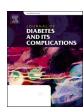


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Impact of aerobic exercise on cardiometabolic health in patients with diabesity: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Purpose: This systematic review and meta-analysis of randomized controlled trials (RCTs) aimed to evaluate the effects of aerobic exercise on cardiometabolic health-related indices in patients with type 2 diabetes and concurrent overweight/obesity (diabesity).

Methods: PubMed, Web of Science, Scopus, Science Direct, Cochrane Library, and Google Scholar databases were searched from inception to October 2024. The search strategy included the following keywords: diabetes, aerobic exercise, and endurance training. RCTs comparing aerobic exercise training ≥ 2 weeks in duration to standard treatment were considered eligible. Participants were adults with diabesity.

Results: A total of 1391 middle-aged/older adult patients (55 % females) were included in 34 RCTs. Body mass index [standardized mean differences (SMD) -0.18 kg/m², 95 % confidence intervals (CI) -0.36 to -0.01]. waist circumference (SMD -0.23 cm, 95 % CI -0.44 to -0.03), body fat (SMD -0.30 %, 95 % CI -0.59 to -0.01), fasting blood glucose (SMD -0.49 mmol/L, 95 % CI -0.72 to -0.27), glycated hemoglobin (SMD -0.79 %, 95 % CI -1.17 to

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-0.41), fasting insulin (SMD -0.44 mIU/L, 95 % CI -0.72 to -0.15), homeostatic model assessment for insulin resistance (SMD -0.72, 95 % CI -1.09 to -0.35), high-density lipoprotein cholesterol (SMD 0.32 mg/dL, 95 % CI 0.01 to 0.63), triglycerides (SMD -0.33 mg/dL, 95 % CI -0.63 to -0.04), and total cholesterol (SMD -0.28 mg/dL, 95 % CI -0.47 to -0.10) improved compared with standard treatment.

Conclusions: These results underscore the beneficial role of aerobic exercise as a non-pharmacological intervention in managing and treating patients with diabesity when compared to standard treatment, despite the presence of considerable uncertainty in several outcomes.

1. Introduction

Diabesity, a complex medical condition, refers to the simultaneous presence of type 2 diabetes and obesity, which are connected by various pathophysiological mechanisms. 1,2 Diabesity is also a significant global health concern that contributes to an elevated risk of cardiovascular disease morbidity and mortality. 1.3,4 As a result, individuals with diabesity often demonstrate metabolic derangements and cardiovascular dysfunction, such as raised blood glucose levels, insulin resistance, elevated levels of visceral fat, impaired lipid profiles, and abnormal blood pressure, or combinations thereof.^{3,4} Patients with diabesity are typically characterized by poor functionality, which leads to diminished musculoskeletal fitness parameters and reduced health-related quality of life.. 5,6 Similarly, populations with glucose homeostasis derangements and excess adiposity generally exhibit low levels of habitual physical activity and cardiorespiratory fitness that are associated with elevated metabolic risk factors. 7,8 Accordingly, there has been a notable shift in focus towards non-pharmacological interventions, such as aerobic exercise training, to enhance overall cardiometabolic health. This has become a pivotal objective for medical practitioners, healthcare professionals, and public health decision-makers, focused on the deleterious health effects and escalating financial costs concomitant with diabesity.5

Exercise interventions are broadly suggested for preventing, managing, and treating diabesity. 10-13 Particularly, aerobic exercise has been identified as a feasible and efficient lifestyle strategy by the American College of Sports Medicine (ACSM) and other leading international scientific authorities. 14 Specifically, regular aerobic exercise, also defined as continuous endurance training, represents exercise designed to improve cardiorespiratory fitness, a strong prognostic indicator, by applying rhythmic and repetitive bodily movement that requires the body to increasingly utilize oxygen as a source of energy, using the large muscle groups. 15 Current guidelines from the ACSM, the American Diabetes Association, and the World Health Organization recommend moderate-intensity aerobic exercise at least three times per week for people with cardiovascular complications and metabolic dysregulation, without accompanying weight loss. 10,11,15,16 In particular, aerobic exercise training may be an effective approach for improving cardiometabolic health-related indicators in individuals with diabesity, with or without other comorbid conditions. 17–19 However, the existing evidence is weak because it is not generalizable and is not focused on individuals with diabesity.

Aerobic exercise interventions appear to provide safe and effective training options for individuals with diabesity to combat the associated metabolic health complications. ^{10,15,20,21} The incorporation of aerobic exercise is a powerful physiological stimulus that may lead to beneficial outcomes for individuals with type 2 diabetes and excess body weight or adiposity, including improvements in glycemic control, resting cardio-vascular hemodynamic responses, indices of low-grade chronic inflammation, and mental health. ^{21–25} Nevertheless, this hypothesis necessitates further validation and investigation to incorporate all pertinent evidence necessary to accurately update the current physical activity guidelines. ^{10,11,15} Unfortunately, previous relevant studies often failed to include a broad spectrum of cardiometabolic health-related indices and to account for the occurrence of overweight or obesity. ^{21,25–27} Moreover, regular moderate-intensity aerobic exercise is

associated with a reduced cardiovascular disease mortality rate compared with non-exercising controls and appears that a combination of muscle strengthening and this modality results in an independent and cumulative effect. ^{28,29} Furthermore, aerobic exercise plays a pivotal role in exercise-based cardiac rehabilitation. ³⁰ A preliminary assessment of the literature suggests further investigation is needed because few data on the influence of aerobic exercise on cardiometabolic health markers outcomes in patients with diabesity are available.

Despite abundant evidence indicating the favorable effect of chronic resistance training in partially mitigating the cardiometabolic risk associated with obesity and type 2 diabetes, \$10,15,16,31,32\$ the effectiveness of aerobic exercise per se, or superimposed on resistance training, for eliciting beneficial adaptations, remains not fully identified. The objective of the present review was to evaluate the influence of aerobic exercise on a broad range of cardiometabolic health outcomes in patients with diabesity. The outcomes included anthropometric characteristics, body composition parameters, glucose homeostasis, blood lipids, as well as resting hemodynamic responses, measures of low-grade chronic inflammation, liver function, adipokines, and physical function, respectively.

2. Methods

2.1. Registration

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement³³ and the Cochrane Handbook for Systematic Reviews of Interventions guidelines.³⁴ The study protocol was registered on the Open Science Framework registry (https://osf.io/hvrk9).Because this study did not include individual patient data and all eligible studies were previously published, approval was not required from our institutional bioethics committee.

2.2. Literature search strategy

A comprehensive electronic search was conducted across databases such as PubMed, Scopus, Web of Science, Cochrane Library, Science-Direct, and Google Scholar. Five authors (S.B.A.M., N.H.A., B.B.S., A.F. A., and A.B.) utilized a targeted combination of keywords and Boolean operators like "AND" and "OR" to systematically search the literature up to October 2024. The search terms ("Diabetes") AND ("Exercise" OR "Training") were employed to identify pertinent studies. The search strategy was structured using the PICOS framework: (P) Population: patients with type 2 diabetes and concurrent overweight/obesity; (I) Intervention: aerobic exercise alone, including continuous endurance training trials; (C) Comparator: no exercise or standard treatment; (O) Outcomes: primary - anthropometric measures (body mass, BMI, waist and hip circumference, waist-to-hip ratio), body composition (body fat, fat mass, fat-free mass), lipid metabolism (HDL-C, LDL-C, total cholesterol, triglycerides), glucose metabolism (fasting blood glucose, HbA1c, fasting insulin, HOMA-IR); secondary – resting hemodynamic responses (resting heart rate, systolic and diastolic blood pressure), markers of low-grade chronic inflammation (hs-CRP, IL-6, TNF-α), liver function (ALT, AST), adipokines (adiponectin, leptin), physical function (VO₂max, sit-to-stand test).; and (S) Study type: randomized controlled

trials (RCTs). Additionally, reference lists of selected reports and relevant systematic reviews were examined to identify further studies meeting the inclusion criteria.

