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Meta-Analysis

Metabolic Efficacy of Time-Restricted Eating in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Lili Liu,[1] Wei Chen,[1] Dan Wu,[1] and Fang Hu[1]

[1]National Clinical Research Center for Metabolic Diseases, Key Laboratory of Diabetes Immunology (Central South University), Ministry of Education, Metabolic Syndrome Research Center, and Department of Metabolism and Endocrinology, Second Xiangya Hospital of Central South University, Changsha, 410011 Hunan, China

Correspondence: Fang Hu, PhD, National Clinical Research Center for Metabolic Diseases, Key Laboratory of Diabetes Immunology (Central South University), Ministry of Education, Metabolic Syndrome Research Center, and Department of Metabolism and Endocrinology, the Second Xiangya Hospital of Central South University, Changsha, 410011 Hunan, China, Email: hu_fang98@csu.edu.cn.

Abstract

Context: Time-restricted eating (TRE), which restricts food intake to a limited duration of the day, is a key regimen of intermittent fasting.

Objective: The aim of our study was to provide an up-to-date meta-analysis and systematic review to evaluate the efficacy of TRE on weight loss and other metabolic-related parameters in adults.

Methods: We searched PubMed, EMBASE, and the Cochrane Library for relevant studies published before February 26, 2022. Study duration of TRE was at least 4 weeks. Body weight and other metabolic-related continuous parameters were described as weighted mean difference (WMD) with 95% CI.

Results: Seventeen randomized controlled trials involving 899 participants were analyzed. The pooled meta-analysis has shown that TRE contributed to a significant decrease in body weight with a WMD of −1.60 kg (95% CI −2.27 to −0.93) and fat mass with WMD −1.48 kg (95% CI −1.59 to −1.38). Subgroup analysis showed that TRE could reduce body weight and fat mass especially in overweight participants with WMD −1.43 kg (95% CI −2.05 to −0.81) and −1.56 kg (95% CI −1.67 to −1.44), respectively. TRE also showed beneficial effects on the lipid spectrum in overweight participants, including decreased levels of triglyceride (WMD −12.71 mg/dL, 95% CI −24.9 to −0.52), total cholesterol (WMD −6.45 mg/dL, 95% CI −7.40 to −5.49), and low-density lipoprotein cholesterol (WMD −7.0 mg/dL, 95% CI −9.74 to −4.25). However, compared with control, TRE had no significant effects on waist circumference, body mass index, glycosylated hemoglobin, or blood pressure.

Conclusion: This updated meta-analysis found that TRE may be an effective approach to improve the metabolic state of nonobese subjects, especially in overweight participants.

Key Words: time-restricted eating, overweight, obesity, weight loss

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; HDL, low-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; IF, intermittent fasting; LDL-C, low-density lipoprotein cholesterol; RCT, randomized controlled trial; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; TRE, time-restricted eating; WC, waist circumference; WMD, weighted mean difference.

The global prevalence of overweight and obesity has become a major public health problem. Over the past ∼50 years, obesity rates have nearly doubled in 73 countries worldwide, with ap-proximately 40% of the adult population overweight and 10% to 15% of the population obese (1, 2). According to the World Health Organization, 650 million people world-wide suffer from overweight/obesity. Overweight and obesity are risk factors of many diseases, including coronary heart dis-ease (3), hypertension (4, 5), stroke (6), diabetes (7, 8), kidney disease (9), cancer (10, 11), and a series of noncommunicable chronic diseases. Therefore, reducing the body weight of over-weight/obese people and preventing normal-weight individu-als from gaining weight have become urgent issues to resolve. Initially, lifestyle interventions, anti-obesity pharmacother-apy, and bariatric surgery were considered optional strategies to prevent or treat obesity (12). However, it is difficult to en-sure long-term compliance with lifestyle interventions, and most weight loss drugs have certain side effects (13) that limit their applications in clinical practice. Additionally, although bariatric surgery has been proven to be the most effective treatment for patients with morbid obesity, the eligibility cri-teria and safety risks may also limit its application (14). Therefore, it is urgent to find applicable strategies to overcome obesity.

In recent years, intermittent fasting (IF), a dietary regi-men consisting of a typical cycle of fasting and eating for a period, has become an innovative and feasible treatment strategy to prevent the progression of obesity and metabolic disorders (15). Many studies have shown that IF can reduce body weight, prolong life span, and improve aging-related

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diseases (16), as well as increase resistance to various oxi-dative stresses (17). In addition, it has been shown that IF enhances cancer treatment outcomes (18). IF is mainly div-ided into 4 types according to various fasting approaches (19): (1) 0-calorie alternate-day fasting, (2) modified alternate-day fasting, (3) the 5:2 diet, which refers to 5 days of eating ad libitum and 1 to 2 days per week of cal-oric restriction, and (4) time-restricted eating (TRE). The first 3 types of IF are involved in caloric restriction. However, TRE involves fasting for 12 to 21 hours per day without caloric restriction (20, 21). Hence, TRE has be-come an attractive and easily adoptable lifestyle intervention.

As a key regimen of IF, TRE allows ad libitum eating without caloric restrictions in controlled time durations. Usually, the TRE regimen has a 4- to 12-hour eating win-dow, and the most common fasting to eating window is 16:8, with 16 hours of fasting and an 8-hour eating window each day (20). According to whether the eating window includes breakfast or dinner, TRE can be divided into 2 types: early TRE and late TRE (22). Animal research has provided strong evidence on the beneficial metabolic- related effects of TRE. For example, TRE can reduce body weight and cholesterol levels, increase insulin sensitivity in mice (23, 24), and restore muscle function in *Drosophila* (25).

Although the beneficial effects of TRE have been consist-ently observed in animal studies, the impacts on human par-ticipants have been illusive. Several clinical studies have reported that TRE could improve metabolic parameters such as reducing body weight (26, 27), but some others showed no metabolism-related benefits (28, 29). A recent meta-analysis found that TRE could improve metabolic dys-functions compared to the baseline. However, the beneficial effects of TRE disappeared when compared with the non-TRE group (30), indicating that diverse designs may re-sult in the divergent outcomes of TRE. Randomized con-trolled trials (RCTs) are regarded as the highest level of evidence to establish causal connections in clinical research. Many new RCTs about TRE have emerged in recent years. In this study, we aimed to provide an up-to-date meta- analysis and systematic review of RCTs to evaluate and com-pare the efficacy of TRE on weight loss and other metabolic-related parameters in normal-weight, overweight, and obese adults.

Materials and Methods

This meta-analysis was performed according to the outlines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) (31).

Literature Search Strategy

We selected relevant studies published before February 26, 2022, in PubMed, EMBASE, and the Cochrane Library. Searching language, publication year, and regions had no restrictions. We used search terms including combina-tions of "time restricted eating," "time restricted diet," "time restricted fasting," or "time restricted feeding," and "obesity," "weight," "fat mass," "blood pressure," "trigly-ceride," "cholesterol," or "glucose." Detailed database search strategies are shown elsewhere (Appendix S1 (32)).

Inclusion and Exclusion Criteria

The inclusion criteria of this meta-analysis were as follows: (1) a population of adults aged 18 years or older; (2) studies with RCTs; (3) intervention with TRE for fasting for at least 12 hours daily; (4) a follow-up duration of at least 4 weeks; (5) studies reporting outcomes including at least 1 of the fol-lowing items: weight loss, waist circumference (WC), body mass index (BMI), fat mass, fasting glucose, glycosylated hemoglobin (HbA1c), systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), or triglycerides (TGs); (6) trials that have been published.

The exclusion criteria included (1) duplications of the searched studies; (2) crossover studies, non-RCTs, and nonor-iginal articles including editorials, review articles, case reports, or letters to the editor; (3) animal studies; (4) studies involving cases with diseases that may influence the outcome; and (5) other studies that did not meet the above inclusion criteria.

Data Extraction

Two experienced authors (Liu and Chen) independently ex-tracted the following items: first author, publication year, time of follow-up, stirrup size, characteristics of the partic-ipants, sex, mean age, blood pressure, body composition, mean weight, fasting glucose, HbA1c, homeostatic model assessment of insulin resistance (HOMA-IR), and lipid profile.

For our continuous variables of interest, changes from base-line were extracted in both the TRE and non-TRE groups. If studies reported the mean and SD values at both baseline and postintervention, we used a correlation coefficient meth-od to calculate changes in the mean and SD from baseline. In studies providing SEM or CI for our continuous variables of interest, the SD was transformed using reported approaches (33). Disagreements were resolved by discussion with a third party.

