

## ORIGINAL ARTICLE

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# The effects of intermittent fasting on body composition and cardiometabolic health in adults with prediabetes or type 2 diabetes: A systematic review and meta-analysis

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## Abstract

**Aim:** To perform a meta-analysis to investigate the effects of intermittent fasting (IF), as compared with either a control diet (CON) and/or calorie restriction (CR), on body composition and cardiometabolic health in individuals with prediabetes and type 2 diabetes (T2D).

**Methods:** PubMed, Web of Science, and Scopus were searched from their inception to March 2024 to identify original randomized trials with parallel or crossover designs that studied the effects of IF on body composition and cardiometabolic health. Weighted mean differences (WMDs) or standardized mean differences with 95% confidence intervals (CIs) were calculated using random-effects models.

**Results:** Overall, 14 studies involving 1101 adults with prediabetes or T2D were included in the meta-analysis. IF decreased body weight (WMD  $-4.56$  kg [95% CI  $-6.23$  to  $-2.83$ ];  $p = 0.001$ ), body mass index (BMI; WMD  $-1.99$  kg.m<sup>2</sup> [95% CI  $-2.74$  to  $-1.23$ ];  $p = 0.001$ ), glycated haemoglobin (HbA1c; WMD  $-0.81\%$  [95% CI  $-1.24$  to  $-0.38$ ];  $p = 0.001$ ), fasting glucose (WMD  $-0.36$  mmol/L [95% CI  $-0.63$  to  $-0.09$ ];  $p = 0.008$ ), total cholesterol (WMD  $-0.31$  mmol/L [95% CI  $-0.60$  to  $-0.02$ ];  $p = 0.03$ ) and triglycerides (WMD  $-0.14$  mmol/L [95% CI  $-0.27$  to  $-0.01$ ];  $p = 0.02$ ), but did not significantly decrease fat mass, insulin, low-density lipoprotein, high-density lipoprotein, or blood pressure as compared with CON. Furthermore, IF decreased body weight (WMD  $-1.14$  kg [95% CI  $-1.69$  to  $-0.60$ ];  $p = 0.001$ ) and BMI (WMD  $-0.43$  kg.m<sup>2</sup> [95% CI  $-0.58$  to  $-0.27$ ];  $p = 0.001$ ), but did not significantly affect fat mass, lean body mass, visceral fat, insulin, HbA1c, lipid profiles or blood pressure.

**Conclusion:** Intermittent fasting is effective for weight loss and specific cardiometabolic health markers in individuals with prediabetes or T2D. Additionally, IF is associated with a reduction in body weight and BMI compared to CR, without effects on glycaemic markers, lipid profiles or blood pressure.

## KEYWORDS

body composition, cardiovascular disease, dietary intervention, dyslipidaemia, insulin resistance, type 2 diabetes

## 1 | INTRODUCTION

Diabetes and prediabetes are major global health problems and the prevalence of both has been increasing globally<sup>1–5</sup> in conjunction with increased cardiovascular diseases (CVDs) and all-cause mortality.<sup>6–8</sup> Type 2 diabetes (T2D) is characterized by elevated fasting blood glucose (FBG) concentrations of >7.0 mmol/L, or 2-h glucose (2hG) of >11.1 mmol/L, whereas with prediabetes, FBG is 6.1–6.9 mmol/L and 2hG levels are between 7.8 and 11 mmol/L.<sup>2,9,10</sup> These elevations in glucose are due to the progressive loss of insulin secretion subsequent to the development of insulin resistance.<sup>2,11</sup> With the rising prevalence of diabetes and prediabetes, more effective and safe treatments are required, for which lifestyle interventions are common first-line strategies, used alone or in combination with antidiabetic medications. Dietary therapy is an important non-pharmacological intervention,<sup>12–14</sup> with daily calorie restriction (CR) a central component, defined as reducing daily energy intake by 20%–50%. CR improves glycaemic control, insulin sensitivity, myocardial function, hepatic fat content, oxidative stress, and lipid profiles.<sup>15–18</sup> Despite the effectiveness of CR, poor adherence rates, especially in the long term,<sup>19,20</sup> limit its effectiveness in diabetic patients. Intermittent fasting (IF) may therefore be a more flexible dietary strategy and has become popular for patients with varied conditions and diseases.<sup>21–23</sup>

Intermittent fasting is characterized by periods of fasting in combination with periods of ad libitum feeding, with the most prevalent forms being alternate-day fasting (ADF; i.e., 0–500 kcal on fasting days, with ad libitum intake on feeding days), the 5:2 diet (i.e., 2 days of fasting with 5 days of feeding), and time restricted-eating (TRE; i.e., eating during a period of 6–10 h, and fasting for the remaining hours each day).<sup>24</sup> Previous research indicates that IF can be both effective and safe for weight loss and improves some cardiometabolic health markers including lipid profiles, glycaemic markers, and inflammation.<sup>22,24–28</sup> Although several meta-analyses have investigated the potential role of IF on body composition and cardiometabolic health,<sup>29–32</sup> those in patients with T2D have been limited by small numbers of studies with few health markers.<sup>33,34</sup> One meta-analysis of seven studies in individuals with T2D showed that IF was not associated with superior effects on glycaemic control, despite large effects on weight loss,<sup>33</sup> whilst another including four studies showed similar effects on glycaemic control when compared with CR.<sup>34</sup> The beneficial effects of IF in patients with T2D have been challenged due to the modest effects on glycaemic parameters and lack of superiority over control diets (CON).<sup>28</sup> There are now many new published randomized clinical trials that extend previous results by including lipid profiles, blood pressure, glycaemic control (i.e., fasting insulin, glucose and glycated haemoglobin [HbA1c]), as well as body composition.<sup>26,35–42</sup> Furthermore, additional evidence is required through systematic review and meta-analysis to further strengthen the existing literature. The aim of this study, therefore, was to undertake an in-depth analysis of the current available data. We compared the effects of IF with CON and/or CR on body composition and cardiometabolic health in adults with prediabetes or T2D.

