Original Article

Effects of intermittent fasting on cardiometabolic risk factors in patients with metabolic syndrome: A systematic review and meta-analysis of randomized controlled trials

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Background and Objectives: Evidence showed that intermittent fasting may have beneficial effects on metabolic syndrome. However, the results are controversial and indefinite. This study intends to investigate and assess the effects of intermittent fasting (IF) on cardiometabolic risk factors in patients with metabolic syndrome. **Methods and Study Design:** We searched PubMed, Web of Science, Embase, and Cochrane Library databases up to July 31, 2022. Primary outcomes included body mass index, fat mass, fat free mass, body weight, blood pressure, the homeostasis model assessment of insulin resistance (IR), fasting blood glucose, fasting insulin, and lipid profiles. **Results:** Of 4997 retrieved records, 6 met the inclusion criteria. The meta-analysis showed that IF can significantly reduce BMI (mean difference=-1.56 kg/m2, 95% CI: -2.62 to -0.51), fat mass (mean difference=-1.35%, 95% CI: -2.03 to -0.67), fat free mass (mean difference=-0.63%, 95% CI: -1.22 to -0.04), body weight (mean difference=-2.49 kg, 95% CI: -3.11 to -1.88), waist circumference (mean difference=-3.06 cm, 95% CI: -4.21 to -1.92), and HOMA-IR (mean difference=-0.62, 95% CI: -0.84 to -0.40) compared with non-fasting. However, no statistical difference was found in the SBP, DBP, TC, TG, LDL-C, HDL-C, fasting blood glucose, and fasting insulin comparing fasting and non-fasting group. Subgroup analyses suggested that study duration and sample size may be the source of heterogeneity for LDL-C. Sensitivity analysis indicated that our results are reliable and robust. **Conclusions:** IF could be used for patients with metabolic syndrome. Further studies with a larger sample size are needed to verify the effectiveness and safety of IF in patients with metabolic syndrome.

Key Words: intermittent fasting, metabolic syndrome, biomarkers, meta-analysis, evidence synthesis

INTRODUCTION

Metabolic syndrome (MetS) is a pathological condition characterized by abdominal obesity, insulin resistance, hypertension, and hyperlipidemia.[1] MetS is often associated with an increased risk of type 2 diabetes, cardiovascular disease, and dementia.[2-4] Due to lifestyle changes along with economic development, the increasing prevalence of MetS occurs, which has been a public health issue worldwide.[5,6] According to the international diabetes federation (IDF), it has been estimated that around 25% of the global adult population suffers from MetS.[7] In addition, it has been shown that the prevalence of MetS among US citizens has risen over the last decade for all sociodemographic groups.[8] Several large-scale population studies have shown that the prevalence of MetS increases with age.[9-12] To combat the age-related increases in health risks, major health organizations promote dietary and physical activity behaviors as preventive strategies. Therefore, the development of effective treatments with fewer side effects such as dietary changes for MetS is currently highly warranted.[13,14]

Recently, intermittent fasting (IF) has garnered much public attention as a unique dietary strategy.[15] IF involves repeated intentional interruptions or significant reductions in energy expenditure over a period.[16] Although IF interventions have not been standardized, several protocols exist, like alternate-day fasting (ADF), modified fasting, and energy restriction intermittent fasting die (IER).[17,18]

Although it has been proven that continuous energy restriction improves metabolism and prevents chronic diseases,[19-24] its long-term effects are indefinite, and patients have difficulty adhering to it.[25-28] In general, IF refers to consuming a very low calorie diet (500-700 kcal) for 2–4 days a week.[29] Since IF requires strict energy restriction for only a few days per week, it is more easily accepted by patients.[30] Several studies have indicated that intermit-

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tent fasting has many beneficial effects on chronic non-communicable diseases.[31-36] A recent meta-analysis conducted by Enríquez et al[37] concluded that an intermittent fasting diet may be beneficial to improve anthropometry, body composition, and lipid profiles in overweight or obese adult populations, likewise a continuous energy restriction diet. Meng et al[38] performed a systematic review and meta-analysis and indicated that IER can significantly improve circulating TC, LDL-C, and TG concentrations when compared with a non-diet control. In addition, Borgundvaag et al[39] found that IF can contribute to weight loss in type 2 diabetic patients when compared to the standard diet. An umbrella review from Patikorn et al[40] also concluded that IF may have a beneficial role in improving anthropometric and cardiometabolic outcomes. However, few meta-analyses focused on exploring the effects of IF on MetS. Therefore, we systematically reviewed randomized controlled trials (RCTs) assessing the metabolic effects of IF in patients with MetS.

METHODS

This research was performed according to the preferred 2020 reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[41]

Search strategy and eligibility criteria

We searched PubMed, Web of Science, Embase, and Cochrane Library for relevant articles up to 23 February 2022, using a combination of the following terms "Fasting", "Intermittent Fasting", "Hunger Strike", "Hunger Strikes", "Time Restricted Feeding", "Metabolic Syndrome", "Metabolic Syndromes", "Metabolic Syndrome X", "Insulin Resistance Syndrome X", "Metabolic X Syndrome", "Dysmetabolic Syndrome X", "Reaven Syndrome X", "Metabolic Cardiovascular Syndrome", "Cardiometabolic Syndrome", "Cardiometabolic Syndromes". We only included the published literature in English. The reference lists of the relevant articles were also retrieved for additional articles.

Eligibility criteria

For this meta-analysis, inclusion criteria were as follows: (a) the study design is limited to randomized controlled trials; (b) Adult participants with metabolic syndrome aged ≥18 years; (c) the intervention group underwent any type of IF intervention alone or in conjunction with a standard dietary intervention;(d) the comparator group underwent standard dietary intervention, standard diet including calorie-deficient healthy dietary advice or normal caloric intake; (e) Primary outcomes included body mass index (BMI), fat mass, body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), waist circumference, the homeostasis model assessment of IR(HOMA-IR), fasting blood glucose, fasting insulin, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) or fat free mass. We excluded trials for these reasons: (a) uncontrolled trials or other research designs; (b) animal or cell experiments, case reports, comments, letters, editorials, conference papers, and literature with unavailable or unconverted data.

Data extraction

Data extraction and quality assessment were independently performed by 2 reviewers (L.Z and H.R.Li) and checked by another reviewer (M.W.Liu). The following information was extracted from the included studies: (1) study characteristics (e.g., first author, year, sample size, age), (2) treatments, (3) methodological aspects, and (4) clinical outcomes. We converted the units from mg/dL to mmol/L for the network meta-analysis. For blood glucose, 1 mg/dL was converted to 0.0555 mmol/L; for serum TC, LDL-c, and HDL-c, 1 mg/ dL was converted to 0.0259 mmol/L; for serum TG, 1 mg/dL was converted to 0.0113 mmol/L. We tried our best to contact the corresponding authors to obtain potential specific raw data if the outcome data were missing or presented graphically. We obtained the mean net change of relevant indexes (endpoint minus baseline value) from each arm. We used the last end value When the trial was with multiple endpoints. Any disagreements during data extraction were resolved through rigorous discussion by two reviewers, and a third reviewer, if necessary, was invited for the final adjudication.

Risk of bias assessment

We used the Cochrane risk-of-bias tool to assess the risk of bias in these included randomized trials.[42] The assessed items covered seven domains, namely detection bias (outcome assessment blinding), selection bias (random sequence generation and allocation concealment), attrition bias (incomplete outcome data), and reporting bias (selective reporting).[43] Each item could be rated as "high risk," "low risk," or "unclear" for included literature. We determined the overall risk-of-bias judgment as low risk of bias, some concerns, or high risk of bias considering the risk-of-bias judgment in seven domains above.

