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Effect of physical activity and different exercise modalities on glycemic control in people with prediabetes: a systematic review and meta-analysis of randomized controlled trials

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Background: Numerous studies have shown the beneficial effects of exercise on glycemic control in people with prediabetes. However, the most effective exercise modality for improving glycemic control remains unclear. We aimed to assess which exercise training modality is most effective in improving glycemic control in a population with prediabetes.

Methods: We conducted searches in Pubmed/MEDLINE, EMBASE, SPORTDiscus, Web of Science, PEDro, BVS, and the Cochrane Library from inception to June 2022. Included studies reported fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), and 2-hour postprandial (2hPP) levels and implemented an exercise program lasting at least 12 weeks in adults with prediabetes. We performed a direct meta-analysis using a random-effects model and a network meta-analysis. Cochran's Q statistic and the inconsistency I^2 test were used to assess the heterogenicity between studies.

Results: Twenty trials were included, with 15 trials (comprising 775 participants with prediabetes) combined in the meta-analysis, and 13 in the network meta-analysis. The meta-analysis results did not show a statistically significant reduction in fasting plasma glucose (FPG) after aerobic training (AT) intervention compared to a control group (mean (95%CI) difference = -5.18 (-13.48; 3.12) mg/dL, Z=1.22, p=0.22). However, a difference of -7.25 (-13.79; -0.71) mg/dL, p=0.03, in FPG after interval training (IT) intervention was detected compared to a control group. After resistance

training (RT) intervention, FPG was significantly lower -6.71 (-12.65,-0.77) mg/dL, Z=2.21, p=0.03, and HbA1c by -0.13 (-0.55, 0.29), p=0.54, compared to the control group. The impact of RT compared to no intervention on 2hPP was not statistically significant (p=0.26). The network meta-analysis did not show statistical significance. Most of the studies presented an unclear risk of bias, and a low and very low-quality of evidence. According to the GRADE criteria, the strength of the body of evidence was low.

Conclusion: Resistance training and IT had demonstrated benefits on glycemic indices, especially on FPG, in a population with prediabetes. Further studies with larger sample sizes and a more robust methodology that compare different types of exercise modalities, frequencies, and durations, are needed to establish a beneficial exercise intervention.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=370688, identifier CRD42022370688.

KEYWORDS

prediabetes, exercise, aerobic training, resistance training, interval training

Introduction

Type 2 diabetes (T2D) is a public health problem whose prevalence has increased during recent decades (1, 2), causing an important financial burden on the healthcare system (3). According to the International Diabetes Federation, the global prevalence of diabetes is currently 10.5% (463 million people), and it is projected to rise to 12.2% (783 million people) by 2045 (4). It is predicted that the global economic burden of diabetes will increase from U.S. $1.3 trillion (95% CI 1.3–1.4) in 2015 to $2.5 trillion (2.4–2.6) in 2030 under the past trends (5).

Some risk factors contribute to the development of T2D, including age, overweight/obesity, physical inactivity, family history of diabetes, history of gestational diabetes, and prediabetes (6). Among these factors, prediabetes is the preceding phase for developing diabetes (7), which is characterized by a metabolic state with higher blood glucose levels than normal but below the criteria for a diagnosis of T2D. Prediabetes has been defined by impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and/or increased glycated hemoglobin (HbA1c). People with IGT have increased postprandial blood glucose levels (8), while insulin resistance and beta-cell dysfunction are the main causes of IGT and IFG (9, 10). The American Diabetes Association (ADA) defines prediabetes using IFG defined as fasting plasma glucose (FPG) of 100-125 mg/dL and IGT defined as 2-hour post prandial glucose (2hPP) of 140-200 mg/dL after ingestion of 75 g of oral glucose load and HbA1c based criteria of a level of 5.7% to 6.4% (11). The World Health Organization (WHO), on the other hand, has the same cut-off value for IGT but has a high cut-off value for IFG (FPG 110-125 mg/dL) and did not consider HbA1c (12).

People with prediabetes are at a high risk of developing T2D, especially those who are overweight or obese (13). Lifestyle modifications, including regular physical activity (PA), play a crucial role in preventing the progression to T2D and even reversing prediabetes to normoglycemia (6, 14, 15). Approximately 70% of people with prediabetes will progress to T2D, with an annual progression rate of 5-10% (16, 17).

Several studies have shown the beneficial effects of PA on glycemic control in people with prediabetes (18–20), but there is relatively limited knowledge regarding the effect of structured exercise on glycemic control in this population (21). Moreover, there are few studies comparing the effects of different exercise modalities on glycemic control with an appropriate sample size to generalize the results (22–24). Consequently, it remains unclear which exercise modality and duration is most effective in reducing T2D risk, particularly in individuals with prediabetes.

Among different exercise modalities, aerobic training (AT) and resistance training (RT) improves glycemic control in people with and without prediabetes and T2D through multiple mechanisms (25). These mechanisms include the use of glucose for energy, leading to decreased blood glucose levels over time due to reduced muscle glycogen caused by exercise. Other mechanisms involve enhancing endothelial function; improving pancreatic β-cell functions; enhancing glucose metabolism, reducing visceral adipose tissue (VAT), increasing lean tissue, and increasing the production of glucose transporter type 4 (GLUT-4), which improves insulin sensitivity and enhances glucose uptake, ultimately leading to improved glycemic control (26–31).

Even though the WHO recommends performing moderate-vigorous physical activity (MVPA), accumulating between 150-300 minutes/week, and combining aerobic exercise with resistance training at least 2 days/week (32), few adults comply with these recommendations (33). High-intensity interval training (HIIT) has shown beneficial effects on VO_2max, insulin resistance (34), and

muscle strength (35) in adults and seems to produce positive effects on glycemic control in people with prediabetes (20). Additionally, moderate-intensity interval training (IT) has shown positive results in multiple measures of glycemic variability (36). Furthermore, vigorous-intensity exercise may provide similar or even greater benefits than moderate-intensity exercise for glycemic control in individuals with T2D (37).

Considering these findings, exercise prescription should be a priority in clinical practice to prevent or delay T2D. However, there is a lack of sufficient evidence to determine which exercise modality works best for preventing diabetes in people with prediabetes. Therefore, the purpose of this systematic review with metanalysis is to provide evidence regarding the effect of different exercise modalities on glycemic control in people with prediabetes and to assess which exercise training modality is most effective in improving glycemic control. The research question is as follows: Which exercise modality is more effective in improving glycemic control in people with prediabetes?