## 2 | METHODS

The current meta-analysis was registered a priori in the International Prospective Register of Systematic Reviews (PROSPERO) with the ID number: CRD42024527104, and was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines.<sup>43</sup>

### 2.1 | Search strategy

Three main electronic databases were searched (PubMed, Web of Science and Scopus) from their inception to March 2024 using the following keywords: ('time-restricted feeding' OR 'time restricted feeding' OR 'time-restricted eating' OR 'time restricted eating' OR 'time-restricted diet' OR 'time restricted diet' OR 'time-restricted fasting' OR 'time restricted fasting' OR 'intermittent fasting' OR 'intermittent energy restriction' OR 'alternate fasting' OR 'periodic fasting' OR 'reduced meal frequency' OR 'alternate-day fasting' OR 'alternate day fasting') and ('diabetes' OR 'type 2 diabetes' OR 'T2D' OR 'prediabetes' OR 'pre diabetes'). Filters for English language and human participants were applied when available in the database. In addition, Google Scholar and the reference lists of included studies were manually searched to make sure no eligible studies were missed. Full details of the search strategy are provided in Table S1. The searches were performed independently by two reviewers (M.K. and A.H.M.).

### 2.2 | Inclusion and exclusion criteria and study selection

Studies were included if they were full-text, original, English-language and peer-reviewed articles that met the selection criteria based on participants, intervention, comparator, outcome, and study design (PICOS). For participants, studies that included adults with prediabetes or T2D regardless of their age, or biological sex were included. For the purposes of our systematic review and meta-analysis, prediabetes was defined as FBG ranging between 6.1 and 6.9 mmol/L and 2hG between 7.8 and 11 mmol/L, and T2D was defined as FBG >7.0 mmol/L or 2hG of >11.1 mmol/L.<sup>2,9,10</sup> For intervention, studies that included any mode of IF including ADF, the 5:2 diet, TRE, or other fasting regimens with intervention durations ≥2 weeks were included. For comparator, studies involving usual diet or CON and/or CR were included. For outcomes, studies including results for body composition (i.e., body weight, BMI, fat mass, fat%, waist circumference and lean body mass (LBM), or fat-free mass when LBM was not reported); lipid profile (i.e., triglycerides [TG], total cholesterol [TC], low-density lipoprotein [LDL] and high-density lipoprotein [HDL]); glycaemic outcomes including fasting glucose and insulin, HbA1c, and blood pressure including systolic blood pressure (SBP) and diastolic blood pressure

(DBP). For study design, only randomized trials comparing IF versus either CON and/or CR with parallel or crossover designs were included. Studies were excluded if any of following applied: participants had gestational diabetes or type 1 diabetes; use of carbohydrate fasting diets or durations <2 weeks; or comparison of IF with other types of diets, such as a Mediterranean diet. Study selection processes were performed in two steps by two independent reviewers (M.K. and A.H.M.), and any disagreements were resolved through consultation with other reviewers. All retrieved studies were exported into EndNote (version 20.2.1) and, after removing duplicate records, screening was performed against study selection criteria. In the first step, articles were screened based on titles and abstracts, and subsequently in the second step, based on review of the full texts.

## 2.3 | Data extraction and synthesis

The following information and data were extracted from each eligible study: author names and publication year; study design; participant characteristics (number age, biological sex, BMI, health status); characteristics of the IF intervention (type of IF, protocol, and intervention duration); and outcome variables. To calculate the effect size, means and standard deviations (SDs) pre- and post-intervention, or mean changes and their SDs and sample sizes were used. When required, these data were extracted from figures or were calculated from other available data, such as standard errors (SEs), medians, and interquartile ranges. Otherwise, the corresponding authors were contacted to request missing data. When required, lipid profile and glucose values expressed in mg/dL were converted to mmol/L,<sup>44</sup> for glucose using  $\text{mg/dL} \times 0.0555 = \text{mmol/L}$ , for LDL, HDL and TC using  $\text{mg/dL} = 0.0259 \text{ mmol/L}$ , and for TG using  $\text{mg/dL} = 0.0113 \text{ mmol/L}$ .<sup>44</sup> In addition, for HbA1c, units in mmol/mol were converted to percentages with the following formula:  $(0.09148 \times \text{HbA1c in mmol/mol}) + 2.152$ .<sup>45</sup> When required, mean changes (post-values – pre-values) and SD changes were calculated using a formula recommended in the Cochrane handbook in which conservative values of 0.5 for correlations were assumed. In addition, if a study included multiple IF interventions, each IF intervention was included as a separate arm and the sample size of the comparator group was divided accordingly. Two authors (A.H.M. and M.E.) independently extracted and reported the information and data, with conflicts resolved by other co-authors.

## 2.4 | Quality assessment

An independent assessment of the risks of bias was performed by two reviewers (A.H.M. and M.E.), with conflicts resolved by a third reviewer (M.K.). Consistent with several meta-analyses, the Physiotherapy Evidence Database (PEDro) scale was used to assess the quality of the included studies. This scale assesses the risks of bias using 11 domains which are summarized in Table S2. Risk of bias scores ranged from 5 to 9, with higher scores representing higher quality. There were no studies excluded based on the risk of bias score.

## 2.5 | Data analysis

Two separate meta-analyses were conducted to compare the effects of IF versus CON and/or CR for each outcome. Standardized mean differences (SMDs; when units of measurement varied) or weighted mean differences (WMDs; when units of measurement were consistent) and 95% confidence intervals (CIs) were calculated using random-effect models with the DerSimonian and Laird approach. Random-effect models were chosen due to the assumption of heterogeneity amongst the included clinical trials that may influence the results.<sup>46</sup> Subgroup analyses were performed based on IF mode (TRE vs. other), intervention duration (less than 16 weeks vs. more than 16 weeks) and participant characteristics (prediabetes vs. T2D) when there were sufficient data available. Therefore, subgroup analyses were only conducted for body weight and HbA1c considering IF versus CON. Interpretation of SMDs was as follows: values < 0.20, 0.20–0.39, 0.40–0.80, and >0.80 were defined as trivial, small, moderate, and large, respectively.  $I^2$  statistics were used to determine heterogeneity among included studies, which was interpreted as follows:  $I^2$  values of <25%, 50%, 75%, and >75% defined low, moderate, high, and considerable.<sup>47</sup> Publication bias was assessed using visual interpretation of funnel plots, and Egger's tests were used as secondary determinants, with a  $p$  value < 0.10 taken to indicate statistical significance. In addition, when publication bias was detected by visual interpretation of funnel plots, the trim-and-fill method was used to address the potential effect of publication bias.<sup>48</sup> Sensitivity analyses were performed by removing individual studies when there were more than 10 trials for any outcome. All analyses were conducted using comprehensive meta-analysis version 3 (CMA3).

