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Original Research Article

The effects of time-restricted eating versus habitual diet on inflammatory cytokines and adipokines in the general adult population: a systematic review with meta-analysis

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A B S T R A C T

Background: Time-restricted eating (TRE) may facilitate weight loss, but its impact on inflammation remains unclear. Chronic inflammation can detrimentally increase risk of obesity-associated comorbidities.

Objectives: The aim of this systematic review was to synthesize and determine the effects of TRE on cytokine and adipokines (C-reactive protein [CRP], TNF alpha [TNF-α], interleukin-6 [IL-6], leptin, and adiponectin) in adults.

Methods: PubMed, Scopus, Cochrane CENTRAL, and Web of Science were systematically searched for randomized controlled trials (RCTs) and non-RCTs to determine the effects of TRE on cytokines and adipokines in adults up to 23 June, 2023. Risk of bias was assessed using risk of Bias 2 tool for RCTs and the ROBINS-I for non-RCTs. The standardized mean differences (SMDs) and their 95% confidence intervals (CIs) were estimated with the DerSimonian–Laird method through random-effect models. The PRISMA recommendations were followed.

Results: A total of 25 studies (13 RCTs, 12 non-RCTs) involving 936 participants were included. The pooled SMD for the effect of TRE compared with the control group on cytokines and adipokines was −0.11 (95% CI: −0.33, 0.12; $I^2 = 19.7\%$; $n = 10$ comparisons) for CRP; −0.25 (95% CI: −0.47, −0.03; $I^2 = 0\%$; $n = 11$ comparisons) for TNF-α; −0.09 (95% CI: −0.39, 0.21; $I^2 = 16.4\%$; $n = 8$ comparisons) for IL-6; −0.81 (95% CI: −1.37, −0.24; $I^2 = 65.3\%$; $n = 5$ comparisons) for leptin; and 0.07 (95% CI: −0.40, 0.54; $I^2 = 56.9\%$; $n = 6$ comparisons) for adiponectin.

Conclusions: Time-restricted eating may be an effective approach to reduce TNF-α and leptin levels in the general adult population.
This review was registered at PROSPERO as CRD42022358162.

Keywords: time-restricted eating, inflammation, cytokines, adipokines

Introduction

Obesity is strongly associated with an increased prevalence for chronic conditions such as cardiometabolic diseases and cancer [1]. The pathogenesis of obesity-associated comorbidities is intricately linked with local and systemic inflammation, which may partially stem from adipose tissue inflammation [2,3]. Through excessive fat accumulation, adipocytes undergo hypertrophy to accommodate excess lipids. However, hypertrophic adipocytes tend to become dysfunctional and secrete various inflammatory markers as well as chemotactic factors, causing the infiltration and activation of immune cells, most notably macrophages [2–5]. The increased presence of macrophages not only elevates inflammation in adipose tissue, but also further exacerbate adipocyte dysfunction, causing profound morphological and functional changes [6]. Consequently, whole-body metabolic and immune derangements follow, thus making obesity a chronic low-grade inflammatory disease.

Weight loss plays a pivotal role in reducing the overall inflammatory burden in those with obesity. However, the effectiveness of dietary interventions is often heterogeneous and only recently has timing of food intake been considered as a key factor in modulating the results of dietary approaches. The duration over which food is consumed has

Abbreviations: CI, confidence interval; CRP, C-reactive protein; GRADE, Grades of Recommendations Assessment Development and Evaluation; IL-6, interleukin-6; RCT, randomized controlled trial; RoB2, Risk-of-Bias 2 tool; SMD, standardized mean difference; TRE, time-restricted eating.

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marked effects on many physiological and metabolic processes including the regulation of circadian rhythms [7,8]. There is increasing evidence that circadian clocks at both central and peripheral levels control the responses of the innate and adaptive immune systems [9,10]. However, it is likely that the metabolic dysfunctions associated with obesity disrupt circadian clocks, which may exacerbate the inflammatory profiles in those with obesity [11].

Time-restricted eating (TRE) is a dietary strategy that restricts food consumption to a specific time window, typically ranging from 6 to 10 h [12]. In mice, TRE facilitated weight loss, restored circadian amplitude, and protected against high-fat diet-induced obesity, hyperinsulinemia, hepatic steatosis, and inflammation [8]. TRE also reduced the expression of inflammatory mediators in visceral adipose tissue and key regulators of metabolic and inflammatory processes in mice with induced arthritis [13]. Conversely, the evidence for the anti-inflammatory properties of TRE in humans is inconsistent. TRE reduced key inflammatory biomarkers such TNF-α, interleukin-1β, and leptin and increased adiponectin in trained individuals compared with control after 8 wk [14]. To the contrary, another study found that 6 wk of TRE did not elicit significant changes in inflammatory cytokines and adipokines in resistance-trained firefighters [15].

The potential benefits of TRE on inflammation in humans remain unclear. Therefore, this systematic review and meta-analysis aims to synthesize the available evidence and determine the effects of TRE on cytokines and adipokines (C-reactive protein [CRP], TNF-α, interleukin 6 [IL-6], leptin, and adiponectin) in the general adult population.

Methods

Data sources and searches

The present study was conducted in accordance with the 2020 PRISMA guidelines [16] and the Cochrane Handbook for Systematic Reviews of Interventions [17]. Details of the bibliographic search are presented according to PRISMA-S guidelines [18]. This review was registered in the PROSPERO database (registration number: CRD42022358162).

A systematic search of the literature was performed in 4 databases: MEDLINE (via PubMed), Scopus, Web of Science, and the Cochrane CENTRAL from inception to the 23 June, 2023. We searched for articles assessing the effects of TRE protocols on cytokines and adipokines (CRP, TNF-α, IL-6, leptin, and adiponectin) in adults. The search strategy was built according to the PI(E)COS approach, including the following free and controlled (MeSH) terms: (“time-restricted eating” OR “time-restricted feeding” OR “time limited eating”) AND (inflammation OR inflammatory OR inflamm*). The complete search strategy for each database is available in Supplemental Table 1.

Study selection

Two reviewers (LT and RC) independently examined the titles and abstracts of the retrieved studies, and a third reviewer (RF-R) was consulted in case of disagreements. For studies in which titles and abstracts were related to the objective of our review, we screened them against eligibility criteria. The inclusion criteria were as follows: *1*) type of study: RCTs with parallel or crossover design, non-RCTs and pre-post studies; *2*) type of participants: individuals aged ≥18 y; *3*) type of intervention: different protocols of TRE (i.e., early, mid or late TRE) but with an eating window <12 h; *4*) comparison: control condition (i.e., usual diet, ad libitum), energy-restricted diets without TRE; and *5*) outcomes: cytokines and adipokines (i.e., CRP, TNF-α, IL-6, leptin, and adiponectin). No language restrictions were applied. We excluded studies when TRE was not undertaken daily or undertaken in the context of religious fasting. Letters, gray literature, unpublished results, and conference abstracts were also excluded.

Data extraction and quality assessment

Two independent reviewers (LT and RF-R) performed the data extraction and quality assessment procedures, and a third co-author (LKH) was consulted in case of disagreement between the initial reviewers. We extracted the following information from the included studies: first author name and year; study design, country, total sample size and sample size in each arm, characteristics of the population (i.e., comorbidities/health status, female percentage, mean age, mean weight, mean BMI), TRE protocol, length of the intervention, cytokine and adipokine measured as well as the tests used to measure their levels, and adherence to the TRE protocol (compliance and method of assessment).