2.3. Eligibility criteria

The inclusion criteria for the studies were: a) participants: adults (≥18 years) diagnosed with type 2 diabetes and concurrent overweight or obesity (BMI \geq 25 kg/m²), with or without additional comorbidities; b) intervention: studies implementing standard treatment combined with aerobic exercise interventions, including continuous endurance training; c) outcomes: assessment of at least one primary outcome related to anthropometric measures, body composition, lipid metabolism, or glucose metabolism in human participants. Secondary outcomes associated with cardiometabolic health indices were also considered; d) publication criteria: full-text articles published in refereed journals up to October 2024, with no language restrictions, and adherence to the Declaration of Helsinki; and e) study design: randomized controlled trials (RCTs). The exclusion criteria included: a) studies involving mixed samples of patients with type 2 diabetes, overweight/obesity, and other chronic conditions within the same intervention arm; b) research including children and/or adolescents (<18 years); c) investigations where the effects of the aerobic exercise intervention could not be isolated due to its inclusion as part of a multidimensional treatment regimen (e.g., combined diet and aerobic exercise), d) publications that did not assess any of the primary outcome measures of interest; e) studies employing acute exercise interventions (<2 weeks); f) review articles, case reports, studies lacking a control group, and those with ambiguous or unclear data. This structured approach ensures the inclusion of high-quality evidence to assess the efficacy of aerobic exercise interventions in managing type 2 diabetes among adults with overweight or obesity.

2.4. Study selection

Four researchers (S.B.A.M., N.H.A., B.B.S., and A.F.A.) conducted a linear evaluation to determine study eligibility. They began by reviewing titles and abstracts, proceeding to full-text assessments as necessary. Studies meeting the inclusion criteria underwent comprehensive evaluation. In cases of disagreement or uncertainty, a fifth researcher (A.B.) provided an independent assessment. To manage the search results, the team utilized EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA), a reference-management software that facilitates organizing and sharing research materials.

2.5. Data extraction

Two independent authors (S.B.A.M. and A.B.) conducted data extraction from the selected randomized controlled trials (RCTs) after thorough full-text reviews. The 34 included RCTs provided comprehensive datasets, detailing information such as lead author, publication year, demographic characteristics, gender distribution, sample size, specifics of the exercise intervention (frequency, intensity, duration, type), study duration, and predefined outcome measures. These details were systematically organized and summarized in Table 1.

2.6. Risk of Bias assessment

Two authors (S.B.A.M. and A.B.) independently evaluated the risk of bias in each study using the Cochrane Collaboration's risk of bias tool. ³⁵ In cases of disagreement or uncertainty, a third author (N.O.) was consulted for resolution. The assessment criteria included: a) random sequence generation; b) allocation concealment; c) welcome; d) blinding of participants and personnel; d) blinding of outcome assessors; e) completeness of outcome data; f) selective outcome reporting; and g) other potential biases. These criteria align with the domains specified in

the Cochrane Handbook for Systematic Reviews of Interventions. 36 Based on these assessments, studies were categorized into three risk levels: low, some concerns, or high. 37

2.7. Data analysis

All statistical analyses were conducted using Review Manager (RevMan) 5.4, a software developed by the Cochrane Collaboration. A random-effects model was employed to account for variability among studies. The presence of heterogeneity among studies was assessed through the implementation of the Cochran's Q-test and the I2 statistic as previously articulated. ¹⁹ The I² statistic quantifies the proportion of total variation across studies attributable to heterogeneity, with values interpreted as follows: low heterogeneity (0 %-40 %), moderate heterogeneity (30 %-60 %), and substantial heterogeneity (50 %-90 %), and considerable heterogeneity (75 %–100 %). Effect sizes were calculated using mean differences (MD) or standardized mean differences (SMD), each accompanied by 95 % confidence intervals (CI). MD was employed when outcome measures were consistent and measured on the same scale across studies, whereas SMD was used when outcome measures varied in scales or units. A two-sided p-value of less than 0.05 was considered statistically significant.

2.8. Grading quality of evidence

Two authors (S.B.A.M. and A.B.) independently evaluated the quality of evidence for both primary and secondary outcomes using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework, with one author (S.B.A.M.) providing access to the framework (available at https://www.gradepro.org). ³⁸The factors evaluated included risk of bias, inconsistency, indirectness, imprecision, publication bias, and the classification of evidence into categories of very low, low, moderate, or high quality. In cases of disagreements or uncertainties, a third author (N.O.) was consulted to help address and resolve these issues. Evidence may be upgraded based on factors like a substantial effect size, a clear dose-response relationship, or when potential confounders would either reduce a demonstrated effect or suggest a false effect in the absence of any real effect. On the other hand, factors that could lead to downgrading include risk of bias, inconsistency in results, indirect evidence, imprecision, and publication bias. Additionally, Egger's regression test was used to detect asymmetry in the funnel plot, which can indicate bias or heterogeneity in specific outcomes, especially when fewer than 10 studies of varying sizes contribute to each outcome. ^{37,39} This analysis was performed using Comprehensive Meta-Analysis software version 4 (Biostat, Englewood, NJ, USA) (Borenstein, 2022).

2.9. Subgroup analysis

A subgroup analysis was conducted when the I2 statistic surpassed 50 %. Given the considerable diversity in the duration of the interventions employed in RCTs investigating aerobic exercise in type 2 diabetes, 40 a subgroup analysis was conducted to identify potential differences in primary outcomes based on the duration of the intervention ($\leq\!16$ weeks vs. $>\!16$ weeks) in studies examining the impact of aerobic exercise on body mass, FBG, and HbA1c.

2.10. Sensitivity analysis

A sensitivity analysis was performed to evaluate the impact of potential bias on the assessment of performance and detection results.

2.11. Equity, diversity and inclusion

The author team was varied in terms of age, gender, academic background, and geographic origin, with representation from

Table 1
Characteristics of the included studies.

