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

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Abstract

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

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

Results: Forty-six studies were included. Compared to the ones within control groups, participants exposed to the IF intervention reduced their body weight (WMD, -1.78 kg; 95% CI, -2.21 to -1.35; $p < 0.05$), waist circumference (WMD, -1.19 cm; 95% CI, -1.8 to -0.57; $p < 0.05$), fat mass (WMD, -1.26 kg; 95% CI, -1.57 to -0.95; $p < 0.05$), body mass index (WMD, -0.58 kg/m^2; 95% CI, -0.8 to -0.37; $p < 0.05$), systolic blood pressure (WMD, -2.14 mmHg; 95% CI: -3.54 to -0.73; $p < 0.05$), diastolic blood pressure (WMD: -1.38 mmHg, 95% CI, -2.35 to -0.41, $p < 0.05$), fasting blood glucose (WMD, -0.96 mg/dL; 95% CI, -1.89 to -0.03; $p < 0.05$), fasting insulin (WMD, -0.8 μU/mL; 95% CI, -1.15 to -0.44; $p < 0.05$), insulin resistance (WMD, -0.21; 95% CI, -0.36 to -0.05; $p < 0.05$), total cholesterol (WMD, -3.75 mg/dL; 95% CI, -6.64 to -0.85; $p < 0.05$), triglycerides (WMD, -7.54 mg/dL; 95% CI, -11.45 to -3.63; $p < 0.05$). No effects were observed for low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or glycosylated hemoglobin.

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

Introduction

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

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

Table 1
Types of intermittent fasting and description

Type of Fast	Description
Alternate-day fasting (ADF)	A circular diet that requires fasting for a day (consumption of no calories) and then eating freely for a day [73].
Alternate-modified-day fasting (AMDF)	A circular feeding pattern that requires fasting (consumption of 20-25% of energy needs) for a day, and then eating freely for a day; the popular 5:2 diet includes a discontinuous strict energy limit of 2 days a week and 5 other days of random eating [14, 73].
Time-restricted feeding (TRF)	Complete fast (no calories) for at least 12 hours a day, and eating freely the rest of the time; the 16:8 fasting pattern currently prevails [14, 106, 107].
Periodic fasting (PF)	A circular weekly eating pattern that consists of fasting 1 to 2 days a week (burning 25% or less of the calories required) and eating freely the rest of the week on a 6:1 or 5:2 scale [106].
Common religious fasts	These include: 1. The Islamic Ramadan fast: during the 30-day fasting holy month of Ramadan, worshippers fast from sunrise to sunset and eat freely after sunset [108]. 2. Greek Orthodox fasts: During fasting, people fast dairy products, eggs, and meat for 40 days [109]. 3. Daniel fast: This is a biblical fast, usually for 10 to 40 days [109]. 4. Jewish fast: one of the major fasts in the Jewish calendar is the Yom Kippur fast [108].

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

sample size, a variety of IF types, and multiple effect indicators to determine the effectiveness of IF interventions in improving health outcomes and modifiable risk factors for people with MetS.

Methods

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

Data source and search strategy

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

Inclusion and Exclusion Criteria

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

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

Data extraction and study quality assessment

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

Quality assessment and publication bias

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

Data statistical and analysis

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

In order to determine the influence of IF on various effect indicators, it is necessary to change the mean value before and after intervention as well as the SD of the changes. Therefore, we used a method outlined in the Cochrane handbook [22, 24] to determine the SD of changes between time points. $SD_{change}=\sqrt{[SD_{baseline}^2+ SD_{final}^2- (2 \times R \times SD_{baseline}\times SD_{final})]}$. In addition, we performed some conversion of data units through international calculation formulas to ensure that results are clinically significant.

Results

Characteristics of included studies

The PRISMA statement flow diagram is shown in Fig. 1[25]. A total of 9087 studies were part of the initial database search (PubMed: 6128, EMBASE: 40, Cochrane Library: 2919), after the removal of 1540 duplicate studies. After filtering the titles and abstracts to exclude irrelevant articles, we found 106 studies that met the topic of interest. The full texts of the 106 records were reviewed. Of them, 60 records were excluded for the following reasons: data not available (n= 15), literature review, letter, or case report (n= 34), unrelated to relevant predictive factors (n= 2), related to protocol (n = 2), and meta-analyses (n = 7). Finally, 46 studies from the database searches were included in the meta-analysis[15, 26-71]. A total of 2681 participants were randomized in the IF

intervention group (n = 1423) and the control group (n = 1258). The characteristics of the eligible trials are summarized in Table 2. All the results calculated using Stata are shown in Table3.

Table 2
Characteristics of studies included in the meta-analysis

Study and publication year	Country	RCT design (blinding)	Total sample (case: control)	Participants	Intervention and intervention details	Control	Duration	Mean age	Sex (F: M)	O
Chow et al. (2020)[35]	USA	A randomized clinical trial	11:9	People with overweight or obesity	TRF: 11:8 hour window, with unrestricted eating within the window	Unrestricted (non-TRE) control	12w	46.5 ±12.4	9:2	w FI D LI H
Cienfuegos et al. (a) (2020) [36]	USA	A randomized controlled trial	16:14	Adults with obesity	4-hour TRF: eating only between 3 and 7 pm (without having to count calories)	The control group continued their usual diet pattern with no meal timing restrictions	8w	47 ± 8	14:2	FI D LI H FI H H
Cienfuegos et al. (b) (2020) [36]	USA	A randomized controlled trial	19:14	Adults with obesity	6-hour TRF: eating only between 1 and 7 pm (without having to count calories)	The control group continued their usual diet pattern with no meal timing restrictions	8w	47 ± 13.8	18:1	FI D LI H FI H H
de Oliveira Maranhao Pureza et al. (2020)[39]	Brasil	A randomized, parallel, controlled clinical trial	31:27	Obesity people	TRF and a hypoenergetic diet: meals only in a 12-hour feeding window and fasting for the other 12 hours.	Hypo energetic diet	12w	31.03 ±7.16	NA	w W SI
Domaszewski et al. (2020) [40]	Poland	A randomized clinical trial	25:20	Overweight women over 60 years of age	Experimental group involved completely abstaining from food for 16 hours a day, from 8 pm to 12 am (the next day)	Followed their previous eating plan	6w	65 ± 4	25f	w FI
Finlayson et al. (2020)[41]	USA	A parallel-group controlled-feeding randomized controlled trial	24:22	Overweight and obesity Women	IER: alternating ad libitum and 75% energy restriction days	CER	12w	34 ± 10	24f	W BI
Lowe et al. (2020)[15]	USA	A randomized clinical trial	59:57	Adults with obesity	TRF: Eat 8 hours a day and fast the rest of the day	Consistent meal timing	12w	46.8 ±10.8	24:35	w W
Martens et al. (2020)[50]	USA	A randomized controlled crossover trial	14:10	Healthy middle-aged and older men and postmenopausal women	TRF: Eat 8 hours a day and fast the rest of the day	Chronic calorie restriction	6w	66 ± 6.92	7:5	T LI H FI
Pinto et al. (2020)[69]	UK	A parallel-arm randomized controlled trial	21:22	Non-smoking men and women	Short-term effects of IER: 48 hours, 600 kcal/day, followed by 5-day healthy eating advice	CER: 500 kcal/day, healthy eating advice	4w	50 ± 12	15:6	w W SI T Fi H
Pureza et al. (2020)[54]	Brazil	A randomized, parallel, controlled trial	31:27	Women with obesity	Hypoenergetic diet with TRF. women were instructed to eat only	A diet with the same energy restriction but without TRF	21d	31.8 ± 7.25	31f	W W SI FI H

					during a 12 hour and fasted during the other 12 hours					
Stratton et al. (2020)[57]	USA	A randomized controlled trial	13:13	Active males	TRF: 8 hours eating window, 25% caloric deficit, 1.8 g/kg/day protein, and body resistance training	Normal diet and body resistance training	4w	22.9 ± 3.6	13m	w FI
Cai et al. (a) (2019)[29]	China	A randomized clinical trial	90:79	Adults with nonalcoholic fatty liver disease (NAFLD)	ADF: 25% baseline energy needs, mealtime between 12.00 p.m. and 2.00 p.m	Control group	12w	35.50±4.417	60:35	w W BI T(C, FI
Cai et al. (b) (2019)[29]	China	A randomized clinical trial	95:79	Adults with nonalcoholic fatty liver disease (NAFLD)	TRF: 16:8 fasting window	Control group	12w	33.56 ± 6.23	66:29	w W BI T(C, FI
Cho et al. (a) (2019)[34]	Korea	A randomized, controlled, parallel-arm diet trial	9:9	Asian population with overweight or obesity	ADF and exercise	Continued their regular eating and exercise habits	8w	34.5 ± 5.7	4:5	w FI T(LI H FI H
Cho et al. (b) (2019)[34]	Korea	A randomized, controlled, parallel-arm diet trial	8:9	Asian population with overweight or obesity	ADF	CER	8w	33.5 ± 5	6:2	w FI T(LI H FI H
Gabel et al. (a) [42]	USA	Secondary analysis of a study	11:17	Individuals with overweight and obesity	ADF: participants consumed 25% of their baseline energy needs at lunch (between 12 and 2 pm)	Control group	12m	43±9.95	9:2	w FI SI T(LI H FI
Gabel et al. (b) (2019)[42]	USA	Secondary analysis of a study	11:15	Individuals with overweight and obesity	ADF: participants consumed 25% of their baseline energy needs at lunch (between 12 and 2 pm)	CR: consumed 75% baseline energy	12m	43±9.95	9:2	w FI SI T(LI H FI
Hirsh et al. (2019)[46]	USA	A randomized clinical trial	10:12	Overweight individuals	Nutrition program group: two fasting days of balanced shake and dietary supplements, 5 days of habitual diet	Habitual diet	52d	43.4±13	8:2	w SI T(LI H Fi
Panizza et al. (2019)[52]	USA	A randomized active comparator pilot study	30:30	BMI 25–40 kg/m^2, VAT ≥ 90 cm for men and women	IER and a Mediterranean diet: 2 consecutive days with 70% energy restriction and 5 days of a Mediterranean diet	Dietary Approaches to Stop Hypertension diet	12w	48.4±4.7	21:9	w W BI D T(C, FI
Parvaresh et	Iran	A single-	35:34	Patients with	ADF: 25% of	CR	8w	44.6±9.08	14:20	w

al. (2019)[53]		center, randomized clinical trial		MetS and overweight	the individual's energy needs					W Sl T LI H FI H
Stekovic et al. (2019)[71]	Austria	An embedded randomized controlled trial	30:30	Healthy study participants	ADF: eat every second-day ad libitum, refrain from calorie intake on the fast days	Ad libitum number of meals	4w	48	17:12	w FI Sl H
Tinsley et al. (2019)[63]	USA	A randomized controlled trial	13:14	Healthy females	TRF: consume all calories between 12 and 8 pm each day	Control diet	8w	22.1 ± 7.27	13f	w FI D T C, FI
Antoni et al. (2018)[30]	UK	A randomized, parallel-arm trial	15:12	Individuals with overweight and obesity	IER: 25% of the energy requirements for two consecutive days. On the remaining 5 normal days	CER	7d	45±15.49	7:8	w W Sl T C, FI H
Bowen et al. (2018)[27]	Australia	A randomized parallel study	82:81	Adults with overweight and obesity	ADF + Daily energy restriction (DER); 3 days of ADF, 3 days of alternate DER, and one ad libitum day	Daily energy restriction	16w	40.0 ± 8.3	67:15	w FI Sl T LI H FI
Byrne et al. (2018)[28]	Australia	A single-center, parallel-group, randomized controlled trial	26:25	Males with obesity	IER: alternating ad libitum and 75% energy restriction days	CER	16w	39.9± 9.2	26m	w FI
Carter et al. (2018)[32]	Australia	A randomized noninferiority trial	70:67	Adults with type 2 diabetes who were overweight or obese	IER: 500-600 kcal/day, followed for 2 nonconsecutive days per week (their usual diet for the other 5 days)	CER	12m	61±9	39:31	w FI H
Conley et al. (2018)[37]	Australia	A single-center, parallel-group randomized controlled trial	11:12	Veterans: males with a BMI greater than or equal to 30 kg/m^2 and stable weight	IER: 2 non-consecutive days per week (restrict calorie intake to 600 calories) and eat ad libitum on the remaining 5 days	Standard energy-restricted diet	3m	68 ± 2.7	11m	w W Sl T LI H FI
Corley et al. (2018)[68]	Australia	A randomized controlled trial	19:18	Participants with type 2 diabetes who were taking medication for diabetes	Non-consecutive days caloric restriction: 5:2 schedule a VLCD for 2 days per week	CR	12w	58 (42 to 74)	8:11	w W Bl D T C, FI H
Coutinho et al. (2018)[38]	Norway	A randomized controlled trial	14:14	Adults with obesity	IER: 3 non-consecutive days (followed a commercial very low-calorie diet (550 and 660 kcal/day for women and	CER: followed a low-calorie diet	12w	39.4±11.0	10:4	w FI