Assessment of Study Quality and Publication Bias

We used a modified Cochrane risk of bias instrument to assess the risk of bias of the included RCTs (34). The biases were se-lection bias, performance bias, detection bias, attrition bias, and reporting bias. The specific items were involved in 6 as-pects as follows: random sequence generation, allocation con-cealment, blinding of the participants and researchers, incomplete outcome data, selective reporting, and other bias. Publication bias was evaluated by funnel plot asymmetry and quantified by Egger's test (35).

Statistical Analysis

All statistical analyses were performed by using Stata version 12.0 software (Stata Corp, College Station, TX, USA), and Review Manager Version 5.3 was used to draw a risk of bias graph. The results of continuous variables were reported with WMDs with 95% CI.

Forest plots were used to examine the overall effects. Statistical heterogeneity was evaluated by using the chi-square test with significance set at $P \leq .10$, and heterogeneity was quantified by the I^2 statistic. $I^2 > 50\%$ indicated high hetero-geneity (36). The random-effects model was adopted if there was significant heterogeneity among studies; otherwise, the

fixed-effects model was employed. Subgroup analyses were performed to sort out potential sources of heterogeneity, which included different ratios of daily fasting to eating (12:12, 14:10, 16:8, 18:6, 20:4) and mean baseline BMI (≤25 kg/m^2 as normal, 25-30 kg/m^2 as overweight, or ≥ 30 kg/m^2 as obese) (37). Considering that the duration of intervention of TRE could affect the outcomes, we performed subgroup analysis according to study duration. Short-term study duration was defined as less than 12 weeks and long-term study duration as 12 weeks or more.

Results

Characteristics of Included Studies

A flow chart of the study process is shown in Fig. 1. A total of 1365 studies were retrieved after an initial search of electronic databases. After 357 duplicates were eliminated, 1007 records were screened. After further exclusion of 960 studies by checking titles and abstracts, 47 articles remained, of which 28 were excluded by reading the full text that did not meet the inclusion criteria, and 2 studies were excluded due to lack of relevant data. Finally, we included 17 studies for systematic evaluation and meta-analysis.

A total of 899 participants were enrolled in this study. The largest study recruited 174 individuals (26), while the smallest recruited 16 subjects (38). There were 4 studies (38–41) involving healthy individuals with BMI < 25 kg/m^2, 9 studies (26, 28, 42–48) enrolling overweight participants with BMI of 25-30 kg/m^2, and 4 studies (29, 49–51) including obese individuals with BMI ≥ 30 kg/m^2. The duration of the studies ranged from 4 weeks to 12 months. The most common form of TRE is "16:8," with 16 hours of fasting and an 8-hour eating window each day. Table 1 shows the demographic and clinical characteristics of the participants.

Risk of Bias and Publication Bias in the Enrolled Studies

The risk of bias for the RCTs is shown in Fig. 2. Of the 17 studies identified for analysis in this study, 3 trials (42, 44, 47) lacked information on randomization procedures. Allocation protocol concealment was not mentioned in 5 studies (29, 41, 42, 44, 47). Blinding of all participants was not feasible due to the interventional nature of the study. However, 4 studies (26, 47, 50, 51) did not mention it. Three studies (26, 50, 51) did not mention the blinding of the investigator and the statistical analysis of the data. All trials did not appear to have selective results reporting. Tisnley (47) reported unmatched baseline characteristics of the enrolled participants between TRE and non-TRE groups.

Efficacy of TRE on Body Weight

All 17 included studies (26, 28, 29, 38–51) reported body weight. Compared with that in the control group, significant mean weight reduction was found in the TRE group with a WMD of −1.60 kg (95% CI −2.27 to −0.93) (I^2 = 90.2%) (P < .001) (Fig. 3). There was no publication bias (Egger's test: P = .69) (Fig. S1A (32)).

Subgroup analysis using the time of fasting to eating ratio was performed. There was no significant weight loss in the subgroup with 12:12 (WMD −0.21, 95% CI −5.26 to 4.84) (P = .935), while there was markedly decreased body weight in the other 4 subgroups with 14:10 (WMD −2.15, 95% CI −2.29 to −2.01), 16:8 (WMD −1.16, 95% CI −1.52 to −0.8), 18:6 (WMD −3.3, 95% CI −3.66 to −2.94), and 20:4 (WMD −3.3, 95% CI −3.67 to −2.93) (all P < .001) (Table 2).

In the subgroup with lean (mean baseline BMI < 25 kg/m^2) and overweight (mean baseline BMI ≥ 25 kg/m^2 and < 30 kg/m^2) subjects, TRE significantly reduced body weight compared with non-TRE with WMD −1.23 kg (95% CI −1.9 to −0.56) (I^2 = 0%) (P < .001) and −1.43 kg (95% CI −2.05 to −0.81) (I^2 = 84.9%) (P < .001), respectively. However, in obese (mean baseline BMI ≥ 30 kg/m^2) participants, body weight loss was not significant, with a WMD of −1.73 kg (95% CI −4.76 to 1.29) (I^2 = 92.7%) (P = .261) (Table 2).

In exploratory analysis, we performed subgroup analysis based on study duration. TRE showed reduced body weight both in short-term and long-term duration of intervention with a WMD of −1.91 kg (95% CI −3.47 to −0.36) (I^2 = 85.4%) (P < .001) and −1.29 kg (95% CI −1.96 to −0.61) (I^2 = 87.7%) (P < .001), respectively (Table 2).

Efficacy of TRE on Fat Mass

Changes in fat mass from baseline to endpoint were reported in 13 studies (26, 29, 38–41, 43–45, 47, 48, 50, 51). As shown in Fig. 4, fat mass markedly decreased in the TRE group compared with the control group, with a WMD of −1.48 kg (95% CI −1.59 to −1.38) (I^2 = 32%) (P < .001). Publication bias was significant (Egger's test: P = .034), so we performed trim and fill analysis. Five default study data were assumed, and the filled meta-analysis showed that TRE reduced fat mass with a WMD of −1.40 kg (95% CI −1.67 to −1.14) (P < .001) (Fig. S2 (32)).

In the subgroup analysis according to the time of fasting to eating ratio, 3 subgroups with different fasting to eating ratios (16:8, 18:6, 20:4) all showed reduced fat mass (all P < .001) (Table 2). However, the reduced fat mass was not in a fasting time–dependent manner. TRE reduced fat mass with a WMD of −1.09 kg (95% CI −1.47 to −0.72) (I^2 = 43.1%), −0.8 kg (95% CI −1.05 to −0.55), and −2.2 kg (95% CI −2.48 to −1.91) (I^2 = 0%) after fasting for 16 hours, 18 hours, and 20 hours, respectively. The 18:6 group included 1 study only, so the heterogeneity was unknown (Table 2).

In exploratory analysis, subgroup analysis based on mean baseline BMI showed that there was significantly reduced fat mass in the normal, overweight, and obesity groups (all P < .001). In the subgroup with BMI < 25 kg/m^2, fat mass was reduced with WMD −0.94 kg (95% CI −1.33 to −0.54) (I^2 = 0%). The largest reduction in fat mass among the 3 subgroups was seen in the overweight group (BMI ≥ 25 kg/m^2 and < 30 kg/m^2), with a WMD of −1.56 kg (95% CI −1.67 to −1.44) (I^2 = 0%). Compared with the non-TRE control, the subgroup with a mean baseline BMI ≥ 30 kg/m^2 also showed a significant decrease (P < .001) in fat mass, with a WMD of −1.07 kg (95% CI −1.87 to −0.28) (I^2 = 51.7%). (Table 2).

To explore the effect of intervention duration on fat mass, we performed subgroup analysis based on study duration (<12 weeks or ≥12 weeks). Results showed that, compared with control, TRE led to significant weight loss both in short-term (WMD −1.24 kg, 95% CI −1.49 to −0.99) (I^2 = 0%) (P < .001) and long-term duration of intervention (WMD −1.04 kg, 95% CI −1.78 to −0.31) (I^2 = 56.2%) (P = .006) (Table 2).