Study (first author)	Country (year)	MCC	Length (weeks)	Sample (N / F / M)	Age (yrs) (Mean ± SD)	BMI (kg/m ²) (Mean ± SD)	ADH to AE	AE interventions' training parameters	Outcome measures	
1. Ligtenberg et al.	Netherlands (1997)	No	26	58/20/ 38 ST = 28 AE = 30	62.0 ± 5.0	30.0 ± 4.0	83 %	$3\times$ /week; 60 %–80 % VO $_2$ max; cycling, swimming, treadmill, rowing;	HbAlc, FI, VO ₂ max, TC, HDL—C, LDL-C, TG	
2. Kadoglou et al.	Greece (2010)	No	52	60/60/ 0 ST = 30 AE = 30	56.9 ± 7.1	30.7 ± 4.8	93 %	$4\times$ /week; 50 %–80 % $VO_2peak;$ 30–45 min	BMI, FM, TG, HDL—C, LDL-C, TC, VO ₂ max, hs-CRP, HbA1c, FI, IL-10, IL-18, SBP, DBP	
3. Rönnemaa et al.	Finland (1986)	Yes	16	25/20/ 5 ST = 12 AE = 13	52.5 ± 7.5	$\begin{array}{c} 28.0\ \pm \\ 2.7\end{array}$	85 %	5-7×/week; 70 % $\rm VO_2max$; 45 min; walking, jogging, or skiing.	FBG, HbA1c, FI	
4. O'Donovan et al.	United Kingdom (2005)	No	24	64/0/ 64 $ST = 20$ $AE = 44$	41.5 ± 1.5	28.7 ± 4.9	96 %	$3\times$ /week; 60 %–80 % VO_2max ; cycling.	BMI, WC, BF, TG, FBG, FI, HOMA-IR, VO $_2$ max	
5. Motahari- Tabari et al.	Iran (2015)	No	8	53/53/ 0 $ST = 26$ $AE = 27$	49.3 ± 8.2	30.3 ± 4.8	93 %	3×/week; 60 % HRmax; 30 min; walking.	BMI, WC, HC, WHR, FBG, FI, HOMA-IR	
6. Brun et al.	France (2008)	No	52	53/0/ 53 $ST = 26$ $AE = 27$	59.7 ± 2.0	32.8 ± 6.2	100 %	2×/week; 45 min; brisk walking, jogging, or gymnastics at the ventilatory threshold.	BMI, SBP, DBP, WC, HC, WHR, FBG, FI, HOMA-IR, HbA1c, TC, HDL—C, LDL-C, TG, VO ₂ max	
7. Kadoglou et al. Original study	Greece (2007a)	No	24	60/60/0 ST = 30 AE = 30	61.6 ± 4.9	$32.1\ \pm$ 3.2	97 %	$4\times$ /week; 50 %–75 % VO $_2$ peak; 45–60 min, walking, jogging, cycling, and calisthenics.	FBG, FI, HOMA-IR, TC, HDL—C, LDL-C, TG, hs-CRP,	
8. Kadoglou et al. ⁶² Report of #7	Greece (2007)	No	16	60/60/ 0 ST = 30 AE = 30	56.8 ± 6.7	$31.8 \pm \\3.8$	93 %	$4\times$ /week; 50 %–85 % VO $_2$ max; 45–60 min; walking, jogging, cycling, and calisthenics.	BM, BMI, WHR, FI, L-6, SBP, DBP	
9. Sridhar et al.	India (2010)	Yes	52	105/ $58/47$ $ST = 50$ $AE = 55$	$\begin{array}{c} \textbf{61.8} \pm \\ \textbf{3.1} \end{array}$	$\begin{array}{c} \textbf{27.0} \; \pm \\ \textbf{0.2} \end{array}$	100 %	$7\times\!\!/\text{week};$ 30 min; cycling or walking (treadmill).	BMI, SBP, DBP, HbA1c	
10. Conners et al.	United States (2019)	No	12	26/10/ 16 $ST = 13$ $AE = 13$	58.0 ± 5.0	28.2 ± 6.9	100 %	3×/week; 40 %–70 % HRpeak; 30–60 min; underwater treadmill training.	BMI, WC, TC, HDL—C, LDL-C TG, HbA1c, SBP, DBP.	
11. Middlebrooke et al.	United Kingdom (2006)	No	24	52/28/ 24 $ST = 30$ $AE = 22$	61.8 ± 7.7	31.8 ± 4.5	68 %	3×/week; 70 %–80 % HRmax; 30 min; two supervised group exercise and one home-based sessions.	BMI, WC, HC, WHR, TC, HDL—C, LDL-C, TG, FBG, FI, SBP, DBP	
12. Ribeiro et al.	Brazil (2008)	No	16	21/7/ 14 $ST = 10$ $AE = 11$	59.0 ± 7.0	$\begin{array}{c} 29.0\ \pm\\ 3.0 \end{array}$	100 %	3×/week; 40 min; exercise intensity was adjusted between the anaerobic threshold and the respiratory compensation point; cycling.	BMI, WC, FBG, FI, HOMA-IR, HbA1c, VO_2 max	
13. Ku et al.	South Korea (2010)	No	12	31/31/ 0 $ST = 16$ $AE = 15$	55.7 ± 6.2	$\begin{array}{c} 27.1\ \pm\\ 2.3\end{array}$	100 %	$5\times$ /week; 3.6–5.2 METs; 60 min; walking.	BMI, WC, TC, HDL—C, LDL-C TG, HbA1c, ADPN, LEP, SBP, DBP	
14. Dela et al.	Denmark (2004)	No	12	24/0/ 24 $ST = 10$ $AE = 14$	54.0 ± 2.0	$31.0\ \pm$ 1.0	100 %	$5\times$ /week; 50 %–75 % $VO_2max;$ 30–40 min; cycling.	BMI, FBG, FI, HbA1c	
15. Wilson et al.	New Zealand (2019)	No	12	$16/7/9 \\ ST = 5 \\ AE = 11$	52.0 ± 2.0	32.1 ± 3.3	100 %	3×/week; 70 %–90 % HRpeak; 20–30 min; cycling.	BMI, FM, HbA1c, VO ₂ peak,	
16. Boudou et al.	France (2000)	No	8	20/0/ 20 $ST = 8$ $AE = 8$	46.8 ± 7.7	28.0 ± 4.0	75 %	3×/week; 75 % VO₂peak; 45 min; cycling.	BMI, WG, WHR, FM, FI, HbA1c, VO_2 peak	
17. Yan et al.	Mozambique (2014)	Yes	12	32/0/ 32 $ST = 10$ $AE = 22$	53.0 ± 2.0	27.2 ± 0.7	100 %	$3\text{-}5\times/\text{week}; 50 \%\text{-}75 \% \text{ VO}_2\text{peak}; 45 min; walking.}$	BMI, WC, HC, WHR, SBP, DBP, BF, FBG, VO ₂ max	
18. Shenoy et al. Original study	India (2009)	No	16	$\begin{array}{c} 20/14/\\ 6\\ ST=10 \end{array}$	52.2 ± 9.3	$\begin{array}{c} 26.2 \pm \\ 3.2 \end{array}$	100 %	3×/week, 30 min, walking.	FBG, HbA1c, SBP, DBP, RHR	
				AE = 10					(continued on next page)	

Table 1 (continued)

