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Review

Intermittent fasting versus continuous energy-restricted diet for patients with type 2 diabetes mellitus and metabolic syndrome for glycemic control: A systematic review and meta-analysis of randomized controlled trials

Xue Wang [a], *Qifei Li* [a], *Yan Liu* [a], *Hua Jiang* [b,c,d], *Wei Chen* [a,*]

[a] *Department of Clinical Nutrition, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 1 Shuai fu yuan Wang fu jing Dong cheng District, Beijing 100730, China*

[b] *Institute for Emergency and Disaster Medicine, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, No. 32 Yi Huan Lu Xi Er Duan, Chengdu 610072, Sichuan Province, China*

[c] *Emergency Intensive Care Unit, Emergency Medicine Center, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, No. 32 Yi Huan Lu Xi Er Duan, Chengdu 610072, Sichuan Province, China*

[d] *Department of Acute Care Surgery, Emergency Medicine Center, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, No. 32, Yi Huan Lu Xi Er Duan, Chengdu 610072, Sichuan Province, China*

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ABSTRACT

Aims: To compare the safety of intermittent fasting (IF) with that of continuous energy-restricted diets (CERD) in patients with T2DM and metabolic syndrome who were overweight or obese and assess their effects on glycemic control and weight loss.

Materials and methods: We searched MEDLINE (Ovid), Embase, and SINOMED databases up to September 13, 2020. The major outcome was glycemic control and secondary outcomes were change in weight, fasting insulin, and lipid profile.

Results: Of 84 retrieved studies, 5 met our inclusion criteria. Of these, four studies comprising 355 participants were included in the *meta*-analysis. Based on changes in HbA1c (-0.06, 95% confidence interval [CI] −0.27 to 0.16) and fasting plasma glucose (-0.27, 95% CI −0.76 to 0.22), IF and CERD had similar effects on glycemic control. Moreover, IF had a better effect on weight loss (-1.70, 95% CI −3.28 to −0.11 kg). Patients in both groups experienced similar improvements in fasting insulin and lipid profile as well as similar hypoglycemic events.

Conclusions: IF is a safe diet pattern and could be implemented for patients with T2DM or metabolic syndrome. Further studies with a larger sample size are needed to verify the effectiveness and safety of IF in patients with T2DM.

* Corresponding author.
E-mail address: chenw@pumch.cn (W. Chen).

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Contents

1. Introduction

Cases of adult type 2 diabetes mellitus (T2DM) are increasing rapidly, with its global prevalence rising from 4.7% in 1980 to 8.5% in 2014. The growing burden of diabetes in low- and middle-income countries is higher than that in high-income countries [1]. Obesity is a known independent risk factor for T2DM [2] and was redefined as an adiposity-based chronic disease in 2017 by the American Association of Clinical Endocrinologists [3]. It is suggested that 3–10% weight loss is beneficial for glycemic control [4]; therefore, implementing methods to control and maintain healthy weight is crucial for controlling, and even remitting T2DM. Dietary intervention is an important foundation for weight control, including the continuous energy-restricted diet (CERD), Mediterranean diet, and intermittent fasting (IF). However, the effectiveness and safety of very low-calorie diets (VLCDs) in T2DM remain debatable and controversial.

A conventional diet for a patient with diabetes, recommended by most guidelines, is a balanced diet with continuous, moderate calorie restriction [5,6]. Although continuous energy restriction has been confirmed to be effective in improving metabolism and preventing chronic diseases [7–14], it is difficult for patients to adhere to, and its long-term effects are indefinite [15–19]. IF generally refers to consuming a VLCD (500–700 kcal) for 2–4 days a week [20], which is more conveniently accepted by patients since it requires strict energy restriction for only a few days in the week [21]. Several reviews and *meta*-analyses [22–25] have shown that the effect of intermittent and continuous energy restriction on weight loss, lipid profile, and insulin resistance in participants with overweight or obesity was comparable. However, the effect of IF on glycemic control in patients with T2DM remains inconclusive [26–34], with limitations regarding large-scale, multicenter-based clinical trials. We systematically reviewed randomized controlled trials (RCTs) comparing IF with CERD for safety, glycemic control, and weight loss in patients with overweight or obesity with metabolic syndrome or T2DM.

2. Materials and methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [35].

2.1. Databases and search strategy

The present *meta*-analysis was conducted and reported based on the PRISMA guidelines. We performed an extensive search of electronic databases including MEDLINE, Embase, and SINOMED without restrictions on language, region, and publication time up to September 13, 2020. In addition to this, reference lists of selected articles were also screened.

