Cardiorespiratory fitness in individuals with type 2 diabetes mellitus: a systematic review and meta-analysis

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ABSTRACT

Objective: To conduct a systematic review and meta-analysis assessing the cardiorespiratory fitness (CRF) among individuals with and without type 2 diabetes **Materials and methods:** The current review was registered in PROSPERO under the number CRD42018082718. MEDLINE, EMBASE, and Cochrane Library databases were searched from inception through February 2022. Eligibility criteria consisted of observational or interventional studies that evaluated CRF through cardiopulmonary exercise testing or six-minute walk test in individuals with type 2 diabetes compared with individuals without type 2 diabetes. For data extraction, we used baseline CRF assessments of randomized clinical trials or follow-up CRF assessments in observational studies. We performed a meta-analysis using maximal oxygen consumption (VO_2max), and distance walked in the 6MWT as primary outcomes. They were extracted and expressed as mean differences (MDs) and 95% CIs between treatment and comparator groups. The meta-analysis was conducted using Review Manager (RevMan) software. **Results:** Out of 8,347 studies retrieved, 77 were included. Compared with individuals without type 2 diabetes, individuals with diabetes achieved a lower VO_2max (-5.84 mL.kg^{-1}.min^{-1}, 95% CI -6.93, -4.76 mL.kg^{-1}.min^{-1}, p = <0.0001; I^2 = 91%, p for heterogeneity < 0.0001), and a smaller distance walked in 6MWT (-93.30 meters, 95% CI -141.2, -45.4 meters, p > 0.0001; I^2: 94%, p for heterogeneity < 0.0001). **Conclusion:** Type 2 diabetes was associated with lower cardiorespiratory fitness, as observed by lower VO_2max on maximal tests, and smaller distance walked in 6MWT, however the quality of studies was low.

Keywords

Exercise tolerance; review; meta-analysis; diabetes mellitus

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Received on Jan/1/2023
Accepted on May/30/2023

DOI: 10.20945/2359-4292-2023-0040

INTRODUCTION

Cardiorespiratory fitness (CRF) appraises an individual's exercise capacity, it is directly linked to the integrated function of several body systems and may be a marker of total body health (1). Low CRF is associated with an increased risk of cardiovascular disease among patients with type 2 diabetes (2). Balducci and cols. (3) observed that increasing maximal oxygen consumption (VO_2max) by approximately 2 mL.kg^{-1}.min^{-1} can significantly reduce 10-year risk of coronary heart disease in these individuals. Moreover, a 9% lower relative risk of all-cause mortality was shown among adult men with VO_2max of 1 mL.kg^{-1}.min^{-1} higher (4). The annual cost savings per person were $5,193 in type 2 diabetes for each 1-metabolic equivalent (MET) higher fitness (5).

The cardiopulmonary exercise test – by gas analysis – is the gold standard assessment of CRF. It evaluates the VO_2max or peak oxygen uptake (VO_2 peak) during an incremental exercise test (6). Several protocols use a cycle ergometer or a treadmill (7), but these devices are expensive and require a trained team, being unfeasible in some situations such as population-based studies and in clinical practice. Therefore, other tests, such as six-minute walk test (6MWT), are also useful as they can estimate oxygen consumption (8).

Previous studies have shown controversial results when comparing CRF between individuals with and without diabetes: some showed comparable results (9-11), whereas others showed lower CRF in individuals with diabetes compared to those without diabetes (12-14). These differences could be methodological and derive from different protocols used for the evaluations. However, there are physiopathological mechanisms to justify the lower levels of exercise capacity observed among individuals with type 2 diabetes, which may occur from insulin action, mitochondrial dysfunction, skeletal muscle microvasculature, and cardiac dysfunction (15). Moreover, poor glycemic control can reduce CRF (15) because of diabetes itself or diabetes-associated sedentary behavior (16). Thus, it is essential to understand the magnitude of VO_2max impairments observed in these individuals during planning of appropriate interventions to improve exercise performance and avoid increasing disability in this population. However, it is uncertain whether the magnitude of this difference and age, sex, body mass index (BMI), diabetes duration and control of the disease could negatively affect exercise capacity.

We aimed to conduct a systematic review with meta-analysis to summarize studies that assessed CRF measured by VO_2 peak or VO_2max in individuals with and without type 2 diabetes. We also evaluated the differences in distance walked in the 6MWT among them.

MATERIALS AND METHODS

A systematic review and meta-analysis was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions (17) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (18). This review was registered in the international prospective register of systematic reviews (PROSPERO: CRD42018082718).

Eligibility criteria

The eligibility criteria were as follows: 1) participants: adults with type 2 diabetes, > 18 years old; 2) outcomes: CRF measured by maximal exercise tests and expressed as VO_2 (peak or maximal), or distance walked evaluated by the 6MWT; and 3) control group: individuals without type 2 diabetes; 4) study design: observational design (i.e., cohort or cross-sectional studies) and baseline data from quasi-experimental, randomized, or non-randomized clinical trials. Only studies in English, Portuguese, and Spanish were included. Studies were excluded if the participants had peripheral arterial disease, heart failure, chronic neurological diseases. Also, studies reporting that individuals without diabetes took any medication were excluded as well as studies when groups were matched by CRF.

Outcomes definition

The primary outcome was VO_2 (peak or maximal) measured by direct expired gas analysis. The secondary outcome was distance walked evaluated by the 6MWT.

Databases and search strategy

Three electronic databases (i.e., PubMed/MEDLINE, EMBASE and Cochrane Library) were searched using a combination of MeSH headings, keywords and related entry terms, such as "type 2 diabetes" and "cardiorespiratory fitness". The search strategies are presented in Supplementary File 1. Besides, the reference list of studies was manually searched. The search strategy was conducted from inception until December 2017, updated in March 2021 and February 2022.

Selection process

Two pairs of authors (ACPM/MBP and PMB/CEB) independently evaluated the titles and abstracts of all studies based on eligibility criteria. All studies with abstracts lacking enough information regarding the eligibility criteria were included to full text evaluation. Finally, the full-text studies were evaluated by the same reviewers according to the inclusion and exclusion criteria and any disagreement between them was resolved by a third reviewer (DU).

Data collection process

Data were extracted independently by two pairs of authors (ACPM/CWS and PMB/CEB) using a

standardized and pre-tested data extraction form (Microsoft Excel). Missing data were requested to the authors by email (two out of seven requests were answered).

The information extracted from the included studies were sex, age, body mass index (BMI), medications, diabetes duration, hemoglobin A1c (HbA1c), physical activity level, exercise capacity test used and evaluated outcomes.

Risk of bias and publication bias assessment

The risk of bias of the included studies was assessed by two pairs of authors (PMB/CEB and CWS/MBP), previously trained and qualified. The Newcastle-Ottawa Scale (NOS) version for cohort studies was adapted and used (19). The quality score was calculated by assessing three domains: selection of the study groups (0-3 points); comparability, which represent the quality of adjustment for confounding factors (0-2 points); evaluation of the outcomes of interest (0-3 points). The maximum score was eight and the classification of the studies were: (1) good quality: 2-3 points in the selection domain, 1-2 points in the comparability domain and 2-3 points in the outcome domain; (2) fair quality: 1 point in the selection domain, 1-2 points in the comparability domain and 1-2 points in the outcome domain; and (3) poor quality: 0 points in any domains. Disagreement between reviewers were resolved by consensus, and, in cases of persistent disagreement, the assessment was made by a third reviewer (ACPM).