Methods and analysis

Study protocol and registration

The protocol of this systematic review and meta-analysis was registered on the Prospective Register of Systematic Reviews (PROSPERO) website (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=370688) and PROSPERO registration number is CRD42022370688.

The protocol of this systematic review was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statements (38), and the systematic review was equally reported according to PRISMA guidelines (39).

Search strategy

We performed a systematic literature search of the main databases: MEDLINE (via PubMed), EMBASE, SPORTDiscus (via EBSCO), Web of Science, PEDro, BVS, and the Cochrane Library from the inception to June 2022. There were no restrictions in terms of the language of publication.

Search terms included controlled terms from MeSH in PubMed/MEDLINE and EMtree in EMBASE as well as free text terms. The key search terms were prediabetic state, exercise, and clinical trial. The search strategy was performed in cooperation with an information scientist which is shown in the supplementary information (Additional File 1).

Unpublished literature was identified through Clinical Trials (https://clinicaltrials.gov), the Information System on Gray Literature in Europe (Open Gray), Conference Proceedings of the Web of Science and ProQuest Dissertations, and Theses Global. Data from conference proceedings were not included in the review due to the limited information available to carry out the methodological quality assessment.

Eligibility criteria

Inclusion criteria

Our inclusion criteria, framed in terms of PICO (population, intervention, comparator, and outcome) questions are the following:

- Population: Participants at least 18 years old with prediabetes as defined by ADA (11) and/or WHO criteria (12).

- Intervention: We focused on the following exercise training modalities: AT, IT, RT, combined exercise, and no exercise. The definition of each exercise training modality is shown in the supplementary information (Additional File 2). Studies were included if the implementation of an exercise program last at least 12 weeks in duration [as most studies agree on long-term interventions of at least 12 weeks to be able to assess changes in many physiological variables, such as anthropometric, biochemical, physical fitness variables (22, 33, 40) and blood glucose (20, 41, 42)]. In addition, HbA1c reflects half of the glucose concentration during the previous 8-12 weeks (43), consequently, a period of 12 weeks or more is necessary to detect changes in HbA1c.

- Comparator: Placebo control/Different exercise modality.

- Outcome: Our primary outcome was the glycemic control therefore we included FPG, HbA1c, and 2hPP measures.

In terms of study design, we only included randomized control trials (RCTs).

Exclusion criteria

Study protocols for RCTs and studies focused on pregnant women.

Study selection

References of the studies identified were imported into EndNote 20 (Clarivate Analytics, Philadelphia, USA) to manage the literature search records. Duplicates were subsequently removed. To ensure the quality of the process, two blinded reviewers (IH- and MB-V) independently screened the title, abstract, or both, in each record for relevance according to the eligibility criteria. Any disagreements or conflicts between the reviewers were resolved through consensus. After this initial screening, all potentially eligible references were evaluated at the full-text level to confirm their eligibility.

Data extraction and management

We extracted and registered the data about the characteristics of the studies and study results in Microsoft Excel 2019 (Microsoft Corp, Redmond, WA, www.microsoft.com) and Review Manager software (RevMan version 5.4.1, Copenhagen, Denmark: The Nordic Cochrane Centre, the Cochrane Collaboration 2014), respectively. Two reviewers (IH-B and MB-V) independently extracted the data of the characteristics of the studies (e.g., publication year, country, journal title, participants, sample size, diagnostic criteria for prediabetes and study period) and outcomes (FPG, HbA1c, and 2hPP). Since the data for anthropometric variables, fitness level, and health status were not available for all the

studies, we did not include them in the present meta-analyses. The reviewers contacted the authors to resolve doubts or questions or request missing or incomplete data. Data were presented as the mean and standard deviation (SD) at the end of the study.

Risk of bias and quality of evidence assessment

Both reviewers (IH-B and MB-V) independently assessed the risk of bias in the included according to the Cochrane Handbook version 5.1.0 (44). This assessment considered aspects such as adequate sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective reporting, and other sources of bias (e.g., extreme baseline imbalance). The methodological quality was classified as having a low, high, or unclear risk of bias. Additionally, another reviewer (AY), with methodological expertise, independently supervised the risk of bias assessment, and any disagreements were resolved by consensus. The quality of the body of evidence was evaluated based on the GRADE criteria (45). We also assessed the potential for publication bias using Egger's test (46).

Data analysis

For direct meta-analysis, we analyzed the data using Review Manager software (RevMan version 5.4; Cochrane Collaboration, Copenhagen, Denmark, 2014). Weights and mean difference (95% CI) were determined using random-effects models. Post-intervention values of FPG, 2hPP, and HbA1c between the control and intervention groups were used to calculate the mean differences. Studies that did not report the post-intervention levels of FPG, 2hPP, and HbA1c were excluded from the final analysis. We converted FPG values from mmol/dL to mg/dL. Further, we used the 95%CI or interquartile range to determine SD in studies that did not report the value of SD. Studies with interventions other than AT, RT, and IT were excluded from the final meta-analysis due to the small number of eligible studies.

We used Cochran's Q statistic and the inconsistency I^2 test to assess the heterogenicity between studies. I^2 values of 25, 50, and 75% are considered indicative of low, moderate, and high heterogeneity, respectively (47).

Since the direct meta-analysis could only provide pairwise comparisons of exercise treatments, a network meta-analysis was used to evaluate the efficacies of the three exercise regimens. To run the network meta-analysis, we used Meta-Insight software (48). Random effect models were chosen based on Cochrane's Q statistic. We used the mean difference to summarize the effects of the continuous outcome variables.

Results

Literature selection

A total of 1,419 studies were initially identified in this study after duplicates were removed. After reviewing the title and abstract, 126 studies were selected for further review. Among these, 5 studies were excluded because authors did not respond to data requests and 103 did not meet the review eligibility criteria. Finally, 20 studies met our inclusion criteria (20, 22–24, 36, 41, 42, 49–62), of which 15, comprising 775 participants with prediabetes, were combined in the meta-analysis, and 13 in the network meta-analysis. A flow chart of the screening process was presented in accordance with the PRISMA flow diagram of study selection (Figure 1).

Study characteristics of eligible studies

The characteristics of the included studies are illustrated in Table 1. The final analysis consisted of 15 studies published between 2012 and 2022, with a total of 775 participants with prediabetes (52% of them were women). In the study by Dai et al., the sex of participants was not reported (23). The total mean (SD) age of the participants in the intervention group was 51.66 (13.36) years and, for the control group, it was 53.1 (12.16) years. The study by Die et al., and Hansen et al., did not report the age of the participants (23, 55).

