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WORLDVIEWS ON EVIDENCE-BASED NURSING

ORIGINAL ARTICLE

The effectiveness of lifestyle interventions for diabetes remission on patients with type 2 diabetes mellitus: A systematic review and meta-analysis

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Abstract

Background: Conventional wisdom affirmed that diabetes was irreversible, but current research shows that lifestyle interventions may achieve diabetes remission among patients with type 2 diabetes mellitus. Recently, many original studies have examined the effectiveness of lifestyle interventions. However, great heterogeneity in intervention approaches resulted in inconsistent intervention effects.

Aims: The aim of this study was to determine the effectiveness of lifestyle interventions for diabetes remission among patients with type 2 diabetes mellitus.

Methods: PubMed, CINAHL, Embase, Web of Science Core Collection, and Cochrane Library were searched for relevant articles from their inceptions to March 26, 2021. Reference lists and a relevant journal were searched manually as well. Both randomized controlled trials and quasi-experimental studies were included. The quantitative data extracted from the selected studies included diabetes remission rate, weight, and quality of life score. The risk of bias was assessed by the Cochrane and Joanna Briggs Institute's tool. RevMan version 5.3. was used to carry out the meta-analysis.

Results: This systematic review included 12 studies involving 3997 patients with type 2 diabetes mellitus. Lifestyle interventions included in the studies were mainly divided into diet-only interventions and diet combined with physical activity interventions. Among them, there were three types of diet: (1) low-energy diet, (2) low carbohydrate diet, and (3) Mediterranean diet. Moderate-intensity aerobic and resistance physical activity, walking, and maintaining habitual physical activity were the three types of physical activity interventions employed in the included studies. The results indicated that lifestyle interventions were effective for achieving diabetes remission, reducing weight, and improving quality of life in patients with type 2 diabetes mellitus.

Linking Evidence to Action: Lifestyle interventions were associated with significant effects on diabetes remission, reducing weight, and improving quality of life. As an important part of lifestyle interventions, diet and physical activity have a significant effect on blood glucose and weight control in patients with type 2 diabetes mellitus. It is therefore suggested that the contents of lifestyle interventions should focus on diet and physical activity.

Yating Zhang and Yajie Yang contributed equally to this work.

KEYWORDS
diabetes remission, lifestyle, meta-analysis, systematic review, type 2 diabetes

INTRODUCTION

Diabetes is a worldwide public health concern. According to the 9th edition of the International Diabetes Federation [IDF] (2019) Diabetes Atlas 9, approximately 463 million people worldwide suffered from diabetes in 2019. Among these diagnosed patients, type 2 diabetes mellitus (T2DM) is the most common type, accounting for 90%–95% of the patients with diabetes (Zheng et al., 2018). T2DM is characterized by insulin resistance driven by chronic hyperglycemia and is commonly diagnosed by measures of glycemia such as fasting blood glucose (FBG) concentrations of 7.0 mmol/L or above or glycated hemoglobin (HbA1c) values of 6.5% or above (American Diabetes Association, 2021). T2DM is associated with various risk factors including genetics and lifestyle influences, but by far the most common risk factor is overweight or obesity (GBD 2015 Obesity Collaborators et al., 2017). Consequently, T2DM leads to many medical complications and eventually causes the death of patients (Jansson et al., 2010).

T2DM has conventionally been considered a lifelong, incurable disease (World Health Organization and International Diabetes Federation, 2016). In the early 1990s, it was found that some patients with T2DM could achieve *remission* through some treatments, that is, the blood glucose could be restored to normal levels without medication and maintained for a period of time (Pories et al., 1992). With the deepening of research and the development of medical technology, more and more studies about diabetes intervention use the term *diabetes remission* as one of the outcomes of treatment (Buse et al., 2009). Diabetes remission has become an ideal treatment goal for most patients with T2DM.

Lifestyle interventions are the cornerstone of treating T2DM (American Diabetes Association, 2019). Several major randomized controlled trials, including the Diabetes Prevention Program (DPP; Knowler et al., 2002), the Finnish Diabetes Prevention Study (DPS; Lindström et al., 2006), and the DaQing Diabetes Prevention Study (Da Qing study) (Li et al., 2014), demonstrated that lifestyle interventions featuring individualized reduced-calorie meal plans and moderate-intensity physical activity were highly effective in controlling blood glucose and weight. Therefore, the American Diabetes Association (2021) guideline suggests that diet and physical activity should be important in lifestyle interventions.

What's more, with *The twin-cycle hypothesis* proposed by Taylor (2021), researchers found that diabetes remission might be achieved through lifestyle interventions. Therefore, in recent years, proliferate studies have paid more attention to achieving diabetes remission through lifestyle interventions in T2DM. (Dave et al., 2019; Taheri et al., 2020; Walton et al., 2019). However, the results of these studies have been inconsistent. On the one hand, Hammer et al. (2008) found that a caloric restriction diet could achieve diabetes remission in T2DM patients with obesity during the first three months of intervention. Likewise, other studies also reported similar results (Paisey et al., 1998; Snel et al., 2012). On the other hand, the Action for Health in Diabetes (The Look AHEAD) study concluded that intensive lifestyle interventions in patients with T2DM were unsatisfactory, especially with regard to long-term maintenance of glycemic control and weight loss (Look AHEAD Research Group, 2013). Hence, it is necessary to integrate these results quantitatively through meta-analysis.

A previous systematic review demonstrated the efficacy of a low-carbohydrate diet (LCD) intervention in diabetes remission among T2DM patients (Goldenberg et al., 2021). However, this review merely focused on efficacy of LCD intervention, whereas patients with T2DM often received not a single dietary intervention, but comprehensive lifestyle interventions. In addition, a few relevant studies have been published recently, which might provide new evidence for lifestyle intervention to achieve diabetes remission (Taheri et al., 2020; Umphonsathien et al., 2019; Unwin et al., 2020). Therefore, the effectiveness of lifestyle interventions in achieving diabetes remission are still unclear.

The current systematic review and meta-analysis aimed to review the lifestyle intervention strategies and quantitatively evaluate the effectiveness of lifestyle interventions on diabetes remission, weight, and quality of life (QoL) through included randomized controlled trials and quasi-experimental studies.

METHODS

This study was registered in the PROSPERO international prospective register of systematic reviews and conducted based on the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines.

Inclusion and exclusion criteria for literature selection

Population

Studies with participants meeting the international diagnosis of T2DM were included, and there were no limitations of age and sex. Patients who had undergone bariatric surgery, were treated with injectable insulin, or had serious complications were excluded.

Intervention

Lifestyle interventions included were diet or physical activity interventions for a defined period (at least 12 weeks). But interventions

involving medication, surgery, or single diet components (such as vitamin D supplementation) were excluded.

Comparison

The control group only received usual care (standard care with no formalized, structured, or tailored intervention for adherence) or no intervention.