The Cochrane’s Risk-of-Bias 2 tool (RoB2) [19] was used to assess the quality of the RCTs included. Subsequently, the following 5 domains were evaluated: *1*) randomization process, *2*) deviations from intended interventions, *3*) missing outcome data, *4*) measurement of the outcome, and *5*) selection of the reported results. Each of these domains were graded individually as “low risk of bias,” “some concerns,” or “high risk of bias.” Lastly, using the RoB2 instructions, each study was given a score according to their overall risk of bias (e.g., “low risk of bias,” “some concerns,” or “high risk of bias”).

The Cochrane’s ROBINS-I tool was used for the included non-RCTs [20]. The tool evaluates 7 domains: *1*) confounding, *2*) selection of participants into the study, *3*) classification of the interventions, *4*) biases due to deviations from intended interventions, *5*) missing data, *6*) measurement of outcomes, and *7*) selection of the reported results. Each of these domains were scored as having either a low, moderate, serious, or critical risk of bias. Subsequently, each study was classified according to their overall risk of bias following the ROBINS-I instructions [20]. Finally, risk-of-bias VISualization (robvis) tool was used to develop the figures for risk of bias assessments for RCTs and non-RCTs [21].

Grading the quality of evidence

The “Grades of Recommendations, Assessment, Development, and Evaluation” (GRADE) tool was used to determine the certainty of the evidence in the present systematic review and meta-analysis [22]. Each included outcome (i.e., CRP, TNF-α, IL-6, leptin, and adiponectin) was rated as having high-, moderate-, low-, or very low-quality evidence based on study design, risk of bias, inconsistency, indirect evidence, imprecision, and publication bias. For the GRADE report, we considered the RCTs included in the meta-analysis of each outcome. The score was downgraded one when ≤60% of the studies were at low risk of bias as well as when inconsistency (I^2 >50%), indirect evidence, imprecision (wide CIs), and publication bias were reported.

Dealing with missing data

The authors of 2 studies [23,24] were contacted at least 3 times by e-mail to request information on missing data; only one answered and provided additional data on one of the outcomes of interest [23]. Furthermore, whenever possible, data from the available figures were also extracted to be used in this study [25,26]. Otherwise, when it was impossible to extract the data from figures or when authors did not send

additional data, the study's main results and conclusions were described.

Data synthesis

Primary data from trials, including pre-post mean, SD, and sample size of intervention and control groups were extracted. For studies not reporting the aforementioned data, we collected the mean difference and SE or SD of the change. Subsequently, the standardized mean difference (SMD) and their related 95% CIs were calculated for each study according to the DerSimonian and Laird random effects method [27]. We conducted a meta-analysis only considering RCTs when at least 4 studies reported valid data for the outcomes of interest. Furthermore, a sensitivity analysis was conducted to determine the robustness of the summary estimates removing each included study one by one. Subgroup analyses based on the health status of the participants (overweight/obesity versus healthy/trained) were performed. Meta-regression models were performed considering age, weight, BMI, and length of the intervention to determine its influence in our estimates. We evaluated the heterogeneity using the I^2 statistic with I^2 values of 0% to 40% considered to be "not important" heterogeneity, 30% to 60% representing "moderate" heterogeneity, 50% to 90% representing "substantial" heterogeneity, and 75% to 100% representing "considerable" heterogeneity, considering the corresponding P values and 95% CIs [28]. Finally, the assessment of small study effects was evaluated through visual inspection of funnel plots and Egger's regression asymmetry test [28]. All statistical analyses were performed using StataSE v. 15 (StataCorp).

Results

Study selection

A total of 850 nonduplicated studies were retrieved across the consulted databases. An initial screening by title and abstract resulted in 77 studies that were assessed in full text. The excluded studies along with the reasons for exclusion are available in Supplemental Table 2. As such, 25 studies with a total of 936 participants met the eligibility criteria and were considered for the qualitative synthesis; of these, 13 were RCTs [7,14,24,25, 29–36], and 12 were non-RCTs [15,23, 37–44]. Finally, there were a total of 10 RCTs included for the meta-analysis (6 for CRP, 6 for TNF-α, 5 for IL-6, 4 for leptin, and 5 for adiponectin) (Figure 1). Overall, the included studies were performed

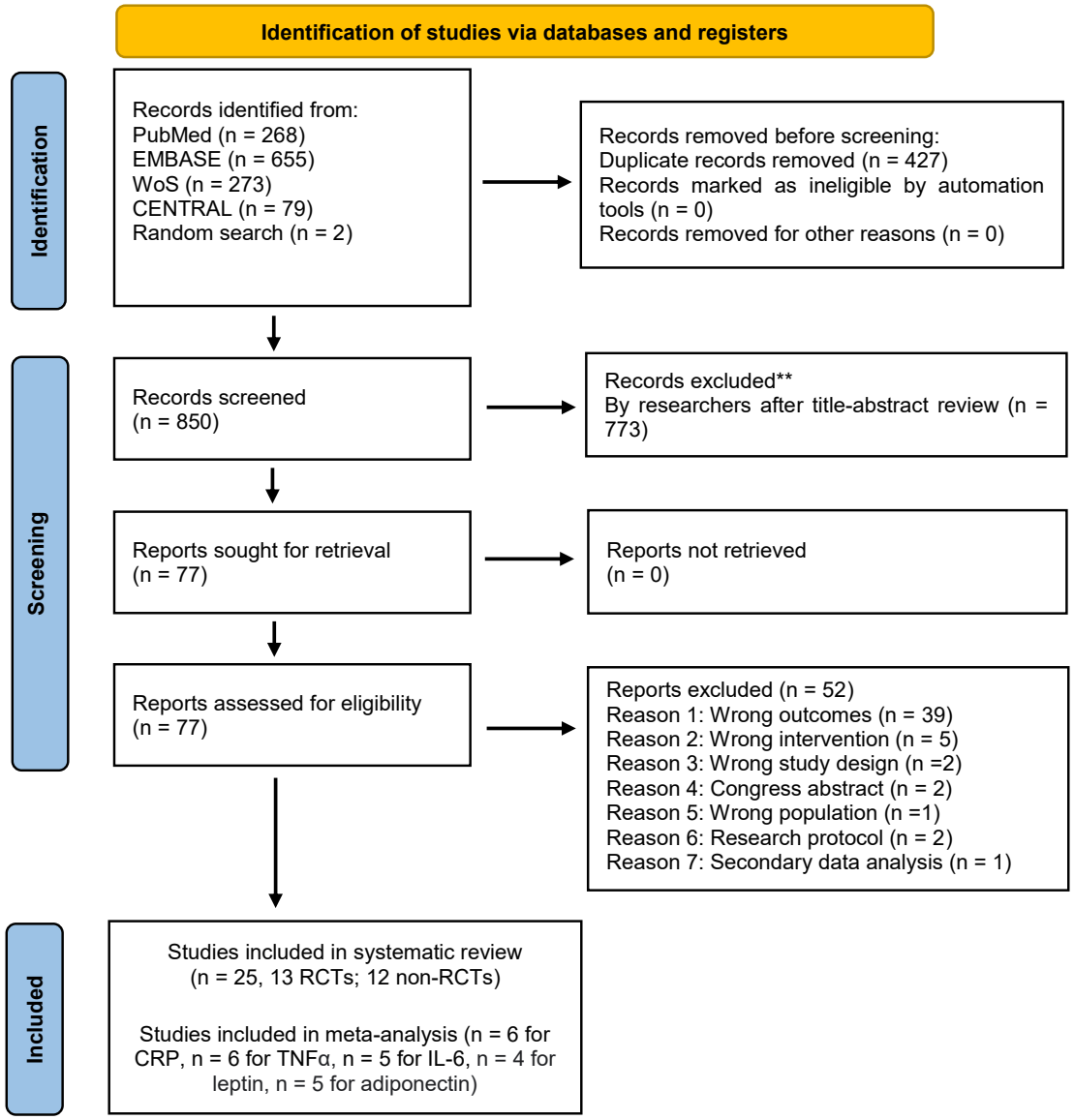

FIGURE 1. Flow diagram of the studies (PRISMA).