## 3 | RESULTS

### 3.1 | Search results and study characteristics

The initial search yielded 337 records from PubMed, 567 records from Web of Science and 574 records from Scopus. After removal of duplicates, 991 records remained. After the first stage of screening, 937 records were excluded, and 54 articles were included in the full-text review. Subsequently, 40 articles were excluded after the second stage of screening for the reasons presented in Figure 1. Finally, 14 studies were included the current meta-analysis.<sup>26,35–42,49–53</sup> Amongst the 14 studies, seven studies included IF versus CON,<sup>26,37,39,40,42,49,51</sup> four studies included IF versus CR,<sup>35,50,52,53</sup> and two studies included IF versus both CON and CR.<sup>38,41</sup> In addition, two studies used two modes of IF.<sup>35,49</sup> All included studies were randomized trials, two studies used crossover designs,<sup>40,52</sup> and all other articles used parallel-group designs.

### 3.2 | Participant and IF characteristics

Overall, 1101 participants were included, with mean ages ranging from 17 to 65 years and BMIs ranging from 24 to 39 kg/m<sup>2</sup>. Except

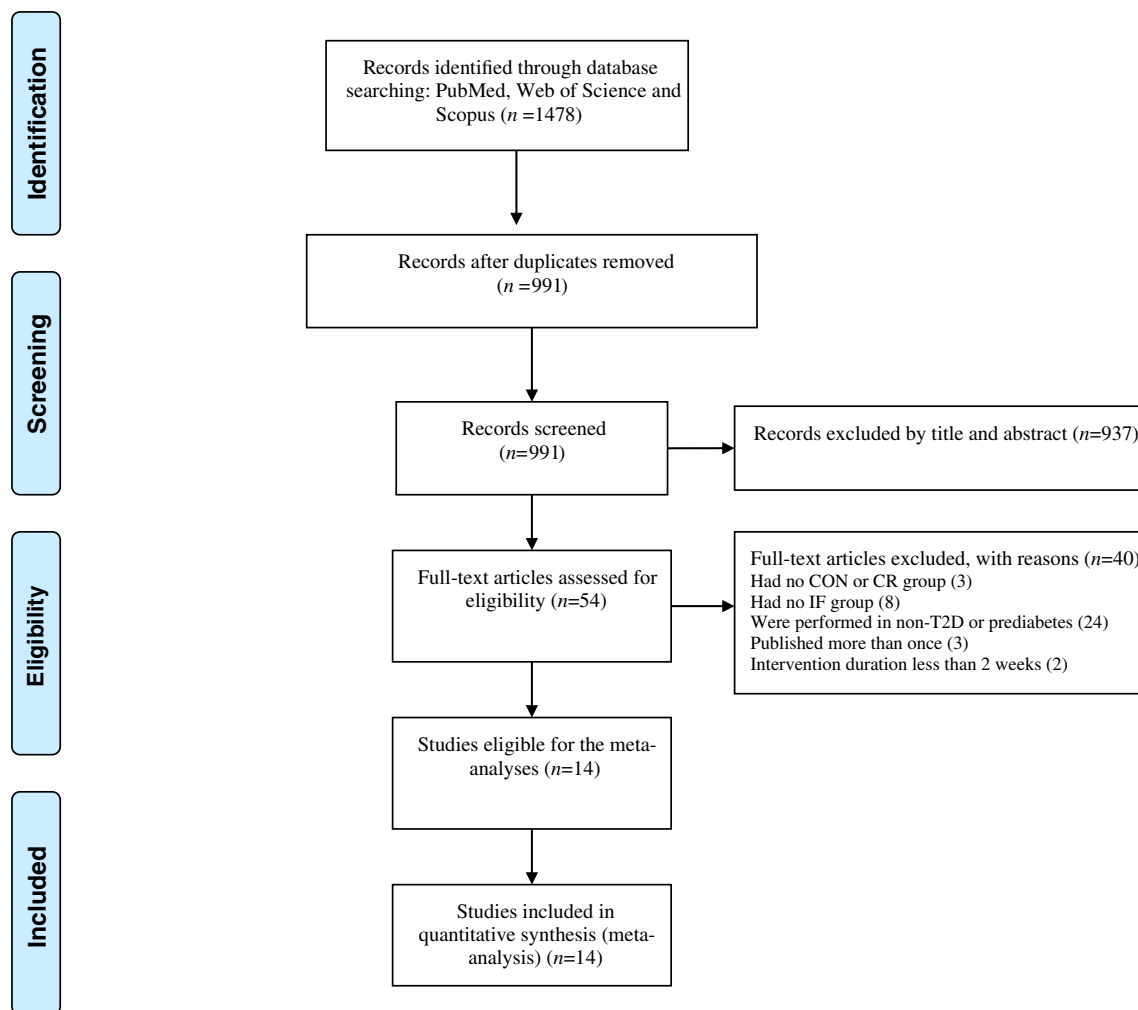


**FIGURE 1** Flow diagram of systematic literature search. CON, control diet; CR, calorie restriction; IF, intermittent fasting; T2D, type 2 diabetes.

one,<sup>40</sup> the studies included both male and female participants. Nine studies included patients with T2D,<sup>25,36,37,41,49–52,54</sup> and five included participants with prediabetes.<sup>35,36,39–41</sup> The IF intervention modes varied, with seven studies using TRE,<sup>37–41,51,52</sup> two studies using 5:2 fasting and feeding,<sup>35,52</sup> one study using 4:3 fasting and feeding,<sup>26</sup> one study using both TRE and ADF<sup>35</sup> and three studies using other modes of IF.<sup>42,49,53</sup>

### 3.3 | Meta-analysis

#### 3.3.1 | IF versus CON

##### Body composition

Intermittent fasting decreased body weight (WMD  $-4.56$  kg [95% CI  $-6.23$  to  $-2.83$ ],  $p = 0.001$ ; 11 trials) and BMI (WMD  $-1.99$  kg.m<sup>2</sup> [95% CI  $-2.74$  to  $-1.23$ ],  $p = 0.001$ ; five trials) significantly more than CON, but there were no significant differences between IF and CON for fat mass (WMD  $-2.17$  kg [95% CI  $-4.50$  to  $0.15$ ],  $p = 0.06$ ;

four trials [Figures S1–S3]). There was significant heterogeneity among the included studies for body weight ( $I^2 = 90.03$ ,  $p = 0.001$ ), BMI ( $I^2 = 87.02$ ,  $p = 0.001$ ) and fat mass ( $I^2 = 86.42$ ,  $p = 0.001$ ). Visual interpretation of funnel plots suggested publication bias for body weight and fat mass. However, the Egger's tests indicated publication bias for body weight ( $p = 0.03$ ), but not for BMI ( $p = 0.10$ ) or fat mass ( $p = 0.80$ ). In addition, after adjusting the results using trim and fill, the effect size was as follows: body weight (WMD  $-6.00$  kg [95% CI  $-8.68$  to  $-0.32$ ]; four trials from the left side of the mean) and fat mass (WMD  $-1.68$  kg [95% CI  $-4.16$  to  $0.80$ ]; one trial from the right side of the mean). Sensitivity analysis for body weight did not change the significance or effect size.