Outcome

The primary outcome was the rate of diabetes remission defined as: (1) absence of glucose-lowering therapy (GLT), (2) normoglycaemia, and (3) for a duration ≥ of 3 months (American Diabetes Association, 2021; Buse et al., 2009; Herdzik et al., 2002).

Secondary outcomes included weight and QoL (the measuring tools of QoL include HRQOL, EQ-5D, and SF-36).

Study design

The review included randomized controlled trials (RCT) and quasi-experimental studies in English.

Search strategy

A three-step search strategy was applied in this review. First, based on the population, intervention, comparison, outcomes, and study design (PICOS) framework, an initial limited search of PubMed was conducted to identify search terms. Second, all identified free-text words and MeSH terms across PubMed, CINAHL, Embase, Web of Science Core Collection, Cochrane Library were used: "diabetes mellitus, type 2" [MeSH Terms], "type 2 diabetes", "T2DM", "life style" [MeSH Terms], "Diet" [MeSH Terms], "diet*", "Exercise" [MeSH Terms], "exercise", "remission", and "reversal". The full search strategy is available in Appendix S1. Third, the reference lists of all identified articles were examined manually. Only studies published in English from the database inception to March 26, 2021, were included.

Selection process

All the retrieved studies were sent to EndNote to eliminate duplication of studies. Two reviewers (YZ and YY) who had been trained in evidence-based medicine courses screened the titles, abstracts, and full texts of possibly relevant studies independently. The disagreements between two reviewers (YZ and YY) were solved by a third reviewer (ML).

Study risk of bias assessment

Two trained reviews (YZ and YY) independently evaluated the quality of eligible studies. The RCTs were evaluated by using the Cochrane Collaboration Risk of Bias Tool (Higgins et al., 2011), which assessed random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective report, and other biases. The reviewers were asked to make a "yes" (low bias), "no" (high bias), or "unclear" (lack of relevant information or uncertainty of bias) judgment for each item. For quasi-experimental studies, the appraisal instrument for quasi-experimental studies from Joanna Briggs Institute (JBI) was used (Tufanaru et al., 2020). This instrument assessed seven areas, including clarity of causality, comparability of baseline and treatment between groups, the existence of control groups, multiple measurements of the outcome, completeness of follow-up, consistency and reliability of measurement methods, and soundness of statistical analysis. The disagreements regarding the quality assessment between two reviewers (YZ and YY) were solved by a third reviewer (ML).

Data extraction

Data were extracted independently by two trained reviewers (YZ and YY) into the standard data extraction form. The extracted data included the first author, year, country, study design, sample size, mean age, disease duration, intervention description (component and does), control description, timepoint, and outcomes (diabetes remission rate, weight, and the score of QoL). Authors of studies were contacted when the data of outcome could not be found in the article or calculated based on accessible data. Studies were excluded if ultimately these data were unavailable.

Statistical analysis

Statistical analyses were performed using Review Manager (RevMan) version 5.3. For the dichotomous outcome, the rate of diabetes remission, odds ratio (OR), and 95% confidence interval (95% CI) were calculated. For continuous variables which included weight and QoL, mean difference (MD) or standardized mean difference (SMD) with 95% CI was calculated. A p-value $< .05$ was considered to be statistically significant. Statistical heterogeneity was estimated using p-values and I^2 tests: $p \leq .05$ or $I^2 \geq 50\%$ were considered heterogeneous and random effects models were used for statistical analysis; $p \geq .05$ and $I^2 \leq 50\%$ were considered not heterogeneous and fixed effects models were used. Subgroup analysis was conducted in terms of the study design and the duration of follow-up. Publication bias was identified through a funnel plot.