Keywords used for searching included intermittent fasting, intermittent energy restriction, prediabetes, type 2 diabetes, HbA1c, fasting glucose, and metabolic syndrome. The search strategy employed in the MEDLINE (Ovid) database is shown in Table S1, with numbers 1–8 depicting the study type limited to RCTs, point 9 showing the interventions, and numbers 10–14 describing the subjects.

2.2. Inclusion and exclusion criteria

We selected articles that met all the following conditions:

(1) The participants included were adult patients (aged $\geq$ 18 years) with T2DM or metabolic syndrome.
(2) The intervention measures implemented in experimental groups included intermittent fasting, including the 5:2 mode (wherein participants were fasting for 2 days per week and habitually dieting for the remaining 5 days) or fasting on alternate days, and the control groups adopted a CERD.
(3) The study design was an RCT.
(4) The changes in HbA1c, fasting blood glucose, or fasting insulin levels were reported.
(5) The duration of the study was longer than 6 weeks.

However, we excluded articles if:

(1) It was an animal study, a non-randomized trial, an observational study, a review, or a case report.
(2) The intervention group adopted continuous VLCD diet ($\geq$1 week) or time restricted fasting.
(3) The duration of intervention was shorter than 6 weeks.

2.3. Data extraction

Two researchers (X.W. and Q.L.) independently searched databases, and duplicated studies were removed. Pairs of independent reviewers screened the titles and abstracts of each study that met the inclusion criteria prior to screening the full text of candidate studies. Any discrepancy regarding the decision made on a particular study was dealt with via discussion and, if necessary, arbitration by a third reviewer. Reference lists of selected articles were also evaluated. Two researchers independently extracted data, including general information (first author, year, title, and country), clinical characteristics (baseline characteristics of the subjects, dietary pattern, follow-up time of the intervention, and outcomes), and method and design (randomization regimen and data analysis strategy), for all included studies. The major outcome was glycemic control, including the change in HbA1c and fasting glucose levels. While the secondary outcomes were change in weight, change in fasting insulin, and lipid profile (total cholesterol, triacylglycerol, low-density lipoprotein cholesterol [LDL], and high-density lipoprotein cholesterol [HDL]), patients' compliance and safety outcomes such as hypoglycemia and other adverse events were also included.

2.4. Risk of bias assessment

Two reviewers independently assessed the risk of bias in trials according to the revised Cochrane risk of bias tool for randomized trials (RoB 2) on the outcome levels (HbA1c or fasting glucose). Bias arising due to the randomization process, deviation from intended interventions, missing outcome data, or measurement of the outcome selection of the reported result was calculated as "high risk," "low risk," or "some concerns" based on the signal questions in each item.

2.5. Data analysis

The effect of the intervention was presented as mean difference (MD) and standard deviation (SD) before and after intervention. When the SD could not be extracted directly, it was estimated according to the Cochrane Handbook [36]. If the study only provided the SD of the baseline and final outcome, the correlation coefficient was used to estimate the SD of the changes. The main outcome was glycated hemoglobin (HbA1c) presented as MD, while the secondary outcomes were weight loss (presented as MD), fasting glucose, fasting insulin, and lipid profile, of which the scales were not the same as standard mean difference (SMD). Heterogeneity was tested with I^2.

Due to differences in eligible study populations, the effect of the intervention may vary depending on ethnicity and disease background. Therefore, weighted MD and SMD were combined with random-effects models. Sensitivity analyses were completed to detect the robustness of the statistical results and analyze possible sources of heterogeneity, excluding studies in sequence, followed by the exclusion of those with a high risk of bias.

A two-sided P value of < 0.05 was considered statistically significant. We used funnel plots to evaluate publish bias. Meta-analysis and funnel plots were implemented using RevMan 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark).

Table 1 – Characteristics of the studies included in the systematic review.

