                                      | TRF: 8 hours eating window, 25% caloric deficit, 1.8 g/kg/day protein, and body resistance training | 4w       | 22.9 ± 3.6 | 13m    | w           |
| Cai et al. (a) (2019) [29]              | China   | A randomized clinical trial   | 90:79           | Adults with nonalcoholic fatty liver disease (NAFLD) | ADF: 25% baseline energy needs, mealtime between 12.00 p.m. and 2.00 p.m            | 12w      | 35.50±4.417 | 60:35  | w           |
| Cai et al. (b) (2019) [29]              | China   | A randomized clinical trial   | 95:79           | Adults with nonalcoholic fatty liver disease (NAFLD) | TRF: 16:8 fasting window                                                             | 12w      | 33.56 ± 6.23 | 66:29  | w           |
| Cho et al. (a) (2019) [34]              | Korea   | A randomized, controlled, parallel-arm diet trial | 9:9             | Asian population with overweight or obesity       | ADF and exercise Continued their regular eating and exercise habits                   | 8w       | 34.5 ± 5.7  | 4:5    | w           |
| Cho et al. (b) (2019) [34]              | Korea   | A randomized, controlled, parallel-arm diet trial | 8:9             | Asian population with overweight or obesity       | ADF CER                                                                               | 8w       | 33.5 ± 5    | 6:2    | w           |
| Gabel et al. (a) [42]                   | USA     | Secondary analysis of a study | 11:17           | Individuals with overweight and obesity           | ADF: participants consumed 25% of their baseline energy needs at lunch (between 12 and 2 pm) | 12m      | 43±9.95   | 9:2    | w           |
| Gabel et al. (b) (2019) [42]            | USA     | Secondary analysis of a study | 11:15           | Individuals with overweight and obesity           | ADF: participants consumed 25% of their baseline energy needs at lunch (between 12 and 2 pm) | 12m      | 43±9.95   | 9:2    | w           |
| Hirsh et al. (2019) [46]                | USA     | A randomized clinical trial   | 10:12           | Overweight individuals                             | Nutrition program group: two fasting days of balanced shake and dietary supplements, 5 days of habitual diet | 52d      | 43.4±13    | 8:2    | w           |
| Panizza et al. (2019) [52]              | USA     | A randomized active comparator pilot study | 30:30           | Patients with ADF: 25% of CR                     | Dietary Approaches to Stop Hypertension diet                                         | 12w      | 48.4±4.7   | 21:9   | w           |
| Parvaresh et                            | Iran    | A single-                     | 35:34           |                                                   |                                                                       | 8w       | 44.6±9.08 | 14:20  | w           |
| Study Authors | Country | Study Design | Participants | Intervention | Comparison | Duration | Results |
|---------------|---------|--------------|--------------|--------------|------------|----------|---------|
| al. (2019)[53] |         | center, randomized clinical trial | MetS and overweight | the individual's energy needs | | | |
| Stekovic et al. (2019)[71] | Austria | An embedded randomized controlled trial | Healthy study participants | ADF: eat every second day ad libitum, refrain from calorie intake on the fast days | Ad libitum number of meals | 4w | 48 | 17:12 |
| Tinsley et al. (2019)[63] | USA | A randomized controlled trial | Healthy females | TRF: consume all calories between 12 and 8 pm each day | Control diet | 8w | 22.1 ± 7.27 | 13f |
| Antoni et al. (2018)[30] | UK | A randomized, parallel-arm trial | Individuals with overweight and obesity | IER: 25% of the energy requirements for two consecutive days. On the remaining 5 normal days | CER | 7d | 45±15.49 | 7:8 |
| Bowen et al. (2018)[27] | Australia | A randomized parallel study | Adults with overweight and obesity | ADF + Daily energy restriction (DER); 3 days of ADF, 3 days of alternate DER, and one ad libitum day | Daily energy restriction | 16w | 40.0 ± 8.3 | 67.15 |
| Byrne et al. (2018)[28] | Australia | A single-center, parallel-group randomized controlled trial | Males with obesity | IER: alternating ad libitum and 75% energy restriction days | CER | 16w | 39.9± 9.2 | 26m |
