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Effects of Time-Restricted Eating with Different Eating Duration on Anthropometrics and Cardiometabolic Health: A Systematic Review and Meta-Analysis.

Zaman MK *et al.* TRE on Cardiometabolic Health: Meta-analysis

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Abstract

BACKGROUND

Time-restricted eating (TRE) is a dietary approach that limits eating to a set number of hours per day. Human studies on the effects of TRE intervention on cardiometabolic health have been contradictory. Heterogeneity in subjects and TRE interventions have led to inconsistency in results. Furthermore, the impact of the duration of eating/fasting in the TRE approach has yet to be fully explored.

AIM

This study aims to analyze the existing literature on the effects of TRE with different eating durations on anthropometrics and cardiometabolic health markers in adults with excessive weight and obesity-related metabolic diseases.

METHODS

We reviewed a series of prominent scientific databases, including Medline, Scopus, Web of Science, Academic Search Complete, and Cochrane Library articles to identify

published clinical trials on daily time-restricted eating in adults with excessive weight and obesity-related metabolic diseases. RCTs were assessed for methodological rigor and risk of bias using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB-2). Outcomes of interest include body weight, waist circumference, fat mass, lean body mass, fasting glucose, insulin, HbA1c, HOMA-IR, lipid profiles, C-reactive protein, blood pressure, and heart rate.

RESULTS

Fifteen studies were included in our systematic review. TRE significantly reduces body weight, waist circumference, fat mass, lean body mass, blood glucose, insulin, triglyceride, LDL-C, and heart rate. However, no significant changes were observed in HbA1c, HOMA-IR, total cholesterol, HDL-C, systolic and diastolic blood pressure. Furthermore, subgroup analyses based on the duration of the eating window revealed significant variation in the effects of TRE intervention depending on the length of the eating window.

CONCLUSION

TRE is a promising chrononutrition-based dietary approach for improving anthropometric and cardiometabolic health. However, further clinical trials are needed to determine the optimal eating duration in TRE intervention for cardiovascular disease prevention.

Key Words: Cardiovascular diseases; cardiometabolic health; time-restricted eating; chrononutrition; intermittent fasting; obesity.

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Core Tip: Beneficial effects of time-restricted eating (TRE) on adults with excessive weight and obesity-related metabolic diseases remain under investigation, and results are conflicting. We explored the effectiveness of TRE on anthropometric and cardiometabolic health in adults with excessive weight and obesity-related metabolic diseases. We found that TRE is an effective and sustainable dietary strategy for reducing body weight, body composition, blood glucose, insulin, triglyceride, LDL-C, and heart rate in individuals with excessive weight or weight-related metabolic disorders. Moreover, the meta-analysis demonstrates the varying effects of fasting duration on the outcomes of interest.

INTRODUCTION

The global prevalence of overweight and obesity has become a major public health problem. High body mass was responsible for over five million deaths and 160 million disability-adjusted life years (DALYs) worldwide^[1]. According to the World Health Organization (WHO) reports, the number of overweight and obese individuals has doubled globally since 1980, affecting both developed and developing countries. As a result, weight-related diseases, including obesity and related conditions such as type 2 diabetes, cardiovascular disease, and certain cancers, have become a major public health challenge worldwide and a burden on healthcare systems^[2, 3]. Researchers and healthcare professionals have explored multiple dietary strategies to improve weight and cardiometabolic health and prevent cardiovascular diseases (CVD) through caloric and macronutrient restriction, specific foods or nutrients, adherence to selected dietary patterns, and fasting. Continuous energy restriction (CER) has been frequently used to manage the body weight of individuals with excessive weight^[4]. However, adherence to this diet pattern is challenging due to the daunting task of reducing daily caloric intake^[5]. Additionally, CER may promote adaptive responses such as decreased physical activity, increased hunger, and deactivation of the hypothalamic-pituitary-

thyroid axis, hindering weight and fat loss^[6]. Moreover, CER increases the risk of adverse effects such as hypoglycemia, nutrient deficiencies, and extreme fatigue.

In recent years, intermittent fasting (IF) has emerged as an alternative weight loss and CVD prevention strategy. It refers to a cyclic eating pattern that rotates between periods of abstinence from consuming any caloric-containing food or drinks and periods of eating ^[7]. Current human research indicates that chrononutrition-based dietary interventions, such as time-restricted eating, have gained substantial interest from the public as one of the sustainable strategies for CVD prevention^[8]. Time-restricted eating (TRE) is a lifestyle approach that limits eating duration to a set number of hours per day (typically within 4–12 h) during waking hours, allowing for adequate fasting^[9, 10]. Time-restricted eating aims to align dietary intake with daily circadian rhythms. It is considered a more sustainable approach than caloric restriction, as it involves lower-intensity adaptation for long-term lifestyle modifications to reduce weight^[8]. Animal studies have linked TRE to lower body weight, total cholesterol, triglycerides, glucose, insulin, interleukin-6, tumor necrosis factor, and improved insulin sensitivity^[11-13].