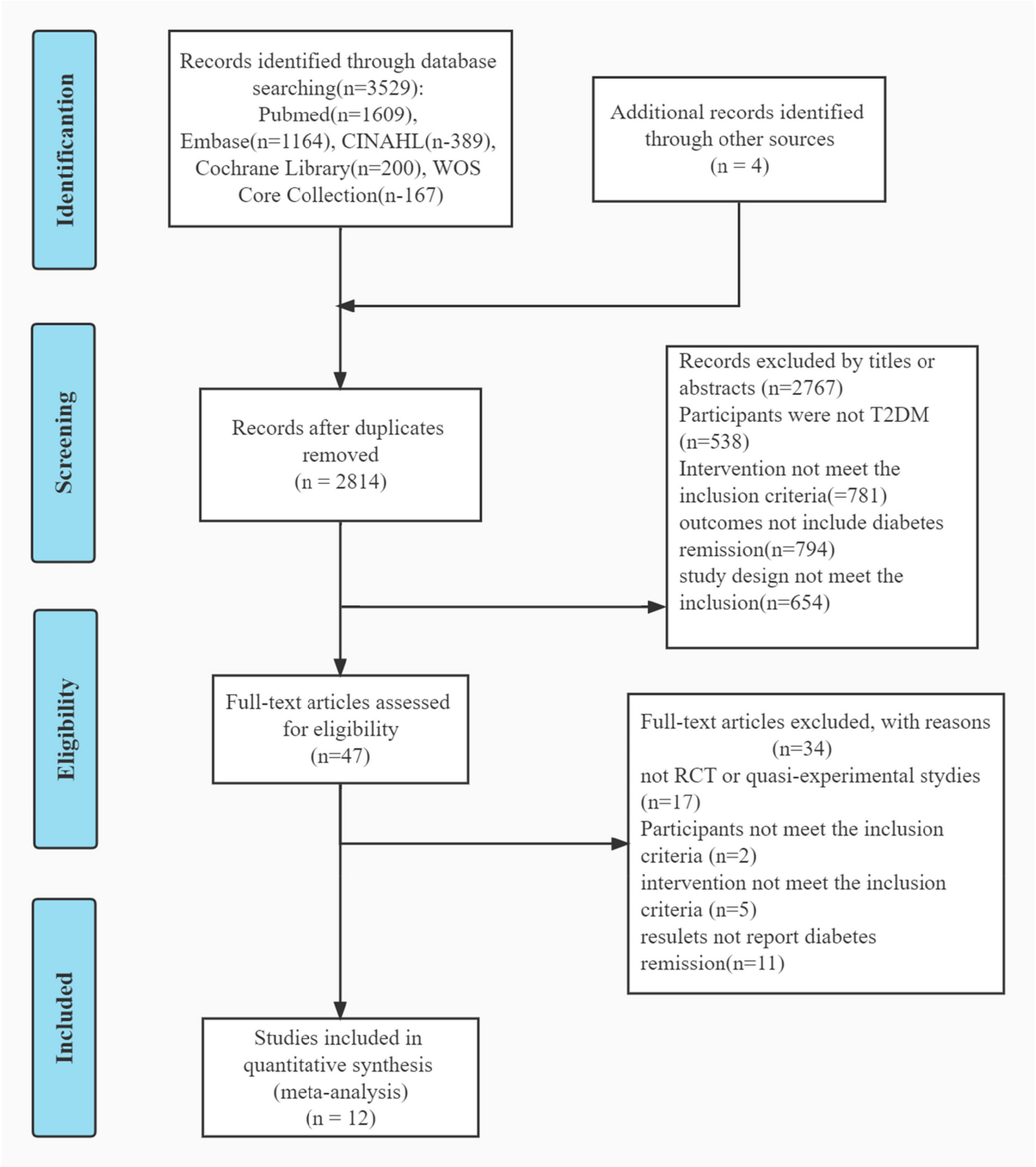

FIGURE 1 The PRISMA flow diagram

RESULTS

Study selection

A total of 3533 relevant records were retrieved, of which 719 duplicate records were removed by EndNote. Manually, 2767 irrelevant documents were removed by reading titles and abstracts. Then, the full-text of the remaining 47 articles were screened. Finally, 12 articles (Bhatt et al., 2017; Dave et al., 2019; Esposito et al., 2009, 2014; Gow et al., 2017; Gregg et al., 2012; Lean et al., 2018, 2019; Ried-Larsen et al., 2019; Taheri et al., 2020; Umphonsathien et al., 2019; Unwin et al., 2020) were included. The PRISMA flow diagram was shown in Figure 1.

TABLE 1 Characterizations of the included studies

Author, year, country	Study design	Size (total [I/C])	Age (I/C)	Male (total% or I/C)	Disease duration (year/month)
Bhatt et al. (2017), India	Quasi-experimental study	12 (n/a)	38.5[a]	66.7	1.5/4.0[a] years
Dave et al. (2019), India	Quasi-experimental study	45 (n/a)	45.1 (10.1)[b]	66.7	1.9 (2.7)[b] years
Esposito et al. (2009), Italy	RCT	215 (108/107)	52.4 (11.2)/51.9 (10.7)[b]	50.0/48.5	newly diagnosed without medication
Esposito et al. (2014), Italy	RCT	215 (108/107)	52.4 (11.2)/51.9 (10.7)[b]	50.0/48.5	newly diagnosed without medication
Gow et al. (2017), Australia	Quasi-experimental study	8 (5/3)	14.4[a]	75.0	from < 1 month to 3.25 years
Gregg et al. (2012), USA	RCT	2503 (2241/2262)	59.1 (6.9)/58.6 (6.7)[b]	41.4/41.9	5 (7)/5 (8)[a] years
Lean et al. (2018), UK	RCT	306 (157/149)	52.9 (7.6)/55.9 (7.3)[b]	56.0/62.0	3.0 (1.7)/3.0 (1.8)[b] years
Ried-Larsen et al. (2019), Denmark	RCT	93 (62/31)	53.5 (9.2)/56.7 (8.3)[b]	53.0/55.0	4.7 (2.8)/5.6 (3.2)[b] years
Taheri et al. (2020), USA	RCT	147 (70/77)	41.9 (5.4)/42.3 (5.8)[b]	70.0/75.0	21.9 (11.5)/20.5 (13.0)[b] month
Umphonsathien et al. (2019), Thailand	Quasi-experimental study	19 (n/a)	48.2 (1.7)[b]	5.0	2.0[b] years

Intervention group					
Diet	**Exercise**	**Other**	**Duration**	**Timepoint**	**Control group**
Low carbohydrate diet meal replacement protein formula: 378.5 kcal, 48 g whey protein, 41 g of CHO, and 2.5 g of fat along with micronutrients. CHO: 60%; Protein: 30%; Fat: 10%	Advised moderate intensity aerobic and resistance exercise from the 2nd week	/	12 weeks	12 weeks	Before and after treatment
American Diabetes Association diet	Minimum target duration of 45 min, 6 days/ week	Education and monitoring	1 year	5 years	Before and after treatment
Mediterranean-style diet: 50% of daily calories from CHO	Advised 175 minutes of moderate-intensity physical activity per week	Monthly sessions in the first year and bimonthly sessions thereafter	4 years	4 years	Low-fat diet, fat no more than 30%, and saturated fat no more than 10%
Low-carbohydrate Mediterranean diet: 1500 kcal/d (female), 1800 kcal/d (male); CHO no more than 50%, Fat: no less than 30%, with the main source of added fat 30-50 g of olive oil	175 min of moderate-intensity physical activity per week	Monthly sessions in the first year and bimonthly sessions thereafter	4 years	8 years	Low-fat diet, Fat no more than 30%, and saturated fat no more than 10%
Very low energy diet: 800 kcal/day, CHO <40%, Protein 40–55%, Fat <20%	/	Weekly reviewed by the dietitian	/	34 weeks	Before and after treatment
Reduce total caloric intake to 1200 to 1800 kcal/d by reducing in total and saturated fat intake	Increasing physical activity levels to a goal of 175 min/wk.	/	/	/	DSE
0–12 weeks (TDR phase): low energy formula diet (825–853 kcal/day; 59% CHO, 13% fat, 26% protein, 2% fiber, with 2.25 L fluids) 13–18 weeks (FR phase): step down to low fat diet (about 50% CHO, 35% total fat, and 15% protein) 19–104 weeks (Weight loss maintenance phase): individually tailored calorie prescription to support weight stabilization	0-12 weeks: maintain usual physical activities >12 weeks: step counters and physical activity, up to 15,000 steps/day	All oral antidiabetic and antihypertensive drugs were discontinued on day 1	18 weeks	12 months	Standard diabetes care
0–4 months: individual dietary plans (45%–60% CHO, 15%–20% Protein, and 20%–35% Fat, with <7% saturated fat) 5–8 months: energy balance	Supervised resistance and aerobic exercise;30-60 min, 5–6 days/week	Standard care (the same as control group)	12 months	24 months	Standard care (pharmaceutical therapy & lifestyle advice)
1–12 weeks (TDR phase): formula low-energy diet meal replacement products (800–820 kcal/day, 57% CHO, 26% protein, 14% fat, 3% fiber, ≥2 L water); 13–24 weeks (FR phase): appropriate energy (based on body weight), protein-rich food, low-glycaemic-index foods; 25–48 weeks: own food/ participants managed their own energy-restricted food intake	Walking at least 10,000 steps per day initially; followed by advised unsupervised activity at least 150 min/ week	Discontinued all diabetes medications; behavioral support	12 months	24 months	Usual medical diabetes care
(−2)-8 weeks: very low calorie diet: 54%–65% CHO, 23%–30% protein, and 12%–13% fat with a total daily calorie of 600 kcal; one tablet of multivitamins and a minimum of 2500 ml of water daily was encouraged. 8–12 weeks: higher caloric intake in a stepwise fashion (800 kcal/day on week 9, 1000 kcal/day on week 10, 1200 kcal/day on week 11, and 1500 kcal/day on week 12)	/	Continue habitual lifestyle pattern	2 + 8 weeks	12 weeks	Before and after treatment

(Continues)

TABLE 1 (Continued)

Author, year, country	Study design	Size (total [I/C])	Age (I/C)	Male (total% or I/C)	Disease duration (year/month)
Unwin et al. (2020), UK	Quasi-experimental study	128 (n/a)	63.0 (54.0, 73.0)[a]	63.0	/
Lean et al. (2019), UK	RCT	306 (157/149)	52.9 (7.6)/55.9 (7.3)[b]	56.0/62.0	3.0 (1.7)/3.0 (1.8)[b] years

Abbreviations: CHO, carbohydrate; DSE, diabetes support and education intervention; FR, food reintroduction; I/C, intervention/control; n/a, not available; TDR, totally diet replacement; UK, The United Kingdom; USA, The United States of America.

