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Review

Effect of exercise interventions on oxygen uptake in people with chronic obstructive pulmonary disease: A network meta-analysis of randomized controlled trials

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ABSTRACT

Background: Although aerobic training leads to physiological improvements in people with chronic obstructive pulmonary disease (COPD), measured by the VO2 peak, there is no evidence as to which type of physical exercise intervention is the most effective in improving the VO_2 peak or max.
Objective: A network meta-analysis (NMA) was performed to determine the effects of different physical interventions on oxygen uptake in people with COPD.
Methods: A literature search was performed from database inception to February 2024. Randomized controlled trials on the effectiveness of exercise programs on oxygen uptake with COPD were included. We assessed the risk of bias using the Cochrane Risk of Bias (RoB 2.0) tool and the quality of the evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool. Pairwise meta-analyses and NMAs were performed for direct and indirect evidence.
Results: A total of 22 studies were included in this NMA. The highest effects for improvement in oxygen uptake scores were for continuous, moderate-intensity endurance exercise versus a control (effect size [ES]: 1.17; 95% CI 0.59 to 1.74), followed by continuous, high-intensity endurance exercise versus a control (ES: 0.47; 95% CI 0.08 to 0.85), and combined exercise versus a control (ES: 0.41; 95% CI 0.18 to 0.64).
Conclusions: Continuous, moderate-intensity endurance exercise should be considered the most effective strategy to improve oxygen uptake in people with COPD, followed by continuous, high-intensity endurance exercise and combined exercise. Due to the importance of VO_2 as a predictor of quality of life and mortality in people with COPD, it is essential to include its assessment in clinical guidelines and to include the most effective physical activity interventions to improve it.
Trial Registration: PROSPERO database: CRD42023425893

Introduction

Maximal oxygen uptake (measured as VO2max or VO_2 peak) is an index of cardiovascular performance, as well as a measure of aerobic capacity, and is a fundamental measure in exercise physiology [1]. Aerobic exercise capacity is an important outcome measure for people with chronic obstructive pulmonary disease (COPD), as many of them present with breathlessness, exercise intolerance [2], and

Abbreviations: AMBMT, active mind-body movement therapies; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise test; ES, effect size; FEV1, forced expiratory volume in one second; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; NMA, network meta-analysis; RCTs, randomized clinical trials; RoB, risk of bias; SUCRA, surface under the cumulative ranking; VO2 max, maximal oxygen consumption or maximal oxygen uptake; 6MWT, 6-minute walking test

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limited activities of daily living because of dyspnea and reduced exercise capacity [3-5]. People with COPD have a limited tolerance to effort, which is multifactorial, related both to central and peripheral oxygen transport and to the capacity to use oxygen at the mitochondrial level. Exercise intolerance due to dyspnea leads to physical inactivity, deconditioning, and reduced exercise capacity [5,6], which can be directly measured by the VO_2 peak.

A relationship has been found between the reduction in exercise capacity measured by the VO_2 peak and the ventilatory limitation [7,8], pulmonary gas exchange abnormalities [9], and peripheral and muscle dysfunction [10,11]. Peripheral muscle dysfunction is an important comorbidity in people with COPD, and peripheral muscle strength is correlated with peak VO_2, indicating that people with greater muscle weakness in the extremities have lower aerobic capacity [12]. Among the parameters of lung function, forced expiratory volume in one second (FEV1) is the most strongly correlated with peak VO_2. FEV1 (% predicted) is also strongly positively correlated with peak VO_2. Finally, peak VO_2 is a better predictor of health-related quality of life [13] and survival than FEV1 [14].

Reduced peak VO_2 values, assessed by cardiopulmonary exercise testing (CPET), have been related to higher mortality in people with COPD [13]. Although CPET is the gold standard for measuring peak VO_2 [15], it requires expensive equipment. Therefore, field tests, such as the 6MWT, which is strongly correlated with peak VO_2, may be used. However, the strength of the relationship between the VO_2 peak and the distance covered in field tests may be affected by the exercise capacity of people with COPD, highlighting the importance of using multiple exercise tests [16].

There is controversy as to whether physical training can improve peak VO_2 in people with COPD [17-20], and whether this improvement depends on the type of exercise performed or the degree of severity of the disease. Researchers have found physiological improvements, measured by the VO_2 peak, after aerobic training in people with COPD [21,22]. There is an inverse relationship between the severity of the disease and the change in the VO_2 max, suggesting that people with greater disease severity are more likely to have exercise ventilation limitation, which may imply less gain after exercise compared to people with less severe disease. However, there is no evidence as to which type of physical exercise intervention is the most effective in improving VO_2 peak or max.

Therefore, the objective of this network meta-analysis (NMA) was to evaluate the effect of physical exercise programs on maximal oxygen uptake in people with COPD and to determine which type of intervention most effectively improves it.

Methods

This systematic review and NMA is reported in accordance with the Preferred reporting items for systematic reviews (PRISMA-NMA) that incorporate Network meta-analysis (Supplementary Table S.1) [23] and was conducted in accordance with the Cochrane Collaboration Manual [24]. The study protocol was registered in PROSPERO (registration number CRD42023425893).

Search strategy and selection criteria

Two reviewers (S.P.-J., C.A.-B.) independently searched PubMed, SCOPUS, Physiotherapy Evidence Database, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Web of Science databases from their inception to February 2024.

The aim of the study was to identify randomized control trials (RCTs) of the effect of different exercise modalities on oxygen uptake in people with COPD. The search strategy included combined relevant terms: "physical activity", "pulmonary rehabilitation", active mind-body movement therapies", "aerobic exercise", “exercise training”, "oxygen uptake", "VO_2", "COPD", "chronic obstructive pulmonary disease", and "randomized clinical trials". The full search strategy is included in the supplementary material (Table S.2).