Author (year)	Country	Participants	Sample size (T/C)	Female sex (%)	Age (y) (Mean ± SD)	Baseline BMI (kg/m^2) (Mean ± SD)	Study duration	Outcomes	Loss ratio of follow-up (%)	Intervention diet	Control diet	Adjustment of hypoglycemic agents during intervention
Ash 2003 [37]	Australia	T2DM	14/17	0	T:54.3 ± 9.4 C:54.9 ± 9.3	T:31.2 ± 3.4 C:32.7 ± 2.4	12 weeks	①③④ †	0	IF for 4 consecutive days each week (liquid meal replacement formula, 1000 cal/d), ad libitum eating for the remaining 3 days (homemade, 1400–1700 cal). Mean energy intake was 1412 ± 578 cal/d	1400–1700 cal/d. Mean energy intake at 12 weeks was 1427 ± 437 cal/d	None
Carter 2018 [34]	Australia	T2DM	70/67	56.2	T:61.0 ± 9.0 C:61.0 ± 9.2	T:35 ± 5.8 C:37 ± 5.7	12 months	①③	29.2	IF for 2 inconsecutive days (500–600 cal/d), participants followed their usual diet for the other 5 days. Mean energy intake was 1643 cal/d	1200–1500 cal/d	Baseline HbA1c < 7%, sulfonylureas and insulin for all participants were discontinued; 7% <baseline HbA1c < 10%, sulfonylureas and insulin were discontinued on IF days only, and long-acting insulin was discontinued the night before an IF day. Medications could be reduced in the control group depending on dose, at the endocrinologist's discretion; baseline HbA1c > 10%, sulfonylurea medications remained unchanged, but long-acting insulin was decreased by approximately 10 units on IF days only.
Parvaresh 2019 [38]	Iran	MS	35/35	40.6	T:44.6 ± 9.08 C:46.4 ± 7.94	T:31.1 ± 3.35 C:31.6 ± 3.82	8 weeks	②③④⑤	1.4	IF for Saturday, Monday and Wednesday (75% energy restriction), ate a diet providing 100% energy on Sunday, Tuesday and Thursday; on Friday, ate ad libitum without limitation.	75% of energy needs each day.	/
Sundfør 2018 [27]	Norway	Abdominal obesity with at least one MS criteria met	54/58	50	T:49.9 ± 10.1 C:47.5 ± 11.6	T:35.5 ± 3.5 C:35.1 ± 3.9	6 months	①②③④	2.7	IF for 2 discontinuous days (female 400 cal/d, male 600 cal/d), consumed food as usual the remaining 5 days. Participants reduced estimated energy intake by 28%(SD18%).	Total daily energy expenditure (TDEE) minus 400 cal/600 cal (female/male). Participants reduced estimated energy intake by 26%(SD17%)	/
Williams 1998 [39]	United States	T2DM, not receiving insulin	18/18	57.4	T:51.4 ± 7.9 C:54.1 ± 7.0	T:35.4 ± 5.4 C:35.0 ± 5.2	20 weeks	①②④⑤	13.9	IF for one day a week (400–600 cal/d), 1500–1800 cal/d for the remaining days. Mean energy intake estimated was 1486 cal/d.	1500–1800 cal/d. Took in more energy than IF group.	Oral diabetes medications were stopped 2 weeks before participation in the study. Subjects with FPG levels > 16.7 mmol/1 when medications were discontinued were excluded. oral diabetes medications were resumed at half of the dose prescribed before the study.

† The differences between groups were not available.

Abbreviations: T: treatment group; C: control group; BMI: body mass index; T2DM: type 2 diabetes mellitus; MS: metabolic syndrome; IF: intermittent fasting.
①HbA1c ②fasting glucose ③weight change ④lipids profile ⑤ fasting insulin.

3. Results

3.1. Study characteristics

A flow diagram of the literature search is shown in Fig. S1. We obtained a total of 68 studies after searching the databases and removing duplicates, of which 10 were potentially eligible after title and abstract screening. Finally, 5 RCTs (6 articles) were included in the systematic review [27,29,34,37–39]. One of the studies did not report the difference within the studied groups; therefore, four studies were included in quantitative synthesis, with a total of 355 subjects.

The characteristics of the five selected studies are presented in Table 1 and Table S2. Among those studies, the sample size ranged from 31 to 137, while the duration of intervention was between 8 weeks and 12 months. Two studies enrolled patients with T2DM, and the other two enrolled patients with metabolic syndrome [34,39].

3.2. Study quality and risk of bias assessment

The risk of bias assessments of the included studies are summarized in Fig. 1. One study was rated as high risk, three as some concerns, and one as low risk. Detailed results of the signal questions corresponding to each study can be found in supplementary materials. The intervention was diet, for which blinding was highly difficult; however, outcomes were detected entirely using machines, suggesting that the risk arising from blinding of outcome assessment (part of deviations from intended interventions assessment) was low. However, Parvaresh et al. and Williams et al. adopted the per-protocol (PP) analysis, and bias could occur owing to deviations from the intended intervention [38,39]. The detailed results of signaling questions can be found in the supporting file.