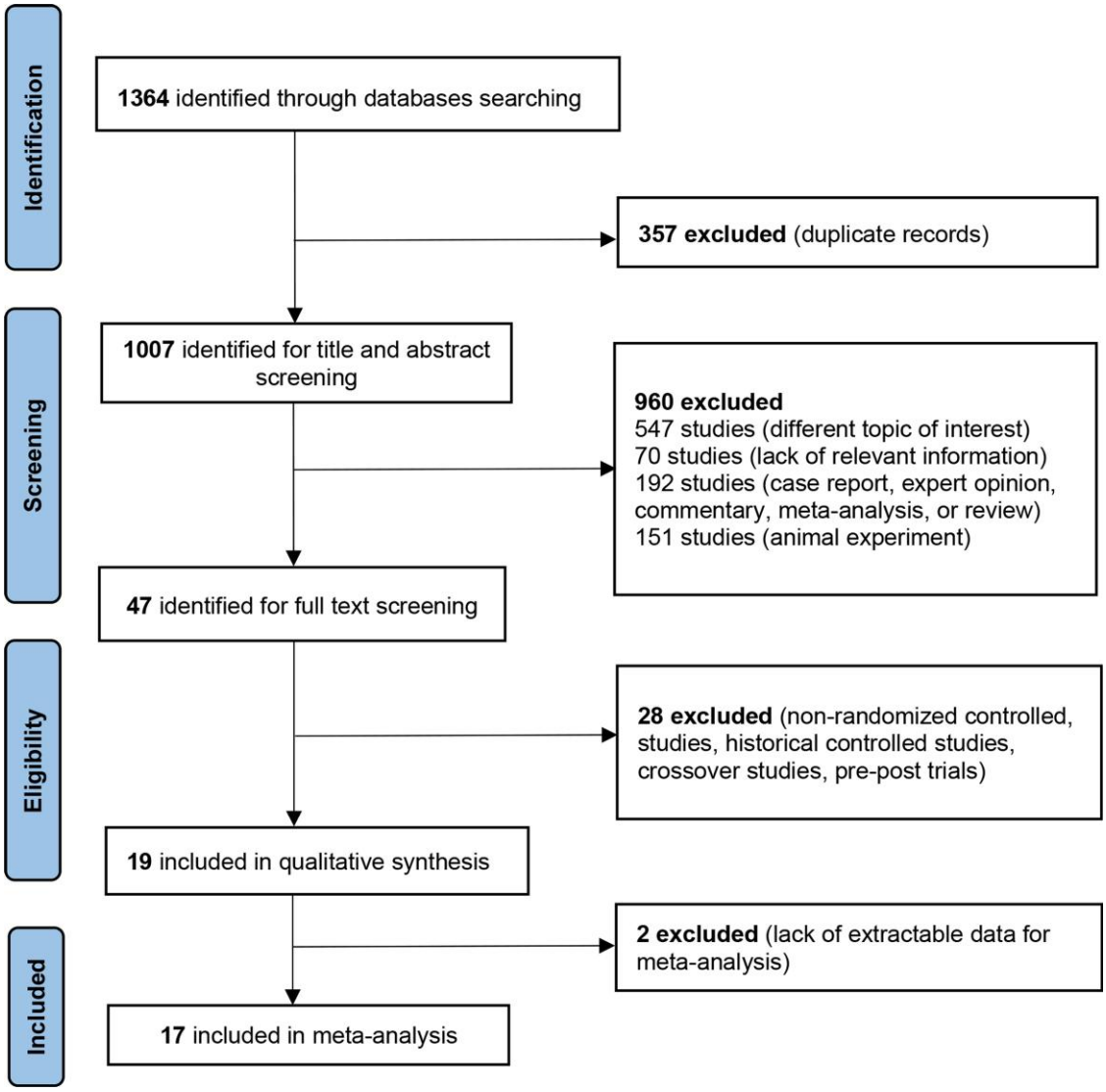

Figure 1. Schema of the search strategy.

Efficacy of TRE on Body Mass Index and Waist Circumference

Eight studies (26, 28, 29, 42, 44–46, 49) reported BMI. We performed a meta-analysis and found that there was no difference between the TRE and non-TRE groups (WMD −0.53 kg/m^2, 95% CI −1.1 to 0.04) ($P = .07$), with high heterogeneity ($I^2 = 84.8\%$) (Fig. 5A). We performed sensitivity analysis to determine the reason for the high heterogeneity, and Che et al., 2021 (46) was identified. When this study was removed, I^2 was reduced to 0%, and statistical significance was found (WMD −0.27 kg/m^2, 95% CI −0.53 to −0.01) ($P = .04$).

Seven studies (26, 28, 29, 42, 44, 45, 49) with 438 participants reported the efficacy of TRE on WC. We did not find a significant difference between the TRE and non-TRE groups (WMD −0.07 cm, 95% CI −0.98 to 0.83) ($P = .93$). The heterogeneity was low ($I^2 = 0\%$) (Fig. 5B).

Efficacy of TRE on Glucose and Blood Pressure

Twelve studies (26, 28, 29, 38–40, 42, 43, 46, 48, 50, 51) reported the effect of TRE on fasting glucose concentration. Compared with the non-TRE control, TRE lowered the fasting glucose concentration (WMD −4.08 mg/dL, 95% CI −7.74 to −0.42) ($I^2 = 96.6\%$) ($P = .03$) (Fig. 6A). Significant publication bias was not observed (Egger's test: $P = .12$) (Fig. S1B (32)). Six studies (28, 29, 44, 46, 50, 51) reported hemoglobin (HbA1c), and there were no significant differences between the TRE and non-TRE groups (WMD −0.11%, 95% CI −0.51 to 0.28) ($I^2 = 98.9\%$) ($P = .58$) (Fig. 6B).

Eight studies (28, 29, 41, 42, 44, 49–51) provided detailed information about SBP and DBP. TRE did not reduce either SBP or DBP, with WMDs of −2.46 mmHg (95% CI −6.43 to 1.51) ($I^2 = 77.4\%$) ($P = .22$) and −1.78 mmHg (95% CI −4.72 to 1.16) ($I^2 = 72.2\%$) ($P = .24$), respectively (Fig. 6C and 6D). As the number of included studies was fewer than 10, we did not perform publication bias of HbA1c and blood pressure.

Efficacy of TRE on Lipid Profile

Thirteen studies (26, 28, 29, 38–43, 46, 48, 50, 51) with 693 cases reported changes in TGs. The pooled data did not show beneficial effects of TRE on TG (WMD −8.64 mg/dL, 95% CI

Table 1. Characteristics of the 17 included studies

Author	Year	Geographic region	Participants	Study duration	TRE regimen (fasting: eating)	Study groups (TRE/non-TRE)	Age (year)	Sex (men/ women)	Weight (kg)	BMI (kg/m^2) WC (cm)	SBP DBP (mmHg)	Fasting glucose (mg/dL) Hb1Ac (%)	TC TG (mg/dL)	HDL-c LDL-c (mg/dL)
Xie et al (41)	2022	China	Healthy adults	5 weeks	16:08	eTRE: 28 mTRE: 26 non-TRE: 28	28.7 ± 9.7 31.1 ± 8.4 33.6 ± 11.6	4/24 7/19 7/21	61.1 ± 8.8 61.0 ± 11.7 61.2 ± 9.9	22.7 ± 3.1 UN 21.4 ± 2.2 UN 21.5 ± 2.9 UN	UN	UN	UN	UN
Lin et al (42)	2022	China	Overweight or obese females	8 weeks	16:08	TRE 30 non-TRE: 33	50.1 ± 7.5 54.2 ± 7.9	0/63	65.9 ± 9.7 65.8 ± 8.8	25.9 ± 9.7 87.0 ± 8.0 25.7 ± 3.8 89.7 ± 9.5	121.2 ± 16.1 75.3 ± 11.2 121.1 ± 12.9 71.2 ± 10.1	88.3 ± 7.6 UN 89.5 ± 8.6 UN	186.6 ± 41.4 104.1 ± 38.8 188.3 ± 27.9 107.9 ± 47.3	63.9 ± 14.2 108.3 ± 32.5 63.2 ± 11.8 110.9 ± 26.4
Phillips et al (28)	2021	Switzerland	Participants with 1 component of MS	6 months	12:12	TRE 25 non-TRE: 20	40.1 ± 13.3	UN	79.6 ± 15.9 77.5 ± 13.8	28.0 ± 4.1 92.4 ± 11.6 27.0 ± 4.0 90.1 ± 11.0	123.8 ± 11.2 79.3 ± 11.0 126.4 ± 10.5 81.0 ± 9.6	96.39 ± 10.36 5.3 ± 0.44 95.65 ± 12.4 5.23 ± 0.35	UN 119.61 ± 58.48 UN 105.43 ± 44.3	56.89 ± 14.32 UN 55.73 ± 11.22 UN
Moro et al (43)	2021	USA	Trained adults	12 months	16:08	TRE: 10 non-TRE: 10	UN	UN	83.2 ± 5.9 84.6 ± 5.7	UN	UN	95.1 ± 5.3 UN 95.5 ± 4.33 UN	194.9 ± 8.44 123.2 ± 6.94 198.3 ± 13.28 122.1 ± 11.06	53.7 ± 2.67 118.3 ± 15.08 53.6 ± 2.07 119.9 ± 11.01
Kotarsky et al (44)	2021	USA	Overweight adults	8 weeks	16:08	TRE 11 non-TRE: 10	45 ± 9.9 44 ± 6.3	3/18	82 ± 10 83 ± 9.5	29.8 ± 2.7 98.0 ± 6.3 29.4 ± 2.5 95.3 ± 39.5	122 ± 9.9 UN 120 ± 6.3 UN	UN 4.6 ± 0.7 UN 4.7 ± 0.6	202 ± 39.8 UN 200 ± 38 UN	55 ± 19.9 UN 55 ± 9.5 UN
Isenmann et al (45)	2021	Germany	Overweight adults	14 weeks	16:08	TRE 18 non-TRE: 17	27.9 ± 5.3 27.4 ± 5.8	8/10 6/11	80.0 ± 17.1 74.9 ± 12.0	26.3 ± 3.0 80.6 ± 11.8 25.7 ± 3.3 78.7 ± 10.5	UN	UN	UN	UN
de Oliveira et al (49)	2021	Brazil	Obese females	12 months	12:12	TRE: 31 non-TRE: 27	31.8 ± 7.0 31.0 ± 7.2	0/58	81.3 ± 13.5 80.3 ± 9.4	33.5 ± 4.5 102.8 ± 10.8 33.1 ± 3.6 98.9 ± 9.6	127.1 ± 15.29 86.2 ± 13.2 124.0 ± 0.4 86.5 ± 10.1	UN	UN	UN
Che et al (46)	2021	China	Participants with type 2 diabetes	12 weeks	14:10	TRE: 54 non-TRE: 50	48.2 ± 9.3 48.8 ± 9.6	UN	75.1 ± 4.4 74.7 ± 4.4	26.4 ± 2.0 UN 26.1 ± 2.1 UN	UN	180.01 ± 25.53 8.68 ± 1.21 176.49 ± 23.31 8.34 ± 1.09	215.17 ± 42.57 229.4 ± 108.09 205.88 ± 42.57 217.96 ± 104.55	47.99 ± 12 142.03 ± 47.99 46.05 ± 13.16 138.16 ± 40.25
Brady et al (40)	2021	USA	Trained males	8 weeks	16:08	TRE: 10 non-TRE: 7	35.9 ± 8.6	10/0 7/0	72.17 ± 6.68	Mean 22.5 UN	UN	96.57 ± 7.77 UN	UN 65.5 ± 20.1	UN