itudy first author)	Country (year)	MCC	Length (weeks)	Sample (N / F / M)	Age (yrs) (Mean ± SD)	BMI (kg/m ²) (Mean ± SD)	ADH to AE	AE interventions' training parameters	Outcome measures
9. Arora et al.									BMI, HDL-C
Report of #18 20. Church et al.	United States (2010)	No	36	113/ 51/62 ST = 41 AE = 72	55.8 ± 8.7	$34.8 \pm \\6.2$	93 %	$3\text{-}5\times/\text{week}$; 12 kcal/kg per week; 50 %–80 % VO $_2$ max; 150 min/week; walking.	BM, HbA1c
21. Swift et al. 102				nL - 72			93 %		FM, FFM
Report of #20 22. Lambers et al.	Belgium (2008)	No	12	35/35/ 0 ST = 16	55.8 ± 9.7	30.9 ± 4.0	95 %	3×/week; 60 %–85 % HRpeak; 60 min; walking, jogging, cycling, or stepping.	BMI, WC, HbA1c, SBP, DBP VO_2 peak
23. Jorge et al. Original study	Brazil (2011)	No	12	AE = 19 23/9/ 14 ST = 12	57.9 ± 9.8	30.0 ± 4.0	82 %	$3\times$ /week; intensity at the lactate threshold; 60 min; cycling.	BMI, WHR, FBG, HOMA-IR, HbA1c, TC, HDL—C, LDL-C TG, SBP, DBP, ADPN,
4. Oliveira et al.				AE = 11			82 %		VO_2 max, hs-CRP, IL-6, TNF BM, WC, BF, LDL-C, AST, A
Report of #23 25. Sigal et al. Original study	Canada (2007)	No	22	122/ 79/43 ST = 62	53.5 ± 7.3	$35.6 \pm \\10.1$	87 %	3×/week; 60 %–75 % HRmax; 15–45 min; walking, jogging, or cycling.	BM, BMI, BF, FM, FFM, HbA1c, TC, HDL—C, LDL-C TG, SBP, DBP
6. Reid et al.				AE = 60			87 %		ВМІ
Report of #25 7. Yavari et al.	Iran (2012)	No	52	40 /28/ 32	50.9 ± 9.8	$32.0 \pm \\ 4.9$	85 %	3×/week; 60 %–75 % HRmax; 20–60 min; walking, jogging, cycling, or	HbA1c, VO ₂ max
28. Cuff et al.	Canada (2003)	No	16	ST = 20 $AE = 20$ $18/18/$ 0 $ST = 9$	$63.4 \pm \\2.2$	$36.7 \pm \\2.0$	100 %	elliptical trainer. 3×/week; 75 min; walking/running, cycling, recumbent steppers, elliptical trainer, and rowing machines.	$ m VO_2$ peak
29. Sabouri et al.	Iran (2021)	No	12	AE = 9 29/15/ 14 ST = 13	52.5 ± 4.8	$\begin{array}{c} \textbf{28.0} \pm \\ \textbf{2.8} \end{array}$	100 %	$3\times$ /week; 70 % HRmax; 30 min; cycling.	BM, BMI, SBP, DBP, FBG, F HOMA-IR, HbA1c, TC, HDL—C, LDL-C, TG, VO ₂ ma
30. Ranasinghe et al. ⁶⁵	Sri Lanka (2021)	Yes	12	AE = 16 58/27/ 31 ST = 30 AE = 28	50.1 ± 8.7	26.4 ± 4.0	100 %	$2\times$ /week; 60 %–75 % HRmax; 75 min; walking, stepping, and cycling.	BM, BMI, TC, HDL—C, LDL TG, AST, ALT, hs-CRP
31. Findikoglu et al. ⁶⁶	Turkey (2023)	No	12	40/6/ 34 ST = 20 AE = 20	57.5 ± 7.8	$33.2 \pm \\3.5$	100 %	$3\times$ /week; 50 % VO ₂ peak, cycling.	BM, WC, BF, FM, FFM, HbA: TC, HDL—C, LDL-C, TG, SB DBP
32. Mitranun et al. ⁶⁷	Thailand (2014)	No	12	29/10/ 19 ST = 15 AE = 14	60.9 ± 2.4	$\begin{array}{c} 29.7 \pm \\ 0.4 \end{array}$	93 %	$3\times$ /week; 50 % VO2max; 30–40 min, walking.	BM, BMI, WC, HC, WHR, FE HOMA-IR, HbA1c, TC, HDL—C, LDL-C, TG, SBP, DBP, VO ₂ max
33. Way et al. ⁵⁶	Australia (2020)	Yes	12	23/14/ 9 ST = 11 AE = 12	56.9 ± 2.1	37.5 ± 5.4	83 %	$3\times$ /week; 60 % VO_2peak ; 45 min; cycling.	BM, BMI, WC, FBG, FI, HbA, TC, HDL—C, LDL-C, TG, SB DBP, VO_2max
34. Karstoft et al. ⁵⁷	Denmark (2013)	No	16	20/13/ 7 $ST = 8$ $AE = 12$	60.8 ± 2.2	$\begin{array}{c} 29.0 \ \pm \\ 1.3 \end{array}$	92 %	$5\times$ /week; $55~\%$ VO ₂ peak; 60 min; walking.	BM, BMI, WC, HC, WHR, B FM, FFM, FBG, HbA1c, TC, HDL—C, LDL-C, TG, SBP, DBP, VO ₂ max
35. Ghardashi Afousi et al. ⁷⁴	Iran (2018)	No	12	34/16/ 18 ST = 17 AE = 17	54.8 ± 6.2	$29.3 \pm \\1.3$	100 %	$3\times$ /week; 70 % VO2peak; 42 min, cycling.	BM, BMI, BF, FM, FFM, FBG FI, HOMA-IR, HbA1c, TC, HDL—C, LDL-C, TG, SBP, DBP, VO ₂ max
36. Gildea et al. ⁵⁸	Ireland (2021)	No	12	19/11/ 8 ST = 9 AE = 10	53.0 ± 10.0	30.0 ± 5.7	80 %	3×/week; 70 % HRpeak; 47 min; cycling.	BMI, and VO ₂ max
37. Li et al. ⁶⁸	China (2022)	No	12	AE = 10 $24/0/$ 24 $ST = 12$	$\begin{array}{c} \textbf{39.0} \pm \\ \textbf{5.0} \end{array}$	$\begin{array}{c} 26.8 \; \pm \\ 4.2 \end{array}$	92 %	$5\times$ /week; 50 %–70 % VO $_2$ max; 30 min; cycling.	BM, BMI, FBG, FI, HbA1c, SBP, DBP, VO $_2$ max

(continued on next page)

Table 1 (continued)

Study (first author)	Country (year)	MCC	Length (weeks)	Sample (N / F / M)	Age (yrs) (Mean ± SD)	BMI (kg/m ²) (Mean ± SD)	ADH to AE	AE interventions' training parameters	Outcome measures
38. Hwang et al. ⁵⁹	United States (2019)	No	8	35/27/ 8 ST = 16 AE = 19	63.0 ± 1.0	32.4 ± 0.8	84 %	4×/week; 70 % HRmax; 45 min, cycling.	BM, BMI, WC, WHR, BF, FM, FFM, FBG, FI, HbA1c, HOMA-IR, TC, HDL—C, LDL-C, TG. SBP, DBP, VO ₂ max
39. Winding et al. ⁶⁰	Denmark (2018)	No	11	19/12/ 7 $ST = 7$ $AE = 12$	58.0 ± 8.0	$28.3 \pm \\3.2$	100 %	$3\times/\text{week};$ 50 % $\text{VO}_2\text{peak};$ 40 min; cycling.	BM, BMI, FM, FFM, RHR, SBP, DBP, VO ₂ max, FBG, FI, HbA1c, HOMA-IR, TC, HDL, LDL, TG, FBG

ADH: Adherence, ADPN: Adiponectin, AE: Aerobic Exercise, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, BF: Body Fat, BM: Body Mass, BMI: Body Mass Index, hs-CRP: High Sensitivity C-Reactive Protein, DBP: Diastolic Blood Pressure, F: Females, FFM: Fat-Free Mass, FBG: Fasting Glucose, FI: Fasting Insulin, FM: Fat Mass, HbA1c: Glycated Hemoglobin, HC: Hip Circumference, HDL-C: High-Density Lipoprotein Cholesterol, IL: Interleukin, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, HRmax: Maximum Heart Rate, HRpeak: Peak Heart Rate, LDL-C: Low-Density Lipoprotein Cholesterol, M: Males, MCC: Major Complications or Comorbidities, N: Sample Size, RHR: Resting Heart Rate, SBP: Systolic Blood Pressure, SD: Standard Deviation, ST: Standard Treatment, TC: Total Cholesterol, TG: Triglycerides, TNF- α : Tumor Necrosis Factor α , VO₂max: Maximum Oxygen Consumption, VO₂peak: Peak Oxygen Consumption, WC: Waist Circumference, WHR: Waist-to-Hip Ratio.

researchers at different stages of their careers. The study population was inclusive, not limited by factors like region, race, education, socioeconomic status, or other demographic attributes.

3. Results

3.1. Literature search and selection

A total of 24,417 studies were initially retrieved from the specified databases, including PubMed, Scopus, Web of Science, Cochrane Library, Science Direct, and Google Scholar (Fig. 1). Subsequent to the removal of duplicates, the total number of studies decreased to 19,594,

which were then subjected to further assessment. Subsequent to a thorough review of titles and abstracts based on predefined inclusion and exclusion criteria, 19,543 studies were excluded. The remaining 51 reports were then subjected to thorough review, resulting in the exclusion of 17 for specific reasons (Table S2). Additionally, five investigations were identified as follow-up studies of the original trials reviewed (Table S3). Consequently, 34 studies were included in this systemic review and meta-analysis, with data extracted from 1391 patients [55/45 female/male ratio; mean (SD) age, 56.2 (7.8) years; mean (SD) BMI, 30.4 (4.2) kg/ m^2] who met the eligibility criteria.

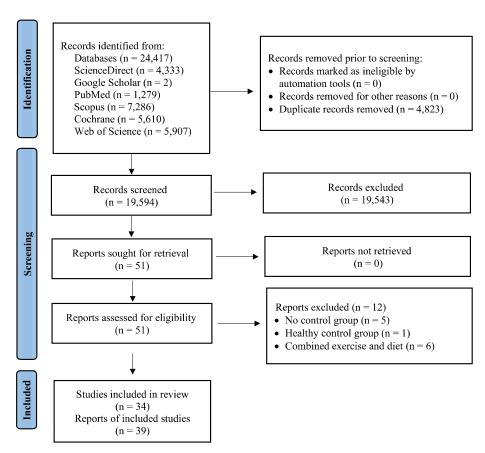


Fig. 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram. RCT, randomized controlled trial.