Publication bias was assessed using a contour-enhanced funnel plot with each study effect size against the standard error of the estimate.

Synthesis methods

The quantitative assessment of the included studies was performed by meta-analysis using the Review Manager (RevMan) software (Cochrane Review Manager, version 5.3). Each outcome (VO_2max/peak, and distance walked) was expressed as mean differences (MDs) and 95% confidence interval (CI) between individuals with and without type 2 diabetes. The results were pooled using a random-effects model.

Statistical heterogeneity was assessed by the Cochran's Q test, at 0.1 significance level, and inconsistency I^2 test. Considerable heterogeneity was indicated when I^2 value was > 75%, according to the Cochrane Handbook for Systematic Reviews of Interventions (17). Heterogeneity among studies was investigated based on two strategies: (1) the meta-analysis was re-run by removing each study to check if one specific study explained the heterogeneity and (2) stepwise meta-regression analyses were conducted. Univariate meta-regression models were performed in STATA software (version 20) to assess clinical and methodological variables associated with CRF, i.e., BMI, age, HbA1c, and diabetes duration, based on R^2 values and statistical significance $p < 0.05$. Subgroup analysis was conducted by type of ergometer (i.e., cycle ergometer and treadmill) and sex.

Data treatment

In studies that presented the results as standard deviation (n = 31), the conversion to standard error was made by the equation SD = SEM.√sample size. The VO_2max unit was converted from absolute (mL/min) to relative weight values ($mL.kg^{-1}.min^{-1}$) in six studies. The metabolic equivalents were converted into relative weight values (mL.kg–1.min–1) in three studies, based on the standard equation ($VO_2 = METS \times 3{,}5$) (20).

The data were combined in an unique group in studies with more than one group of individuals with and without type 2 diabetes (e.g., men and women), as suggested by the Cochrane's handbook.

RESULTS

Study selection

In total, 77 out of 8,347 studies identified in the data search (databases 7,146 + manual searching 13 + update 1,188) met the eligibility criteria and were included in our review. Figure 1 shows the flowchart of inclusion and exclusion criteria of studies. Meta-analysis for the VO_2max and distance walked in the 6MWT included 72 and 5 studies, respectively.

Study characteristics

The included studies were published from 1984 to 2022 and the sample sizes ranged from 10 (21,22) to 3,770 participants (23). A total of 8,725 individuals were included in the meta-analysis, 2,007 in the diabetes group and 6,718 in the group without diabetes. The participants were aged < 60 years in 89% of the studies. Twenty-two studies included only men,

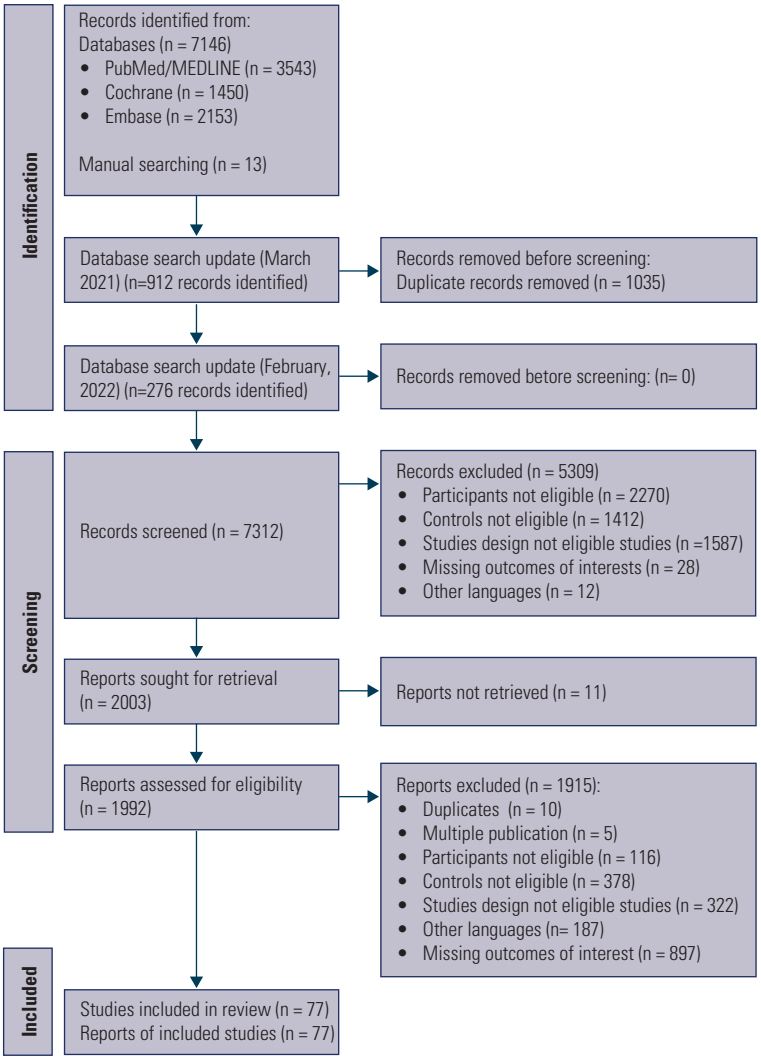

Figure 1. Flow diagram of included studies.

eight studies included only women, and 42 studies included both men and women. The baseline HbA1c ranged from 5.8% to 12.2% in individuals with diabetes (data available in 64 studies) and the duration of the disease ranged from 2.5 to 12.5 years (data available in 54 studies). Most of the included studies (n = 43) presented matched groups by age, sex and/or BMI. Tables 1 and 2 show the characteristics of the studies included in the VO_2max and distance walked meta-analyses, respectively.

A total of 73 included studies reported the BMI. Among the type 2 diabetes group, 1.3% (n = 1), 43.8% (n = 32), and 54.8% (n = 40) were classified as normal weight, overweight and obese, whereas lean and obese individuals with diabetes were pooled to be analyzed in four studies. We observed a high prevalence of patients classified as overweight (59.2%, n = 40) and obese (22.2%, n = 17) in the group without diabetes.

A total of 46 out of the 77 included studies reported habitual physical activity (PA). Eight studies reported that participants did not participate in regular exercise programs (21,24-30), 22 studies reported that participants were sedentary or physically inactive (9,11,12,31-49), 10 studies reported similar PA level in groups with and without diabetes (50-59), two studies reported that habitual PA scores were higher in the diabetes group (60,61), three studies showed higher levels of PA in the group without diabetes (13,62,63) and one study reported that individuals practiced physical exercises for more than six months (64).