(*continued*)

Table 1. Continued

Author	Year	Geographic region	Participants	Study duration	TRE regimen (fasting: eating)	Study groups (TRE/non-TRE)	Age (year)	Sex (men/ women)	Weight (kg)	BMI (kg/m^2) WC (cm)	SBP DBP (mmHg)	Fasting glucose (mg/dL) Hb1Ac (%)	TC TG (mg/dL)	HDL-c LDL-c (mg/dL)
							39.9 ± 3.0		73.13 ± 6.06	Mean 22.3 UN		91.95 ± 6.66 UN	UN 69.2 ± 13.7	
Moro et al (38)	2020	Italy	Healthy young males	4 weeks	16:08	TRE: 8 non-TRE: 8	19.4 ± 2.4 19.4 ± 1.6	8/0 8/0	67.0 ± 5.0 72.3 ± 6.2	21.85 ± 1.65 UN 22.47 ± 1.83 UN	UN	94.63 ± 5.45 UN 91 ± 5.15 UN	171 ± 18.52 69.75 ± 26.13 176.25 ± 17.56 70.5 ± 54.51	UN
Lowe et al (29)	2020	USA	Obese adults	12 weeks	16:08	TRE: 59 non-TRE: 57	46.8 ± 10.8 46.1 ± 10.3	35/24 35/22	99.3 ± 16.9 99.1 ± 15.1	32.9 ± 4.9 106.3 ± 15.2 32.6 ± 3.4 106.6 ± 15.3	119.8 ± 13.2 76.9 ± 13.2 122.6 ± 13.0 74.6 ± 13.5	91.7 ± 8.72 5.28 ± 0.5 93.9 ± 8.72 5.3 ± 0.5	203.7 ± 35.37 127.2 ± 60.69 202.5 ± 35.37 133.4 ± 60.69	54.7 ± 13 122.1 ± 27.74 50.1 ± 13 126.4 ± 28
Cienfuegos et al (50)	2020	USA	Obese adults	8 weeks	20:04 18:06	4h-TRE: 16 6h-TRE: 19 non-TRE: 14	49 ± 8 46 ± 13 45 ± 7	2/14 1/18 2/12	101 ± 20 99 ± 21 93 ± 18	36 ± 4 UN 37 ± 4 UN 36 ± 4 UN	135 ± 20 88 ± 8 128 ± 14 84 ± 9 122 ± 19 81 ± 11	88 ± 8 5.9 ± 0.8 94 ± 8.7 5.9 ± 0.4 96 ± 18.7 5.9 ± 0.7	UN 91 ± 44 UN 95 ± 30.5 UN 84 ± 41.2	57 ± 20 95 ± 24 54 ± 13.1 104 ± 34.9 56 ± 15 108 ± 22.5
Chow et al (51)	2020	USA	Obese adults	12 weeks	16:08	TRE: 11 non-TRE: 9	46.5 ± 12.4 44.2 ± 12.3	2/9 1/8	95.2 ± 22.6 100.9 ± 28.1	33.8 ± 7.6 UN 34.4 ± 7.8 UN	132 ± 13.0 85 ± 4 123 ± 13.0 79 ± 8	95 ± 10 5.4 ± 0.4 95 ± 13 5.6 ± 0.4	UN 144 ± 54 UN 87 ± 21	50 ± 14 95 ± 24 60 ± 18 105 ± 19
Tinsley et al (39)	2019	USA	Healthy females	8 weeks	16:08	TRE: 13 non-TRE: 14	22.1 ± 7.6 22.0 ± 9.0	0/13 0/14	63.8 ± 7.93 64.7 ± 7.86	Mean 23.8 UN Mean 22.5 UN	113 ± 7 67 ± 4 108 ± 7 64 ± 4	89 ± 10.82 UN 93 ± 11.22 UN	179 ± 36.06 88 ± 36.06 179 ± 33.67 83 ± 33.67	64 ± 14.42 97 ± 25.24 69 ± 14.97 92 ± 26.19
Cai et al (26)	2019	China	Adults with NAFLD	12 weeks	16:08	TRE: 95 non-TRE: 79	33.6 ± 6.2 34.5 ± 7.0	29/66 23/56	75.0 ± 8.0 72.9 ± 8.0	26.8 ± 1.6 91.5 ± 4.4 26.3 ± 2.7 92.6 ± 5.0	UN	94.72 ± 15.17 UN 94.17 ± 16.65 UN	175.31 ± 59.21 256.94 ± 155.05 188.86 ± 53.41 234.79 ± 149.73	44.89 ± 17.42 105.65 ± 34.06 44.89 ± 19.35 98.69 ± 30.57
Tinsley et al (47)	2017	USA	Healthy active males	8 weeks	20:04	TRE: 10 non-TRE: 8	22.9 ± 4.1 22.0 ± 2.4	10/0 8/0	87.4 ± 19.2 79.0 ± 13.5	Mean 27.2 UN Mean 24.3 UN	UN	UN	UN	UN
Moro et al (48)	2016	USA	Trained males	8 weeks	16:08	TRE: 17 non-TRE: 17	29. ± 4.1 28.5 ± 3.4	17/0 17/0	83.9 ± 12.8 85.3 ± 13	Mean 26.4 UN Mean 27.2 UN	UN	96.64 ± 5.1 UN 95.21 ± 4.77 UN	193.45 ± 6.6 123.78 ± 15.12 196.33 ± 9.93 137.1 ± 16.98	54.11 ± 5.89 114.58 ± 11.33 53.33 ± 9.67 115.58 ± 9.9

Abbreviations: BMI, body mass index; cm, centimeter; DBP, diastolic blood pressure; eTRE, early time-restricted eating; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MS, metabolic syndrome; mTRE, mid-day time-restricted eating; NAFLD, nonalcoholic fatty liver disease; non-TRE, nontime-restricted eating; SBP, systolic blood pressure; TC, total cholesterol; TRE, time-restricted eating; TG, triglycerides; UN, unknown; WC, waist circumference.