The included studies used different exercise modalities, with a wide variation in session duration ranging from 20 to 85 minutes. These exercise modalities can be divided into three main categories: AT, RT, and IT. The duration of the studies ranged between 12 to 96 weeks.

Studies with more than one mode of exercise intervention were analyzed in different meta-analysis groups with the same control group. Studies that consisted of interventions with a combination of two exercise modalities (e.g., IT+RT vs. control) and studies with diet or exercise interventions as control groups were excluded due to the impossibility of comparison with other studies.

Risk of bias and quality of evidence

The quality of the included studies was assessed as moderate (Figure 2). Blinding of participants and personnel was not

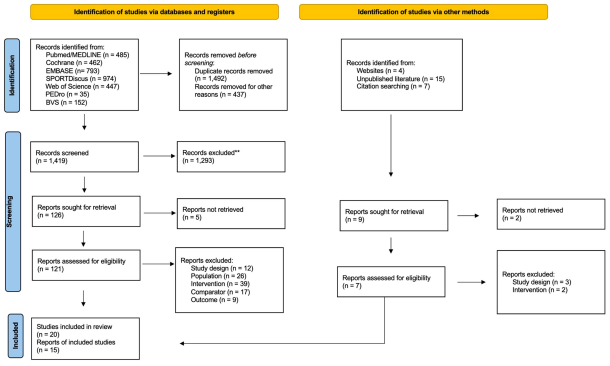

FIGURE 1
PRISMA Flow diagram of literature search and study selection process.

TABLE 1 Characteristics of included studies.

Author	Year	Country	Diagnostic criteria	Groups	Sample size (% female)	Age (SD)	Duration (frequency)	Type of intervention	Length/ session	Intensity	Dropout	Adherence
Alvarez et al.[a]	2012 (49)	Chile	FPG (ADA)	IT Control	12 (100%) 13 (100%)	39.2 (9.5) 40.1 (11.4)	12 weeks (3 days/week) -	Running races Lifestyle advice	20' -	>85% HR max	nd nd	85% nd
Alvarez et al.[b]	2012 (49)	Chile	FPG (ADA)	RT Control	8 (100%) 13 (100%)	33.9 (9.3) 40.1 (11.4)	12 weeks (2 days/week) -	Free weigh Lifestyle advice	45' -	VI	nd nd	95% nd
Alvarez et al.[c]	2012 (49)	Chile	FPG (ADA)	IT+RT Control	10 (100%) 13 (100%)	43.3 (8.1) 40.1 (11.4)	12 weeks (5 days/week) -	Combined training Lifestyle advice	20-45' -	Both combinations	nd nd	74% nd
Burtscher et al.	2009 (50)	Austria	FPG (WHO)	AT Control	18 (55.5%) 18 (55.5%)	59.1 (7.8) 55.8 (5.5)	48 weeks (2.7 days/ week) 48 weeks (1.3 days/ week)	Jogging, swimming, running, dancing… Lifestyle advice	81' 85'	Lactate 2-3 mmol/L	nd nd	nd nd
Burtscher et al.[a]	2012 (63)	Austria	FPG (WHO)	AT+RT Control	12 (66.7%) 18 (50%)	57.8 (6.5) 57.8 (7.9)	48 weeks (2 days/week)	Jogging, swimming, strength training… nd	60'	MI (HR or PE)	nd nd	nd nd
Burtscher et al.[b]	2012 (63)	Austria	FPG + IGT (WHO)	AT+RT Control	12 (66.7%) 18 (50%)	54.0 (8.0) 57.6 (5.8)	48 weeks (2 days/week)	Jogging, swimming, strength training… nd	60'	MI (HR or PE)	nd nd	nd nd
Chen et al.	2021 (51)	China	FPG (ADA) IGT (ADA) HbA1c (ADA)	AT RT Control	83 (71.1%) 82 (63.4%) 83 (60.2%)	60.9 (5.7) 59.9 (5.9) 60.7 (5.8)	12 and 24 months (3 days/week) 12 and 24 months (3 days/week)	Aerobic dance Elastic bands Maintain usual habits	60' 50'	60-70% HRmax -	18.3%; 26.8% 18.1% 30.1% 14.5%; 33.7%	81.7%; 73.2% 81.9%; 69.9% 85.5%; 66.3%
Dai et al. [a]	2019 (23)	China	ADA	AT Control	41 (nd) 45 (nd)	55-75 (nd) 55-75 (nd)	96 weeks (3 days/week)	Dancing Lifestyle advice	60'	60-70% HR max	17.1% 22.2%	nd nd
Dai et al. [b]	2019 (23)	China	ADA	RT Control	43 (nd) 45 (nd)	55-75 (nd) 55-75 (nd)	96 weeks (3 days/week)	Leg and chest press, pull downs… Lifestyle advice	60'	60-80% 1RM	27.9% 22.2%	nd nd
Dai et al. [c]	2019 (23)	China	ADA	AT+RT Control	43 (nd) 45 (nd)	55-75 (nd) 55-75 (nd)	96 weeks (3 days/week)	Combined training Lifestyle advice	30'+30'	Both combinations	13.9% 22.2%	nd nd
Desch et al.	2010 (23)	Germany	IGT FPG	AT Control	14 (21.4) 12(33.3)	62.3 (6.2) 62.3 (6.5)	6 months (1 o 2 days/ week)	Bicycle ergometer	90'-120'	75% HRmax	nd	nd
Færch et al.	2021 (36)	Denmark	HbA1c (ADA)	IT Control	30 (50%) 30 (60%)	57.8 (9.9) 57.2 (9.9)	13 weeks (5 days/week)	Walking, cycling, running… Lifestyle advice	30'	≥75%/≤60% HR max	nd nd	93% nd
Fritz et al.**	2013 (36)	Stockholm	IGT (8.9-12.1 mmol/L)	AT Control	14 (64.3%) 21 (52.4%)	59.1 (6.2) 61.8 (3.4)	16 weeks (nd)	Nordic walking nd	300'	MI (HR or PE)	nd nd	>80% nd