Table 1. Characteristics of the maximal cardiopulmonary test studies included in the VO_2 meta-analysis (n = 70)

Study	Sample size (n)		Sex	Diabetes duration (years)	Matched groups	Medication	Ergometer	Protocol	VO_2peak/ max
	DM	C							
Andrade-Mayorga and cols. (2020) (79)	13	32	M/W	NR	NR	NR	Cycle ergometer	Modified Astrand	VO_2 peak
Baldi and cols. (2003) (24)	11	12	M/W	5.4 ± 3.1	Age, BMI, and habitual physical activity	Antidiabetics and antihypertensives	Cycle ergometer	Initial workloads 25 or 50 Wt, increments 15-25 W	VO_2 max
Baldi and cols. (2006) (80)	13	15	M/W	5.4 ± 3.1	Age and BMI	Antidiabetics and antihypertensives	Cycle ergometer	Initial workloads 25 or 50 Wt, increments 15-25 W	VO_2 max
Bauer and cols. (2007) (60)	11	11	M/W	NR	No	NR	Cycle ergometer	Incremental 10-20 Wt/min	VO_2 peak
Baynard and cols. (2005) (50)	9	6	W	NR	Age	Antidiabetics	Treadmill	Starting at 2.5 mph, increased 2%mph 3.5mph reached	VO_2 peak
Bergman and cols. (2015) (31)	15	14	M/W	NR	No	Antidiabetics	Cycle ergometer	Workload adjusted to maintain determined intensity	VO_2 max
Boon and cols. (2007) (32)	10	10	M	7.0 ± 3.1	Weight	Antidiabetics	Cycle ergometer	Workload at 0.75 to 1.5 $W.KgFFM^{-1}$, cadence 60 rpm	VO_2 max
Borghouts and cols. (2002) (12)	8	8	M	NR	Weight and body composition	Antidiabetics	Cycle ergometer	Workload at 0.75 to 1.5 $W.KgFFM^{-1}$, cadence 60 rpm	VO_2 max
Brandenburg and cols. (1999) (33)	8	19	W	3.0 ± 2.0	Age and activity levels	NR	Cycle ergometer	Workload increases 10Wt/min.	VO_2 max
Chance and cols. (2008) (81)	69	45	M/W	7.8 ± 5.8	Age	Antidiabetics and insulin	Cycle ergometer	Incremental 20-30 Wt/3 min.	VO_2 peak
Colberg and cols. (2005) (35)	9	10	M/W	NR	No	NR	Cycle ergometer	Initial workload 0 Wt or 20 Wt, incremental 20 Wt/3 min., cadence of 50 rpm	VO_2 peak
Colberg and cols. (2006) (34)	10	9	M/W	NR	No	NR	Cycle ergometer	Initial workload 0 Wt or 20 Wt, incremental 20 Wt/3 min., cadence of 50 rpm	VO_2 peak
Cusi and cols. (2001) (25)	8	6	M/W	NR	No	Antidiabetics	Cycle ergometer	NR	VO_2 max
Dela and cols. (1999) (21)	4	6	NR	NR	No	Antidiabetics	Cycle ergometer	NR	VO_2 max
Devlin and cols. (1987) (26)	5	12	M	NR	No	Antidiabetics	Cycle ergometer	NR	VO_2 max
Durrer and cols. (2017) (82)	10	9	M/W	NR	Age	Antidiabetics	Cycle ergometer	Ramp protocol (15 Wt/min at 50 rpm)	VO_2 peak
Fluckey and cols. (1994) (83)	10	3	M/W	2.8 ± NR	Age	NR	Treadmill	Modified Naughton-Balke	VO_2 max
Fujii and cols. (2017) (84)	12	12	M	7.5 ± 4.4	No	Antidiabetics, insulin, statins, and antihypertensives	Cycle ergometer	NR	VO_2 peak

Study	Sample size (n)		Sex	Diabetes duration (years)	Matched groups	Medication	Ergometer	Protocol	VO_2peak/ max
	DM	C							
Green and cols. (2003) (27)	15	16	NR	NR	No	Antidiabetics, insulin, statins, and antihypertensives	Cycle ergometer	Initial workload 20 and 60 Wt, increased 20-25 Wt increments each 3 min	VO_2 peak
Groen and cols. (2019) (85)	9	8	M/W	8 ± 3	No	Antidiabetics	Cycle ergometer	Initial workload 50-100 Wt, increases 25 Wt each 1min	VO_2 peak
Gulsin and cols. (2020) (86)	87	36	M/W	4.7 ± 3.8	No	Antidiabetics, insulin, and antihypertensives	Cycle ergometer	Incremental	VO_2 peak
Hansen and cols. (2014) (28)	33	18	M	5.2 ± 4.4	No	Antidiabetics, insulin, statins, and antihypertensives	Cycle ergometer	Initial workload 45 Wt, increments 45 Wt each 3-min.	VO_2 peak
Hernández-Alvarez and cols. (2010) (9)	12	7	M/W	2.5 ± 1.9	Age and BMI	Antidiabetics and insulin	Treadmill	Stepwise	VO_2 max
Holton and cols. (2003) (36)	9	10	M/W	NR	Age, gender, and BMI	NR	Cycle ergometer	Initial workload 0 Wt or 20 Wt, 20 Wt increment every 3 min., cadence 50 rpm.	VO_2 peak
Huebschmann and cols. (2009) (37)	13	26	W	3.9 ± 3.9	No	Antidiabetics	Cycle ergometer	Initial workload 0 Wt, increments 10 Wt/min., cadence at 60 rpm	VO_2 peak
Iborra and cols. (2008) (29)	14	12	M/W	9.0 ± 4.0	No	Antidiabetics, insulin, and antihypertensives	Cycle ergometer	Workload increased 10-15 Wt/min.	VO_2 peak
Jae and cols. (2016) (23)	170	3600	M	NR	No	NR	Treadmill	Bruce	VO_2 peak
Karavelioglu and cols. (2013) (87)	67	68	M/W	5.2 ± 4.1	Age and gender	Antidiabetics and insulin	Treadmill	Bruce	VO_2 peak
Kasumov and cols. (2015) (38)	10	14	M/W	NR	No	Insulin	Treadmill	Incremental	VO_2 max
Kennedy and cols. (1999) (22)	5	5	M/W	NR	No	Antidiabetics	Cycle ergometer	Incremental (2-min. stages)	VO_2 max
Lalande and cols. (2008) (39)	8	11	M	5.0 ± 8.4	Weight and habitual activity level	Antidiabetics	Cycle ergometer	Initial workload 40 Wt, increases 15 Wt/min.	VO_2 max
Larsen and cols. (2009) (51)	8	15	M	4.0 ± 2.8	Age and BMI	Antidiabetics	Cycle ergometer	NR	VO_2 max
Mac Ananey and cols. (2011) (40)	9	20	W	1-5years	No	Antidiabetics, insulin, statins, and antihypertensives	Cycle ergometer	Initial workload 40 Wt, increases 20 Wt each 3 min., cadence 60 rpm	VO_2 peak
Madsen and cols. (2015) (41)	10	13	M/W	NR	Age, height, and weight	Antidiabetics, statins, and antihypertensives	Cycle ergometer	Initial workload 80-100 Wt, increases 15 W/ min., cadence 60 rpm.	VO_2 max
Martin and cols. (1995) (10)	8	7	M	4.7 ± 3.6	Age and weight	Antidiabetics	Cycle ergometer	NR	VO_2 max