| Carter et al. (2018)[32] | Australia | A randomized noninferiority trial | Adults with type 2 diabetes who were overweight or obese | IER: 500-600 kcal/day, followed for 2 nonconsecutive days per week (their usual diet for the other 5 days) | CER | 12m | 61±9 | 39:31 |
| Conley et al. (2018)[37] | Australia | A single-center, parallel-group randomized controlled trial | Veterans: males with a BMI greater than or equal to 30 kg/m² and stable weight | IER: 2 nonconsecutive days per week (restrict calorie intake to 600 calories) and eat ad libitum on the remaining 5 days | Standard energy-restricted diet | 3m | 68 ± 2.7 | 11m |
| Conley et al. (2018)[68] | Australia | A randomized controlled trial | Participants with type 2 diabetes who were taking medication for diabetes | Nonconsecutive days caloric restriction: 5.2 schedule a VLCD for 2 days per week | CR | 12w | 58 (42 to 74) | 8:11 |
| Coutinho et al. (2018)[38] | Norway | A randomized controlled trial | Adults with obesity | IER: 3 nonconsecutive days (followed a commercial very low-calorie diet (550 and 660 kcal/day for women and | CER; followed a low-calorie diet | 12w | 39.4±11.0 | 10:4 |
| Study                          | Country | Study Design             | Participants | Intervention                                                                 | Follow-up | Outcome 1  | Outcome 2  | Outcome 3  | Outcome 4  |
|-------------------------------|---------|--------------------------|--------------|-------------------------------------------------------------------------------|-----------|------------|------------|------------|------------|
| Gasmi et al. (young) (2018)   | Italy   | A randomized controlled trial | Young men | TRF: young and older were asked to fast for 2 days separated by 48 hours (Monday and Thursday) for 3 months (February, March, April) | Normal meals | 12w | 26.90±1.97 | 10m         | w          |
| Gasmi et al. (old) (2018)     | Italy   | A randomized controlled trial | Aged men    | TRF: young and older were asked to fast for 2 days separated by 48 hours (Monday and Thursday) for 3 months (February, March, April) | Normal meals | 12w | 51.60±5.87 | 10m         | w          |
| Hutchison et al. (a) (2018)   | Australia | A randomized controlled trial | Overweight women | IF70: an IF diet at 70% of calculated baseline energy requirements per week | Dietary restriction (DF70) | 8w | 49 ± 10 | 25f     | w          | D Ti C F H |
| Hutchison et al. (b) (2018)   | Australia | A randomized controlled trial | Overweight women | IF100: an IF diet at 100% of calculated baseline energy requirements per week | Continuous energy intake at 100% of baseline energy | 8w | 51 ± 10 | 25f     | w          | D Ti C F H |
| Schübel, et al. (2018)        | Germany | A randomized controlled trial | Men and women with overweight and obesity | IER: 5:2 diet (2 days with 75% energy deficit and 5 days without energy restriction) | No advice to restrict energy | 12w | 49.4±9.0 | 24:25       | T I L H F I H |
| Sundfor et al. (2018)         | Norway  | A randomized controlled clinical trial | Men and women with overweight and obesity | IER: 5:2 diet | CER | 6m | 49.9±10.1 | 26:28       | w          | W SI T I L H F I H |
| Trepanowski et al. (a) (2018) | USA     | A randomized controlled trial | Men and women with overweight and obesity | ADF: repeatedly alternate between consuming 25% of energy needs over 24-hour | CR | 24w | 46 ± 10 | 22:3         | F H |
| Trepanowski et al. (b) (2018) | USA     | A randomized controlled trial | Men and women with overweight and obesity | ADF: repeatedly alternate between consuming 25% of energy needs over 24-hour | Consumed 100% of energy needs every day | 24w | 46 ± 10 | 22:3         | F H |
| Li et al. (2017)              | Germany | A randomized controlled clinical pilot study | Persons with a manifest and treated type 2 diabetes | A 7-day fasting program (an initial fasting program followed a Mediterranean diet) | A Mediterranean diet | 4m | 64.7 ± 7.0 | NA          | w          | W SI T I L H F I H |
| Wei et al. (2017)             | USA     | A randomized crossover design | Healthy participants | Fasting-mimicking diet: a plant-based diet designed to attain | Unrestricted diet | 3m | 43.3 ± 11.7 | 33:19       | w          | W SI T I L |