##### Lipid profile

Intermittent fasting significantly decreased TC (WMD  $-0.31$  mmol/L [95% CI  $-0.60$  to  $-0.02$ ],  $p = 0.03$ ; nine trials) and TG (WMD  $-0.14$  mmol/L [95% CI  $-0.27$  to  $-0.01$ ],  $p = 0.02$ ; 10 trials), but not LDL (WMD  $0.11$  mmol/L [95% CI  $-0.19$  to  $-0.42$ ],  $p = 0.45$ ; 10 trials) or HDL (WMD  $0.01$  mmol/L [95% CI  $-0.02$  to  $0.04$ ],  $p = 0.47$ ;

10 trials), when compared with CON (Figures S4–S7). There was significant heterogeneity among included studies for TC ( $I^2 = 78.18$ ,  $p = 0.001$ ), LDL ( $I^2 = 89.48$ ,  $p = 0.001$ ) and TG ( $I^2 = 49.82$ ,  $p = 0.03$ ), but not for HDL ( $I^2 = 24.96$ ,  $p = 0.21$ ). Visual interpretation of funnel plots suggested publication bias for TC, LDL, HDL and TG. However, the Egger's tests indicated publication bias for HDL ( $p = 0.05$ ), not for TC ( $p = 0.42$ ), LDL ( $p = 0.12$ ) and TG ( $p = 0.12$ ). In addition, after adjusting the results using trim and fill, the effect size was as follows: TC (WMD  $-0.48$  mmol/L [95% CI  $-0.79$  to  $-0.18$ ]; two trials from the left side of the mean), LDL (WMD  $0.31$  mmol/L [95% CI  $-0.06$  to  $-0.68$ ]; four trials from the right side of the mean), HDL (WMD  $0.00$  mmol/L [95% CI  $-0.03$  to  $0.04$ ]; three trials from the left side of the mean), and TG (WMD  $-0.16$  mmol/L [95% CI  $-0.30$  to  $-0.03$ ]; two trials from the left side of the mean).

#### Glycaemic markers

Intermittent fasting significantly decreased HbA1c (WMD  $-0.81\%$  [95% CI  $-1.24$  to  $-0.38$ ],  $p = 0.001$ ; nine trials) and fasting glucose (WMD  $-0.36$  mmol/L [95% CI  $-0.63$  to  $-0.09$ ],  $p = 0.008$ ; 10 trials), but not insulin (SMD  $-0.63$  [95% CI  $-1.81$  to  $0.55$ ],  $p = 0.29$ ; six trials) when compared with CON (Figures S8–S10). There was significant heterogeneity amongst include studies for HbA1c ( $I^2 = 97.69$ ,  $p = 0.001$ ), glucose ( $I^2 = 86.74$ ,  $p = 0.001$ ) and insulin ( $I^2 = 95.17$ ,  $p = 0.001$ ). Visual interpretation of funnel plots suggested publication bias only for insulin. However, Egger's tests did not confirm bias for HbA1c ( $p = 0.58$ ), glucose ( $p = 0.45$ ) or insulin ( $p = 0.84$ ). In addition, after adjusting the results using trim and fill, the effect size was as follows: insulin (SMD  $-1.16$  [95% CI  $-2.26$  to  $-0.06$ ]; one trial from the right side of the mean) and glucose (WMD  $-0.36$  [95% CI  $-0.63$  to  $-0.10$ ]; one trial from the left side of the mean).

#### Blood pressure

Intermittent fasting did not decrease SBP (WMD  $-2.31$  mmHg [95% CI  $-6.39$  to  $1.77$ ],  $p = 0.26$ ; five trials) or DBP (WMD  $-1.88$  mmHg [95% CI  $-4.58$  to  $0.97$ ],  $p = 0.20$ ; five trials), when compared with CON (Figures S11 and S12). There was significant heterogeneity amongst the included studies for SBP ( $I^2 = 59.91$ ,  $p = 0.04$ ) and DBP ( $I^2 = 62.10$ ,  $p = 0.03$ ). Visual interpretation of funnel plots suggested publication bias only for SBP. However, the Egger's tests did not confirm bias for SBP ( $p = 0.62$ ) and did not indicate bias for DBP ( $p = 0.52$ ). In addition, after adjusting the results using trim and fill, the effect size was as follows: SBP (WMD  $-0.48$  mmHg [95% CI  $-4.37$  to  $3.40$ ]; two trials from the right side of the mean).

### 3.3.2 | IF versus CR

#### Body composition

Intermittent fasting decreased body weight (WMD  $-1.14$  kg [95% CI  $-1.69$  to  $-0.60$ ],  $p = 0.001$ ; six trials) and BMI (WMD  $-0.43$  kg.m<sup>2</sup> [95% CI  $-0.58$  to  $-0.27$ ],  $p = 0.001$ ; four trials) significantly more than CR, but did not decrease fat mass (WMD  $-0.78$  kg [95% CI  $-1.54$  to  $0.07$ ],  $p = 0.07$ ; four trials), FFM (WMD  $-0.11$  kg [95% CI

