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Title page

Title. Effectiveness of combined exercise on overweight or obese type 2 diabetes: a systematic review and meta-analysis

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Abstract

Objective. To synthesize the available scientific evidence on the effects of combined exercise on glycemic control, weight loss, insulin sensitivity, blood pressure, and serum lipids among overweight/obese patients with type 2 diabetes (T2D). **Design and Sample.** Relevant literature was retrieved from seven electronic databases to identify randomized controlled trials (RCTs) that reported the effects of combined exercise in overweight/obese individuals with T2D. **Methods.** The mean difference (MD) with its corresponding 95% confidence interval (CI) was used to estimate the effect size. Meta-analysis was performed using Review Manager 5.3. **Results.** A total of 10 RCTs with 978 participants were included in the meta-analysis. Pooled results demonstrated that combined exercise significantly reduced the concentration of hemoglobin A1c (MD=-0.16%, 95%CI: -0.28 to -0.05, P=0.006); body mass index (MD=-0.98 kg/m^2, 95%CI: -1.41 to -0.56, P<0.001); homeostasis model assessment of insulin resistance (MD=-1.19, 95%CI: -1.93 to -0.46, P=0.001); serum insulin (MD=-2.18 μIU/mL, 95%CI: -2.99 to -1.37, P<0.001); and diastolic blood pressure (MD=-3.24 mmHg, 95%CI: -5.32 to -1.16, P=0.002). **Conclusions.** Combined exercise exerted significant effects in improving glycemic control, influencing weight loss, and enhancing insulin sensitivity among overweight/obese patients with T2D.

Strengths and limitations of this study

► To our knowledge, this is the first systematic review and meta-analysis of RCTs investigating the effects of combined exercise on overweight/obese patients with T2D.

► A total of seven electronic databases were searched to provide a comprehensive range of studies.

► This study reports data on a range of factors including glycemic control, insulin sensitivity, weight loss, BP, and serum lipids, thereby providing a detailed comparison of the effects of combined exercise.

► Most included studies did not estimate the exercise adherence objectively, which is a vital variable to evaluate the implementation of exercise interventions.

► Although we performed subgroup analyses, the subgroup of <150 min/week in exercise duration and the subgroups of 3 weeks and 52 weeks in exercise intervention time were addressed in only one study, which may have caused the deviation of results.

Introduction

The number of patients with diabetes is increasing globally, with an estimated 463 million adults diagnosed with diabetes. This number is predicted to exceed 700 million by 2045.[1] Type 2 diabetes (T2D), characterized by hyperglycemia resulting from hyposecretion of insulin and/or insulin resistance, accounts for nearly 90% of all types of diabetes.[1] Propelling the surge of diabetes is the growing prevalence of overweight and obesity. Data from the World Health Organization[2] shows that nearly 2 billion adults are overweight and more than half a billion worldwide are obese. Furthermore, obesity accounts for 50.9–98.6% of adults with T2D in Europe and 56.1% in Asia.[3] Overweight and obesity contribute to the increasing development of cardiovascular disease (CVD), cancer, T2D, hypertension, dyslipidemia, and mental health

disorders. The coexistence of excess body weight and diabetes further aggravates the quality of life of individuals and imposes a tremendous burden on the healthcare system. Although there are several available treatment options targeting individuals with either T2D or excess weight, not many options are available for those with T2D and overweight/obesity. Measures to support individuals to optimize glycemic control and weight management remain elusive.

Physical activity (defined as all body movement that increase energy use) and exercise (defined as a structured form of physical activity)[4] have been recommended as the key components of lifestyle management for patients with T2D and overweight/obesity. Compelling evidence shows that aerobic exercise has an active effect on receptor affinity (adipose tissue, skeletal muscle, and insulin receptors), thereby inducing insulin sensitivity and glucose homeostasis.[1 5 6] Resistance exercise can enhance muscle strength, which in turn improves insulin sensitivity and muscle rehabilitation.[5 6] Current national and international guidelines recommend that people with diabetes should perform combined exercise, which integrates both aerobic (at least 150 min per week of moderate-vigorous aerobic activities) and resistance exercise (two sessions per week at least 60 min).[6] However, in reality, the adoption rate of the combined exercise is quite low, and the combined modes have the potential to become excessively burdensome. Moreover, it remains unclear whether the combined exercise modes can exert benefits on glycemic control and body weight among individuals with T2D and overweight/obesity.

Therefore, the aim of this systematic review and meta-analysis is to synthesize the best available evidence and explore the effectiveness of combined exercise on glycemic control,

weight loss, insulin sensitivity blood pressure (BP), and serum lipids among overweight/obese T2D patients.

Materials and Methods

Inclusion and exclusion criteria

Eligibility was defined according to the PICOs (Patient, Intervention, Comparison, Outcome) framework:

Type of participants:

(1) T2D patients aged ≥18 years; (2) overweight or obesity was indicated by body mass index (BMI) (BMI≥25 kg/m^2 for Caucasians or BMI≥23 kg/m^2 for Asian subjects).[7]

Type of intervention and comparison:

(1) included an intervention group of combined form of exercise, which included both aerobic (e.g., jogging, running, cycling, brisk walking) and resistance (e.g., push-ups, abdominal crunch, chest press, leg press, squats knee extensions) exercise with predefined intensity, frequency, and duration; (2) exercise intervention time ≥3 weeks;[7] and (3) potential comparison groups included placebo, any format of exercise intervention, or usual care.

Outcomes:

Primary outcomes included hemoglobin A1c (HbA1c) and BMI at the data collection timepoint. Secondary outcomes included serum insulin, homeostasis model assessment of insulin resistance (HOMA-IR), systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-

density lipoprotein cholesterol (LDL-C), or psycho-behavioral outcomes such as exercise performance, muscle strength or performance, exercise adherence, exercise self-efficacy, emotional well-being, anxiety, depression, and objective measures (e.g., pedometers or accelerometers).

Type of studies:

Randomized controlled trials (RCTs).

Exclusion criteria:

Studies were excluded if (1) participants were diagnosed with type 1 diabetes or gestational diabetes; (2) participants suffered from severe complications that impeded exercise engagement, such as acute infection, diabetic foot, diabetes ketoacidosis, severe hepatorenal insufficiency, diabetic retinopathy, or obstacle of limb movement; (3) vague description of exercise intervention in terms of time and type; and (4) full texts were not available.

Search strategy and literature selection

The literature retrieval was performed in major English and Chinese electronic databases, including PubMed, EMBASE, Web of Science, the Cochrane library, WANFANG, CNKI, and SinoMed from inception through April 2020. The reference lists of eligible publications were also retrieved to identify additional eligible studies. Keywords with the combination of medical subject heading terms were used in the search strategy: aerobic, exercise, training, isometric exercise, physical activity, physical exercise, resistance, strength training, strength exercise, weight lifting, weight bearing, combined exercise, diabetes, DM, T2D, NIDDM, overweight, obese, obesity, body mass index, BMI, body weight, and adiposity. After removing duplicate

records, two reviewers independently selected potential articles by assessing titles and abstracts. Then, full texts were further screened to identify the eligibility; at this stage, the two reviewers checked whether the participants were human subjects with T2D and overweight/obese instead of animal model studies or people without T2D and overweight/obesity, and they eliminated articles that had no desired results shown in the inclusion criteria. Any disagreements or discrepancies regarding the selection of potential studies were resolved through discussion, and a third reviewer was consulted in case of any disagreement.

Data extraction

Two reviewers independently extracted details of the included studies using a structured data extraction form, including the study design, sample size, exercise intervention details, data collection time points, participant characteristics, and outcomes (Table 1). Any disagreements or discrepancies regarding data extraction were resolved through discussion, and a third reviewer was consulted in case of any disagreement.

Quality assessment

The risk of bias of included studies was assessed using the Cochrane Collaboration's Risk of Bias assessment tool.[9] The quality of studies was judged to be with low, unclear, or high risk of bias.

Data analysis

All analyses were performed using RevMan5.3 (Cochrane Collaboration, http://ims.cochrane.org/revman). Heterogeneity was assessed using Cochran's Q statistic and I^2-test. A random effect model was applied to calculate the pooled results if $I^2 \geq 50\%$; otherwise, a

fixed effect model was used. Subgroup analyses on primary outcomes stratified by exercise duration per week, exercise frequency, and the time of exercise intervention were conducted, respectively. The mean difference (MD) with its corresponding 95% confidence interval (CI) was used to calculate the effect size. A two-sided $p<0.05$ was considered to indicate statistical significance.

Patient and public involvement

No patient involved.

Results

Search outcome

A total of 10,342 records were identified. After duplicate deletion, 8,140 articles were screened for titles and abstracts, and 50 articles were further screened for full-text. Finally, 10 studies were deemed eligible and included in this meta-analysis (Figure 1).

An overview of the characteristics of included studies is summarized in Table 1. Across the included studies, the sample size ranged from 20 to 606; the intervention duration ranged from 3 to 52 weeks; the mean (SD) age of participants was similar across the included studies (range: 53.6 [9.1]–66.6 [7.5]) years; the mean (SD) HbA1c ranged from 6.44 (0.33) to 9.50 (0.90); and the mean (SD) BMI ranged from 28.15 (3.72) to 39.9 (7.3) kg/m^2.

Quality of the included studies

Figure 2 shows the quality assessment of the included studies: six studies were judged to have a low risk of bias,[11 12 13 16 17 18] while the remaining four studies showed uncertain risk of

Table 1. characteristics of the included studies.

Author Year	Country	Sample size (EX/CON)	Combined exercise intervention							Control	Time points of data collection（week）	Participant characteristics			Dropout rate (%)	Outcomes	Adverse events
			Exercise format	Supervision/ Facilitator	Exercise type	Intensity	Frequency (Days/week)	Duration /session (min)	Intervention time (week)			Age（year）	BMI (kg/m^2)	T2D duration（years）			
AminiLari 2017	Iran	30 (15/15)	Center-based and group-based: each exercise session consisted of three phases--warm up, the main stage and a cool-down period	NR/NR	AE: cycle ergometer RE: leg extension, prone leg curl, abdominal crunch	AE: 50%-55% of HR_{max} RE: 50%-55% 1 RM	3	45-70	12	NR	0,12	45-60	EX 29.01±2.57 CON 28.15±3.72	＞2	6.67	HOMA-IR, BMI	NR
Balducci 2010a	Italy	606 (303/303)	Center-based and group-based: in metabolic fitness center	Yes/Exercise specialist	AE: treadmill, step, elliptical, cycle ergometer RE: 4 resistance exercises (eg, chest press, lateral pull down, leg press, trunk flexion for the abdominals) and 3 stretching position standard care: same as control group	Low~high intensity	2	75	48	Standard care (counseling and diet management) Counseling: encouraging any type of commuting, occupational, home and leisure time physical activity, counseling was reinforced every 3 months; Diet management: caloric intake reduction, adherence to diet was verified by using food diaries, and dietary prescriptions were adjusted at each intermediate visit.	0,48	EX 58.8±8.6 CON 58.8±8.5	EX 31.2±4.6 CON 31.9±4.6	6(3–10)	7.10	HbA1c, HOMA-IR, SBP, DBP, TG, TC, HDL-C, LDL-C, BMI	Shoulder pain, low back pain, Aggravation of pre-existing osteoarthritis, musculoskeletal discomfort
Balducci 2010b	Italy	42 （22/20）	Center-based and group-based: NR	Yes/NR	AE: treadmill, cycloergometer RE: 4 resistance exercises (eg, chest press, lateral pull down, leg press, trunk flexion for the abdominals) and 3 stretching position Dietary prescriptions	AE: 70-80% VO_{2max} RE: 80% 1 RM	2	60	48	Dietary prescriptions	0,12,24, 36,48	EX 60.6±9.3 CON 61.1±7.1	EX 30.5±0.9 CON 30.9±1.1	EX 8.5±5.7 CON 7.8±5.2	4.76	HbA1c, HOMA-IR, SBP, DBP, TG, TC, HDL-C, LDL-C, BMI	Musculo-skeletal injury