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TABLE 1 Continued

Author	Year	Country	Diagnostic criteria	Groups	Sample size (% female)	Age (SD)	Duration (frequency)	Type of intervention	Length/ session	Intensity	Dropout	Adherence
Gidlund et al.[a]	2016 (22)	Finland	FPG (ADA) IGT (ADA) Findrisk (>12)	AT Control	20 (0%) 17 (0%)	54 (6.2) 54(6.9)	12 weeks (3 days/week)	Nordic walking Lifestyle advice	60’	55% to 75% HRR	nd nd	nd nd
Gidlund et al.[b]	2016 (22)	Finland	FPG (ADA) IGT (ADA) Findrisk (>12)	RT Control	18 (0%) 17 (0%)	56 (5.6) 54(6.9)	12 weeks (3 days/week)	Leg and bench press, leg extension… Lifestyle advice	60’	50% to 85% 5RM	nd nd	nd nd
Gilbertson et al.	2019 (54)	EEUU	ADA	AT IT	12 (41.4%) 17 (58.6%)	50.8 (4.4) 45.7 (4.4)	16 weeks (3 days/week) 16 weeks (3 days/week)	Walk and run-on treadmill Walk and run-on treadmill	30-60’ 45’	45-55% HRR 10 bpm of HRmax/PE[1]	38.0% 10.3%	89.6% 91.7%
Hansen et al.	2012 (55)	Norway	IGT (WHO)	RT RT	9 (77.8%) 9 (77.8%)	33-69 (nd) 33-69 (nd)	16 weeks (3 days/week) 16 weeks (3 days/week)	Leg and chest press, pull downs… Leg and chest press, pull downs…	nd nd	60%-85% 1RM 45%-65% 1RM	nd nd	nd nd
Herzig et al.	2014 (56)	Finland	FPG or IGT (WHO)	AT Control	33 (72.7%) 35 (74.3%)	58.1 (9.9) 59.5 (10.8)	12 weeks (3 days/week)	Indoor sports nd	60’	MI (walk at 3-4 km/h)	13.1% 12.5%	67% nd
Liao et al.	2015 (41)	nd	FPG (ADA)	AT Control	60 (47%) 60 (41.7%)	42.4 (5.8) 44.1 (6.6)	12 weeks (5 days/week)	Jogging or brisk walking Lifestyle advice	30’	MI	13.3% 6.7%	nd nd
Liu et al.[a]	2013 (57)	China	IGT (7.8-10 mmol/L)	AT Control	20 (nd) 21 (nd)	49.8 (4.8) 49.8 (4.8)	24 weeks (4 days/week)	Walk and run-on treadmill nd	60’	60%-70% HRmax	nd	nd
Liu et al.[b]	2013 (57)	China	IGT (7.8-10 mmol/L)	AT+RT Control	20 (nd) 21 (nd)	49.8 (4.8) 49.8 (4.8)	24 weeks (4 days/week)	Walk/upper arm, chest and waist … nd	50’ (30’ RT +20’AT)	nd	nd	nd
Malin et al.	2012 (58)	EEUU	IGT (ADA)	AT+RT Control	8 (62.5%) 8 (75.0%)	45.4 (8.0) 49.8 (10.9)	12 weeks (3 days/week)	Cycling, free weigh Placebo	60-75’	70% HR/70% of 1RM	nd nd	nd nd
RezkAllah et al.[a]	2019 (20)	Egypt	FPG (ADA)	IT Control	20 (45%) 20 (40%)	31.8 (5.3) 35.9 (5.8)	12 weeks (3 days/week)	Uphill running on treadmill Lifestyle advice	25’	90% HRmax	nd nd	nd nd
RezkAllah et al.[b]	2019 (20)	Egypt	ADA	IT Control	20 (50%) 20 (40%)	31.0 (5.3) 35.9 (5.8)	12 weeks (3 days/week)	Uphill running on treadmill Lifestyle advice	45’	90% HRmax	nd nd	nd nd
Rowan et al.	2017 (59)	Canada	HbA1c (ADA)	IT+RT AT+RT	10 (33.3%) 11 (63.6%)	47.7 (6.9) 53.6 (8.2)	16.6 weeks (3 days/ week)	Running on treadmill, push-ups, squats	38’ 38’	90% HRR 60-70% HRR	20% 0%	80% 100%

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TABLE 1 Continued

Author	Year	Country	Diagnostic criteria	Groups	Sample size (% female)	Age (SD)	Duration (frequency)	Type of intervention	Length/ session	Intensity	Dropout	Adherence
								Running on treadmill, push-ups, squats				
Slentz et al. [a] **	2016 (60)	EEUU	FPG (5.28 -6.94 mmol/l)	AT Control	40 (57.5%) 37 (54.0%)	61.4 (7.1) 57.6 (8.1)	24 Weeks (8.6 milles/ week) 24 Weeks (8.6 milles/ week)	Cardiovascular machines Clinical lifestyle	≤ 60'	50% VO_2 reserve 50% VO_2 reserve	18% 14%	82% 86%
Slentz et al. [b] **	2016 (60)	EEUU	FPG (5.28 -6.94 mmol/l)	AT Control	38 (60.5%) 37 (54.0%)	60.4 (7.0) 57.6 (8.1)	24 Weeks (13.8 milles/ week) 24 Weeks (8.6 milles/ week)	Cardiovascular machines Clinical lifestyle	≤ 60'	50% VO_2 reserve 50% VO_2 reserve	15% 14%	85% 86%
Slentz et al. [c] **	2016 (60)	EEUU	FPG (5.28 -6.94 mmol/l)	AT Control	35 (62.8%) 37 (54.0%)	56.9 (7.8) 57.6 (8.1)	24 Weeks (13.8 milles/ week) 24 Weeks (8.6 milles/ week)	Cardiovascular machines Clinical lifestyle*	≤ 60'	75% VO_2 reserve 50% VO_2 reserve	15% 14%	85% 86%
Venojärvi et al.	2013 (61)	Finland	FPG (ADA) IGT (ADA)	AT RT CG	48 (0) 49 (0) 47 (0)	55 (6.2) 54 (6.1) 54 (7.2)	12 weeks (3 days/week) 12 weeks (3 days/week)	Nordic walking Strength and power exercise Lifestyle advice	60' 60'	55-75% HRmax 50-85% 1RM	18.7% 26.5% 14.9%	81.3% 73.5% 85.1%
Viskochil et al.	2017 (61)	EEUU	IGT (ADA)	AT+RT Control	9 (55.5%) 8 (75.0%)	46.2 (2.6) 49.8 (3.9)	12 weeks (3 days/week)	Cycling, free weigh Placebo	60-75'	65% VO_2 max./60%-70% 1RM -	nd nd	nd nd
Yan et al.[a]	2019 (62)	China	IGT (ADA)	AT Control	35 (71.4%) 35 (57.1%)	64.2 (5.7) 60.3 (7.6)	48 weeks (3 days/week)	Aerobic dancing Lifestyle advice	50'	60-70% HRmax	11.4% 5.7%	88.6% 94.3%
Yan et al.[b]	2019 (62)	China	IGT (ADA)	RT Control	35 (57.1%) 35 (57.1%)	62.1 (8.1) 60.3 (7.6)	48 weeks (3 days/week)	Leg and chest press, pull downs… Lifestyle advice	60'	60% 1RM	17.2% 5.7%	82.8% 94.3%
Yuan et al.[a]	2019 (62)	China	FPG (ADA) IGT (ADA) HbA1c (ADA)	AT Control	83 (71.1%) 83 (60.2%)	59.9 (5.9) 60.7 (5.8)	24 weeks (3 days/week)	Aerobic exercises Lifestyle advice	60'	60-70% HRmax	12% 12%	88% 88%
Yuan et al.[b]	2019 (62)	China	FPG (ADA) IGT (ADA) HbA1c (ADA)	RT Control	82 (63.4%) 83 (60.2%)	60.9 (5.7) 60.7 (5.8)	24 weeks (3 days/week)	Leg and chest press, pull downs… Lifestyle advice	50'	60% 1RM	13.4% 12%	86.6% 88%

FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; 2hPP, 2-hour postprandial; AT, Aerobic training; RT, Resistance training; IT, Interval training; IT+RT, a combination of IT and RT; AT+RT, a combination of AT and RT; VI, vigorous intensity; MI, moderate intensity; HRmax, maximum heart rate; HRR, heart rate reserve; VO_2 max., maximum consumption of oxygen; 1RM, one repetition maximum. 5RM, five repetitions maximum; PA, physical activity; PE, perceived exertion.$_2$ max.: maximum consumption of oxygen; 1RM: one repetition maximum. 5RM: five repetitions maximum; PA: physical activity; PE: perceived exertion.

Vigorous intensity can be determined by HR ≥85% HRmax. or by VO_2 max. ≥60% (64–67).

[1]The Borg Rating of Perceived Exertion scale is a tool for measuring an individual's effort and exertion, breathlessness, and fatigue during exercise practice (68), a perceived exertion of 19-20 on the Borg scale corresponds to "extremely hard and maximal exertion" respectively (69).

*Clinical lifestyle: Diet + cardiovascular machines.

**This study was not included in the meta-analysis.

nd = not determined.

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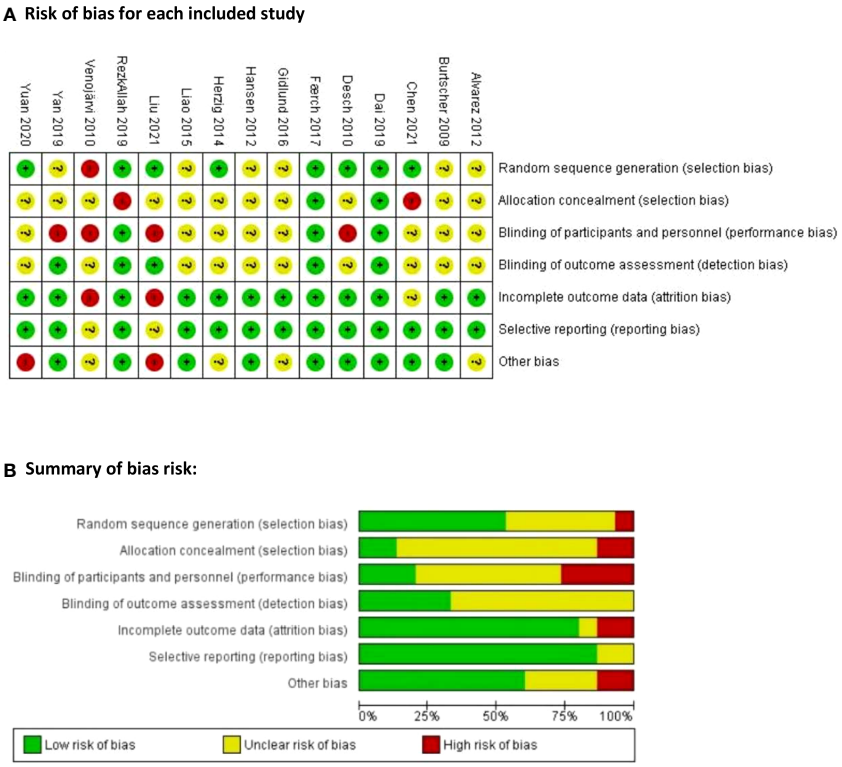

FIGURE 2
Risk of bias assessment for the included studies. **(A)** Risk of bias for each included study: "+" represents low risk of bias; "−" represents high risk of bias; and "?" represents unclear risk of bias **(B)** Summary of bias risk:.

applicable in most studies due to the nature of the intervention, but unfortunately, they did not report any description of it. Random sequence generation, allocation concealment, and blinding of outcome assessors presented an unclear risk of bias in several studies. However, it was noted that most of the studies had a low risk of attrition and reporting bias. According to the GRADE criteria, the strength of the body of evidence was determined to be low. As only RCTs were included, the strength of the body of evidence was initially considered to be high in terms of the primary outcomes (45). However, due to the small sample size and the risk of bias observed in a considerable proportion of studies, the rating was downgraded to moderate.

Description of exercise modalities

Direct meta-analysis

Fasting plasma glucose (FPG)

Meta-analysis results did not show a statistically significant reduction in FPG after different types of AT compared to the control group (p=0.22). However, studies evaluating RT showed a significant reduction of -6.71 in FPG levels compared to the control group (p=0.03). Similarly, IT resulted in a significant reduction of -7.25 in FPG levels (p=0.03). Detailed information is shown in Figure 3.

Glycated hemoglobin (HbA1c)

Both, AT and RT as exercise modalities (Figure 4) did not show a significant effect on HbA1c levels (p>0.05). However, IT resulted in a significant reduction in HbA1c levels compared to the control group (mean difference [95%CI]: -1.33 [-1.53,-1.12], p<0.0001).

2-Hour postprandial glucose (2hPP)

Results from the studies that used AT and RT as interventions showed no significant reduction in 2hPP levels (Figure 5).

In total AT, RT and IT had a significant effect on reducing FPG levels (Z=2.56, p=0.01). Similarly, the general effect of AT, RT, and IT was statistically significant in reducing HbA1c levels (Z=2.68, p=0.008). However, this effect was not observed in studies that evaluated 2hPP levels using AT and RT as interventions (Z=1.77, p=0.08).