					men, respectively)					
Gasmi et al. (young) (2018)[43]	Italy	A randomized controlled trial	10:10	Young men	TRF: young and older were asked to fast for 2 days separated by 48 hours (Monday and Thursday) for 3 months (February, March, April)	Normal meals	12w	26.90±1.97	10m	w
Gasmi et al. (old) (2018) [43]	Italy	A randomized controlled trial	10:10	Aged men	TRF: young and older were asked to fast for 2 days separated by 48 hours (Monday and Thursday) for 3 months (February, March, April)	Normal meals	12w	51.60±5.87	10m	w
Hutchison et al. (a) (2018) [47]	Australia	A randomized controlled trial	25:26	Overweight women	IF70: an IF diet at 70% of calculated baseline energy requirements per week	Dietary restriction (DF70)	8w	49 ± 10	25f	w W D T C, F H
Hutchison et al. (b) (2018) [47]	Australia	A randomized controlled trial	25:12	Overweight women	IF100: an IF diet at 100% of calculated baseline energy requirements per week	Continuous energy intake at 100 % of baseline energy	8w	51 ± 10	25f	w W D T C, F H
Schübel, et al. (2018)[55]	Germany	A randomized controlled trial	49:49	Men and women with overweight and obesity	IER: 5:2 diet (2 days with 75% energy deficit and 5 days without energy restriction)	No advice to restrict energy	12w	49.4 ± 9.0	24:25	T LI H FI H
Sundfor et al. (2018)[58]	Norway	A randomized controlled clinical trial	54:58	Men and women with overweight and obesity	IER: 5:2 diet	CER	6m	49.9±10.1	26:28	w W SI T LI H FI H
Trepanowski et al. (a) (2018)[64]	USA	A randomized controlled trial	25:29	Men and women with overweight and obesity	ADF: repeatedly alternate between consuming 25% of energy needs over 24-hour	CR	24w	46 ± 10	22:3	FI Fi H
Trepanowski et al. (b) (2018)[64]	USA	A randomized controlled trial	25:25	Men and women with overweight and obesity	ADF: repeatedly alternate between consuming 25% of energy needs over 24-hour	Consumed 100% of energy needs every day	24w	46 ± 10	22:3	FI Fi H
Li et al. (2017)[49]	Germany	A randomized controlled clinical pilot study	23:23	Persons with a manifest and treated type 2 diabetes	A 7-day fasting program (an initial fasting program followed a Mediterranean diet)	A Mediterranean diet	4m	64.7 ± 7.0	NA	w W SI T LI H FI H H
Wei et al. (2017)[66]	USA	A randomized crossover design	52:48	Healthy participants	Fasting-mimicking diet: a plant-based diet designed to attain	Unrestricted diet	3m	43.3 ± 11.7	33:19	w W SI T LI

					fasting-like effects					H FI
Carter et al. (2016)[31]	Australia	A parallel randomized controlled trial	31:32	Obesity adults with type 2 diabetes mellitus; BP of <160/100 mmHg	IER: an ER of 1670-2500kJ/day for 2 days each week, and the remaining 5 days included habitual eating	CER	12w	61 ± 7.5	17:14	w FI H
Catenacci et al. (2016)[33]	USA	A randomized pilot study	13:12	Individuals with obesity	ADF: zero-calories	Caloric restriction (2400 kcal/day)	8w	39.6±9.5	9:3	w FI T(LI H FI
Moro et al. (2016)[51]	Italy	A randomized controlled trial	17:17	Resistance-trained males	TRF: participants consumed 100% of energy needs in an 8-hour	Normal diet group	8w	29.94 ± 4.07	17m	FI T(C, FI
Tinsley et al. (2016)[62]	USA	A randomized controlled trial	10:8	Generally healthy, recreationally active men	Resistance training and TRF: consuming all calories within a four-hour period, 4 days per week. Resistance training program was performed 3 days per week	Resistance training and normal diet	8w	22.9 ± 4.1	10m	w FI
Keogh et al. (2014)[48]	Australia	A parallel, randomized controlled trial	19:17	Women with overweight or obesity	IER: 1-week normal diet followed by 1 week of energy restriction	CER	52w	59.5 ± 8.7	19f	w W
Harvie et al. (b) (2013)[44]	USA	A single-center, randomized study	37:40	Women with overweight or obesity	IECR: restrict energy and carbohydrates on 2 consecutive days each week and Mediterranean-type diet for the remaining 5 days of the week	Daily energy restriction	3m	45.6±8.3	37f	w W T(C, FI H H(
Harvie et al. (a) (2013)[44]	USA	A single-center, randomized study	38:40	Women with overweight or obesity	IECR and ad libitum protein and fat	Daily energy restriction	3m	48.6 ±7.3	38f	w W T(C, FI H H(
Teng et al. (2013)[61]	Malaysia	A randomized controlled trial	28:28	Healthy (non-diabetic and no history of cardiovascular diseases) Malay men	Fasting calorie restriction	Maintain their present lifestyle	6w	59.6±5.4	28m	w FI SI T(LI H FI
Varady et al. (2013)[65]	USA	A randomized, controlled, parallel-arm feeding trial	15:15	Healthy people	ADF: 25% of their baseline energy needs on the fast day and then ate ad libitum on each alternating feed day	Ad libitum	12w	47±7.74	10:5	SI T(LI H
Bhutani et al. (2013)[70]	US	A randomized,	25:16	Adults with obesity	A 4-week controlled	Ad libitum number of	12w	42 ± 10	24:1	w W

		controlled, parallel-arm feeding trial			feeding period: 25% of their baseline energy needs on the “fast day” and an 8-week self-selected “feeding period”	meals				Bl D T(C, FI H(
Arguin et al. (2012)[26]	USA	A randomized pilot study	12:10	Postmenopausal women with sedentary obesity	IF: food was self-selected with dietitian supervision on macronutrient composition (55%, 30%, and 15% of energy intake from carbohydrates, fats, and proteins, respectively	Continuous diet	30w	60.5 ±6.0	12f	w W T(LI H FI
Harvie et al. (2011)[45]	USA	A randomized trial	53:54	Premenopausal women with overweight	IER: 25% restriction delivered as a VLCD for 2 days per week, with no restrictions on the other 5 days of the week.	CER	6m	40 ±14.1	53f	w W D T(C, FI H(
Teng et al. (2011)[60]	USA	A randomized controlled trial	13:12	Healthy Malay men	Fasting calorie restriction: reduce daily energy intake by 300-500 kcal/day and fast two days a week for three months	Maintenance of present lifestyle	12w	59.3 ± 3.4	13m	w Bl
Stote et al. (2007)[56]	USA	A randomized crossover design	Total (15)	Healthy, normal-weight, middle-aged adults	1 meal/d	3 meals/d	8w	45 ±2.71	10:5	w FI D T(C, FI
Williams et al. (a) (1998)[67]	USA	A parallel Arms	18:18	T2DM patients	IER (1 day/ week): 400– 600 kcal/day on fast day and 1500–1800 kcal/ day on feed day	CER:1500– 1800 kcal/day every day	20w	51 ± 8	9:9	w T(LI H Fi
Williams et al. (b) (1998)[67]	USA	A parallel Arms	18:18	T2DM patients	IER (5 days/ week): 400– 600 kcal/day on fast day every 5 weeks and 1500–1800 kcal/ day on feed days	CER:1500– 1800 kcal/day every day	20w	50 ± 9	11:7	w T(LI H Fi

Table 3
All the results calculated using Stata

Characteristic	Trials	Participants	WMD	95% CI	z	p	I^2 (%)	p for heterogeneity
body composition								
Weight (kg)	45	2225	-1.78	(-2.21, -1.35)	8.11	0.000	0	0.960
WC (cm)	23	1385	-1.19	(-1.80, -0.57)	3.77	0.000	23.8	0.148
FM (kg)	33	1610	-1.26	(-1.57, -0.95)	7.87	0.000	22.9	0.121
BMI (kg/m^2)	26	1590	-0.58	(-0.80, -0.37)	5.24	0.000	0	0.886
glycemic control								
FBG (mg/dL)	34	1863	-0.96	(-1.89, -0.03)	2.02	0.044	44.4	0.003
Fins (μU/mL)	26	1161	-0.80	(-1.15, -0.44)	4.40	0.000	24.3	0.130
HbA1c (%)	9	544	-0.06	(-0.18, 0.05)	1.07	0.287	0	0.974
HOMA-IR	19	866	-0.21	(-0.36, -0.05)	2.66	0.008	38.4	0.046
blood pressure								
SBP (mmHg)	29	1393	-2.14	(-3.54, -0.73)	2.97	0.003	36.2	0.028
DBP (mmHg)	27	1277	-1.38	(-2.35, -0.41)	2.79	0.005	0	0.588
lipid panel								
TC (mg/dL)	33	1766	-3.75	(-6.64, -0.85)	2.54	0.011	14.6	0.233
TG (mg/dL)	34	1750	-7.54	(-11.45, -3.63)	3.78	0.000	5.5	0.377
LDL-C (mg/dL)	36	1850	-2.15	(-4.42, 0.12)	1.85	0.064	0	0.967
HDL-C (mg/dL)	36	1852	-0.54	(-1.46, 0.38)	1.15	0.250	0	0.858

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

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

Risk of bias and quality assessment of studies

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

Meta-analysis results

Effect of IF on body composition

Body composition was operationalized in weight, WC, FM, and BMI. Forty-five studies, with 2225 participants (case = 1136, control = 1089), showed a consistent effect of IF on weight (Fig. 3a). The fixed-effect analysis showed significant weight reduction (WMD, -1.78 kg, 95% CI: -2.21 to -1.35, $p < 0.05$), thus, indicating significant weight loss. There was no evidence of effect heterogeneity ($I^2 = 0.0\%$, $p = 0.96$). Regarding funnel plot symmetry and Egger's test, $p = 0.547$ (Fig. 4a).

Pooled data from 23 studies (1385 participants: case = 714, control = 671) showed a consistent effect of IF on WC (Fig. 3b). While the fixed-effect analysis showed a significant WC reduction (WMD: -1.19 cm, 95% CI: -1.8 to -0.57, $p < 0.05$), there was also evidence of effect heterogeneity ($I^2 = 23.8\%$, $p = 0.148$). Regarding funnel plot symmetry and Egger's test, $p = 0.576$ (Fig. 4b).

A pooled meta-analysis including 33 studies with 1610 participants, found a significant effect of IF on FM when compared to placebo (WMD: -1.26 kg, 95% CI: -1.57 to -0.95, $p < 0.05$) (Fig. 3c). There was a slight effect heterogeneity ($I^2 = 22.9\%$, $p = 0.121$). Regarding funnel plot symmetry and Egger's test, $p = 0.498$ (Fig. 4c).

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

Effect of IF on glycemic control

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

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

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

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

Effect of IF on BP

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

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

Effect of IF on blood lipid panel

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

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

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

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

Sensitivity analysis

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

Discussion

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

Overall, in terms of body composition, there was a significant positive correlation between BMI and weight loss during IF (i.e., the higher the starting BMI, the greater the weight loss during the fasting period). This suggests that IF may be more effective for people with a higher BMI. The results for the effect of IF on body composition were similar to those obtained in a previous meta-analysis, by [72], which involved 11 trials that found that TRF was effective in promoting weight loss and reducing FBG compared to not limiting meal times approaches. In addition, IER was more effective in reducing weight than a regular control diet. Moreover, it was also more effective in reducing FM level than CER [73]. In a meta-analysis on religious fasting [74], it was found that overweight participants had a greater reduction in weight and percentage of fat than normal people. A recent meta-analysis of RCTs showed that ADF effectively lowered body composition and TC in overweight adults within 6 months compared to the control group [75]. However, in another meta-analysis of 12 RCTs, researchers confirmed that lean mass was relatively conserved in the IF group and no significant weight reduction was identified [34]. In addition, a recent study by Lowe, D.A., et al [15] on 16:8 time-restricted eating (TRE), an IF plan encouraging the consumption of all dietary intake within an 8-hour eating window, demonstrated that IF does not play a significant role in weight loss in the absence of controlled food intake. In turn, it may lead to a reduction in muscle mass. There were no significant differences in FM, Fins, glucose level, HbA1C, or blood lipids between the TRE and control groups. The results of Lowe's study are contrary to the results of most studies related to fasting. This may have been brought about by the time window of fasting. Meantime, our meta-analysis is also included in this study, but a comprehensive assessment of IF in body composition is beneficial.

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

Previous studies have shown that IF is not only beneficial in reducing the production of free radicals or weight loss; it also has several health benefits [7, 78-80]. IF can cause an evolutionarily conservative adaptive cellular response, improve blood glucose regulation, enhance anti-stress ability, and inhibit inflammation between and within organs. During fasting, cells activate pathways that enhance the body's defense against oxidation and metabolic stress as well as remove or repair damaged molecules. IF causes the organism to reach the stage of an alternative metabolism, which lays the foundation for improving the metabolic characteristics and healthy lifespan of the animal [78, 81]. Fat is the main energy source for cells and is stored in the adipose tissue in the form of TGs after meals. During fasting, TGs are broken down into fatty acids and glycerol, which are used to provide energy consumption by the organism [82]. Physiologically, fasting is defined as a change in the cell's response to food restriction, resulting in less glucose dependence and more reliance on ketone bodies as a fuel source. According to animal and human studies, ketone bodies can not only improve glucose homeostasis, mitochondrial function, and DNA repair but also stimulate autophagy, stem cell renewal, stress resistance, and inflammation inhibition [82, 83]. Thus, accelerated metabolic changes lead to fat consumption and weight loss [84].