Author Year	Design Country	Sample size (EX/CON)	Exercise intervention							Control	Time points of data collection（week）	Participants characteristics			Dropout rate (%)	Outcomes	Adverse events
			Exercise format	Supervision/ Facilitator	Exercise type	Intensity	Frequency (Days/week)	Duration /session (min)	Intervention time (week)			Age（year）	BMI (kg/m^2)	T2D duration（years）			
Bjorgaas 2005	Norway	29 (15/14)	Center-based and group-based: each exercise session consisted of three phases--warm up, the main stage, a cool-down and stretching period	Yes/Physio-therapist	AE: light jogging, co-ordination exercises, knee bends and stretching RE: NR Diet information: same as control group	50–85% HR_{max}	2	90	12	Diet information: a plenary session by a clinical nutritionist	0,12	EX 57.9±8.0 CON 56.9±7.8	EX 31.7±2.6 CON 31.8±3.0	EX 2.5 (0.1-17) CON 1.5 (0.1-15)	10.34	HbA1c, SBP, DBP	Achilles tendinitis
Leehey 2016	USA	36 （18/18）	Participants underwent 12 weeks of center-based exercise followed by 40 weeks of home-based exercise. Center-based: developing an individualized exercise prescription Home-based and individual-based: patients received weekly phone calls and were encouraged to meet with their trainer on a monthly basis	Yes/ Trainer	AE: treadmill, elliptical trainer and cycle ergometer RE: using elastic bands, hand-held weights or weight machine Diet management: same as control group	AE: Interval RE: progressive	Center-based exercise: 3 Home-based exercise: 3or 6	Center-based exercise: 80-90 Home-based exercise: 60 (3 times) 30 (6 times)	52	Diet management: nutritional counseling session at baseline with 9 follow-up telephone calls	0,12,52	EX 65.4±8.7 CON 66.6±7.5	EX 36.2±4.8 CON 37.4±4.2	NR	11.11	HbA1c, SBP, TG, TC, HDL-C, LDL-C, BMI	Cardiovascular disease, cervical myelopathy

Author Year	Design Country	Sample size (EX/CON)	Exercise intervention							Control	Time points of data collection（week）	Participants characteristics			Dropout rate (%)	Outcomes	Adverse events
			Exercise format	Supervision/ Facilitator	Exercise type	Intensity	Frequency (Days/week)	Duration /session (min)	Intervention time (week)			Age（year）	BMI (kg/m^2)	T2D duration（years）			
Lucotti 2011	Italy	50 （30/20）	Center-based and group-based: in a hospital	Yes/ Physician	AE: row ergometer and bicycle ergometer RE: 5 exercises for the upper part of the body (arm curls, military press, push-ups, upright rowing, back extension) and 4 exercises for the lower part of the body (squats knee extensions, heel raises and bent knee sit-ups) Diet management: same as control group	AE: 70% HR_{max} RE：40–50% of 1RM	5	45	3	AE plus diet management: AE: 70%HR max 5days/wk,30min/session； Diet management: hypocaloric diet regime administered under a daily supervision of a dietician.	0,3	EX 61.5±11.5 CON 58.1±9.9	EX 39.9±7.3 CON 38.8±4.5	NR	6.00	HbA1c SBP, DBP, TG, TC, HDL-C, BMI	NR
Vinetti 2015	Italy	20 (10/10)	Center-based: in a hospital-based setting	Yes/ Trainer	AE: cycling on mechanically braked cycle ergometers RE: major muscle groups (upper limb, lower limb, chest, back and core), using calisthenics, repetitions with ankle weights, dumbbells and elastic bands Standard care: same as control group	AE：Interval RE：progressive	NR	55-85	48	Standard care: dietary regimen prescribed by the diabetologist	0,48	EX 60.56 ±5.94 CON 57.5±9.46	EX 29.65±4.08 CON 29.2±3.11	≥2	0	HbA1c, SBP, DBP, TG, TC, HDL-C, BMI	NR

Abbreviations: RCT, randomized controlled trial; T2D, type 2 Diabetes; EX, exercise group; CON, control group; AE, aerobic exercise; RE, resistance exercise; NR: not reported; CKD, chronic kidney disease; RM: repetition maximum; HR: heart rate; VO_{2max}: maximal oxygen consumption; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

bias. [10 14 15 19] The following were main sources of bias: lack of blinding of participants and personnel, absence of random sequence generation and allocation concealment, and incomplete outcome data. In summary, the quality of the included studies was considered as moderate risk of bias.

Pooled results

(1) Glycemic control (HbA1c)

Nine studies provided data about the effect of combined exercise on HbA1c. The pooled results showed the combined intervention significantly reduced the HbA1c level of participants, favoring the intervention group, as compared with the control group (MD=-0.16%, 95%CI: -0.28 to -0.05, P=0.006) (Figure 3).

(2) Weight loss (BMI)

Eight studies reported changes in BMI. The pooled results showed that combined exercise significantly reduced BMI in the intervention group than in the control group (MD=-0.98 kg/m^2, 95%CI: -1.41 to -0.56, P<0.001) (Figure 3).

(3) Insulin sensitivity (HOMA-IR, serum insulin)

Four of the 10 studies examined the effectiveness of combined exercise on HOMA-IR index. The pooled result revealed a significant reduction in HOMA-IR index favoring the intervention group (MD=-1.19, 95%CI: -1.93 to -0.46, P=0.001) (Figure 4).

Six studies examined the value of serum insulin. The difference in mean of serum insulin significantly favored the intervention group (MD=-2.18 μIU/mL, 95%CI: -2.99 to -1.37, P<0.001) (Figure 4).

(4) Blood pressure (SBP and DBP)

Eight of the 10 studies measured SBP and seven studies measured DBP. The pooled results showed no difference in SBP between the intervention and control groups (MD=-2.33 mmHg, 95%CI: -6.01 to 1.35, P=0.21); whereas, the result revealed a significant reduction in DBP favoring the intervention group (MD=-3.24 mmHg, 95%CI: -5.32 to -1.16, P=0.002) (Figure 5).

(5) Serum lipids (TG, TC, HDL-C, and LDL-C)

Seven studies measured the effectiveness of combined exercise on lipid profiles. The pooled results demonstrated that combined exercise had no significant effect on TG, TC, HDL-C, and LDL-C levels (TG: MD=-7.57 mg/dL, 95%CI: -16.42 to 1.28, P=0.09; TC: MD=-8.29 mg/dL, 95%CI: -22.18 to 5.60, P=0.24; HDL-C: MD= 2.69 mg/dL, 95%CI: -0.72 to 6.10, P=0.12; LDL-C: MD=0.14 mg/dL, 95%CI: -19.87 to 20.14, P=0.99) (Figure 6).

Subgroup analysis (exercise duration)

The results demonstrated that the combined exercise for a duration ≥150 min/week yielded a significant reduction in HbA1c (MD=-0.16%, 95%CI: -0.28 to -0.04, P=0.01) and BMI (MD=-1.35 kg/m^2, 95%CI: -2.02 to -0.69, P<0.001). The subgroup of <150 min/week favored the intervention group with a lower BMI concentration than the control group (150 min/week: MD=-0.80 kg/m^2, 95%CI: -1.39 to -0.21, P=0.008) (Table 2).

Subgroup analysis (exercise frequency)

The results showed that combined exercise with frequency <3 days/week significantly lowered the HbA1c (MD=-0.31%, 95%CI: -0.50 to -0.13, P<0.001) and BMI (MD=-1.03 kg/m^2, 95%CI: -1.49 to -0.57, P<0.001) (Table 2).

Table 2. Subgroup analyses on primary outcomes

Subgroups		HbA1c						BMI					
		Included study (n)	Sample size (EX)	Sample size (CON)	Mean Difference (95% CI)	*P*	I^2	Included study (n)	Sample size (EX)	Sample size (CON)	Mean Difference (95% CI)	*P*	I^2
Exercise duration (min/week)	<150	1	22	20	-0.28(-1.01, 0.45)	0.45	/	1	22	20	-0.80(-1.39, -0.21)	0.008	/
	≥150	5	343	341	-0.27(-0.44, -0.10)	0.002	0%	5	345	345	-1.10(-1.76, -0.44)	0.001	0%
Exercise frequency (days/week)	<3	3	321	306	-0.31(-0.50, -0.13)	<0.001	0%	2	310	295	-1.03(-1.49, -0.57)	<0.001	36%
	≥3	3	44	55	0.03(-0.45, 0.51)	0.90	0%	4	57	70	0.18(-1.34, 1.71)	0.81	0%
Intervention time (weeks)	3	1	20	27	0.40(-0.57, 1.37)	0.42	/	1	20	27	1.10(-2.43, 4.63)	0.54	/
	12	3	47	49	0.07(-0.49, 0.62)	0.81	0%	3	49	53	-0.29(-0.84, 0.27)	0.31	0%
	48	3	320	305	-0.31(-0.48, -0.13)	<0.001	0%	3	320	305	-1.02(-1.47, -0.56)	<0.001	0%
	52	1	14	18	0.50(-0.83, 1.83)	0.46	/	1	14	18	-0.40(-4.65, 3.85)	0.85	/

Abbreviations: EX, exercise group; CON, control group; CI = confidence intervals; I^2 = I-squared.

Subgroup analysis (exercise intervention time)

The results showed that combined exercise for 48 weeks significantly reduced the HbA1c (MD=-0.31%, 95%CI: -0.48 to -0.15, P<0.001) and BMI (MD=-1.06 kg/m^2, 95%CI: -1.52 to -0.62, P<0.001) in the intervention group as compared with the control group. (Table 2).

Discussion

The results from this meta-analysis showed that combined exercise was associated with a significant decline in HbA1c, BMI, HOMA-IR index, serum insulin, and DBP, indicating the important role of combined exercise in improving glycemic and weight control and enhancing insulin sensitivity among overweight/obese T2D patients. However, at this time, combined exercise had no effect on serum lipids.

Previous meta-analyses of exercise in diabetic patients with/without overweight/obesity have found a positive effect on glycemic control. Hou[20] assessed the effect of combined exercise compared with aerobic exercise among T2D patients. Their results showed a significant reduction of HbA1c by 0.31%, which was consistent with our finding that combined exercise decreased HbA1c by 0.16%. The meta-analysis by Zou[21] identified 13 eligible studies investigating the effect of exercise on obese T2D patients; moreover, the researchers performed subgroup analysis stratified by intervention time, suggesting that longer term exercise (48 weeks) achieved a pronounced reduction in HbA1c by 0.27%, a

magnitude similarity with our results that longer term combined exercise (48 weeks) decreased HbA1c by 0.31%.

Our result showed that combined exercise exerted a significant effect on insulin sensitivity on T2D patients with overweight/obesity, which was in line with the results of Thaane[22], wherein exercise appeared to improve insulin sensitivity among T2D adults with overweight/obesity. Way[23] also found that regular exercise had a significant benefit in insulin sensitivity on T2D adults. They concluded this by synthesizing the outcomes of clamps, insulin infusion sensitivity tests, insulin tolerance test, and oral glucose tolerance test. The results of Way[23] indicated that the durability of training-induced improvement in insulin sensitivity could persist beyond 72 h after the last exercise session. However, there was a potential heterogeneity by diverse measurement techniques in insulin sensitivity.

It is generally more difficult for diabetic patients to lose weight and/or maintain weight loss. The results of our study suggested that overweight/obese individuals with T2D who wish to lose weight should engage in combined exercise. Our results showed that combined exercise achieved a pronounced decrease in BMI among overweight/obese adults with T2D. Previous reviews also showed the effect of combined exercise on weight-loss by using other obesity indicators. The review by Hou[20] showed that combined exercise significantly reduced subcutaneous and visceral adipose tissue; the results of Pan[24] showed that combined exercise safely accentuated reduction in body weight; while the results of Thaane[22] suggested that short-term exercise training exerted no significant effect in body weight, BMI, and body fat.

Cardiovascular disease was one of the leading reasons for frequent medical consultation

and rehospitalization for adults with T2D and overweight/obesity.[25] BP and serum lipids are vital risk factors for CVD, and the importance of managing and maintaining blood pressure and cholesterol levels has been emphasized by the ADA guideline.[26] Evidence has shown the benefits of simultaneous control of HbA1c, BP, and lipid levels. Our study found that combined exercise had no effect on SBP and serum lipids, which was contradictory with the finding of Albalawi[27] and Bersaoui[28], which reported that combined exercise was related to a statistically significant decline in BP and lipid control among T2D patients. The possible reason for the discrepancy may be related to the differences of participants' characteristics. In the current meta-analysis, participants had T2D and were overweight or obese. Compared with patients with normal weight, overweight and obese patients were less likely to engage in self-management activities and maintain therapeutic lifestyles[29]. Hence, T2D patients with overweight/obesity were more likely to have poor BP and lipid control. More strategies need to be explored to facilitate patients with T2D and overweight/obesity to simultaneously manage HbA1c, BP, and cholesterol levels.