Study	Sample size (n)		Sex	Diabetes duration (years)	Matched groups	Medication	Ergometer	Protocol	VO_2peak/ max
	DM	C							
Meex and cols. (2010) (42)	18	20	M	3.9 ± 16.5	Age, weight, and BMI	Antidiabetics	Cycle ergometer	Constant cadence 80 ± 5 rpm. At Wmax previously estimated.	VO_2 max
Meneilly and cols. (1996) (88)	33	25	M/W	3.0 ± 5.7	Age and weight	Antidiabetics and antihypertensives	Cycle ergometer	Workload increases 16.6 Wt each 30s.	VO_2 max
Meneilly and cols. (1999) (89)	34	19	M/W	3.0 ± 4.3	Age and weight	Antidiabetics and antihypertensives	Cycle ergometer	Workload increases 16.6 Wt each 30s.	VO_2 max
Mogensen and cols. (2009) (52)	12	11	M	3.9 ± 3.1	Age and weight	Antidiabetics, statins, and antihypertensives	Cycle ergometer	Initial workload 60-70% HRmax, increases 30 Wt each 3 min., cadence of 60 rpm	VO_2 max
Oberbach and cols. (2006) (67)	10	15	M/W	NR	Age and BMI	NR	Cycle ergometer	Graded	VO_2 max
O'Connor and cols. (2012) (54)	32	32	M/W	5.1 ± 2.6	Age and BMI	Antidiabetics	Cycle ergometer	Initial workload 40 Wt, increases 30 Wt each 3 min., cadence 60 rpm	VO_2 peak
O'Connor and cols. (2015) (53)	33	21	M	3.9 ± 2.5	Age	Antidiabetics	Cycle ergometer	Incremental	VO_2 peak
Pinna and cols. (2021) (90)	13	13	M/W	At least 1 year	Age and sex	Antidiabetics	Cycle ergometer	Incremental	VO_2 max
Regensteiner and cols. (1995) (55)	10	10	M/W	6.7 ± 6.8	Age, gender, weight, and physical activity	Antidiabetics	Treadmill	Modified Naughton	VO_2 max
Regensteiner and cols. (1998) (56)	10	20	W	3.0 ± 2.0	Age, gender, weight, and physical activity	Antidiabetics	Cycle ergometer	Workload increases 10 Wt/min.	VO_2 max
Regensteiner and cols. (2009) (57)	10	10	W	3.6 ± 0	No	Antidiabetics	Cycle ergometer	Workload increases 10 Wt/min.	VO_2 peak
Regensteiner and cols. (2015) (43)	29	34	M/W	3.1 ± 2.8	No	Antidiabetics and statins	Cycle ergometer	Workload increases 10-25 Wt/min.	VO_2 peak
Ribeiro and cols. (2008) (11)	21	11	M/W	8.6 ± 8.2	No	Antidiabetics, statins, and antihypertensives	Cycle ergometer	Workload increases 10-15 Wt/min.	VO_2 max
Scalzo and cols. (2018) (44)	31	21	M/W	NR	BMI	Antidiabetics	Cycle ergometer	Workload increases 10-20 Wt/min.	VO_2 peak
Scalzo and cols. (2022) (49)	19	22	M/W	NR	No	Antidiabetics	Cycle ergometer	Incremental	VO_2 peak
Scheede-Bergdahl and cols. (2009) (91)	12	9	M	5.1 ± 3.8	Age, weight, and body fat	Antidiabetics, statins, and antihypertensives	Cycle ergometer	NR	VO_2 peak
Scheede-Bergdahl and cols. (2014) (45)	12	9	M	5.1 ± 3.8	No	Antidiabetics, statins and antihypertensives	Cycle ergometer	NR	VO_2 peak
Schneider and cols. (1984) (46)	20	11	M	NR	Age, gender, and weight	None	Cycle ergometer	Workload increments of 25 Wt, each 3 min.	VO_2 max
Schneider and cols. (1988) (30)	16	9	M/W	NR	Age, gender, and weight	None	Cycle ergometer	NR	VO_2 max

Study	Sample size (n)		Sex	Diabetes duration (years)	Matched groups	Medication	Ergometer	Protocol	VO_2peak/ max
	DM	C							
Schreuder and cols. (2014) (68)	27	9	M	NR	Age, gender, and weight	Antidiabetics, insulin, statins, and antihypertensives	Cycle ergometer	Initial workload 10 Wt, increases 10 Wt/min., cadence 60-80 rpm	VO_2 max
Segerstrom and cols. (2011) (69)	39	53	M	NR	Age	Antidiabetics and insulin	Cycle ergometer	Initial workload 30 Wt, increases 15 Wt/min., cadence 60 rpm	VO_2 peak
Simões and cols. (2010) (13)	10	10	NR	NR	No	Antidiabetics	Cycle ergometer	Initial workload 15 Wt, increases 15 Wt each 3 min.	VO_2 max
Simões and cols. (2013) (47)	10	10	M/W	6.0 ±1.1	Age, weight, and BMI	Antidiabetics and antihypertensives	Cycle ergometer	Initial workload 15 Wt, increases 15 Wt each 3 min.	VO_2 peak
Suk and cols. (2015) (92)	12	12	W	7.8 ± 2.1	BMI	None	Cycle ergometer	Initial workload 20% of Wmax, increments 30-60% Wmax each 3 min.	VO_2 max
Tadic and cols. (2021) (65)	30	55	M/W	NR	No	Antidiabetics and insulin	Treadmill	Modified Bruce	VO_2 peak
Tobin and cols. (2008) (93)	8	7	M	4.9 ± 3.3	Age, gender, and BMI	Antidiabetics	Cycle ergometer	Graded	VO_2 max
Van Tienen and cols. (2012) (61)	8	12	M	12.5 ± 7.7	Age, weight, and BMI	NR	Cycle ergometer	Incremental	VO_2 peak
Vind and cols. (2011) (94)	13	13	M	3.7 ± 2.8	Age and BMI	Antidiabetics and antihypertensives	Cycle ergometer	Initial workload 60-70% HRmax, increases 30 Wt each 3 min., cadence of 60 rpm	VO_2 peak
Vukomanovic and cols. (2020) (95)	64	72	M/W	NR	No	NR	Treadmill	Modified Bruce	VO_2 peak
Vukomanovic and cols. (2019) (96)	70	80	M/W	3 (1-5)	No	Antidiabetics and insulin	Treadmill	Modified Bruce	VO_2 peak
Vukomanovic and cols. (2019) (97)	53	62	M/W	NR	No	Antidiabetics	Treadmill	Modified Bruce	VO_2 peak
Wilkerson and cols. (2011) (48)	12	12	M	<5 years	Age and weight	Antidiabetics and antihypertensives	Cycle ergometer	Ramp (15 Wt/min.)	VO_2 max
Wilmot and cols. (2014) (14)	20	20	M/W	4.7 ± 4.0	Age	Antidiabetics and antihypertensives	Cycle ergometer	NR	VO_2 max
Wilson and cols. (2017) (58)	17	16	M/W	8.3 ± 9.5	Age, gender, BMI, physical activity	Antidiabetics and insulin	Cycle ergometer	Initial workload 25-50 Wt, increases 25-50 Wt each 1min	VO_2 peak
Yu and cols. (2016) (70)	180	1594	NR	NR	Age and gender	NR	Treadmill	Bruce	VO_2 peak
Zbinden-Foncea and cols. (2013) (63)	10	5	NR	NR	No	Antidiabetics	Cycle ergometer	Incremental	VO_2 max
Zierath and cols. (1996) (72)	7	7	M	5 ± 5.2	Age and BMI	Antidiabetics	Cycle ergometer	Initial workload 50 Wt, increases 50 Wt each 5 min.	VO_2 max