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

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

Even though, many experiments have shown that IF is beneficial to human health and suitable for a wide range of metabolic diseases, this dietary pattern is rarely used in practice. The main reason for this is the three-meals-a-day habit in our daily lives. Second, when switching to an IF program, some people feel hungry, irritable, and lose concentration. Finally, doctors are required to prescribe specific training for IF interventions, which requires a standardized use of IF.

There are some limitations to this meta-analysis. As this is the case with some studies, some of the included ones have a small sample size, and there are several studies with a high risk of bias. Second, the number of long-term studies conducted is very limited, and larger long-term trials with a longer duration are needed to understand the effects of IF on weight loss and long-term weight management. Moreover, different types of IF have different characteristics in various metabolic diseases, and we did not analyze each of them individually. Finally, although IF has a variety of components, a comparison with other types of IF could not be conducted due to the lack of RCT research on religious fasting and lack of data on other kinds of fasting.

Conclusions

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

Abbreviations

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

Declarations

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Author contributions

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

Availability of data and materials

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

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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References

1. Cornier M, Dabelea D, Hernandez T, Lindstrom R, Steig A, Stob N, Van Pelt R, Wang H, Eckel R: **The metabolic syndrome**. *Endocrine reviews* 2008, **29**(7):777-822.
2. Alberti K, Zimmet P, Shaw J: **The metabolic syndrome--a new worldwide definition**. *Lancet (London, England)* 2005, **366**(9491):1059-1062.
3. Eckel R, Alberti K, Grundy S, Zimmet P: **The metabolic syndrome**. *Lancet (London, England)* 2010, **375**(9710):181-183.
4. Eckel R, Grundy S, Zimmet P: **The metabolic syndrome**. *Lancet (London, England)* 2005, **365**(9468):1415-1428.
5. Khunti K, Davies M: **Metabolic syndrome**. In.: British Medical Journal Publishing Group; 2005.
6. An N, Gao Y, Si Z, Zhang H, Wang L, Tian C, Yuan M, Yang X, Li X, Shang H *et al*: **Regulatory Mechanisms of the NLRP3 Inflammasome, a Novel Immune-Inflammatory Marker in Cardiovascular Diseases**. *Front Immunol* 2019, **10**:1592.
7. Grundy SM: **Metabolic syndrome update**. *Trends Cardiovasc Med* 2016, **26**(4):364-373.
8. Collier R: **Intermittent fasting: the next big weight loss fad**. In.: Can Med Assoc; 2013.
9. Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM: **Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes**. *Cell Metab* 2018, **27**(6):1212-1221.e1213.
10. Kim K, Kim Y, Son J, Lee J, Kim S, Choe M, Moon J, Zhong J, Fu K, Lenglin F *et al*: **Intermittent fasting promotes adipose thermogenesis and metabolic homeostasis via VEGF-mediated alternative activation of macrophage**. *Cell research* 2017, **27**(11):1309-1326.
11. Haluzík M, Mráz M: **Intermittent Fasting and Prevention of Diabetic Retinopathy: Where Do We Go From Here?** *Diabetes* 2018, **67**(9):1745-1747.
12. Lamos EM, Malek R, Munir KM: **Effects of Intermittent Fasting on Health, Aging, and Disease**. *N Engl J Med* 2020, **382**(18):1771.
13. Stekovic S, Hofer S, Tripolt N, Aon M, Royer P, Pein L, Stadler J, Pendl T, Prietl B, Url J *et al*: **Alternate Day Fasting Improves Physiological and Molecular Markers of Aging in Healthy, Non-obese Humans**. *Cell metabolism* 2020, **31**(4):878-881.
14. Patterson RE, Sears DD: **Metabolic Effects of Intermittent Fasting**. *Annu Rev Nutr* 2017, **37**:371-393.
15. Lowe DA, Wu N, Rohdin-Bibby L, Moore AH, Kelly N, Liu YE, Philip E, Vittinghoff E, Heymsfield SB, Olgin JE *et al*: **Effects of Time-Restricted Eating on Weight Loss and Other Metabolic Parameters in Women and Men With Overweight and Obesity: The TREAT Randomized Clinical Trial**. *JAMA Intern Med* 2020.
16. Carlson O, Martin B, Stote KS, Golden E, Maudsley S, Najjar SS, Ferrucci L, Ingram DK, Longo DL, Rumpler WV *et al*: **Impact of reduced meal frequency without caloric restriction on glucose regulation in healthy, normal-weight middle-aged men and women**. *Metabolism* 2007, **56**(12):1729-1734.
17. Soeters MR, Lammers NM, Dubbelhuis PF, Ackermans M, Jonkers-Schuitema CF, Fliers E, Sauerwein HP, Aerts JM, Serlie MJ: **Intermittent fasting does not affect whole-body glucose, lipid, or protein metabolism**. *Am J Clin Nutr* 2009, **90**(5):1244-1251.
18. Moon S, Kang J, Kim SH, Chung HS, Kim YJ, Yu JM, Cho ST, Oh C-M, Kim T: **Beneficial Effects of Time-Restricted Eating on Metabolic Diseases: A Systemic Review and Meta-Analysis**. *Nutrients* 2020, **12**(5).
19. Faris MAE, Jahrami HA, Alsibai J, Obaideen AA: **Impact of Ramadan Diurnal Intermittent Fasting on Metabolic Syndrome Components in Healthy, Non-Athletic Muslim People Aged Over 15 Years: A Systematic Review and Meta-Analysis**. *Br J Nutr* 2019:1-51.
20. McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, Clifford T, Cohen JF, Deeks JJ, Gatsonis C, Hooft L *et al*: **Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement**. *Jama* 2018, **319**(4):388-396.
21. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ: **GRADE: an emerging consensus on rating quality of evidence and strength of recommendations**. *BMJ (Clinical research ed)* 2008, **336**(7650):924-926.
22. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA: **Cochrane handbook for systematic reviews of interventions**: John Wiley & Sons; 2019.
23. Egger M, Davey Smith G, Schneider M, Minder C: **Bias in meta-analysis detected by a simple, graphical test**. *BMJ (Clinical research ed)* 1997, **315**(7109):629-634.
24. Hozo SP, Djulbegovic B, Hozo I: **Estimating the mean and variance from the median, range, and the size of a sample**. *BMC Med Res Methodol* 2005, **5**:13.
25. Moher D, Liberati A, Tetzlaff J, Altman DG: **Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement**. *PLoS Med* 2009, **6**(7):e1000097.
26. Arguin H, Dionne IJ, Senechal M, Bouchard DR, Carpentier AC, Ardilouze JL, Tremblay A, Leblanc C, Brochu M: **Short- and long-term effects of continuous versus intermittent restrictive diet approaches on body composition and the metabolic profile in overweight and obese postmenopausal women: a pilot study**. *Menopause* 2012, **19**(8):870-876.
27. Bowen J, Brindal E, James-Martin G, Noakes M: **Randomized Trial of a High Protein, Partial Meal Replacement Program with or without Alternate Day Fasting: Similar Effects on Weight Loss, Retention Status, Nutritional, Metabolic, and Behavioral Outcomes**. *Nutrients* 2018, **10**(9).
28. Byrne NM, Sainsbury A, King NA, Hills AP, Wood RE: **Intermittent energy restriction improves weight loss efficiency in obese men: the MATADOR study**. *Int J Obes (Lond)* 2018, **42**(2):129-138.
29. Cai H, Qin YL, Shi ZY, Chen JH, Zeng MJ, Zhou W, Chen RQ, Chen ZY: **Effects of alternate-day fasting on body weight and dyslipidaemia in patients with non-alcoholic fatty liver disease: a randomised controlled trial**. *BMC Gastroenterol* 2019, **19**(1):219.
30. Antoni R, Johnston KL, Collins AL, Robertson MD: **Intermittent v. continuous energy restriction: differential effects on postprandial glucose and lipid metabolism following matched weight loss in overweight/obese participants**. *British Journal of Nutrition* 2018, **119**(5):507-516.

31. Carter S, Clifton PM, Keogh JB: **The effects of intermittent compared to continuous energy restriction on glycaemic control in type 2 diabetes; a pragmatic pilot trial**. *Diabetes Research and Clinical Practice* 2016, **122**:106-112.
32. Carter S, Clifton PM, Keogh JB: **Effect of Intermittent Compared With Continuous Energy Restricted Diet on Glycemic Control in Patients With Type 2 Diabetes: A Randomized Noninferiority Trial**. *JAMA Netw Open* 2018, **1**(3):e180756.
33. Catenacci VA, Pan Z, Ostendorf D, Brannon S, Gozansky WS, Mattson MP, Martin B, MacLean PS, Melanson EL, Troy Donahoo W: **A randomized pilot study comparing zero-calorie alternate-day fasting to daily caloric restriction in adults with obesity**. *Obesity (Silver Spring)* 2016, **24**(9):1874-1883.
34. Cho AR, Moon JY, Kim S, An KY, Oh M, Jeon JY, Jung DH, Choi MH, Lee JW: **Effects of alternate day fasting and exercise on cholesterol metabolism in overweight or obese adults: A pilot randomized controlled trial**. *Metabolism* 2019, **93**:52-60.
35. Chow LS, Manoogian ENC, Alvear A, Fleischer JG, Thor H, Dietsche K, Wang Q, Hodges JS, Esch N, Malaeb S *et al*: **Time-Restricted Eating Effects on Body Composition and Metabolic Measures in Humans who are Overweight: A Feasibility Study**. *Obesity* 2020, **28**(5):860-869.
36. Cienfuegos S, Gabel K, Kalam F, Ezpeleta M, Wiseman E, Pavlou V, Lin S, Oliveira ML, Varady KA: **Effects of 4- and 6-h Time-Restricted Feeding on Weight and Cardiometabolic Health: A Randomized Controlled Trial in Adults with Obesity**. *Cell Metab* 2020, **32**(3):366-378 e363.
37. Conley M, Le Fevre L, Haywood C, Proietto J: **Is two days of intermittent energy restriction per week a feasible weight loss approach in obese males? A randomised pilot study**. *Nutr Diet* 2018, **75**(1):65-72.
38. Coutinho SR, Halset EH, Gasbakk S, Rehfeld JF, Kulseng B, Truby H, Martins C: **Compensatory mechanisms activated with intermittent energy restriction: A randomized control trial**. *Clin Nutr* 2018, **37**(3):815-823.
39. de Oliveira Maranhao Pureza IR, da Silva Junior AE, Silva Praxedes DR, Lessa Vasconcelos LG, de Lima Macena M, Vieira de Melo IS, de Menezes Toledo Florencio TM, Bueno NB: **Effects of time-restricted feeding on body weight, body composition and vital signs in low-income women with obesity: A 12-month randomized clinical trial**. *Clin Nutr* 2020.
40. Domaszewski P, Konieczny M, Pakosz P, Bączkowicz D, Sadowska-Krępa E: **Effect of a Six-Week Intermittent Fasting Intervention Program on the Composition of the Human Body in Women over 60 Years of Age**. *International Journal of Environmental Research and Public Health* 2020, **17**(11).
41. Finlayson G, Blundell J, Varady K, Hopkins M, Gibbons C, Turicchi J, Oustric P, Casanova N, Beaulieu K: **Matched Weight Loss Through Intermittent or Continuous Energy Restriction Does Not Lead To Compensatory Increases in Appetite and Eating Behavior in a Randomized Controlled Trial in Women with Overweight and Obesity**. *The Journal of Nutrition* 2020, **150**(3):623-633.
42. Gabel K, Kroeger CM, Trepanowski JF, Hoddy KK, Cienfuegos S, Kalam F, Varady KA: **Differential Effects of Alternate-Day Fasting Versus Daily Calorie Restriction on Insulin Resistance**. *Obesity (Silver Spring)* 2019, **27**(9):1443-1450.
43. Gasmi M, Sellami M, Denham J, Padulo J, Kuvacic G, Selmi W, Khalifa R: **Time-restricted feeding influences immune responses without compromising muscle performance in older men**. *Nutrition* 2018, **51-52**:29-37.
44. Harvie M, Wright C, Pegington M, McMullan D, Mitchell E, Martin B, Cutler RG, Evans G, Whiteside S, Maudsley S *et al*: **The effect of intermittent energy and carbohydrate restrictionv. daily energy restriction on weight loss and metabolic disease risk markers in overweight women**. *British Journal of Nutrition* 2013, **110**(8):1534-1547.
45. Harvie MN, Pegington M, Mattson MP, Frystyk J, Dillon B, Evans G, Cuzick J, Jebb SA, Martin B, Cutler RG *et al*: **The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women**. *Int J Obes (Lond)* 2011, **35**(5):714-727.
46. Hirsh SP, Pons M, Joyal SV, Swick AG: **Avoiding holiday seasonal weight gain with nutrient-supported intermittent energy restriction: a pilot study**. *J Nutr Sci* 2019, **8**:e11.
47. Hutchison AT, Liu B, Wood RE, Vincent AD, Thompson CH, O'Callaghan NJ, Wittert GA, Heilbronn LK: **Effects of Intermittent Versus Continuous Energy Intakes on Insulin Sensitivity and Metabolic Risk in Women with Overweight**. *Obesity (Silver Spring)* 2019, **27**(1):50-58.
48. Keogh JB, Pedersen E, Petersen KS, Clifton PM: **Effects of intermittent compared to continuous energy restriction on short-term weight loss and long-term weight loss maintenance**. *Clinical Obesity* 2014, **4**(3):150-156.
49. Li C, Sadraie B, Steckhan N, Kessler C, Stange R, Jeitler M, Michalsen A: **Effects of A One-week Fasting Therapy in Patients with Type-2 Diabetes Mellitus and Metabolic Syndrome – A Randomized Controlled Explorative Study**. *Experimental and Clinical Endocrinology & Diabetes* 2017, **125**(09):618-624.
50. Martens CR, Rossman MJ, Mazzo MR, Jankowski LR, Nagy EE, Denman BA, Richey JJ, Johnson SA, Ziemba BP, Wang Y *et al*: **Short-term time-restricted feeding is safe and feasible in non-obese healthy midlife and older adults**. *Geroscience* 2020, **42**(2):667-686.
51. Moro T, Tinsley G, Bianco A, Marcolin G, Pacelli Q, Battaglia G, Palma A, Gentil P, Neri M, Paoli A: **Effects of eight weeks of time-restricted feeding (16/8) on basal metabolism, maximal strength, body composition, inflammation, and cardiovascular risk factors in resistance-trained males**. *Journal of translational medicine* 2016, **14**(1):290.
52. Panizza CE, Lim U, Yonemori KM, Cassel KD, Wilkens LR, Harvie MN, Maskarinec G, Delp EJ, Lampe JW, Shepherd JA *et al*: **Effects of Intermittent Energy Restriction Combined with a Mediterranean Diet on Reducing Visceral Adiposity: A Randomized Active Comparator Pilot Study**. *Nutrients* 2019, **11**(6).
53. Parvaresh A, Razavi R, Abbasi B, Yaghoobloo K, Hassanzadeh A, Mohammadifard N, Safavi SM, Hadi A, Clark CCT: **Modified alternate-day fasting vs. calorie restriction in the treatment of patients with metabolic syndrome: A randomized clinical trial**. *Complementary Therapies in Medicine* 2019, **47**.
54. Pureza I, Melo ISV, Macena ML, Praxedes DRS, Vasconcelos LGL, Silva-Junior AE, Florencio T, Bueno NB: **Acute effects of time-restricted feeding in low-income women with obesity placed on hypoenergetic diets: Randomized trial**. *Nutrition* 2020, **77**:110796.
55. Schübel R, Nattenmüller J, Sookthai D, Nonnenmacher T, Graf ME, Riedl L, Schlett CL, von Stackelberg O, Johnson T, Nabers D *et al*: **Effects of intermittent and continuous calorie restriction on body weight and metabolism over 50 wk: a randomized controlled trial**. *The American Journal of Clinical Nutrition* 2018, **108**(5):933-945.