3.2. Literature characteristics

Table 1 delineates the characteristics of the included studies. The reports were published between 1986 and 2024, with 17 studies (50 %) published from 1986 to 2010 and another 17 studies (50 %) published from 2011 to 2024. Trials were conducted in 21 countries: Asia (n = 10[29 %]), Europe (n = 15 [44 %]), North America (n = 5 [15 %]), South America (n = 2 [6 %]), Australia (n = 1 [3 %]), and Africa (n = 1 [3 %]). In accordance with the World Bank's classification system (http://data. worldbank.org/about/country-and-lending-groups), 19 of the 34 trials were from high-income countries, 41-59 eight were from upper-middleincome countries, 60-67 and seven were from lower-middle-income countries.^{68–74} A total of 34 trials were reported; however, only four of these trials documented the presence of comorbidities. 43,64,69,70 Nineteen studies involved short-term exercise interventions with a duration of 8–12 weeks. 45,46,48–50,52,55,57–59,63–68,70,73,74 In contrast. fifteen studies focused on long-term exercise interventions with a duration of 16–48 weeks. 41–44,47,51,53,54,56,60–62,69,71,72 The mean attendance rate was 93 %, with a range of 68 % to 100 % across all aerobic exercise intervention groups. The most frequently reported exercise training protocol was a 12-week walking or cycle ergometer routine, conducted three times a week (45 min/session) at 70 %-75 % of maximum heart rate, requiring a weekly time commitment of 135 min.

3.3. Risk of Bias assessment results

As illustrated in Fig. 2, a comprehensive summary of the risk of bias assessment is provided. A substantial proportion of the eligible studies have indicated concerns regarding the processes of randomization, allocation concealment, and blinding of outcome assessment. The primary concern pertains to the inability to make a definitive bias determination, particularly in the context of randomization and allocation. The determination of high risk of bias was exclusively observed in the domains of performance, detection, and attrition bias, with minimal instances identified in the latter two domains. Conversely, a limited number of studies exhibited a high risk of bias with regard to blinding of participants/personnel, a practice that is commonly observed in human exercise training studies. Conversely, the majority of studies demonstrated a low risk of bias concerning incomplete outcome data and selective reporting. Fig. S1 and Table S4 provide details of the risk of bias judgment per domain for each eligible study. The certainty of the outcomes varied from very low to low, with evidence being downgraded for specific reasons. These included small sample sizes in both the standard treatment and aerobic exercise groups across the included studies, a high risk of bias, and moderate to substantial heterogeneity (Table 2).

3.4. Primary outcomes

3.4.1. Anthropometrics

Body mass and BMI were reported in 26 and 23 trials, involving 1029 and 795 participants, respectively. No significant changes were observed between aerobic exercise and standard treatment groups in body mass (Figs. S2a and S2b). Aerobic exercise cohorts demonstrated a significant reduction in BMI compared with standard treatment (SMD -0.18 kg/m^2 , 95 % CI -0.36 to -0.01; $I^2 = 32 \text{ %}$; p = 0.04; very low certainty). Waist and hip circumferences and WHR were reported in 14, four, and six trials, involving 691, 178, and 208 participants, respectively (Figs. S2c, S2d, and S2e). Aerobic exercise was associated with a significant reduction in waist circumference, although the evidence was of very low certainty (SMD -0.23 cm, 95 % CI -0.44 to -0.03; $I^2 = 42$ %; p = 0.03) compared with standard treatment. No significant changes were observed between aerobic exercise and standard treatment with respect to hip circumference and WHR. A sensitivity analysis reported a change in the effect estimate for body mass (SMD -0.17, 95 % CI -0.32 to -0.02; $I^2 = 19$ %; $p = 0.03)^{64,65}$ while no notable alterations were yielded in the effect estimate for hip⁴⁴⁶⁵ and waist circumferences^{64,53} Nevertheless, aggregate sensitivity analyses of BMI revealed an alteration in the estimated effect (SMD -0.19, 95 % CI -0.43 to 0.06; $I^2 = 45$ %; p = 0.13)⁶⁴⁴⁴⁵³⁷³⁶⁷.⁷²

3.4.2. Body composition

Potential changes in fat mass were assessed in only one trial involving 126 patients. No significant difference was found between in aerobic exercise and standard treatment groups. Fat-free mass and body fat were assessed in seven and nine trials, involving 420 and 520 participants, respectively. No significant differences were found in fat-free mass between aerobic exercise and standard treatment cohorts (Fig. S2f). Aerobic exercise groups demonstrated a significant reduction in body fat compared with standard treatment (SMD -0.30 %, 95 % CI -0.59 to -0.01; $\rm I^2=59$ %; p=0.04; very low certainty) (Fig. S2g). A sensitivity analysis conducted on fat-free mass and body fat revealed no significant alterations in the effect estimates $^{64}.53$

3.4.3. Glucose metabolism

FBG, HbA1c, fasting insulin, and HOMA-IR were evaluated in 24 (n=915), 27 (n=1117), 17 (n=623), and 11 trials (n=417), respectively. Aerobic exercise induced significant reductions in FBG (SMD -0.49 mmol/L, 95 % CI -0.72 to -0.27; $I^2=62$ %; p<0.01; very low certainty) (Fig. S2h), HbA1c (SMD -0.79 %, 95 % CI -1.17 to -0.41; $I^2=88$ %; p<0.01; very low certainty) (Fig. S2i), fasting insulin (SMD -0.44 mIU/L, 95 % CI -0.72 to -0.15; $I^2=68$ %; p=0.003; very low certainty) (Fig. S2j), and HOMA-IR (SMD -0.72, 95 % CI -1.09 to -0.35; $I^2=67$ %; p=0.001; very low certainty) (Fig. S2k) compared with standard treatment. Subgroup analyses involving patients participating in aerobic exercise for 16 weeks or less (FBG: n=547; HbA1c: 18 trials, n=464)

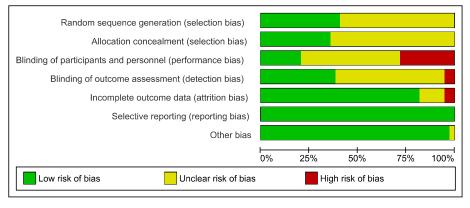


Fig. 2. Summary of the risk of bias assessment.

 Table 2

 Summary of findings using GRADE quality assessment.

Outcome	Certainty	assessment						Nº of patients		Effect	Certainty
	Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AE	ST	Absolute (95 % CI)	
BM (kg)	26	RCT	serious ^d	not serious	not serious	serious ^c	none	542	487	SMD 0.13 lower (0.28 lower to 0.03 higher)	⊕⊕⊖C Low ^{c,d}
BM (≤16 weeks)	20	RCT	serious ^d	not serious	not serious	serious ^c	none	311	278	SMD 0.19 lower (0.4 lower to 0.02 higher)	⊕⊕⊖(Low ^{c,d}
BM (>16 weeks)	6	RCT	very serious ^{e,a}	not serious	not serious	serious ^c	none	231	209	SMD 0.04 lower (0.23 lower to 0.15 higher)	⊕⊖⊖(Very low a
BMI (kg/m²)	23	RCT	very serious ^{e,d}	not serious	not serious	serious ^c	none	433	392	SMD 0.18 lower (0.36 lower to 0.01 lower)	⊕⊖⊖(Very low d
WC (cm)	14	RCT	serious ^d	serious ^b	not serious	serious ^c	none	365	326	SMD 0.23 lower (0.44 lower to 0.03 lower)	⊕⊖⊖(Very low
HC (cm)	4	RCT	serious ^d	not serious	not serious	serious ^c	none	96	82	SMD 0.11 lower (0.48 lower to	⊕⊕⊖C Low ^{c,d}
WHR	6	RCT	serious ^a	serious ^b	not serious	serious ^c	none	108	100	0.25 higher) SMD 0.06 higher (0.43 lower to 0.54 higher)	⊕⊖⊖(Very low
FM (kg)	1	RCT	serious ^e	not serious	not serious	serious ^c	none	64	62	MD 2.5 lower (8.91 lower to 3.91 higher)	⊕⊕⊖(Low ^{c,e}
FFM (kg)	7	RCT	very serious ^{e,a}	serious ^b	not serious	serious ^c	none	230	190	SMD 0.28 higher (0.01 lower to 0.56 higher)	⊕⊖⊖(Very low e,a
3F (%)	9	RCT	very serious ^{e,a}	serious ^b	not serious	serious ^c	none	279	241	SMD 0.3 lower (0.59 lower to 0.01 lower)	⊕⊖⊖ Very low e,a
BG (mmol/L)	24	RCT	serious ^d	serious ^f	not serious	serious ^c	none	497	418	SMD 0.49 lower (0.72 lower to 0.27 lower)	⊕⊖⊖(Very low f
FBG (mmol/L) (≤16 weeks)	18	RCT	serious ^d	serious ^b	not serious	serious ^c	none	301	246	SMD 0.56 lower (0.82 lower to 0.31 lower)	⊕⊖⊖(Very low d
FBG (mmol/L) (>16 weeks)	6	RCT	very serious ^{e,a}	serious ^f	not serious	serious ^c	none	196	172	SMD 0.34 lower (0.81 lower to 0.12 higher)	⊕⊖⊖(Very low f,a
HbA1c (%)	27	RCT	serious ^d	serious ^f	not serious	serious ^c	none	590	527	SMD 0.79 lower (1.17 lower to 0.41 lower)	⊕⊖⊖(Very low f
HbA1c (%) (≤16 weeks)	18	RCT	serious ^d	serious ^f	not serious	serious ^c	none	249	215	SMD 0.5 lower (0.81 lower to 0.2 lower)	⊕⊖⊖(Very low f
HbA1c (%) (>16 weeks)	9	RCT	very serious ^{e,a}	very serious ⁸	not serious	serious ^c	none	341	312	SMD 1.27 lower (2.08 lower to 0.46 lower)	⊕⊖⊖(Very low g,a
FI (mIU/L)	17	RCT	serious ^d	serious ^f	not serious	serious ^c	none	329	294	SMD 0.44 lower (0.72 lower to 0.15 lower)	OC Very low
HOMA-IR	11	RCT	very serious ^{d,e}	serious ^f	not serious	serious ^c	none	226	191	SMD 0.72 lower (1.09 lower to 0.35 lower)	⊕⊖⊖(Very low e,f