between 2016 and 2023 and in different countries: 11 in the United States, 4 in China, 3 in Greece and Italy, 2 in Brazil, and 1 in Germany and Iran. These studies included participants with a mean age range between 18 and 59 y, a mean baseline weight between 61 and 101 kg, and a mean baseline BMI range between 21 and 36 kg/m^2 (Table 1). The methods employed to determine change in each inflammatory marker level are available in the supplementary material (Supplemental Table 3). Finally, the assessment and results of adherence and compliance during the intervention are shown in Supplemental Table 4. Although the methods for assessment were diverse, most studies used daily or 3-d food records and smartphone applications to document the beginning and end of food intake. A total of 14 studies reported data for the adherence/compliance of the TRE intervention [7,15,23,24,26,29–32,39,41,43,45].

CRP

Among the 18 studies reporting data for CRP, 9 were non-RCTs [33,37–40,43–46], and 9 were RCTs [7,24,26,29–34]. Overall, these studies included 673 participants, of which 437 followed TRE protocols, and 236 were in the control groups. Most studies (10 of 17) were conducted in participants with overweight, obesity, and metabolic disorders (i.e., prediabetes, metabolic syndrome, polycystic ovary syndrome, chronic kidney disease), and 7 studies were conducted in healthy adults, including 2 in firefighters [31,41] and 1 in elite cyclists [34] (Table 1).

The mean length of the intervention was 7.9 wk (range: 4–12). The TRE protocols were different, but 13 of 18 applied an 8-h eating window (16:8), 3 of 18 followed a 10-h window (14:10) and 2 of 18 followed a 6-h window (18:6). Most of the control groups followed their usual ad libitum diets without any time restriction, though 2 studies compared TRE with hypocaloric orthodox fasting [37,38] (Table 1). The methods employed to determine change in CRP levels are available in the supplementary material (Supplemental Table 3).

There were only 3 studies in which CRP levels decreased significantly after TRE [29,33,41]. Two of them were RCTs [29,33] and one was a pre-post study design [40]. The pooled SMD considering only RCTs for the effect of TRE compared with the control group on CRP was −0.11 (95% CI: −0.33, 0.12; I^2 = 19.7%; n = 8 comparisons) (Figure 2A). The subgroup analysis by health status did not modify the SMD estimate (Supplemental Table 5). The sensitivity analysis showed that when studies were removed one by one, none modified the SMD estimate (Supplemental Table 6). None of the covariates explored influenced our estimates in the meta-regression models (Supplemental Table 7). Finally, after exploring funnel plot asymmetry and the Egger test, there was no evidence of publication bias (P = 0.30) (Supplemental Table 8).

TNF-α

Among the 10 studies reporting data for TNF-α, 7 were RCTs [7,14,24–26,34,35], and 3 were non-RCTs [41,45,46]. Overall, these studies included 323 participants, of which 213 followed TRE protocols, and 110 were in the control groups. Four studies were conducted in participants with overweight or obesity or with prediabetes, and 6 studies were conducted in healthy participants, 3 of which included physically active adults (resistance-trained firefighters and elite cyclists) (Table 1).

The mean length of the intervention was 10.8 wk (range: 4–48). TRE protocols differed with 6 studies applying an 8-h eating window (16:8), 3 had a 6-h eating window (18:6), 1 compared a 6-h eating window to a 4-h eating window (20:4) [25], and 1 had a 10-h eating window (12:10) (Table 1). The control groups mostly included ad libitum normal diets without any time restriction. The most employed method to assess the changes on TNF-α levels was immunoassay kits (Supplemental Table 3).

Three RCTs showed significant TNF-α reductions after TRE [14,25,35]. According to the quantitative synthesis, the pooled SMD for RCTs on the effect of TRE compared with the control on TNF-α was −0.25 (95% CI: −0.47, −0.03; I^2 = 0%; n=9 comparisons) (Figure 2B). The subgroup analysis by health status did not modify the SMD estimate (Supplemental Table 5). The sensitivity analysis showed that when studies were removed one by one, all 3 of them modified the SMD estimate [14,25,35] (Supplemental Table 6). None of the covariates explored influenced our estimates in the meta-regression models (Supplemental Table 7). Finally, after exploring funnel plot asymmetry and the Egger test, there was no evidence of publication bias (P = 0.37) (Supplemental Table 8).

IL-6

Among the 8 studies reporting data for IL-6, 5 were RCTs [14,25,32,34,35], and 3 were non-RCTs [15,41,45]. Overall, these studies included 196 participants, of which 133 followed TRE protocols, and 63 were in the control groups. There were 2 studies conducted in participants with overweight or obesity and 6 in healthy participants, 2 of which were in firefighters and 2 in athletes (resistance and cyclist) (Table 1).

The mean length of the intervention was 14.1 wk (range: 4–48). Five of 8 studies followed an 8-h eating window (16:8), 2 followed a 10-h eating window (12:10), and 1 was a 3-arm trial assessing the effects of 4-h and 6-h eating windows compared with no mealtime restrictions [25] (Table 1). The control groups followed their usual ad libitum diets without any time restriction. The most employed method to assess the changes on IL-6 levels was immunoassay kits (Supplemental Table 3).

Only 1 study reported significant improvements in IL-6 after the TRE intervention compared with the control group [35]. The pooled SMD for RCTs on the effect of TRE compared with the control group on IL-6 levels was −0.09 (95% CI: −0.39, 0.21; I^2 = 16.4%; n = 7 comparisons) (Figure 2C). The subgroup analysis by health status did not modify the SMD estimate (Supplemental Table 5). The sensitivity analysis showed that when studies were removed one by one, none modified the SMD estimate (Supplemental Table 6). None of the covariates explored influenced our estimates in the meta-regression models (Supplemental Table 7). Finally, after exploring funnel plot asymmetry and the Egger test, there was evidence of publication bias (P = 0.03) (Supplemental Table 8).

Leptin

Among the 7 studies reporting data for leptin levels, 5 were RCTs [14,24,26,35,36], and 2 were non-RCTs [15,42]. Overall, these studies included 258 participants, of which 161 followed TRE protocols, and 97 were in the control groups. There were 2 studies conducted in participants with overweight and/or obesity [26,42], and 5 studies were performed in healthy individuals, of which 2 were in resistance-trained males [15,35] (Table 1).