56. Stote KS, Baer DJ, Spears K, Paul DR, Harris GK, Rumpler WV, Strycula P, Najjar SS, Ferrucci L, Ingram DK *et al*: **A controlled trial of reduced meal frequency without caloric restriction in healthy, normal-weight, middle-aged adults**. *The American journal of clinical nutrition* 2007, **85**(4):981-988.
57. Stratton MT, Tinsley GM, Alesi MG, Hester GM, Olmos AA, Serafini PR, Modjeski AS, Mangine GT, King K, Savage SN *et al*: **Four Weeks of Time-Restricted Feeding Combined with Resistance Training Does Not Differentially Influence Measures of Body Composition, Muscle Performance, Resting Energy Expenditure, and Blood Biomarkers**. *Nutrients* 2020, **12**(4).
58. Sundfor TM, Svendsen M, Tonstad S: **Effect of intermittent versus continuous energy restriction on weight loss, maintenance and cardiometabolic risk: A randomized 1-year trial**. *Nutr Metab Cardiovasc Dis* 2018, **28**(7):698-706.
59. Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM: **Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes**. *Cell Metab* 2018, **27**(6):1212-1221 e1213.
60. Teng NI, Shahar S, Manaf ZA, Das SK, Taha CS, Ngah WZ: **Efficacy of fasting calorie restriction on quality of life among aging men**. *Physiol Behav* 2011, **104**(5):1059-1064.
61. Teng NI, Shahar S, Rajab NF, Manaf ZA, Johari MH, Ngah WZ: **Improvement of metabolic parameters in healthy older adult men following a fasting calorie restriction intervention**. *Aging Male* 2013, **16**(4):177-183.
62. Tinsley GM, Forsse JS, Butler NK, Paoli A, Bane AA, La Bounty PM, Morgan GB, Grandjean PW: **Time-restricted feeding in young men performing resistance training: A randomized controlled trial**. *European Journal of Sport Science* 2016, **17**(2):200-207.
63. Tinsley GM, Moore ML, Graybeal AJ, Paoli A, Kim Y, Gonzales JU, Harry JR, VanDusseldorp TA, Kennedy DN, Cruz MR: **Time-restricted feeding plus resistance training in active females: a randomized trial**. *Am J Clin Nutr* 2019, **110**(3):628-640.
64. Trepanowski JF, Kroeger CM, Barnosky A, Klempel M, Bhutani S, Hoddy KK, Rood J, Ravussin E, Varady KA: **Effects of alternate-day fasting or daily calorie restriction on body composition, fat distribution, and circulating adipokines: Secondary analysis of a randomized controlled trial**. *Clinical Nutrition* 2018, **37**(6):1871-1878.
65. Varady K, Bhutani S, Klempel M, Kroeger C, Trepanowski J, Haus J, Hoddy K, Calvo Y: **Alternate day fasting for weight loss in normal weight and overweight subjects: a randomized controlled trial**. *Nutr J* 2013, **12**(1):146.
66. Wei M, Brandhorst S, Shelehchi M, Mirzaei H, Cheng C, Budniak J, Groshen S, Mack W, Guen E, Di Biase S *et al*: **Fasting-mimicking diet and markers/risk factors for aging, diabetes, cancer, and cardiovascular disease**. *Science translational medicine* 2017, **9**(377).
67. Williams KV, Mullen ML, Kelley DE, Wing RR: **The effect of short periods of caloric restriction on weight loss and glycemic control in type 2 diabetes**. *Diabetes Care* 1998, **21**(1):2-8.
68. Corley BT, Carroll RW, Hall RM, Weatherall M, Parry-Strong A, Krebs JD: **Intermittent fasting in Type 2 diabetes mellitus and the risk of hypoglycaemia: a randomized controlled trial**. *Diabet Med* 2018, **35**(5):588-594.
69. Pinto AM, Bordoli C, Buckner LP, Kim C, Kaplan PC, Del Arenal IM, Jeffcock EJ, Hall WL: **Intermittent energy restriction is comparable to continuous energy restriction for cardiometabolic health in adults with central obesity: A randomized controlled trial; the Met-IER study**. *Clin Nutr* 2020, **39**(6):1753-1763.
70. Bhutani S, Klempel MC, Kroeger CM, Trepanowski JF, Varady KA: **Alternate day fasting and endurance exercise combine to reduce body weight and favorably alter plasma lipids in obese humans**. *Obesity (Silver Spring)* 2013, **21**(7):1370-1379.
71. Stekovic S, Hofer SJ, Tripolt N, Aon MA, Royer P, Pein L, Stadler JT, Pendl T, Prietl B, Url J *et al*: **Alternate Day Fasting Improves Physiological and Molecular Markers of Aging in Healthy, Non-obese Humans**. *Cell Metabolism* 2019, **30**(3):462-476.e466.
72. Pellegrini M, Cioffi I, Evangelista A, Ponzo V, Goitre I, Ciccone G, Ghigo E, Bo S: **Effects of time-restricted feeding on body weight and metabolism. A systematic review and meta-analysis**. *Rev Endocr Metab Disord* 2020, **21**(1):17-33.
73. Harris L, Hamilton S, Azevedo LB, Olajide J, De Brun C, Waller G, Whittaker V, Sharp T, Lean M, Hankey C *et al*: **Intermittent fasting interventions for treatment of overweight and obesity in adults: a systematic review and meta-analysis**. *JBI Database System Rev Implement Rep* 2018, **16**(2):507-547.
74. Fernando H, Zibellini J, Harris R, Seimon R, Sainsbury A: **Effect of Ramadan Fasting on Weight and Body Composition in Healthy Non-Athlete Adults: A Systematic Review and Meta-Analysis**. *Nutrients* 2019, **11**(2).
75. Park J, Seo YG, Paek YJ, Song HJ, Park KH, Noh HM: **Effect of alternate-day fasting on obesity and cardiometabolic risk: A systematic review and meta-analysis**. *Metabolism* 2020, **111**:154336.
76. O'Keefe JH, Torres-Acosta N, O'Keefe EL, Saeed IM, Lavie CJ, Smith SE, Ros E: **A Pesco-Mediterranean Diet With Intermittent Fasting**. *Journal of the American College of Cardiology* 2020, **76**(12):1484-1493.
77. Most J, Gilmore LA, Smith SR, Han H, Ravussin E, Redman LM: **Significant improvement in cardiometabolic health in healthy nonobese individuals during caloric restriction-induced weight loss and weight loss maintenance**. *Am J Physiol Endocrinol Metab* 2018, **314**(4):E396-e405.
78. Mattson MP, Longo VD, Harvie M: **Impact of intermittent fasting on health and disease processes**. *Ageing Res Rev* 2017, **39**:46-58.
79. Longo VD, Mattson MP: **Fasting: molecular mechanisms and clinical applications**. *Cell Metab* 2014, **19**(2):181-192.
80. Panda S: **Circadian physiology of metabolism**. *Science* 2016, **354**(6315):1008-1015.
81. Weindruch R, Sohal R: **Seminars in medicine of the Beth Israel Deaconess Medical Center**. In: *Caloric intake and aging.* vol. 337; 1997: 986-994.
82. de Cabo R, Mattson MP: **Effects of Intermittent Fasting on Health, Aging, and Disease**. *N Engl J Med* 2019, **381**(26):2541-2551.
83. Chung H, Chou W, Sears DD, Patterson RE, Webster NJ, Ellies LG: **Time-restricted feeding improves insulin resistance and hepatic steatosis in a mouse model of postmenopausal obesity**. *Metabolism* 2016, **65**(12):1743-1754.
84. Ren J, Hu D, Mao Y, Yang H, Liao W, Xu W, Ge P, Zhang H, Sang X, Lu X *et al*: **Alteration in gut microbiota caused by time-restricted feeding alleviate hepatic ischaemia reperfusion injury in mice**. *J Cell Mol Med* 2019, **23**(3):1714-1722.