Data are presented in mean ± SD or (range); DM: diabetes; C: control; W: women; M: men; NR: not reported; Wt: watts; min.: minutes; mph: miles per hour; KgFFM: kilogram of free fat mass; rpm: rotations per minute; Wmax: maximal workload; HRmax: maximal heart rate; Tmax.: maximal exercise test duration; VO_2 peak: peak oxygen consumption; VO_2max: maximal oxygen consumption.

Table 2. Characteristics of the six-minute walk test studies included in the meta-analysis (n = 5)

Study	Sample Size		Sex	Diabetes duration (years)	Medications	Protocol	Estim.VO_2 (mL/kg/min)	
	DM	C					DM	C
Awotidebe and cols. (2014) (98)	35	35	M/W	NR	NR	ATS	10.2 ± 1.5	10.9 ± 1.3
Awotidebe and cols. (2016) (99)	125	125	M/W	<5 years	Antidiabetics	ATS	7.6 ± 0.6	9.6 ± 0.6
Heberle and cols. (2021) (64)	13	13	W	11.92 ± 10.77	Antidiabetics and statins	NR	NR	NR
IJzerman and cols. (2012) (59)	137	19	M/W	NR	NR	NR	NR	NR
Ozdirenc and cols. (2003) (62)	30	30	M/W	7.1 ± 6.2	Antidiabetics and insulin	NR	14.6 ± 2.9	17.0 ± 1.8

Data are presented in mean ± SD; DM: diabetes; C: control; M: men; W: women; NR: not reported; ATS: American Thoracic Society; VO_2: maximal oxygen consumption; Estim.VO_2: Estimated VO_2.

We classified all 77 included studies as poor quality and they achieved a mean score of 2.4/8 in the modified NOS (Supplementary File 2). No study has reached the maximum score (3 points) in the selection domain, although seven studies scored 2 points and 46 studies scored 1 point. Eight studies reached maximal score (2 points) and 33 scored 1 point in the comparability domain. Finally, 22 studies reached the maximal score (2 points) and 35 studies scored 1 point in the outcome domain. Mac Ananey and cols. (40) reached the highest score (5 points), whereas four studies scored zero points (9,21,25,65).

We evaluated the publication bias using a funnel plot for the VO_2max (Supplementary File 3). The points for the missing studies would be on the bottom of the plot. Since most of this area contains regions of small sample size, publication bias is unlikely to be the cause of this asymmetry. The analyzed studies did not run further tests to distinguish chance from real asymmetry.

Results of syntheses

Figure 2 shows the data about the meta-analysis of VO_2max, which shows that individuals with diabetes had lower VO_2max/peak [–5.84 mL.kg^{-1}.min^{-1} (95% CI –6.93, –4.76 mL.kg^{-1}.min^{-1}, p = <0.0001); I^2 = 91%, p for heterogeneity < 0.0001] compared to the group without diabetes. We included 8,183 individuals from 72 studies in this analysis. Most studies used cycle ergometer (n = 44) and 26 studies reported VO_2max.

Heterogeneity in VO_2max analyses was classified as high (I^2 = 91%). We did not observe substantial change in heterogeneity at each study removal. Subgroup analyses (Supplementary File 4) showed that heterogeneity remained unchanged when studies were exclusively conducted with men (I^2 = 82.6%; p < 0.001) or women (I^2 = 93.9%; p < 0.001).

Meta-regression analyses of studies included in VO_2max analyses indicated that BMI partly explained the heterogeneity among studies [adjusted R^2 = 10.75%; coefficient –0.4988; 95%CI (–0.94; –0.05); p=0.03]. Age (adjusted R^2 = –2.10%; p = 0.99), HbA1c (adjusted R^2 = 4.48%; p = 0.08), and diabetes duration (adjusted R^2 = –4.21%; p = 0.69) were not associated with differences among studies (Supplementary File 5).

We included five studies in the meta-analysis of the distance walked evaluated by 6MWT. Subjects with diabetes walked –93.30 meters (95% CI –141.2, –45.4 meters, p > 0.0001; I^2 = 94%, p for heterogeneity < 0.0001) compared to the group without diabetes (Figure 3).

DISCUSSION

To our knowledge, this systematic review with meta-analysis was the first study comparing CRF between individuals with and without diabetes, in which we observed that individuals with type 2 diabetes presented lower CRF evaluated by VO_2max. This is essential because VO_2max is a measure associated with health and this review included studies with different designs to broadly analyze this variable in diabetes and non diabetes groups. The lower VO_2max values indicated may be useful to qualify future studies about physical rehabilitation and physical activity for individuals with type 2 diabetes.

Cardiac, respiratory, and skeletal muscular systems determine VO_2max (66). This assumption is supported by studies that indicate that VO_2max reduction is associated with diastolic dysfunction and/or impaired myocardium perfusion during exercise (57), as well as with abnormalities in skeletal muscle morphology (67), VO_2 kinetics (O_2 uptake/use) (54,56), endothelial