The mean length of the intervention was 12.4 wk (range: 4–48). Five of 7 studies reported a TRE protocol with an 8-h eating window (16:8), 1 applied a 10-h eating window (12:10), and 1 compared a 6-h (18:6) eating window in an early eating protocol with late TRE and the control group [24] (Table 1). The control groups followed their usual ad libitum diets without any time restriction, but 2 studies matched the caloric restriction in their control conditions (25%) [36,42]. The most

TABLE 1
Characteristics of the included studies in the systematic review

Reference	Design	Country	Participants (% females)	*N*	nTRE/CON	Age (y)	Weight (kg)	BMI (kg/m^2)	Δ weight, fat mass, and visceral fat in TRE groups	TRE protocol	Length (wk)	Control protocol	Outcomes
Cienfuegos et al. [25]	Three arm-parallel RCT	United States	Adults with Ob (91%)	49	4-TRE=16; 6-TRE=19; CON=14	4-TRE: 49 (2); 6-TRE: 46 (3); CON 45 (2)	4-TRE: 101 (5); 6-TRE: 99 (5); CON 93 (5)	4-TRE: 36 (1); 6-TRE: 37 (1); CON: 36 (1)	4-TRE: weight ↓3.2% ± 0.4%[1]; fat mass ↓2.8 ± 0.4 kg[1]; visceral fat mass ↓0.18 ± 0.07 kg 6-TRE: weight ↓3.2% ± 0.4%[1]; fat mass ↓1.4 ± 0.3 kg[1]; visceral fat mass ↓0.14 ± 0.06 kg	4-TRE (15:00–19:00) ad libitum; 6-TRE (13:00–19:00) ad libitum	8	No mealtime restrictions	TNF-α, IL-6
Karras et al. [38]	non-RCT	Greece	Adults with OW (76%)	45	TRE=16; OF=29	TRE=45.4 (9.2); OF=49.9 (8.9)	TRE= 77.2 (18.8); OF=77.6 (17.1)	TRE= 28.5 (6.3); OF=29 (6)	—	TRE (08:00–16:00) energy-restricted 1200–1500 kcal/d	7	Hypocaloric Orthodox fasting	hs-CRP
Karras et al. [37]	non-RCT	Greece	Adults with OW (72%)	60	TRE=23; OF=37	TRE=46.4 (9.2); OF=50.1 (8.7)	TRE= 72 (12.5); OF=78.1 (16.4)	TRE= 26.4 (4.1); OF= 28.5 (5.5)	—	TRE (08:00–16:00) energy-restricted 1200–1500 kcal/d	7	Hypocaloric Orthodox fasting	hs-CRP
Karras et al. [23]	non-RCT	Greece	Premenopausal females with OW (100%)	97	TRE=42; OF=55	TRE=46.7 (8.7); OF=48.3 (3.9)	TRE= 78.4 (20.2); OF=77.9 (17.1)	TRE= 28.6 (7.2); OF= 29.5 (5.4)	—	TRE (08:00–16:00) energy-restricted 1200–1500 kcal/d	7	Hypocaloric Orthodox fasting (from 08:00 to 20:00) (1200–1500 kcal)	adiponectin
Kesztyüs et al. [39]	Pre-post trial	Germany	Primary care patients with abdominal Ob (78%)	37	TRE=37	TRE= 49.1 (12.4)	TRE= 88.8 (21.1)	TRE= 31.3 (5.9)	TRE: weight ↓1.7 ± 2.5 kg[1]; fat mass - ; visceral fat mass -	TRE (10:00–18:00) usual diet	12	—	hs-CRP
Kotarsky et al. [30]	RCT-parallel	United States	Individuals with OW/Ob (not mentioned)	21	TRE=11; CON=10	TRE=45 (3); CON= 44 (2)	TRE=82 (3); CON=83 (3)	TRE= 29.8 (0.8); CON= 29.4 (0.8)	TRE: weight ↓3.3%[1]; fat mass ↓9.0%[1]; visceral fat mass -	TRE (from 12:00 to 20:00) ad libitum + 8 wk of aerobic exercise and supervised resistance training (between 13:00–19:00) in nonconsecutive days, aerobic exercise 3 or more days per week, 50–60 min in same schedule or after lifting days	8	Maintained dietary habits + 8 wk of aerobic exercise and supervised resistance training (between 9:00–19:00) in nonconsecutive days, aerobic exercise 3 or more days per week, 50–60 min in same schedule or after lifting days	hs-CRP

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TABLE 1 (*continued*)

Reference	Design	Country	Participants (% females)	*N*	nTRE/CON	Age (y)	Weight (kg)	BMI (kg/m^2)	Δ weight, fat mass, and visceral fat in TRE groups	TRE protocol	Length (wk)	Control protocol	Outcomes
Lao et al. [45]	non-RCT	China	Individuals with OW/Ob and chronic kidney disease (48%)	27	TRE=13; CON=14	TRE= 51.8 (7.7); CON=52.2 (11.3)	TRE= 79.4 (10.6); CON= 73.3 (10.5)	TRE= 29.3 (2.3); CON= 28.0 (2.4)	TRE: weight ↓2.8 ± 2.9 kg^{1}; fat mass ↓1.8 ± 2.4 kg^{1}; visceral fat area −8.4 ± 12.1 cm$^{2\ 1}$	TRE (from 7:00 to 12:00) with a high-quality low-protein diet	12	High-quality low-protein diet without time restriction	hs-CRP, IL-6, TNF-α
Li et al. [40]	Pre-post trial	China	Females with PCOS (100%)	15	TRE=18	TRE= 18–31	TRE= 74.7 (69.8 to 97.5)	TRE= 29.8 (4.3)	TRE: weight ↓1.3kg^{1}; fat mass ↓1%^{1}; visceral fat mass -	TRE (8:00–16:00) ad libitum	5	—	hs-CRP
Manoogian et al. [31]	RCT	United States	Firefighters with 24-h work schedule (9%)	137	TRE=70; CON=67	TRE= 41.1 (8.7); CON= 39.6 (9.4)	TRE=87.3; CON=89.3	TRE=27.8; CON=27.7	TRE: weight ↓0.94 kg^{1}; fat mass ↓0.08%; visceral fat mass -	TRE: participants were instructed to follow a Mediterranean diet and eat within a 10-h eating window	12	Standard-of-care control (Mediterranean diet)	hs-CRP
Martens et al. [32]	RCT crossover	United States	Healthy adults (55%)	22	TRE=22	TRE= 67 (1)	TRE= 70.2 (2.8)	TRE= 24.7 (0.6)	—	TRE (10:00–11:00 to 18:00–19:00) usual diet	6	Non-TRE (eating window around 12 h) usual diet	hs-CRP, IL-6
McAllister et al. [33]	2-arm-parallel RCT	United States	Active young males (0%)	22	TRE ad libitum=12; TRE isocaloric=10	TRE= 22 (2.5)	TRE= 90.3 (24)	TRE= 28.5 (8.3)	—	TRE (16:8)	4	TRE ad libitum vs. isocaloric	hs-CRP , adiponectin
McAllister et al. [41]	Pre-post trial	United States	Firefighters (0%)	13	TRE=13	TRE= 36.5 (6.9)	TRE=89.5 (12.5)	TRE= 27.8 (2.8)	—	TRE (14:10) + standardized training program	8	—	Salivary CRP, IL-6, and IL-1β (before and after a fire ground test)
McAllister et al. [15]	Pre-post trial	United States	Resistance-trained firefighters (0%)	15	10-TRE=15	TRE= 37 (6)	TRE= 91.7 (11.3)	TRE= 28.1 (2.7)	—	TRE (14:10) + standardized training program	6	—	IL-6, IL-8, IL-1β, IL-10, TNF-α, leptin and adiponectin
Moro et al. [14]	2-arm-parallel RCT	Italy	Resistance-trained males (0%)	34	TRE=17; CON=17	TRE= 29.9 (4.1); CON= 28.5 (3.5)	TRE= 83.9 (12.8); CON=85.3 (13)	—	TRE: weight ↓0.40 ± 1.76 kg^{1}; fat mass ↓0.96 ± 1.72 kg^{1}; visceral fat mass -	TRE (16:8) with 3 meals and 100% energy requirements	8	Normal diet without time restriction (3 meals and 100% energy requirements)	IL-6, IL-1β, TNF-α, leptin, adiponectin
Moro et al. [34]	2-arm-parallel RCT	Italy	Elite cyclists (0%)	16	TRE=8; CON=8	TRE= 19.4 (2.4); CON= 19.4 (1.6)	TRE= 67.0 (5) CON=72.3 (6.2)	TRE= 21.9 (1.7); CON= 22.5 (1.8)	TRE: weight ↓2%^{1}; fat mass ↓11%; visceral fat mass -	TRE (16:8) with 3 meals (1 snack) and 100% energy requirements from 10:00 to 18:00	4	Normal diet without time restriction (3 meals and 100% energy requirements)	IL-6, TNF-α, hs-CRP, adiponectin