Note: CR = Caloric restriction, DF70 = Dietary restriction at 70% of baseline energy requirements, DF100 = Dietary restriction at 100% of baseline energy requirements, IER = Intermittent Energy Restriction, TRF = Time Restricted Feeding, ADF = Alternate Day Feeding.
| Study                  | Country | Type of Study          | Subjects | Design Description                                                                                                                                                                                                 | Energy Regimen                                                                 | Follow-up | Baseline | Follow-up |
|------------------------|---------|------------------------|----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-----------|----------|-----------|
| Carter et al. (2016)[31] | Australia | A parallel randomized controlled trial | Obesity adults with type 2 diabetes mellitus; BP of <160/100 mmHg | IER: an ER of 1670-2500kJ/day for 2 days each week, and the remaining 5 days included habitual eating | CER                                                                                           | 12w       | 61 ± 7.5 | 17:14     |
| Catenacci et al. (2016)[33] | USA     | A randomized pilot study | Individuals with obesity | ADF: zero-calories (2400 kcal/day)                                                                                                           | Normal diet group                                                              | 8w        | 39.6±9.5  | 9:3       |
| Moro et al. (2016)[51]  | Italy   | A randomized controlled trial | Resistance-trained males | TRF: participants consumed 100% of energy needs in an 8-hour day                                                                                   | Normal diet group                                                              | 8w        | 29.94 ± 4.07 | 17m     |
| Tinsley et al. (2016)[62] | USA     | A randomized controlled trial | Generally healthy, recreationally active men | Resistance training and TRF: consuming all calories within a four-hour period, 4 days per week. Resistance training program was performed 3 days per week | Resistance training and normal diet                                                                 | 8w        | 22.9 ± 4.1 | 10m      |
| Keogh et al. (2014)[48] | Australia | A parallel, randomized controlled trial | Women with overweight or obesity | IER: 1-week normal diet followed by 1 week of energy restriction | CER                                                                                           | 52w       | 59.5 ± 8.7 | 19f      |
| Harvie et al. (b) (2013)[44] | USA     | A single-center, randomized study | Women with overweight or obesity | IECR: restrict energy and carbohydrates on 2 consecutive days each week and Mediterranean-type diet for the remaining 5 days of the week | Daily energy restriction                                                            | 3m        | 45.6 ± 8.3 | 37f       |
| Harvie et al. (a) (2013)[44] | USA     | A single-center, randomized study | Women with overweight or obesity | IECR and ad libitum protein and fat                                                                                                           | Daily energy restriction                                                            | 3m        | 48.6 ± 7.3 | 38f       |
| Teng et al. (2013)[61]  | Malaysia | A randomized controlled trial | Healthy (non-diabetic and no history of cardiovascular diseases) Malay men | Fasting calorie restriction                                                                                                                  | Maintain their present lifestyle                                                   | 6w        | 59.6 ± 5.4 | 28m      |
| Varady et al. (2013)[65] | USA     | A randomized, controlled, parallel-arm feeding trial | Healthy people | ADF: 25% of their baseline energy needs on the fast day and then ate ad libitum on each alternating feed day | Ad libitum                                                                        | 12w       | 47±7.74  | 10:5      |
| Bhutani et al. (2013)[70] | US      | A randomized,       | Adults with obesity | A 4-week controlled Ad libitum number of                                                                                                           |                                                                                     | 12w       | 42 ± 10   | 24:1      |
| Study | Location | Study Design | Duration | Intervention | Baseline | Results |
|-------|----------|--------------|----------|--------------|----------|---------|
| Arguin et al. (2012)[26] | USA | A randomized pilot study | 12:10 | IF: food was self-selected with dietitian supervision on macronutrient composition (55%, 30%, and 15% of energy intake from carbohydrates, fats, and proteins, respectively) | Continuous diet | 30w | 60.5 ± 6.0 | 12f |
| Harvie et al. (2011)[45] | USA | A randomized trial | 53:54 | IER: 25% restriction delivered as a VLCD for 2 days per week, with no restrictions on the other 5 days of the week. | CER | 6m | 40 ± 14.1 | 53f |
| Teng et al. (2011)[60] | USA | A randomized controlled trial | 13:12 | Fasting calorie restriction: reduce daily energy intake by 300-500 kcal/day and fast two days a week for three months | Maintenance of present lifestyle | 12w | 59.3 ± 3.4 | 13m |
| Stote et al. (2007)[56] | USA | A randomized crossover design | Total (15) | 1 meal/d | 3 meals/d | 8w | 45 ± 2.71 | 10:5 |
| Williams et al. (a) (1998)[67] | USA | A parallel Arms | 18:18 | T2DM patients | IER (1 day/week): 400–600 kcal/day on fast day and 1500–1800 kcal/day on feed day | CER: 1500–1800 kcal/day every day | 20w | 51 ± 8 | 9:9 |
| Williams et al. (b) (1998)[67] | USA | A parallel Arms | 18:18 | T2DM patients | IER (5 days/week): 400–600 kcal/day on fast day every 5 weeks and 1500–1800 kcal/day on feed days | CER: 1500–1800 kcal/day every day | 20w | 50 ± 9 | 11:7 |
Table 3