The effects of TRE with different eating durations, ranging from four to 12 h, have been studied on humans ^[14]. These studies have reported varying results, with some showing improvements in weight loss, insulin sensitivity, and cardiovascular markers, while others exhibiting no significant changes. Several recent systematic reviews have been conducted to review the effects of TRE interventions on anthropometric and cardiometabolic health^[15-23]. The most consistent findings from these reviews were significant weight reduction with TRE intervention, with mixed results for the TRE effects on cardiometabolic health. This inconsistency is mainly due to heterogeneity in subjects and the implemented TRE interventions.

Additionally, combining results from individuals with normal BMI and those with metabolic dysregulation may obscure differences in the effectiveness of the intervention. To our knowledge, no systematic review has evaluated the effects of variation in TRE's eating duration on anthropometric and cardiometabolic health.

Therefore, this systematic review and meta-analysis aimed to examine the effects of varying eating durations in TRE interventions on body weight and composition, waist circumference, biomarkers of glucose metabolism, lipid metabolism, inflammatory marker, blood pressure, and heart rate in adults with excessive weight and obesity-related metabolic diseases. The findings of this review will shed light on the overall effectiveness of TRE and its optimal eating duration as a potential dietary approach for weight loss and improved cardiometabolic health in individuals with excessive weight and obesity-related metabolic diseases.

MATERIALS AND METHODS

Protocol and registration

This systematic review was reported according to the updated version of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement^[24]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (<http://www.crd.york.ac.uk/PROSPERO>), with a record number of CRD42022341232. Before conducting the review, PROSPERO and the Cochrane Library were searched to identify existing or ongoing similar work by other researchers.

Search strategy

Multiple electronic databases were queried using selected search terms until May 2022. MEDLINE Complete, Web of Science, Scopus, the Cochrane Library, Academic Search Complete, Food Science Source, OpenDissertations, Education Research Complete, and Psychology and Behavioural Sciences Collection were used for the systematic search (Supplementary Table 1). The search strategy was tailored to each database's keywords to identify literature for the intervention of interest, time-restricted eating. The search terms included "time-restricted diet" OR "time-restricted eating" OR "time-restricted feeding" OR "time-restricted fasting" OR "time-restricted meal", which have been identified in previous systematic reviews ^[19, 21, 22]. The search was not limited to specific

years of publication or languages, and no additional terms were used to avoid filtering out relevant literature. All search outputs were exported to reference manager software (Endnote 20; endnote.com). After removing duplicates, two independent reviewers screened the articles for eligibility based on title, abstract, and full text (Zaman MK and Teng NIMF). A consensus was reached for included articles through discussions after each screening round, and a third reviewer resolved any disagreements (Juliana N).

Study selection

The eligibility criteria for this systematic review were based on the predetermined inclusion and exclusion criteria. We included studies with the following characteristics: (1) Population: adults with excess weight and obesity-related metabolic diseases; (2) Intervention: time-restricted eating, which involves daily (seven days per week) eating window restriction; (3) Comparator: the comparator accepted for this study were dietary intake with ad libitum eating window or eating window of 12 h or more; (4) Outcomes: changes in body weight, waist circumference, fat mass, lean body mass, fasting glucose, insulin, HbA1c, HOMA-IR, lipid profile (total cholesterol (TC), HDL-C, LDL-C, and triglycerides), inflammatory markers, blood pressure (systolic and diastolic), and heart rate were identified as outcomes of interest—studies with any reported outcomes of interest were included; (5) Study design: only controlled/clinical trials with at least one outcome measurement performed within two weeks to 6 mo of intervention commencement were included in this review.

We excluded studies based on the following characteristics: (1) Population: studies involving subjects younger than 18 years of age, animal models, or studies including adult subjects with normal body mass index (BMI) were excluded; (2) Intervention: studies with intermittent time-restricted eating (e.g., ad libitum dietary intake during selected days) were excluded ; (3) Study design: abstracts, and non-original articles such as expert opinions and reviews were excluded from this systematic review.

Risk of bias assessment

Risk of bias (RoB) assessments of the included studies were conducted and graded using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB-2)^[25]. This tool evaluates the risk of bias across five key domains: randomization process, deviation from intended interventions, missing outcome data, outcome measurement, and selection of reported results. Trials were classified as having either low risk, unclear risk, or high risk of bias for each domain and overall. Two reviewers were involved independently in the risk of bias assessments of the included studies (Zaman MK and Teng NIMF). Disagreements were resolved through consensus or discussion with a third reviewer (Kasim SS).

Data extraction

Data collection forms were used to extract data from each study. The extraction form was piloted in at least one study included in this review. Two reviewers were involved in the data extraction from included studies (Zaman MK and Teng NIMF). Data extracted include: 1. Information of the trial: authors, publication year, study design, sample size, and study duration; 2. Study participants: population characteristics, location, age, gender, and body mass index (BMI); 3. Intervention characteristics: description of intervention and control arm, eating window, and timing of intervention; 5. Outcome measures: body weight, waist circumference, fat mass, lean body mass, fasting glucose, insulin, HbA1c, HOMA-IR, lipid profile (TC, HDL-C, LDL-C, and triglycerides), C-reactive protein, blood pressure (systolic and diastolic), and heart rate.