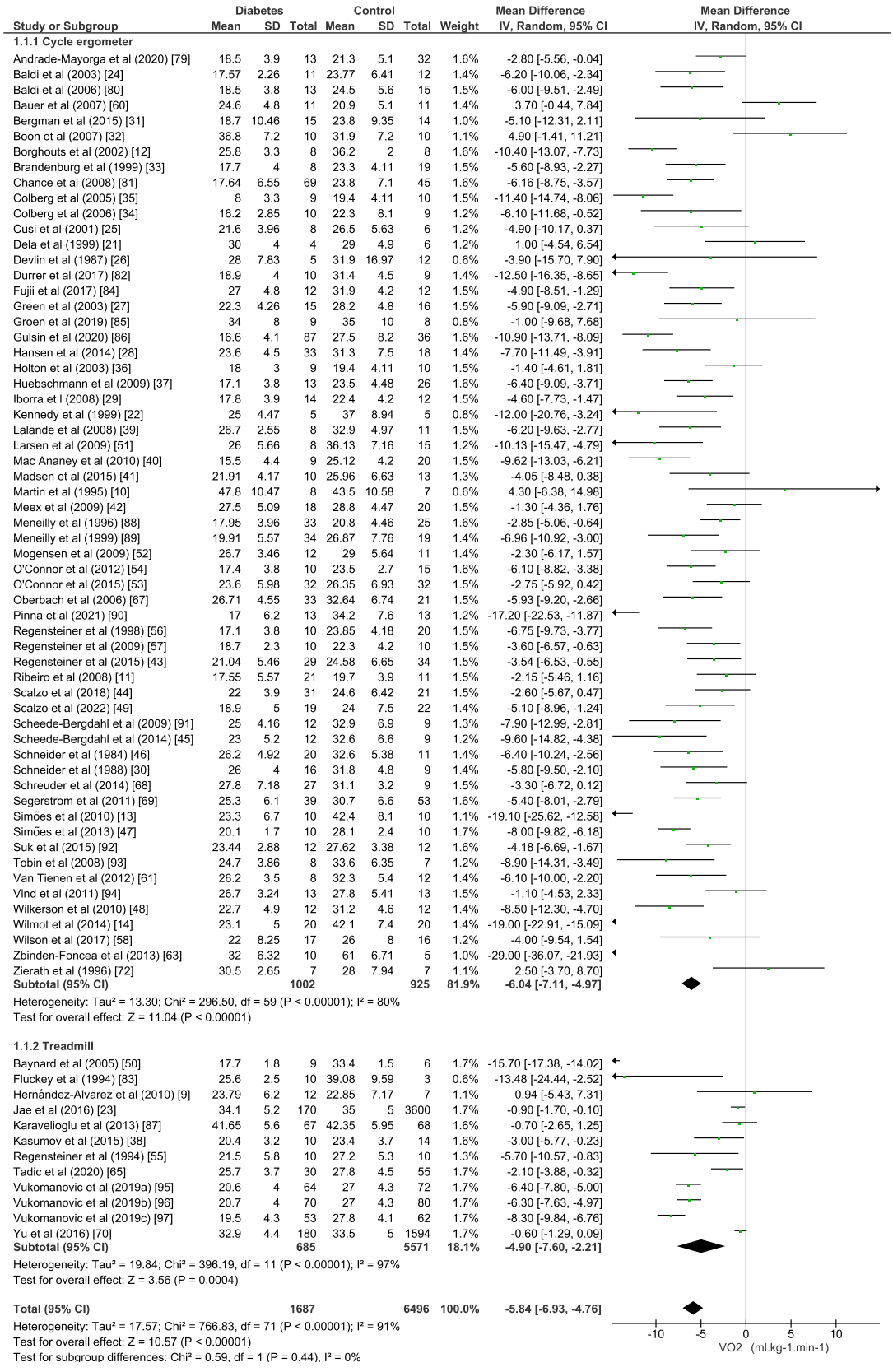

Figure 2. Forest plot of the maximal oxygen consumption (VO_2max) evaluated in maximal cardiopulmonary exercise tests.

Absolute changes in VO_2max in studies conducted with type 2 diabetes patients compared with group without type 2 diabetes. Squares represent study-specific estimates; diamonds represent pooled estimates of random-effects meta-analyses

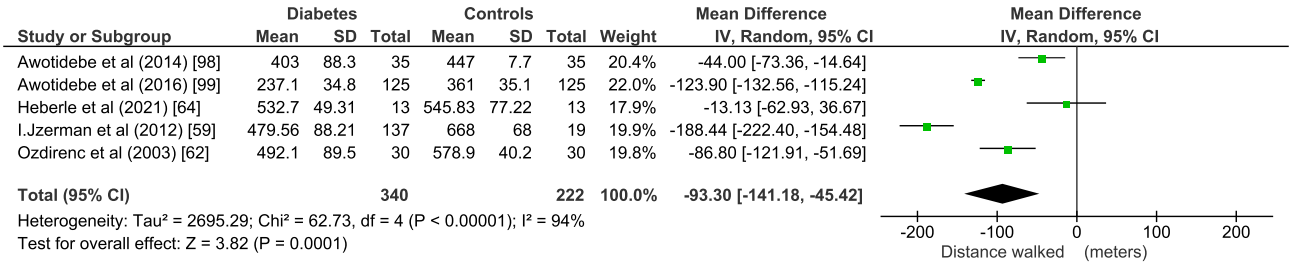

Figure 3. Forest plot of the distance walked in the six minute walk test (6MWT).

Absolute changes in the distance walked in the 6MWT in studies conducted with type 2 diabetes patients compared with control group. Squares represent study-specific estimates; diamonds represent pooled estimates of random-effects meta-analyses

dysfunction (43,68,69), blood viscosity (55), and glycemic profile/control (69). Changes in these components and in their integration can lead to VO_2max impairment. Our study only assessed glycemic control based on HbA1c. However, meta-regression results did not associate HbA1c with VO_2max in patients with diabetes.

We observed lower values of VO_2max in individuals with diabetes compared with the other group, however, 22 out of the 70 included studies did not show differences between the groups. This could be explained by: 1. One study had a diabetes group with higher levels of physical activity than the group without diabetes (61); 2. Another study included only individuals with obesity in the group without diabetes with VO_2max values lower than predicted for normal weight individuals (25); 3. One study included a 10 times smaller sample size in the diabetes group than in the group without diabetes (70); and 4. Four studies did not control for comorbidities, such as cardiovascular, endocrine or renal diseases, in groups with and without diabetes (14,25,71,72).

The 6MWT has been used to estimate exercise capacity in adults with diabetes. However, results have shown moderate correlation between estimated VO_2max and 6MWT (73), which suggest that 6MWT can be used to assess the patients' ability to maintain the exercise, but not to estimate VO_2max. We observed a mean reduction of 93 meters in the distance walked among individuals with diabetes compared to the group without diabetes. Studies showed that reductions of 25-30 meters in distance walked in patients with coronary artery diseases and pulmonary diseases were associated with increased risk of death (74,75). However, the minimal clinically significant difference values of distance walked are not established among patients with diabetes. Although our study found significant reduction in distance walked evaluated by 6MWT in patients with diabetes, our results have limited generalizability due to few included studies.

The first strategy adopted to explore heterogeneity was to remove each study from the analyses, which did not cause changes. Despite the group without diabetes being restricted to individuals without diabetes, we cannot assert their health status. Moreover, factors such as obesity and/or age could explain similar VO_2max between the diabetes group and the group without diabetes in one third of the analyzed studies.

The high heterogeneity in the VO_2max meta-analysis was explored by sensitive analyses considering the ergometer and sex and also by performing a meta-regression analysis. The type of ergometer used in the tests did not change the results of the meta-analysis, as well as the subgroup analyses based on sex. Besides, meta-regression analysis applied to VO_2max showed that age, HbA1c and diabetes duration could not explain the high heterogeneity presented in VO_2max meta-analysis, but BMI partly explained it. We believe that the high I^2 in the VO_2max analysis is related to different magnitudes of these effects in the different studies shown. However, most of them present the same direction of effects. Therefore, the practical/clinical implications are that despite the high heterogeneity, the direction of effect shows lower cardiorespiratory fitness in individuals with diabetes, but we cannot estimate the exact magnitude of the difference between type 2 diabetes and control groups.

Higher levels of CRF may coexist with higher BMI (76). Hemmingsson and cols. observed a reduction of the normal weight and high CRF category (relative

change –30%) when analyzing time trends combinations between CRF and BMI (1995-2020), an increase in overweight and low CRF (relative change +34%) and in obesity and low CRF (relative change +154%) categories. Studies show that the risk of cardiovascular disease and all-cause mortality in individuals with obesity varied by CRF (77), such as among individuals with diabetes (78).