Data synthesis

A series of calculations were executed to standardize the data in terms of standard deviation (SD) as some articles reported confidence intervals (CI).[43] The net change of standard deviation (SD) was calculated by the formula as follows:

$$SD_{\text{net change}} = \sqrt{[(SD(\text{baseline})^2 + SD(\text{endpoint})^2 - 2R \times SD(\text{baseline}) \times SD(\text{endpoint})]}$$

When required, we calculated a correlation coefficient R to impute the standard deviation of changes from baseline according to the formula from the Cochrane handbook. We assumed R=0.5 if the study did not provide or have sufficient data to calculate the correlation coefficient. The formula of the correlation coefficient was as below:

$$R = [SD(\text{baseline})^2 + SD(\text{end point})^2 - SD(\text{change})^2] / [2 * SD(\text{baseline}) * SD(\text{endpoint})].$$

All analyses were repeated using correlation coefficients of 0.2 and 0.834 to test the sensitivity of the meta-analysis. RevMan V5.4.1 and stata 15.0 SE was used for statistical analysis. For continuous variables, we used mean difference (MD) and 95% CI for analysis. The I^2 statistic was used to assess heterogeneity. I^2 values of 25%, 50%, and 75% were considered as low, moderate, and high heterogeneity, respectively. We planned to use a random-effects model to examine potential sources of heterogeneity between studies, subgroup analyses were

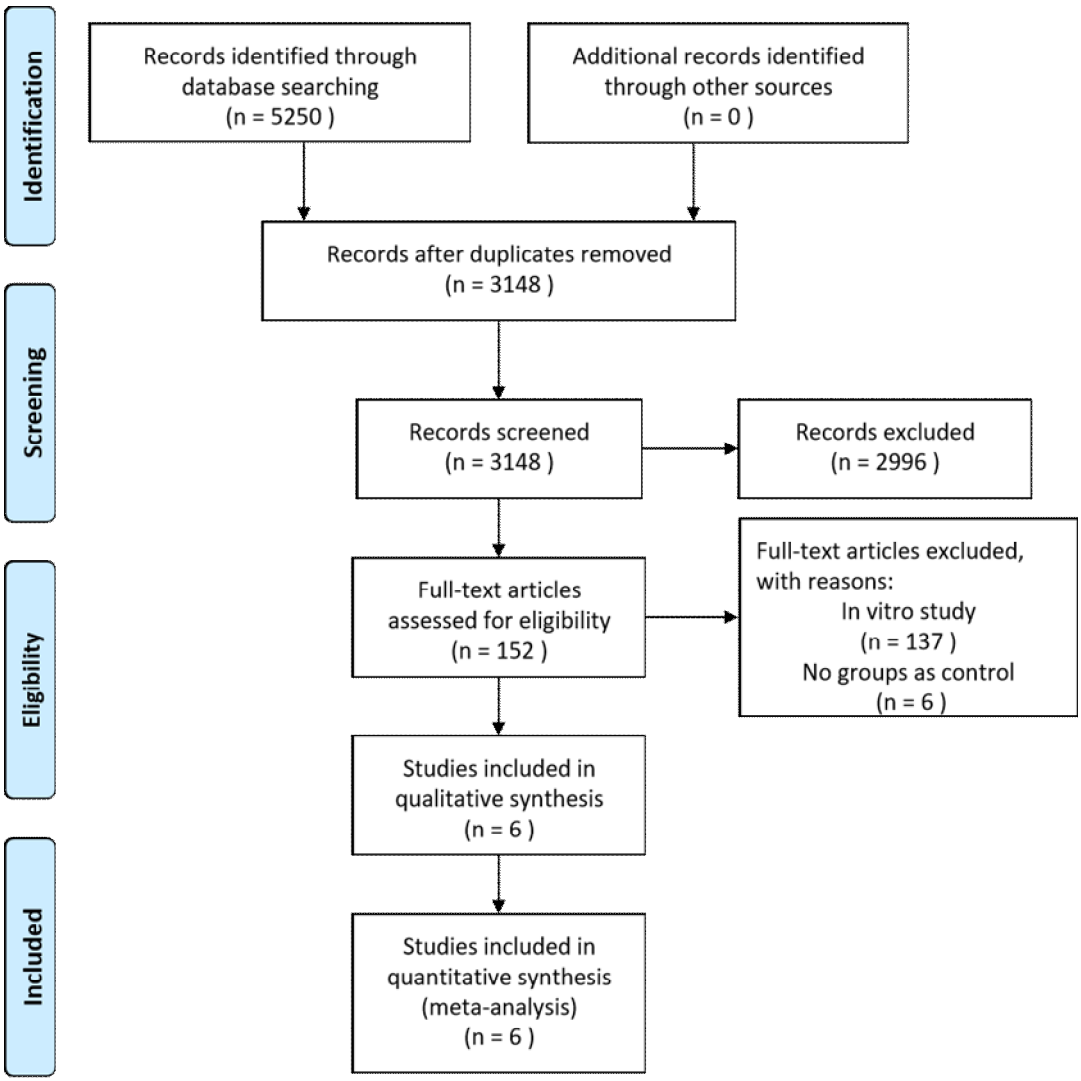

Figure 1. Flow chart.

performed according to study duration (≥12 weeks vs <12 weeks), and sample size (≥50 vs <50). The rationale for these analyses was to assess potential sources of heterogeneity. Sensitivity analyses were conducted by excluding studies from the analysis one by one to assess the susceptibility of the findings of this meta-analysis. The risk of publication bias for studies will be assessed using funnel plots, and the Egger's test was employed to examine the publication bias when there were at least 10 studies.[44] RevMan V5.4.1 and stata 15.0 SE were used for statistical analysis. Two-sided $p<0.05$ were defined statistical significance.

RESULTS

Study selection and characteristic

A PRISMA flow diagram of the included trials is shown in Figure 1. A total of 4997 potentially relevant articles were retrieved after the initial search of four databases (PubMed, Web of Science, EMBASE, and Cochrane Central), of which 6 studies met the inclusion criteria after duplicates, title, abstract screening, and reading the full text.

The general characteristics of the study subjects are summarized in Table 1. From the six included studies, two each were performed in Germany[45,46] and Iran,[47,48] one each in China[49] and Turkey.[50] The mean age of participants ranged from 18 years to 72 years. Sample sizes ranged from 32 to 75, and the total number of participants in included studies was 351 (177 participants in the experimental group, and 174 participants in the control group).

Quality assessment and risk of bias assessment

The majority of RCTs were at low risk of bias, and 4 RCTs was judged as unclear risk of bias for allocation concealment,[45,48-50] 2 RCTs were judged as unclear risk of bias in blinding participants and personnel,[48,50] 3 RCTs were judged as unclear risk of bias in blinding of outcome assessment.[45,48,49] In addition, 1 RCT was judged to have a high risk of bias for incomplete outcome data.[46] The complete results of the risk of bias assessment are shown in Figure 2 and Figure 3.

The effect of empagliflozin on body composition

BMI

Six studies reported BMI levels in 351 patients,[45-50] 177 with fasting, and 174 with non-fasting. When they were included for the meta-analysis, the result showed that fasting can significantly reduce BMI in patients with MetS compared to Non-fasting (MD=-1.56 kg/m^2, 95%

Table 1. characteristics of the included studies

Reference	Country	Sample size (T/C)	Definition of MetS	Age (y)	Intervention diet	Control diet	Duration	Outcomes
Guo Y et al,[49] 2021	China	21/18	IDF diagnostic criteria (2005)	T: 40.2±5.7 C: 42.7±4.1	involved a 75% of energy restriction for two nonconsecutive days a week and an ad libitum diet the other five days.	maintained a routine diet without dietary instructions.	8 weeks	BMI, FM, FFM, BW, WC, SBP, DBP, TC, TG, HDL-C, LDL-C, FBG, FINS, HOMA-IR
Li C et al,[45] 2017	Germany	16/16	greater or equal to 3 MetS risk factors	T: 64.7±7.0 C: 65.4±5.7	performed according to the method of Buchinger with a nutritional energy intake of 300kcal/day by liquids only and stepwise re-introduction of solid food thereafter. The fasting group received an initial fasting program followed by recommendations for a Mediterranean diet.	Mediterranean diet.	4 months	BMI, BW, WC, SBP, DBP, TC, TG, HDL-C, LDL-C, FBG, FINS, HOMA-IR
Maifeld A et al,[46] 2021	Germany	35/36	RNCEP: ATPIII	T: 58±8 C: 62±8	Periodic fasting and modified DASH diet intervention. Intervention within the fasting arm started with two calorie-restricted vegan days (max 1200 kcal/day), followed by 5-days with a daily nutritional energy intake of 300–350 kcal/day, derived from vegetable juices and vegetable broth.	DASH diet	10 weeks	BMI, BW, SBP, DBP
Parvaresh A et al,[47] 2019	Iran	35/34	RNCEP: ATPIII	T: 44.6±9.08 C: 46.4±7.94	Patients in the ADF group were asked to consume a very low calorie diet (75% energy restriction) during the 3 fast days (Saturday, Monday, Wednesday) and then ate a diet that providing 100% of their energy needs on each feed day.	consumed 75% of their energy needs each day.	8 weeks	BMI, BW, WC, SBP, DBP, TC, TG, HDL-C, LDL-C, FBG, FINS, HOMA-IR
Razavi R et al,[48] 2021	Iran	38/37	RNCEP: ATPIII	T: 41.3±8.65 C: 43.1±9.26	During the 4 months ADF period, subjects consumed a very low-calorie diet (75% energy restriction, ranging from 400–600 kcal) during the 3 fast days (Saturday, Monday, Wednesday) and then consumed ad libitum without limitation on each feed day (4 days a week).	consumed 75% energy needs each day.	4 months	BMI, FM, FFM, BW, WC
Kunduraci YE et al,[50] 2020	Turkey	32/33	RNCEP: ATPIII	T: 47.44±2.17 C: 48.76±2.13	All participants needed to adhere to a dietary regime, with a reduction of 25% from habitual energy intake for the 12-week intervention period, and maintain their present lifestyle without any change in physical activity levels. For the other 8 h, participants followed an energy restriction diet. For a 16-h period, such as at 04.00–08.00 a.m., 05.00 p.m.–09.00 a.m., 06.00 p.m.–10.00 a.m., or 07.00 p.m.–11.00 a.m. fasting hours, no food and calorie drinks were consumed.	continuous energy restriction.	12 weeks	BMI, FM, FFM, BW, SBP, DBP, TC, TG, HDL-C, LDL-C, FBG, FINS, HOMA-IR

T, treatment group; C, control group; MS, metabolic syndrome; IF, intermittent fasting; ADF, alternate day fasting; BMI,body mass index; IDF:International Diabetes Federation; RNCEP:ATP-Ⅲ, Revised National Cholesterol Education Program Third Adult Treatment Panel; FM, fat mass; FFM, fat free mass; BW, body weight; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, Triglycerides; HDL-C, high density lipoprotein; LDL-C, low density lipoprotein; FINS, fasting insulin; FBG, fasting blood glucose; Fins, fasting insulin; HOMA-IR, Homeostasis model assessment-insulin resistance; DASH, dietary approaches to stop hypertension.