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TABLE 1 (*continued*)

Reference	Design	Country	Participants (% females)	*N*	nTRE/CON	Age (y)	Weight (kg)	BMI (kg/m^2)	Δ weight, fat mass, and visceral fat in TRE groups	TRE protocol	Length (wk)	Control protocol	Outcomes
Moro et al. [35]	2-arm-parallel RCT	Italy	Healthy adults (0%)	20	TRE=10; CON=10	—	TRE= 83.2 (5.9); CON=84.6 (5.8)	—	TRE: weight ↓3.36%[1]; fat mass ↓11.81%[1]; visceral fat volume ↓18.8%[1]	TRE (16:8) with 3 meals and 100% energy requirements (from 13:00 to 20:00) + resistance training	48	Ad libitum without any time restriction (3 meals from 08:00 to 20:00), matched for kcal and macronutrient at baseline	IL-6, IL-1β, TNF-α, leptin, and adiponectin
Ribeiro et al. [42]	non-RCT	Brazil	Physically active adults with OW/Ob (83%)	21	TRE=11; CON=10	TRE= 32.4(5.5); CON= 33(8.7)	TRE= 83.3(13.5); CON=84(14.3)	TRE= 30.5(3.5); CON= 31.7(5.6)	TRE: weight ↓6.8%[1]; fat mass ↓17.0%[1]; visceral fat mass -	TRE (from 12:00 to 20:00) + continuous energy restriction 20% during the study, the subjects performed 3 sessions of the standardized training (20 min aerobics exercises + resistance training + exercises to balance and proprioception, total ~1 h) weekly	8	Continuous energy restriction 20% during the study, the subjects performed 3 sessions of the standardized training (20 min aerobics exercises + resistance training + exercises to balance and proprioception, total ~1 h) weekly	leptin
Schroder et al. [44]	non-RCT	Brazil	Middle-aged females with Ob (100%)	32	TRE=20; CON=12	TRE= 36.6 (1.6) CON= 42.3 (3.5)	TRE= 83.6 (3.9); CON= 87.1 (3.25)	TRE= 32.5 (1.1); CON= 34.5 (1.2)	—	Ad libitum for 8 h (12:00 to 20:00)	12	Habitual diet	CRP
Stratton et al. [36]	RCT	United States	Active males (0%)	26	TRE=13; CON=13	TRE= 22.9 (3.6); CON= 22.5 (2.2)	TRE= 82 (10.6); CON=83.3 (15)	—	—	TRE (from 12:00–13:00 to 20:00–21:00) with 25% caloric restriction + supervised full body resistance training (3 d/wk with 50 g hydrolyzed whey protein isolate post workout)	4	Normal diet (25% caloric restriction) + supervised full body resistance training (3 d/wk with 50 g hydrolyzed whey protein isolate post workout)	Serum adiponectin, plasma leptin
Sutton et al. [7]	RCT crossover	United States	Males with prediabetes (0%)	8	eTRE=8	56 (9)	eTRE= 100.7 (18.4)	eTRE= 32.2 (4.4)	—	eTRE (breakfast: 06:30–08:30; 3 h after lunch, and dinner before	5	12 eating period, 6 h between meals (food provided),	hs-CRP, IL-6, leptin, and adiponectin. Data not

(*continued on next page*)

TABLE 1 (*continued*)

Reference	Design	Country	Participants (% females)	*N*	nTRE/CON	Age (y)	Weight (kg)	BMI (kg/m^2)	Δ weight, fat mass, and visceral fat in TRE groups	TRE protocol	Length (wk)	Control protocol	Outcomes
										15:00) food provided isocaloric and eucaloric controlled feeding: 50% CHO, 35% fat and 15% protein (each meal 1/3 of each participant's daily energy)		wash-out of 7 wk	shown for TNF-α
Varkaneh et al. [29]	RCT	Iran	Patients with OW/Ob and NAFLD (46/35%)	45	TRE=22; CON=23	TRE= 41.4 (10.5) CON= 44.2 (4.9)	TRE= 83.8 (12.7); CON= 89.3 (18.5)	TRE= 29.1 (2.7); CON= 30.6 (3.09)	—	TRE (plus low sugar diet: limiting monosaccharides (i.e., glucose and fructose) and disaccharides (e.g., sucrose/table sugar) added to foods and drinks by the manufacturer, cook, or consumer, and sugars naturally present in honey, syrups, fruit juices, and fruit juice concentrates according to the WHO guidelines)	12	Usual diet adhering to their specific isocaloric diet plan, adhering to the caloric intake, macronutrient, and fruits and vegetables as intervention	hs-CRP
Wilkinson et al. [43]	Pre-post trial	United States	Patients with MS (32%)	19	TRE=19	TRE= 59 (11.1)	TRE= 97.8 (19.7)	TRE= 33.1 (4.8)	TRE: weight ↓3.30 (3.20)[1]; fat mass ↓1.01 (0.91)[1]; visceral fat rating ↓0.58 (0.77)[1]	TRE (self-selected eating window (08:00–10:00 to 18:00–20:00) + ad libitum)	12	—	hs-CRP
Xie et al. [24]	3-arm-parallel RCT	China	Healthy adults (78%)	82	eTRE=28; mTRE=26; CON=28	eTRE= 28.7 (9.7); mTRE= 31.1 (8.4); CON= 33.6 (11.6)	eTRE= 61.1 (8.8); mTRE= 61 (11.7); CON= 61.2 (9.9)	eTRE= 22.7 (3.1); mTRE= 21.4 (2.2); CON= 21.5 (2.9)	eTRE: weight ↓1.6 ± 1.4 kg[1]; fat mass ↓0.76 ± 1.01 kg[1]; visceral fat mass - mTRE: weight ↓0.2 ± 2.2 kg; fat mass ↓0.30 ± 1.25 kg; visceral fat mass -	eTRE=8-h eating window between 06:00–15:00; mTRE=8-h eating window between 11:00 and 20:00	5	Ad libitum without any time restriction	hs-CRP, TNF-α, IL-8, and leptin