All the results calculated using Stata

| Characteristic   | Trials | Participants | WMD  | 95% CI      | z    | p    | I² (%) | p for heterogeneity |
|------------------|--------|--------------|------|-------------|------|------|--------|-------------------|
| body composition |        |              |      |             |      |      |        |                   |
| Weight (kg)      | 45     | 2225         | -1.78| (-2.21, -1.35) | 8.11 | 0.000| 0      | 0.960             |
| WC (cm)          | 23     | 1385         | -1.19| (-1.80, -0.57) | 3.77 | 0.000| 23.8   | 0.148             |
| FM (kg)          | 33     | 1610         | -1.26| (-1.57, -0.95) | 7.87 | 0.000| 22.9   | 0.121             |
| BMI (kg/m²)      | 26     | 1590         | -0.58| (-0.80, -0.37) | 5.24 | 0.000| 0      | 0.886             |
| glycemic control |        |              |      |             |      |      |        |                   |
| FBG (mg/dL)      | 34     | 1863         | -0.96| (-1.89, -0.03) | 2.02 | 0.044| 44.4   | 0.003             |
| Fins (μU/mL)     | 26     | 1161         | -0.80| (-1.15, -0.44) | 4.40 | 0.000| 24.3   | 0.130             |
| HbA1c (%)        | 9      | 544          | -0.06| (-0.18, 0.05)  | 1.07 | 0.287| 0      | 0.974             |
| HOMA-IR          | 19     | 866          | -0.21| (-0.36, -0.05) | 2.66 | 0.008| 38.4   | 0.046             |
| blood pressure   |        |              |      |             |      |      |        |                   |
| SBP (mmHg)       | 29     | 1393         | -2.14| (-3.54, -0.73) | 2.97 | 0.003| 36.2   | 0.028             |
| DBP (mmHg)       | 27     | 1277         | -1.38| (-2.35, -0.41) | 2.79 | 0.005| 0      | 0.588             |
| lipid panel      |        |              |      |             |      |      |        |                   |
| TC (mg/dL)       | 33     | 1766         | -3.75| (-6.64, -0.85) | 2.54 | 0.011| 14.6   | 0.233             |
| TG (mg/dL)       | 34     | 1750         | -7.54| (-11.45, -3.63)| 3.78 | 0.000| 5.5    | 0.377             |
| LDL-C (mg/dL)    | 36     | 1850         | -2.15| (-4.42, 0.12)  | 1.85 | 0.064| 0      | 0.967             |
| HDL-C (mg/dL)    | 36     | 1852         | -0.54| (-1.46, 0.38)  | 1.15 | 0.250| 0      | 0.858             |

WC, waist circumference; FM, fat mass; BMI, body mass index; SBR, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FBG, fasting blood glucose; Fins, fasting insulin; HbA1c, glycosylated hemoglobin; HOMA-IR, insulin resistance

ADF, Alternate-day fasting; CR, Caloric restriction; TRF, time-restricted feeding; IER, Intermittent energy restriction; CER, Continuous energy restriction; WC, waist circumference; FM, fat mass; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FBG, fasting blood glucose; Fins, fasting insulin; HbA1c, glycosylated hemoglobin; HOMA-IR, insulin resistance; MetS, metabolic syndrome; VLCD, very low-calorie diet; IECR, Intermittent energy and carbohydrate restriction;

Risk of bias and quality assessment of studies

Fig. 2 summarizes the risk of bias for RCTs. Twenty-three studies (50%) had a low risk of selection bias. This was because of the intervention type, as no RCT adequately performed blinding of the participants (blinding of dietary interventions is impossible); however, 18 studies (39%) were judged as having a low risk of bias for outcome assessment blinding, 38 studies (82%) were judged as having a low risk of bias for incomplete outcome data, 40 studies (86%) were judged as having a low risk of bias for selective reporting, and 43 studies (93%) showed a low risk of other biases. Overall, 16 studies (35%) were rated with a high risk of bias due to random sequence generation, allocation concealment, outcome assessment blinding, incomplete outcome data, and selective reporting.