Our study has some limitations. Although the search was not limited by language, the included studies were only in Portuguese, English, and Spanish. It was a challenge to summarize the results of this review, since different protocols were used to evaluate CRF. Moreover, there was a considerable variation among the studies about pharmacological treatments that diabetes patients received, some studies did not mention the drugs used to treat health conditions other than diabetes, and most studies did not mention the drug doses used. Most of the included studies were carried out in participants with a mean age of less than 60 years, and the highest prevalence of type 2 diabetes is found in older adults. Another challenge was the wide range of duration of diabetes, because the CRF can change along with diabetes duration. Therefore, these are limitations that could affect the generalization of our outcomes. Additionally, the overall quality of the studies was low, indicating increased risk of bias in many of them, however, there are fewer instruments to evaluate risk of bias of observational studies and they are less accurate compared to those evaluating clinical trials.

The strength of this systematic review is that we could summarize how lower the VO_2max is reduced in individuals with type 2 diabetes compared with the group without type 2 diabetes, due to many included studies (n = 77). Furthermore, the exploratory analyses to explore the high heterogeneity followed all guidelines for systematic reviews.

In conclusion, individuals with type 2 diabetes showed lower CRF than the group without diabetes. CRF was evaluated by the VO_2max individuals attained in maximal cardiopulmonary exercise testing, and was partially influenced by the BMI, but not influenced by age or sex of this population. Moreover, lower distance walked was observed in the group with diabetes. This review emphasizes exercise as a component to treat and to control diabetes that should be evaluated and prescribed individually.

Data availability: data are available on request from the authors.

Contribution statement: BDS had full access to all of the data in the study, supervised study and takes responsibility for the integrity of the data and the accuracy of the data analysis. ACPM, PMB, CEB, DU and BDS designed study. ACPM, CWS, PMB, MBP and CEB acquired data. ACPM and CWS analysed data. ACPM, CWS, PBM, CEB, DU and BDS interpreted data. ACPM and CWS drafted the manuscript. ACPM, CWS, PBM, MBP, CEB, DU and BDS revised the manuscript for important intellectual content and approved the version to be published.

Funding: we thank the Research Incentive Fund (Fipe) of the *Hospital de Clínicas de Porto Alegre* and National Council for Scientific and Technological Development (CNPq) for partly funding this study. This study was partly supported by the Coordination for the Improvement of Higher Education Personnel – Brazil (Capes) – Finance Code 001.

Disclosure: no potential conflict of interest relevant to this article was reported.

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Supplemental file 1. Literature search strategy

PubMed
#1("Diabetes Mellitus, Type 2"[title] OR "Diabetes Mellitus"[title] OR "Diabetes Mellitus, Noninsulin-Dependent"[title] OR "Diabetes Mellitus, Ketosis-Resistant"[title] OR "Diabetes Mellitus, Ketosis Resistant"[title] OR "Ketosis-Resistant Diabetes Mellitus"[title] OR "Diabetes Mellitus, Non Insulin Dependent"[title] OR "Diabetes Mellitus, Non-Insulin-Dependent"[title] OR "Non-Insulin-Dependent Diabetes Mellitus"[title] OR "Diabetes Mellitus, Stable"[title] OR "Stable Diabetes Mellitus"[title] OR "Diabetes Mellitus, Type II"[title] OR "NIDDM"[title] OR "Diabetes Mellitus, Noninsulin Dependent"[title] OR "Diabetes Mellitus, Maturity-Onset"[title] OR "Diabetes Mellitus, Maturity Onset"[title] OR "Maturity-Onset Diabetes Mellitus"[title] OR "Maturity Onset Diabetes Mellitus"[title] OR "MODY"[title] OR "Diabetes Mellitus, Slow-Onset"[title] OR "Diabetes Mellitus, Slow Onset"[title] OR "Slow-Onset Diabetes Mellitus"[title] OR "Type 2 Diabetes Mellitus"[title] OR "Noninsulin-Dependent Diabetes Mellitus"[title] OR "Noninsulin Dependent Diabetes Mellitus"[title] OR "Maturity-Onset Diabetes"[title] OR "Diabetes, Maturity-Onset"[title] OR "Maturity Onset Diabetes"[title] OR "Type 2 Diabetes"[title] OR "Diabetes, Type 2"[title] OR "Diabetes Mellitus, Adult-Onset"[title] OR "Adult-Onset Diabetes Mellitus"[title] OR "Diabetes Mellitus, Adult Onset"[title] OR "DM2"[title] OR "diabetics"[tiab])
#2("Exercise Therapy"[Mesh] OR "Resistance Training"[Mesh] OR "Muscle Stretching Exercises"[Mesh] OR "Exercise Movement Techniques"[Mesh] OR "Exercise"[Mesh] OR "Cardiorespiratory Fitness"[Mesh] OR "evaluation cardiopulmonary" OR "Ergospirometry" OR "Functional capacity" OR "Tests of exercise endurance" OR "six-minute walk" OR "Exercise testing" OR "stress testing" OR "Oxygen Consumption" OR "Cardiopulmonary exercise testing" OR "Exercises" OR "Physical Exercise" OR "Physical Exercise" OR "Physical Exercises" OR "Isometric Exercises" OR "Isometric Exercise" OR "Warm Up Exercise" OR "Aerobic Exercises" OR "Aerobic Exercise" OR "Exercise Therapies" OR "Pilates Training" OR "Strength Training" OR "Strengthening Programs" OR "Weight Lifting Exercise Program" OR "Weight Bearing Strengthening Program" OR "Weight Bearing Exercise Program" OR "Effort test" OR "Fitness, Cardiorespiratory" OR "peak oxygen uptake" OR "maximal oxygen consumption" OR "peak oxygen consumption")
#1 AND #2
Embase
#1 'non insulin dependent diabetes mellitus'/exp
#2'exercise'/exp OR 'exercise tests'/exp OR 'cardiorespiratory fistness'/exp OR cardiopulmonary exercise test'/exp OR 'ergoespirometry'/exp OR 'six-minute walk test'/exp OR 'maximal oxygen uptake'/exp OR functional status assessment'/exp or 'treadmill exercise test'/exp
#3'non diabetic patient'/exp OR 'control group'/exp OR 'normal human'/exp
#1 AND #2 AND #3
Cochrane
"exercise"
AND
"diabetes mellitus, type 2"