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Table 2 (continued)

Outcome	Certainty	assessment						Nº of patie		Effect	Certainty
	Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AE	ST	Absolute (95 % CI)	
HDL-C (mg/dL)	19	RCT	serious ^d	serious ^f	not serious	serious ^c	none	403	401	SMD 0.32 higher (0.01 higher to 0.63 higher)	⊕○○○ Very low ^{c,d}
LDL-C (mg/Dl)	17	RCT	serious ^d	serious ^f	not serious	serious ^c	none	374	373	SMD 0.27 lower (0.58 lower to 0.04 higher)	⊕⊖⊖⊖ Very low ^{c,c}
TG (mg/dL)	19	RCT	serious ^d	serious	not serious	serious ^c	none	403	399	SMD 0.33 lower (0.63 lower to 0.04 lower)	⊕○○○ Very low ^{c,c}
TC (mg/dL)	19	RCT	serious ^d	not serious	not serious	serious ^c	none	403	399	SMD 0.28 lower (0.47 lower to 0.1 lower)	⊕⊕⊖⊖ Low ^{c,d}
hs-CRP (mg/dL)	4	RCT	serious ^d	not serious	not serious	serious ^c	none	78	78	SMD 0.38 lower (0.72 lower to 0.04 lower)	⊕⊕⊖⊖ Low ^{c,d}
IL-6 (pg/mL)	2	RCT	serious ^a	very serious ^g	not serious	serious ^c	none	52	60	SMD 0.74 lower (2.99 lower to 1.52 higher)	⊕○○○ Very low ^{c,8} a
TNF-α (pg/mL)	1	RCT	serious ^a	not serious	not serious	serious ^c	none	11	12	MD 0.28 lower (1.25 lower to 0.69 higher)	$\bigoplus_{\text{Low}^{c,a}} \bigcirc$
SBP (mm Hg)	19	RCT	very serious ^{e,a}	very serious ^g	not serious	serious ^c	none	416	394	SMD 0.71 lower (1.24 lower to 0.18 lower)	⊕⊖⊖⊖ Very low ^{c,e} a,g
DBP (mm Hg)	19	RCT	very serious ^{a,e}	serious ^f	not serious	serious ^c	none	416	394	SMD 0.62 lower (1.04 lower to 0.2 lower)	⊕⊖⊖⊖ Very low ^{c,f,} a,e
RHR (bpm)	6	RCT	very serious ^{e,a}	serious ^f	not serious	serious ^c	none	91	83	SMD 0.03 higher (0.81 lower to 0.88 higher)	⊕○○○ Very low ^{c,e} f,a
ALT (U/L)	2	RCT	serious ^e	not serious	not serious	serious ^c	none	39	42	SMD 0.46 higher (0.02 higher to 0.91 higher)	⊕⊕⊖⊖ Low ^{c,e}
AST (U/L)	1	RCT	serious ^e	not serious	not serious	serious ^c	none	28	30	MD 5.6 higher (4.26 higher to 6.94 higher)	$\bigoplus_{Low^{c,e}}\bigcirc$
ADPN (ug/mL)	2	RCT	serious ^a	not serious	not serious	serious ^c	none	26	28	SMD 0.08 lower (0.61 lower to 0.46 higher)	⊕⊕⊖⊖ Low ^{c,a}
Leptin (ng/mL)	1	RCT	serious ^a	not serious	not serious	serious ^c	none	15	16	MD 5.37 lower (8.52 lower to 2.22 lower)	$\bigoplus_{Low^{c,a}}\bigcirc$
VO ₂ max (mL/kg/ min)	20	RCT	very serious ^{e,d}	serious ^f	not serious	serious ^c	none	319	291	SMD 1.09 higher (0.67 higher to 1.51 higher)	⊕⊖⊖⊖ Very low ^{c,e} f,d
STS (repetitions)	1	RCT	not serious	not serious	not serious	serious ^c	none	19	16	MD 4 higher (2.67 higher to 5.33 higher)	⊕⊕⊕⊖ Moderate ^c

ADPN: Adiponectin, AE: Aerobic Exercise, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, BF: Body Fat, BM: Body mass, BMI: Body Mass Index, ST: Standard treatment, CI: Confidence Intervals, hs-CRP: High Sensitivity C-Reactive Protein, DBP: Diastolic Blood Pressure, FFM: Fat-Free Mass, FBG: Fasting Glucose, FI: Fasting Insulin, FM: Fat Mass, HC: Hip Circumference, HDL-C: High-Density Lipoprotein Cholesterol, IL-6: Interleukin, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, LDL-C: Low-Density Lipoprotein Cholesterol, SMD: Standardized Mean Difference, MD: Mean Difference, RCT: Randomized Controlled Trial, RHR: Resting Heart Rate, SBP: Systolic Blood Pressure, SMD: Standardized Mean Difference, ST: Standard Treatment, STS: Sit-to-Stand Test, TC: Total Cholesterol, TG: Triglycerides, TNF-α: Tumor Necrosis Factor α, VO₂max: Maximal Oxygen Consumption, WC: Waist Circumference, WHR: Waist-to-Hip Ratio.

^a An unclear risk of bias was reported among the included studies.

b There is moderate heterogeneity in the studies.

 $^{^{\}rm c}$ The included studies recorded a small sample size for both the control and intervention groups.

^d Bias arising due to deviation from the intended intervention, unclear risk of bias was reported among the included studies, and bias in the measurement of the outcome.