85. Patke A, Young M, Axelrod S: **Molecular mechanisms and physiological importance of circadian rhythms**. *Nature reviews Molecular cell biology* 2020, **21**(2):67-84.
86. Challet E: **The circadian regulation of food intake**. *Nat Rev Endocrinol* 2019, **15**(7):393-405.
87. Huang W, Ramsey KM, Marcheva B, Bass J: **Circadian rhythms, sleep, and metabolism**. *The Journal of clinical investigation* 2011, **121**(6):2133-2141.
88. Morris CJ, Yang JN, Garcia JI, Myers S, Bozzi I, Wang W, Buxton OM, Shea SA, Scheer FA: **Endogenous circadian system and circadian misalignment impact glucose tolerance via separate mechanisms in humans**. *Proc Natl Acad Sci U S A* 2015, **112**(17):E2225-2234.
89. Garaulet M, Gómez-Abellán P, Alburquerque-Béjar JJ, Lee YC, Ordovás JM, Scheer FA: **Timing of food intake predicts weight loss effectiveness**. *Int J Obes (Lond)* 2013, **37**(4):604-611.
90. Jamshed H, Beyl RA, Della Manna DL, Yang ES, Ravussin E, Peterson CM: **Early Time-Restricted Feeding Improves 24-Hour Glucose Levels and Affects Markers of the Circadian Clock, Aging, and Autophagy in Humans**. *Nutrients* 2019, **11**(6).
91. Sunderram J, Sofou S, Kamisoglu K, Karantza V, Androulakis IP: **Time-restricted feeding and the realignment of biological rhythms: translational opportunities and challenges**. *J Transl Med* 2014, **12**:79.
92. Manoogian ENC, Panda S: **Circadian rhythms, time-restricted feeding, and healthy aging**. *Ageing Res Rev* 2017, **39**:59-67.
93. Zheng X, Sehgal A: **AKT and TOR signaling set the pace of the circadian pacemaker**. *Current biology : CB* 2010, **20**(13):1203-1208.
94. Lamia K, Sachdeva U, DiTacchio L, Williams E, Alvarez J, Egan D, Vasquez D, Juguilon H, Panda S, Shaw R *et al*: **AMPK regulates the circadian clock by cryptochrome phosphorylation and degradation**. *Science (New York, NY)* 2009, **326**(5951):437-440.
95. Asher G, Gatfield D, Stratmann M, Reinke H, Dibner C, Kreppel F, Mostoslavsky R, Alt F, Schibler U: **SIRT1 regulates circadian clock gene expression through PER2 deacetylation**. *Cell* 2008, **134**(2):317-328.
96. Masri S, Sassone-Corsi P: **The circadian clock: a framework linking metabolism, epigenetics and neuronal function**. *Nature reviews Neuroscience* 2013, **14**(1):69-75.
97. Kohsaka A, Laposky A, Ramsey K, Estrada C, Joshu C, Kobayashi Y, Turek F, Bass J: **High-fat diet disrupts behavioral and molecular circadian rhythms in mice**. *Cell metabolism* 2007, **6**(5):414-421.
98. Hatori M, Vollmers C, Zarrinpar A, DiTacchio L, Bushong E, Gill S, Leblanc M, Chaix A, Joens M, Fitzpatrick J *et al*: **Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet**. *Cell metabolism* 2012, **15**(6):848-860.
99. Koike N, Yoo S, Huang H, Kumar V, Lee C, Kim T, Takahashi J: **Transcriptional architecture and chromatin landscape of the core circadian clock in mammals**. *Science (New York, NY)* 2012, **338**(6105):349-354.
100. Thaiss C, Zeevi D, Levy M, Zilberman-Schapira G, Suez J, Tengeler A, Abramson L, Katz M, Korem T, Zmora N *et al*: **Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis**. *Cell* 2014, **159**(3):514-529.
101. Zarrinpar A, Chaix A, Yooseph S, Panda S: **Diet and feeding pattern affect the diurnal dynamics of the gut microbiome**. *Cell Metab* 2014, **20**(6):1006-1017.
102. Heath-Heckman EA, Peyer SM, Whistler CA, Apicella MA, Goldman WE, McFall-Ngai MJ: **Bacterial bioluminescence regulates expression of a host cryptochrome gene in the squid-Vibrio symbiosis**. *mBio* 2013, **4**(2).
103. Chapnik N, Genzer Y, Froy O: **Relationship between FGF21 and UCP1 levels under time-restricted feeding and high-fat diet**. *J Nutr Biochem* 2017, **40**:116-121.
104. Li G, Xie C, Lu S, Nichols RG, Tian Y, Li L, Patel D, Ma Y, Brocker CN, Yan T *et al*: **Intermittent Fasting Promotes White Adipose Browning and Decreases Obesity by Shaping the Gut Microbiota**. *Cell Metab* 2017, **26**(4):672-685.e674.
105. Parkar SG, Kalsbeek A, Cheeseman JF: **Potential Role for the Gut Microbiota in Modulating Host Circadian Rhythms and Metabolic Health**. *Microorganisms* 2019, **7**(2).
106. Cioffi I, Evangelista A, Ponzo V, Ciccone G, Soldati L, Santarpia L, Contaldo F, Pasanisi F, Ghigo E, Bo S: **Intermittent versus continuous energy restriction on weight loss and cardiometabolic outcomes: a systematic review and meta-analysis of randomized controlled trials**. *J Transl Med* 2018, **16**(1):371.
107. Allaf M, Elghazaly H, Mohamed OG, Fareen MFK, Zaman S, Salmasi A-M, Tsilidis K, Dehghan A: **Intermittent fasting for the prevention of cardiovascular disease**. *Cochrane Database of Systematic Reviews* 2019.
108. Adler-Lazarovits C, Weintraub A: **Physicians' attitudes and views regarding religious fasting during pregnancy and review of the literature**. *European journal of obstetrics, gynecology, and reproductive biology* 2019, **233**:76-80.
109. Trepanowski JF, Bloomer RJ: **The impact of religious fasting on human health**. *Nutr J* 2010, **9**:57.