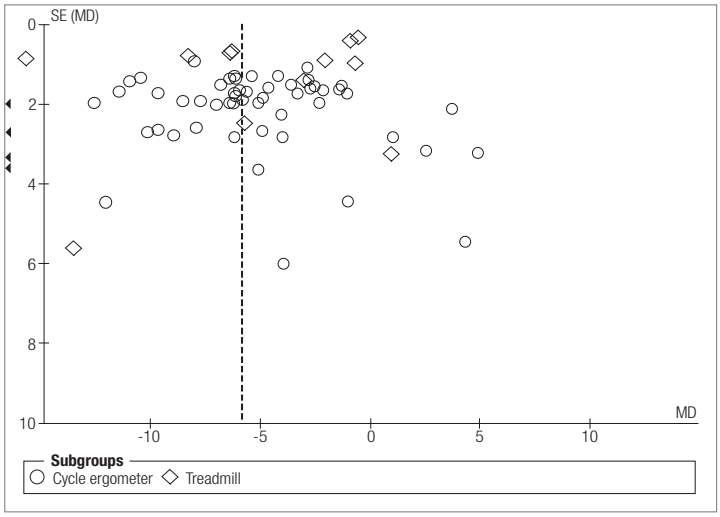
Supplemental file 2. Risk of bias by Newcastle-Ottawa Scale (n = 77 studies)

Study	Year	Selection	Comparability	Outcome	Total score
Andrade-Mayorga and cols. (79)	2020	1	0	2	3
Awotidebe and cols. (98)	2014	1	1	1	3
Awotidebe and cols. (99)	2016	2	0	1	3
Baldi and cols. (24)	2003	0	0	1	1
Baldi and cols. (80)	2006	1	0	0	1
Bauer and cols. (60)	2007	1	0	1	2
Baynard and cols. (50)	2005	1	0	1	2
Bergman and cols. (31)	2015	0	0	1	1
Boon and cols. (32)	2007	1	0	1	2
Borghouts and cols. (12)	2002	0	0	1	1
Brandenburg and cols. (33)	1999	2	2	0	4
Chance and cols. (81)	2008	0	1	0	1
Colberg and cols. (35)	2005	0	0	1	1
Colberg and cols. (34)	2006	0	0	1	1
Cusi and cols. (25)	2001	0	0	0	0
Dela and cols. (21)	1999	0	0	0	0
Devlin and cols. (26)	1987	0	1	0	1
Durrer and cols. (82)	2017	2	0	2	4
Fluckey and cols. (83)	1994	1	1	0	2
Fujii and cols. (84)	2017	0	0	2	2
Green and cols. (27)	2003	2	0	1	3
Groen and cols. (85)	2019	1	0	2	3
Gulsin and cols. (86)	2020	1	0	1	1
Hansen and cols. (28)	2014	0	0	2	2
Heberle and cols. (64)	2021	1	1	1	3
Hernández-Alvarez and cols. (9)	2010	0	0	0	0
Holton and cols. (36)	2003	1	1	1	3
Huebschmann (37)	2009	1	0	1	2
Iborra and cols. (29)	2008	1	1	1	3
IJzerman and cols. (59)	2012	1	1	1	3
Jae and cols. (23)	2016	1	0	1	2
Karavelioglu and cols. (87)	2013	1	0	1	2
Kasumov and cols. (38)	2015	1	0	0	1
Kennedy and cols. (22)	1999	1	0	1	2
Lalande and cols. (39)	2008	0	0	1	1
Larsen and cols. (51)	2009	0	2	0	2
Mac Ananey and cols. (40)	2011	2	2	1	5
Madsen and cols. (41)	2015	0	2	1	3
Martin and cols. (10)	1995	0	2	0	2
Meex and cols. (42)	2010	1	2	0	3
Meneilly and cols. (88)	1996	1	1	1	3
Meneilly and cols. (89)	1999	0	1	1	2
Mogensen and cols. (52)	2009	2	1	1	4

Study	Year	Selection	Comparability	Outcome	Total score
Oberbach and cols. (67)	2006	1	1	1	3
O'Connor and cols. (54)	2012	0	1	2	3
O'Connor and cols. (53)	2015	1	1	2	4
Ozdirenc and cols. (62)	2003	1	1	2	4
Pinna and cols. (90)	2021	1	1	2	4
Regensteiner and cols. (55)	1995	1	2	0	3
Regensteiner and cols. (56)	1998	1	1	2	4
Regensteiner and cols. (57)	2009	1	1	2	4
Regensteiner and cols. (43)	2015	1	1	2	4
Ribeiro and cols. (11)	2008	1	1	1	3
Scalzo and cols. (44)	2018	1	1	1	3
Scalzo and cols. (49)	2022	2	0	1	3
Scheede-Bergdahl and cols. (91)	2009	1	1	1	3
Scheede-Bergdahl and cols. (45)	2014	1	1	1	3
Schneider and cols. (46)	1984	1	2	0	3
Schneider and cols. (30)	1988	1	1	2	4
Schreuder and cols. (68)	2014	0	1	2	3
Segerstrom and cols. (69)	2011	1	1	2	4
Simões and cols. (13)	2010	0	0	2	2
Simões and cols. (47)	2013	1	0	2	3
Suk and cols. (92)	2015	1	1	2	4
Tadic and cols. (65)	2021	0	0	0	0
Tobin and cols. (93)	2008	0	1	2	3
Van Tienen and cols. (61)	2012	1	1	1	3
Vind and cols. (94)	2011	1	1	2	4
Vukomanovic and cols. (95)	2020	1	1	0	2
Vukomanovic and cols. (96)	2019	1	0	0	1
Vukomanovic and cols. (97)	2019	1	0	0	1
Wilkerson and cols. (48)	2011	1	1	0	2
Wilmot and cols. (14)	2014	1	0	1	2
Wilson and cols. (58)	2017	0	1	0	1
Yu and cols. (70)	2016	1	0	2	3
Zbinden-Foncea and cols. (63)	2013	1	0	1	2
Zierath and cols. (72)	1996	0	0	2	2

Domain selection checked: the representativeness of the sample, sample size and diagnosis of type 2 diabetes (maximum score: 3 points); domain comparability checked: confounding factors, i.e. if groups (diabetes and controls) were matched by body mass index (BMI), age and/or sex (maximum score: were 2 points); domain outcome checked: the blinded assessment and statistical tests employed (maximum score: 2 points). The maximum score was eight and the classification of the studies were: (1) good quality: 2-3 points in the selection domain, 1-2 points in the comparability domain and 2-3 points in the outcome domain; (2) fair quality: 1 point in the selection domain, 1-2 points in the comparability domain and 1-2 points in the outcome domain; and (3) poor quality: 0 points in any domains.

Supplemental file 3. Funnel plot for the VO_2max



Supplemental file 4. Subgroup analyses

	N. of studies	VO_2			
		MD	95% CI	p	I^2
Overall results	72	-5.84	(-6.93; -4.76)	<0.001	91.0%
Men	22	-4.84	(-6.60; -3.08)	<0.001	82.6%
Women	7	-7.45	(-11.52; -3.39)	<0.001	93.9%

MD: mean difference; CI: confidence interval; VO_2: maximal oxygen consumption; I^2: inconsistency I^2 test.

Supplemental file 5. Meta-regression analyses

Covariates	N of obs.	Coefficient	95%IC	p	Adjusted R^2
BMI	68	-0.4988	-0.94; -0.05	0.03	10.75%
Age	72	0.0005	-0.13; 0.13	0.99	-2.10%
HbA1c	62	-0.7480	-1.58; 0.08	0.08	4.48%
Duration of diabetes	40	0.1221	-0.49; 0.73	0.69	-4.21%

BMI: body mass index; HbA1c: glycated haemoglobin.