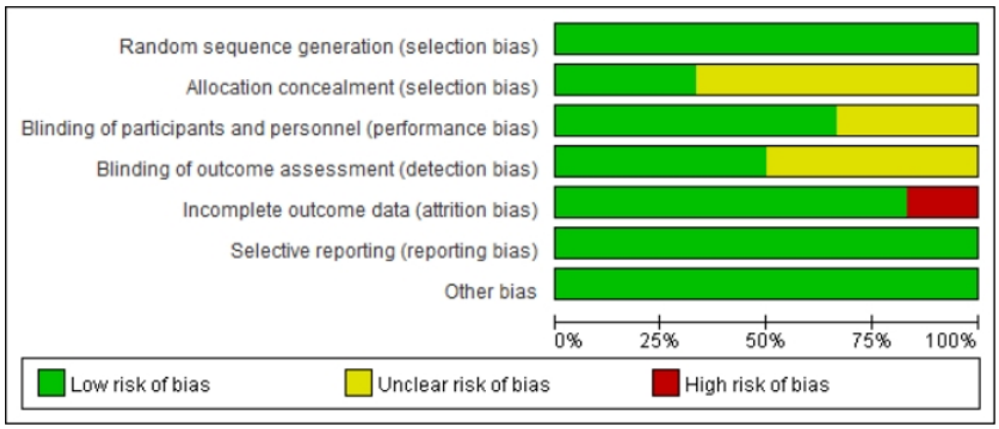

Figure 2. Risk of bias summary review authors' judgments about each risk of bias item for each included study.

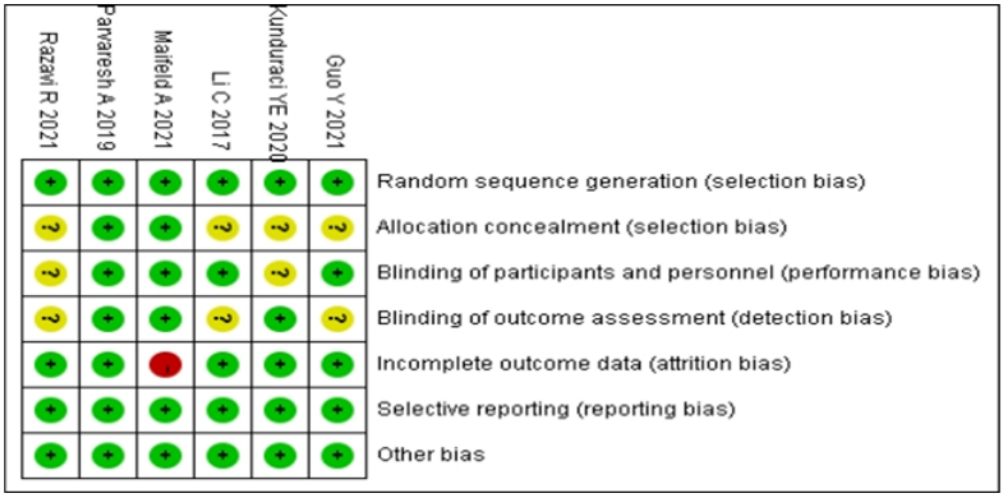

Figure 3. Risk of bias graph review authors' judgments about each risk of bias item presented as percentages across all included studies

CI: -2.62 to -0.51, p=0.004). There was significant heterogeneity exhibited between studies (I^2=85%, p<0.001) (Figure 4).

Fat mass

Three RCTs[48-50] involved 179 patients with fat mass level. The overall result indicated that fasting can significantly reduce fat mass in patients with MetS compared to Non-fasting (MD=-1.35%, 95% CI: -2.03 to -0.67, p<0.001). There was no heterogeneous difference between studies (I^2=0%, p=0.89) (Figure 4).

Fat free mass

Three RCTs with 179 participants reported fat free mass.[48-50] The overall result showed that fasting can significantly reduce fat free mass in patients with MetS compared to Non-fasting (MD=-0.63%, 95% CI: -1.22 to -0.04, p=0.04). There was no heterogeneous difference between studies (I^2=0%, p=0.82) (Figure 4).

Body weight

Six RCTs reported body weight on 351 patients,[45-50] 177 with fasting and 174 with non-fasting. The result showed that fasting can significantly reduce body weight in patients with MetS compared to Non-fasting (MD=-2.49 kg, 95% CI: -3.11 to -1.88, p<0.001). There was no heterogeneous difference between studies (I^2=0%, p=0.88) (Figure 5).

Waist circumference

Four RCTs involved 215 patients reported waist circumference.[45,47-49] The result revealed that fasting can significantly reduce waist circumference in patients with MetS compared to Non-fasting (MD=-3.06 cm, 95% CI: -4.21 to -1.92, p<0.001). There was no heterogeneous difference between studies (I^2=0%, p=0.56) (Figure 5).

The effect of empagliflozin on blood pressure

SBP

Five RCTs involved 244 patients with SBP levels.[45-47,49,50] The result showed that fasting cannot significantly reduce SBP in patients with MetS compared to non-fasting (MD=-3.98 mmHg, 95% CI: -11.08 to 3.12, p=0.27). Significant heterogeneity was found between studies (I^2=66 %, p=0.02) (Figure 6).

DBP

Five RCTs reported DBP levels in 276 patients,[45-47,49,50] 139 with fasting and 137 with non-fasting. The result indicated that fasting cannot significantly reduce DBP in patients with MetS compared to Non-fasting (MD=-1.44 mmHg, 95% CI: -5.51 to 3.23, p=0.61). Significant heter-

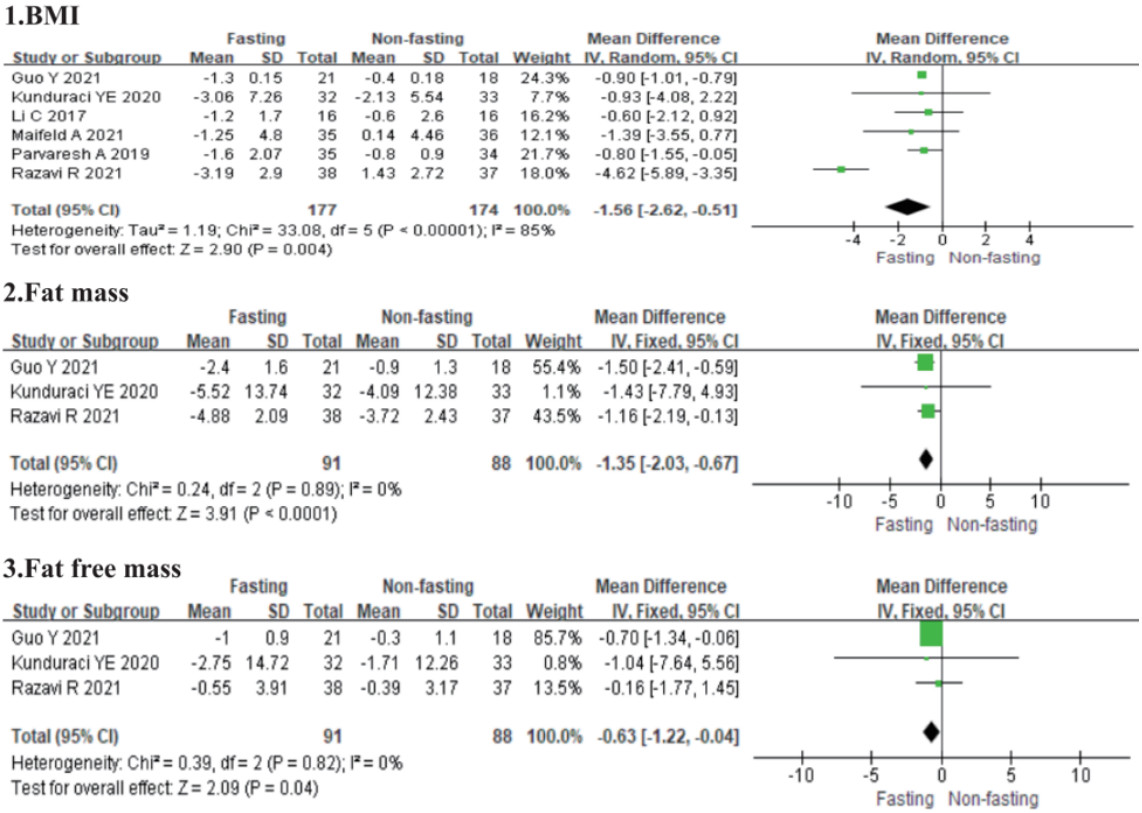

Figure 4. Risk of bias graph review authors' judgments about each risk of bias item presented as percentages across all included studies.