Data synthesis and analysis

Standardized mean differences, or mean differences with 95% confidence intervals (CI), were used to report intervention effects for each study based on pre-and post-TRE intervention. Meta-analyses were conducted, if feasible, using a minimum of two included studies with similar outcomes for each outcome of interest. Forest plots were constructed for all studies included in the meta-analysis. A two-sided P value of <0.05

was considered statistically significant. The heterogeneity was evaluated statistically using the I^2 statistic, with a value greater than 50% indicating substantial heterogeneity. The random-effects model was employed when substantial heterogeneity was present. Publication bias was examined using a funnel plot visualization for outcomes with ten or more studies. Considering the heterogeneity protocol and duration of the eating window in TRE intervention, subgroup analyses were performed by applying a different range of TRE duration. All analyses were conducted using RevMan software, version 5.4.

RESULTS

Search results

The systematic search process identified 2067 articles (Figure 1) from multiple resources, including Medline ($n = 425$), Scopus ($n = 567$), Web of Science ($n = 483$), Academic Search Complete ($n = 224$), Cochrane Library ($n = 216$), Food Science Source ($n = 126$), OpenDissertations ($n = 10$), Education Research Complete ($n = 9$), and Psychology and Behavioural Science collection ($n = 7$). After removing duplicates, 829 records were screened, and 51 were assessed for eligibility after excluding articles not meeting the inclusion criteria. Further screening and quality assessment resulted in 15 studies being selected for the systematic review and meta-analysis, involving 927 subjects^[26-40]. The largest study recruited 139 subjects, while the smallest enrolled eight subjects^[32, 39]. Most studies were conducted in the United States of America ($n = 7$), followed by Brazil ($n = 3$), China ($n = 3$), Switzerland ($n = 1$), and Germany ($n = 1$).

Study characteristics

Table 1 displays the characteristics of the participants in the included studies. The participants were adults with overweight/obesity, prediabetes, or Type 2 Diabetes Mellitus. The participants ranged from 27 to 74 years old^[26, 30], with a BMI above the normal cut-off, ranging from 26.4 to 38.9 kg/m². The majority of the included studies were parallel-arms randomized controlled trials (RCT) ($n = 13$), cross-over randomized

controlled trials (RXT) ($n = 1$), and non-randomized controlled trials (NRCT) ($n = 1$). All studies involved an intervention group with a TRE regimen and a comparator group with an unrestricted time of food intake. The interventions were conducted over three weeks to twelve months, with the fasting period lasting between 12 and 20 h per day and the eating period lasting from four to 12 h daily. The timing of the start of the fasting period was either self-selected by participants or predetermined by the study (Table 1). Most TRE interventions in the included studies restricted food intake during the day, with the last meal completed by 20:00^[27, 29-34, 37-39].

Risk of bias assessment

The risk of bias assessments for the RCTs is summarized in Figure 2. Overall, seven studies posed a high risk of bias^[30-33, 35, 38, 40], and eight studies posed concerns regarding the overall risk of bias^[26-29, 34, 36, 37, 39]. In the domain of the randomization process, all included studies were identified as randomized studies except for one. Ten studies had limited or no information on randomization and concealment, leading to concerns in the domain of the randomization process^[28-34, 37, 38, 40]. Due to the nature of the intervention of interest, blinding participants may not be feasible. Information on blinding of the participants, carers, and personnel assessing in the laboratory or statistical analyses was often unknown or limited, introducing possible risk due to deviations from the intended intervention. Most studies showed a low risk of bias due to missing outcome data ^[26-29, 31-34, 36, 37, 40] and outcomes measurement^[26-37, 39, 40]. In the domain of selection of the reported result, most studies were classified as posing concern^[26-30, 36-39] or high risk ^[31-33, 35, 40] due to the limited availability of a prespecified analysis plan (i.e., protocol) or/and missing outcomes measurement.

Effects of TRE on weight and body composition

Body weight:

A total of 15 studies were included in the analysis to assess the effect of TRE on body weight (kg) (Figure 3). ¹ Individuals assigned to the TRE intervention showed a

significant reduction in body weight levels compared to the comparator group (MD -2.26; 95%CI [-3.10, -1.43], $p < 0.00001$; $I^2 = 93\%$). Random-effects subgroup analysis was conducted based on the duration of TRE intervention revealed no significant changes in body weight in TRE intervention ranging from ten to 12 h (MD -1.11; 95%CI [-2.31, 0.10], $p = 0.07$; $I^2 = 84\%$). Meanwhile, a significant reduction was observed in TRE intervention ranging from seven to nine hours (MD -2.36; 95%CI [-4.37, -0.35], $p = 0.02$; $I^2 = 79\%$) and TRE intervention ranging from four to six hours (MD -3.85; 95%CI [-4.29, -3.41], $p < 0.00001$; $I^2 = 58\%$).