Meta-analysis results

Effect of IF on body composition

Body composition was operationalized in weight, WC, FM, and BMI. Forty-five studies, with 2225 participants (case = 1136, control = 1089), showed a consistent effect of IF on weight (Fig. 3a). The fixed-effect analysis showed significant weight reduction (WMD: -1.78 kg, 95% CI: -2.21 to -1.35, p < 0.05), thus, indicating significant weight loss. There was no evidence of effect heterogeneity (I² = 0.0%, p = 0.96). Regarding funnel plot symmetry and Egger's test, p = 0.547 (Fig. 4a).

Pooled data from 23 studies (1385 participants: case = 714, control = 671) showed a consistent effect of IF on WC (Fig. 3b). While the fixed-effect analysis showed a significant WC reduction (WMD: -1.19 cm, 95% CI: -1.8 to -0.57, p < 0.05), there was also evidence of effect heterogeneity (I² = 23.8%, p = 0.148). Regarding funnel plot symmetry and Egger's test, p = 0.576 (Fig. 4b).
A pooled meta-analysis including 33 studies with 1610 participants, found a significant effect of IF on FM when compared to placebo (WMD: -1.26 kg, 95% CI: -1.57 to -0.95, p < 0.05) (Fig. 3c). There was a slight effect heterogeneity ($I^2 = 22.9\%$, p = 0.121). Regarding funnel plot symmetry and Egger's test, p = 0.498 (Fig. 4c).

The effects of IF on changes in BMI were assessed in 26 RCTs with 1590 participants (case = 806, control = 784). The results showed a significant effect on the BMI (a fixed-effects model, WMD: -0.58 kg/m$^2$, 95% CI: -0.8 to -0.37, p < 0.05) (Fig. 3d). There was no evidence of effect heterogeneity ($I^2 = 0.0\%$, p = 0.886). Regarding funnel plot symmetry and Egger's test, p = 0.734 (Fig. 4d).

**Effect of IF on glycemic control**

A meta-analysis of the effect of IF on glycemic control was performed including the relevant studies. A cumulative meta-analysis of 34 studies with 1863 participants (case = 947, control = 916) evaluated changes in FBG during IF (Fig. 5a). The WMD was -0.96 mg/dL (95% CI: -1.89 to -0.03, p < 0.05, a fixed-effects model), which indicates significant FBG reduction. We observed a moderate effect heterogeneity ($I^2 = 44.4\%$, p = 0.003). Regarding funnel plot symmetry and Egger's test, p = 0.502 (Fig. 6a).

A pooled meta-analysis including 26 studies with 1160 participants (case = 584, control = 576) showed significant Fins reduction (WMD: -0.8 μU/mL, 95% CI: -1.15 to -0.44, p < 0.05) (Fig. 5b). There was evidence of effect heterogeneity ($I^2 = 24.3\%$, p = 0.13). Regarding funnel plot symmetry and Egger's test, p = 0.279 (Fig. 6b).

A pooled meta-analysis including nine studies with 544 participants (case = 280, control = 264) reported changes in HbA1c during IF (Fig. 5c). The WMD was -0.06 % (95% CI: -0.18 to 0.05, p > 0.05, a fixed-effects model), which indicates no tangible effect in HbA1c. There was no evidence of effect heterogeneity ($I^2 = 0.0\%$, p = 0.974). Regarding funnel plot symmetry and Egger's test, p = 0.167 (Fig. 6c).

Pooled data from 19 studies with 866 participants (case = 443, control = 423) reported the effect of IF on HOMA-IR (Fig. 5d). The WMD using a fixed-effects model was -0.21 (95% CI: -0.36 to -0.05, p < 0.05), which indicates significant HOMA-IR reduction. We observed a mild level of heterogeneity among the studies ($I^2 = 38.4\%$, p = 0.046). Regarding funnel plot symmetry and Egger's test, p = 0.065 (Fig. 6d).

**Effect of IF on BP**

BP was operationalized in SBP and DBP. In a pooled meta-analysis including 29 studies with 1393 participants, we found a tangible effect of IF on SBP level when compared to placebo (a fixed-effects model, WMD: -2.14 mmHg, 95% CI: -3.54 to -0.73, p < 0.05) (Fig. 7a). We found mild effect heterogeneity ($I^2 = 36.2\%$, p = 0.028). Regarding funnel plot symmetry and Egger's test, p = 0.111 (Fig. 8a).

Twenty-seven studies with 1277 participants (case = 640, control = 637) indicated an IF effect on DBP (Fig. 7b). The WMD using a fixed-effects model was -1.38 mmHg (95% CI: -2.35 to -0.41, p < 0.05), which indicates significant DBP reduction. There was no evidence of effect heterogeneity among the studies ($I^2 = 0.0\%$, p = 0.588). Regarding funnel plot symmetry and Egger's test, p = 0.639 (Fig. 8b).