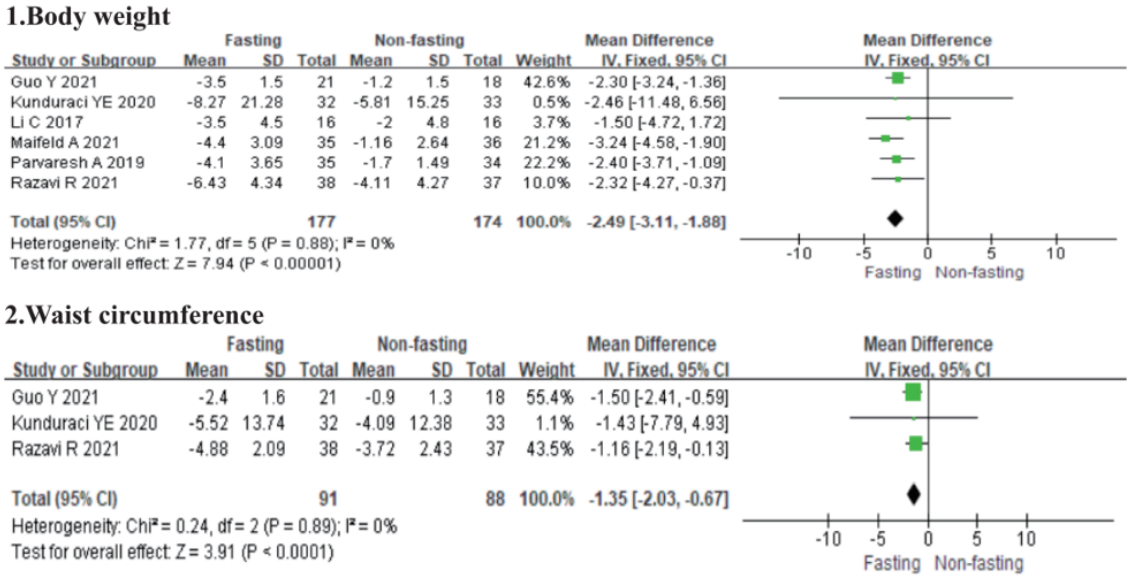

Figure 5. Forest plot comparing the effects of intermittent fasting with non-fasting on body weight and waist circumference.

ogeneity was found between studies (I^2=67 %, p=0.02) (Figure 6).

The effect of fasting on lipids profiles

TC

Four RCTs involved 205 patients with TC levels.[45,47,49,50] The overall result showed that fasting cannot significantly reduce TC in patients with MetS compared to Non-fasting (MD=0.12 mmol/L, 95% CI: -0.16 to 0.41, p=0.40). There was no heterogeneous difference between studies (I^2=5%, p=0.37) (Figure 7).

TG

Four RCTs reported TG levels in 205 patients, 104 with fasting and 101 with non-fasting.[45,47,49,50] The result indicated that fasting cannot significantly reduce TG in patients with MetS compared to Non-fasting (MD=-0.09 mmol/L, 95% CI: -0.37 to 0.18, p=0.51). There was no heterogeneous difference between studies (I^2=0%, p=0.92) (Figure 7).

HDL-C

Four RCTs reported HDL-C levels in 205 patients,[45,47,49,50] 104 with fasting and 101 with non-fasting,

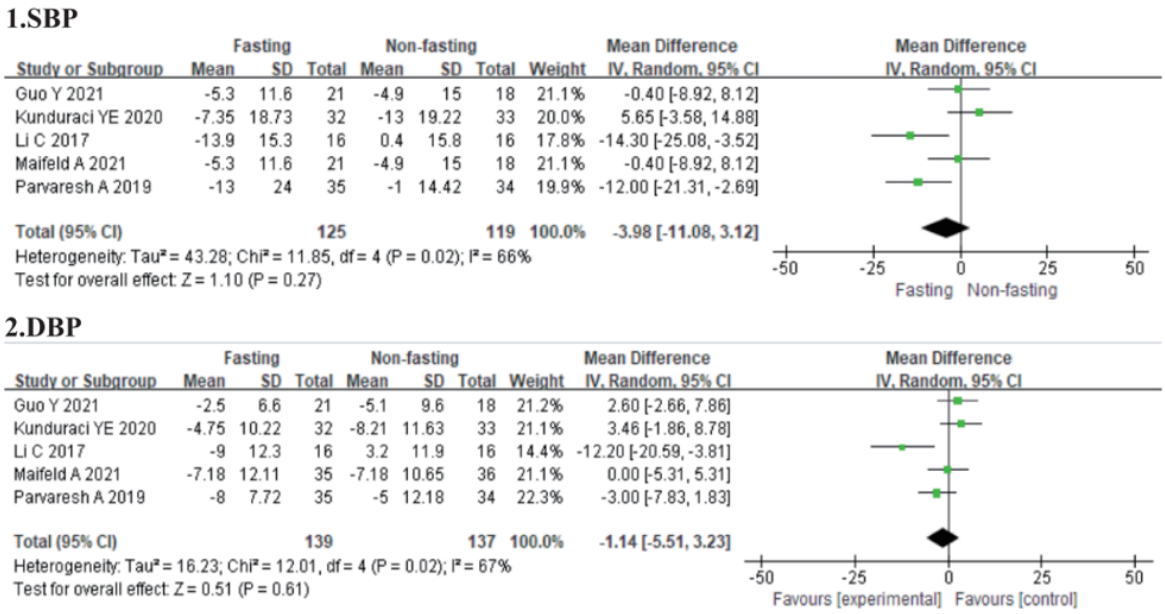

Figure 6. Forest plot comparing the effects of intermittent fasting with non-fasting on SBP and DBP