Waist circumference:

A meta-analysis of nine studies demonstrated a significant overall effect of TRE on waist circumference reduction compared to 261 subjects in the comparator group (MD -2.35; 95%CI [-4.43, -0.27], $p = 0.03$; $I^2 = 81\%$) (Figure 4). Random-effects subgroup analyses were conducted based on the duration of TRE intervention showed no significant changes in waist circumference following TRE intervention ranging from ten to 12 h (MD -1.11; 95%CI [-2.83, 0.60], $p = 0.20$; $I^2 = 0\%$). However, a significant reduction in waist circumference was observed in TRE intervention ranging from seven to nine hours (MD -2.70; 95%CI [-5.24, -0.17], $p = 0.04$; $I^2 = 84\%$). The effect of TRE ranging from four to six hours on the measured outcome was not reported in any of the included studies.

Total fat mass:

A meta-analysis of ten studies evaluated the effect of TRE on total fat mass. ¹ Individuals assigned to TRE intervention showed a significant reduction in total fat mass levels compared to the comparator group (SMD -0.63; 95%CI [-1.10, -0.17], $p = 0.008$; $I^2 = 83\%$) (Figure 5). Random-effects subgroup analyses were conducted based on the duration of TRE intervention, which revealed a reduction in total fat mass following TRE intervention ranging from ten to 12 h (MD -0.41; 95%CI [-0.75, -0.08], $p = 0.02$; $I^2 = 0\%$). However, no significant change was observed in TRE intervention ranging from seven

to nine hours (MD -0.13; 95%CI [-0.35, 0.09], $p = 0.25$; $I^2 = 0\%$), while a significant reduction was observed in TRE intervention ranging from four to six hours (MD -3.73; 95%CI [-6.76, -0.70], $p = 0.02$; $I^2 = 91\%$).

Lean body mass:

A meta-analysis of nine studies was included to evaluate the effect of TRE on lean body mass. Individuals assigned to TRE intervention showed a significant overall reduction in lean body mass compared to the comparator group (MD -0.64; 95%CI [-1.11, -0.16], $P = 0.009$; $I^2 = 75\%$) (Figure 6). Random-effects subgroup analyses were conducted based on the duration of TRE intervention demonstrated no significant changes in lean body mass following TRE interventions ranging from seven to nine hours (MD -0.23; 95%CI [-0.90, 0.43], $P = 0.49$; $I^2 = 0\%$). Significant reduction in lean body mass was observed in the TRE intervention group compared to the comparator following TRE intervention ranging from four to six hours (MD -0.86; 95%CI [-1.54, -0.17], $P = 0.01$; $I^2 = 96\%$). Subgroup analysis for TRE intervention ranging from ten to 12 h was not calculated since only one study reported this outcome.

Effects of TRE on biomarkers of glucose metabolism.

Glucose:

A meta-analysis of eleven studies reported a significant overall effect of TRE on glucose levels reduction compared to the comparator group (MD -4.13; 95%CI [-6.98, -1.28], $P = 0.005$; $I^2 = 89\%$) (Figure 7). Random-effects subgroup analyses were conducted based on the duration of TRE intervention showed no significant changes in glucose levels following TRE intervention ranging from ten to 12 h (MD -5.91; 95%CI [-13.29, 1.48], $P = 0.12$; $I^2 = 82\%$). However, a significant reduction was reported in TRE intervention ranging from seven to nine hours (MD -2.20; 95%CI [-3.64, -0.77], $P = 0.003$; $I^2 = 0\%$) and TRE intervention ranging from four to six hours (MD -5.79; 95%CI [-8.18, -3.41], $P = 0.00001$; $I^2 = 54\%$).

HbA1c:

A meta-analysis of six studies revealed the effect of TRE on HbA1c. There was no significant difference in HbA1c levels between the test and comparator groups (MD -0.12; 95%CI [-0.46, 0.21], $P = 0.47$; $I^2 = 99\%$) (Figure 8). Random-effects subgroup analyses were conducted based on the duration of TRE intervention demonstrated no significant changes in HbA1c following TRE intervention ranging from ten to 12 h (MD -0.27; 95%CI [-0.96, 0.42], $P = 0.45$; $I^2 = 99\%$) and TRE intervention ranging from seven to nine hours (MD 0.09; 95%CI [-0.28, 0.47], $P = 0.63$; $I^2 = 0\%$). However, a significant reduction was reported in TRE intervention ranging from four to six hours.

HOMA-IR:

A meta-analysis of seven studies reported the effect of TRE on HOMA-IR. There was no significant difference in HOMA-IR levels compared to the comparator group (MD -0.24; 95%CI [-0.52, 0.05], $P = 0.10$; $I^2 = 76\%$) (Figure 9). Random-effects subgroup analyses were conducted based on the duration of TRE intervention showed no significant changes in HOMA-IR following TRE intervention ranging from ten to 12 h (MD -0.21; 95%CI [-0.58, 0.16], $P = 0.27$; $I^2 = 96\%$) and TRE intervention ranging from seven to nine hours (MD -0.32; 95%CI [-0.84, 0.20], $P = 0.23$; $I^2 = 0\%$). Subgroup analysis for TRE intervention ranging from four to six hours was not calculated since it was reported in only one study.