It is generally well-accepted that increasing the exercise duration per week is associated with greater long-term health benefits.[30] We found that combined exercise showed a pronounced benefit on HbA1c and BMI reduction when exercise duration ≥150 min /week, which is in line with the finding of Umpierre.[31] Figueira[32] also found that it was beneficial to perform exercise for >150 min/week to magnify the effect of BP reduction. We also found that combined exercise exerted a significant effect on weight loss (BMI) when exercise duration <150 min/week. The plausible explanation would seem to be that weight loss is

influenced by various elements such as diet, regular exercise, pharmacologic therapy, and frequent contact with health professionals.[1 23] Furthermore, the subgroup of <150 min/week exercise only included one study, which may have caused the deviation of results.

Exercise frequency is a major determinant of glycemic control in T2D patients.[33 34] Our study showed that combined exercise had significant effects on HbA1c and BMI only when performed <3 days/week. We would attribute such results to fundamental differences between studies of the subgroups of <3 days/week and ≥3 days/week. More specifically, most researches in the subgroup of <3 days/week performed long-term (48 weeks) and supervised exercise. It is also important to mention that because supervised exercise is associated with greater improvement of glycemic and weight control,[24] Balducci[11 12] even considered physical activity counseling and diet adherence, thus making exercise intervention more efficient. However, in the subgroup of ≥3 days/week exercise, subjects in some studies[10 17] performed short-term exercise, which was likely underpowered to detect a difference in outcomes.

Our finding showed that combined exercise for 48 weeks exerted significant effects on glycemic control and weight loss, which was consistent with the results of Franz,[35] in that physical activity and/or diet had a beneficial effect on glycemic control and weight loss at 12 months. However, our results revealed that combined exercise for 52 weeks had no effect on either HbA1c or BMI. A likely explanation is that participants in the subgroup of 52 weeks suffered from chronic kidney disease and might therefore not exercise effectively, which could lead to an attenuation of the difference between the intervention and control groups. On

the other hand, it is also essential to consider that compliance with exercise regimens would reduce in the long term, thus reducing the effect of exercise on clinical outcomes.

Direction for future research and practice

Considering the benefits of combined exercise, it might be helpful to recommend combined exercise for T2D patients with overweight/obesity to improve glycemic and weight control and decrease insulin resistance. We also recommend long exercise duration (≥150 min/week) to magnify the effect. Physical activity counseling, psycho-educational interventions, mobile technologies, and peer support groups could be integrated into the exercise to improve the adoption rate of combined exercise.[36] Although there are guideline recommendations for diabetic patients, there is little evidence to indicate the ideal exercise duration, exercise intensity, and exercise time that would be most appropriate for overweight/obese T2D patients. Whether frequent exercise and long intervention time of exercise proves beneficial for overweight/obese patients with T2D requires further investigation. According to the features of effective exercise interventions on glycemic and weight control among included studies, most researches performed center-based exercise with supervision. Hence, we recommend this kind of intervention in future studies to achieve greater metabolic effects. Objective measures such as pedometers and accelerometers should be utilized to assess the exercise level more accurately.

Conclusions

This systematic review provides useful information for the clinical application of combined exercise in the management of overweight/obese patients with T2D. The results

show clear evidence that combined exercise intervention has positive effects on improving glycemic and weight control, thus enhancing insulin sensitivity among overweight or obese T2D patients. We recommend an exercise duration of >150 min/week to magnify the effect. More RCTs with robust methodological design, large sample size, and more comprehensive body composition measurements are needed to elaborate the mechanisms and strengthen this conclusion. This review also highlights the need for further RCTs to investigate the ideal exercise duration, exercise intensity, and exercise time for overweight/obese T2D patients.

Contributors XZ, QH, YZ, LC conceived the research; XZ, QH, YZ, LC established eligibility criteria and Search strategy; XZ, QH worked on literature selection, data extraction and quality assessment; XZ, QH, LC performed statistical analysis; XZ wrote paper; XZ, LC had primary responsibility for final content; All authors read the manuscript and approved the final draft.

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Competing interests None declared.

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Figure Captions

Figure 1 Flow chart for study selection according to PRISMA Declaration 2009

Figure 2 Quality assessment of the included studies. (A) as percentages across all included

studies in risk of bias graph; (B) Bias risk of the included studies. "+" indicates Low risk of bias; "?"represents unclear risk of bias; "−" indicates high risk of bias.

Figure 3 Comparison of HbA1c and body mass index (BMI) between intervention group and control group in overweight or obese T2D patients. (A) Forest plot of HbA1c; (B) Forest plot of BMI; Unit of HbA1c is "%". Unit of BMI is "kg/m^2".

Figure 4 Comparison of homeostasis model assessment of insulin resistance (HOMA-IR) and serum insulin between intervention group and control group in overweight or obese T2D patients. (A) Forest plot of HOMA-IR; (B) Forest plot of serum insulin. HOMA-IR has no units. Unit of serum insulin is "μIU/mL".

Figure 5 Comparison of systolic blood pressure (SBP) and diastolic blood pressure (DBP) between intervention group and control group in overweight or obese T2D patients. (A) Forest plot of SBP; (B) Forest plot of DBP. Units of SBP and DBP are both "mmHg".

Figure 6 Comparison of triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) between intervention group and control group in overweight or obese T2D patients. (A) Forest plot of TG; (B) Forest plot of TC; (C) Forest plot of HDL-C; (D) Forest plot of LDL-C. Units of TG, TC, HDL-C and LDL-C are "mg/dL".

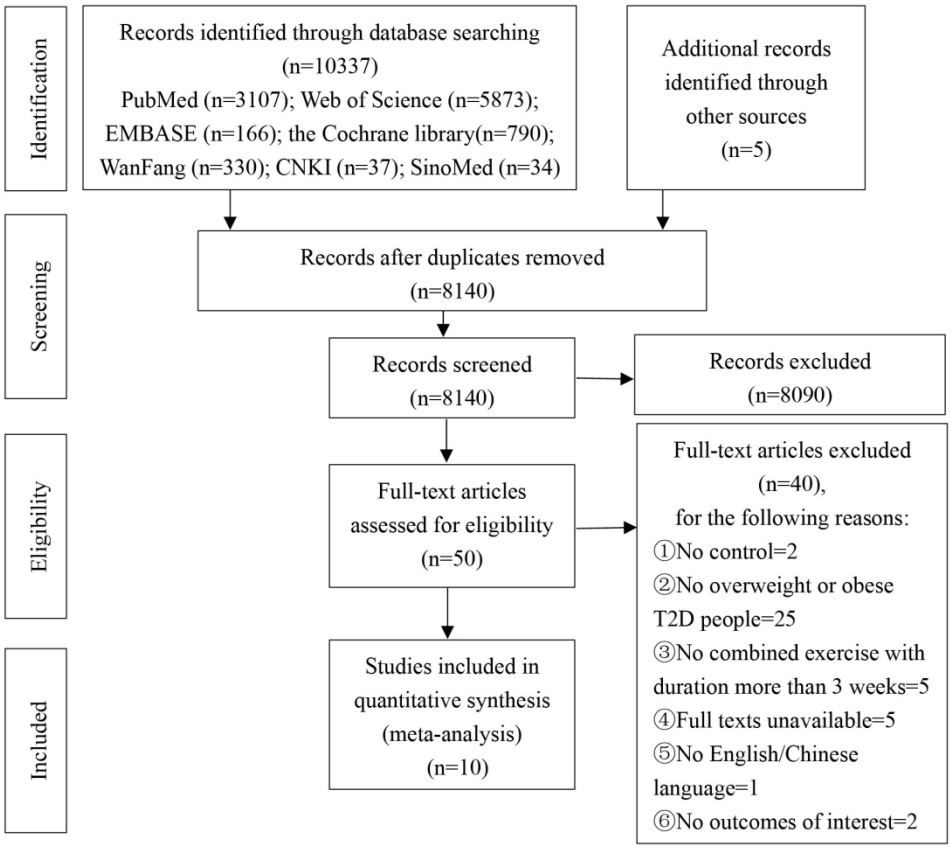

Figure 1 Flow chart for study selection according to PRISMA Declaration 2009

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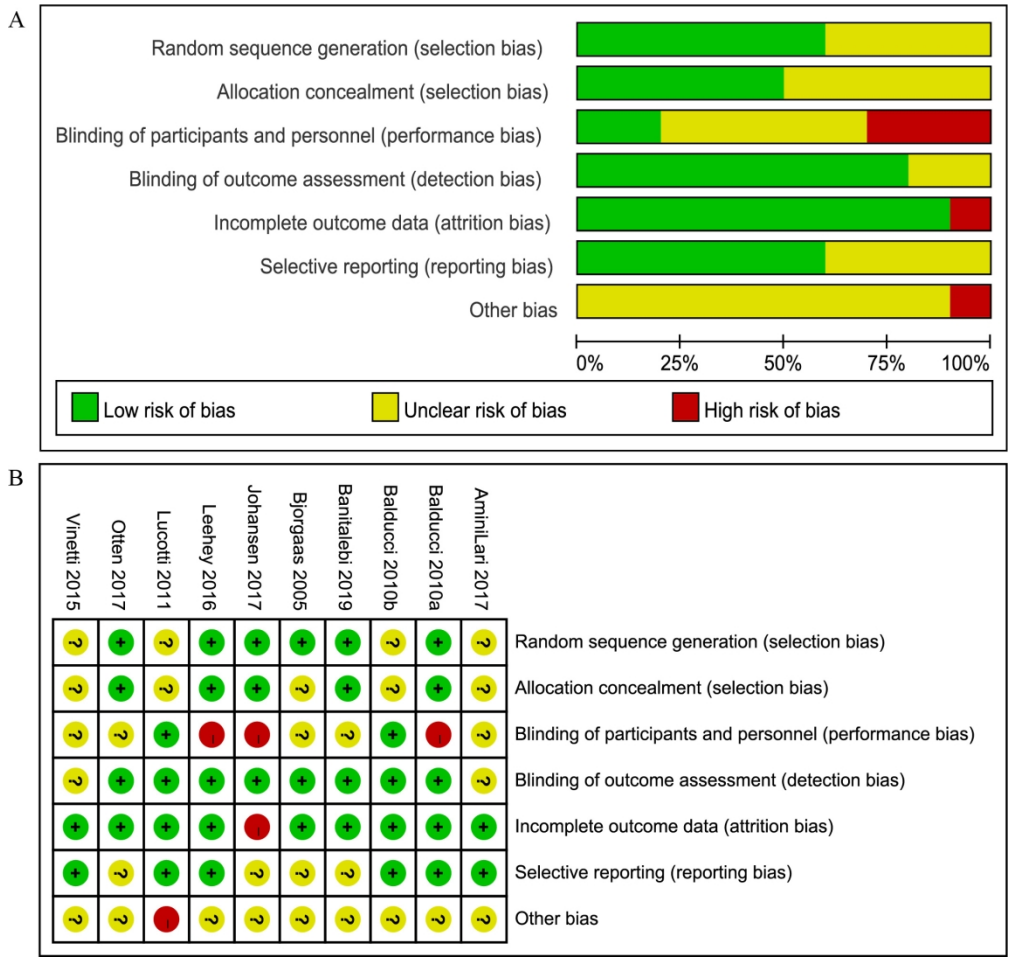