Network meta-analysis

Thirteen studies were included in the network meta-analysis. When comparing different types of physical activity to no exercise, all exercise modalities showed a decrease in glycemic indices (Figure 6). The effect of exercise modalities on lowering FPG and HbA1c was higher for IT compared to other exercise modalities (Mean Difference: -6.70, 95%CI: -18.56, 5.16 for FPG, Mean Difference: -1.25, 95%CI: -1.82,-0.69 for HbA1c). This effect was statistically significant for the reduction of HbA1c. However, for 2hPP levels, the studies included in the network meta-analysis involved AT and RT. Nevertheless, both exercise modalities did not have a notable effect in reducing 2hPP levels in participants with prediabetes (Figure 6C).

The size of the nodes is related to the number of participants in that intervention type, and the thickness of the lines connecting

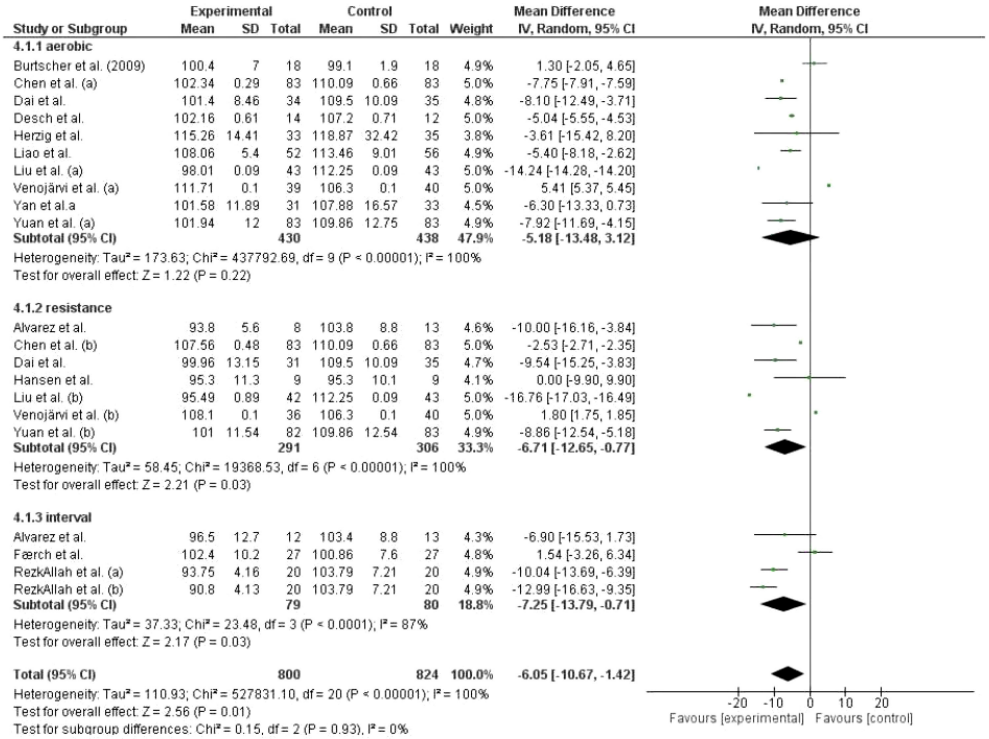

FIGURE 3
Effect of different exercise modalities versus control (no intervention) on FPG.

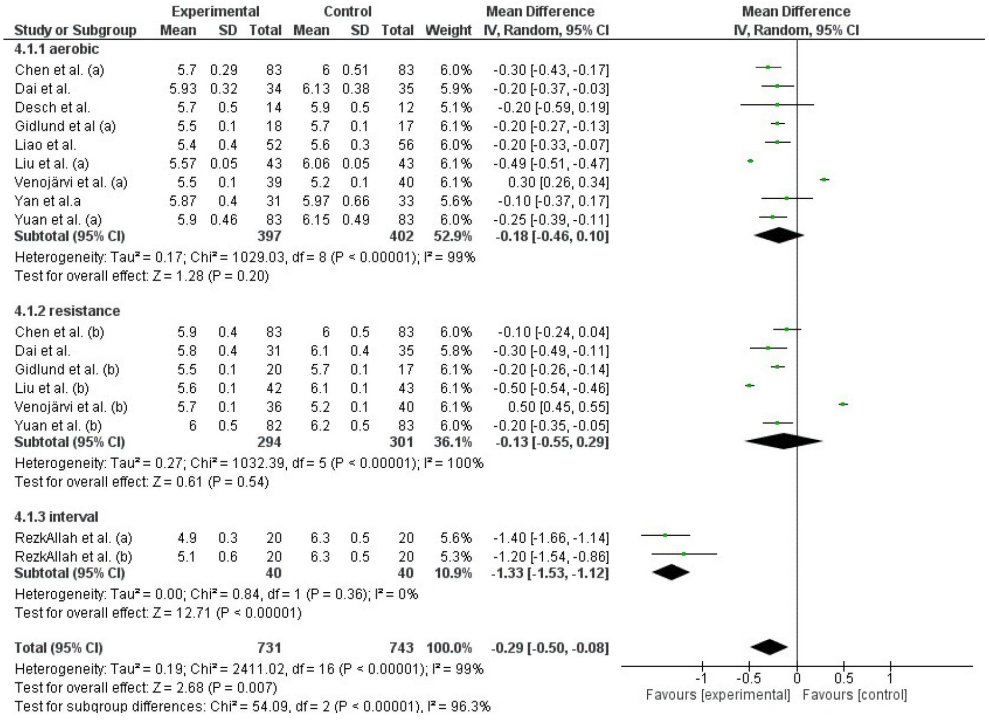

FIGURE 4
Effect of different exercise modalities versus control (no intervention) on HbA1c.