Insulin:

A meta-analysis of eight studies revealed a significant overall reduction of insulin levels with TRE compared to the comparator group (SMD -1.39; 95%CI [-2.54, -0.25], $P = 0.02$; $I^2 = 95\%$) (Figure 10). Random-effects subgroup analyses were conducted based on the duration of TRE intervention showed no significant changes in insulin in TRE intervention ranging from ten to 12 h (MD -1.60; 95%CI [-4.85, 1.65], $P = 0.34$; $I^2 = 99\%$), and TRE intervention ranging from seven to nine hours (MD -0.35; 95%CI [-1.17, 0.47], P

= 0.41; $I^2 = 74\%$). A slight significant reduction was observed in TRE intervention ranging from four to six hours (MD -2.75; 95%CI [-5.49, -0.01], $P = 0.05$; $I^2 = 94\%$).

Effects of TRE on biomarkers of lipid metabolism

Total cholesterol:

A meta-analysis of eight studies evaluated the effect of TRE on total cholesterol. ² There was no significant difference in total cholesterol levels between the test and comparator groups (MD 4.08; 95%CI [-4.73, 12.89], $P = 0.36$; $I^2 = 75\%$) (Figure 11). Random-effects subgroup analyses were conducted based on the duration of TRE intervention showed a significant reduction in total cholesterol following TRE intervention ranging from ten to 12 h (MD -5.63; 95%CI [-9.86, -1.39], $P = 0.009$; $I^2 = 31\%$). Meanwhile, a significant reduction was observed in the comparator group following TRE intervention ranging from seven to nine hours (MD 9.38; 95%CI [0.59, 18.18], $P = 0.04$; $I^2 = 22\%$). Subgroup analysis for TRE intervention ranging from four to six hours was not calculated since it was reported only in one study.

Triglycerides:

A meta-analysis of ten studies evaluated the effect of TRE on triglycerides (Figure 12). Individuals assigned to TRE intervention exhibited significantly reduced triglyceride levels compared to the comparator group (MD -15.79; 95%CI [-28.93, -2.66], $P = 0.02$; $I^2 = 97\%$). Random-effects subgroup analyses were conducted based on the duration of TRE intervention revealed a significant reduction in triglycerides following TRE intervention ranging from ten to 12 h (MD -27.51; 95%CI [-40.12, -14.90], $p < 0.0001$; $I^2 = 45\%$). However, there were no significant changes observed following TRE intervention ranging from seven to nine hours (MD -21.84; 95%CI [-44.23, 0.55], $P = 0.06$; $I^2 = 56\%$) and TRE intervention ranging from four to six hours (MD -3.85; 95%CI [-8.52, 0.82], $P = 0.11$; $I^2 = 65\%$).

LDL- cholesterol:

A meta-analysis of nine studies evaluated the effect of TRE duration on LDL-C (Figure 13). ¹ Individuals assigned to TRE intervention showed a significant reduction in LDL-C levels compared to the comparator group (MD -3.61; 95%CI [-4.92, -2.30], $p < 0.00001$; $I^2 = 86\%$). Random-effects subgroup analyses were conducted based on the duration of TRE intervention, which showed a significant reduction in LDL-C following TRE intervention ranging from ten to 12 h (MD -7.65; 95%CI [-9.43, -5.88], $p < 0.00001$; $I^2 = 88\%$) and TRE intervention ranging from seven to nine hours (MD 5.98; 95%CI [1.02, 10.94], $P = 0.02$; $I^2 = 0\%$). In contrast, no significant changes were observed in TRE intervention ranging from four to six hours (MD 0.45; 95%CI [-1.68, 2.57], $P = 0.68$; $I^2 = 82\%$).

HDL- cholesterol:

A meta-analysis of ten studies showed no significant overall effect of TRE on HDL-C levels compared to the comparator group (MD -0.17; 95%CI [-1.19, 0.85], $P = 0.74$; $I^2 = 58\%$) (Figure 14). Random-effects subgroup analyses were conducted based on the duration of TRE intervention, which demonstrated no significant changes in HDL-C following TRE intervention ranging from ten to 12 h (MD -0.38; 95%CI [-1.00, 0.24], $P = 0.23$; $I^2 = 0\%$), TRE intervention ranging from seven to nine hours (MD 1.62; 95%CI [-2.48, 5.71], $P = 0.44$; $I^2 = 53\%$), and TRE intervention ranging from four to six hours (MD -0.88; 95%CI [-2.28, 0.52], $P = 0.22$; $I^2 = 75\%$).

Effects of TRE on biomarkers of inflammation

C-reactive protein:

A meta-analysis of three studies evaluated the effect of TRE on C-reactive protein (Figure 15). ² There was no significant difference in C-reactive protein levels between the test and comparator groups (MD -0.35; 95%CI [-1.79, 1.08], $P = 0.63$; $I^2 = 0\%$). No subgroup analysis was conducted due to the limited included studies reporting this outcome.