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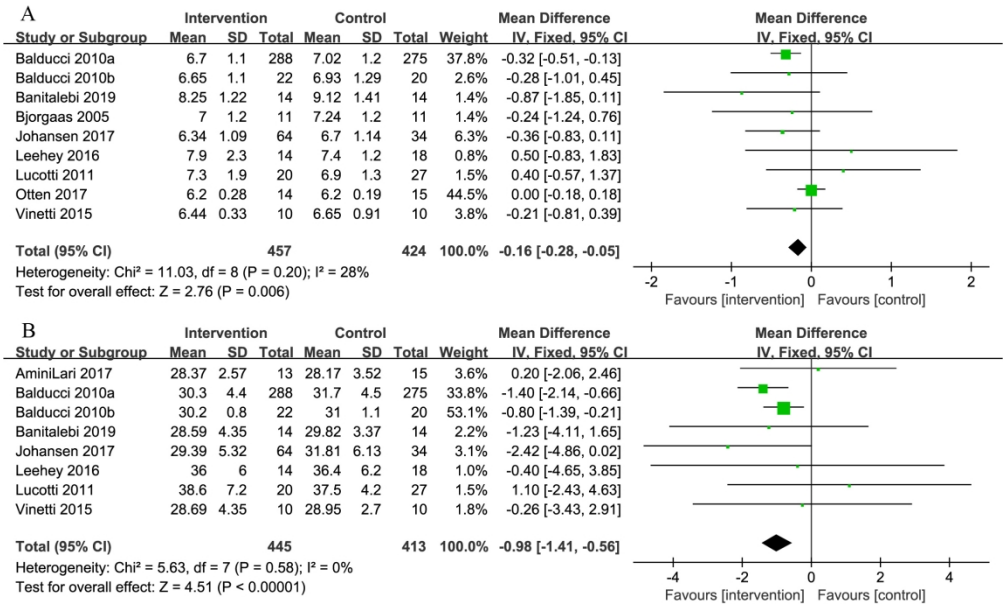

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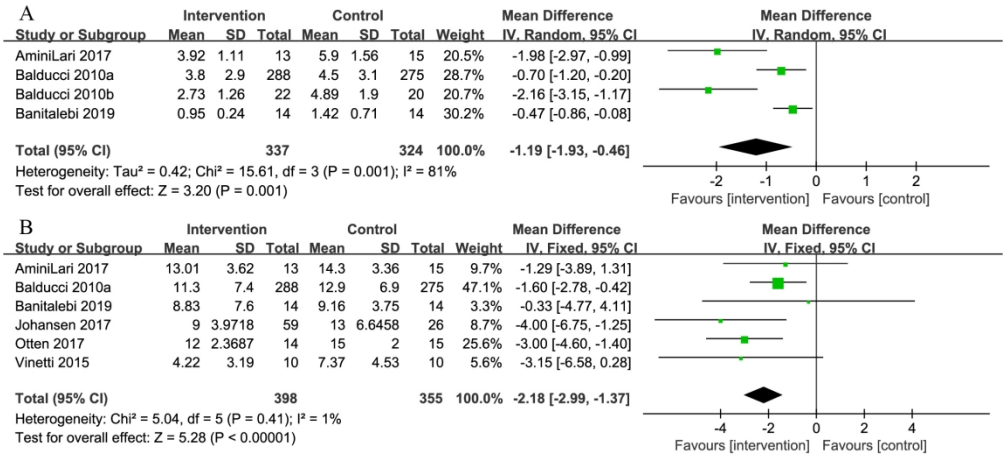

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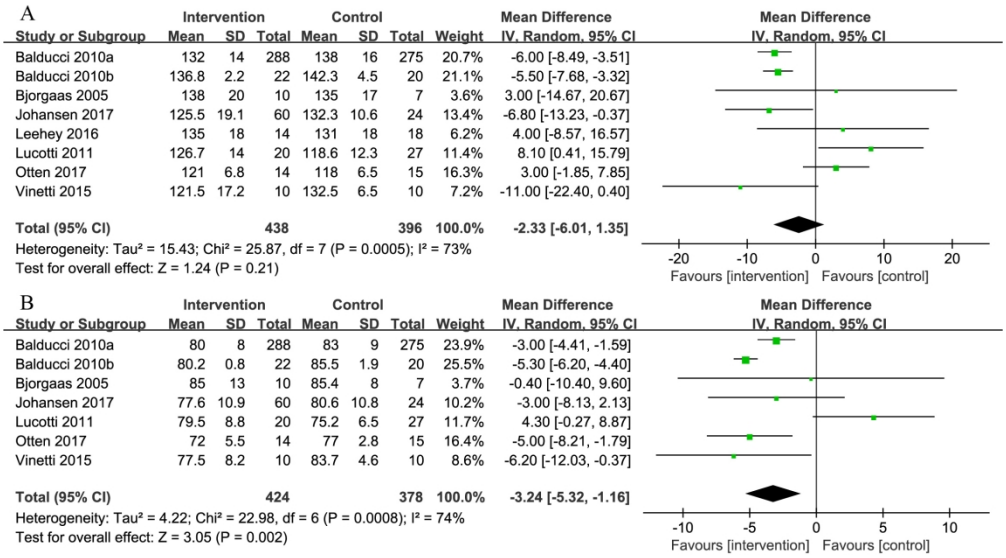

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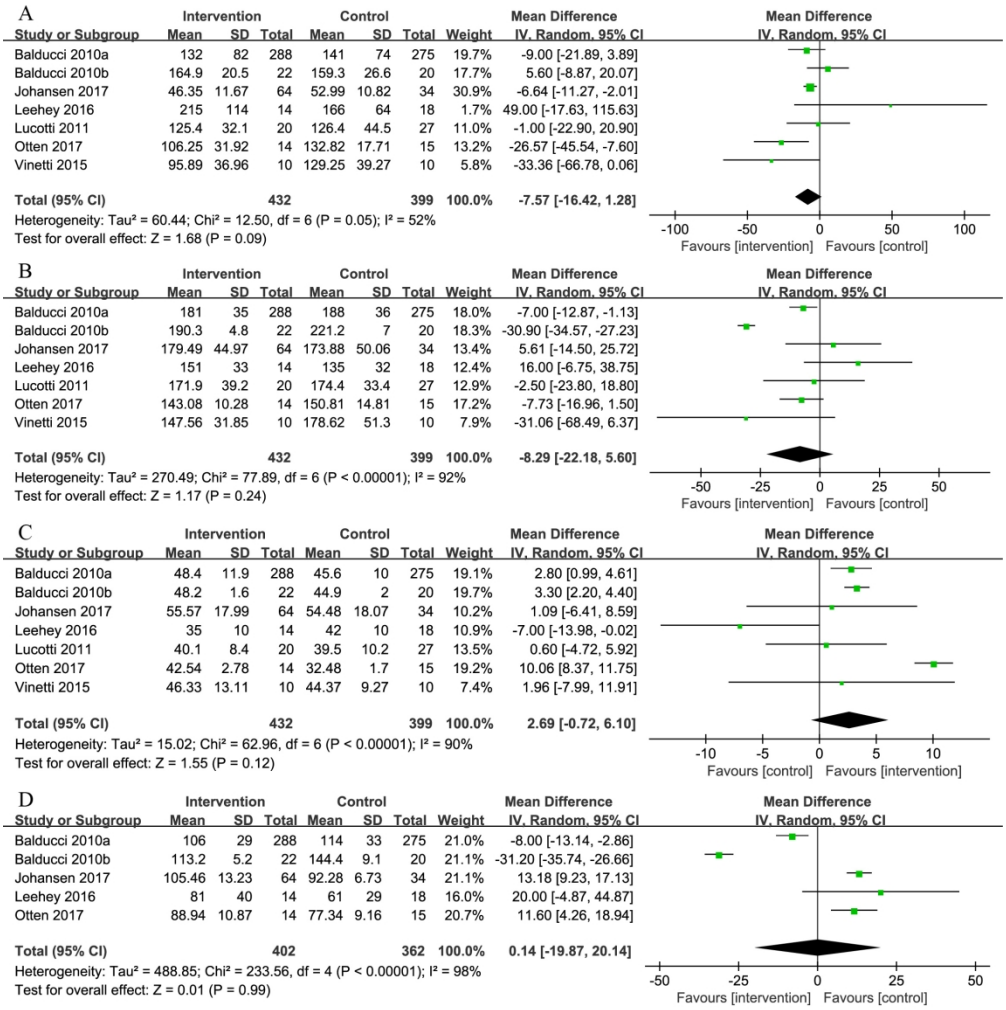

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PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Reported on page #
Administrative information			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Not applicable*
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 21
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 21
Sponsor	5b	Provide name for the review funder and/or sponsor	Page 21

Section and topic	Item No	Checklist item	Reported on page #
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Not applicable
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 5
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 6-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 7-8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 7
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 8

Section and topic	Item No	Checklist item	Reported on page #
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 6-7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 6-7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Page 8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Not applicable
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 9

Section and topic	Item No	Checklist item	Reported on page #
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 8

*The protocol is described in the Methods. Registration does not apply.

BMJ Open

Effectiveness of combined exercise in people with type 2 diabetes and concurrent overweight/ obesity: a systematic review and meta-analysis

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Secondary Subject Heading:	Sports and exercise medicine
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, MEDICAL EDUCATION & TRAINING, PUBLIC HEALTH

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Title page

Title. Effectiveness of combined exercise in people with type 2 diabetes and concurrent overweight/ obesity: a systematic review and meta-analysis

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Keywords. Diabetes, Type 2; Combined exercise; Obesity; Overweight.

Word count. 3,049

Abstract

Objective. To synthesize the available scientific evidence on the effects of combined exercise on glycemic control, weight loss, insulin sensitivity, blood pressure, and serum lipids among patients with type 2 diabetes (T2D) and concurrent overweight/obesity. **Design and Sample.** PubMed, EMBASE, Web of Science, the Cochrane library, WANFANG, CNKI, SinoMed, OpenGrey, and ClinicalTrials.gov were searched from inception through April 2020 to identify randomized controlled trials (RCTs) that reported the effects of combined exercise in individuals with T2D and concurrent overweight/obesity. **Methods.** Quality assessment was performed using the Cochrane Collaboration's risk of bias tool. The mean difference (MD) with its corresponding 95% confidence interval (CI) was used to estimate the effect size. Meta-analysis was performed using Review Manager 5.3. **Results.** A total of 10 RCTs with 978 participants were included in the meta-analysis. Pooled results demonstrated that combined exercise significantly reduced hemoglobin A1c (MD=−0.16%, 95%CI: −0.28 to −0.05, P=0.006); body mass index (MD=−0.98 kg/m^2, 95%CI: −1.41 to −0.56, P<0.001); homeostasis model assessment of insulin resistance (MD=−1.19, 95%CI: −1.93 to −0.46, P=0.001); serum insulin (MD=−2.18 μIU/mL, 95%CI: −2.99 to −1.37, P<0.001); and diastolic blood pressure (MD=−3.24 mmHg, 95%CI: −5.32 to −1.16, P=0.002). **Conclusions.** Combined exercise exerted significant effects in improving glycemic control, influencing weight loss, and enhancing insulin sensitivity among patients with T2D and concurrent overweight/obesity.

Strengths and limitations of this study

►This study provided a comprehensive assessment of the effect of combined exercise in patients with T2D and concurrent overweight/obesity.

►Nine electronic databases were searched to provide a comprehensive range of studies.

►Because of strict inclusion and exclusion criteria, potential selection bias was minimized.

►A limitation is the substantial heterogeneity among the included studies.

►There were insufficient data to undertake subgroup analyses for some types of tests.

Introduction

The number of patients with diabetes is increasing globally, with an estimated 463 million adults diagnosed with diabetes. This number is predicted to exceed 700 million by 2045.[1] Type 2 diabetes (T2D), characterized by hyperglycemia resulting from hyposecretion of insulin and/or insulin resistance, accounts for nearly 90% of all types of diabetes.[1] Propelling the surge of diabetes is the increasing prevalence of overweight and obesity. Data from the World Health Organization[2] show that nearly 2 billion adults are overweight and more than half a billion worldwide are obese. Furthermore, obesity accounts for 50.9–98.6% of adults with T2D in Europe and 56.1% in Asia.[3] Overweight and obesity contribute to the development of cardiovascular disease, cancer, T2D, hypertension, dyslipidemia, and mental health disorders. The coexistence of excess body weight and diabetes further aggravates the quality of life of individuals and imposes a tremendous burden on the healthcare system. Although various exercise options are available for individuals with either T2D or excess weight, individuals with

T2D and concurrent overweight/obesity receive little attention. Measures to support individuals to optimize glycemic control and weight management remain elusive.