[a]Median (IQR).

[b]Mean (*SD*).

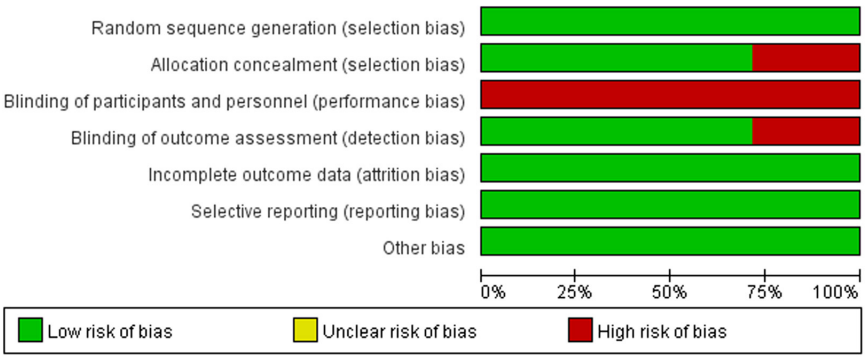

FIGURE 2 Risk of bias graph

TABLE 2 Risk of bias of the included studies (quasi-experimental studies)

Author, year	1	2	3	4	5	6	7	8	9
Bhatt et al. (2017)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dave et al. (2019)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Gow et al. (2017)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Umphonsathien et al. (2019)	yes	yes	Not applicable	no	yes	yes	yes	yes	yes
Unwin et al. (2020)	Yes	Yes	Not applicable	No	Yes	Unclear	Yes	Yes	Yes

Note: 1 = Is it clear in the study what is the "cause" and what is the "effect" (i.e., there is no confusion about which variable comes first)?; 2 = Were the participants included in any comparisons similar?; 3 = Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?; 4 = Was there a control group?; 5 = Were there multiple measurements of the outcome both pre and post the intervention/exposure?; 6 = Was follow up complete and if not, were differences between groups in terms of their follow-up adequately described and analyzed?; 7 = Were the outcomes of participants included in any comparisons measured in the same way?; 8 = Were outcomes measured in a reliable way?; 9 = Was appropriate statistical analysis used?

Study characteristics

This study included 12 studies (seven RCTs and five quasi-experimental studies) with 3997 participants (Table 1). Three studies were implemented in the United Kingdom (Lean et al., 2018, 2019; Unwin et al., 2020), two each in the United States of America (Gregg et al., 2012; Taheri et al., 2020), Italy (Esposito et al., 2009, 2014) and India (Bhatt et al., 2017; Dave et al., 2019), and the remaining three studies were from Denmark (Ried-Larsen et al., 2019), Australia (Gow et al., 2017) and Thailand (Umphonsathien et al., 2019). The mean age of participants ranged from 38.5–63.0 years, and the percentage of males ranged from 5% to 75%.

Intervention group					
Diet	**Exercise**	**Other**	**Duration**	**Timepoint**	**Control group**
lower CHO diet educational resources: outline low glucose index sources of food; reduce the intake of sugary and starchy foods	/	"one-to-one" general practice consultations and group consultations approximately once every 6 weeks	23 (16.8)[b] months	6 years	Before and after treatment
3-5 months (TDR phase): 825–853 kcal/day, 59% CHO, 13% fat, 26% protein, 2% fiber 6–8 weeks (FR phase): step down to low fat diet (about 50% CHO), 35% total fat, and 15% protein maintenance phase: structured support for weight-loss maintenance	TDR phase: maintain usual physical activities FR phase: step counters and physical activity strategies were introduced, up to 15,000 steps/day	All oral antidiabetic and antihypertensive drugs were discontinued	18 weeks	12 months, 24 months	Standard diabetes care