3.3. Compliance of intermittent fasting

The attrition rates reported were from 0.0 to 29.2%, which were similar between the intervention and control groups (Table 1) [34,37]. Compliance with dietary intervention was not reported in any of the studies; however, Carter et al. reported two individuals in the experimental group and five in the control group who dropped out as they could not follow the diet [34].

3.4. Safety of intermittent fasting

(1) Hypoglycemia: In the study conducted by Carter et al., all events related to hypoglycemia occurred in patients using sulfonylureas and/or insulin, and all participants who experienced hypoglycemia were uncertain whether it had occurred before beginning the trial [34]. The average number of hypoglycemic events did not differ between the groups (mean [SEM]: control group 2.0 [1.0] vs. treatment group 2.5 [0.8], $P = 0.74$).

(2) Other adverse events: Carter et al. also reported that there were seven and three participants who experienced hyperglycemia in the IF and control groups, respectively [34]. Sundfør et al. reported some adverse events, such as mild headache (treatment group 20% vs. control group 5%), dizziness (treatment group 11% vs. control group 3%), mild nausea (treatment group 6% vs. control group 2%), and temporary sleep disturbance (treatment group 2% vs. control group 0%) [27]. Both Williams et al. and Parvaresh et al. reported that there were no adverse events, while Ash et al. did not mention any adverse events [34,37,39].

3.5. Antidiabetic drugs

Ash et al. did not compare the antidiabetic drugs used between the groups [37], while Williams et al. excluded patients administered insulin and whose fasting plasma glucose levels were > 16.7 mmol/L when medications were discontinued [39]. In the third week, three patients in the experimental group and one patient in the control group had fasting glucose levels of > 13.9 mmol/L; therefore, oral hypoglycemic drugs were resumed. Carter et al. implemented a drug reduction plan during intervention based on the patients' HbA1c levels (Table S2) and compared the change

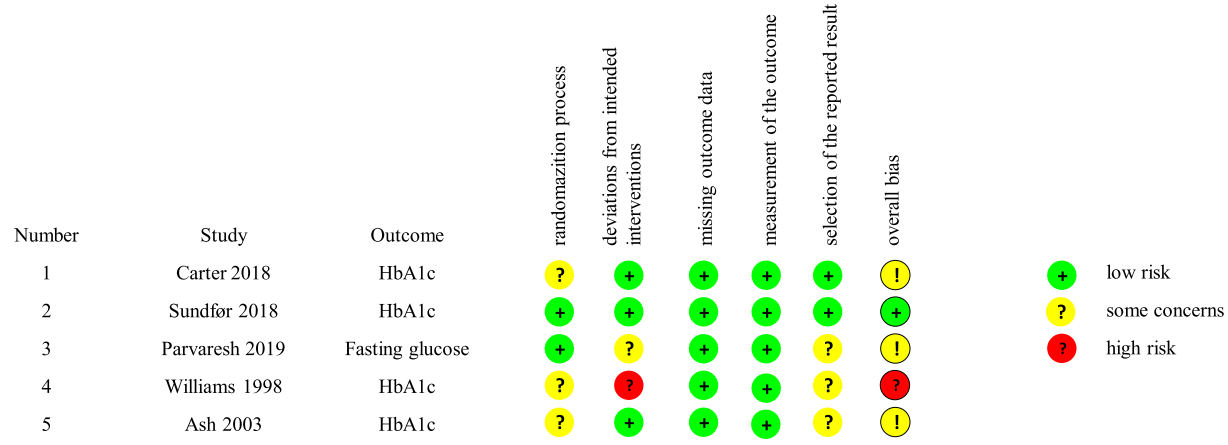

Fig. 1 – Risk of bias judgments of the included studies using the revised Cochrane risk of bias tool for randomized trials on glucose outcomes across five domains.

in medication effect score (MES) between the groups [34]. An MES is calculated as follows [40]:

(actual drug dose/maximum drug dose)
× drug mean adjustment factor.

The MES value is directly proportional to the dose of the antidiabetic drug. No significant difference was found between the groups (IF group −0.6 [SE = 0.1] vs. control group −0.3 [SE = 0.1], $P = 0.11$).

3.6. *Meta-analysis*

3.6.1. *Glycemic control*

Fig. 2 depicts the effect of IF on glycemic control. Three studies [27,34,39] reported changes in HbA1c levels. No statistical difference was found between the IF and control groups (MD = −0.06, 95% confidence interval [CI] [−0.27, 0.16] %, $P = 0.62$, $I^2 = 16\%$). Three trials [27,38,39] reported changes in fasting glucose levels. Meta-analysis showed no difference between the two groups (MD = −0.27, 95% CI [−0.76, 0.22], $P = 0.28$, $I^2 = 64\%$). Sensitivity analyses were performed owing to high heterogeneity. Two studies reported a change in fasting insulin levels, and there was no significant difference observed between the groups (MD = −0.17, 95% CI [−0.57, 0.22], $P = 0.39$, $I^2 = 0\%$) [38,39].