Physical activity (defined as all body movement that increases energy use) and exercise (defined as a structured form of physical activity)[4] have been recommended as the key components of lifestyle management for patients with T2D and concurrent overweight/obesity. Combined exercise involves aerobic exercise (repeated and continuous movement of large muscle groups when oxygen supply is sufficient) and resistance exercise (a strength-training workout that uses some form of resistance or tension) performed within the same or separate exercise sessions of a training program.[5 6] Compelling evidence shows that aerobic exercise has an active effect on receptor affinity (adipose tissue, skeletal muscle, and insulin receptors), thereby inducing insulin sensitivity and glucose homeostasis.[1 7 8] Resistance exercise can enhance muscle strength, insulin sensitivity and muscle rehabilitation.[7 8] Current national and international guidelines recommend that people with diabetes should perform combined exercise, integrating both aerobic (at least 150 min per week of moderate-vigorous aerobic activities) and resistance exercise (two sessions per week at least 60 min).[8 9] However, in reality, the adoption rate of combined exercise is quite low, and the combined modes have the potential to become excessively burdensome. Moreover, it remains unclear whether the combined exercise modes can exert benefits on glycemic control and body weight among individuals with T2D and concurrent overweight/obesity.

Therefore, the aim of this systematic review and meta-analysis is to synthesize the best available evidence and explore the effectiveness of combined exercise on glycemic control,

weight loss, insulin sensitivity, blood pressure (BP), and serum lipids among patients with T2D and concurrent overweight/obesity.

Materials and Methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[10]

Inclusion and exclusion criteria

Eligibility was defined according to the PICOs (Patient, Intervention, Comparison, Outcome) framework:

Type of participants:

(1) T2D patients aged ≥18 years; (2) overweight or obesity indicated by body mass index (BMI) (BMI≥25 kg/m^2 for Caucasians or BMI≥23 kg/m^2 for Asian subjects).[11]

Type of intervention and comparison:

(1) Included an intervention group performing the combined form of exercise, which included both aerobic (e.g., jogging, running, cycling, brisk walking) and resistance (e.g., push-ups, abdominal crunch, chest press, leg press, squats, knee extensions) exercise with predefined intensity, frequency, and duration; (2) exercise intervention time ≥3 weeks;[12] and (3) potential comparison groups included any format of exercise intervention, general health counseling, or usual care.

Outcomes:

Primary outcomes included hemoglobin A1c (HbA1c) and BMI at the data collection

timepoint. Secondary outcomes included serum insulin, homeostasis model assessment of insulin resistance (HOMA-IR), systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), or psycho-behavioral outcomes such as exercise performance, muscle strength or performance, exercise adherence, exercise self-efficacy, emotional well-being, anxiety, depression, and objective measures (e.g., pedometers or accelerometers).

Type of studies:

Randomized controlled trials (RCTs).

Exclusion criteria:

Studies were excluded if (1) participants were diagnosed with type 1 diabetes or gestational diabetes; (2) participants suffered from severe complications that impeded exercise engagement, such as acute infection, diabetic foot, diabetes ketoacidosis, severe hepatorenal insufficiency, diabetic retinopathy, or obstacles to limb movement; (3) vague description of exercise intervention in terms of time and type; and (4) full texts were not available.

Search strategy and literature selection

The literature retrieval was performed in PubMed, EMBASE, Web of Science, the Cochrane library, WANFANG, CNKI, and SinoMed from inception through April 2020 for published studies; OpenGrey and ClinicalTrials.gov were also searched for unpublished studies. The reference lists of eligible publications were also retrieved to identify additional eligible studies. Keywords with the combination of medical subject heading (MeSH) terms were used in

the search strategy: aerobic, exercise, training, isometric exercise, physical activity, physical exercise, resistance, strength training, strength exercise, weight lifting, weight bearing, combined exercise, diabetes, DM, T2D, NIDDM, overweight, obese, obesity, body mass index, BMI, body weight, and adiposity (Supplementary file). After removing duplicate records, two reviewers independently selected potential articles by assessing titles and abstracts. Then, full texts were further screened to identify study eligibility; at this stage, the two reviewers checked whether the participants were human subjects with T2D and concurrent overweight/obesity instead of animal model studies or people without T2D and concurrent overweight/obesity, and they eliminated articles that had no desired results shown in the inclusion criteria. Any disagreements or discrepancies regarding the selection of potential studies were resolved through discussion, and a third reviewer was consulted in case of any disagreement.

Data extraction

Two reviewers independently extracted details of the included studies using a structured data extraction form, including the study design, sample size, exercise intervention details, data collection time points, participant characteristics, and outcomes (Table 1). Any disagreements or discrepancies regarding data extraction were resolved through discussion, and a third reviewer was consulted in case of any disagreement.

Quality assessment

The risk of bias of included studies was assessed using the Cochrane Collaboration's Risk of Bias assessment tool.[13] The quality of studies was judged to have low, unclear, or high risk of bias.

Data analysis

All analyses were performed using RevMan5.3 (Cochrane Collaboration, http://ims.cochrane.org/revman). Heterogeneity was assessed using Cochran's Q test and the I^2-test. A random effects model was applied to calculate the pooled results if $I^2 \geq 50\%$; otherwise, a fixed effects model was used. Subgroup analysis on primary outcomes stratified by exercise frequency was conducted. The mean difference (MD) with its corresponding 95% confidence interval (CI) was used to calculate the effect size. A two-sided $p<0.05$ was considered to indicate statistical significance.

Patient and public involvement

No patient involved.

Results

Search outcome

A total of 10,580 records were identified. After duplicate deletion, 8,383 articles were screened for titles and abstracts, and 50 articles were further screened for full text. Finally, 10 studies were deemed eligible and included in this meta-analysis (Figure 1).

An overview of the characteristics of included studies is summarized in Table 1. Across the included studies, the sample size ranged from 20 to 606; the intervention duration ranged from 3 to 52 weeks; the mean (SD) age of participants was similar across the included studies (range: 53.6 [9.1]–66.6 [7.5]) years; the baseline mean (SD) HbA1c ranged from 6.44 (0.33) to 9.50 (0.90); and the baseline mean (SD) BMI ranged from 28.15 (3.72) to 39.9 (7.3) kg/m^2.

Table 1. characteristics of the included studies.

Author Year	Country	Sample size (EX/CON)	Combined exercise intervention							Control	Time points of data collection（week）	Participant characteristics			Dropout rate (%)	Outcomes	Adverse events
			Exercise format	Supervision/ Facilitator	Exercise type	Intensity	Frequency (Days/week)	Duration /session (min)	Intervention time (weeks)			Age（year）	BMI (kg/m^2)	T2D duration（years）			
AminiLari 2017	Iran	30 (15/15)	Center-based and group-based: each exercise session consisted of three phases--warm up, the main stage and a cool-down period	NR/NR	AE: cycle ergometer RE: leg extension, prone leg curl, abdominal crunch	AE: 50–55% of HR_{max} RE：50–55% 1 RM	3	45-70	12	NR	0,12	45-60	EX 29.0±2.6 CON 28.2±3.7	＞2	6.7	HOMA-IR, serum insulin, BMI	NR
Balducci 2010a	Italy	606 (303/303)	Center-based and group-based: in metabolic fitness center	Yes/Exercise specialist	AE: treadmill, step, elliptical, cycle ergometer RE: 4 resistance exercises (eg, chest press, lateral pull down, leg press, trunk flexion for the abdominals) and 3 stretching position standard care: same as control group	Low~high intensity	2	75	48	Standard care (counseling and diet management) Counseling: encouraging any type of commuting, occupational, home and leisure time physical activity, counseling was reinforced every 3 months; Diet management: caloric intake reduction, adherence to diet was verified by using food diaries, and dietary prescriptions were adjusted at each intermediate visit.	0,48	EX 58.8±8.6 CON 58.8±8.5	EX 31.2±4.6 CON 31.9±4.6	6(3–10)	7.1	HbA1c, HOMA-IR, serum insulin, SBP, DBP, TG, TC, HDL-C, LDL-C, BMI	Shoulder pain, low back pain, Aggravation of pre-existing osteoarthritis, musculoskeletal discomfort
Balducci 2010b	Italy	42 （22/20）	Center-based and group-based: NR	Yes/NR	AE: treadmill, cycloergometer RE: 4 resistance exercises (eg, chest press, lateral pull down, leg press, trunk flexion for the abdominals) and 3 stretching position Dietary prescriptions	AE：70–80% VO_{2max} RE：80% 1 RM	2	60	48	Dietary prescriptions	0,12,24, 36,48	EX 60.6±9.3 CON 61.1±7.1	EX 30.5±0.9 CON 30.9±1.1	EX 8.5±5.7 CON 7.8±5.2	4.8	HbA1c, HOMA-IR, SBP, DBP, TG, TC, HDL-C, LDL-C, BMI	Musculo-skeletal injury
Banitalebi 2019	Iran	35 (17/18)	Center-based and group-based: in a hospital gym	Yes/Exercise physiologists	AE: treadmill, cycle ergometer RE: bilateral leg press, lateral pull down, bench press, bilateral biceps curl, and bilateral triceps push down	AE: 60–70% of HR_{max} RE：10-15 RM	3	50	10	Usual medical care and diabetes recommendations for self-management	0,10	EX 54.1±5.4 CON 55.7±6.4	EX 28.7±4.3 CON 30.1±3.5	NR	20.0	HbA1c, HOMA-IR, serum insulin, BMI	muscle soreness
Bjorgaas 2005	Norway	29 (15/14)	Center-based and group-based: each exercise session consisted of three phases--warm up, the main stage, a cool-down and stretching period	Yes/Physio-therapist	AE: light jogging, co-ordination exercises, knee bends and stretching RE: NR Diet information: same as control group	50–85% HR_{max}	2	90	12	Diet information: a plenary session by a clinical nutritionist	0,12	EX 57.9±8.0 CON 56.9±7.8	EX 31.7±2.6 CON 31.8±3.0	EX 2.5 (0.1-17) CON 1.5 (0.1-15)	10.3	HbA1c, SBP, DBP	Achilles tendinitis

Author Year	Country	Sample size (EX/CON)	Exercise intervention							Control	Time points of data collection（week）	Participant characteristics			Dropout rate (%)	Outcomes	Adverse events
			Exercise format	Supervision/ Facilitator	Exercise type	Intensity	Frequency (Days/week)	Duration /session (min)	Intervention time (weeks)			Age（year）	BMI (kg/m^2)	T2D duration（years）			
Johansen 2017	Zealand and Denmark	98 (64/34)	Group-based: the geographical location of the participants' home address	Yes/ physiotherapist and trainer	AE: power walking, cycling, jogging uphill or on stairs RE: anterior chain (thigh), posterior chain (thigh), chest, back and shoulders standard care: same as control group	AE: 60–90% HR_{max} RE: 10–12 RM	5-6	30-60	48	Standard care: medical counseling, education in type 2 diabetes, and lifestyle advice by the study nurse at baseline and every 3 months for 12months	0,48	EX 53.6±9.1 CON 56.6±8.1	EX 31.4±3.9 CON 32.5±4.5	EX 5 (3-8) CON 6 (3-9)	5.1	HbA1c, serum insulin, SBP, DBP, TG, TC, HDL-C, LDL-C, BMI	Musculoskeletal pain or discomfort, mild hypotension, insomnia, peripheral edema
Leehey 2016	USA	36 （18/18）	12 weeks of center-based exercise followed by 40 weeks of home-based exercise	Yes/ Trainer	AE: treadmill, elliptical trainer and cycle ergometer RE: using elastic bands, hand-held weights or weight machine Diet management: same as control group	AE: Interval RE: progressive	Center-based exercise: 3 Home-based exercise: 3or 6	Center-based: 80-90 Home-based: 60 (3 times) 30 (6 times)	52	Diet management: nutritional counseling session at baseline with 9 follow-up telephone calls	0,12,52	EX 65.4±8.7 CON 66.6±7.5	EX 36.2±4.8 CON 37.4±4.2	NR	11.1	HbA1c, SBP, TG, TC, HDL-C, LDL-C, BMI	Cardiovascular disease, cervical myelopathy
Lucotti 2011	Italy	50 （30/20）	Center-based and group-based: in a hospital	Yes/ Physician	AE: row ergometer and bicycle ergometer RE: arm curls, military press, push-ups, upright rowing, back extension, squats knee extensions, heel raises and bent knee sit-ups Diet management: same as control group	AE: 70% HR_{max} RE：40–50% of 1RM	5	45	3	AE plus diet management: AE: 70%HR max 5days/wk,30min/session；Diet management: hypocaloric diet regime administered under a daily supervision of a dietician.	0,3	EX 61.5±11.5 CON 58.1±9.9	EX 39.9±7.3 CON 38.8±4.5	NR	6.0	HbA1c SBP, DBP, TG, TC, HDL-C, BMI	NR
Otten 2017	Sweden	32 (16/16)	Center-based: in a Sports Medicine unit	Yes/ Trainer	AE: cross trainer, cycle-ergometer, cycle-ergometer RE: leg presses, leg curls, hip raises, seated rows, dumbbell rows, shoulder raises, back extensions, burpees, sit-ups, and wall ball shots Paleolithic diet: same as control group	AE: 40-100% HR_{max} RE：NR	3	60	12	Paleolithic diet, education about the diet and cooked food by a trained dietician at baseline and once a month	0,12	EX 61 (58-66) CON 60 (53-64)	EX 31.7 (29.2-35.4) CON 31.4 (29.4-33.1)	EX 5.5 (1-8) CON 3 (1-5)	9.4	HbA1c, serum insulin, SBP, DBP, TG, TC, HDL-C, LDL-C	NR
Vinetti 2015	Italy	20 (10/10)	Center-based: in a hospital-based setting	Yes/ Trainer	AE: cycling on mechanically braked cycle ergometers RE: major muscle groups (upper limb, lower limb, chest, back and core), using calisthenics, repetitions with ankle weights, and dumbbells Standard care: same as control group	AE：Interval RE：progressive	NR	55-85	48	Standard care: dietary regimen prescribed by the diabetologist	0,48	EX 60.56 ±5.94 CON 57.5±9.46	EX 29.7±4.1 CON 29.2±3.11	≥2	0	HbA1c, serum insulin, SBP, DBP, TG, TC, HDL-C, BMI	NR