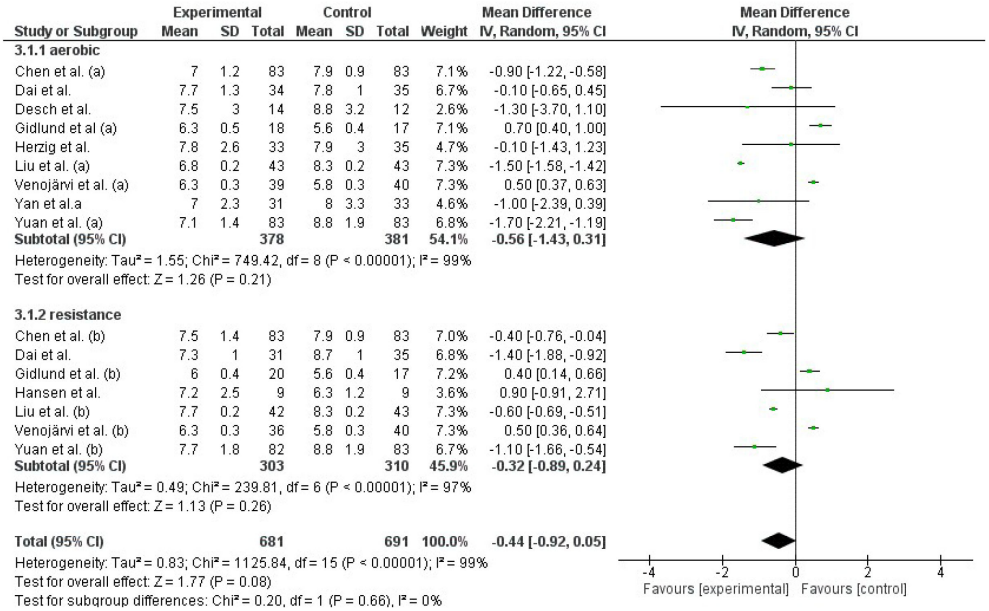

FIGURE 5
Effect of different exercise modalities versus control (no intervention) on 2hPP.

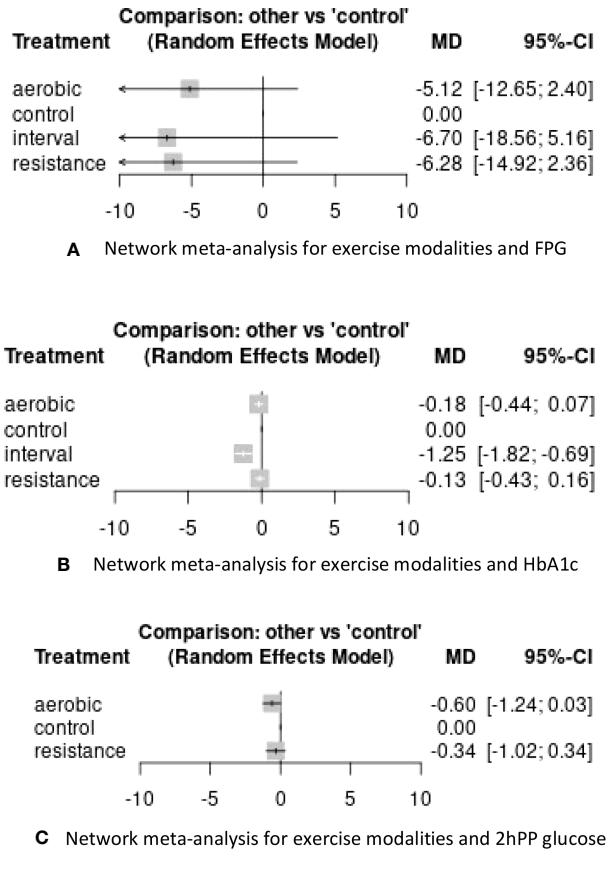

FIGURE 6
Results of network meta-analysis for exercise modalities and glycemic control variables. **(A)** Network meta-analysis for exercise modalities and FPG **(B)** Network meta-analysis for exercise modalities and HbA1c **(C)** Network meta-analysis for exercise modalities and 2hPP glucose.

interventions is linked to the number of studies for that comparison (Figure 7).

Inconsistency between direct and indirect comparisons

The assessment of inconsistency between direct and indirect comparison (Table 2) revealed that no studies had inconsistencies (p value> 0.05).

Discussion

The main findings of the present meta-analysis indicate that IT and RT are useful interventions to control FPG levels in people with prediabetes. In contrast, AT does not show significant differences in FPG levels compared to a control group, and neither does RT in terms of HbA1c or 2hPP glucose levels. Additionally, the network meta-analysis shows that any type of PA in comparison with no exercise achieves lower glycemic indices, and IT shows differences with all other modalities for HbA1c. However, no significant differences were found between AT and RT in any glycemic indexes.

A previous meta-analysis performed with a population with T2D and prediabetes compared HIIT with moderate-intensity continuous training, and found no significant differences in FPG or HbA1c (70). In that meta-analysis, only one study include a population with prediabetes (71), and no differences were also found as well. Another meta-analysis showed that both AT and RT led to reductions in HbA1c compared to a control group (72). In our meta-analysis, we only identified three studies that compared AT with RT, but no significant differences were found. This could be due to the small sample size, or the limited number of studies included in the analysis.

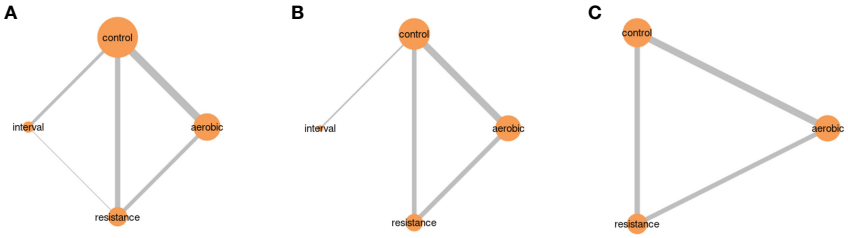

FIGURE 7
Network plots for studies included in network meta-analysis. **(A)** Exercise modalities and FPG **(B)** Exercise modalities and HbA1c **(C)** Exercise modalities and 2hPP glucose.

Interestingly, some evidence suggests that AT appeared to be more effective in isolated IGT as it conferred benefits in 2hPP (73). However, a previous systematic review with diabetic patients concluded that, despite differences in some glycemic control reaching statistical significance in favor of AT, there was no evidence that these differences were of clinical importance or had an impact on cardiovascular risk markers or safety (74). On the other hand, there are contradictions in the role of RT on glycemic control (75–77). In a meta-analysis with the T2D population, RT showed reductions in HbA1c, but there were no correlations between RT intensity, duration, frequency, and changes in HbA1c levels (76). Another meta-analysis with the T2D population observed greater reductions in HbA1c when RT was performed at a moderate-vigorous intensity compared to light intensity, indicating that the training component with the greatest effect on HbA1c is intensity, rather than frequency or duration (77, 78). Another study conducted with an adult population with T2D showed that RT was more effective than AT in HbA1c control (75). However, the small sample size of the study (n=20) and the short duration of the intervention (only 10 weeks) could limit the changes in HbA1c. In contrast, a recent meta-analysis with a prediabetic population that compared AT with RT or a combination of both, concluded that all modalities exerted beneficial effects, but AT or a combination of AT and RT provided better glycemic control than RT alone (72). Moreover, there is evidence suggesting that a combination of AT+RT could provide greater benefits in glycemic control than both modalities separately (79).