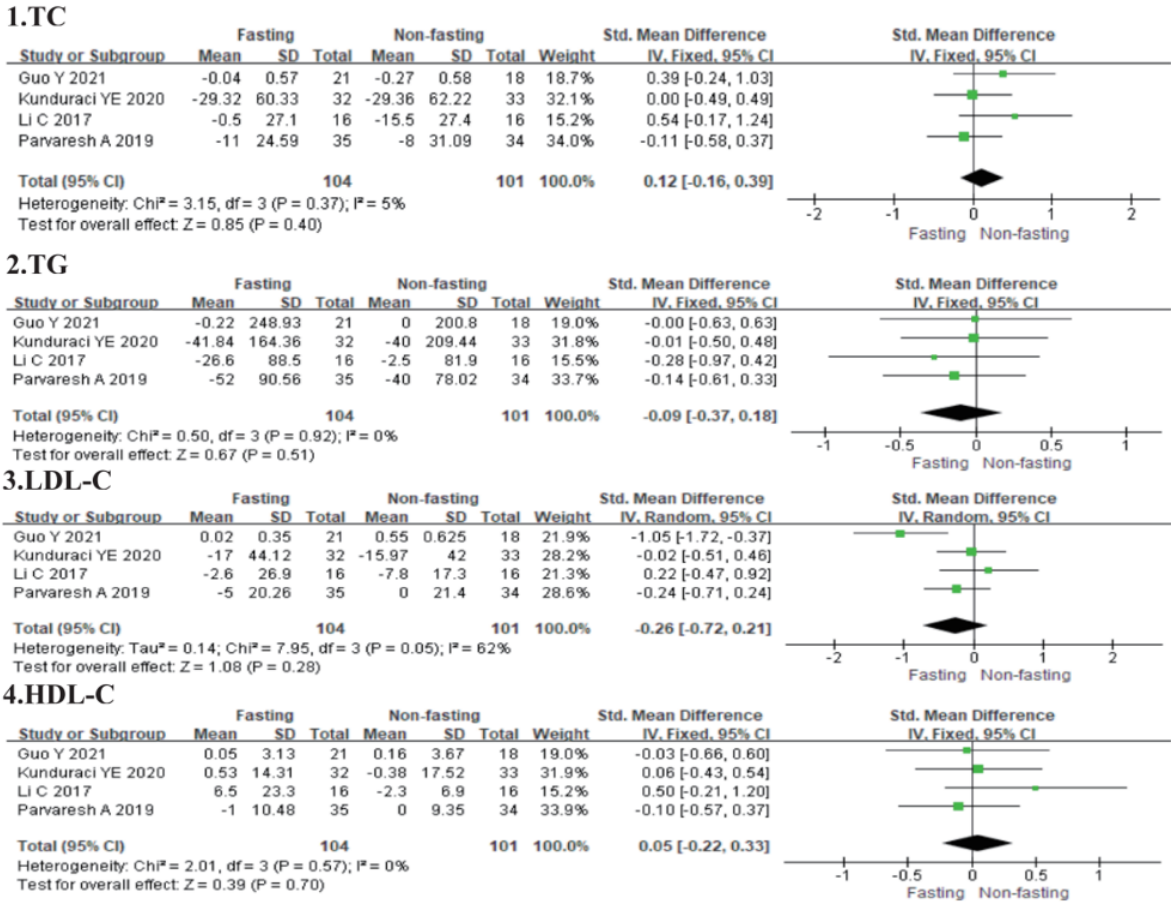

Figure 7. Forest plot comparing the effects of intermittent fasting with non-fasting on TC, TG, LDL-C and HDL-C.

the result revealed that fasting cannot significantly reduce HDL-C in patients with MetS compared to Non-fasting (MD=0.05 mmol/L, 95% CI: -0.22 to 0.33, p=0.70). There was no heterogeneous difference between studies (I^2=0%, p=0.57) (Figure 7).

LDL-C

Four studies were included for analysis, the result showed that fasting cannot significantly reduce HDL-C in patients with MetS compared to Non-fasting (MD=-0.26 mmol/L, 95% CI: -0.72 to 0.21, p=0.28).[45,47,49,50] There was significant heterogeneous difference between studies (I^2=62%, p=0.05) (Figure 7).

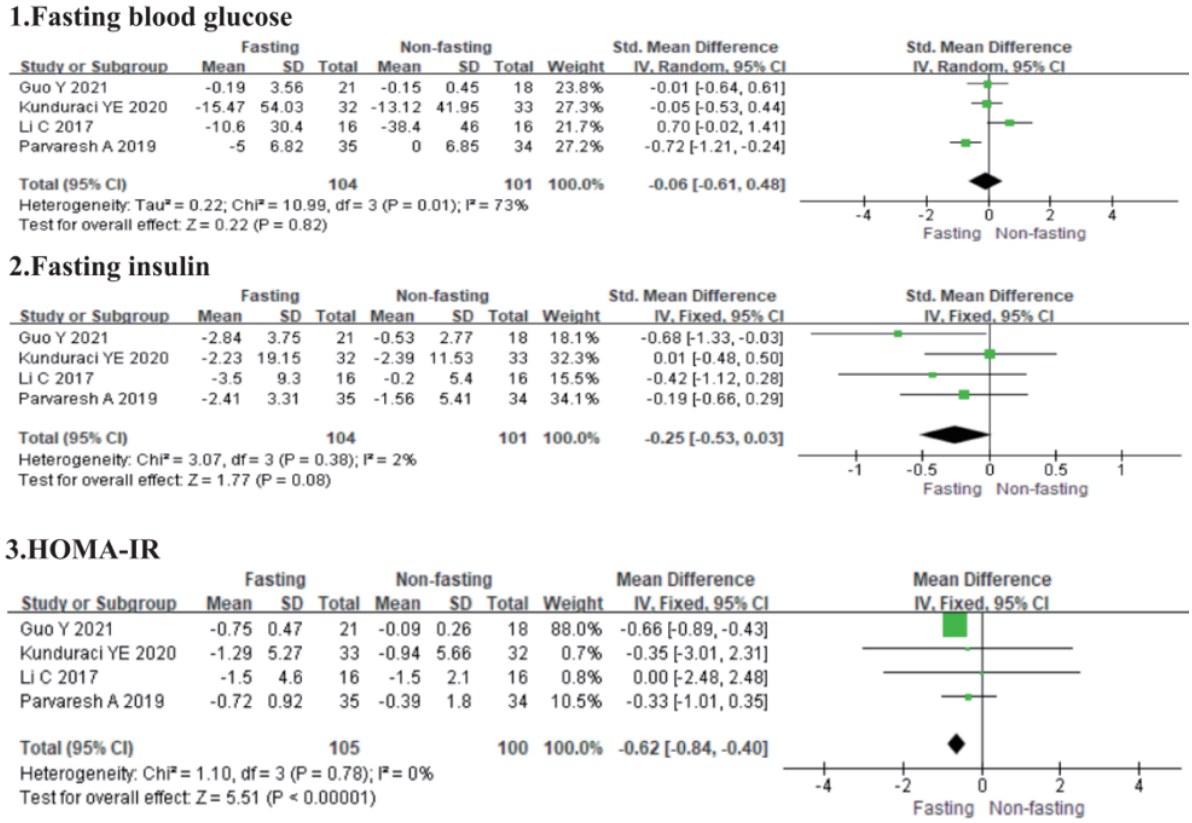

Figure 8. Forest plot comparing the effects of intermittent fasting with non-fasting on Fasting blood glucose, Fasting insulin, and HOMA-IR.

The effect of fasting on glycemic indices

Fasting blood glucose

Four RCTs were included in the meta-analysis, and the result indicated that fasting cannot significantly reduce fasting blood glucose in patients with MetS compared to Non-fasting (MD=-0.06 mmol/L, 95% CI: -0.61 to 0.48, p=0.82).[45,47,49,50] Significant heterogeneity was found between studies (I^2=73 %, p=0.01) (Figure 8).

Fasting insulin

Four RCTs were chosen for the meta-analysis. the result showed that fasting cannot significantly reduce fasting insulin fasting insulin in patients with MetS compared to Non-fasting (MD=-0.25 mmol/L, 95% CI: -0.53 to 0.03, p=0.08).[45,47,49,50] There was no heterogeneous difference between studies (I^2=2%, p=0.38) (Figure 8).

HOMA-IR

Four RCTs reported HOMA-IR levels in 205 patients, 104 with fasting and 101 with non-fasting.[45,47,49,50] The result showed that fasting can significantly reduce HOMA-IR in patients with MetS compared to Non-fasting (MD=-0.62, 95% CI: -0.84 to -0.40, p<0.001). There was no heterogeneous difference between studies (I^2=0%, p=0.78) (Figure 8).

Subgroup analysis and sensitivity analysis

Subgroup analyses were conducted to determine the underlying clinical heterogeneity. The results of subgroup analysis of BMI, SBP, DBP, LDL-C, fasting blood glucose were summarized in Table 2. For LDL-C, we found that study duration and sample size may be the source of heterogeneity. However, for BMI, SBP, DBP, and fasting blood glucose, we did not find the sources of significant heterogeneity in the subgroup analysis. We performed a sensitivity analysis to evaluate the stability of our present results. The results of sensitivity analysis indicated our results are reliable and robust.

Publication bias

Based on visual inspection of the funnel plot, slight asymmetry of funnel plot was observed due to fewer number of studies (Supplementary figure 1 to 14).

DISCUSSION

To our knowledge, this study was the first meta-analysis to focus on evaluating the effectiveness of IF on metabolic syndrome biomarkers in patients with Mets. In our meta-analysis, the results showed that IF can significantly reduce BMI, fat mass, fat free mass, body weight, waist circumference, and HOMA-IR compared with Non-fasting. However, no statistical difference was observed in the SBP, DBP, TC, TG, LDL-C, HDL-C, fasting blood glucose, and fasting insulin compared to the non-fasting group. The results of subgroup analysis suggested that study duration and sample size may be the source of heterogeneity for LDL-C, and we did not find the sources of significant heterogeneity for BMI, SBP, DBP, and fasting blood glucose. Also, the sensitivity analysis indicated that our current results are robust.