Abbreviations: RCT, randomized controlled trial; T2D, type 2 Diabetes; EX, exercise group; CON, control group; AE, aerobic exercise; RE, resistance exercise; NR: not reported; RM: repetition maximum; HR: heart rate; VO_{2max}: maximal oxygen consumption; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Quality of the included studies

Figure 2 shows the quality assessment of the included studies: six studies were judged to have a low risk of bias,[14-19] while the remaining four studies showed uncertain risk of bias. [20-23] The following were main sources of bias: lack of blinding of participants and personnel, absence of random sequence generation and allocation concealment, and incomplete outcome data. In summary, the quality of the included studies was considered as having moderate risk of bias.

Pooled results

(1) Glycemic control (HbA1c)

Nine studies provided data about the effect of combined exercise on HbA1c. The pooled results showed the combined intervention significantly reduced the HbA1c level of participants, favoring the intervention group, as compared with the control group (MD=−0.16%, 95%CI: −0.28 to −0.05, P=0.006) (Figure 3).

(2) Weight loss (BMI)

Eight studies reported changes in BMI. The pooled results showed that combined exercise significantly reduced BMI in the intervention group as opposed to the control group (MD=−0.98 kg/m^2, 95%CI: −1.41 to −0.56, P<0.001) (Figure 3).

(3) Insulin sensitivity (HOMA-IR, serum insulin)

Four of the 10 studies examined the effectiveness of combined exercise on the HOMA-IR index. The pooled result revealed a significant reduction in the HOMA-IR index favoring the intervention group (MD=−1.19, 95%CI: −1.93 to −0.46, P=0.001) (Figure 4).

Six studies examined serum insulin. The difference in mean of serum insulin significantly

favored the intervention group (MD=−2.18 μIU/mL, 95%CI: −2.99 to −1.37, P<0.001) (Figure 4).

(4) Blood pressure (SBP and DBP)

Eight of the 10 studies measured SBP and seven studies measured DBP. The pooled results showed no difference in SBP between the intervention and control groups (MD=−2.33 mmHg, 95%CI: −6.01 to 1.35, P=0.21), whereas there was a significant reduction in DBP favoring the intervention group (MD=−3.24 mmHg, 95%CI: −5.32 to −1.16, P=0.002) (Figure 5).

(5) Serum lipids (TG, TC, HDL-C, and LDL-C)

Seven studies measured the effectiveness of combined exercise on lipid profiles. The pooled results demonstrated that combined exercise had no significant effect on TG, TC, HDL-C, and LDL-C levels (TG: MD=−7.57 mg/dL, 95%CI: −16.42 to 1.28, P=0.09; TC: MD=−8.29 mg/dL, 95%CI: −22.18 to 5.60, P=0.24; HDL-C: MD= 2.69 mg/dL, 95%CI: −0.72 to 6.10, P=0.12; LDL-C: MD=0.14 mg/dL, 95%CI: −19.87 to 20.14, P=0.99) (Figure 6).

Subgroup analysis (exercise frequency)

The results showed that combined exercise with frequency <3 days/week significantly lowered the HbA1c (MD=−0.31%, 95%CI: −0.50 to −0.13, P<0.001) and BMI (MD=−1.03 kg/m^2, 95%CI: −1.49 to −0.57, P<0.001), while combined exercise with frequency ≥3 days/week had no effect on HbA1c (MD=0.03%, 95%CI: −0.45 to 0.51, P=0.90) and BMI (MD=0.18 kg/m^2, 95%CI: −1.34 to 1.71, P=0.81) (Table 2).

Table 2. Subgroup analysis on primary outcomes

Subgroups		HbA1c						BMI					
		Included study (n)	Sample size (EX)	Sample size (CON)	Mean Difference (95% CI)	*P*	I^2	Included study (n)	Sample size (EX)	Sample size (CON)	Mean Difference (95% CI)	*P*	I^2
Exercise frequency (days/week)	<3	3	321	306	−0.31(−0.50, −0.13)	<0.001	0%	2	310	295	−1.03(−1.49, −0.57)	<0.001	36%
	≥3	3	44	55	0.03(−0.45, 0.51)	0.90	0%	4	57	70	0.18(−1.34, 1.71)	0.81	0%

Abbreviations: EX, exercise group; CON, control group; CI = confidence intervals; I^2 = I-squared.

Discussion

The results from this meta-analysis showed that combined exercise was associated with a significant decline in HbA1c, BMI, HOMA-IR index, serum insulin, and DBP, indicating the important role of combined exercise in improving glycemic and weight control and enhancing insulin sensitivity among patients with T2D and concurrent overweight/obesity. However, the results showed that combined exercise had no effect on serum lipids.

Our results showed that combined exercise had a significant effect on HbA1c among adults with T2D and concurrent overweight/obesity. It is important to mention that a 1% absolute reduction in HbA1c is associated with a 21% reduction in the risk of any end point or death related to diabetes.[24] Previous meta-analyses of exercise in diabetic patients with or without overweight/obesity have found a positive effect on glycemic control. Hou[25] assessed the effect of combined exercise compared with aerobic exercise among patients with T2D. Their results showed a significant reduction of HbA1c by 0.31%, which was comparable with our finding that combined exercise decreased HbA1c by 0.16%. The meta-analysis by Zou[26] identified 13 eligible studies investigating the effect of exercise on patients with T2D and obesity, and the result showed that exercise had no effect on HbA1c in the 3 months intervention subgroup, whereas exercise significantly reduced HbA1c by 0.25%, 0.93%, and 0.26% when intervention duration were 4 months, 6 months, and 12months, respectively. This may indicate the effect of exercise in patients with type 2 diabetes and obesity tends to be steady and persistent. The pooled effect of combined exercise in patients with T2D and concurrent overweight/obesity, however, seems to be much lower than that reported in the

first adequately powered RCT[27] that examined the effects of aerobic, resistance, and combined exercise in people with T2D. Sigal and colleagues[27] found a pronounced reduction (0.9%) in HbA1c with combined exercise. Such discrepancy might be attributed to the long exercise duration (210−270 min/week) of the combined exercise program, in which participants performed intensive aerobic training program (75−135min/week) as well as resistance training program (135min/week).[28]

Our results showed that combined exercise exerted a significant effect on insulin sensitivity on patients with T2D and concurrent overweight/obesity, which was in line with the results of Thaane[29], wherein exercise appeared to improve insulin sensitivity among adults with T2D and concurrent overweight/obesity. Way[30] also found that regular exercise had a significant benefit in insulin sensitivity in adults with T2D. They concluded this by synthesizing the outcomes of clamps, insulin infusion sensitivity tests, insulin tolerance test, and oral glucose tolerance test. The results of Way[30] indicated that the durability of training-induced improvement in insulin sensitivity could persist beyond 72 hours after the last exercise session. However, potential heterogeneity was introduced by diverse measurement techniques for insulin sensitivity.

It is generally more difficult for patients with diabetes to lose weight and/or maintain weight loss than nondiabetic individuals. Our results showed that combined exercise achieved a statistically and clinically significant decrease in BMI among adults with T2D and concurrent overweight/obesity. Previous reviews also showed the effect of combined exercise on weight loss by using other obesity indicators. The review by Hou[25] showed that combined

exercise significantly reduced subcutaneous and visceral adipose tissue and the results of Pan[31] showed that combined exercise safely accentuated reduction in body weight. While the results of Thaane[29] suggested that short-term exercise training exerted no significant effect on body weight, BMI, and body fat.

Cardiovascular disease was one of the leading reasons for frequent medical consultation and rehospitalization for adults with T2D and concurrent overweight/obesity.[32] BP and serum lipids are vital risk factors for cardiovascular disease, and the importance of managing and maintaining blood pressure and cholesterol levels has been emphasized by the American Diabetic Association (ADA) guideline.[33] Evidence has shown the benefits of simultaneous control of HbA1c, BP, and lipid levels. Our study found that combined exercise had no effect on SBP and serum lipids, which was contradictory to the findings of Albalawi[34] and Bersaoui[35], who reported that combined exercise was related to a statistically significant decline in BP and lipid control among patients with T2D. The possible reason for the discrepancy may be related to the differences of participants' characteristics. In the current meta-analysis, participants had T2D and were overweight or obese. Low-grade metabolic inflammation in this group of people can induce changes in the neural mechanisms (e.g., hypothalamic-pituitary-adrenal axis), which in turn damage the cognitive function of individuals. Cognitive impairments further attenuate individuals' motivation and ability to engage in self-management activities and maintain therapeutic lifestyles.[36-39] Hence, combined exercise may have limited effect on BP and lipid control in people with T2D and concurrent overweight/obesity. More strategies need to be explored to help patients with T2D

and concurrent overweight/obesity to simultaneously manage HbA1c, BP, and cholesterol levels.

Exercise frequency is a pivotal determinant which moderates the effect of combined exercise on glycemic control in patients with T2D and concurrent overweight/obesity.[40 41] Our study showed that combined exercise had significant effects on HbA1c and BMI only in subgroup with exercise frequency less than 3 days/week. We would attribute such results to inherent differences between studies with exercise frequency <3 days/week and ≥3 days/week. Specifically, subjects in the studies with exercise frequency more than 3 days/week tended to perform short-duration exercise (3 weeks, 12 weeks), which was likely not enough to make a difference in outcomes. While subjects [14 15 23] in the study with exercise frequency less than 3 days/week had been offered with long-term (48 weeks) exercise under supervision. Long-term exercise sessions and professional supervision were identified as important factors associated with prominent improvement of glycemic and weight control.[26 31] Additionally, Balducci[14 15] even implemented diet management in addition to physical activity counseling. Thus, the results of subgroup analysis should be interpreted with caution.

Direction for future research and practice

Considering the benefits of combined exercise, it might be helpful to recommend combined exercise for patients with T2D and concurrent overweight/obesity to improve glycemic and weight control and decrease insulin resistance. Physical activity counseling, psycho-educational interventions, mobile technologies, and peer support groups could be integrated into the exercise to improve the adoption rate of combined exercise.[42] Although

there are ADA, American College of Sports Medicine, and International Diabetes Federation exercise recommendations for diabetic patients,[8 9 43] there is little evidence to indicate the ideal exercise duration, exercise intensity, and exercise time that would be most appropriate for patients with T2D and concurrent overweight/obesity. Optimal exercise frequency and duration that would be beneficial for patients with T2D and concurrent overweight/obesity requires further investigation. According to the features of effective exercise interventions among the included studies, most research studies performed center-based exercise with supervision. Hence, we recommend this kind of intervention in future studies to achieve greater metabolic effects.