- ^e High risk of bias was reported among the included studies.
- ^f There is substantial heterogeneity in the studies.
- ^g There is considerable heterogeneity in the studies.

showed significant decreases in FBG (SMD -0.56 mmol/L, 95 % CI -0.82 to $-0.31;\, I^2=50$ %; p<0.01; very low certainty) (Fig. S2h) and HbA1c (SMD -0.50 %, 95 % CI -0.81 to $-0.20;\, I^2=60$ %; p=0.001; very low certainty) (Fig. S2i) compared with standard treatment. Subgroup analyses involving participants who engaged in aerobic exercise for >16 weeks (FBG: six trials, n=368; HbA1c: nine trials, n=653) exhibited meaningful reductions in FBG (SMD -0.34 mmol/L, 95 % CI -0.81 to $-0.12;\, I^2=78$ %; p=0.004; very low certainty) (Fig. S2h), as well as in HbA1c (SMD -1.27 %, 95 % CI -2.08 to $-0.46;\, I^2=95$ %; p=0.002; very low certainty) (Fig. S2i) compared with standard treatment. The effect estimate remained unchanged following sensitivity analyses of FBG, HbA1c, fasting insulin, and HOMA-IR in numerous studies $^{444373677266}, ^{51}$

3.4.4. Lipid metabolism

HDL-C, TG, and TC levels were assessed across 19 trials, with sample sizes of 804, 802, and 802 participants, respectively. Aerobic exercise elicited significant increases in HDL-C (SMD 0.32 mg/dL, 95 % CI 0.01 to 0.63; I² = 76 %; p=0.04; very low certainty) (Fig. S2l), while lowering TG (SMD -0.33 mg/dL, 95 % CI -0.63 to -0.04; I² = 75 %; p=0.03; very low certainty) (Fig. S2m), and TC (SMD -0.28 mg/dL, 95 % CI -0.47 to -0.10; I² = 35; p=0.002; low certainty) (Fig. S2n) compared with standard treatment. Conversely, LDL-C levels, assessed in 17 trials (n=747), showed no significant difference between aerobic exercise and standard treatment groups (Fig. S2o). Sensitivity analyses revealed alterations in the estimated effect of aerobic exercise on HDL-C (SMD 0.29, 95 % CI -0.11 to 0.70; I² = 75 %; p=0.16) and TG (SMD -0.10, 95 % CI -0.35 to 0.14; I² = 42 %; p=0.42) 644453657372 , 66 whereas no changes were observed in LDL-C and TC.

3.5. Secondary outcomes

3.5.1. Low-grade chronic inflammation

hs-CRP, IL-6 and TNF- α were investigated in four (n=156), two (n=112), and one trial (n=23), respectively. Aerobic exercise resulted in a significant reduction in hs-CRP (SMD -0.38 mg/L, 95 % CI -0.72 to -0.04; I² = 11 %; p=0.03; low certainty) (Fig. S2p) compared with standard treatment. No significant differences were observed in IL-6 (Fig. S2q) and TNF- α levels between the aerobic exercise and standard treatment groups.

3.5.2. Resting cardiovascular function

SBP and DBP were reported in 19 trials (n=810). Aerobic exercise significantly reduced SBP (SMD -0.71 mmHg, 95 % CI -1.24 to -0.18; $I^2=91$ %; p=0.009; very low certainty) (Fig. S2r) and DBP (SMD -0.62 mmHg, 95 % CI -1.04 to -0.20; $I^2=87$ %; p=0.004; very low certainty) compared with standard treatment (Fig. S2s). RHR was reported in six trials (n=174), with no significant difference observed between aerobic exercise and standard treatment groups (Fig. S2t). Sensitivity analyses indicated that there were no alterations in the effect estimate for SBP and DBP 4453736772 . 66

3.5.3. Liver function

Changes in ALT and AST were reported in two trials (n = 81) and one trial (n = 58), respectively. Aerobic exercisers demonstrated a significant increase in ALT (SMD 0.46 U/L, 95 % CI 0.02 to 0.91; $I^2 = 0$ %; p = 0.04; low certainty) (Fig. S2u) and AST (MD 5.60 U/L, 95 % CI 4.26 to 6.94; p < 0.001; low certainty) compared with standard treatment. Sensitivity analysis indicated a statistically significant alteration in the estimated effect for ALT (MD 6.90, 95 % CI -9.16 to 22.96; p = 0.40).

3.5.4. Adipokines

Two studies (n = 62) investigated potential changes in adiponectin.

There were no significant differences in adiponectin between aerobic exercise and standard treatment groups (Fig. S2w). Leptin was reported in one trial (n=31). Aerobic exercisers demonstrated a significant decrease in leptin (MD -5.37 ng/mL, 95 % CI -8.52 to -2.22; p=0.008; low certainty) compared with standard treatment.

3.5.5. Physical function

VO₂max and STS were assessed in 20 trials (n=610) and one trial (n=35), respectively. Aerobic exercise significantly increased VO₂max (SMD 1.09 mL/kg/min, 95 % CI 0.67 to 1.52; $I^2=81$ %, p<0.001; low certainty) (Fig. S2x) and STS (MD 4.0 repetitions, 95 % CI 2.67 to 5.33; p<0.001; moderate certainty) compared with standard treatment. Following sensitivity analyses, no alterations were identified in the effect estimate for VO₂max 444365,7372 . 66

3.6. Publication bias

Funnel plots depicting the impact of aerobic exercise on BMI, waist circumference, HDL—C, LDL-C, TC, TG, HbA1c, FBG, fasting insulin, HOMA-IR, SBP, and DBP exhibited symmetrical distributions on both sides, suggesting minimal publication bias in the results. However, the funnel plots for body mass and VO₂max demonstrated asymmetrical distributions, indicating potential publication bias in these outcomes. To further examine publication bias as well as specificity, Egger's linear regression test was applied.⁷⁵ The results showed no significant bias for BMI, waist circumference, HDL—C, LDL-C, TC, TG, HbA1c, FBG, fasting insulin, HOMA-IR, SBP, and DBP, with p-values of 0.14, 0.82, 0.07, 0.33, 0.13, 0.93, 0.17, 0.56, 0.10, 0.90, 0.24, and 0.15, respectively (Fig. S3). However, significant effect estimates of -0.141 and 1.145 (p = 0.006) were found for body mass and VO₂max, respectively. The asymmetry in the funnel plots raised concerns about potential publication bias. To address this, the trim-and-fill method was employed, estimating missing studies to the right of the mean. After adjusting for these missing studies, the revised effect estimates were 0.0190 and 1.228, indicating a negligible and non-significant effect. This observation indicates that the original findings may have been influenced by publication bias and that the true effect, after adjustment, is approximately zero (Fig. S3).

4. Discussion

The present meta-analysis offers a unique insight into the effect of aerobic exercise training on a comprehensive array of cardiometabolic health-related indicators in middle-aged and older adults patients with diabesity. Our findings indicate that aerobic exercise confers beneficial alterations in selected cardiometabolic health-related outcomes, including anthropometric characteristics, glucose metabolism, blood lipid profile, chronic low-grade inflammation markers, blood pressure, cardiorespiratory fitness and physical function, among individuals with diabesity (Fig. 3). A notably high compliance rate was observed across all RCTs, which may be attributed, at least in part, to the supervised aerobic exercise interventions, resulting in a lower weekly time commitment than combined aerobic and resistance training, which is recommended for patients with metabolic complications. ^{10,16,76,77} The favorable outcomes observed in the present review are consistent with those reported in analogous meta-analyses examining the impact of resistance training⁷⁸ and high-intensity interval training⁷⁹ in this demographic. Nevertheless, despite the considerable number of eligible studies, the current findings should be interpreted with caution due to the relatively low quality of evidence in the RCTs included in this quantitative analysis, especially for most secondary outcomes, which were based on a limited number of studies.