Figures

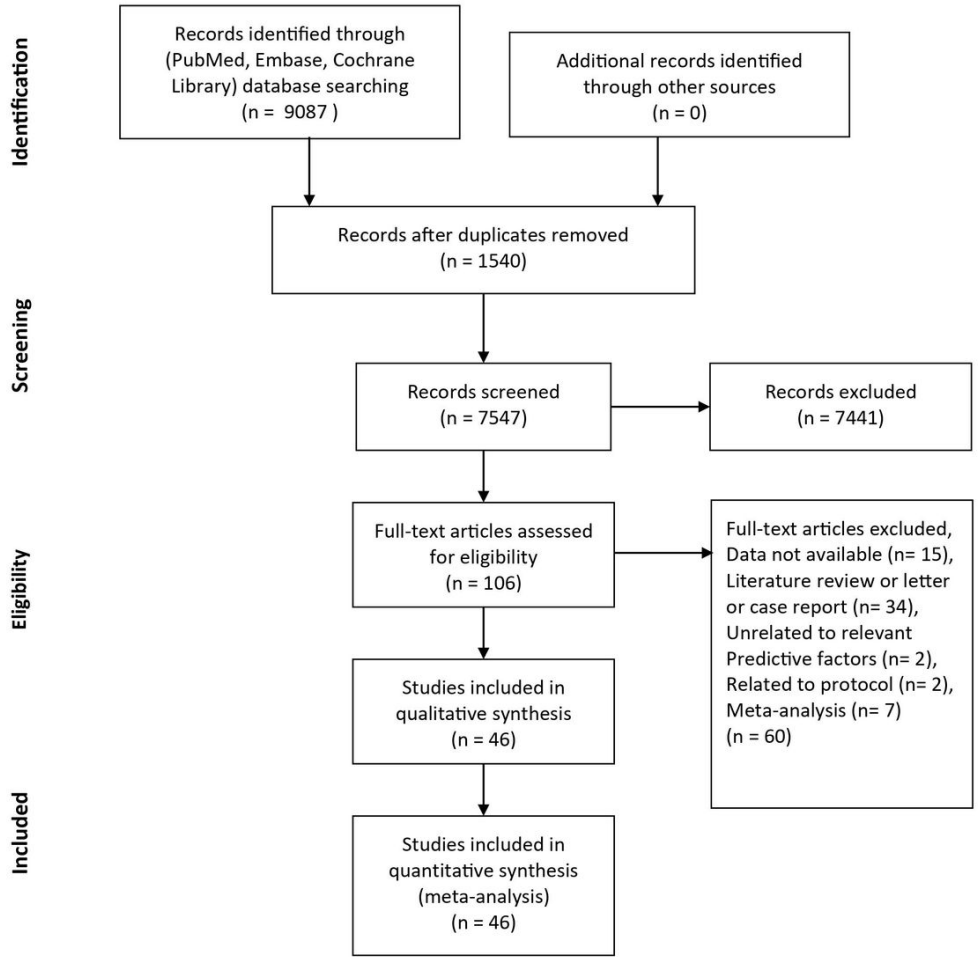

Figure 1

Schema of the search strategy

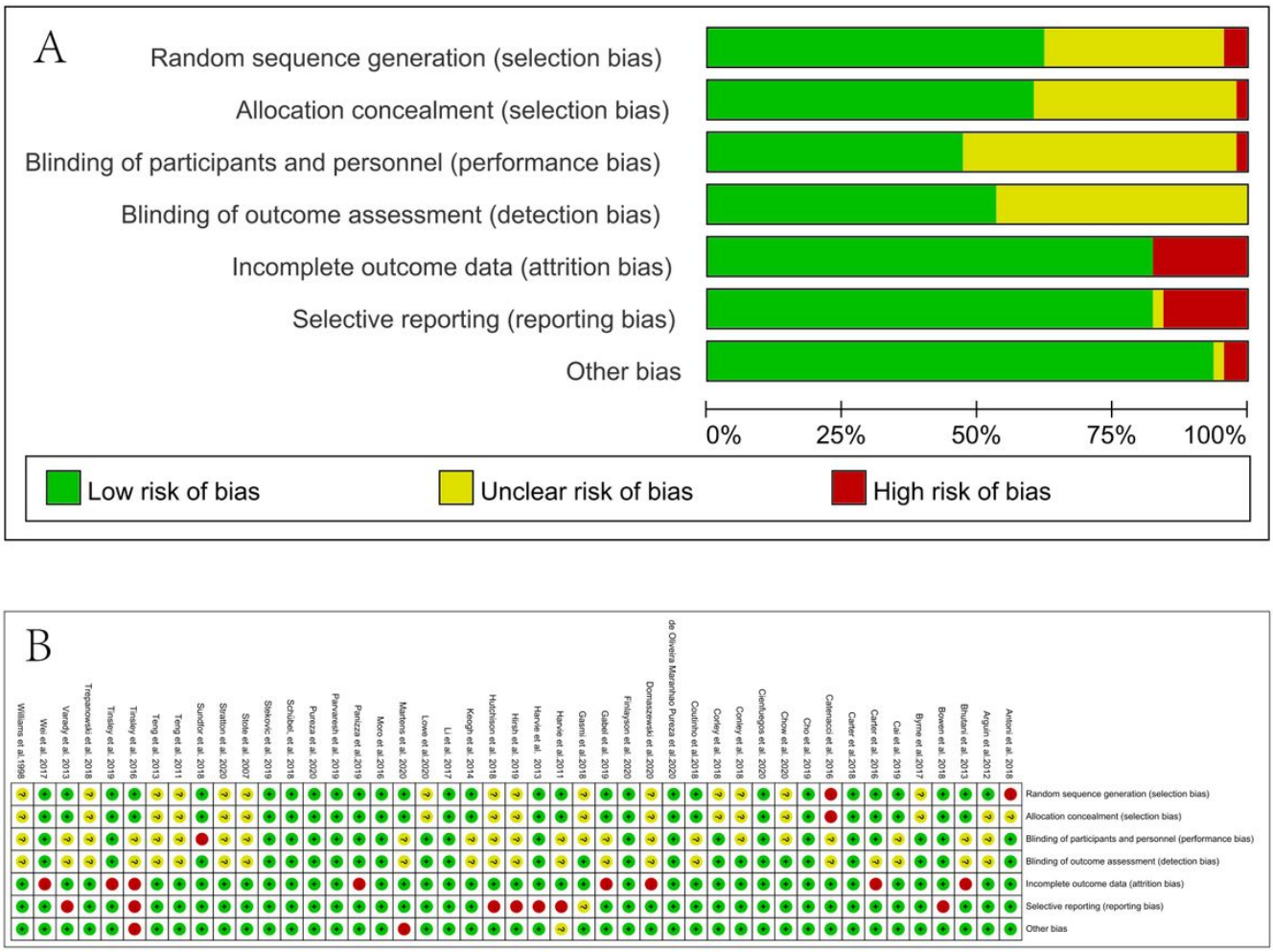

Figure 2

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

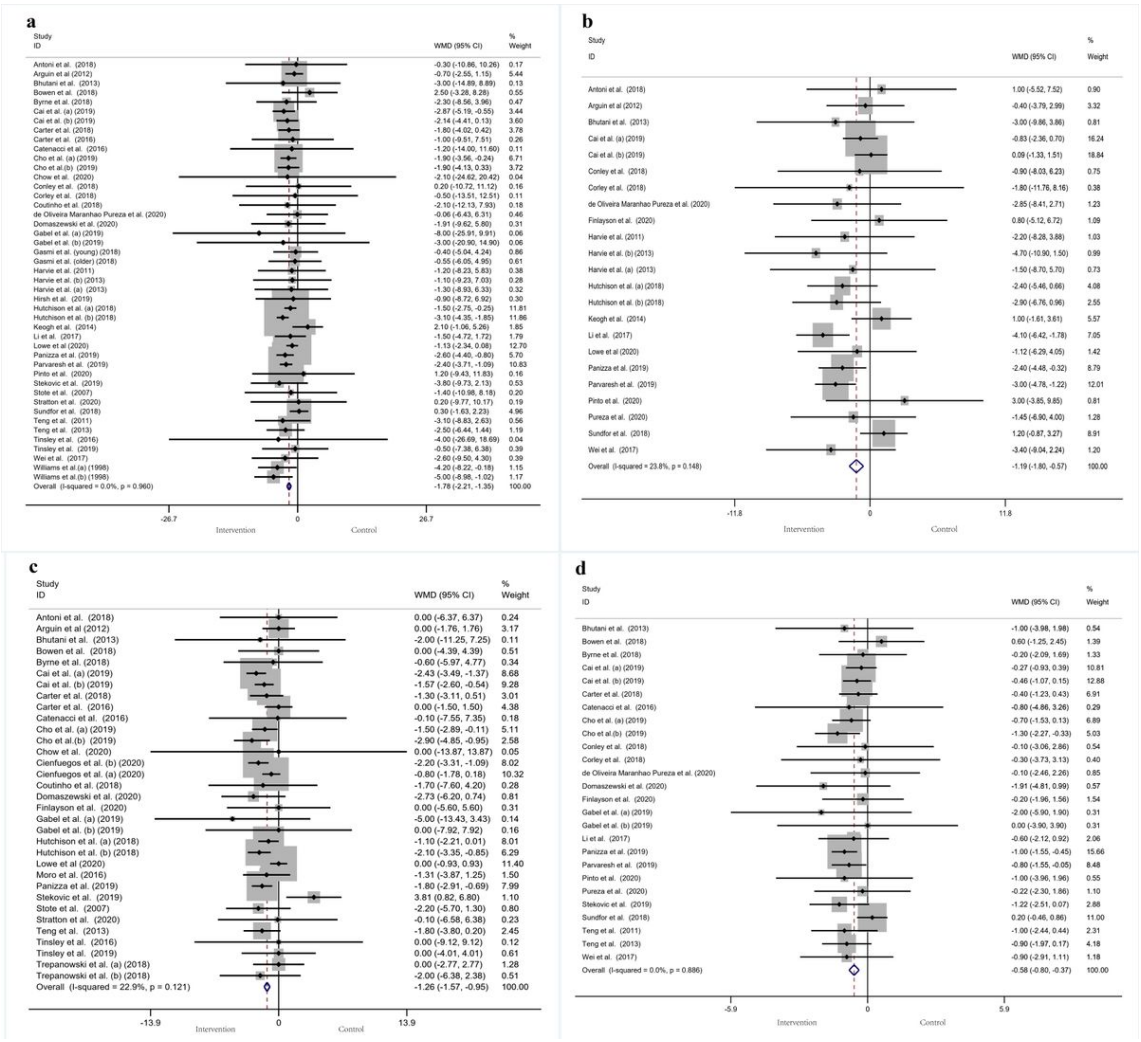

Figure 3

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

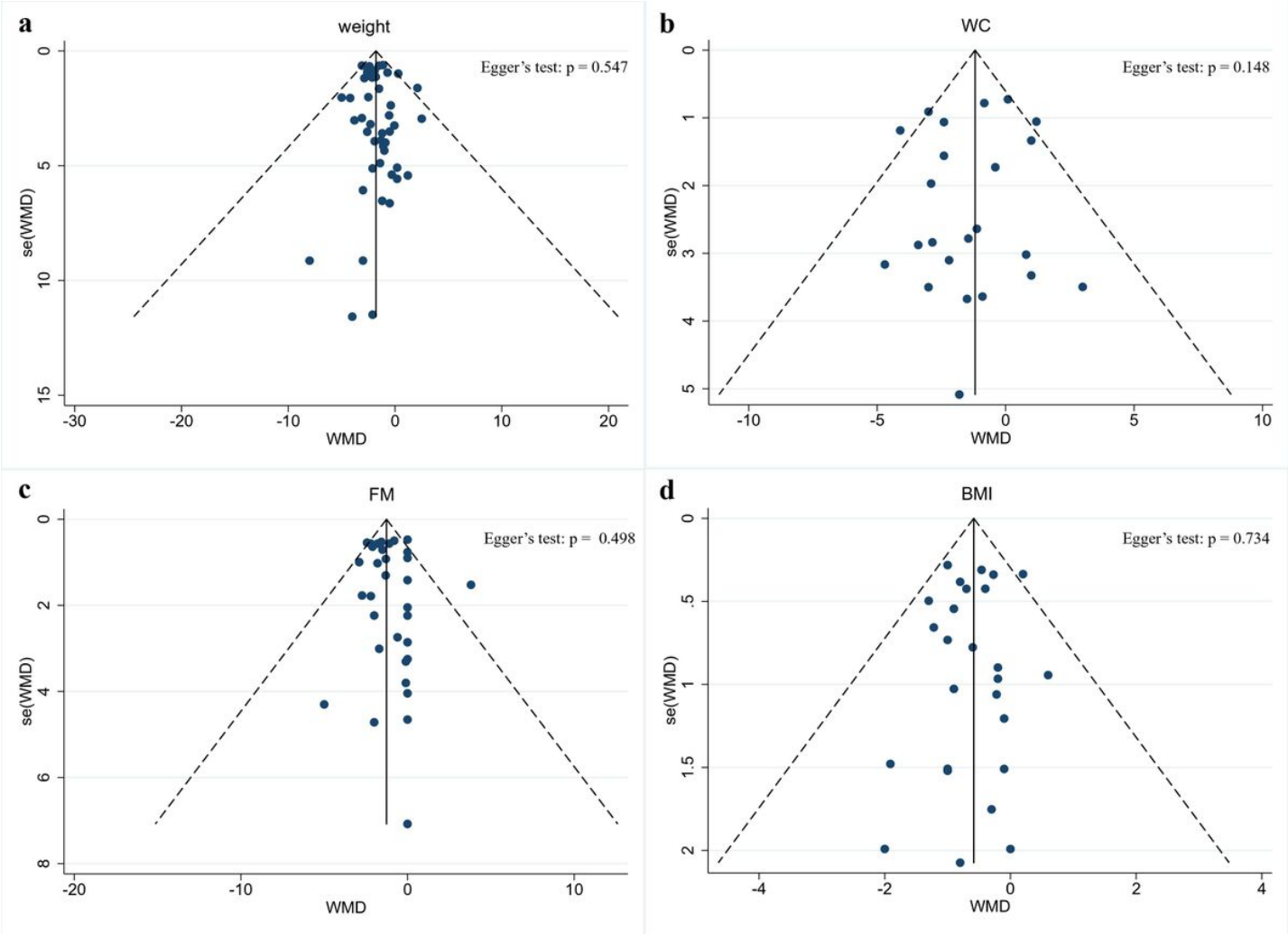

Figure 4

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

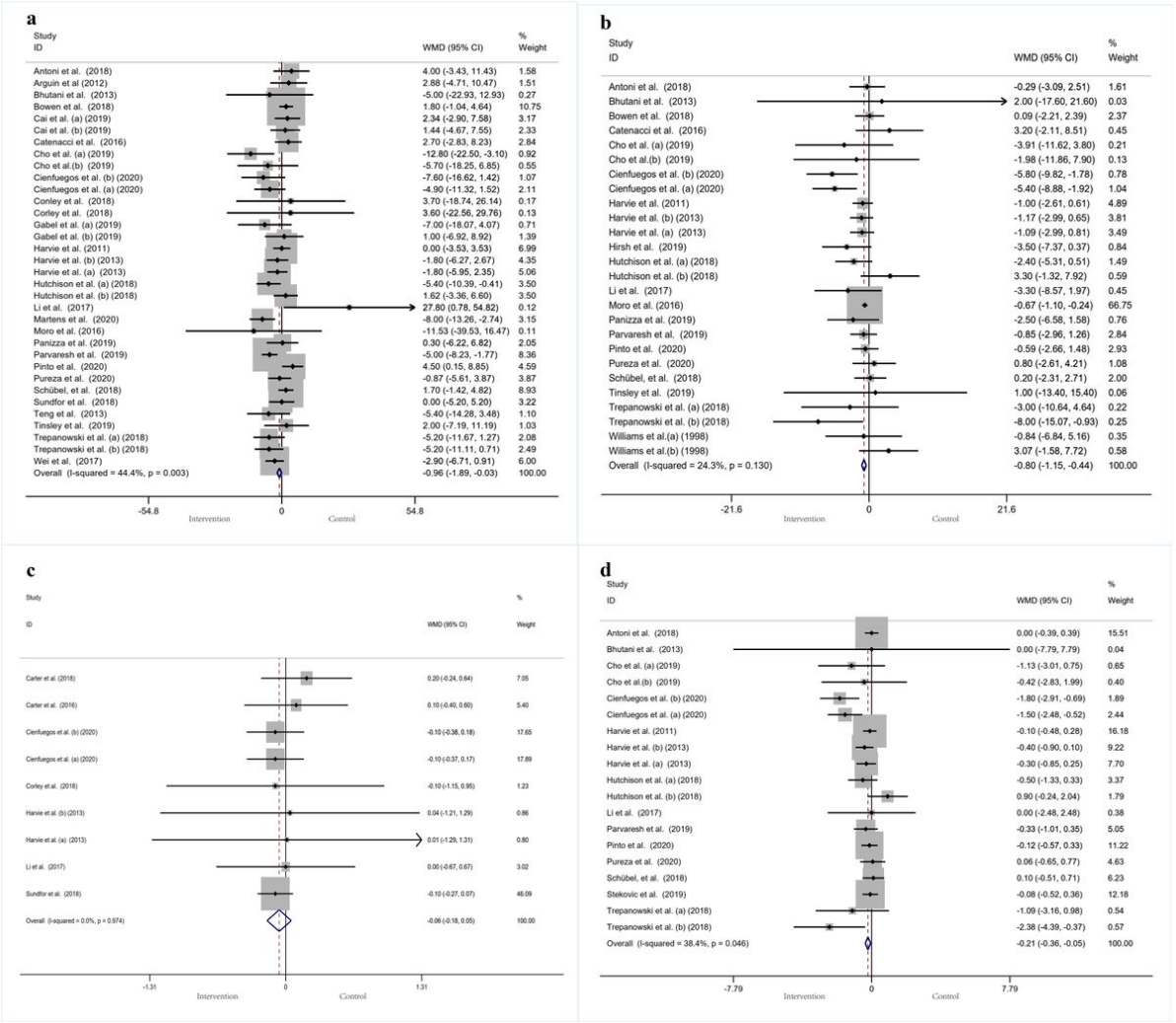

Figure 5

Forest plot of RCTs investigating the effects of intermittent fasting on glycemic control (a) FBG, (b) Fins, (c) HbA1c, (d) HOMA-IR.