Limitations

Our study has some limitations. First, the intervention components of combined exercise in terms of intervention frequency, intensity, duration, and time were inconsistent among the included studies and there was substantial heterogeneity among the trials in the meta-analysis. The results, therefore, should be interpreted with caution. Second, only 10 studies met the inclusion criteria and were eligible for the meta-analysis. Some well-conducted and important RCTs were excluded because of not focusing on combined exercise or targeting patients with T2D and concurrent overweight/obesity.[27 44 45] Third, the effectiveness of combined exercise observed in this meta-analysis should be interpreted with caution as the majority of the participants (~ 62%) included in this analysis were from a single study called the "IDES study" with significant positive findings.[11] Additionally, the patients in our study were mainly middle-aged and elderly subjects; hence, the effect of combined exercise on

young subjects with T2D and concurrent overweight/obesity remains unclear. Finally, the T2D duration varied from 0.1 to 17 years or more and which subgroup of patients could benefit more from the combined exercise remains unclear.

Conclusions

This systematic review provides useful information for the clinical application of the combined exercise in the management of patients with T2D and concurrent overweight/obesity. The results show clear evidence that combined exercise intervention has positive effects on improving glycemic and weight control, and enhancing insulin sensitivity among patients with T2D and concurrent overweight/obesity. More RCTs with robust methodological design, and more comprehensive body composition measurements are needed to elaborate the intervention effects and mechanism. This review also highlights the need for further studies to investigate the ideal duration, intensity, and time of combined exercise for patients with T2D and concurrent overweight/obesity.

Contributors XZ, QH, YZ, LC conceived the research; XZ, QH, YZ, LC established eligibility criteria and Search strategy; XZ, QH worked on literature selection, data extraction and quality assessment; XZ, QH, LC performed statistical analysis; XZ wrote paper; XZ, LC had primary responsibility for final content; All authors read the manuscript and approved the final draft.

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Competing interests None declared.

Ethics statement This study does not require ethics approval as it is a review based on

published studies.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information**.** No additional data available.

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cognitive alterations displayed by animal models of obesity. *Front Neurosci*. 2015; 9:229.

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resistance in women with type 2 diabetes. *Diabetes Care*. 2003; 26:2977–82.

Figure Captions

Figure 1 Flow chart for study selection according to PRISMA Declaration 2009

Figure 2 Quality assessment of the included studies. (A) as percentages across all included studies in risk of bias graph; (B) Bias risk of the included studies. "+" indicates Low risk of bias; "?"represents unclear risk of bias; "–" indicates high risk of bias.

Figure 3 Comparison of HbA1c and body mass index (BMI) between intervention group and control group in patients with T2D and concurrent overweight/obesity. (A) Forest plot of HbA1c; (B) Forest plot of BMI; Unit of HbA1c is "%". Unit of BMI is "kg/m^2".

Figure 4 Comparison of homeostasis model assessment of insulin resistance (HOMA-IR) and serum insulin between intervention group and control group in patients with T2D and concurrent overweight/obesity. (A) Forest plot of HOMA-IR; (B) Forest plot of serum insulin. HOMA-IR has no units. Unit of serum insulin is "μIU/mL".

Figure 5 Comparison of systolic blood pressure (SBP) and diastolic blood pressure (DBP) between intervention group and control group in patients with T2D and concurrent overweight/obesity. (A) Forest plot of SBP; (B) Forest plot of DBP. Units of SBP and DBP are both "mmHg".

Figure 6 Comparison of triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) between intervention group and control group in patients with T2D and concurrent overweight/obesity. (A) Forest plot of TG; (B) Forest plot of TC; (C) Forest plot of HDL-C; (D) Forest plot of LDL-C. Units

of TG, TC, HDL-C and LDL-C are “mg/dL”.

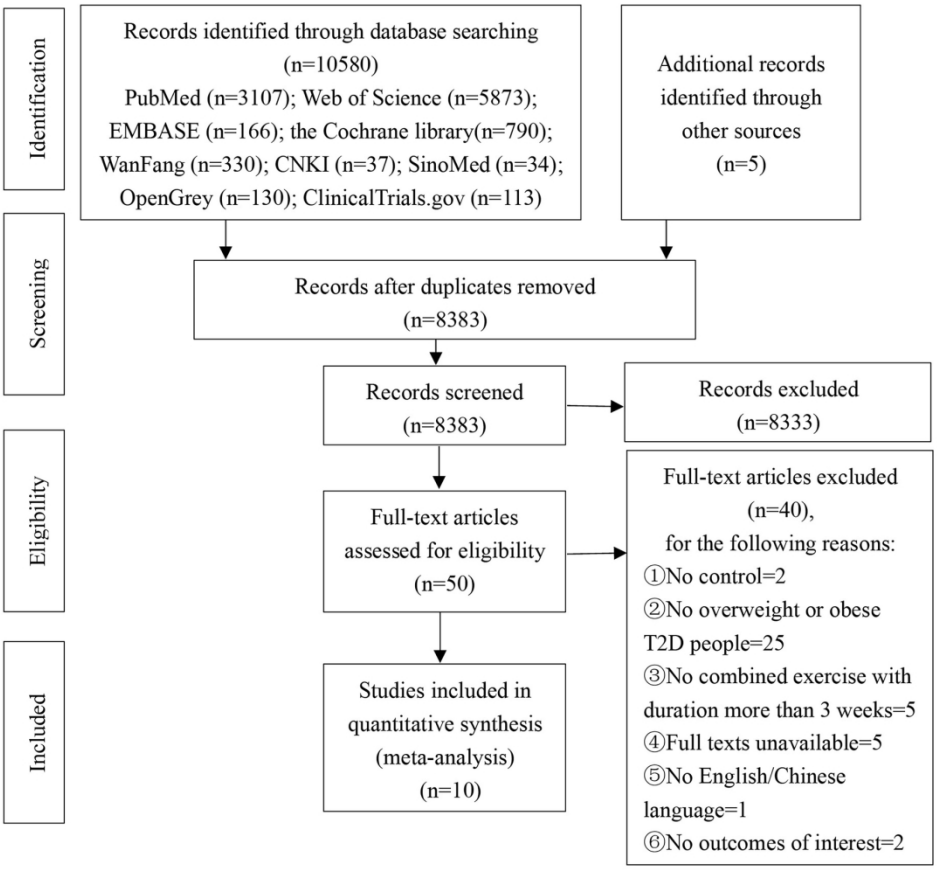

Figure 1 Flow chart for study selection according to PRISMA Declaration 2009

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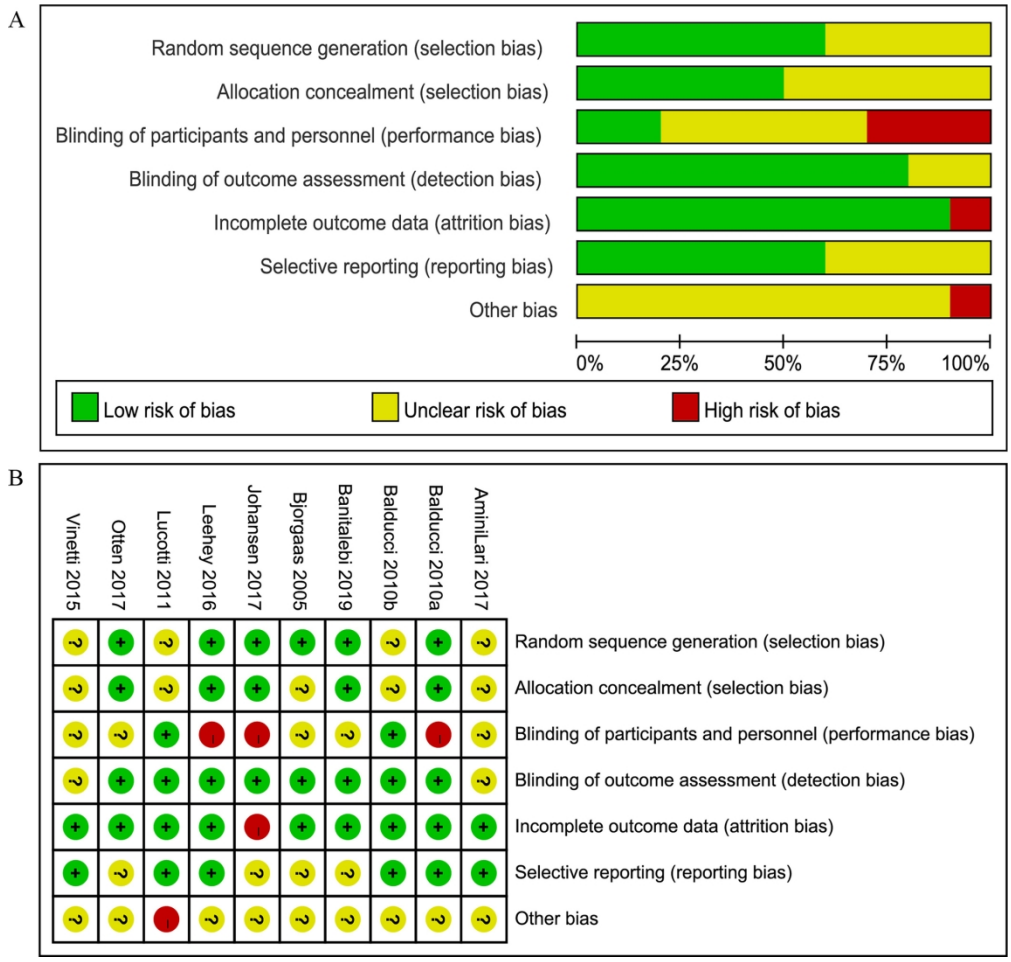

Figure 2 Quality assessment of the included studies. (A) as percentages across all included studies in risk of bias graph; (B) Bias risk of the included studies. "+" indicates Low risk of bias; "?"represents unclear risk of bias; "−" indicates high risk of bias.

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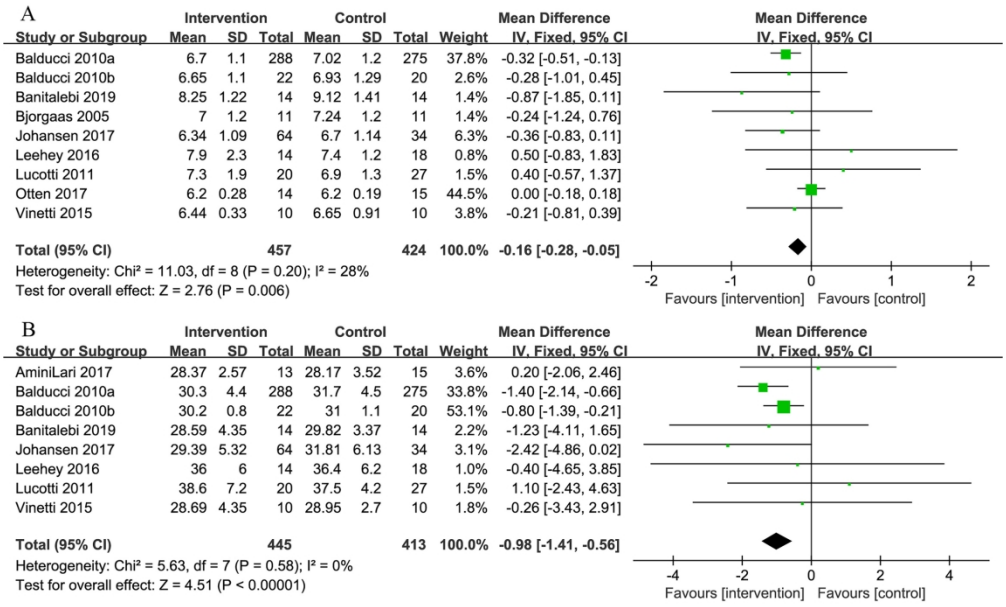

Figure 3 Comparison of HbA1c and body mass index (BMI) between intervention group and control group in patients with T2D and concurrent overweight/obesity. (A) Forest plot of HbA1c; (B) Forest plot of BMI; Unit of HbA1c is "%". Unit of BMI is "kg/m2".