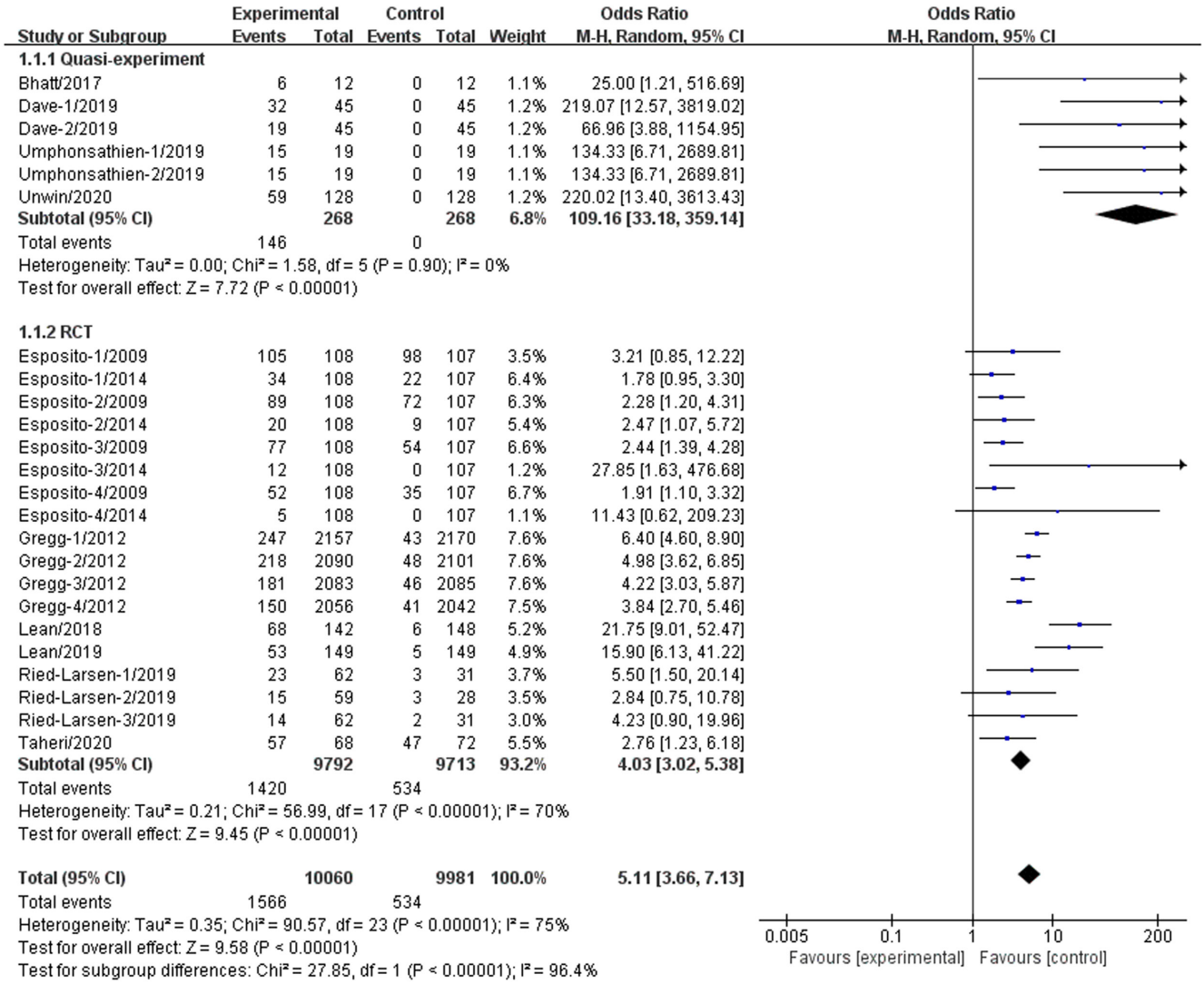

FIGURE 3 Forest plot for diabetes remission

With respect to the use of lifestyle interventions, a diet-only intervention was employed in three studies (Gow et al., 2017; Umphonsathien et al., 2019; Unwin et al., 2020). A diet combined with physical activity intervention was employed in the other nine studies. There were three types of diet in these studies: (1) low-energy diet, (2) LCD, and (3) the Mediterranean diet. Moderate intensity aerobic and resistance physical activity, walking, and maintaining habitual physical activity were the three types of physical activity interventions employed in the included studies. The duration of lifestyle interventions varied from 12 weeks to 4 years.

Risk of bias in studies

Due to the nature of the intervention, it was difficult to blind the participants and implementers. Therefore, this review evaluated "blinding of participants and personnel performance bias" item as high risk of bias in all RCTs. Among seven RCTs, two (Esposito et al., 2009, 2014) had a high risk of selection bias due to inadequate distribution concealment, and two (Lean et al., 2018, 2019) had a high risk of detection bias due to assessments not being blinded. For five quasi-experimental studies, two (Umphonsathien et al., 2019; Unwin et al., 2020) were before-after studies with no control group, and the follow-up information of three studies (Dave et al., 2019; Gow et al., 2017; Unwin et al., 2020) were incomplete or absent. Detailed results were presented in Figure 2 and Table 2.

Meta-analyses

The effect of lifestyle interventions on diabetes remission

Eleven of the included studies reported the rate of diabetes remission (Bhatt et al., 2017; Dave et al., 2019; Esposito et al., 2009, 2014; Gregg et al., 2012; Lean et al., 2018, 2019; Ried-Larsen et al., 2019; Taheri et al., 2020; Umphonsathien et al., 2019; Unwin et al., 2020). For each study, we included data from each follow-up visit. Subgroup analyses based on the study type and random-effect model was used because of the large heterogeneity ($p < .001$, $I^2 = 75\%$). Pooled analysis showed that lifestyle interventions increased remission rates by almost four times compared to control group (OR = 5.11, 95% CI [3.66, 7.13], $p < .001$). Both RCTs and quasi-experimental studies showed that lifestyle interventions could increase remission rates in T2DM (RCTs, OR = 4.03, 95% CI [3.02, 5.38], $p < .001$; quasi-experimental studies, OR = 109.16, 95% CI [33.18, 359.14], $p < .001$; Figure 3).

As the timepoint varied between studies (from 12 weeks to 6 years), subgroup analysis was performed separately for RCTs and quasi-experimental studies based on the timepoint. We divided the data into three groups: (1) ≤ 12 months (Bhatt et al., 2017; Dave et al., 2019; Esposito et al., 2009; Gregg et al., 2012; Lean et al., 2018; Ried-Larsen et al., 2019; Taheri et al., 2020; Umphonsathien et al., 2019), (2) 13–36 months (Esposito et al., 2009; Gregg et al., 2012; Ried-Larsen et al., 2019), and (3) >36 months (Dave et al., 2019; Esposito et al., 2014; Gregg et al., 2012; Lean et al., 2019; Unwin et al., 2020). For RCTs, lifestyle interventions increased remissions at a higher rate when the follow-up duration was ≤12 months (OR = 6.09, 95% CI [3.14, 11.79], $p < .001$). The other two subgroups showed similar lower increases in remission rates when the follow-up was >12 months (13–36 months, OR = 4.04, 95% CI [2.76, 5.92], $p < .001$; >36 months, OR = 2.72, 95% CI [1.71, 4.32], $p < .001$; Figure 4). For quasi-experimental studies, the diabetes remission rate showed greater increase when the follow-up was >36 months (OR = 122.64, 95% CI [16.66, 902.63], $p < .001$), and lower increase when follow-up was ≤36 months (OR = 102.36, 95% CI [23.21, 451.4], $p < .001$; Figure 5).

The effect of lifestyle interventions on weight

Nine of the included studies reported the effect of lifestyle interventions on weight loss. (Bhatt et al., 2017; Dave et al., 2019; Esposito et al., 2009; Gow et al., 2017; Lean et al., 2018, 2019; Taheri et al., 2020; Umphonsathien et al., 2019; Unwin et al., 2020). There was heterogeneity across studies ($p < .001$, $I^2 = 93\%$). Therefore, a random-effect model was conducted. Pooled analysis showed that the lifestyle intervention group achieved greater weight loss when compared with the control (MD = −7.09, 95% CI [−10.58, −3.60], $p < .005$). Subgroup analysis showed similar results in both RCTs (MD = −4.08, 95% CI [−7.67, −0.49], $p = .002$) and quasi-experimental studies (MD = −9.84, 95% CI [−11.00, −8.68], $p < .001$). Both subgroups showed a high level of heterogeneity (RCTs, $p = .03$, $I^2 = 79\%$; quasi-experimental studies, $p < .001$, $I^2 = 0\%$; Figure 6).