(*continued on next page*)

TABLE 1 (*continued*)

Reference	Design	Country	Participants (% females)	*N*	nTRE/CON	Age (y)	Weight (kg)	BMI (kg/m^2)	Δ weight, fat mass, and visceral fat in TRE groups	TRE protocol	Length (wk)	Control protocol	Outcomes
Waldman et al. [46]	Pre-post trial	United States	Physically active males (0%)	12	TRE=12	TRE= 51.9 (8.6)	TRE= 83.2 (13.4)	—	—	TRE: self-selected eating window + habitual diet	4	—	hs-CRP, TNF-α
Zhang et al. [26]	3-arm-parallel RCT	China	Young adults with OW/Ob (45%)	60	eTRE=21; lTRE=20; CON=19	eTRE= 23.8 (0.6); lTRE= 23.2 (0.5); CON= 22.1 (0.4)	eTRE= 78 (2.9); lTRE= 83.5 (4.1); CON= 77.1 (3.4)	eTRE= 27.1 (0.7); lTRE= 28.5 (0.8); CON= 27.8 (0.8)	eTRE: weight ↓3.5 kg[1]; fat mass ↓2.2 kg[1]; visceral fat area ↓13.3 cm^2 [1] lTRE: weight ↓2.9 kg[1]; fat mass ↓2.6 kg[1]; visceral fat area ↓14.2 cm^2 [1]	eTRE: eat ad libitum from 07:00 to 13:00 lTRE: eat ad libitum from 12:00 to 18:00	8	Ad libitum without any time restriction	hs-CRP, IL-6, TNF-α, leptin, adiponectin

Abbreviations: eTRE, early time-restricted eating; hs-CRP, high-sensitivity C-reactive protein; IL interleukin; lTRE, late time-restricted eating; MS, metabolic syndrome; mTRE, mid time-restricted eating; NAFLD, nonalcoholic fatty liver disease; Ob, obesity; OW, overweight; PCOS, polycystic ovarian syndrome; TRE, time-restricted eating.
↓ indicates a reduction; —, not reported/not available
[1]Denotes $P < 0.05$

employed method to assess the changes in leptin levels was immunoassay kits (Supplemental Table 3).

Most studies reported lower leptin levels after the TRE intervention. Indeed, the pooled SMD for RCTs on the effect of TRE compared with the control group on leptin levels was −0.81 (95% CI: −1.37, −0.24; I^2 = 65.3%; n = 5 comparisons) (Figure 3A). The subgroup analysis by health status showed significant leptin decreases in those with overweight/obesity and not for the healthy/trained individuals (Supplemental Table 5). The sensitivity analysis showed that when studies were removed one by one, none modified the SMD estimate (Supplemental Table 6). None of the covariates explored influenced our estimates in the meta-regression models (Supplemental Table 7). Finally, after exploring funnel plot asymmetry and the Egger test, there was no evidence of publication bias (P = 0.88) (Supplemental Table 8).

Adiponectin

Among the 8 studies reporting data for adiponectin levels, 6 were RCTs [7,14,26,34–36], and 2 were non-RCTs [15,23]. Overall, these studies included 276 participants, of which 154 followed TRE protocols, and 122 were in the control groups. There were 2 studies conducted in individuals with overweight and/or obesity [23,26] and 1 in males with prediabetes [7]; 5 studies were performed in healthy individuals, 2 of which were in resistance-trained males [14,15] and 1 in elite cyclists [34] (Table 1).

The mean length of the intervention was 11.3 wk (range: 4–48). Five of 7 studies reported a TRE protocol with an 8-h eating window (16:8), 1 study applied a 10-h eating window (12:10), and 2 used a 6-h eating window (18:6) [7,26] (Table 1). Most of the control groups followed their usual ad libitum diets without any time restriction, but 1 study reported using the same caloric restriction in the control group (25%) [36], and another compared TRE with hypocaloric orthodox fasting [23].The most employed method to assess the changes on adiponectin levels was immunoassay kits (Supplemental Table 3).

Most studies reported non-significant higher adiponectin levels when comparing TRE with the control group. The pooled SMD for RCTs on the effect of TRE compared with the control group on adiponectin levels was 0.07 (95% CI: −0.40, 0.54; I^2 = 56.9%; n = 6 comparisons) (Figure 3B). The subgroup analysis by health status did not modify the SMD estimate (Supplemental Table 5). The sensitivity analysis showed that when studies were removed one by one, none modified the SMD estimate (Supplemental Table 6). None of the covariates explored influenced our estimates in the meta-regression models (Supplemental Table 7). Finally, after exploring funnel plot asymmetry and the Egger test, there was no evidence of publication bias (p=0.88) (Supplemental Table 8).

Risk of bias and quality of the evidence

Based on the RoB2 tool, 7 out of 13 RCTs scored on overall risk of bias at "low risk of bias," and 6 scored at "some concern." Quality details for each domain and a summary of the overall assessment for all RCTs are presented in Supplemental Figure 1.

According to the overall risk of bias for the non-RCTs (ROBINS-I), 5 out 9 studies were rated as "moderate risk of bias," 1 as "serious risk of bias," and 3 as "critical risk of bias." Quality details for each domain and summary overall assessment for all non-RCTs are presented in Supplemental Figure 2.

Finally, the summary of the findings according to the GRADE framework, including only the RCTs in the meta-analysis, showed that the certainty of the evidence was "high" for CRP, TNF-α, and