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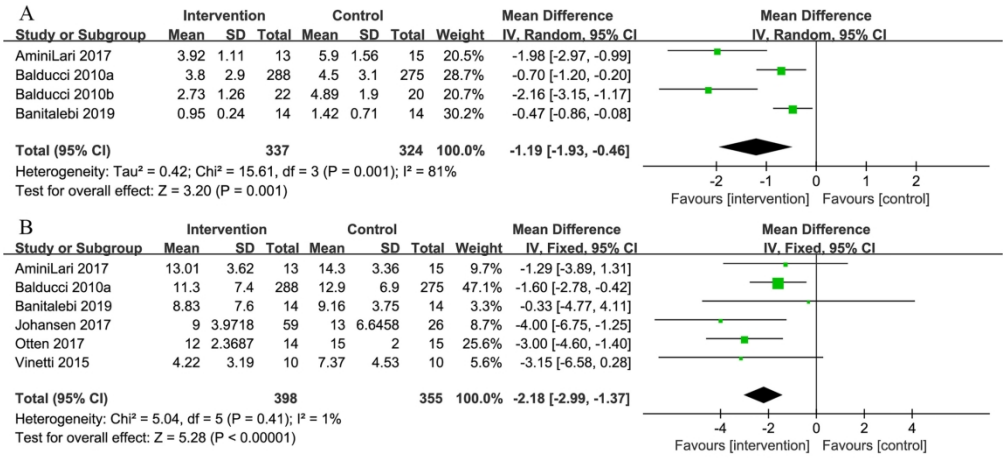

Figure 4 Comparison of homeostasis model assessment of insulin resistance (HOMA-IR) and serum insulin between intervention group and control group in patients with T2D and concurrent overweight/obesity. (A) Forest plot of HOMA-IR; (B) Forest plot of serum insulin. HOMA-IR has no units. Unit of serum insulin is "μIU/mL".

195x89mm (300 x 300 DPI)

Figure 5 Comparison of systolic blood pressure (SBP) and diastolic blood pressure (DBP) between intervention group and control group in patients with T2D and concurrent overweight/obesity. (A) Forest plot of SBP; (B) Forest plot of DBP. Units of SBP and DBP are both "mmHg".

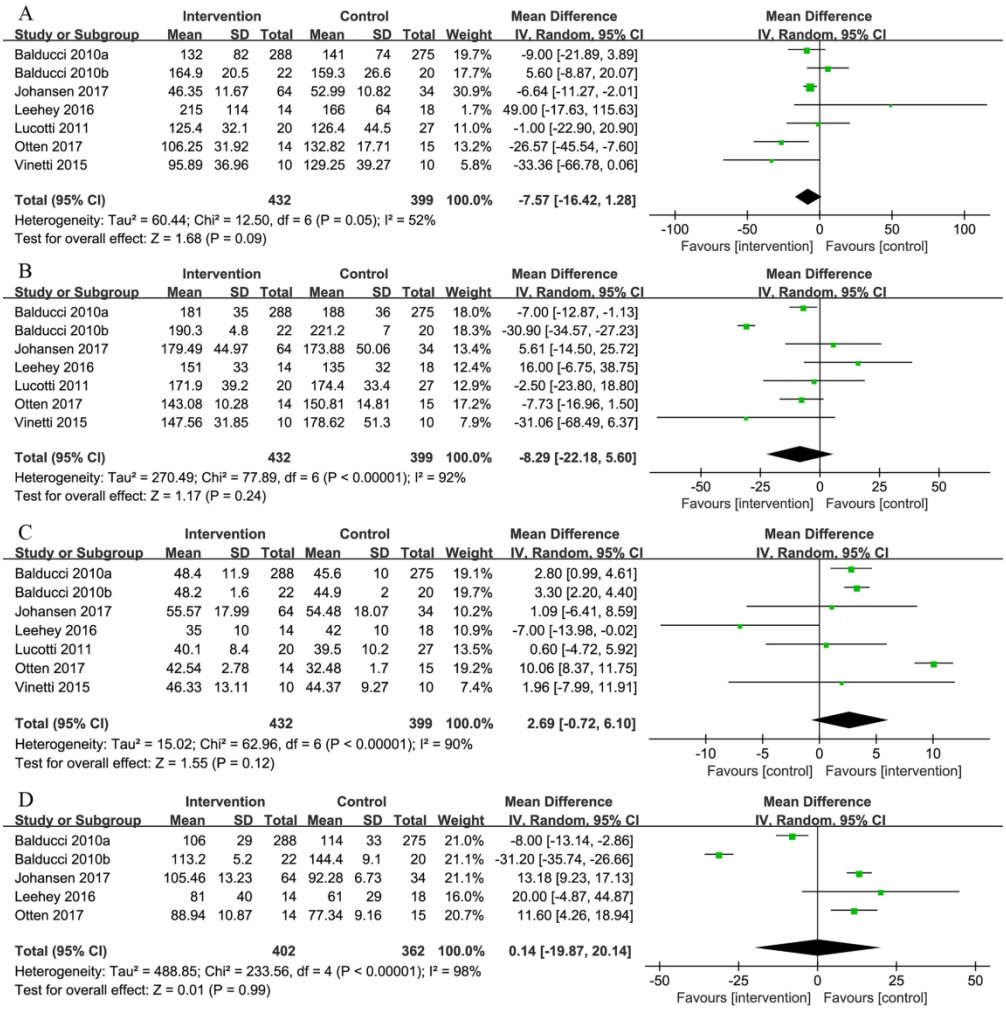

Figure 6 Comparison of triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) between intervention group and control group in patients with T2D and concurrent overweight/obesity. (A) Forest plot of TG; (B) Forest plot of TC; (C) Forest plot of HDL-C; (D) Forest plot of LDL-C. Units of TG, TC, HDL-C and LDL-C are "mg/dL".

195x197mm (300 x 300 DPI)

PubMed

#1 Physical activity[Text Word]

#2 Physical intervention[Text Word]

#3 Exercise [MeSH Terms]

#4 Train*[Text Word]

#5 Aerobic[Text Word]

#6 Isometric[Text Word]

#7 Resistance[Text Word]

#8 Strength*[Text Word]

#9 Weight Lifting[Text Word]

#10 Weight Bearing[Text Word]

#11 Exercise[Text Word]

#12 Physical exercise[Text Word]

#13 Combined exercise[Text Word]

#14 Overweight[MeSH Terms]

#15 Overweight[Text Word]

#16 Obesity[MeSH Terms]

#17 Obes*[Text Word]

#18 Body mass index[Text Word]

#19 BMI[Text Word]

#20 Body weight[Text Word]

#21 Underweight[Text Word]

#22 Adiposity[Text Word]

#23 Body fat distribution[Text Word]

#24 Quetelet index[Text Word]

#25 Diabetes[Title/Abstract]

#26 Diabet*[Text Word]

#27 DM[Text Word]

#28 T2DM[Text Word]

#29 T2D[Text Word]

#30 NIDDM[Text Word]

#31 #1-13/OR

#32 #14-24/OR

#33 #25-30/OR

#34 #31 AND #32 AND #33

EMBASE

#1 'Physical activity':ti,ab,kw

#2 'Physical intervention':ti,ab,kw

#3 'Exercise':ti,ab,kw

#4 'Exercise'/exp

#5 'Train':ti,ab,kw

#6 'Training':ti,ab,kw

#7 'Aerobic':ti,ab,kw

#8 'Resistance':ti,ab,kw

#9 'Strength':ti,ab,kw

#10 'Weight Lifting':ti,ab,kw

#11 'Weight Bearing':ti,ab,kw

#12 'Physical exercise':ti,ab,kw

#13 'Combined exercise':ti,ab,kw

#14 'Overweight'/exp

#15 'Overweight':ti,ab,kw

#16 'Obesity'/exp

#17 'Obese':ti,ab,kw

#18 'Obesity':ti,ab,kw

#19 'Body mass index':ti,ab,kw

#20 'BMI':ti,ab,kw

#21 'Body weight':ti,ab,kw

#22 'Underweight':ti,ab,kw

#23 'Adiposity':ti,ab,kw

#24 'Body fat distribution':ti,ab,kw

#25 'Quetelet index':ti,ab,kw

#26 'Diabetes':ti,ab,kw

#27 'Diabetic':ti,ab,kw

#28 'DM':ti,ab,kw

#29 'T2DM':ti,ab,kw

#30 'T2D':ti,ab,kw

#31 'NIDDM':ti,ab,kw

#32 #1-13/OR

#33 #14-25/OR

#34 #26-31/OR

#35 #32 AND #33 AND #34

Limits: Human, English language

Web of Science

#1 TS=(Physical activity OR Physical intervention OR Exercise OR Train* OR Aerobic OR Isometric OR Resistance OR Strength* OR Weight Lifting OR Weight Bearing OR Physical exercise OR Combined exercise)

#2 TS=(Overweight OR Obes* OR Body mass index OR BMI OR Body weight OR Underweight OR Adiposity OR Body fat distribution OR Quetelet index)

#3 TS=(Diabetes OR Diabetic OR DM OR T2DM OR T2D OR NIDDM)

#4 (#1 AND #2 AND #3) AND LANGUAGE: (English)

the Cochrane library

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#2 "Physical intervention":ti,ab,kw

#3 "Exercise":ti,ab,kw

#4 "Train":ti,ab,kw

#5 "Training":ti,ab,kw

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#7 "Isometric":ti,ab,kw

#8 "Resistance":ti,ab,kw

#9 "Strength":ti,ab,kw

#10 "Weight Lifting":ti,ab,kw

#11 "Weight Bearing":ti,ab,kw

#12 "Physical exercise":ti,ab,kw

#13 "Combined exercise":ti,ab,kw

#14 "Overweight":ti,ab,kw

#15 "Obese":ti,ab,kw

#16 "Obesity":ti,ab,kw

#17 "Body mass index":ti,ab,kw

#18 "BMI":ti,ab,kw

#19 "Body weight":ti,ab,kw

#20 "Underweight":ti,ab,kw

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#26 "DM":ti,ab,kw

#27 "T2DM":ti,ab,kw

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#29 "NIDDM":ti,ab,kw

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WANFANG

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#24 "非胰岛素依赖型糖尿病"[主题]

#25 #1-12/OR

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#27 #22-24/OR

#28 #25 AND #26 AND #27

CNKI

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SinoMed

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#26 #13-21/OR
#27 #22-24/OR
#28 #25 AND #26 AND #27

OpenGrey

((Diabetes OR Diabetic OR DM OR T2DM OR T2D OR NIDDM) AND (Overweight OR Obes* OR Body mass index OR BMI OR Body weight OR Underweight OR Adiposity OR Body fat distribution OR Quetelet index)) AND (Physical activity OR Physical intervention OR Exercise OR Train* OR Aerobic OR Isometric OR Resistance OR Strength* OR Weight Lifting OR Weight Bearing OR Physical exercise OR Combined exercise)

ClinicalTrials.gov

Condition or disease: (Diabetes OR Diabetic OR DM OR T2DM OR T2D OR NIDDM) AND (Overweight OR Obesity OR obese)
Other terms: Physical activity OR Physical intervention OR Exercise OR Train* OR Aerobic OR Isometric OR Resistance OR Strength* OR Weight Lifting OR Weight Bearing OR Physical exercise OR Combined exercise
Study type: Interventional Studies (Clinical Trials)
Study Results: Studies With Results

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	P2L12
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P5L33-41
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P5L53-56
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P6-7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P7L45-50
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P8L12-28
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P8L35-45
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P8L38-40 Table 1
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Table 1
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	P8L51-55
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	P9L17-20
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	P9L6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	P9L7-9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	P9L7-14
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	P9L14-16
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	P9L17-20

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P9L38-42 Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	P20L48
Study characteristics	17	Cite each included study and present its characteristics.	P13L9-12 Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	P13L7-20 Figure 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 3-6
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	P9, P13
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	P13-14
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	P13L12-17
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	P13L17-19
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P16L8-18
	23b	Discuss any limitations of the evidence included in the review.	P19, P20
	23c	Discuss any limitations of the review processes used.	P20
	23d	Discuss implications of the results for practice, policy, and future research.	P19
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Not prepared
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	P21L51-55
Competing interests	26	Declare any competing interests of review authors.	P21L56
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Table 1, Appendix

PRISMA 2020 Checklist

PRIMSA Abstract Checklist

Topic	No.	Item	Reported?
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	No
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	No
Registration	12	Provide the register name and registration number.	No

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71