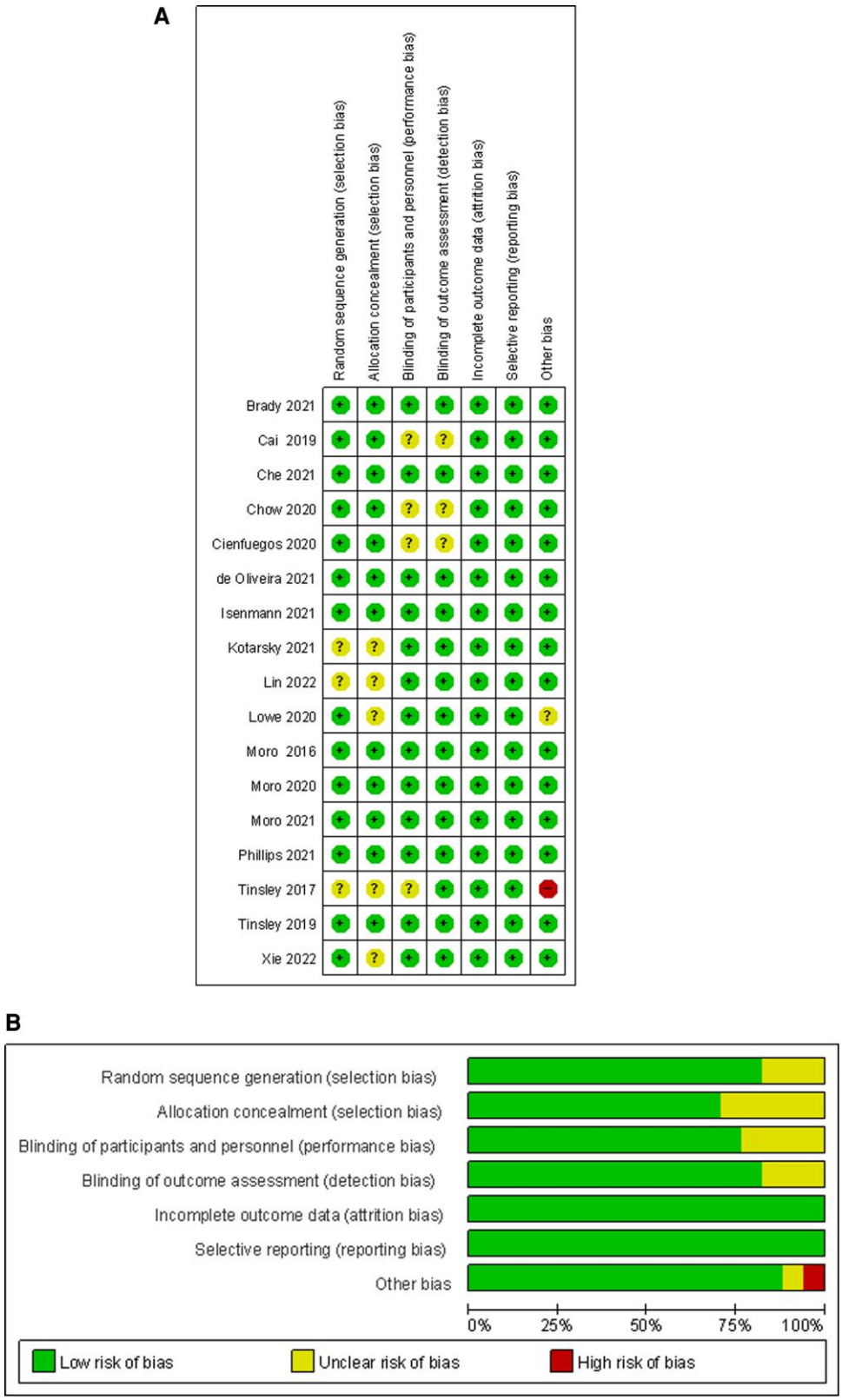

Figure 2. Risk of bias assessment. (A) Summary of risk of bias. (B) Quality assessment percentages in the meta-analysis.

−18.01 to 0.73) ($I^2 = 97.0\%$). However, subgroup analysis found significantly decreased TG in overweight participants (BMI ≥ 25 kg/m^2 and < 30 kg/m^2) with a WMD of −12.71 mg/dL (95% CI −24.90 to −0.52) ($I^2 = 97.5\%$) ($P = .041$), and there were no significant reductions in TG in obesity (BMI ≥ 30 kg/m^2) and lean (BMI < 25 kg/m^2) subjects (Fig. 7A). No publication bias was found (Egger's test: $P = .301$) (Fig. S1C (32)).

TC was reported in 10 studies (26, 29, 38, 39, 41–44, 46, 48) with 587 cases. Lower TC was significant in the TRE group compared with the control (WMD −6.10 mg/dL, 95%

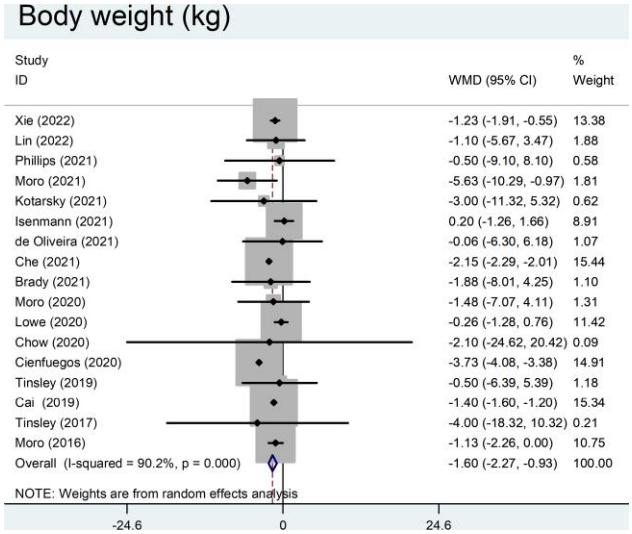

Figure 3. Effects of time-restricted eating on body weight vs controls.

CI −7.86 to −4.34) ($P < .001$), and the heterogeneity was low ($I^2 = 4.6\%$). According to the mean baseline BMI, we performed subgroup analysis and found that TRE tended to decrease TC in overweight participants (BMI ≥ 25 kg/m^2 and < 30 kg/m^2) with a WMD of −6.45 mg/dL (95% CI −7.40 to −5.49) ($I^2 = 0\%$) ($P < .001$). In the subgroups with BMI < 25 kg/m^2 and BMI ≥ 30 kg/m^2, we found no evidence of TRE having an efficacy on TC with WMD −5.15 mg/dL (95% CI −16.48 to 6.18) ($P = .373$) and WMD −4.53 mg/dL (95% CI −17.58 to 8.52) ($P = .496$) separately (Fig. 7B). Publication bias was low (Egger's test: $P = .09$) (Fig. S1D (32)).

Ten (26, 29, 39, 41–43, 46, 48, 50, 51) and 12 (26, 28, 29, 39, 41–44, 46, 48, 50, 51) studies reported LDL-C and HDL-C, respectively. The pooled data showed that there were no significant beneficial effects of TRE on either LDL-C (WMD −3.63 mg/dL, 95% CI −8.05 to 0.78) ($P = .107$) or HDL-C levels (WMD 0.75 mg/dL, 95% CI −0.73 to 2.24) ($P = .319$). However, subgroup analysis found that TRE reduced LDL-C levels (WMD −7.0 mg/dL, 95% CI −9.74 to −4.25) ($P < .001$) in overweight participants with BMI ≥ 25 kg/m^2 and <30 kg/m^2(Fig. 7C and 7D). There was no publication bias in either LDL-C (Egger's test: $P = .41$) or HDL-C (Egger's test: $P = .34$) (Fig. S1E and 1F (32)).

Efficacy of TRE on HOMA-IR

Eight enrolled RCTs (29, 40–43, 46, 50, 51) assessed the change of HOMA-IR between the TRE and non-TRE groups. Pooled data showed significantly improved HOMA-IR by WMD −0.39 (95% CI −0.64 to −0.13) ($I^2 = 95.1\%$) ($P = .003$) in the TRE arm compared with non-TRE. There was no significant publication bias in this analysis and the Egger's test P value was .86 (Fig. S1G (32)). We performed subgroup analysis based on study duration and the results showed noteworthy improved HOMA-IR in the long-term duration of intervention with WMD −0.31 (95% CI −0.45 to −0.17) ($I^2 = 79.4\%$) ($P < .001$), but not in the subgroup of short-term study duration (Fig. 8A). We also performed subgroup analysis based on BMI and found significant alleviated HOMA-IR in overweight participants (BMI ≥ 25 kg/m^2 and < 30 kg/m^2) with WMD −0.27 (95% CI −0.45 to −0.1) ($I^2 = 89.8\%$) ($P = .002$). However, we did not find improved HOMA-IR in normal or obese cases (Fig. 8B).