MetS is associated with multiple risk factors, including elevated blood glucose, insulin resistance, and obesity. Weight loss is beneficial to improving their blood glucose, lipid profile, and blood pressure.[51] Therefore, we included

Table 2. Results of subgroup analysis

Index Subgroup	No. of Trials	Weighted mean difference		*p*	I^2 (%)	*p* value of heterogeneity
		Mean	95% CI			
BMI						
Overall	6	-1.56	-2.62, -0.51	0.004	85	<0.001
Study duration						
≥12 weeks	3	-2.17	-5.20, 0.87	0.162	88.4	0.000
<12 weeks	3	-0.90	-1.00, -0.80	0.000	0	0.875
Sample size						
≥50	4	-2.02	-4.28, 0.23	0.08	88	<0.001
<50	2	-0.9	-1.00, -0.79	<0.00001	0	0.7
SBP						
Overall	5	-3.98	-11.1, 3.12	0.27	66	0.02
Study duration						
≥12 weeks	2	-4.12	-23.7, 15.4	0.679	86.8	0.006
<12 weeks	3	-4.05	-11.4, 3.30	0.280	52.4	0.122
Sample size						
≥50	3	-2.21	-12.1, 7.67	0.662	72.2	0.027
<50	2	-6.94	-20.5, 6.66	0.317	74.6	0.047
DBP						
Overall	5	-1.14	-5.51,3.23	0.61	67	0.02
Study duration						
≥12 weeks	2	-4.02	-19.4, 11.3	0.607	89.5	0.002
<12 weeks	3	-0.27	-3.50, 2.95	0.868	16.1	0.304
Sample size						
≥50	3	0.02	-3.68, 3.72	0.991	35.7	0.211
<50	2	-4.42	-18.9, 10.1	0.549	88.4	0.003
LDL-C						
Overall	4	-0.26	-0.72, 0.21	0.28	62	0.05
Study duration						
≥12 weeks	2	2.97	-9.58, 15.51	0.643	0	0.641
<12 weeks	2	-0.53	-0.86, -0.21	0.001	0	0.373
Sample size						
≥50	2	-4.28	-13.2, 4.62	0.346	0	0.737
<50	2	-0.53	-0.85, -0.20	0.001	0	0.474
FBG						
Overall	4	-0.06	-0.61, 0.48	0.82	73	0.01
Study duration						
≥12 weeks	2	12.0	-17.5, 41.5	0.427	63.2	0.099
<12 weeks	2	-2.31	-7.15, 2.53	0.350	86.5	0.007
Sample size						
≥50	2	-4.95	-8.15, -1.76	0.002	0	0.827
<50	2	10.5	-16.0, 36.9	0.438	75.4	0.044

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL-C: low density lipoprotein; FBG: fasting blood glucose.

studies comprising subjects with MetS. We found that IF can significantly reduce BMI, fat mass, fat free mass, and body weight, which suggests that IF may be more effective than non-fasting for weight loss. Nevertheless, the clinical significance of the differences needs to be further investigated.

Our current findings are consistent with previous meta-analysis studies that showed that IF was beneficial to weight loss and partial metabolic improvement in patients with chronic diseases such as type 2 diabetes, hypertension, and nonalcoholic fatty liver.[34,52-53] Since there are no uniformly accepted treatments for the MetS, and the current treatment of related complications require the long-term use of multiple drugs,[54-57] new diets and lifestyles to improve Mets are necessary.[58]

IF can be effective to lose weight and fat mass in our study, suggesting that fasting could be considered a valid alternative but not superior to non-fasting such as caloric restriction, although there were greater benefits in insulin indexes but no differences in blood lipids or glucose level. Thus, the predominant mechanism for weight loss through IF may be a reduction in total calories consumed, as well as the rise of insulin levels that promote the storage of fat.[59] One of the important pathophysiologic approaches to maintaining physical function is balancing maximizing loss of body fat and the minimizing the loss of lean mass.[60] It has been shown in previous studies that up to 25% of weight loss under continuous energy restriction is lean tissue, but the lean mass has been preserved in most previous studies under an IF diet intervention.[61] Our results, however, showed that IF diets reduced fat free mass in patients with MetS. It may be necessary to conduct further research to verify the underlying mechanism of our findings.

In the subgroup analysis, study duration and sample size may be the source of heterogeneity for LDL-C. Different study duration times may lead to differences in energy intake, resulting in differences in results, thus causing certain heterogeneity in research. In addition, small sample sizes may also have contributed to the extreme results, which caused the heterogeneity. however, we did not find the sources of significant heterogeneity for BMI, SBP, DBP, and fasting blood glucose, so the results of these indexes were hindered by significant heterogeneity.

Obesity caused by overfeeding is the most common reason for insulin resistance, which is a key factor in the etiology of MetS. Insulin resistance is a multifactorial interaction, in which inflammation, lipid metabolism, and microbiota are the main interacting components.[62-66] Studies have shown that the key mechanisms by which IF can improve insulin resistance are likely to be achieved by reducing inflammatory factors, improving lipid metabolism, and the gastrointestinal flora.[67-68]

Healthy dietary patterns, such as the Mediterranean diet and the DASH diet, have been proven to be effective in improving MetS,[69-72] but high-quality healthy foods such as fruits, vegetables, and fish are more expensive and difficult to obtain for low-income people,[73,74] so IF can be used as a supplementary treatment to improve MetS without changing dietary quality.

This meta-analysis has several strengths. Our study examined the efficacy of IF on metabolic syndrome biomarkers in patients with confirmed MetS. In addition, it was performed and reported based on current guidelines, and comprised an evaluation of results employing sensitivity analyses, and an investigation of the risk of bias using an updated assessment tool. There were also potential limitations in our review: firstly, there was high heterogeneity between the trials and the diet plans, therefore, the interpretation of conclusions may be hindered by substantial heterogeneity; secondly, the sample size of the included research was small and limited; thirdly, most of the studies were of short duration. Therefore, further large-scale studies are needed to clarify the role of IF in patients with MetS.

Conclusion

In summary, our current study indicates that IF may be beneficial to patients with MetS. Given the limitations such as heterogeneity and small sample size, more long-term clinical trials are needed to assess the safety and effectiveness of IF in patients with MetS.

AUTHOR DISCLOSURES

The authors declare to have no competing interests. There was no financial support or funding for this study.

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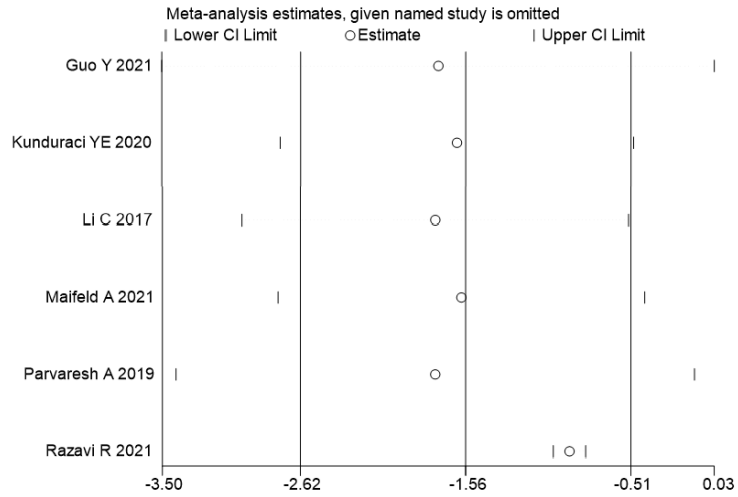
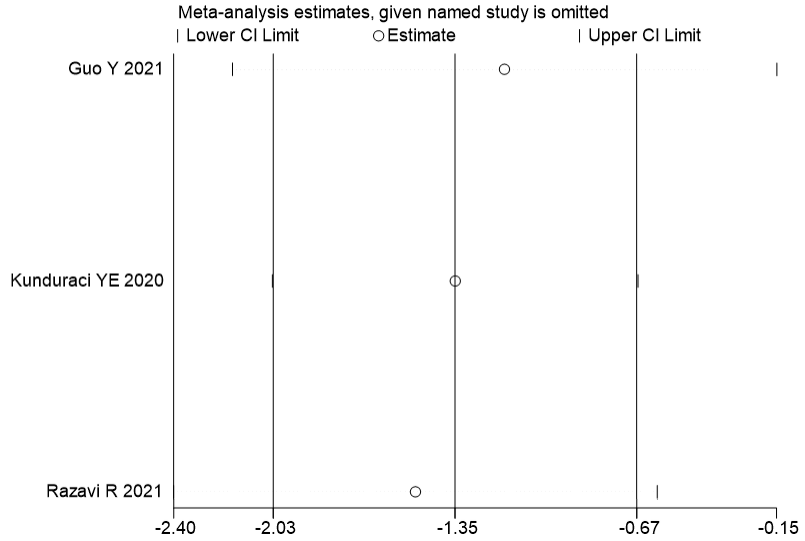
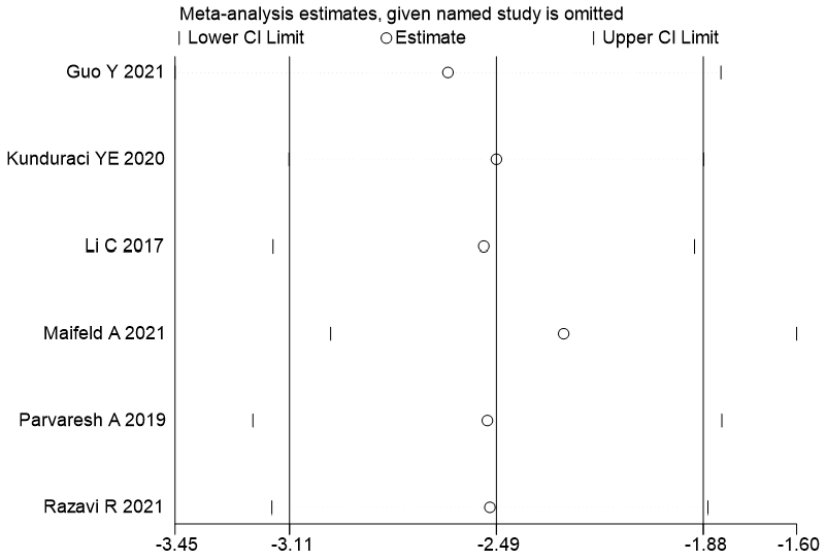