One of the possible explanations for the inconsistency of the results obtained in the literature may be due to small sample sizes and interventions not being implemented in a controlled, supervised, and systematic manner. For instance, Yan et al. (2019) found an improvement in HbA1c levels with AT after 12 months of intervention compared to RT or the control group, with 35 participants in each group (24). Similarly, Dai et al. (2019) observed a reduction in FPG, HbA1c, and 2hPP in all intervention groups (AT, RT, and AT+RT) compared to the control group, with a similar sample size. In this study, the group that showed the most significant reduction in FPG levels was AT+RT, followed by RT and AT, with a TD2 incidence reduction of 74% in AT+RT, 65% in RT, and 72% in AT (23). By contrast, Yuan et al. (2019) compared AT with RT and a control group and found no differences between AT and RT groups in glycemic control to FPG, 2hPP, or HbA1C (62). However, significant improvements were observed in all three glycemic control variables when comparing AT or RT separately with the control group. In this study, each group had a sample size of 80 participants, and the exercise sessions were well-detailed and supervised.

Rezkallah and Takla (2019) compared an intervention with low versus high volume HIIT with a control group (n=20 in each group). Both interventions improved FPG and HbA1c compared to the control group, and high-volume HIIT showed greater reductions in HbA1C (20). The remarkable aspect of this article is the high intensity of the intervention and the detailed description of the sessions, which ensures a systematization of the intervention. This finding is consistent with other studies that have suggested that the reduction in HbA1C after HIIT is the result of a lowering of hepatic endogenous glucose production (80).

Based on the data of the included studies in this systematic review with meta-analysis, physical activity has a positive effect on the parameters of glycemic control. However, there is insufficient evidence to determine which type of exercise, intensity, duration, and frequency is most beneficial for glycemic control in people with prediabetes. Further research with methodological rigor and larger sample sizes, such as the GLYCEX study (81), should be conducted to provide better levels of evidence to determine which exercise modality is most effective for glycemic control in people with prediabetes.

TABLE 2 Results of the consistency test.

Comparison	No. Studies	NMA	Direct	Indirect	Difference	Diff_95CI_lower	Diff_95CI_upper	P
aerobic:control	10	-5.12457	-5.18343	-3.65091	-1.53253	-40.7095	37.6444	0.938886
aerobic:interval	0	1.574538	NA	1.574538	NA	NA	NA	NA
aerobic:resistance	5	1.159878	0.648912	2.800956	-2.15204	-24.1807	19.8766	0.848154
interval:control	4	-6.69911	-7.23204	1.854081	-9.08612	-59.5678	41.39555	0.72426
resistance:control	7	-6.28445	-6.63509	-3.65317	-2.98192	-29.8052	23.84132	0.827517
interval:resistance	1	-0.41466	2.7	-1.78363	4.483629	-25.7406	34.70788	0.771241

NA, not available.

Among the strengths of this study, we would like to highlight the registration of protocol in PROSPERO, the adoption of state-of-the-art analytical methods, and a comprehensive search strategy that enabled the inclusion of a large number of studies. An extensive search for relevant studies was conducted in literature sources, grey literature, and reference lists of eligible articles. When necessary, the authors of potentially eligible studies were contacted to obtain additional data for meta-analyses. Moreover, followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statements.

However, some limitations should also be acknowledged. Firstly, the control group intervention was not described in detail in most of the studies, possibly leading to an underestimation of the beneficial effects of different exercise modalities when compared to an active control group. Secondly, there is currently no consensus regarding the diagnostic criteria for prediabetes. The ADA defined prediabetes as an FPG between 100 to 125 mg/dL (82), while the WHO define it as an FPG of 110 to 125 mg/dL (83, 84). Moreover, the cut-off levels for HbA1c vary across different guidelines (85, 86). As a result, different studies included subjects with IFG or IGT or both, which could have acted as potential confounders that influenced the results of the meta-analysis. Thirdly, it is possible that this review did not include all relevant publications due to insufficient information, unavailability of authors, or unanswered communication attempts. Fourthly, the variations in duration, frequency (2-5 days/week), length of sessions 20-90 minutes) and intensity (45-90% HR max) among the included studies could limit the comparison of intervention effects. Furthermore, different types of activities were included for AT interventions, such as running, brisk walking, aerobic dancing, nordic walking, and cardiovascular machines, among others. Moreover, in some studies, the exercise intensity was not well defined or was described in a vague manner (41, 50, 56, 57, 60). Lastly, most of the studies showed methodological limitations, such as small sample sizes (8-21 participants per group) and lack of clear information in some data.

Conclusion

This review suggests that exercise interventions could be effective in individuals with prediabetes to reduce the risk of developing T2D. However, these results should be taken with caution as the main variable of assessment in this meta-analysis was glycemic control Engaging in any type of physical exercise leads to improved glycemic control compared to no exercise. Our findings showed that AT was not effective in glycemic control, while RT and IT have demonstrated significant benefits, especially in FPG levels, in individuals with prediabetes compared to a control group. Further studies with larger sample sizes and including control groups are needed to determine which exercise modality, frequency, and duration are needed to reverse prediabetes status and prevent the progression to T2D.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

MB-V, IH-B, and AY contributed to the conception and design of the study. MB-V, NM, AG-P, IH-B, and AY contributed to data acquisition. NG-C and AG-P provided expertise on the topic of the review. IR-C provided expertise in systematic review and meta-analysis methodology. NM and AY performed the statistical analysis. MB-V, NM, AG-P, and AY drafted the manuscript. All authors contributed to the interpretation of the data and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1233312/full#supplementary-material

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Glossary

ADA	American Diabetes Association
AT	Aerobic training
FPG	Fasting plasma glucose
GDM	Gestational diabetes
GLUT-4	Glucose transporter type 4
GRADE	Grade of Recommendations, Assessment, Development, and Evaluation
HbA1c	Glycated hemoglobin
HITT	High-Intensive interval training
IEC	International Expert Committee
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IT	Interval training
MVPA	Moderate-to-vigorous physical activity
NICE	National Institute for Health and Care
PA	Physical activity
OGTT	Oral glucose tolerant test
RCTs	Research clinical trials
RT	Resistance Training
SD	Standard deviation
T2D	Type 2 diabetes mellitus
VAT	Visceral adipose tissue
WHO	World Health Organization
2hPP	2-hour post prandial.