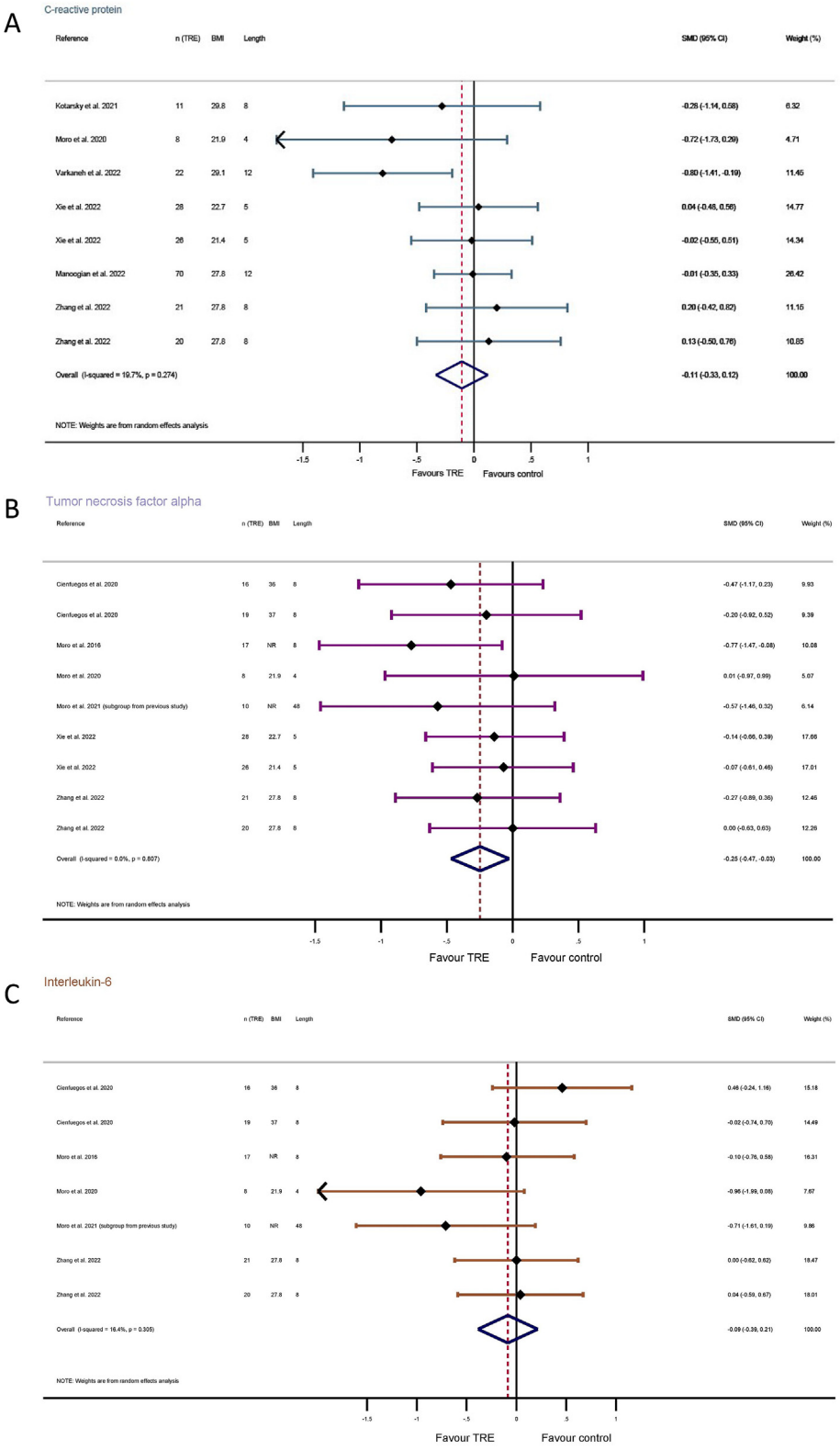

FIGURE 2. Meta-analysis of the standardized mean difference on randomized controlled trials for the effect of time-restricted eating compared with the control group on C-reactive protein (A), tumor necrosis factor α (B), and interleukin-6 (C).

leptin, "low" for IL-6, and "very low" for adiponectin. The scores were downgraded because of imprecisions (adiponectin), indirectness, and risk of bias (IL-6). The summary of findings for the GRADE assessment is available in the supplementary material (Supplemental Table 9).

Discussion

Data from our systematic review and meta-analysis suggest that the different TRE protocols decrease key cytokines and adipokines. Although no changes were observed for CRP, IL-6, and adiponectin,

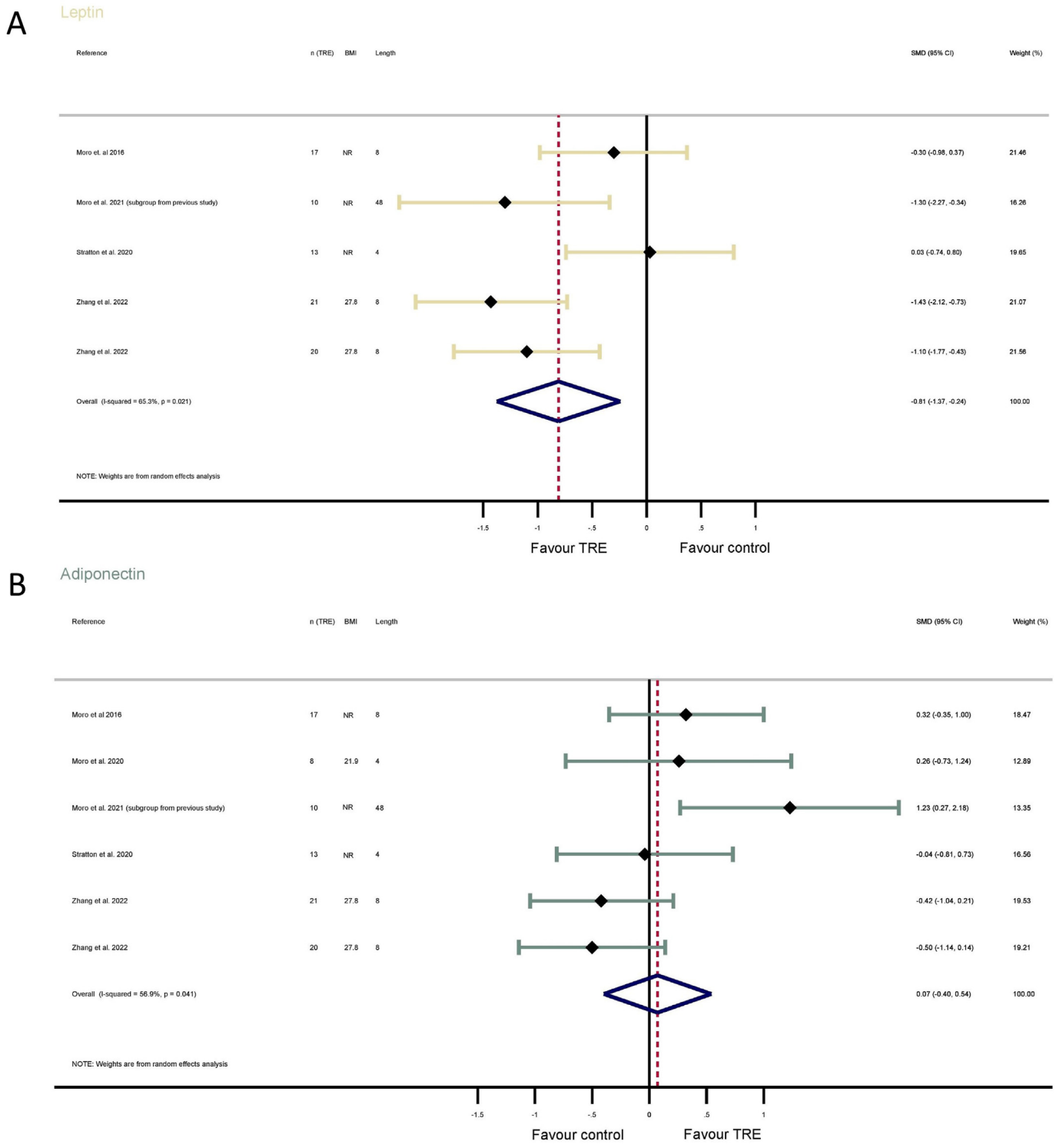

FIGURE 3. Meta-analysis of the standardized mean difference on randomized controlled trials for the effect of time-restricted eating compared with the control group on leptin (A) and adiponectin (B).

TRE significantly reduced TNF-α and leptin levels when compared with control conditions in the general adult population.