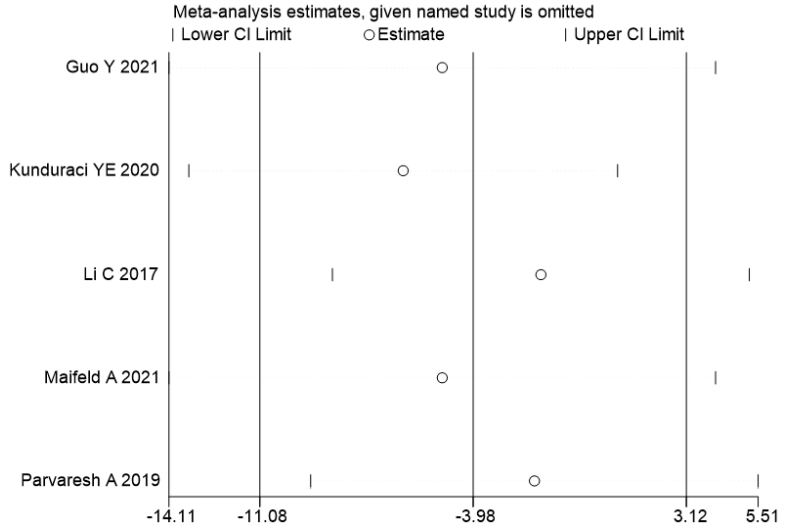
Supplementary figure 1. A sensitivity analysis of the included studies for BMI.



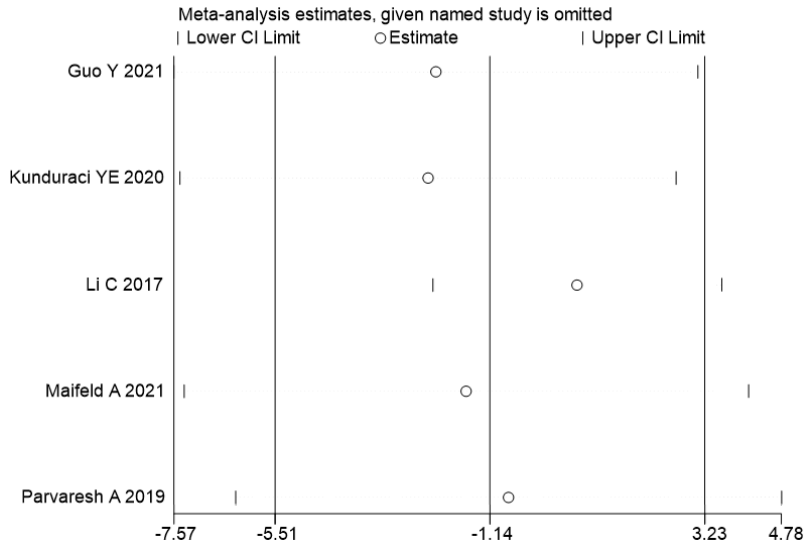
Supplementary figure 2. A sensitivity analysis of the included studies for fat mass.



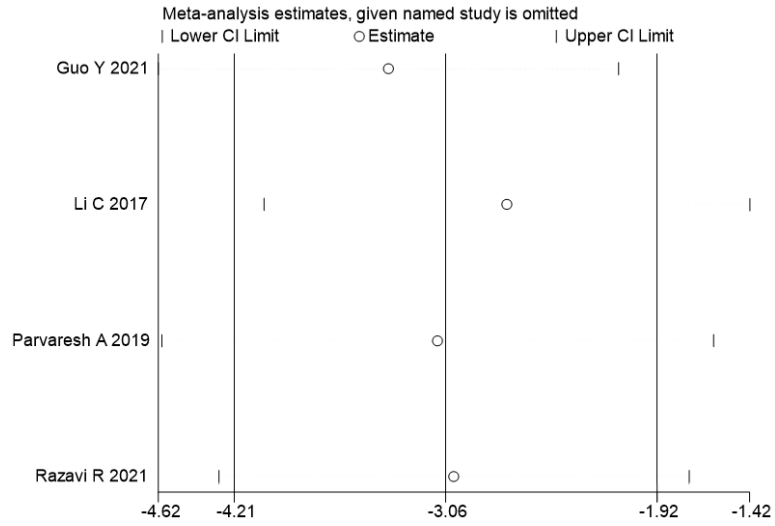
Supplementary figure 3. A sensitivity analysis of the included studies for weight.



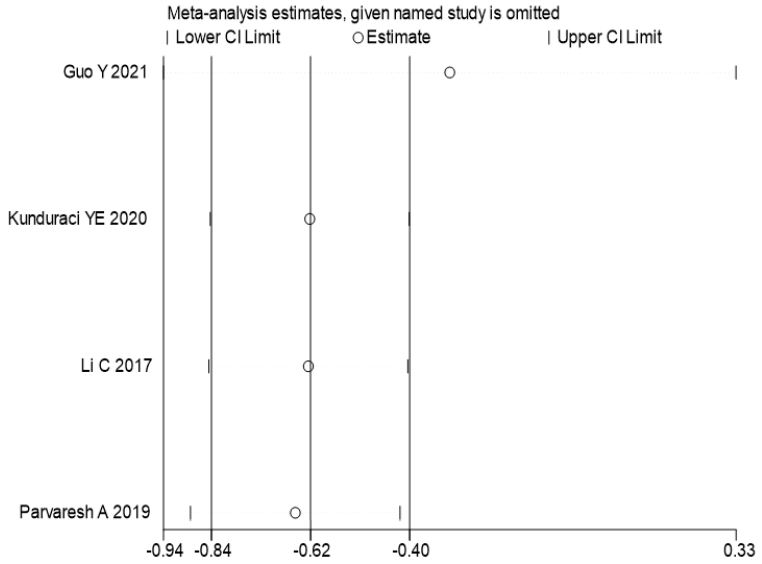
Supplementary figure 4. A sensitivity analysis of the included studies for SBP.



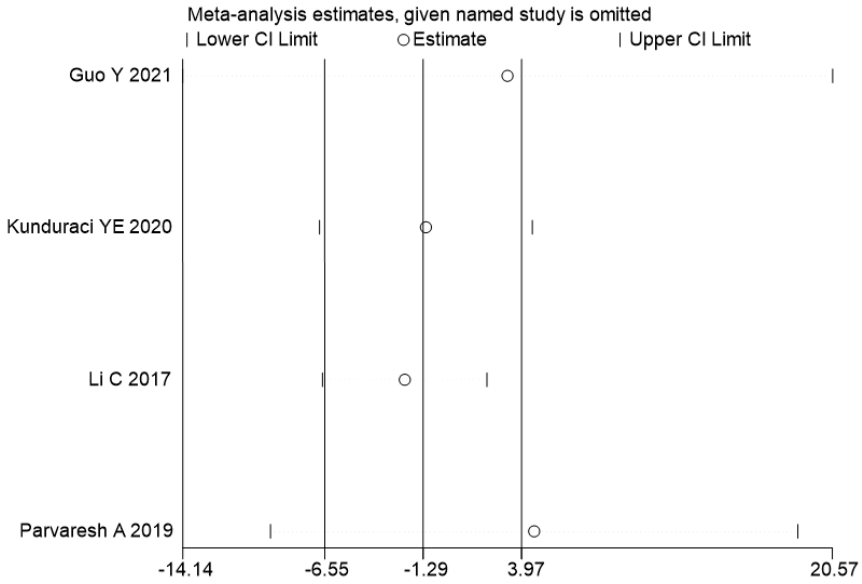
Supplementary figure 5. A sensitivity analysis of the included studies for DBP.