The effect of lifestyle interventions on QoL

Five studies reported the efficacy of lifestyle interventions on the total score of QoL with the measurement of the SF-36 questionnaire (Umphonsathien et al., 2019), Equation 5-D scale (Lean et al., 2018, 2019; Taheri et al., 2020), and HRQOL (Gow et al., 2017). SMD and random-effect models were used due to differences in the measurement of different rating scales and the existence of heterogeneity ($p < .001$, $I^2 = 92\%$). Pooled analysis showed that patients in the intervention group had a higher QoL compared with the control (SMD = 1.10, 95% CI [0.49, 1.70], $p = .007$). On the basis of subgroup analysis, we found that in RCTs, QoL was significantly improved in the intervention group compared to the control group (SMD = .17, 95% CI [0.02, 0.32], $p = .02$) with a low heterogeneity ($p = .52$, $I^2 = 0\%$; Lean et al., 2018, 2019; Taheri et al., 2020), quasi-experimental studies showed significant QoL improvement as well (SMD = 2.09, 95% CI [0.70, 3.47], $p < .001$; Gow et al., 2017; Figure 7).

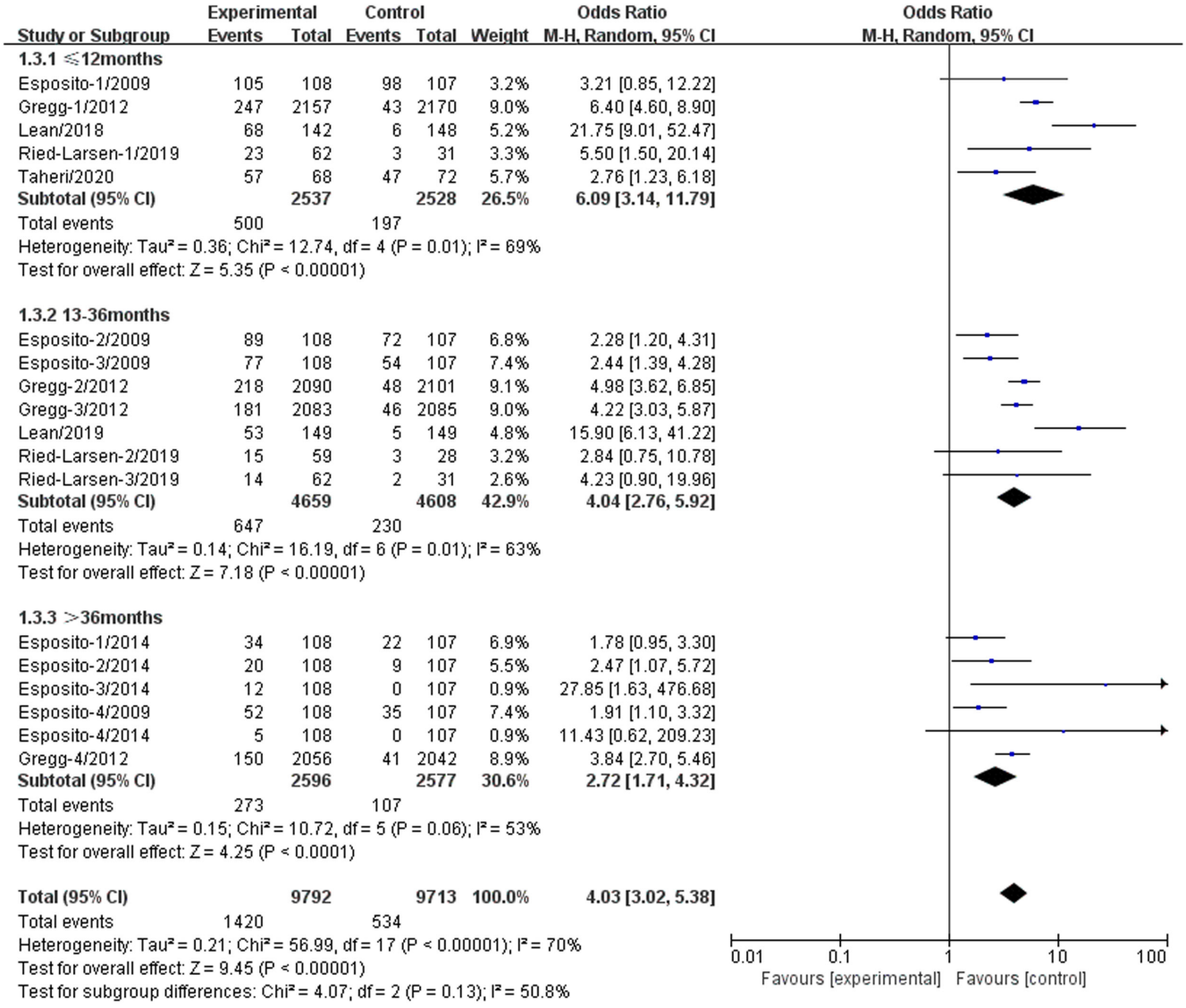

FIGURE 4 Forest plot for diabetes remission (subgroup-RCTs)

Publication bias and sensitivity analyses

The distribution of the studies in the funnel plot was approximately symmetrical, suggesting no publication bias in the studies (Figure 8). Sensitivity analyses showed no significant changes in outcomes by removing studies one by one.

DISCUSSION

Principal findings

Twelve studies that reported 3997 participants with T2DM were pooled in this review to assess the effect of lifestyle interventions on diabetes remission. Lifestyle interventions included in the studies were mainly divided into diet-only interventions and diet combined with physical activity interventions. Among them, the low-energy diet, LCD, and Mediterranean diet were usually employed. Moderate intensity aerobic and resistance physical activity, walking, and maintaining habitual physical activity were usually employed. Results of meta-analysis identified that through lifestyle interventions under strict withdrawal or non-medication conditions in patients with T2DM could reach diabetes remission, reduce weight, and improve QoL. In addition, subgroup analysis based on different follow-up times demonstrated a credible subgroup effect between studies.

The results showed that lifestyle interventions could achieve higher diabetes remission rates. In these included studies, the lifestyle interventions implemented were mainly diet (low-energy diet, LCD, and Mediterranean diet) combined with physical activity (moderate intensity aerobic and resistance physical activity, walking, and maintaining habitual physical activity). It is well known that lifestyle interventions, especially diet and physical activity, are the cornerstone of diabetes management (American Diabetes Association, 2021). According to the twin-cycle hypothesis (Taylor, 2021), the pathogenesis of T2DM can be roughly divided into three stages: (1) glucose desensitization, (2) β-cell fatigue, and (3) irreversible loss of β-cell