Table 2. Subgroup analysis of body weight and fat mass

Outcomes of interest	Studies, no.	WMD (95% CI)	Study heterogeneity I^2, %
Body weight (kg)	17	−1.60 (−2.27 to −0.93)	90.2
Fasting to eating ratio			
12:12	2	−0.21 (−5.26 to 4.84)	0
14:10	1	−2.15 (−2.29 to −2.01)	
16:08	12	−1.16 (−1.52 to −0.80)	13.3
18:06	1	−3.3 (−3.66 to −2.94)	
20:04	2	−3.3 (−3.67 to −2.93)	0
Mean baseline BMI			
BMI < 25 kg/m^2	4	−1.23 (−1.90 to −0.56)	0
BMI ≥ 25 kg/m^2 and <30 kg/m^2	8	−1.43 (−2.05 to −0.81)	84.9
BMI ≥ 30 kg/m^2	4	−1.73 (−4.76 to 1.29)	92.7
Study duration			
<12 weeks	9	−1.91 (−3.47 to −0.36)	85.4
≥12 weeks	8	−1.29 (−1.96 to −0.61)	87.7
Fat mass (kg)	13	−1.48 (−1.59 to −1.38)	32
Fasting to eating ratio			
16:08	11	−1.09 (−1.47 to −0.72)	43.1
18:06	1	−0.80 (−1.05 to −0.55)	
20:04	2	−2.2 (−2.48 to −1.91)	0
Mean baseline BMI			
BMI < 25 kg/m^2	4	−0.94 (−1.33 to −0.54)	0
BMI ≥ 25 kg/m^2 and <30 kg/m^2	5	−1.56 (−1.67 to −1.44)	0
BMI ≥ 30 kg/m^2	3	−1.07 (−1.87 to −0.28)	51.7
Study duration			
<12 weeks	8	−1.24 (−1.49 to −0.99)	0
≥12 weeks	5	−1.04 (−1.78 to −0.31)	56.2

Abbreviations: BMI, body mass index; 95% CI, 95% confidence interval; WMD, weighted mean difference.

Efficacy of 16:8 TRE on Metabolic Parameters

Of the enrolled 17 studies, 12 (26, 29, 38–45, 48, 51) were about 16:8 TRE. Subgroup analysis found that 16:8 TRE decreased body weight in both normal and overweight participants with WMD −1.23 kg (95% CI −1.9 to −0.56) (I^2 = 0%) (P < .001) and −1.36 kg (95% CI −1.56 to −1.17) (I^2 = 17.6%) (P < .001), respectively. Consistent with this, fat mass was also lowered both in normal-weight subjects for WMD −0.94 kg (95% CI −1.33 to −0.54) (I^2 = 0%) (P < .001) and overweight cases for WMD −1.46 kg (95% CI −1.81 to −1.11) (I^2 = 12.2%) (P < .001). However, in the subgroup of obese participants, there was neither significant change in body weight with a WMD of −0.26 kg (95% CI −1.28 to 0.75) (I^2 = 0%) (P = .611) nor fat mass with WMD −0.48 kg (95% CI −1.34 to 0.38) (I^2 = 0%) (P = .274). In short-term or long-term intervention of 16:8 TRE, there were significant reduced body weight and fat mass. Compared with control, 16:8 TRE lowered BMI with WMD −0.27 kg/m^2 (95% CI −0.53 to −0.11) (I^2 = 0%) (P = .042), SBP with WMD −2.92 mmHg (95% CI −5.58 to −0.25) (I^2 = 30.8%) (P = .032), and TC with WMD −4.45 mg/dL (95% CI −8.12 to −0.78) (I^2 = 27%) (P = .02). However, there were no significant changes in WC, fasting blood glucose, HbA1c, DBP, TG, LDL-C, HDL-C, and HOMA-IR (Table S1 (32)).

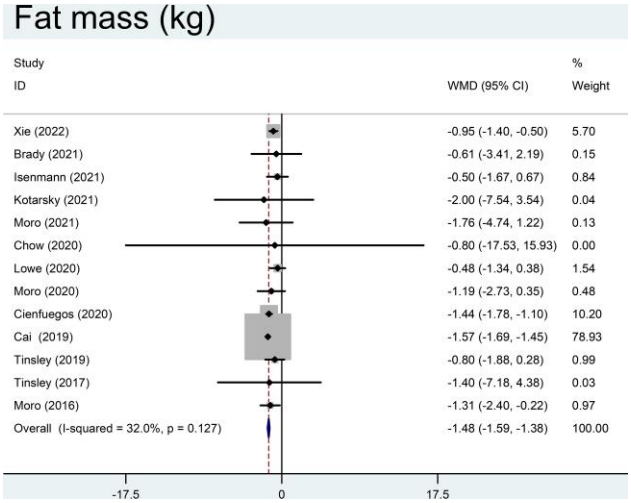

Figure 4. Effects of time-restricted eating on fat mass vs controls.

Discussion

This systematic review and meta-analysis, which included 17 RCTs enrolling 899 participants, has shown that TRE significantly reduced body weight, decreased fat mass, improved fasting blood glucose, HOMA-IR, and changed lipid profiles when compared with the non-TRE group. However, TRE did not lower WC, BMI, HbA1c, or blood pressure. These data suggest that TRE may be an effective strategy to improve certain metabolic states in adults and may reduce the risk of atherosclerotic cardiovascular disease.

This meta-analysis suggested that TRE was an effective approach for reducing body weight. However, this finding is inconsistent with the result of a previous meta-analysis showing that TRE did not significantly reduce body weight compared with the control (30).The small sample size of RCTs in the latter study might be mainly responsible for this inconsistency. However, the latter study reported beneficial metabolic effects of TRE compared with baseline. Our subgroup analysis showed that weight loss was significant in normal and overweight participants butt not in cases of obesity. Five (26, 42, 44–46) studies showed 3.5% ~ 5% mean weight loss in overweight participants and 4 (38–41) studies showed 1% ~ 2% mean weight loss in normal BMI participants. Guidelines (52) have recommended that meaningful clinical benefits can be obtained in modest (3-5%) weight loss. Consistently, we found that overweight individuals benefitted from TRE, with significantly reduced body weight and improved metabolic parameters. Though weight loss of normal BMI subjects did not reach the level of meaningful clinical benefits, they might still benefit from fewer body weight gains and protect themselves from getting overweight. There were 4 studies (29, 49–51) involving 223 obese participants. Only a study by Cienfuegos et al (50), which involved 49 cases, has shown a change in body weight when compared with baseline. The other 3 studies showed significant differences in body weight between the pre- and post-TRE groups, but no change was observed when compared with the non-TRE group. The no significant weight loss of obese people on TRE on can be partly explained by the fewer studies. Two (50, 51) of the 4 studies involved in obesity showed that TRE lowered mean body

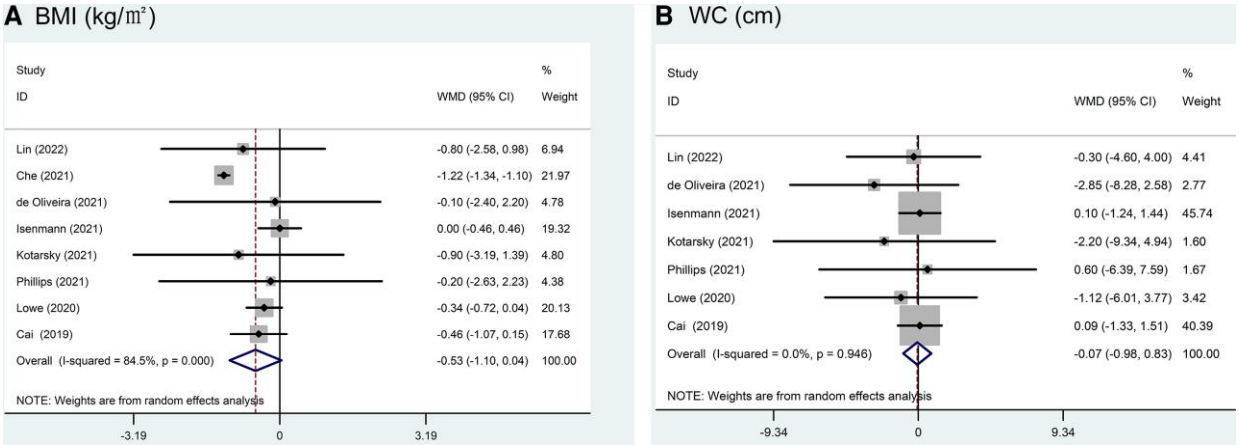

Figure 5. Effects of time-restricted eating on (A) body mass index (BMI), and (B) waist circumference (WC).