$-0.74$  to  $0.51$ ],  $p = 0.71$ ; four trials), or visceral fat (SMD  $-0.02$  [95% CI  $-0.24$  to  $0.20$ ],  $p = 0.85$ ; three trials [Figures S13–S17]). There was no significant heterogeneity amongst the included studies for body weight ( $I^2 = 12.22$ ,  $p = 0.33$ ), BMI ( $I^2 = 0.00$ ,  $p = 0.56$ ), fat mass ( $I^2 = 0.00$ ,  $p = 0.91$ ), FFM ( $I^2 = 45.62$ ,  $p = 0.13$ ) or visceral fat ( $I^2 = 0.00$ ,  $p = 0.94$ ). Visual interpretation of funnel plots suggested publication bias for body weight, BMI and visceral fat. However, Egger's tests did not confirm bias for body weight ( $p = 0.97$ ), BMI ( $p = 0.17$ ) or visceral fat ( $p = 0.42$ ). Both visual interpretation of funnel plots and the Egger's test suggested publication bias for FFM ( $p = 0.04$ ), and both visual interpretation of funnel plots and the Egger's test did not suggest publication bias for fat mass ( $p = 0.49$ ). In addition, after adjusting the results using trim and fill, the effect size was as follows: body weight (WMD  $-1.10$  kg [95% CI  $-1.66$  to  $-0.54$ ]; one trial from the right side of the mean), BMI (WMD  $-0.42$  kg.m<sup>2</sup> [95% CI  $-0.57$  to  $-0.26$ ]; one trial from the right side of the mean), FFM (WMD  $-0.00$  kg [95% CI  $-0.50$  to  $0.52$ ]; one trial from the right side of the mean) and visceral fat (SMD  $-0.05$  [95% CI  $-0.23$  to  $0.11$ ]; two trials from the left side of the mean).

#### Glycaemic markers

Intermittent fasting did not decrease HbA1c (WMD  $0.00\%$  [95% CI  $-0.03$  to  $0.04$ ],  $p = 0.84$ ; six trials) significantly more than CR (Figure S18). There was no heterogeneity among the included studies for HbA1c ( $I^2 = 0.00$ ,  $p = 0.85$ ). Both visual interpretation of funnel plots and Egger's tests did not suggest publication bias for HbA1c ( $p = 0.79$ ).

#### Blood pressure

Intermittent fasting did not decrease SBP (WMD  $-0.05$  mmHg [95% CI  $-1.56$  to  $1.45$ ],  $p = 0.94$ ; four trials) or DBP (WMD  $-1.14$  mmHg [95% CI  $-2.30$  to  $0.01$ ],  $p = 0.05$ ; four trials), more than CR (Figures S19 and S20). There was no significant heterogeneity among the included studies for SBP ( $I^2 = 0.00$ ,  $p = 0.80$ ), but there was high and significant heterogeneity for DBP ( $I^2 = 8.66$ ,  $p = 0.35$ ). Visual interpretation of funnel plots suggested publication bias, however, Egger's tests did not confirm bias for SBP ( $p = 0.51$ ) or DBP ( $p = 0.40$ ). In addition, after adjusting the results using trim and fill, the effect size was as follows: SBP (WMD  $0.14$  mmHg [95% CI  $-1.30$  to  $1.58$ ]; two trials from the right side of the mean) and DBP (WMD  $-0.82$  mmHg [95% CI  $-2.20$  to  $0.55$ ]; two trials from the right side of the mean).

## 3.4 | Subgroup analysis

### 3.4.1 | IF versus CON

Subgroup analysis revealed that body weight was significantly reduced by TRE (WMD  $-3.07$  kg [95% CI  $-4.69$  to  $-1.44$ ],  $p = 0.001$ ; six trials) and other modes of IF (WMD  $-6.53$  kg [95% CI  $-9.00$  to  $-4.06$ ],  $p = 0.001$ ; five trials). In addition, body weight was reduced with both prediabetes (WMD  $-5.35$  kg [95% CI  $-9.23$  to

−1.47],  $p = 0.007$ ; five trials) and T2D (WMD −4.16 kg [95% CI −6.20 to −2.12],  $p = 0.001$ ; six trials). Also, body weight was reduced by intervention duration of less than 16 weeks (WMD −4.71 kg [95% CI −7.01 to −1.40],  $p = 0.001$ ; seven trials) and more than 16 weeks (WMD −4.66 kg [95% CI −5.78 to −3.54],  $p = 0.001$ ; four trials [Table S3]).

Subgroup analysis revealed HbA1c was reduced by other modes of IF (WMD −1.99% [95% CI −3.51 to −0.46],  $p = 0.01$ ; four trials) but not by TRE (WMD −0.37% [95% CI −0.85 to 0.10],  $p = 0.12$ ; five trials) in participants with either prediabetes (WMD −0.11% [95% CI −0.17 to −0.05],  $p = 0.001$ ; two trials) or T2D (WMD −1.21% [95% CI −1.89 to −0.53],  $p = 0.001$ ; seven trials). Also, HbA1c was reduced by intervention duration of less than 16 (WMD −1.11% [95% CI −1.76 to −0.46],  $p = 0.001$ ; five trials) but not by intervention duration of more than 16 (WMD −0.42% [95% CI −0.91 to 0.07],  $p = 0.09$ ; four trials [Table S3]).

## 4 | DISCUSSION

We show that, in individuals with prediabetes or T2D, IF was an effective intervention for reducing body weight, BMI, and glycaemic markers, but had no beneficial effects on fat mass, fasting insulin, lipid profiles or blood pressure. In addition, IF was more effective than CR for weight loss but not for reducing fat mass, glycaemic markers, lipid profile and blood pressure. These findings support growing evidence that IF can serve as an alternate and potentially efficient nutritional intervention for preventing obesity and multiple metabolic disorders.<sup>54,55</sup> Previous meta-analyses have shown the beneficial effects of IF for reducing body weight and body fat,<sup>32,56,57</sup> but less is known about patients with prediabetes or T2D. Our results indicate the effectiveness of IF in reducing body weight and BMI, as shown in a previous meta-analysis including patients with T2D,<sup>33</sup> with the observed weight loss effect size being larger (i.e., −3.82 kg vs. −1.89 kg). This improved weight loss may be due to differences between meta-analyses in participant characteristics and in inclusion criteria.

Importantly, several meta-analyses have compared IF with CR to determine any advantage of IF in overweight and obese subjects,<sup>32,58–60</sup> and we confirm greater effects on some (i.e., weight and BMI) but not all indices of body composition. Some studies have suggested IF is effective for maintaining FFM during weight loss,<sup>32,54</sup> but we did not, although we observed moderate differences in weight loss when comparing IF to CON. This difference may be clinically important because weight loss, especially fat loss, is associated with significant improvements in CVD risk,<sup>61,62</sup> even with modest weight loss.<sup>62</sup>

An important challenge for researchers, is to determine which mode of IF may be most beneficial and acceptable to patients. In overweight and obese individuals, a recent network meta-analysis suggested that ADF is an appropriate method of IF,<sup>63</sup> and may be superior to a low-calorie diet for fat loss.<sup>64</sup> The results of the present meta-analysis include results pooled from several modes of IF, and

due to the small number of studies included, we were unable to elucidate the effectiveness of the individual IF modes, such as ADF versus TRE. In our subgroup analysis for reduced body weight in the IF versus CON groups, we were restricted to studies with TRE; the effect of IF was reduced to −3.07 kg but remained significant and potentially clinically meaningful. In addition to determining the most effective and acceptable mode of IF, the intervention duration required in order to see beneficial effects is important. Previous analyses indicate that intervention duration was a significant moderator of the association between intervention type and effectiveness in studies of shorter duration.<sup>33</sup> However, our subgroup analysis for body weight showed that IF was effective with longer duration, as well as with interventions less than 16 weeks, but no study was longer than 6 months (Table 1).