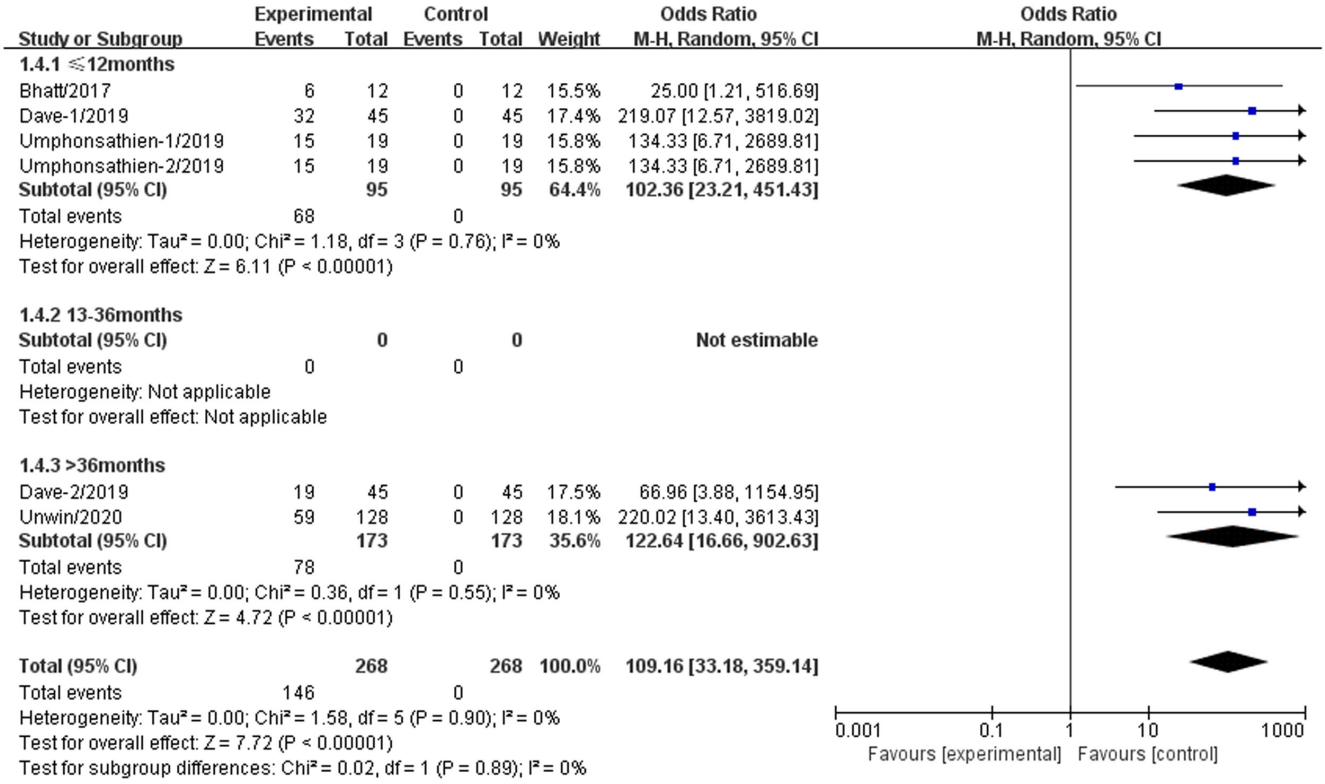

FIGURE 5 Forest plot for diabetes remission (subgroup-quasi experimental studies)

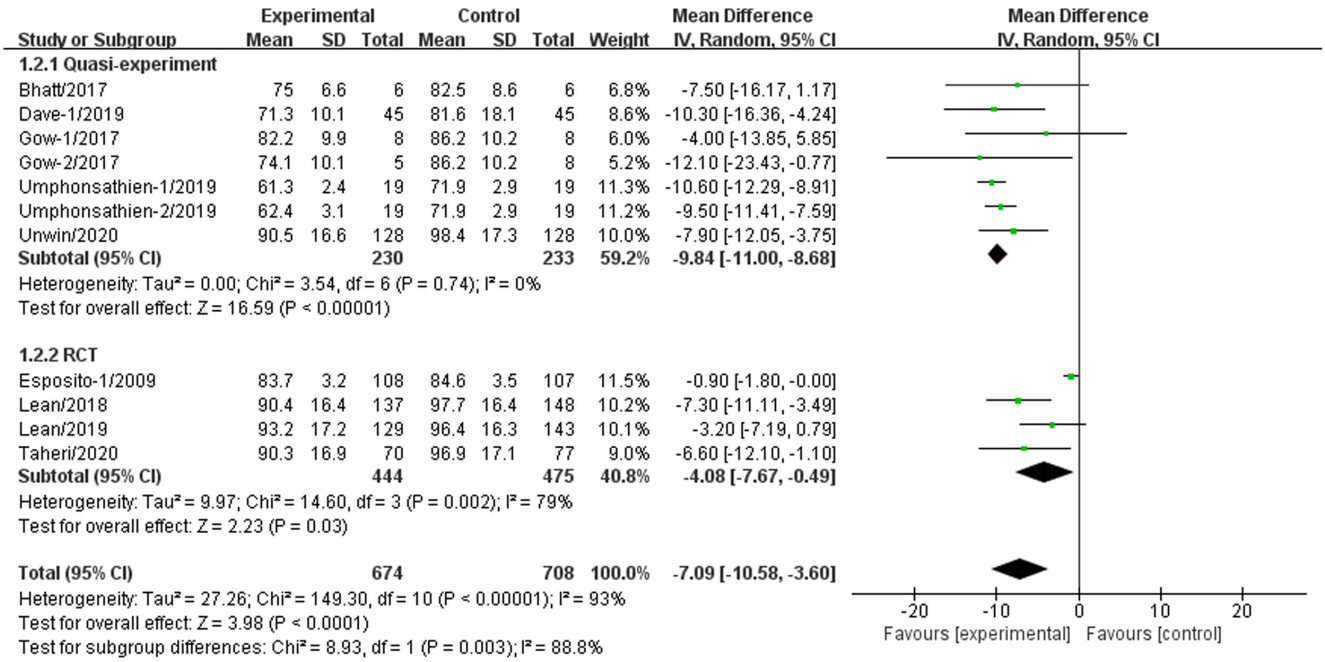

FIGURE 6 Forest plot for weight loss

function. However, timely effective measures (bariatric surgery, intensive insulin therapy, and lifestyle interventions) to reduce body weight to below the personal fat threshold before the irreversible loss of β cells may break the vicious cycle and restore β cells function, thus reversing the development of T2DM (Ding et al., 2020; Kramer et al., 2013). Compared with bariatric surgery and insulin therapy, lifestyle interventions are more widely applicable and non-invasive. This result indicates that lifestyle interventions focused on diet and physical activity may be effective interventions to achieve diabetes remission in T2DM. However, due to the small number of original