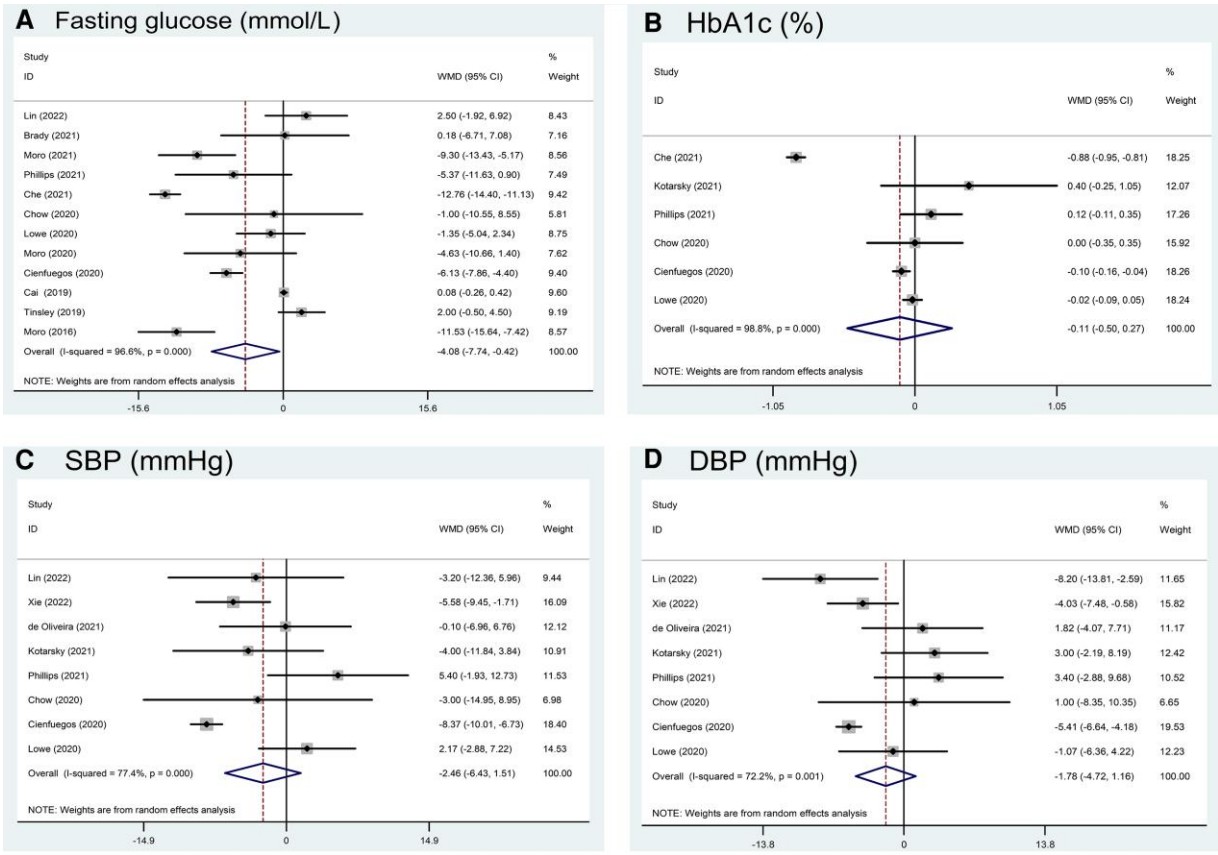

Figure 6. Effects of time-restricted eating on (A) fasting blood glucose, (B), glycosylated hemoglobin (HbA1c), (C) systolic blood pressure (SBP), and (D) diastolic blood pressure (DBP).

weight by 3.6% ~ 3.8%, and the other 2 (29, 49) studies showed less than 1% mean body weight loss. The benefits of TRE on obesity might be offset by the combination of opposing data. Overall, in the subgroup of obese participants, the heterogeneity was high, so the results should be interpreted with caution. Furthermore, subgroup analysis based on the fasting to eating ratio has indicated that TRE seemed to have significant beneficial effects on body weight if the fasting window is 14 hours or more (26, 40, 42, 45, 47, 49). It is interesting to note that significantly reduced body weight and fat mass were seen both in subgroups of the short-term and long-term study duration. Considering the longest study duration of our included RCTs was 12 months, there is a need to perform more trials with longer duration of follow-up in the future to confirm the effects of study duration on body weight.

Although body weight was reduced after intervention with TRE, WC and BMI did not show significant changes. This might be due to the small number of reported studies, or because body weight but not WC or BMI is the most sensitive metabolic related parameter. Our study also found that TRE played an important role in decreasing fat mass regardless of baseline BMI. Although fat mass had significant publication bias, the trim-and-fill method showed the same beneficial effect of TRE on fat mass. Thus, TRE did play a part in reducing fat mass. This result is consistent with a previous meta-analysis by Moon et al (30).

Of the enrolled 17 studies, only 1 (41) refers to early TRE, 13 (26, 29, 39–45, 47, 48, 50) were about late TRE, 1 (51) was not sure due to a self-selected 8-hour eating window for ad libitum intake, and 3 (28, 46, 49) refer to broader TRE, which includes breakfast and dinner, so it is not suitable to perform subgroup analysis of early and late TRE. Interestingly, a very recent RCT reported that, compared with non-TRE plus energy restriction, early TRE plus energy restriction can improve metabolic parameters such as body weight, fat mass, WC, blood pressure, glucose, and HOMA-IR (53). Therefore, it is important to perform more RCTs in the future to confirm the effects of early TRE on the metabolism.

Regarding glycemic profiles, we found that TRE has significantly reduced fasting blood glucose, while changes in HbA1c did not differ between groups. Our meta-analysis did not find evidence that TRE had improved blood pressure. This may be because most included participants had normal HbA1c and blood pressure at baseline. Moreover, the intervention duration of most studies that reported HbA1c was shorter than 12 weeks, which is not sufficient to show an obvious change. Subgroup analysis found that HOMA-IR was significantly improved in overweight but not in normal-weight or obese participants. What is more, in the subgroup of study duration no less than 12 weeks, TRE lowered HOMA-IR compared with control, indicating that TRE could improve insulin sensitivity in overweight patients with long-term intervention. However, since the heterogeneity between groups was high, more relevant large sample studies in the future are needed to confirm the effects of TRE on HOMA-IR.