Lifestyle-induced weight loss is associated with improvements in markers of cardiometabolic health,<sup>65–68</sup> and the effects of IF in patients with prediabetes or T2D are still largely unknown, and often controversial. Previously reported results in these populations are mixed, but several meta-analyses have suggested that IF is effective for improving some markers including lipid profiles, glycaemic markers, and blood pressure in various health conditions and diseases.<sup>29,32,57,69,70</sup> In contrast to one previous meta-analysis in individuals with T2D, we focused on both prediabetic individuals and patients with T2D, and our results suggest that IF may improve fasting glucose and HbA1c. We did not show significant benefits with regard to lipid profiles or blood pressure when comparing IF to either CON or CR.<sup>33</sup> The potential mechanisms by which IF reduces fasting glucose and HbA1c include improved insulin sensitivity,  $\beta$ -cell function, glucose tolerance, fatty acid oxidation, and postprandial glucose level.<sup>26,33,41,71</sup> In addition, weight loss improves cardiometabolic outcomes, but in contrast to previous meta-analyses and systematic reviews in patients with impaired glucose and lipid metabolism and T2D,<sup>72,73</sup> we found no improvements in LDL or HDL or blood pressure and small effects on TC and TG levels with IF. However, the small number of included studies, along with the heterogeneity in the mode of IF should be considered when evaluating these effects. In the case of HbA1c, we performed several subgroup analyses to clarify heterogeneity, and found that IF showed greater improvements in patients with T2D versus prediabetes, demonstrating its effectiveness in patients with greater glycaemic dysregulation, including high fasting glucose levels and insulin resistance, which was in accordance with a previous meta-analysis.<sup>25</sup> Although there are meta-analyses that have investigated the effects of various types of IF on weight loss,<sup>63,64</sup> other indicators have not been investigated. The present meta-analysis showed that, when data from only TRE were pooled, there was no effect on HbA1c. Since subgroup analysis by IF mode showed that other ID modes were effective, it seems ADF or 2:5 fasting/feeding may be more effective and this requires further research in patients with prediabetes and T2D. In addition, IF was not associated with greater improvements in any of the cardiometabolic health markers, consistent with previous meta-analyses.<sup>32,60</sup> One previous meta-analysis that pooled data from four studies in patients with T2D and metabolic syndrome reported that IF and CR had similar effects

TABLE 1 Summary of demographic characteristics of participants and interventions.

| Participant characteristics         |                              |               |                                                             | Intervention characteristics                                |                      |                                                                                                                                                                                                                       |
|-------------------------------------|------------------------------|---------------|-------------------------------------------------------------|-------------------------------------------------------------|----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Source, year                        | Sample size (biological sex) | Health status | Age, years                                                  | BMI, kg/m <sup>2</sup>                                      | Study design         | Duration, weeks or months                                                                                                                                                                                             |
|                                     |                              |               |                                                             |                                                             | IF mode              | IF                                                                                                                                                                                                                    |
| Carter et al., 2018 <sup>50</sup>   | 97 (F and M)                 | T2D           | IF: 61.0 ± 9.2<br>CR: 61.0 ± 9.0                            | IF: 37.0 ± 5.7<br>CR: 37.0 ± 5.8                            | RCT                  | 12 months                                                                                                                                                                                                             |
|                                     |                              |               |                                                             |                                                             |                      | 5:2 fasting/feeding                                                                                                                                                                                                   |
|                                     |                              |               |                                                             |                                                             |                      | Intermittent energy restriction including 500–600 kcal/d followed for 2 nonconsecutive days per week, with the remaining 5 days as habitual eating                                                                    |
|                                     |                              |               |                                                             |                                                             |                      | CON or CR protocol                                                                                                                                                                                                    |
|                                     |                              |               |                                                             |                                                             |                      | CR: Continuous energy restriction diet including 1200–1500 kcal/d                                                                                                                                                     |
|                                     |                              |               |                                                             |                                                             |                      | Outcomes assessed                                                                                                                                                                                                     |
|                                     |                              |               |                                                             |                                                             |                      | Body weight, FFM, body fat%, fat mass, VF, HbA1c, insulin                                                                                                                                                             |
| Che et al., 2021 <sup>51</sup>      | 104 (F and M)                | T2D           | IF: 48.21 ± 9.32<br>CON: 48.78 ± 9.56                       | IF: 26.42 ± 1.96<br>CON: 26.08 ± 2.14                       | RCT                  | 12 weeks                                                                                                                                                                                                              |
|                                     |                              |               |                                                             |                                                             | TRE                  | Ad libitum feeding from 8:00 AM to 6:00 PM; fasting between 6:00 PM and 8:00 AM                                                                                                                                       |
|                                     |                              |               |                                                             |                                                             |                      | CON: Maintain normal diet                                                                                                                                                                                             |
|                                     |                              |               |                                                             |                                                             |                      | Body weight, BMI, HbA1c, insulin, FBG, HOMA-IR, TG, TC, LDL, HDL                                                                                                                                                      |
| Chair et al., 2022 <sup>35</sup>    | 101 (F and M)                | Prediabetes   | IF1: 34.68 ± 4.37<br>IF2: 36.06 ± 7.67<br>CON: 34.97 ± 6.23 | IF1: 26.46 ± 2.36<br>IF2: 26.74 ± 1.58<br>CON: 26.47 ± 1.84 | RCT                  | 3 weeks                                                                                                                                                                                                               |
|                                     |                              |               |                                                             |                                                             | IF1: ADF<br>IF2: TRE | IF1: Consuming 600 kcal on fasting days and a usual diet on eating days.<br>IF2: Ad libitum feeding for an 8-h window during the daytime and then fasting for the remaining 16 h each day throughout the intervention |
|                                     |                              |               |                                                             |                                                             |                      | CON: Received the same individual educational session.                                                                                                                                                                |
|                                     |                              |               |                                                             |                                                             |                      | Body weight, BMI, FBG, TG, TC, LDL, HDL, WC                                                                                                                                                                           |
| He et al., 2021 <sup>36</sup>       | 173 (F and M)                | Prediabetes   | IF: 50.2 ± 8.9<br>CR: 50.7 ± 8.7                            | IF: 28.7 ± 2.6<br>CR: 28.7 ± 2.5                            | RCT                  | 6 months                                                                                                                                                                                                              |
|                                     |                              |               |                                                             |                                                             | 5:2 fasting/feeding  | A very-low-calorie diet for 2 days per week, 500 kcal/day for women and 600 kcal/day for men, along with 5 days of a habitual diet                                                                                    |
|                                     |                              |               |                                                             |                                                             |                      | CR: Continuous energy restriction diet including consuming 1000 kcal/day for women and 1200 kcal/day for men                                                                                                          |
|                                     |                              |               |                                                             |                                                             |                      | Body weight, FFM, BMI, body fat%, fat mass, HbA1c, FBG, TG, TC, LDL, HDL, SBP, DBP                                                                                                                                    |
| Hegedus et al., 2023 <sup>37</sup>  | 27 (F and M)                 | T2D           | IF: 16.9 ± 1.6<br>CON: 16.1 ± 1.7                           | IF: ND<br>CON: 16.1 ± 1.7                                   | RCT                  | 12 weeks                                                                                                                                                                                                              |
|                                     |                              |               |                                                             |                                                             | TRE                  | Ad libitum feeding from 12:00 PM to 8:00 PM without calorie counting, fasting between 8:00 PM and 12:00 PM                                                                                                            |
|                                     |                              |               |                                                             |                                                             |                      | CON: Eating over a period of 12 or more hours per day                                                                                                                                                                 |
|                                     |                              |               |                                                             |                                                             |                      | Fat mass, HbA1c, FBG, average glucose, TG, TC, LDL, HDL                                                                                                                                                               |
| Kahleova et al., 2014 <sup>52</sup> | 54 (F and M)                 | T2D           | 59.4 ± 7                                                    | 32.6 ± 4.9                                                  | RCT (crossover)      | 12 weeks                                                                                                                                                                                                              |
|                                     |                              |               |                                                             |                                                             | TRE                  | A restriction of 2092 kJ/day (500 kcal/day) with 2 meals/day including breakfast 6:00–10:00 AM; lunch 12:00–4:00 PM                                                                                                   |
|                                     |                              |               |                                                             |                                                             |                      | CR: a restriction of 2092 kJ/day (500 kcal/day) with 6 meals/day including (breakfast/ lunch/dinner + 3 snacks)                                                                                                       |
|                                     |                              |               |                                                             |                                                             |                      | Body weight, BMI, HbA1c                                                                                                                                                                                               |