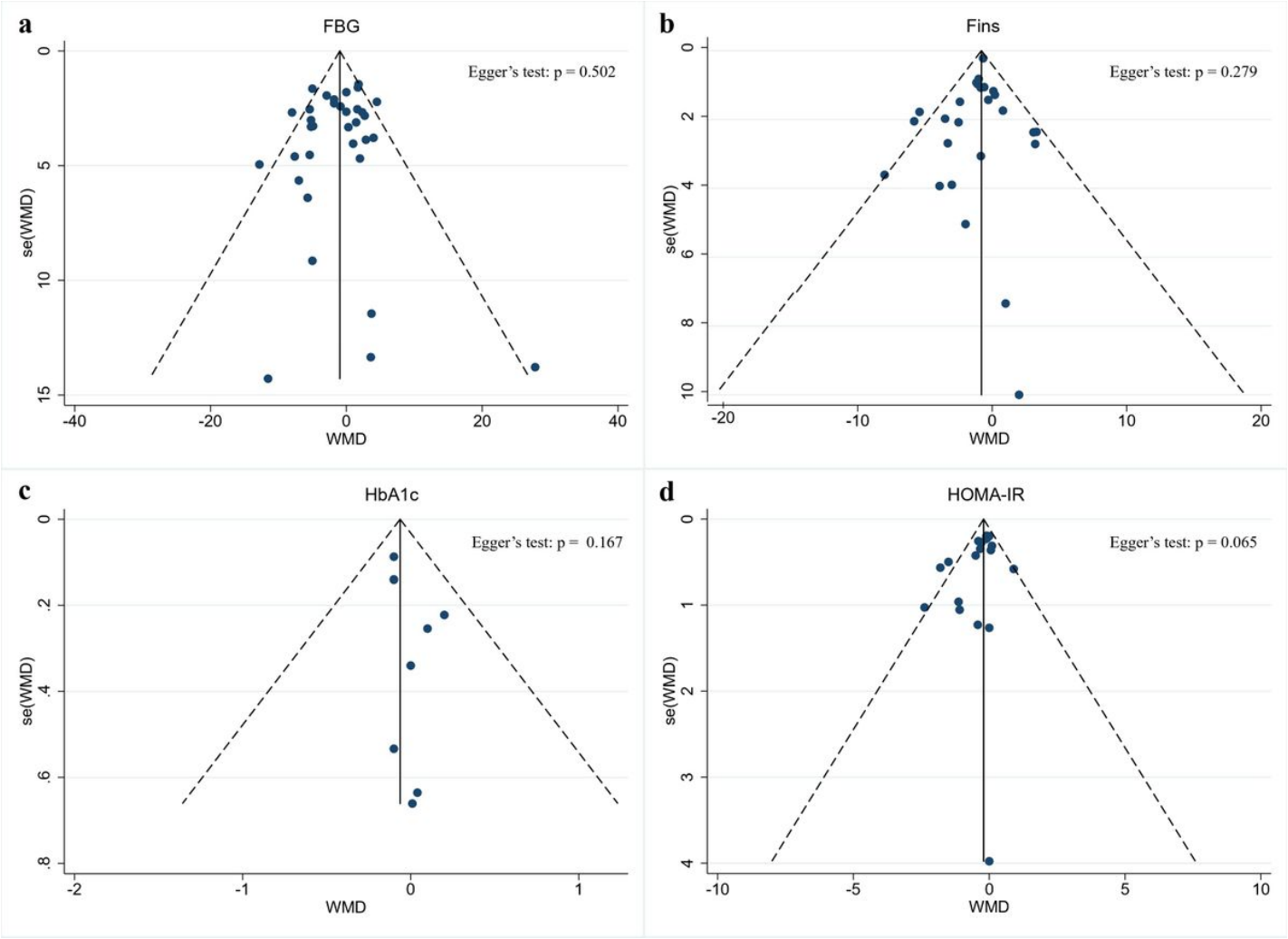

Figure 6

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

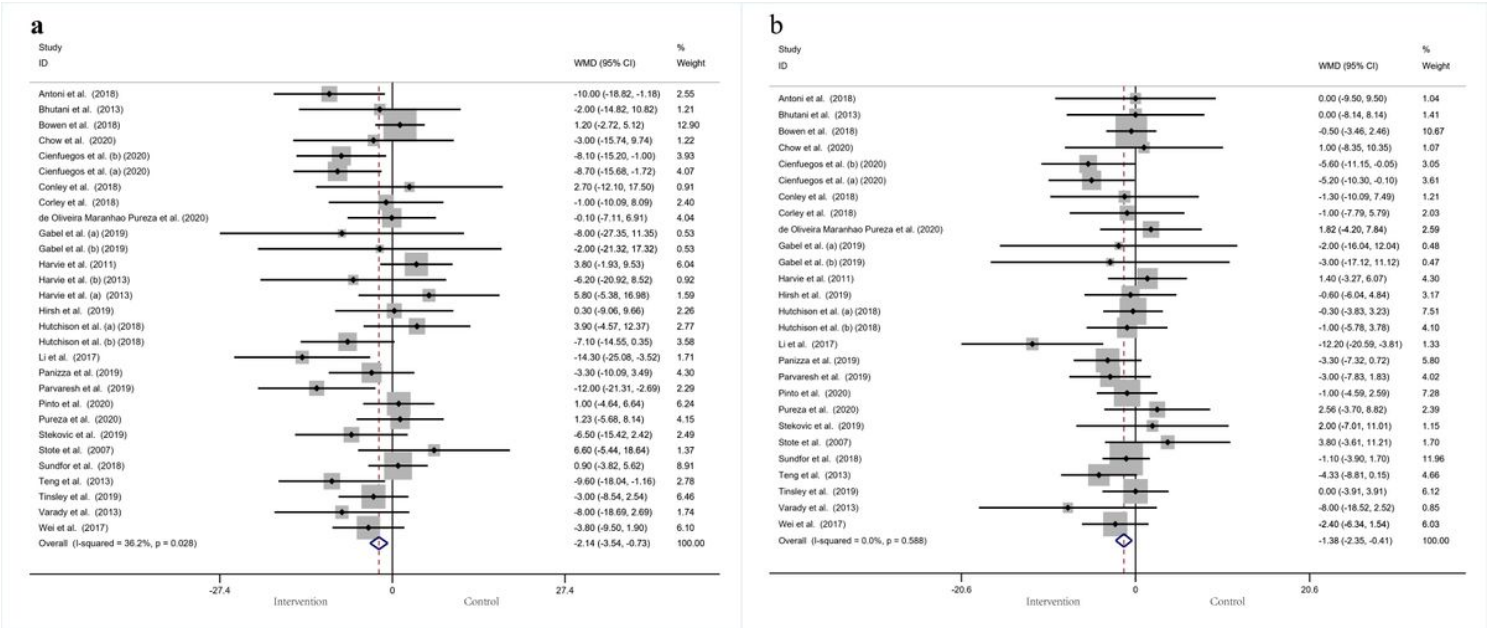

Figure 7

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

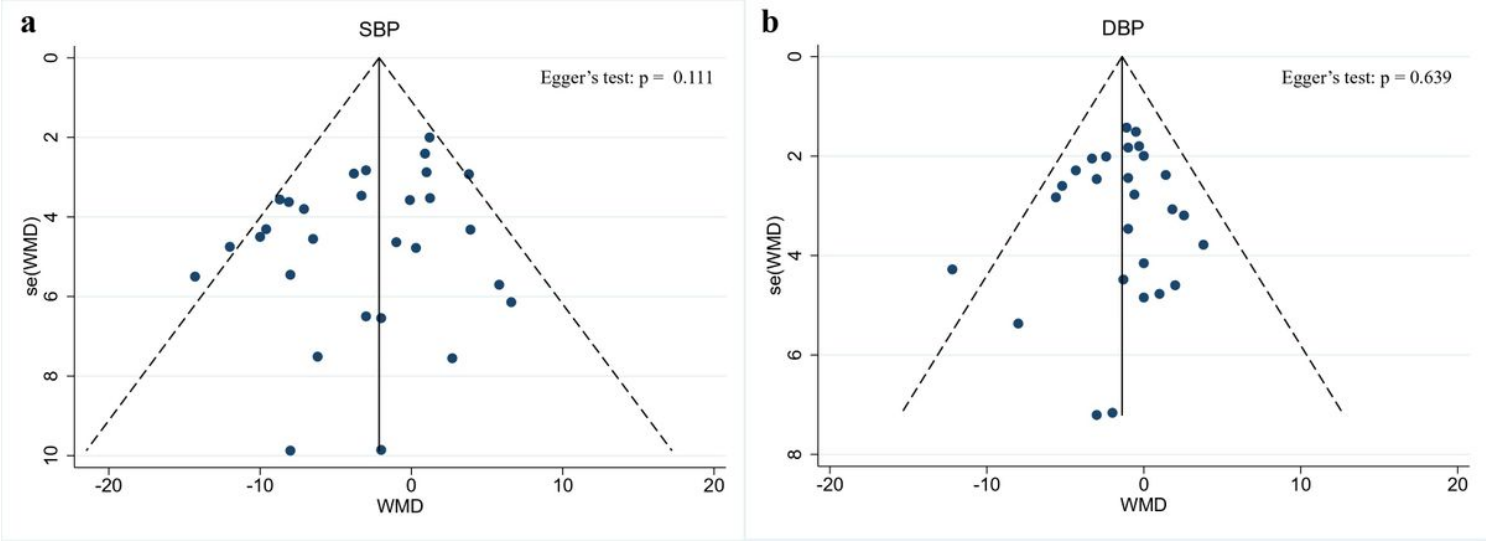

Figure 8

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

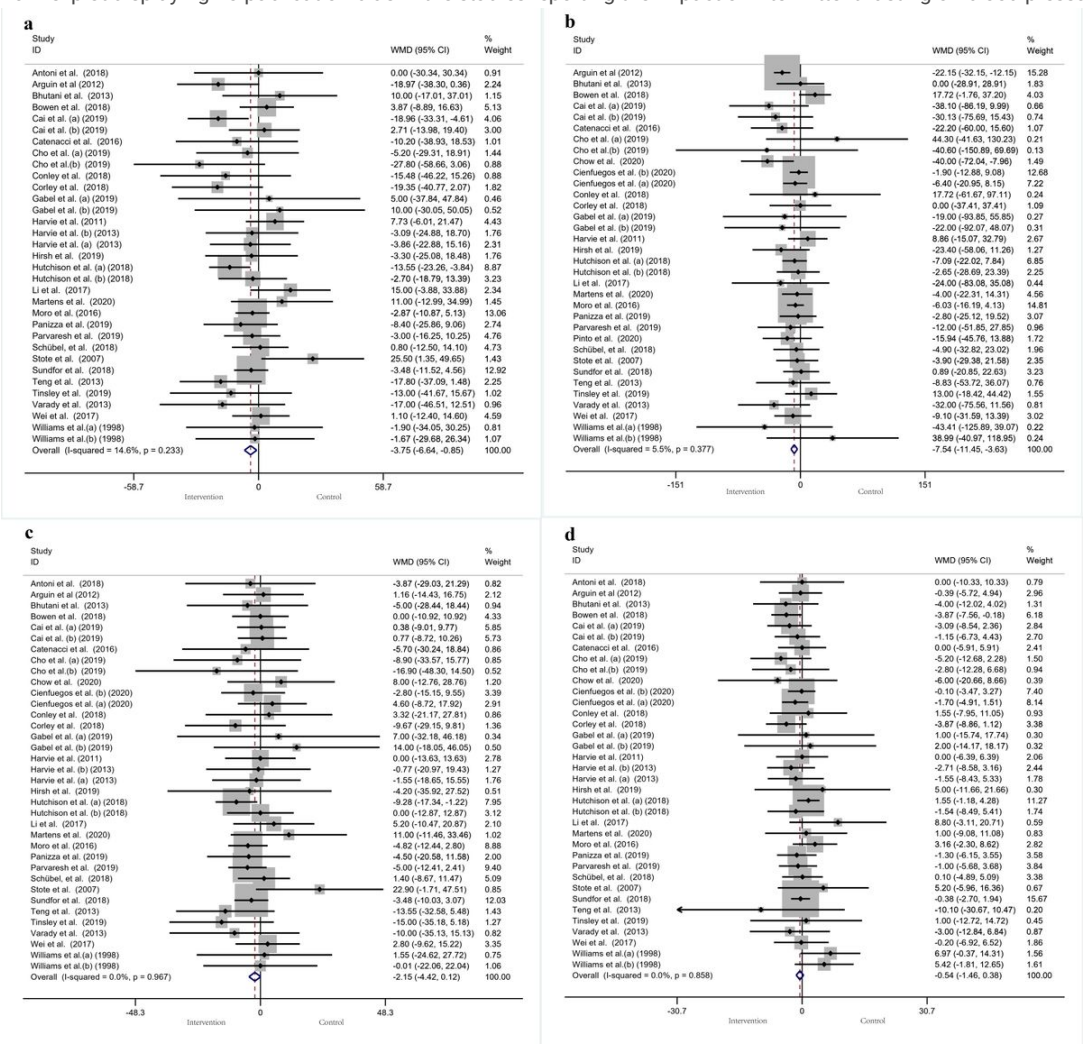

Figure 9

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

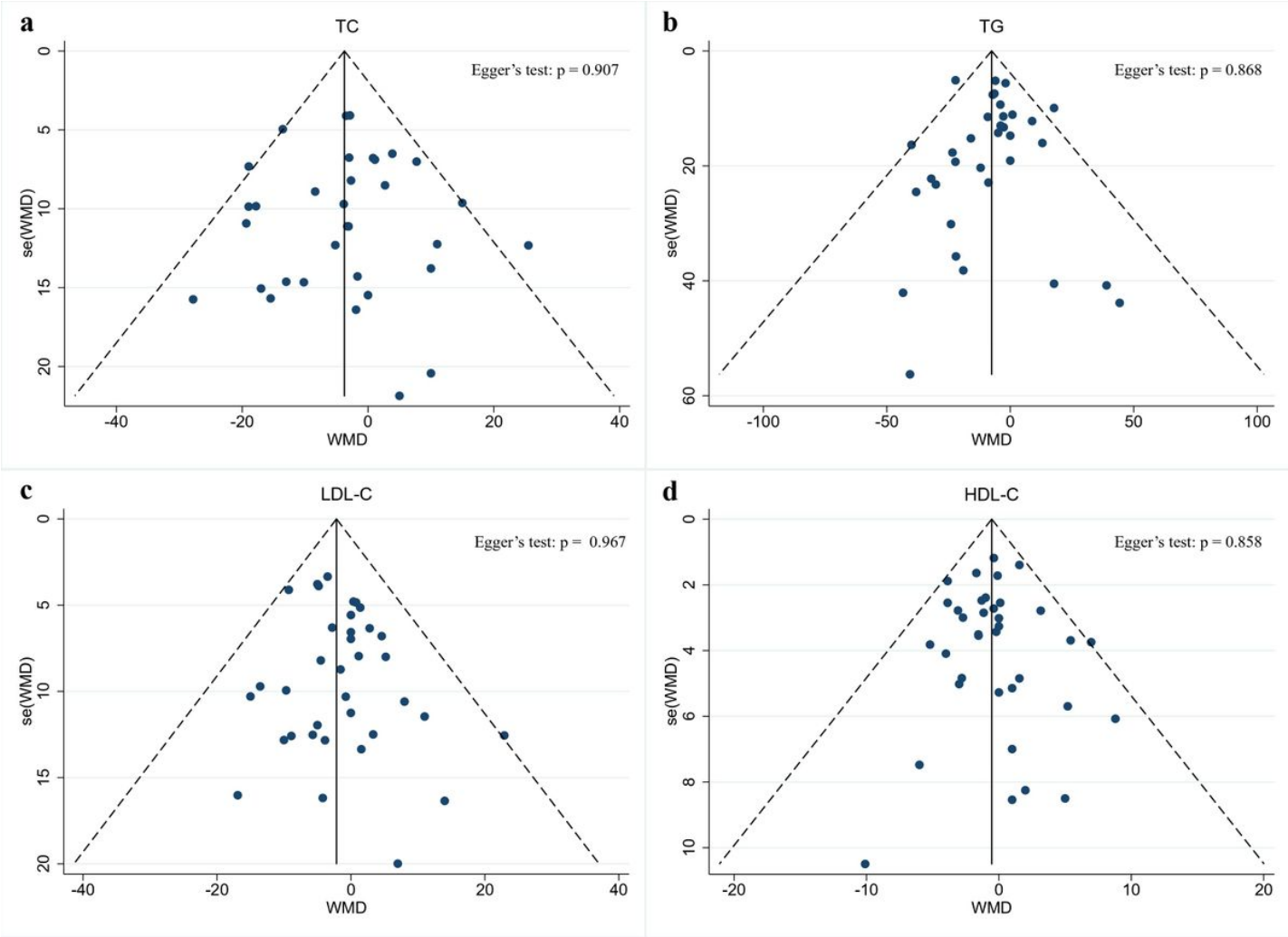

Figure 10

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