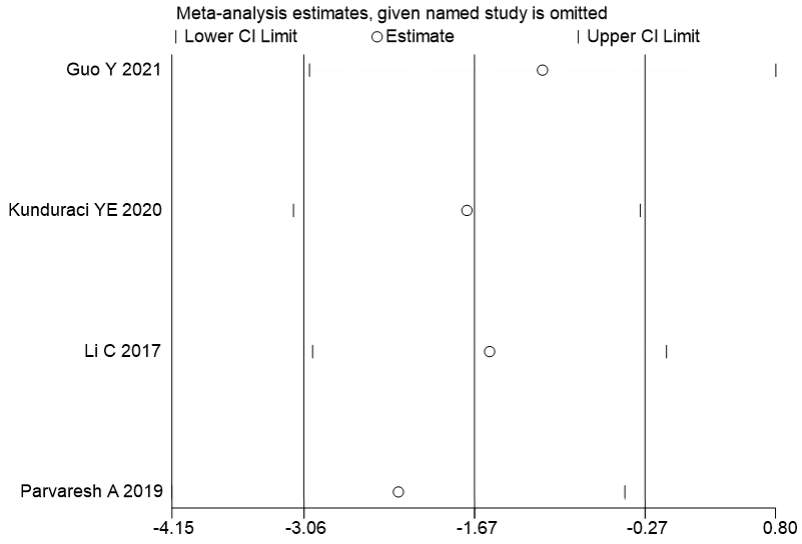
Supplementary figure 6. A sensitivity analysis of the included studies for WC.



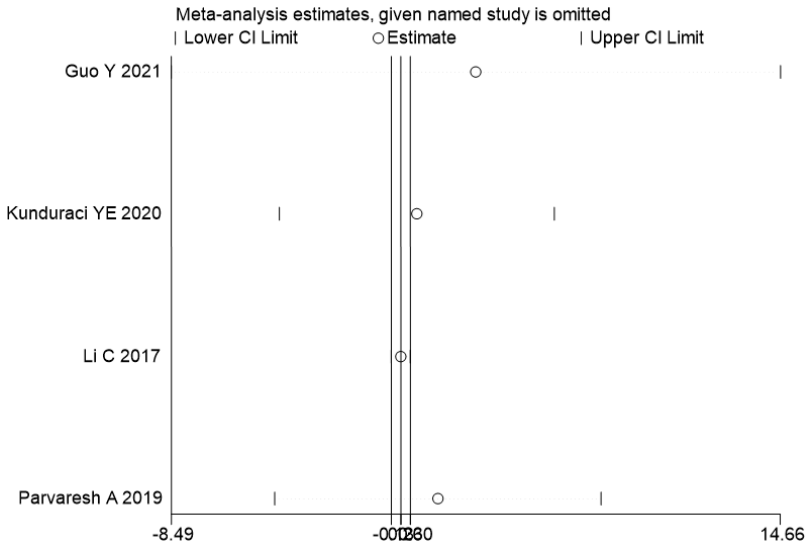
Supplementary figure 7. A sensitivity analysis of the included studies for HOMA-IR.



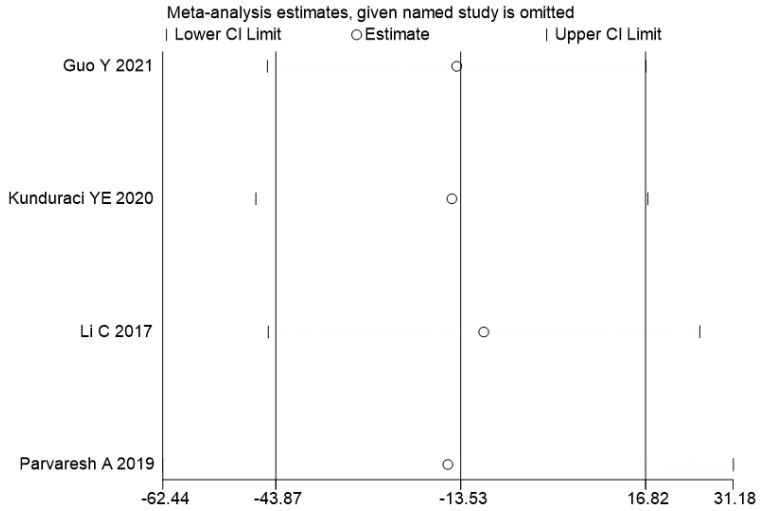
Supplementary figure 8. A sensitivity analysis of the included studies for glucose.



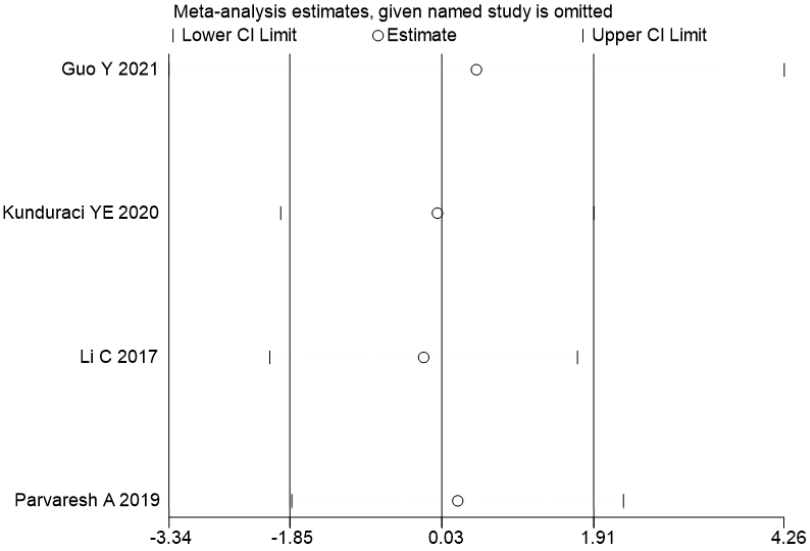
Supplementary figure 9. A sensitivity analysis of the included studies for insulin.



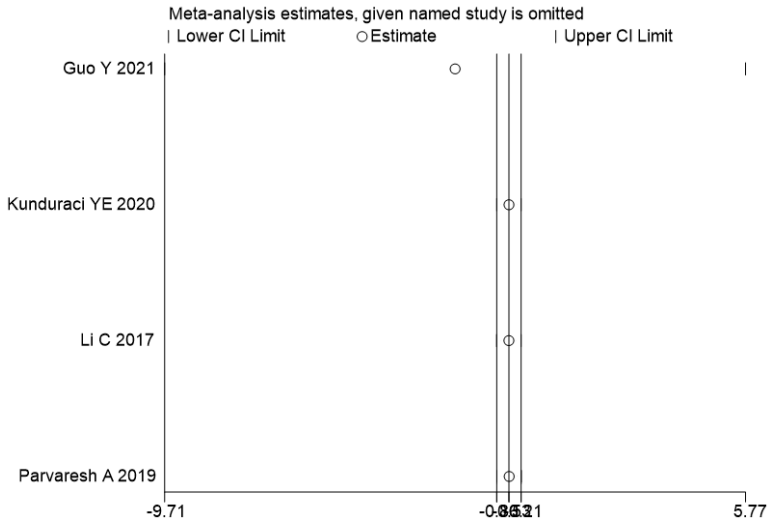
Supplementary figure 10. A sensitivity analysis of the included studies for TC.



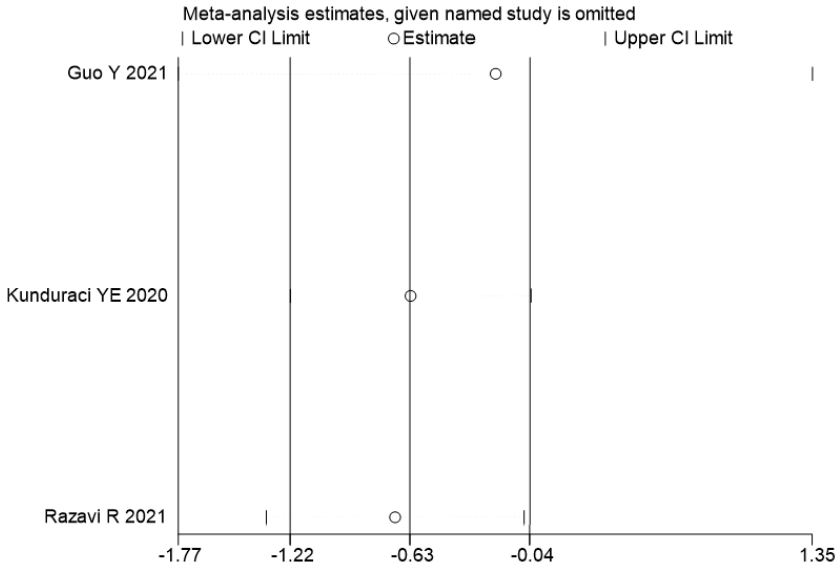
Supplementary figure 11. A sensitivity analysis of the included studies for TG.



Supplementary figure 12. A sensitivity analysis of the included studies for HDL.



Supplementary figure 13. A sensitivity analysis of the included studies for LDL.



Supplementary figure 14. A sensitivity analysis of the included studies for fat free mass.