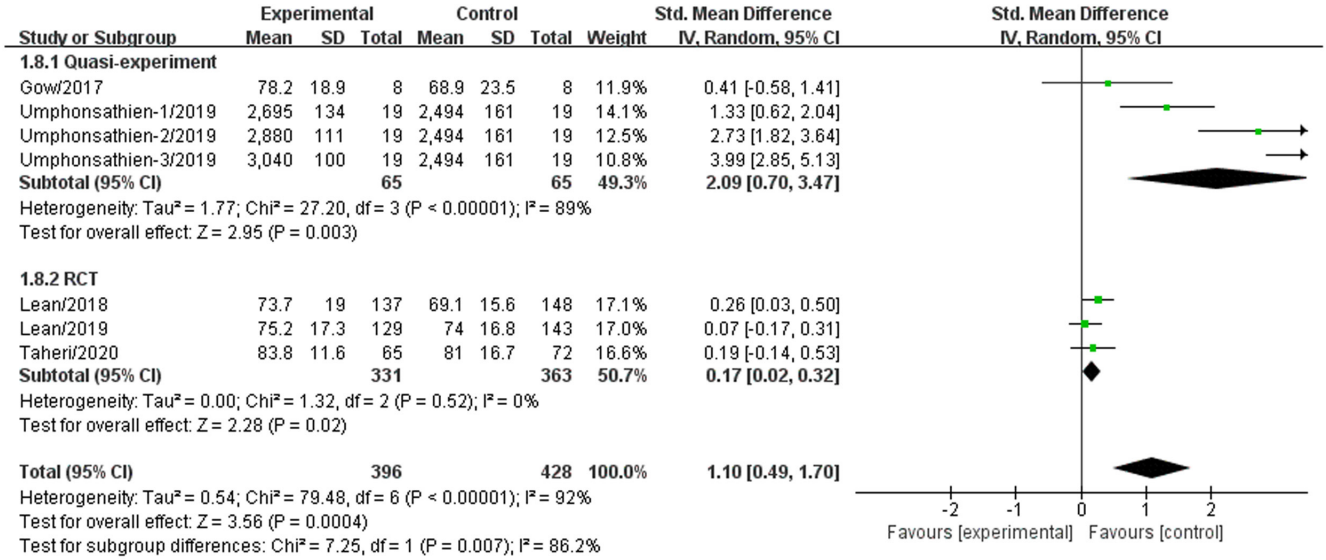

FIGURE 7 Forest plot for QoL. QoL, quality of life

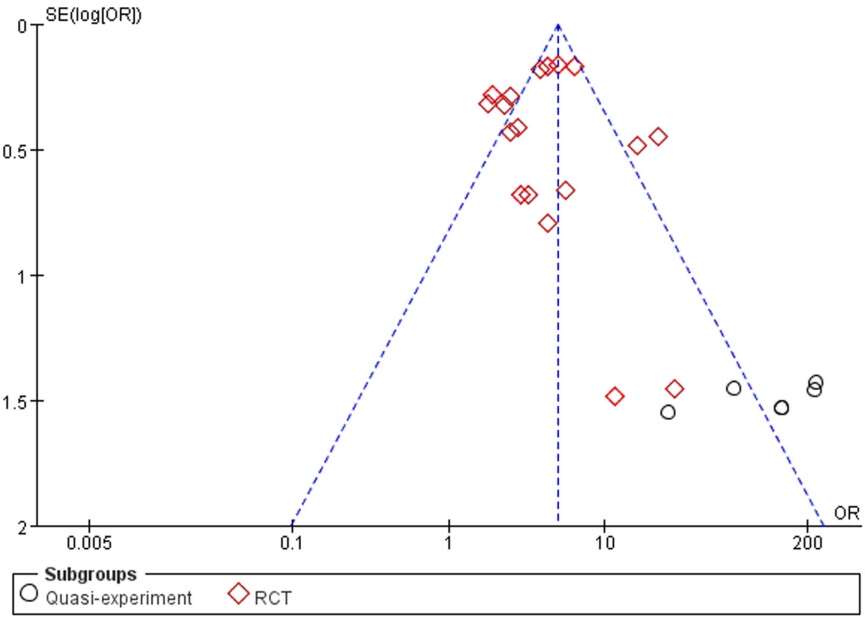

FIGURE 8 Funnel plot for publication bias (diabetes remission)

studies in subgroup analysis, more high-quality studies should be conducted in the future.

Lifestyle interventions exerted a positive impact on reducing weight. These effects were generally supported by previous studies. One synthesis by O'Donoghue et al. (2021) of 25 RCTs comparing lifestyle interventions with usual care found similar body weight reduction. Similarly, another synthesis by Michaud et al. (2021) of 17 randomized trials in T2DM found a reduction in weight. As for T2DM patients, weight loss is an important part of disease management. Reasonable lifestyle interventions are basic treatments for weight loss, which can help to maintain ideal weight and delay disease progression by adjusting total diet energy, diet structure, and meal allocation ratio. Therefore, tailored lifestyle interventions should be provided to those patients with T2DM.

According to the five studies included in the meta-analysis, patients in the intervention group had a higher QoL compared with the control group. However, through retrospective research, there were currently no studies evaluating the impact of lifestyle interventions on QoL in patients with T2DM. To our knowledge, only one systematic review that evaluated the effect of Tai Chi in T2DM patients on their QoL showed a similar result (Qin et al., 2021). Therefore, this suggests that lifestyle interventions may not only reduce weight and improve glycemia and other physiological indicators of T2DM patients, but also improve patients' QoL.

Limitations

This study was not without limitations. Firstly, there is no universally accepted definition of diabetes remission. Thus, we attempted to overcome this by using loose definitions of remission (blood glucose returned to normal after at least three months of discontinuation of hypoglycemic medication). Secondly, because of the wide range of age, disease duration, the length and frequency of intervention, and follow-up time, the results may be affected, so the results should be carefully considered. Thirdly, in the meta-analysis, we found that the results were very heterogeneous, so we used subgroup analysis to address this problem as far as possible. When we performed a subgroup analysis by study type (RCTs or quasi-experimental studies) and duration of follow-up (with ≤12 months, 13–36 months, and >3 months), the heterogeneity of partial outcomes was significantly reduced. Further research can reduce the influence of confounding factors through meta-regression. Fourthly, due to the nature of the intervention, as a result, it is difficult to blind the participants and implementers, so the result of the risk of bias could be affected. Finally, we only limited the language to English, which may lead to some publication bias.

Implications for practice

As lifestyle interventions are advantageous for patients with T2DM, this review suggests that medical workers are recommended to apply lifestyle interventions focused on diet and physical activity to help patients with T2DM achieve diabetes remission.

Linking evidence to action

- Based on the results of this study, lifestyle interventions were effective interventions for achieving diabetes remission, reducing weight, and improving quality of life in patients with T2DM.
- Lifestyle interventions focused on diet and physical activity may be effective interventions to achieve diabetes remission in T2DM.
- The content of the diet and physical activity could be modified with different aims and local context.
- The findings may provide accurate evidence-based guidance for T2DM management.
- In the future, high-quality studies are needed to verify these results.

CONCLUSIONS

Besides the limitations, this study demonstrated that lifestyle interventions could achieve diabetes remission, reduce weight, and improve QoL when patients declined or withdrew their diabetes medication. The focus of lifestyle interventions should be diet and physical activity. Future research designs need to standardize the intervention plan and pay attention to reducing heterogeneity and publication bias as far as possible.

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CONFLICT OF INTEREST

No conflicts of interest are declared by the author(s).

PROSPERO REGISTRATION

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