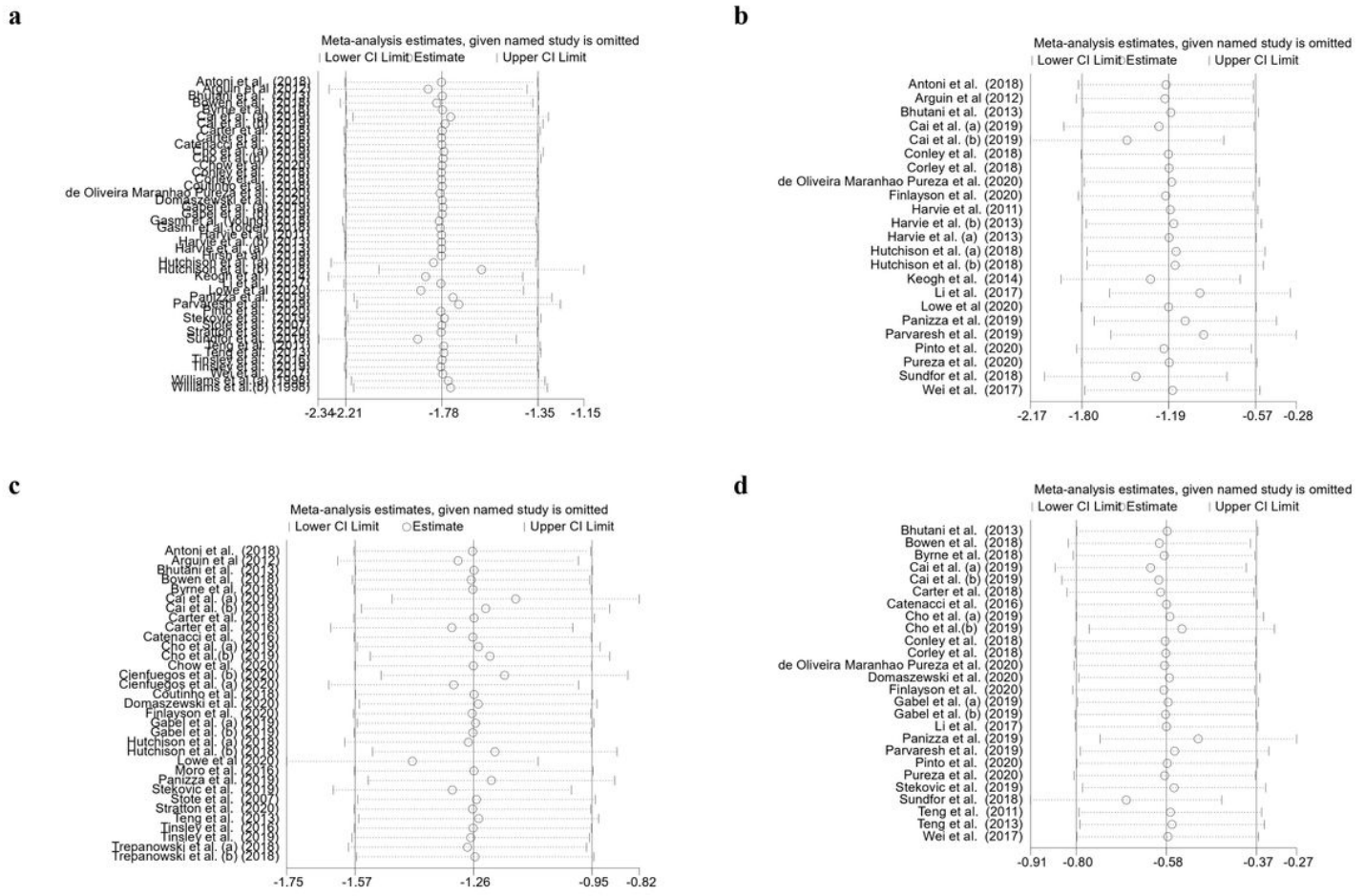

Figure 11

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

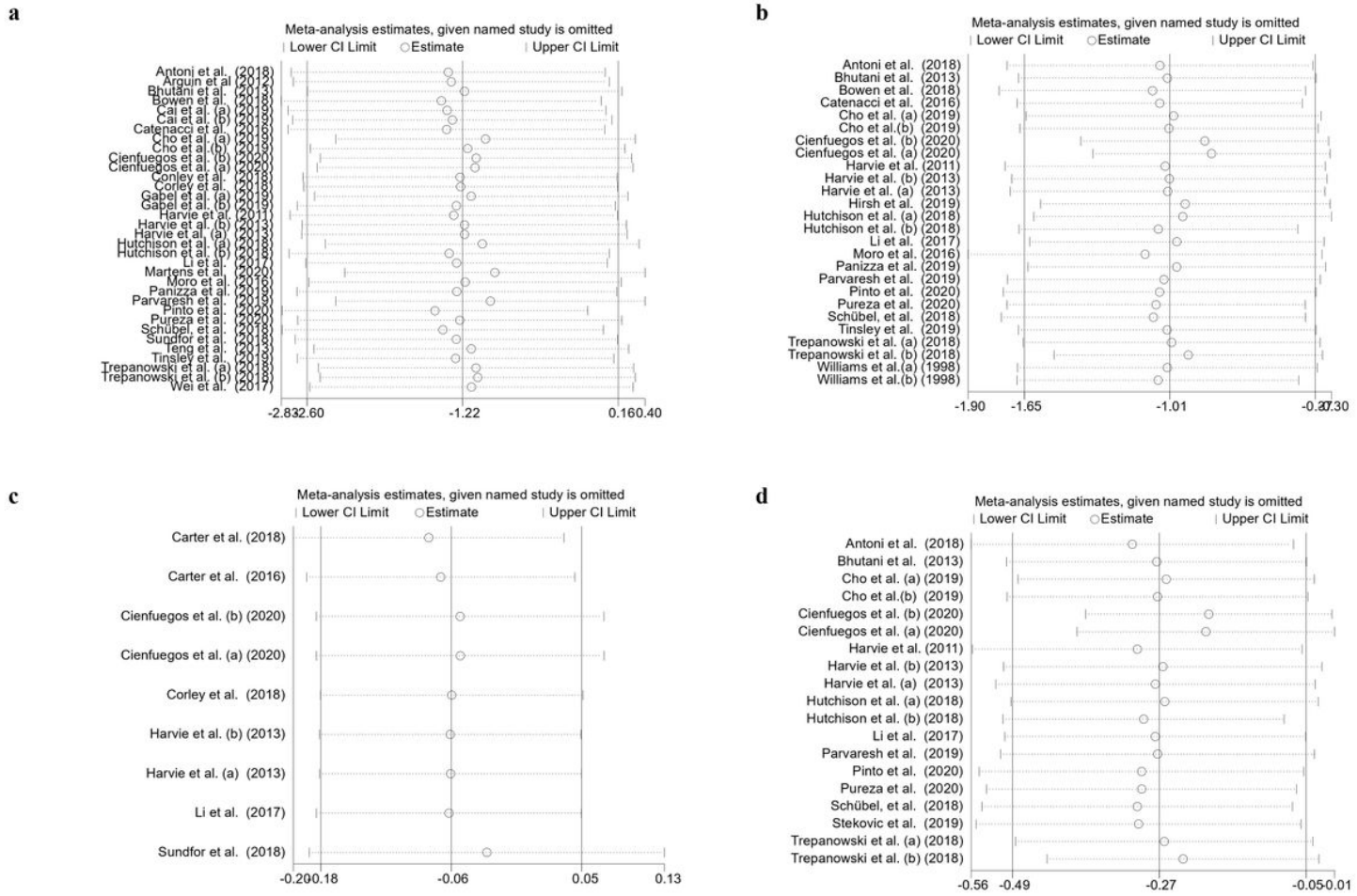

Figure 12

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

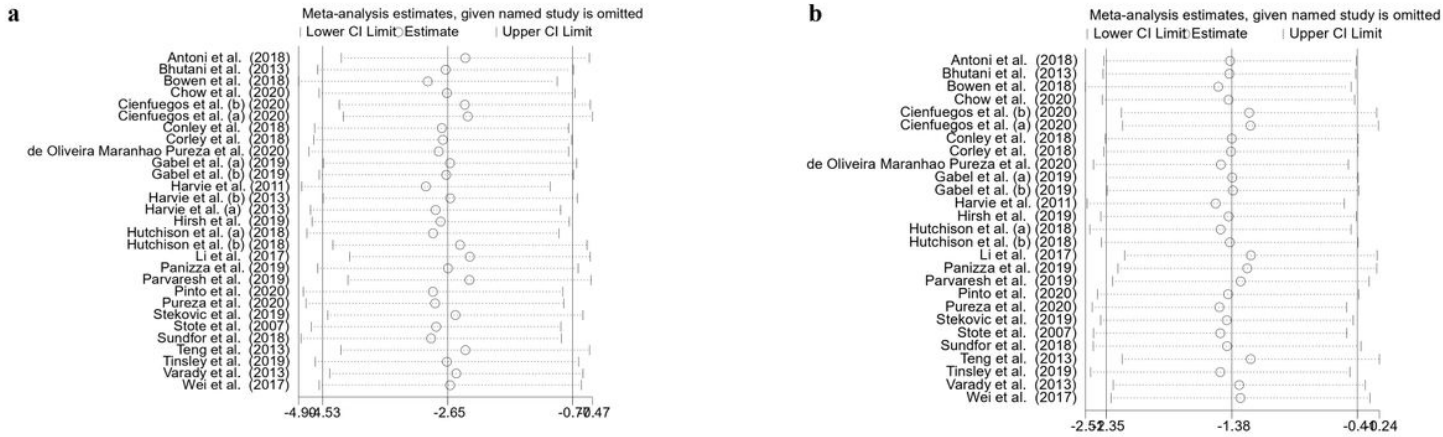

Figure 13

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

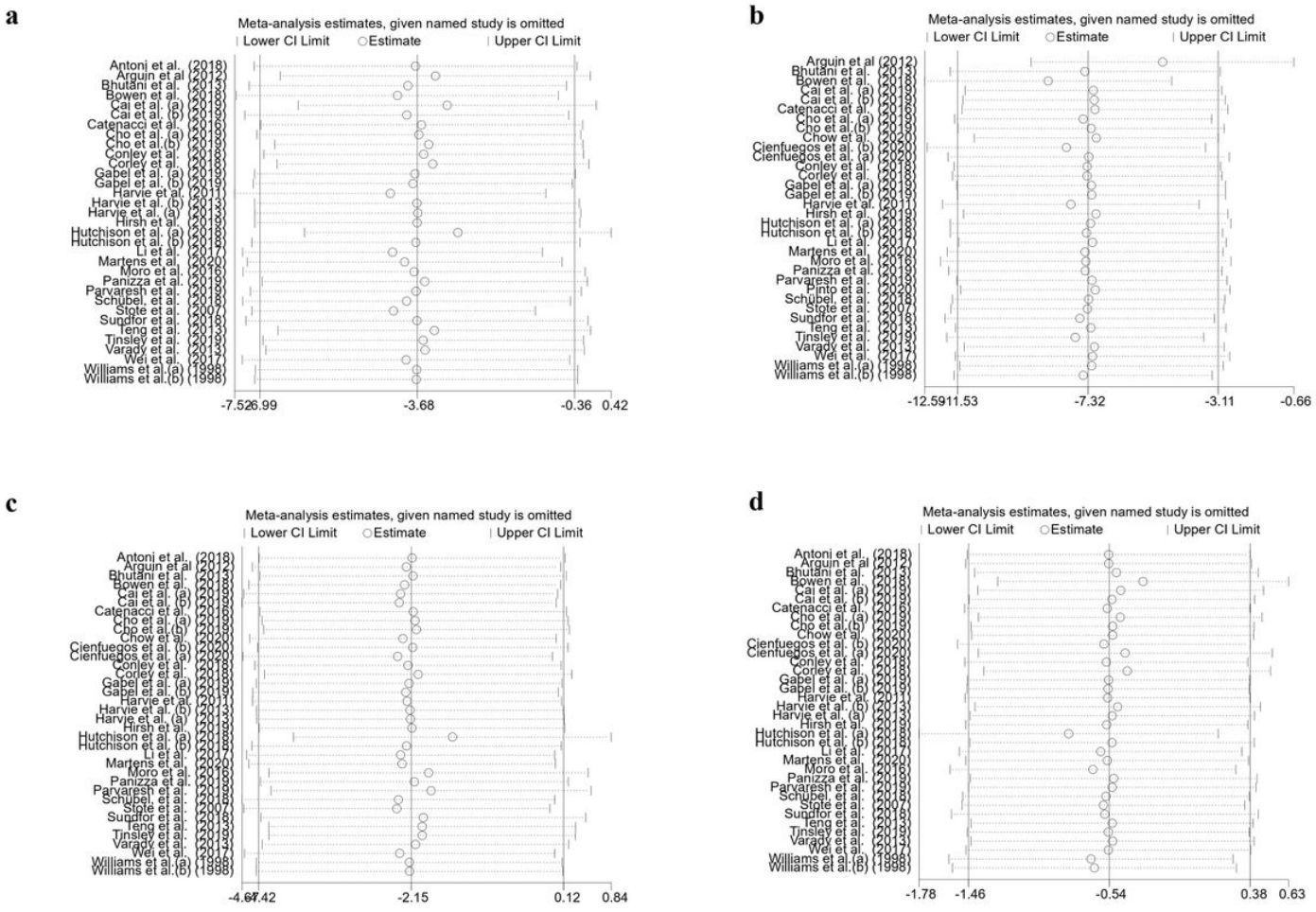

Figure 14

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

Supplementary Files

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