3.6.2. *Change in weight*

All four studies reported changes in weight before and after the diet intervention. Fig. 3 shows a comparison of the effects of IF and CERD on body weight. When statistically pooled, the change in weight was −1.70 (95% CI [−3.28, −0.11] kg, $P = 0.04$, $I^2 = 56\%$), indicating that IF was more effective than continuous energy restriction for successful weight loss.

Three trials [27,34,38] reported an improvement in body mass index (BMI), and the *meta*-analysis showed no difference between the groups (MD = −0.31, 95% CI [−0.91, −0.30] kg/m^2, $P = 0.32$, $I^2 = 50\%$) (Fig. 3).

3.6.3. *Lipid profile*

Fig. 4 shows a forest plot comparing the effects of IF with those of CERD on weight loss. No statistical difference was observed in the lipid profile that included total cholesterol, triacylglycerol, LDL cholesterol, and HDL cholesterol in the three trials [27,38,39].

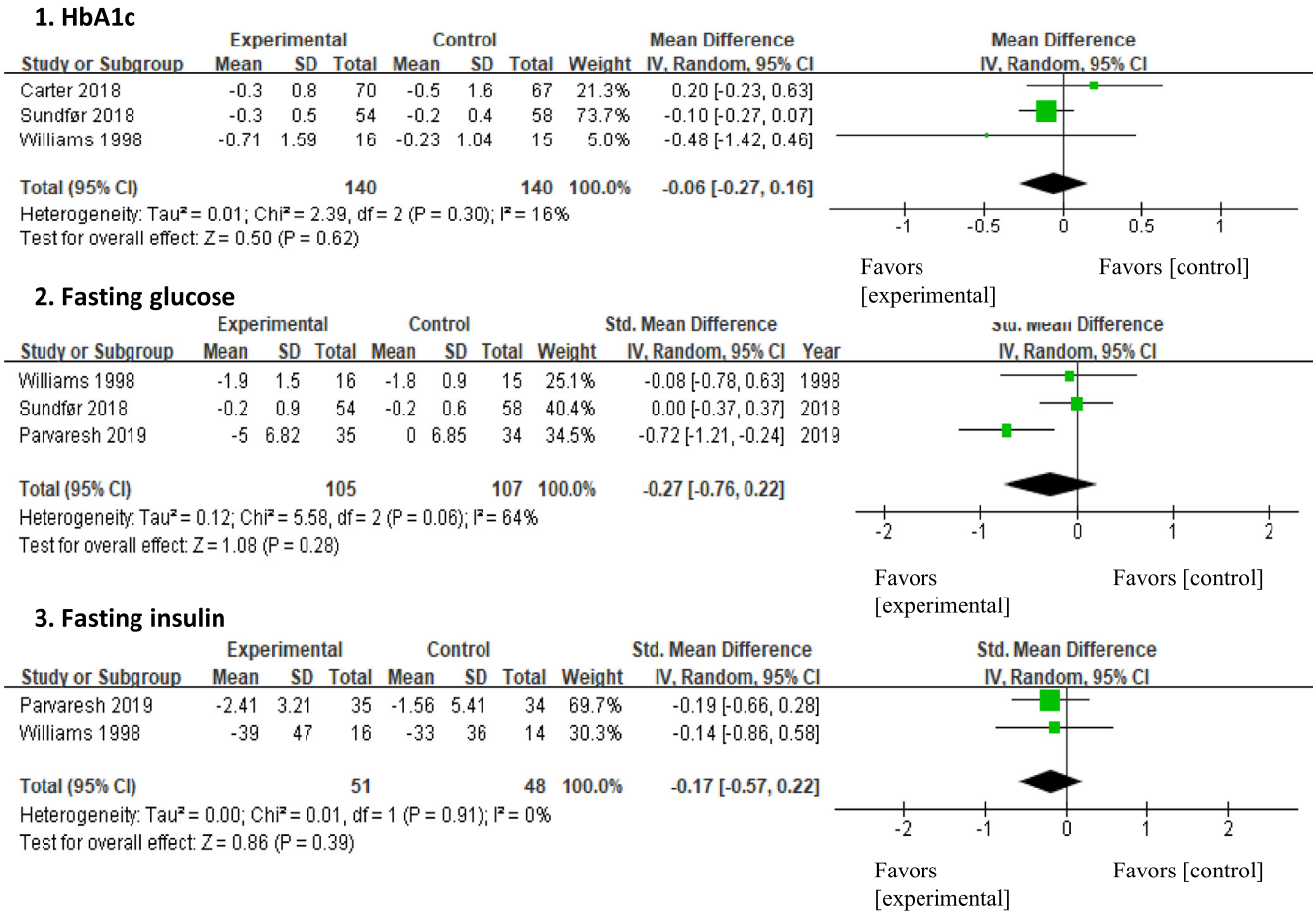

Fig. 2 – Forest plot comparing the effects of intermittent fasting with those of continuous energy restriction on glycemic control (the size of the box represents the weight of each study, and the lateral tips of the diamond show the confidence interval of the pooled result).

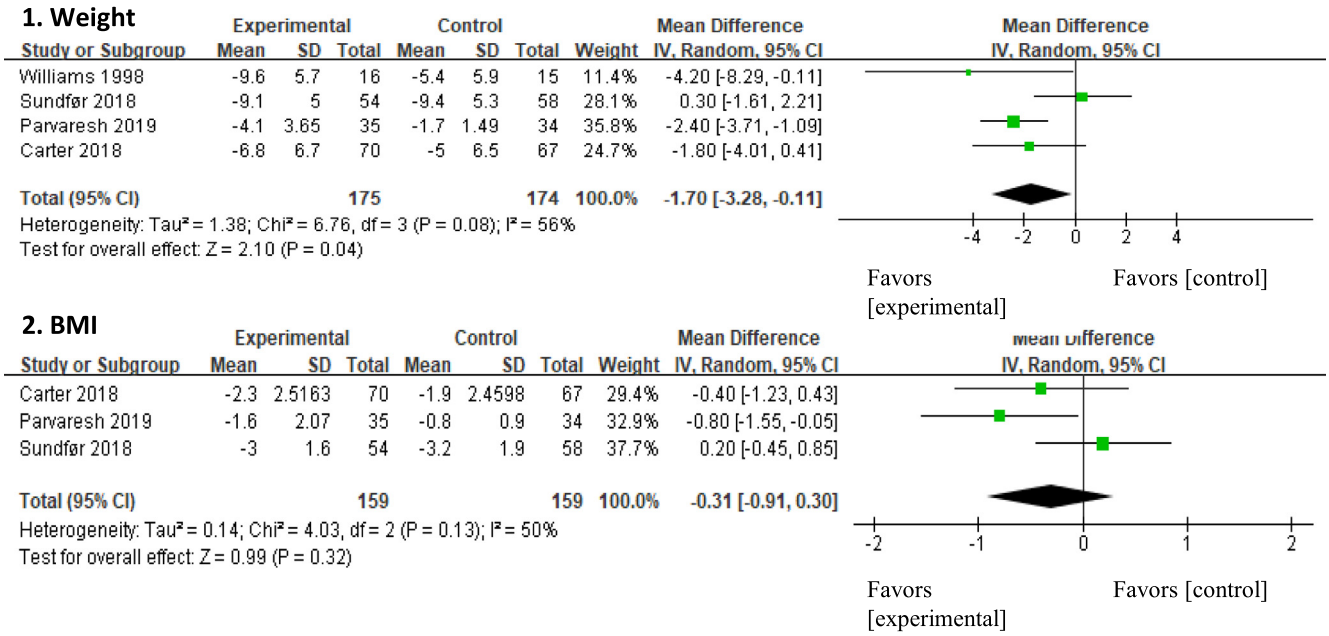

Fig. 3 – Forest plot comparing the effects of intermittent fasting with those of continuous energy restriction on weight change.