TABLE 1 (Continued)

| Participant characteristics              |                              |               |                                                        | Intervention characteristics                        |                 |                           |                         |                                                                                                                                                                      |                                                                                                                 |                                                                                                |
|------------------------------------------|------------------------------|---------------|--------------------------------------------------------|-----------------------------------------------------|-----------------|---------------------------|-------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Source, year                             | Sample size (biological sex) | Health status | Age, years                                             | BMI, kg/m <sup>2</sup>                              | Study design    | Duration, weeks or months | IF mode                 | IF protocol                                                                                                                                                          | CON or CR protocol                                                                                              | Outcomes assessed                                                                              |
| Obermayer et al., 2023 <sup>36</sup>     | 46 (F and M)                 | T2D           | IF: 65.0 ± 6.0<br>CON: 61.0 ± 7.0                      | IF: 33.5 ± 4.7<br>CON: 35.0 ± 4.3                   | RCT             | 12 weeks                  | 4:3 day fasting/feeding | Reducing calories by 75% (i.e., consuming only 25% of the recommended caloric intake) for 3 days each week, with the remaining 4 days as habitual eating.            | CON: Maintain normal diet                                                                                       | Body weight, fat mass, LBM, HbA1c, insulin                                                     |
| Pavlou et al., 2023 <sup>38</sup>        | 69 (F and M)                 | T2D           | IF: 56.0 ± 13.0<br>CR: 55.0 ± 13.0<br>CON: 54.0 ± 11.0 | IF: 39.0 ± 9.0<br>CR: 38.0 ± 5.0<br>CON: 39.0 ± 7.0 | RCT             | 6 months                  | TRE                     | Ad libitum feeding from 12:00 PM to 8:00 PM; fasting between 8:00 PM and 12:00 AM                                                                                    | CR: Reduction of the energy intake by 25% of baseline energy needs every day<br>CON: Maintain their normal diet | Body weight, BMI, LBM, fat mass, VF, FBG, insulin, HbA1c, TG, TC, LDL, HDL, WC                 |
| Suthutvoravut et al., 2023 <sup>39</sup> | 46 (F and M)                 | Prediabetes   | IF: 55.5 ± 7.2<br>CON: 55.2 ± 7.9                      | IF: 29.2 ± 2.9<br>CON: 30.3 ± 3.2                   | RCT             | 12 weeks                  | TRE                     | Restriction of the daily food intake to a 9-h window (between 8:00 AM and 5:00 PM), without any limitation on the types of foods and beverages consumed              | CON: Usual care                                                                                                 | Body weight, HbA1c, HOMA-IR, insulin, FBG, TG, TC, LDL, HDL, SBP, DBP                          |
| Sutton et al., 2023 <sup>40</sup>        | 12 (M)                       | Prediabetes   | 56.0 ± 9.0                                             | 32.2 ± 4.4                                          | RCT (crossover) | 12 weeks                  | TRE                     | 6-h eating period with 18 h of daily fasting, with dinner before 3:00 PM                                                                                             | CON: 12-hr feeding period                                                                                       | Body weight, FBG, insulin, HOMA-IR, TC, TG, LDL, HDL, SBP, DBP                                 |
| Teong et al., 2023 <sup>41</sup>         | 183 (F and M)                | Prediabetes   | IF: 57.0 ± 10.0<br>CR: 58.0 ± 10.0<br>CON: 59.0 ± 11.0 | IF: 34.7 ± 4.6<br>CR: 35.0 ± 4.6<br>CON: 33.8 ± 4.9 | RCT             | 6 months                  | TRE                     | 30% of energy requirements between 8:00 AM and 12:00 PM followed by a 20-h fasting period on three nonconsecutive days per week, and ad libitum eating on other days | CR: 70% of energy requirements daily, without time prescription<br>CON: standard care                           | Body weight, FFM, body fat%, fat mass, VF, HbA1c, FBG, insulin, SBP, DBP, TC, TG, LDL, HDL, WC |
| Williams et al., 1998 <sup>49</sup>      | 47 (F and M)                 | T2D           | IF1: 51.4 ± 7.9                                        | IF1: 35.4 ± 5.4                                     | RCT             | 20 weeks                  | Other                   | IF1: An intermittent very-low-calorie diet for 5 consecutive days during week 2, followed by intermittent very-low-calorie diet therapy                              | CON: standard care                                                                                              | Body weight, HbA1c, FBG, insulin, TG, TC, LDL, HDL                                             |