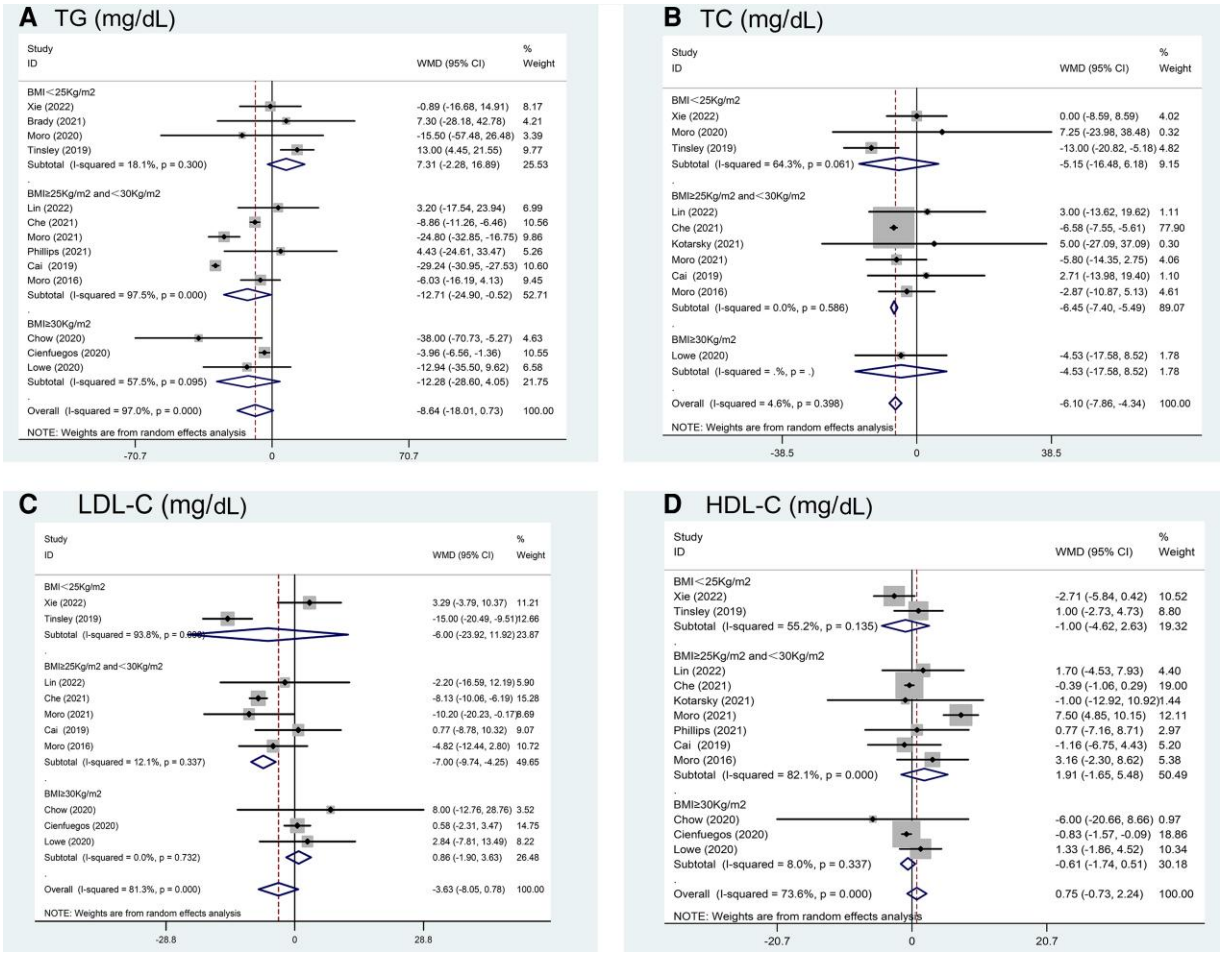

Figure 7. Effects of time-restricted eating on lipid profile versus controls. (A) triglycerides (TG); (B) total cholesterol (TC); (C) low-density lipoprotein cholesterol (LDL-C); (D) high-density lipoprotein cholesterol (HDL-C).

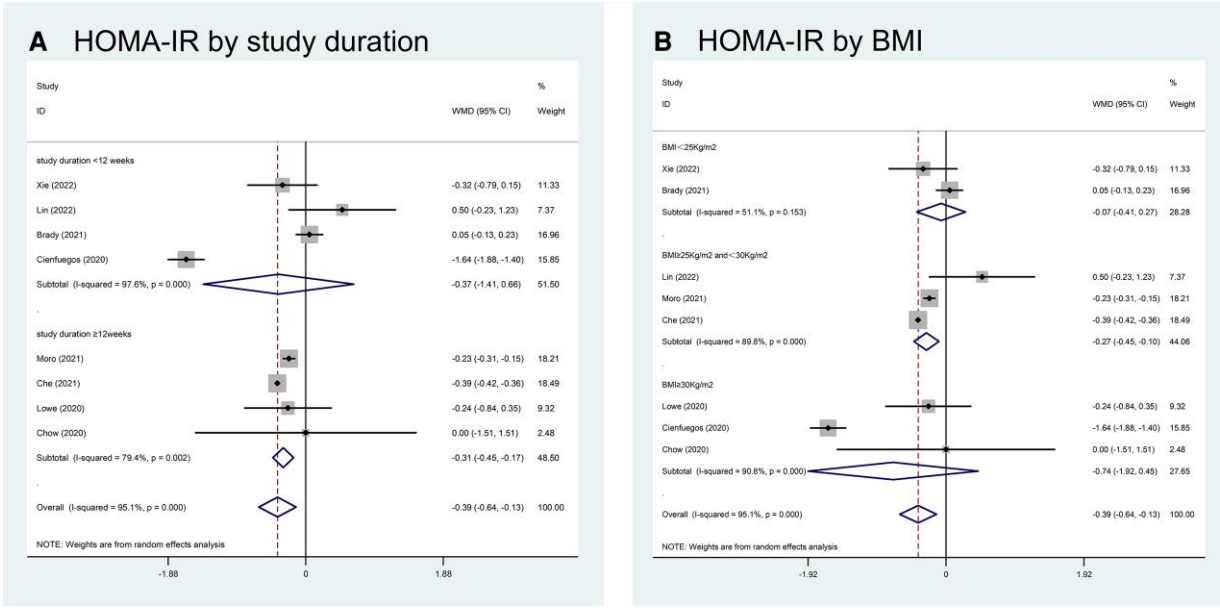

Figure 8. Effects of time-restricted eating on homeostatic model assessment of insulin resistance (HOMA-IR).

Additionally, significantly decreased TC, TG, and LDL-C but not HDL-C levels were observed in overweight participants between TRE and non-TRE groups, indicating alleviated hyperlipidemia. However, except reduced fat mass, all metabolic parameters showed no significant changes in obese participants. This suggests that TRE, without caloric

restriction, may be a mild strategy to combat obesity. In line with this notion, a very recent study showed that calorie restriction with TRE successfully lowered body weight, fat mass, and improved other metabolic parameters in patients who are obese (54). However, calorie restriction with or without TRE had similar effects on weight reduction, indicating that TRE might have no more beneficial effects on metabolic parameters than daily calorie restriction in obese participants (54).

It is well known that most organisms have intrinsic circadian rhythms. Disturbances in circadian rhythms can cause physiological imbalances, metabolic abnormalities, and cardiovascular diseases (19, 20), manifesting morbid conditions and diseases such as sleep disorders (55), obesity (56, 57), diabetes (58), and cancer (59). Accumulating studies have shown that the circadian system can regulate energy expenditure, and glucose and lipid metabolism (60). Animal studies have found that TRE protected the whole body clock gene *Cry1*/*Cry2* or liver-specific Bmal1 knockout mice from high-fat diet induced obesity and metabolic disorders (61). Studies have also shown that the synchronicity of the eating/fasting cycle and light/dark circadian rhythm might have important influences on metabolic regulation pathways and the efficiency of weight loss (62). The above data suggested that the beneficial effects of TRE may be due to reinforced and strengthened circadian rhythms.

To date, this meta-analysis is the most comprehensive study to utilize RCTs to explore the benefits of TRE on weight loss and other metabolic parameters. In 2019, Pellegrini et al (63) and his team conducted a meta-analysis of 5 RCTs and 6 observational studies investigating the efficacy of TRE on body weight and metabolism. The authors concluded that TRE promotes short term weight loss. In 2020, Moon et al (30) performed a meta-analysis of 19 studies to explore the efficacy of TRE on metabolism. They found that, compared with baseline, TRE had beneficial effects on body weight, fat mass, fasting blood glucose, and TGs. However, when compared with the non-TRE group, TRE only decreased fat mass without influencing other metabolic parameters. This may be due to the different types of studies, which included 11 RCTs, 2 non-RCTs, 1 historically controlled trial, and 5 trials with 1 group pretest–post-test design. Our study provided an updated overview, and our meta-analysis only included RCTs with the highest level of evidence.

There are several strengths of our meta-analysis. First, we used multiple strategies to search the latest literature and identify eligible studies. Additionally, we performed subgroup analysis using the fasting window of TRE and the mean baseline BMI of the enrolled participants to explore methodological and statistical heterogeneity. Moreover, the included studies were all RCTs of high quality, which might help to minimize the risk of bias. Finally, clinicaltrials.gov was searched for more detailed information to ensure the accuracy of the extracted data.

However, there are some limitations in our meta-analysis. First, the included studies had a large variation in sample size ranging from 16 to 174 participants. Second, the blinding of participants is impossible due to the nature of behavioral interventions by a fixed ratio of fasting and eating periods. However, this appears unlikely to influence the results we were interested in as they were all measured objectively. Third, the inclusion of only RCTs may have resulted in selection bias. Fourth, some of our results showed high heterogeneity. There were some reasons for the heterogeneity, such as the different numbers of participants, different ratios of fasting and eating duration, and different baseline conditions of the participants. The great heterogeneity implies that more studies are necessary to confirm our study conclusion. Finally, we excluded some studies due to the unavailability of original data about outcomes of interest, which may contribute to inaccuracy of the risk bias estimates.

Conclusions

In summary, the available evidence indicated that TRE could decrease body weight, fat mass, fasting blood glucose, HOMA-IR, and the lipid spectrum of TG, TC, and LDL-C, especially in overweight participants. The 16:8 TRE could reduce body weight and fat mass both in normal-weight and overweight participants. TRE may be an effective approach to improve metabolic state of nonobese subjects, especially in overweight participants. Further studies with greater power are warranted to confirm the impact of TRE on metabolic parameters.

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Author Contributions

F.H. and L.L. designed the study. L.L. and W.C. searched the library, reviewed and selected studies, and performed data extraction. L.L. wrote the manuscript. D.W. and W.C. assisted in manuscript revision. F.H. took full responsibility for the integrity and accuracy of the data. All authors approved the manuscript.

Disclosures

The authors have nothing to disclosure.

Data Availability

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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