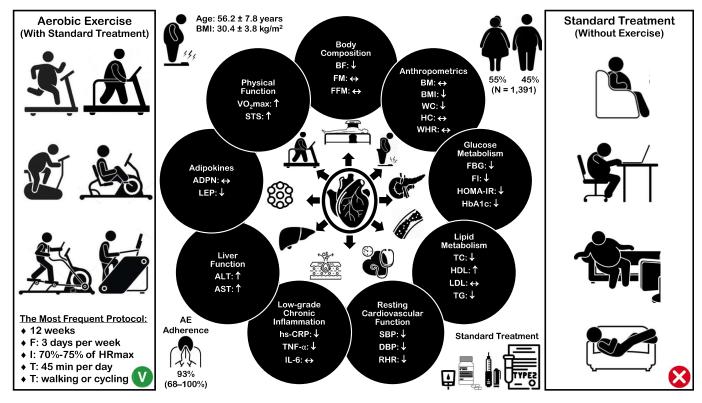


Fig. 3. Graphical representation of the findings. ADPN: Adiponectin, AE: Aerobic Exercise, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, BF: Body Fat, BM: Body Mass, BMI: Body Mass Index, hs-CRP: High Sensitivity C-Reactive Protein, DBP: Diastolic Blood Pressure, FBG: Fasting Blood Glucose, FITT: Frequency–Intensity–Time–Type, FFM: Fat-Free Mass, FI: Fasting Insulin, FM: Fat Mass, HbA1c: Glycated Hemoglobin, HC: Hip Circumference, HDL-C: High-Density Lipoprotein Cholesterol, IL: Interleukin, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, HRmax: Maximum Heart Rate, LEP: Leptin, LDL-C: Low-Density Lipoprotein Cholesterol, RHR: Resting Heart Rate, SBP: Systolic Blood Pressure, STS: Sit-to-Stand, TC: Total Cholesterol, TG: Triglycerides, TNF-α: Tumor Necrosis Factor α, VO₂max: Maximum Oxygen Consumption, WC: Waist Circumference, WHR: Waist-to-Hip Ratio.

4.1. Primary outcomes

4.1.1. Anthropometrics and body composition

This meta-analysis revealed that regular aerobic exercise elicited reductions in waist circumference, BMI, and body fat without improving other anthropometric and body composition parameters. These changes may be associated with potential improvements in ectopic and visceral fat,80 although this was not assessed, which is critical for downregulating low-grade chronic inflammation and has a beneficial effect on glucose management, even in the absence of weight loss in patients with indices of impaired metabolic health.⁴ However, combined aerobic and resistance training as well as concomitant dietary modifications are effective in promoting favorable changes in a broad range of anthropometric and body composition parameters in individuals with diabesity. 81,82 Therefore, additional RCTs are necessary to determine whether aerobic exercise alone can induce beneficial changes in these specific body composition parameters, including visceral adipose tissue, which is linked to cardiovascular disease risk factors affecting diabetes-related morbidity and mortality. This intervention could potentially reduce the cardiovascular disease morbidity and mortality risks associated with diabesity through a treatment approach that is distinguished by its costeffectiveness, non-invasiveness, and non-pharmaceutical nature.

$4.1.2. \ \ Glucose \ and \ lipid \ metabolism$

In general, regular aerobic exercise is a fundamental component of a comprehensive management strategy to reduce visceral fat and insulin resistance in patients with impaired metabolic health, even without favorable changes in body composition ^{80,84}. ^{85,86} Even a 30-min weekly commitment to aerobic exercise can substantially lower HbA1c, with the greatest effect at 100 min per week, whereas longer durations offer no extra benefit. ⁸⁷ Our results showed that aerobic exercise elicits

substantial improvements in glucose and lipid metabolism markers among patients with diabesity, underlining the reduced likelihood of developing diabetes-related sequelae.⁸⁸ Consequently, chronic aerobic exercise may assist in managing glucose levels by triggering processes that favorably modify insulin resistance and diabetes-related comorbidities.⁸⁹ These processes are linked to abdominal fat, as visceral and ectopic fat impair insulin sensitivity, causing inflammation, oxidative stress, and adverse immunologic changes in individuals with diabesity. $^{90-92}$ Patients with metabolic dysregulation frequently exhibit impaired blood lipid profiles and associated cardiometabolic derangements, 93 which increase the likelihood of developing metabolic syndrome and diabetic dyslipidemia 10.94 Others have reported that varied forms of exercise have the potential to improve blood lipids among individuals with impaired metabolic health profiles, which is reinforced by the present findings. This is likely to occur by managing glucose and lipid balance through the reduction of complex, low-grade chronic inflammation, even without weight loss.

4.2. Secondary outcomes

Cardiometabolic dysfunction is common in physically inactive patients with diabesity.³ In the present study, regular aerobic exercise conferred meaningful improvements in cardiovascular hemodynamics, chronic low-grade inflammatory indices, leptin levels, and physical fitness parameters. In contrast, no beneficial alterations were observed in liver enzymes and adiponectin. These results highlight the positive role of aerobic exercise in favorably modifying key cardiometabolic health-related indices associated with improved glucose control and reduced visceral adiposity but without measurable changes in body composition. Increases in cardiorespiratory fitness and physical function are indicative of the influence of regular aerobic exercise on enhancing

the spectrum of activities of daily living and functional capacity, likely reducing sarcopenic obesity and mortality rates in patients with excess adiposity and impaired indices of metabolic health who are at an elevated risk of developing atherosclerotic coronary disease. 101

4.3. Future directions

Despite the existence of contemporary exercise guidelines for type 2 diabetes, ⁷⁶ further investigation is required to clarify the prescribed aerobic exercise dose (frequency, intensity, and duration) to achieve optimal health outcomes. ^{102,103} It would be informing for future studies to investigate the effects of regular aerobic exercise on less-studied indices, including oxidative stress, redox status, and cytokines, as well as their association with major clinical outcomes. Finally, it would be advantageous to examine the potential of longitudinal unsupervised, home-based interventions to explore the implementation of aerobic exercise as a readily accessible, standalone strategy for addressing cardiometabolic health impairments in the community and on a wider scale. Taking this into account, it is important to note that the most extensively investigated aerobic training modalities, such as brisk walking and cycling, as reported in the current review, should be examined in a free-living environment.

4.4. Limitations

This review and meta-analysis have some methodologic limitations, which should be considered when interpreting our findings. The aerobic exercise regimens exhibited considerable heterogeneity across studies, which may have introduced potential bias in the review of RCTs. In addition, the observed heterogeneity in certain outcomes may be ascribed to the limited number of eligible studies, as well as to potential geographic, socioeconomic or cultural differences among the included studies. Furthermore, data regarding the utilization and modification of relevant pharmacological agents for the treatment of type 2 diabetes and related comorbidities during the intervention period were unavailable and could be regarded as potential confounders. These may have potentially heightened the observed influence of aerobic exercise on cardiometabolic health-related indicators, including FBG and HbA1c.

5. Conclusions

This systematic review and meta-analysis offer valuable insights into the significant role of aerobic exercise in influencing various cardiometabolic health-related indices, potentially leading to improved health outcomes in middle-aged and older adults with diabesity. Our findings indicate that aerobic exercise has a positive influence on anthropometric characteristics, glucose metabolism, blood lipid profile, chronic low-grade inflammation, blood pressure, cardiorespiratory fitness and physical function when compared to non-exercising controls. These findings support the implementation of aerobic exercise as a potential adjunctive non-pharmacological treatment option for the clinical management of patients with diabesity. Nevertheless, it is imperative to exercise caution when interpreting the present results, given the considerable uncertainty reported in numerous outcomes. Future RCTs are needed, reflecting a higher quality of evidence, to substantiate and extend these findings to medically supervised group, as well as work and home-based exercise interventions.

CRediT authorship contribution statement

Sameer Badri Al-Mhanna: Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Writing – review & editing, Writing – original draft. Barry A. Franklin: Validation, Methodology, Writing – review & editing. John M. Jakicic: Validation, Methodology, Writing – review & editing. Emmanuel Stamatakis: Validation, Methodology, Writing – review &

editing. Linda S. Pescatello: Validation, Methodology, Writing - review & editing. Deborah Riebe: Validation, Methodology, Writing – review & editing. Walter R. Thompson: Validation, Methodology, Writing review & editing. James S. Skinner: Validation, Methodology, Writing - review & editing. Sheri R. Colberg: Validation, Methodology, Writing - review & editing. Jonathan K. Ehrman: Validation, Methodology, Writing - review & editing. George S. Metsios: Validation, Methodology, Writing - review & editing. Norsuhana Omar: Validation, Methodology, Writing - review & editing. Nouf H. Alkhamees: Validation, Investigation, Formal analysis, Data curation. Bodor Bin Sheeha: Validation, Investigation, Formal analysis, Data curation. Abdullah F. Alghannam: Validation, Investigation, Formal analysis, Data curation. Alexios Batrakoulis: Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Writing - review & editing, Writing original draft.

Ethical approval

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Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2025.109203.

Data availability

The data are available from the corresponding author upon reasonable request.

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