Evidence from a recent systematic review and meta-analysis investigating the effects of intermittent fasting and caloric restriction on inflammatory cytokines indicate that these dietary strategies improve CRP levels [47]. Their analysis also found greater CRP reductions in individuals with overweight and obesity compared with otherwise healthy individuals. Contrastingly, in the present study, it was found that TRE does not lower CRP concentrations in adults of the general population. In addition, the subgroup analysis revealed no significant difference in CRP levels between those with overweight or obesity and the healthy and trained individuals. Despite observing modest weight losses (Table 1), most studies included in this analysis noted no significant changes in CRP levels. This observation is line

a with a recent review of human trials suggesting that, regardless of meal timing and eating window duration, TRE has no effect on circulating levels of CRP with weight loss between 1% and 5% [2].

Previous systematic reviews and meta-analyses found little to no evidence of the effects of intermittent fasting, caloric restriction, or TRE on TNF-α in humans with obesity [47–51]. Conversely, our data indicate that TRE diminishes TNF-α levels in adults regardless of health statuses and even with modest weight losses (Table 1). Previous studies indicate that 11% to 16% weight loss by caloric restriction is necessary to observe changes in systemic biomarkers of inflammation [52]. That data suggests that TRE's health benefits may not entirely be weight loss driven. In fact, there is increasing evidence that TRE may aid to re-establish normal circadian rhythms and improves metabolism as well as several markers of immune function [13,53]; thus, eating in phase with our circadian rhythms promotes health. As such, the plausible realignment of circadian clocks during TRE may be a potential driver for the reduction of TNF-α. However, sensitivity analyses revealed that all 3 studies with significant TNF-α reductions modified the SMD estimates, indicating that our interpretation of the results may be uncertain. More rigorous research is needed to make further conclusions regarding the weight loss-independent effects of TRE.

As for IL-6, our findings are consistent with other systematic reviews and meta-analyses that reported no changes in systemic IL-6 in adults of the general population following intermittent fasting, caloric restriction, or TRE [47,49,50]. In this study, the heterogeneity of the included participants may have been a determining factor. Indeed, 3 studies included in this systematic review measured IL-6 in individuals with obesity, and none found fluctuations of IL-6 levels despite modest changes in weight and body composition. Previous reports indicate that 5% to 16% body weight loss induced either by calorie restriction or TRE are insufficient to reduce systemic IL-6 [2,52]. Contrastingly, Moro et al. [35] found in that in healthy individuals, 12 mo of TRE with significant weight and visceral fat mass losses (−3.4% and −18.8%, respectively) reduced IL-6. Most of the shorter TRE interventions in healthy to obese individuals did not observe any change in IL-6 [7,15,25,26,32,34]. Therefore, longer interventions along with greater weight loss may be necessary to lower IL-6 levels. Of note, significant publication bias was detected for IL-6, and thus, our interpretation of the results may be incorrect. The low statistical power and the scarcity of trials also makes it difficult to draw any conclusions.

Leptin and adiponectin are important homeostatic adipokines produced by adipose tissue and are necessary to maintain whole-body metabolism. While adiponectin regulates glucose levels, lipid metabolism, and insulin sensitivity through its anti-inflammatory effects [54], leptin is primarily a regulator of energy homeostasis [55]. However, there is increasing evidence that leptin modulates both innate and adaptive immune responses by upregulating the secretion of several cytokines [56] as well as promoting immune cell activation, proliferation, and chemotaxis [57]. Furthermore, the circulatory levels of adipokines are dependent upon fat mass [58,59]. As such, weight and fat mass losses may reduce leptin concomitantly with inflammation.

In this study, our analyses indicate that TRE reduced leptin in those with overweight and obesity, but did not significantly increase adiponectin. Fluctuations in leptin levels were concurrently observed with total fat mass loss and particularly visceral fat mass loss. However, only 2 studies measured both leptin and visceral fat mass pre- and post-TRE. For example, Moro et al. [35] found that after 12 mo of TRE, leptin decreased by 25%, which was negatively correlated with both body weight and fat mass. TRE also decreased visceral fat mass by 19%, which may further lower leptin concentrations [35]. Interestingly, another study found that despite similar total body fat and visceral fat area losses, early TRE reduced leptin to a greater extent than late TRE [26], therefore indicating that TRE with different meal timing may impact leptin differently.

With regard to adiponectin, our findings are in line with a previous systematic review and meta-analysis suggesting that fasting and energy-restricted diets have no effects on adiponectin concentrations [60]. Despite observing clinically relevant changes in body weight and fat mass, not all studies found that TRE increases adiponectin concentrations [7,15,32,36]. Overall, inconsistent and limited results preclude definitive conclusions on adiponectin following TRE protocols.

The methods employed to measure CRP, TNF-α, IL-6, leptin, and adiponectin may also partially explain the inconsistency of results. Intra-individual variability [61], the concentration of the markers of interest [62,63] as well as the medium (e.g., plasma compared with serum) [64–66] from which measurements are taken will greatly affect the choice of method to be used and the variability of outcomes. As such, results should be cautiously interpreted, considering that not all methods are equal.

Several factors may underlie the anti-inflammatory and immunomodulatory effects of TRE. Meal timing is a strong entraining cue of circadian rhythmicity and peripheral clocks and may possibly impact markers of inflammation [10]. Since circadian rhythms play a role in regulating inflammation and immune functions [67], eating out of phase with daily circadian rhythms has been shown to exacerbate the chronic low-grade inflammation associated with obesity in mice [68,69]. As such, TRE may dampen inflammation as well as the reactivity of the immune system. Lastly, TRE may exert its anti-inflammatory properties via modulation of the gut microbiome. Several studies indicate that TRE increases gut microbial diversity and health-promoting groups of bacteria [24,70], which, in turn, may also impact positively inflammation and immunity [71].

This systematic review and meta-analysis has several limitations. The vast majority of studies originated from Western countries, and the extrapolation of these results may not be applicable to Eastern populations. Significant heterogeneity in the studies included was encountered due to various regimens, doses, duration, center settings, and populations enrolled. In addition, many of the included studies also suffer from significant sources of bias. Furthermore, on many occasions, the analysis was assessed by only a few studies, and we were unable to perform stratified analyses and meta-regression models to determine the influence of some covariates in our estimates. Although a subgroup analysis was conducted, results should be interpreted with caution.

In summary, our findings suggest that TRE may represent an effective strategy to lower the concentrations of TNF-α and leptin. Although some of the observed changes may be in part weight loss driven, further research is needed to reveal the mechanistic underpinnings of TRE's benefits; some may not be entirely meditated by weight loss. Furthermore, longer and more controlled RCTs with larger sample sizes aiming at comparing various forms of TRE to other fasting and energy-restricted diets in different populations are also necessary.

Author contributions

The authors' responsibilities were as follows—RF-R: conceptualization of the study; LT, RF-R: literature search; LT, RC, RF-R: data extraction; LT, RC, RF-R: quality assessment; RF-R: data analysis; LT,

RF-R: interpretation of results; LT, RF-R: wrote the manuscript; VM-V, AH, LKH: edited the manuscript; RC, VM-V, AH, LKH: reviewed the manuscript; and all authors: read and approved the final manuscript.

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Data availability

Data described in the manuscript, code book, and analytic code will be made available upon reasonable request pending application and approval.

Conflict of interest

The authors report no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2023.10.009.

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