**Effect of IF on blood lipid panel**

A meta-analysis of blood lipid levels was performed involving TC, TG, HDL-C, and LDL-C. In 33 studies with 1766 participants (case = 896, control = 870), a significant reduction in TC concentration (WMD: -3.75 mg/dL, 95% CI: -6.64 to -0.85, p < 0.05) (Fig. 9a) was observed, with slight effect heterogeneity ($I^2 = 14.6\%$, p = 0.233). Regarding funnel plot symmetry and Egger's test, p = 0.907 (Fig. 10a).

A pooled meta-analysis including 34 studies with 1750 participants (case = 887, control = 863) evaluated the effect of IF on TG level (Fig. 9b). The WMD using a fixed-effects model was -7.54 mg/dL (95% CI: -11.45 to -3.63, p < 0.05), which indicates significant TG reduction. There was no evidence of effect heterogeneity among the studies ($I^2 = 5.5\%$, p = 0.377). Regarding funnel plot symmetry and Egger's test, p = 0.868 (Fig. 10b).

A pooled meta-analysis including 36 studies with 1850 participants (case = 943, control = 907) found no tangible effect of IF on LDL-C concentration (WMD: -2.15 mg/dL, 95% CI: -4.42 to 0.12, p > 0.05) (Fig. 9c). There was also no evidence of effect heterogeneity among the studies ($I^2 = 0.0\%$, p = 0.967). Regarding funnel plot symmetry and Egger's test, p = 0.214 (Fig. 10c).

There were 36 RCTs involving 1852 participants (case =943, control = 909) that evaluated the effect of IF on changes in HDL-C. Data pooling showed no significant changes in HDL-C level (WMD: -0.54 mg/dL, 95% CI: -1.46 to 0.38, p > 0.05) (Fig. 9d), with no significant heterogeneity ($I^2 = 0.0\%$, p = 0.858). Regarding funnel plot symmetry and Egger's test, p = 0.711 (Fig. 10d).

**Sensitivity analysis**

In order to determine the impact of each individual study on the effect index, we used a sensitivity analysis in our meta-analysis. Finally, we did not observe the significant effects of any individual study (Fig.11-14).
Discussion

In this study, 46 RCTs were systematically reviewed to evaluate the effects of IF on MetS. The pooled analysis showed that IF had significantly reduced body composition (weight, WC, FM, and BMI), BP (SBP, DBP), lipid panel (TC, TG), and improved glycemic control by reducing FBG, Fins, and HOMA-IR; however, it did not affect the HbA1c level and lipid profile (LDL-C and HDL-C).

Overall, in terms of body composition, there was a significant positive correlation between BMI and weight loss during IF (i.e., the higher the starting BMI, the greater the weight loss during the fasting period). This suggests that IF may be more effective for people with a higher BMI. The results for the effect of IF on body composition were similar to those obtained in a previous meta-analysis, by [72], which involved 11 trials that found that TRF was effective in promoting weight loss and reducing FBG compared to not limiting meal times approaches. In addition, IER was more effective in reducing weight than a regular control diet. Moreover, it was also more effective in reducing FM level than CER [73]. In a meta-analysis on religious fasting [74], it was found that overweight participants had a greater reduction in weight and percentage of fat than normal people. A recent meta-analysis of RCTs showed that ADF effectively lowered body composition and TC in overweight adults within 6 months compared to the control group [75]. However, in another meta-analysis of 12 RCTs, researchers confirmed that lean mass was relatively conserved in the IF group and no significant weight reduction was identified [34]. In addition, a recent study by Lowe, D.A., et al [15] on 16.8 time-restricted eating (TRE), an IF plan encouraging the consumption of all dietary intake within an 8-hour eating window, demonstrated that IF does not play a significant role in weight loss in the absence of controlled food intake. In turn, it may lead to a reduction in muscle mass. There were no significant differences in FM, Fins, glucose level, HbA1C, or blood lipids between the TRE and control groups. The results of Lowe's study are contrary to the results of most studies related to fasting. This may have been brought about by the time window of fasting. Meantime, our meta-analysis is also included in this study, but a comprehensive assessment of IF in body composition is beneficial.