Effects of TRE on blood pressure and heart rate

Systolic blood pressure:

A meta-analysis of eight studies evaluated the effect of TRE on systolic blood pressure (Figure 16). ¹ There was no significant difference in systolic blood pressure levels between groups (MD -0.87; 95%CI [-1.90, 0.16], $P = 0.10$; $I^2 = 0\%$). Random-effects subgroup analyses were conducted based on the duration of TRE intervention showed no changes in systolic blood pressure following TRE intervention ranging from ten to 12 h (MD 2.08; 95%CI [-1.83, 5.99], $P = 0.30$; $I^2 = 0\%$), TRE intervention ranging from seven to nine hours (MD -1.28; 95%CI [-3.74, 1.18], $P = 0.31$; $I^2 = 0\%$), and TRE intervention ranging from four to six hours (MD -1.04; 95%CI [-2.23, 0.14], $P = 0.08$; $I^2 = 0\%$).

Diastolic blood pressure:

A meta-analysis of eight studies evaluated the effect of TRE on diastolic blood pressure (Figure 17). ² There was no significant difference in diastolic blood pressure levels between the test and comparator groups (MD -1.36; 95%CI [-3.83, 1.11], $P = 0.28$; $I^2 = 83\%$). Random-effects subgroup analyses based on the duration of TRE intervention showed no significant changes in diastolic blood pressure following TRE intervention ranging from ten to 12 h (MD 2.87; 95%CI [-0.79, 6.52], $P = 0.12$; $I^2 = 0\%$) and TRE intervention ranging from seven to nine hours (MD 0.25; 95%CI [-1.56, 2.06], $P = 0.79$; $I^2 = 0\%$). In contrast, there was a significant reduction observed in TRE intervention ranging from four to six hours (MD -5.41; 95%CI [-6.25, -4.57], $p = < 0.00001$; $I^2 = 0\%$).

Heart rate:

A meta-analysis of five studies reported no significant overall effect of TRE on heart rate levels in comparison to the comparator group (MD 0.15; 95%CI [-1.86, 2.15], $P = 0.89$; $I^2 = 67\%$) (Figure 18). Random-effects subgroup analyses based on the duration of TRE intervention showed no significant changes in heart rate following TRE intervention ranging from seven to nine hours (MD -1.00; 95%CI [-3.85, 1.84], $P = 0.49$; $I^2 = 0\%$) and TRE intervention ranging from four to six hours (MD 1.04; 95%CI [-2.06, 4.14], $P = 0.51$; $I^2 = 85\%$). Subgroup analysis for TRE intervention ranging from ten to 12

h was not calculated since only one study reported the outcome for this particular duration.

Funnel plots

The potential publication biases were assessed using funnel plots based on the outcomes of interest (Supplementary Figure 1). The funnel plots were generally symmetric, indicating a low probability of publication bias in most outcomes. However, the glucose outcome showed an asymmetric funnel plot, suggesting a possible publication bias.

DISCUSSION

Adopting intermittent fasting, including time-restricted feeding interventions, to potentially optimize metabolic health by altering the duration of food consumption is a topic of increasing interest in research and others^[41]. The present review analyzed the effects of TRE intervention on anthropometrics and cardiometabolic health markers in adults with excessive weight and obesity-related metabolic diseases. The meta-analysis showed that TRE significantly reduced body weight, waist circumference, fat mass, lean body mass, blood glucose, insulin, triglyceride, LDL-C, and heart rate. However, no changes were observed in HbA1c, HOMA-IR, total cholesterol, HDL-C, systolic and diastolic blood pressure. Interestingly, subgroup analyses based on the duration of the eating window revealed that TRE interventions with shorter eating windows (4-6 h) resulted in a more pronounced effect size than longer eating windows as measured for all outcomes. The meta-analysis results suggest that TRE is an effective treatment strategy for adults with excessive weight and obesity-related metabolic diseases as it improves specific metabolic parameters and potentially decreases the risk of atherosclerotic cardiovascular disease.

Limiting food intake to a shorter duration, without explicitly attempting to reduce energy intake, induces fasting physiology. This adaptive mechanism in the human body has evolved to cope with periods of food scarcity and prolonged fasting

and is critical for survival^[42]. A fasting regime, including TRE, activates metabolic switching from energy production through liver-derived glucose to adipose cell-derived ketones^[43, 44]. At the molecular level, TRE triggers circadian coordination with nutrient-sensing pathways to regulate metabolic health and protects against metabolic disorders induced by poor dietary intake^[45]. Findings from this review are consistent with previous meta-analyses where TRE was shown effective in weight reduction despite mixed findings on body composition^[16, 18, 21, 22]. Compared to continuous energy restriction, weight loss achieved through IF is comparable to^[46], if not superior to CER^[47]. TRE may spontaneously decrease energy intake by 20-30% under ad libitum conditions, resulting in weight loss of 1-4%^[48]. During periods of fasting and CER, macro- and micronutrients are less accessible to cells and tissues. Hence, several pathways play comparable roles in mediating CER and IF effects. Decreased glucose levels or decreased protein and amino acid availability, as generated by caloric restriction or fasting, activate AMP-activated protein kinase (AMPK) and inhibit mTOR, resulting in reduced protein synthesis and ribosome biogenesis, as well as the activation of autophagy^[49].