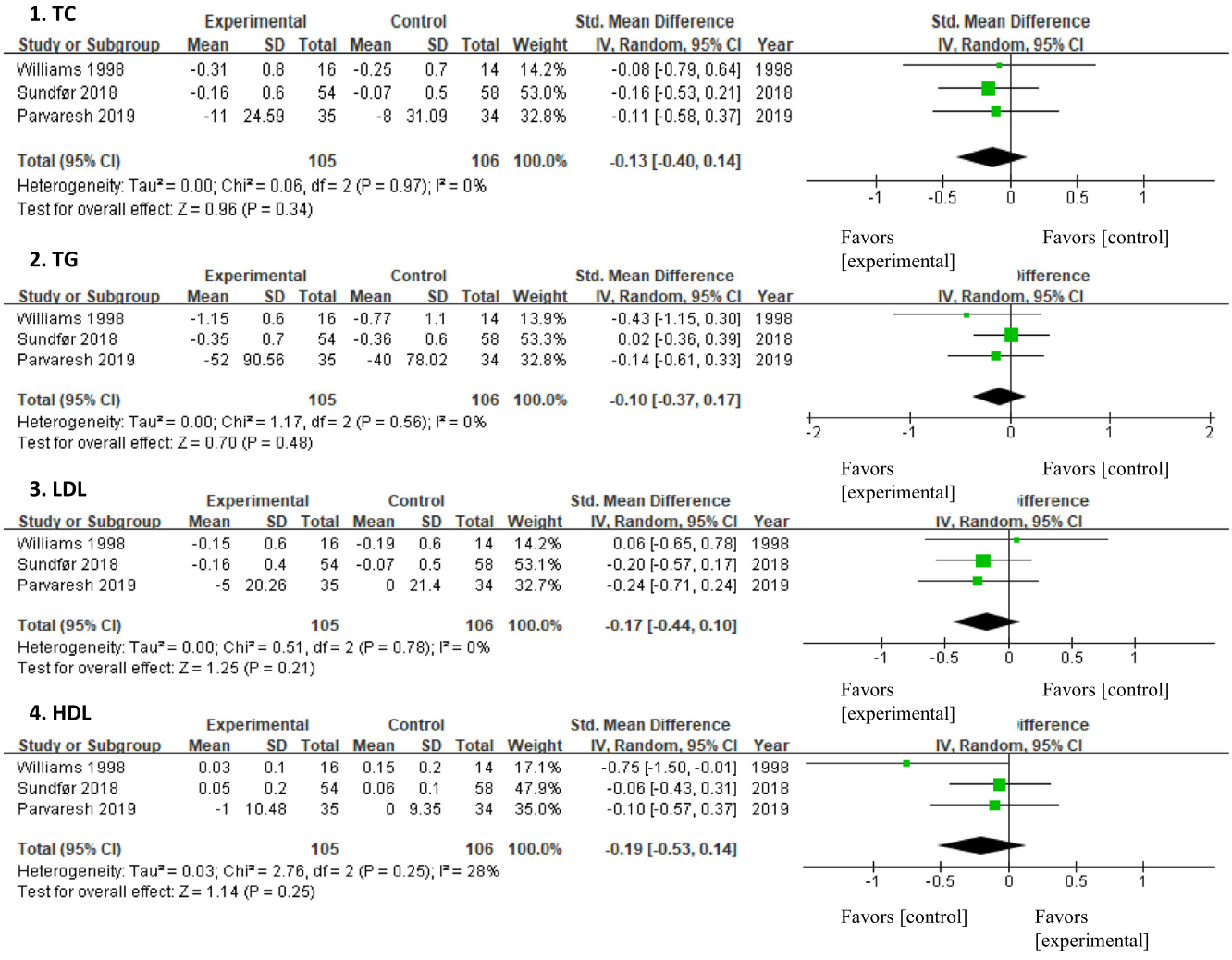

Fig. 4 – Forest plot comparing the effects of intermittent fasting with those of continuous energy restriction on lipid profile (TC: total cholesterol, TG: triglyceride, LDL: low-density lipoprotein, HDL: high-density lipoprotein.

3.7. Publication bias

The funnel plot of the effect of IF on glycemic control presents an approximately symmetric pattern (Fig. S2A), suggesting that the results were less likely to be affected by publication bias. The funnel plot based on the change in body weight also showed considerable symmetry (Fig. S2B).

3.8. Sensitivity analysis

Carter et al. and Williams et al. enrolled patients with T2DM, and the other two studies enrolled patients with metabolic syndrome [34,39]. When the study of Sundfør et al. was dropped on in the analysis on HbA1c levels, leaving two studies researching on T2DM, there is still no difference(MD = −0.01, 95% CI [−0.62, 0.61] kg/m^2, P = 0.20, I^2 = 40%). Similarly, when two studies researching on metabolic syndrome were left on fasting plasma glucose, the difference between two groups remained non-significant (MD = −0.45, 95% CI [−1.08, 0.17] kg/m^2, P = 0.14, I^2 = 54%).

Parvaresh et al. performed a follow-up of the participants for 8 weeks, and when this study was omitted in the pooled analysis on fasting glucose, the heterogeneity decreased from 64% to 0%, while the difference remained non-significant [38,41].