(Continues)

TABLE 1 (Continued)

| Participant characteristics     |                              |               |                   | Intervention characteristics |              |                                                                                                                                                                                                                             |
|---------------------------------|------------------------------|---------------|-------------------|------------------------------|--------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Source, year                    | Sample size (biological sex) | Health status | Age, years        | BMI, kg/m <sup>2</sup>       | Study design | Duration, weeks or months                                                                                                                                                                                                   |
|                                 |                              |               |                   |                              |              | IF mode                                                                                                                                                                                                                     |
| Wing et al., 1994 <sup>53</sup> | 79 (F and M)                 | T2D           | IF2: 50.3 ± 8.6   | IF2: 37.3 ± 4.8              | RCT          | for 1 day/week for 15 weeks, with a 1500–1800 kcal/day diet at other times.                                                                                                                                                 |
|                                 |                              |               | CON: 54.1 ± 7.0   | CON: 35.0 ± 5.2              |              | IF1: An intermittent very-low-calorie diet for 5 consecutive days during Week 2, followed by intermittent very-low-calorie diet therapy for 5 consecutive days every 5 weeks, with a 1500–1800 kcal/day diet at other times |
|                                 |                              |               | IF: 52.3 ± 10.7   | IF: 37.42 ± 6.13             |              | 2 × 12-week periods of 400 to 500 kcal per day alternating with the balanced 1000 to 1200 kcal per day                                                                                                                      |
|                                 |                              |               | CR: 51.3 ± 8.7    | CR: 38.31 ± 6.52             |              | CR: a calorie intake goal of 1000 to 1200 kcal per day throughout the program.                                                                                                                                              |
| Yang et al., 2023 <sup>42</sup> | 63 (F and M)                 | T2D           | IF: 52.2 ± 7.38   | IF: 24.23 ± 2.58             | RCT          | 6 cycles of 15 intervention days in each cycle, the CMNT group was assigned a diet with 5 modified fasting days (~840 kcal/day), with the following 10 days of ad libitum diet                                              |
|                                 |                              |               | CON: 53.4 ± 11.72 | CON: 23.85 ± 2.50            |              | CON: ad libitum diet                                                                                                                                                                                                        |
|                                 |                              |               |                   |                              |              | Body weight, BMI, HbA1c, FBG, insulin, TG, TC, LDL, HDL, SBP, DBP                                                                                                                                                           |
|                                 |                              |               |                   |                              |              |                                                                                                                                                                                                                             |

Abbreviations: BMI, body mass index; CMNT, chinese medical nutrition therapy; CON, control; CR, calorie restriction; DBP, diastolic blood pressure; F, female; FFM, fat free mass; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; IF, intermittent fasting; LBM, lean body mass; LDL, low-density lipoprotein; M, male; ND, not described; RCT, randomized controlled trial; SBP, systolic blood pressure; TC, cholesterol; TG, triglycerides; VF, visceral fat; WC, waist circumference.

on fasting glucose and HbA1c, which aligns with our results.<sup>34</sup> Overall, our results regarding improved lipid profiles and blood pressure, suggest that IF was not more effective as compared with CR, and thus cardiometabolic health was not more improved. Despite the observed positive effect of IF on individuals with prediabetes and T2D, the risk of hyperglycaemia during fasting periods should be considered. However, IF, especially the TRF protocol, is easier and safer, therefore, fasting periods are not long enough to significantly increase the risk of hypoglycaemia.<sup>74</sup> In addition, the risk of hypoglycaemia can be mitigated with insulin dose adjustment protocols during fasting.<sup>26</sup>

The present study has several limitations that should be considered. First, there was a limited number of studies that met our inclusion criteria, thus, we could not comprehensively investigate the role of IF for most outcomes. Therefore, despite the inclusion of important clinical studies, further high-quality investigations are needed in patients with T2D. Second, significant and high heterogeneity was detected for several outcomes, and study methodologies, intervention durations, mode of IF, and disease may be a source of heterogeneity. Third, we could not determine which mode of IF should be prescribed for patients with prediabetes or T2D. Fourth, although comparisons were performed between IF and CR, adherence to the interventions is a concern when prescribing this type of dietary intervention as insufficient data were available in most of the studies to analyse adherence.

In conclusion, our systematic review and meta-analysis provides evidence that IF is effective for reducing body weight and BMI in patients with prediabetes and T2D when compared to CON or CR. Additionally, IF is effective for reducing fasting glucose and HbA1c when compared with CON, but not CR. However, there was little or no evidence for beneficial effects of IF on lipid profiles or blood pressure. Overall, IF may be an alternate and effective dietary intervention in individuals with prediabetes or T2D for weight loss and improving glycaemia. Further randomized clinical trials are needed to elucidate whether there is an appropriate and acceptable mode of IF that would promote cardiometabolic health.

## AUTHOR CONTRIBUTIONS

Mousa Khalafi, Michael E. Symonds, Aref Habibi Maleki, Hadi Rohani, Mahsa Ehsanifar and Sara K. Rosenkranz conceptualized the systematic review and meta-analysis. Mousa Khalafi, Aref Habibi Maleki, Mahsa Ehsanifar and Hadi Rohani carried out the screenings and reviews. Mousa Khalafi, Aref Habibi Maleki and Hadi Rohani analysed the data and performed meta-analyses. Mousa Khalafi drafted the manuscript. Mousa Khalafi, Sara K. Rosenkranz and Michael E. Symonds revised the manuscript. All authors read and approved the final manuscript.

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## CONFLICT OF INTEREST STATEMENT

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.

## PEER REVIEW

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## DATA AVAILABILITY STATEMENT

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

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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