Nutrient timing has been proposed as a potential approach to restoring metabolic health by synchronizing dietary intake with the circadian clock^[50]. TRE intervention consistently improved glucose metabolism by reducing glucose levels in human studies, as confirmed in the current meta-analysis^[16, 18, 19, 21, 22]. The glucoregulatory mechanisms of TRE demonstrate that eating within a limited eating window during the day restores cAMP Response Element-Binding Protein (CREB) phosphorylation, decreases gluconeogenesis, and increases glucogenesis during the fed state *via* enhanced autophagic flux, mild production in ketone bodies, reduced oxidative stress, and promotion of β -cell responsiveness^[51]. However, the effects of TRE on lipid profiles, blood pressure, and heart rate have been inconsistent^[16, 18, 19, 21, 22]. Nonetheless, the meta-analyses revealed that TRE did not worsen any outcomes studied. While it is widely accepted that TRE improves circadian rhythms, it remains unknown whether the metabolic improvements are the result of calorie limitation or time restriction^[52].

The duration of the eating window in TRE interventions on humans varies, which has led to heterogeneous results between studies. This systematic review suggests that TRE's beneficial effects may be time-dependent, with a shorter eating window resulting in better weight management and cardiometabolic health than a longer eating duration. The mechanisms by which this occurs have yet to be fully understood. An animal study revealed that a 4-hour time-restricted feeding could reprogram the circadian clock by restoring the expression phase of clock genes, despite the high-fat diet^[11]. At the cellular level, prolonged fasting leads to increased AMP levels, gene expression, and activation of AMPK, a critical intracellular energy sensor that regulates processes associated with energy metabolism^[11, 53]. This results in reduced fatty acid synthesis and enhanced fatty acid oxidation in the liver^[54]. Similar to AMPK, Sirtuin 1 (SIRT1) activity increases in response to prolonged fasting^[55]. SIRT1 regulates numerous biological processes, such as insulin response, glycolysis, apoptosis, antioxidative defense, DNA repair, inflammatory response, metabolism, cancer, and stress, improving cardiometabolic health and CVD prevention^[56-58].

Jamshed *et al* conducted a 4-day randomized cross-over study to elucidate the possible mechanisms of actions of TRE with short eating duration in humans. This study revealed that TRE with a short eating window improved multiple health aspects *via* circadian and fasting-related mechanisms^[59]. The authors postulated that eating earlier in the day and having shorter inter-meal intervals could help minimize glycemic excursions, suggesting that TRE interventions with longer inter-meal intervals may be less effective in lowering glucose levels. Additionally, the study found that TRE may alter diurnal patterns in fasting cholesterol, ketones, cortisol, and circadian clock genes, particularly by increasing ketone levels in the morning and improving the amplitude of the cortisol rhythm. The study also demonstrated that six hours of TRE may produce a favorable effect on hormones and genes related to lifespan and autophagy, such as brain-derived neurotrophic factor (BDNF), SIRT1, and LC3A, the autophagosome protein.

The findings of this meta-analysis provide evidence to support the hypothesis that longer fasting duration is associated with better weight control^[60, 61]. Contrary to animal studies, restricting eating duration does not affect 24-hour energy expenditure in humans ^[62, 63]. Animal studies have suggested that TRE may increase energy expenditure by enhancing oxidative metabolism and expression of the mitochondrial uncoupling protein, which is responsible for non-shivering thermogenesis in brown and white adipose tissue^[13, 64, 65]. Nevertheless, an increased thermic effect of food (TEF) was detected during the early postprandial period in a human study^[63]. The study demonstrated that short TRE interventions primarily promote weight loss by decreasing appetite, as evidenced by reduced ghrelin levels and normalized hunger, which tend to promote fullness and reduced appetite. Furthermore, TRE with a short eating window leads to alterations in substrate oxidation, with an increase in 24-hour protein oxidation and a decrease in 24-hour non-protein Respiratory Quotient (npRQ), indicative of increased fat oxidation. This metabolic alteration is likely attributed to the prolonged daily fasting phase rather than circadian effects^[43]. Furthermore, the short TRE group showed higher metabolic flexibility, defined as the difference between the maximum and minimum values of the npRQ, indicating a better ability to switch between different oxidizing substrates than the ad libitum group.

It is important to note that the associations between fasting duration and weight and cardiometabolic health may vary depending on the time of fasting and eating^[15]. The early fasting window, characterized by breakfast consumption and early evening meals, may have different metabolic consequences than the late fasting window, characterized by breakfast omission and night-time snacking^[60]. Since humans are diurnal organisms, eating closer to daylight is consistent with the 24-hour circadian rhythms of metabolism, leading to better metabolic health. The alignment of meals with typical circadian oscillations of hormonal profiles is necessary for TRE to be considered a nutritional strategy utilizing chrononutrition concepts. For example, plasma glucose concentration exhibits diurnal fluctuation, with peak values occurring at the start of the activity phase^[66]. Since food intake promotes insulin production, plasma insulin levels

reflect the daily rhythm of food intake. Thus, night eating results in a misalignment of central and peripheral endogenous glucose circadian rhythms, and impaired glucose tolerance while restricting meals to the daytime prevents such dysregulation^[67]. Accordingly, the current pool of evidence suggests that later or self-selected TRE periods are less effective in improving metabolic health markers^[68].