O'Keefe, J. H., et al. [76] found that IF habits can improve glucose metabolism as well as reduce abdominal fat accumulation, free radical production, inflammation, and the risks of diabetes, CVD, cancer, and neurodegenerative diseases. After 12 hours of fasting, insulin levels drop, glycogen reserves are depleted, and the body begins to absorb fatty acids from fat cells to replace glucose for combustion, which improves insulin sensitivity [59, 77].

Previous studies have shown that IF is not only beneficial in reducing the production of free radicals or weight loss; it also has several health benefits [7, 78-80]. IF can cause an evolutionarily conserved adaptive cellular response, improve blood glucose regulation, enhance anti-stress ability, and inhibit inflammation between and within organs. During fasting, cells activate pathways that enhance the body's defense against oxidation and metabolic stress as well as remove or repair damaged molecules. IF causes the organism to reach the stage of an alternative metabolism, which lays the foundation for improving the metabolic characteristics and healthy lifespan of the animal [78, 81]. Fat is the main energy source for cells and is stored in the adipose tissue in the form of TGs after meals. During fasting, TGs are broken down into fatty acids and glycerol, which are used to provide energy consumption by the organism [82].

Physiologically, fasting is defined as a change in the cell's response to food restriction, resulting in less glucose dependence and more reliance on ketone bodies as a fuel source. According to animal and human studies, ketone bodies can not only improve glucose homeostasis, mitochondrial function, and DNA repair but also stimulate autophagy, stem cell renewal, stress resistance, and inflammation inhibition [82, 83]. Thus, accelerated metabolic changes lead to fat consumption and weight loss [84].

Human beings have gradually formed a 24-hour circadian rhythm during evolution [85]. The master clock is mainly produced by the suprachiasmatic nucleus of the hypothalamus, while the peripheral oscillators are found in the esophagus, liver, pancreas, spleen, skin, and thymus. There is an important relationship between the feeding signal and peripheral clock rhythm. Thus, energy consumption outside the normal eating phase (i.e., late-night eating in humans) may disrupt the balance of some peripheral clocks [86]. Meanwhile, irregular mealtimes may cause a shift or an internal desynchronization of the peripheral clock, which may lead to its decoupling, followed by a series of unhealthy consequences such as MetS [87]. Daily rhythms also exist in glucose homeostasis, and the decline of insulin sensitivity and glucose oxidation at night is higher than the decline experienced in the morning [88]. People who eat late lunches are less likely to lose weight because glucose tolerance and insulin function decline at night [89]. This finding is critical because studies have suggested that mealtimes may change the central biological clock [90]. These data highlight that appropriate mealtimes play a key role in health. TRE can improve metabolic dysfunction and weight loss by adjusting circadian rhythms in obese individuals [91, 92].

Some studies have found that the mammalian TOR pathway activated by diets alters the stability of the biological clock [93]. In contrast, fasting activates the AMP-dependent protein kinase pathway to degrade the cryptochrome [94]. Moreover, nicotinamide adenine dinucleotide and sirtuins fluctuate with the cell's energy state, affecting circadian rhythms [95-97]. Therefore, the feeding/fasting cycle enhances the oscillation of circadian activators and repressors, thereby regulating rhythmic tissue-specific transcriptomes [98, 99], and ultimately translating to a healthier phenotype. Meanwhile, researchers have found that the gut microbiota is associated with circadian rhythms and dietary habits [100]. In fact, feeding alters the inherent daily rhythm of the intestinal microbes, and both food content and feeding time play a role in the process [100-102]. Defense against oxidative and metabolic stress as well as clearance of damaged molecules also enhance and provide greater diversity of intestinal flora during fasting [101, 103]. In addition, an earlier study suggested that IF promotes browning of white fat and reduces obesity by shaping the intestinal flora [104]. Another study showed that TRF reduced the number of several obese mice and increased the proportion of hypothetical bacteria protective bacteria [101]. TRF is associated with periodic microorganism fluctuations and improves the intestinal microenvironment [105], resulting a total amount of intestinal bacteria and Firmicutes increased during the awake/eating phase. Further, the bacteroids, proteobacteria, and microbiota increase during the sleep/fasting phase. There is also evidence of diurnal variations in microbial metabolites, which in turn affect host circadian rhythms and metabolism.