Sundfør et al. and Carter et al. adopted intention-to-treat analysis [27,34], while Williams et al. and Parvaresh et al. used the PP analysis [38,39]. When the last two studies were removed from the combination of changes in weight loss, the difference in weight improvement between the two groups became insignificant (P = 0.52, I^2 = 50%).

4. Discussion

4.1. Summary of evidence

To the best of our knowledge, this study is the first *meta*-analysis that compares the effects of IF patterns with those of CERD in patients with T2DM and metabolic syndrome. We found that IF was comparable with CERD. This review revealed that the change in HbA1c, fasting insulin, fasting glucose levels, and lipids profile did not significantly differ between the two groups. And the change in MES through diet intervention showed no statistical difference, suggesting that IF has an approximately similar effect on the prevention and control of diabetes. However, intermittent fasting may have an edge on the effect on weight loss.

Patients with metabolic syndrome have multiple risk factors, including elevated blood glucose levels, insulin resistance, and a high risk of developing T2DM; thus, appropriate weight loss is beneficial to improve their blood glucose, lipid profile, and blood pressure [42]. Therefore, we included studies comprising subjects with metabolic syndrome.

Regarding weight loss, although the pooled results of weight loss showed that IF was superior to CERD, the difference lost its statistical significance after excluding the two studies using PP analysis [38,39]; furthermore, no significant difference was found in BMI. This suggests that IF may be more effective than CERD for weight loss; however, the differences and clinical significance need to be further verified. Energy intake difference between the two groups is also an important factor in weight loss besides diet pattern. However, of the studies included, the differences in energy intake by design or recorded were either of no significance or quite small (approximately 200 cal/d estimated), which would result in little to no differences at a relatively short term.

In this study, a systematic review of the compliance and safety of dietary regimens was carried out, considering that these factors would have a significant impact on glycemic control. With longer intervention time, the rate of attrition increased, which may also be associated with the frequency of follow-up, dietary regimen, and study population. Overall, the subjects followed the diets of each group with good compliance during the period of diet intervention, and the incidences of hypoglycemic events were similar in both groups. In addition, considering the effects of antidiabetic drugs on glycemic control, the study also extracted drug adjustment protocols for individuals with T2DM (Table 1). According to Williams et al. and Carter et al. [27,39], there was no significant difference observed in the amount of medication reduction between the two groups during the intervention, indicating that the effect of IF was comparable with that of CERD on glycemic control. Other adverse events reported by Sundfør et al. [27,44] were subjective and mild, and may be attributed to participants knowing the intervention because blinding was impossible. Therefore, a more rigorous evaluation of a patient's subjective feelings is required.

Our results are similar to those reported by Seimon et al. [24] and Welton et al., [43] which stated that intermittent energy restriction was as effective as continuous energy restriction in reducing blood glucose levels and aiding in weight loss in people with obesity, representing an effective option for weight control. However, Seimon et al. [24] did not perform quantitative synthesis, and the subjects included were healthy people with obesity.

4.2. Limitations

This study had certain limitations. First, there exists certain heterogeneity among the trials and diet regimens, with the duration of intervention probably being the main source of heterogeneity. Therefore, the random-effects models were used for merging in this study, and sensitivity analyses were conducted according to possible sources. Second, there were only a few RCTs whose sample size was not large and met the inclusion criteria, and there were even fewer studies conducted on patients with T2DM [28,34]. In addition, the study focused on alternative outcomes (HbA1c, fasting blood glucose, etc.), and the intervention time ranged from 8 weeks to 12 months; therefore, it was not possible to obtain a definitive conclusion of the effect of IF on glycemic control. Given that the current study is not registered, there may be a small deviation, but we have strictly followed the steps of systematic evaluation as the flow chart described.

5. Conclusions

IF has positive effects on glycemic control in patients with T2DM or metabolic syndrome, and patient compliance and safety are comparable to those in CERD. In addition, the administration of antidiabetic drugs during intervention is similar between both diets. However, due to limitations such as heterogeneity and a small sample size, more long-term clinical trials are needed to assess the safety and effectiveness of IF in patients with T2DM.

CRediT authorship contribution statement

Xue Wang: Formal analysis, Writing – original draft. **Qifei Li:** Investigation. **Yan Liu:** Writing – review & editing. **Hua Jiang:** Methodology. **Wei Chen:** Conceptualization, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data Availability Statement

Data are contained within the article.

Institutional Review Board Approval

Not applicable.

Informed Consent Statement

Not applicable.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2021.109003.

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