Although the findings of this meta-analysis suggest that short TRE may improve cardiometabolic outcomes, it is crucial to consider the sustainability of a restrictive eating pattern. The primary concern with a short eating window is that it may be too limiting for many individuals, making it challenging to adhere to over the long term. Adherence is a crucial factor in the success of any dietary intervention, as a lack of adherence can lead to the failure of the intervention. Additionally, limiting eating periods may lead to disordered eating patterns or restrictive dieting behaviors. A recent study found that individuals who engaged in time-restricted eating were at a higher risk for disordered eating behaviors, such as overeating, losing control, binge eating, vomiting, laxative use, and compulsive exercise^[69]. The application of short TRE may not be suitable for all individuals, particularly those with certain medical conditions or who are pregnant or breastfeeding. Alteration in the metabolism and nutrient needs of these individuals may necessitate a more frequent or longer eating duration than the general population.

We have identified several strengths in our meta-analysis. We utilized multiple databases to search existing literature and identify eligible studies related to TRE conducted on individuals with excessive weight or weight-related metabolic diseases while excluding individuals with a normal BMI. This approach ensured the homogeneity of the population of interest, as this group of individuals may have a higher tendency to experience metabolic disturbances than individuals with a normal BMI. Additionally, we performed subgroup analyses based on arbitrary clustering of the eating window duration of TRE intervention to explore methodological heterogeneity. Furthermore, we only included studies involving clinical trials that lasted two weeks up to six months to reduce heterogeneity from short-term

interventions (i.e., less than seven days) and studies reporting long-term effects of TRE. However, this meta-analysis has some limitations. Most included studies had small sample sizes, with several posing a high risk of bias in some domains. Blinding participants was impossible due to the nature of behavioral interventions. Nonetheless, this factor is unlikely to affect the results as outcomes were objectively measured, with some studies executed blinding of assessors. Additionally, there was high heterogeneity in some of the outcomes, which could be due to differences in population, fasting/eating duration, duration of the intervention, meal timing, meal frequency, co-interventions, and level of adherence. Data on such factors, including dietary intake, physical activity, and adherence level, were unavailable in some reports, which might have resulted in biased conclusions. Future large-randomized-controlled trials with rigorous methodology are necessary to elucidate the role of different TRE duration on cardiometabolic health and determine the optimal TRE duration to translate into clinical practice.

CONCLUSION

In conclusion, findings from this meta-analysis demonstrate that TRE is an effective and sustainable dietary strategy for reducing body weight, body composition, blood glucose, insulin, triglyceride, and LDL-C and improving heart rate in individuals with excessive weight or weight-related metabolic disorders. Moreover, this study demonstrated that the favorable benefits of TRE on health are dependent on eating duration, with shorter durations resulting in more significant changes in anthropometric and cardiometabolic health markers. However, due to the challenges of adhering to a strict regimen, the TRE intervention with short eating windows may only suit specific individuals and must be monitored vigilantly. Therefore, extensive studies with larger sample size and higher quality is required to confirm the findings of this meta-analysis and determine the optimal duration of the eating window for primary and secondary CVD prevention.

ARTICLE HIGHLIGHTS

Research background

There is growing interest in time-based dietary intervention as an alternative to caloric restriction or nutrient-based dietary intervention for cardiovascular disease prevention.

Research motivation

3 Time-restricted eating is considered a mild form of intermittent fasting and has shown conflicting cardiometabolic health outcomes in humans.

Research objectives

Our study aimed to explore the overall effectiveness of TRE and its optimal duration as a potential dietary approach for weight loss and improved cardiometabolic health in individuals with excessive weight and obesity-related metabolic diseases.

Research methods

Systematic searches were conducted *via* multiple databases (MEDLINE Complete, Web of Science, Scopus, the Cochrane Library, Academic Search Complete, Food Science Source, OpenDissertations, Education Research Complete, and Psychology and Behavioural Sciences Collection) to identify the relevant articles till May 2022. The methodological quality of the included studies was assessed using the Cochrane risk-of-bias tool for randomized trials (RoB-2). Meta-analyses were conducted depending on feasibility. Analysis was performed using RevMan software.

Research results

TRE significantly decreased body weight, waist circumference, adipose mass, lean body mass, blood glucose, insulin, triglyceride, LDL-C, and heart rate. HbA1c, HOMA-IR, total cholesterol, HDL-C, systolic and diastolic blood pressure showed no significant changes with the treatment. In addition, subgroup analyses based on the eating

duration revealed significant variation in the effects of the TRE intervention on the measured outcomes.

Research conclusions

TRE is an effective and sustainable dietary strategy to improve the anthropometric and cardiometabolic health of individuals with excessive weight or weight-related metabolic disorders.

Research perspectives

A larger sample size and higher quality studies are necessary to corroborate the findings of this meta-analysis and define the optimal duration of the eating window for CVD prevention.

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