Even though, many experiments have shown that IF is beneficial to human health and suitable for a wide range of metabolic diseases, this dietary pattern is rarely used in practice. The main reason for this is the three-meals-a-day habit in our daily lives. Second, when switching to an IF program, some people feel hungry, irritable, and lose concentration. Finally, doctors are required to prescribe specific training for IF interventions, which requires a standardized use of IF.
There are some limitations to this meta-analysis. As this is the case with some studies, some of the included ones have a small sample size, and there are several studies with a high risk of bias. Second, the number of long-term studies conducted is very limited, and larger long-term trials with a longer duration are needed to understand the effects of IF on weight loss and long-term weight management. Moreover, different types of IF have different characteristics in various metabolic diseases, and we did not analyze each of them individually. Finally, although IF has a variety of components, a comparison with other types of IF could not be conducted due to the lack of RCT research on religious fasting and lack of data on other kinds of fasting.

Conclusions

This systematic review has demonstrated that IF may improve body composition (weight, WC, FM, and BMI) and moderate BP, TC, TG, and blood glucose, but there may be no difference regarding the LDL-C, HDL-C, and HbA1c levels; components of MetS are also risk factors for the development of diabetes and CVDs. Therefore, high-quality and long-term RCTs are needed to provide data on the persistence of the effect and to strengthen the certainty of the evidence.

Abbreviations

IF: Intermittent fasting; RCTs: randomized controlled trials; CVDs: cardiovascular diseases; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; CI: confidence interval; WMD: weighted mean difference; ADF: Alternate-day fasting; AMDF: alternate-modified-day fasting; CR: Caloric restriction; TRF: time-restricted feeding; TRE: time-restricted eating; IER: Intermittent energy restriction; CER: Continuous energy restriction; WC: waist circumference; FM: fat mass; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; TG: triglyceride; HDL: high-density lipoprotein; LDL: low-density lipoprotein; FBG: fasting blood glucose; Fins: fasting insulin; HbA1c: glycosylated hemoglobin; HOMA-IR: insulin resistance; MetS: metabolic syndrome; VLCD: very low-calorie diet; IECR: Intermittent energy and carbohydrate restriction;

Declarations

Acknowledgements

We express our appreciation to the participants of this study.

Author contributions

Y.W.X. and Y.H.G. designed the manuscript. F.Y. wrote the manuscript. F.Y., X.L., and C.L. searched databases, performed the selection of studies. Y.W.X. and X.D.P. revised the manuscript. X.Y.L., L.T., and J.H.S. critically evaluated the review and commented on it. S.J.Y., R.Z., N.A. and X.Y.Y. contributed in revised version. All authors approved the manuscript for publication.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Funding

This work was supported by the National Key R&D Program of China (grants 2018YFC1704900 & 2018YFC1704901).

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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**Figures**
Figure 1
Schema of the search strategy
Figure 2

Risk-of-bias assessment of the studies included in the meta-analysis.
Figure 3

Forest plot of RCTs investigating the effects of intermittent fasting on body composition (a) Weight, (b) WC, (c) FM, (d) BMI.
Figure 4

Funnel plot displaying no publication bias in the studies reporting the impact of intermittent fasting about body composition (a) Weight, (b) WC, (c) FM, (d) BMI.
Figure 5

Forest plot of RCTs investigating the effects of intermittent fasting on glycemic control (a) FBG, (b) Fins, (c) HbA1c, (d) HOMA-IR.
Figure 6
Funnel plot displaying no publication bias in the studies reporting the impact of intermittent fasting on glycemic control (a) FBG, (b) Fins, (c) HbA1c, (d) HOMA-IR.

Figure 7
Forest plot of RCTs investigating the effects of intermittent fasting on blood pressure (a) SBP and (b) DBP.
Figure 8

Funnel plot displaying no publication bias in the studies reporting the impact of intermittent fasting on blood pressure (a) SBP and (b) DBP.

Figure 9

Forest plot of RCTs investigating the effects of intermittent fasting on lipid panel (a) TC, (b) TG, (c) LDL-C, (d) HDL-C.
Figure 10

Funnel plot displaying no publication bias in the studies reporting the impact of intermittent fasting on lipid panel (a) TC, (b) TG, (c) LDL-C, (d) HDL-C.
Figure 11

Sensitivity analysis observed no significant effect of intermittent fasting on body composition (a) Weight, (b) WC, (c) FM, (d) BMI.
Figure 12

Sensitivity analysis observed no significant effect of intermittent fasting on glycemic control (a) FBG, (b) Fins, (c) HbA1c, (d) HOMA-IR.

Figure 13

Sensitivity analysis observed no significant effect of intermittent fasting on blood pressure (a) SBP and (b) DBP.
Figure 14

Sensitivity analysis observed no significant effect of intermittent fasting on lipid panel (a) TC, (b) TG, (c) LDL-C, (d) HDL-C.

Supplementary Files

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