The list of references included in previously published systematic reviews and meta-analyses were reviewed for potentially relevant studies.

Eligibility

Studies on the efficacy of different types of exercise to improve oxygen uptake were included in this NMA. The inclusion criteria were (1) type of study: RCT; (2) type of participants: people diagnosed with COPD at any stage of disease; (3) type of intervention: any form of exercise training (considering exercise as a planned, structured, and repetitive physical activity aiming to improve or maintain one or more components of physical fitness [25] with any frequency, duration, or intensity); (4) type of comparison: control group participants subjected to their usual practice or no exercise; and (5) results: oxygen uptake, either peak or maximal oxygen uptake, standardized in this study into a single concept named maximal oxygen uptake. No language limitation was applied.

The exclusion criteria were (1) studies that compared the same type of exercise; (2) studies combining exercise with other health interventions, in which the effect of each could not be isolated and extracted; (3) studies that included conditions other than COPD, in which data for people with COPD could not be extracted separately; or (4) lack of data in the selected studies to estimate the effect of interventions.

Data extraction

Data from each included article were independently extracted by 2 reviewers (S.P.-J., C.A.-B.): (1) study characteristics (ie, year of publication, country, and sample size); (2) population characteristics (ie, mean age and severity of disease); (3) intervention characteristics (ie, duration, frequency, type, and training modality); and (4) measurement of results (maximal oxygen uptake). Disagreements relating to data extraction were resolved by consensus.

Intervention categorization

The exercise interventions described in the included studies were classified as active mind-body movement therapies (AMBMT), endurance, strength, and combined. AMBMT included interventions focused on deep and controlled breathing, flexibility, and strength, such as Taichi, Yoga, or Qigong, supervised and supplemented mostly with daily walks. Endurance referred to programs that aimed to increase heart rate and energy expenditure to meet the oxygen requirements necessary to keep the muscle activated and included treadmill, cycling, or walking. Within endurance, we subclassified 3 different types of exercise according to the training modality: a) endurance interval training exercise referred to a specific training modality in which the training intensity was varied with “uphill” and “downhill” intervals (ie, at 80% of the peak work uphill and at 30−40% of the peak work downhill) [26]; b) continuous, high-intensity endurance exercise, modality in which the load was constant throughout the training at 70%−80% of the peak work; and c) continuous, moderate-intensity endurance exercise, defined as the use of a constant load throughout the exercise at a moderate intensity of 50−60%. Strength training included different strengthening exercises for the upper and lower limbs. The combined exercise programs included strength and endurance interventions in the same session.

Risk of bias assessment

Two investigators (S.P.-J., C.A.-B.) independently performed the risk of bias assessment of the included RCTs by applying the Cochrane

Collaboration tool to assess risk of bias (RoB2). [27] Any disagreements were resolved by consensus or by discussion with a third reviewer. This tool assesses the risk of bias according to 5 domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of reported results. The classification of the overall risk of bias depended on the classification of the domains, thus, in cases in which all domains were classified as 'low risk', the overall bias was considered at a 'low risk of bias', termed 'some concerns' if at least 1 of the domains was scored as 'some concerns' and at a 'high risk of bias' if at least 1 of the domains was scored as 'high risk' or multiple domains scored as 'some concerns' that could affect the validity of the results.

Classification of the quality of the evidence

To perform the assessment of the quality of the evidence and make recommendations, the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool was used [28]. Each outcome was rated as high, moderate, low, or very low value of evidence depending on the design of the studies, risk of bias, indirect evidence, inconsistency, publication bias, and imprecision.

Data synthesis and statistical analysis

First, 3 assumptions were analyzed: (1) we checked similarity to verify that the studies included in the NMA were similar and comparable. This analysis was run by checking whether samples undergoing the same exercise intervention had similar baseline characteristics that could be considered confounding variables (ie, age, percentage of women in the sample, and baseline values of FEV1% and oxygen uptake). (2) We checked consistency and transitivity: the node-splitting method was used to determine inconsistency. (3) Heterogeneity was analyzed using the I^2 statistic, considering that the heterogeneity was not important (I^2: 0% and 30%), moderate (I^2: 30%–50%), substantial (I^2: 50%–75%), or considerable (I^2: 75%–100%). The size and clinical relevance of heterogeneity were determined using the τ^2 statistic, where a τ^2 estimate of 0.04 was interpreted as a low degree, 0.14 as moderate, and 0.40 as substantial clinically relevant heterogeneity.

After that, frequentist random effects methods were used to perform an NMA. For the study outcome (maximal oxygen uptake), we presented the following: 1) a network diagram was used to represent the included evidence, 2) a league table summarized the estimations for each treatment comparison, 3) a rankogram to graphically present the relative classification between the exercise interventions, and 4) the surface under the cumulative ranking (SUCRA) to present a numerical value for the classification of each intervention. These numbers could range from 0 to 1, with a score close to 1 indicating the best intervention.

Finally, using DerSimonian–Laird random effects methods, we estimated the standard mean differences (effect size [ES]) for a standard pairwise meta-analysis for direct comparisons between interventions and control/no intervention. In addition, data for sensitivity analyses were presented in tables and Egger's regression asymmetry test was used to assess publication bias. All analyses were performed using Stata 16.0.

Results

The selection process of articles included in the NMA is presented in Fig. 1. Of the 4785 full-text articles identified, 22 RCTs with a total

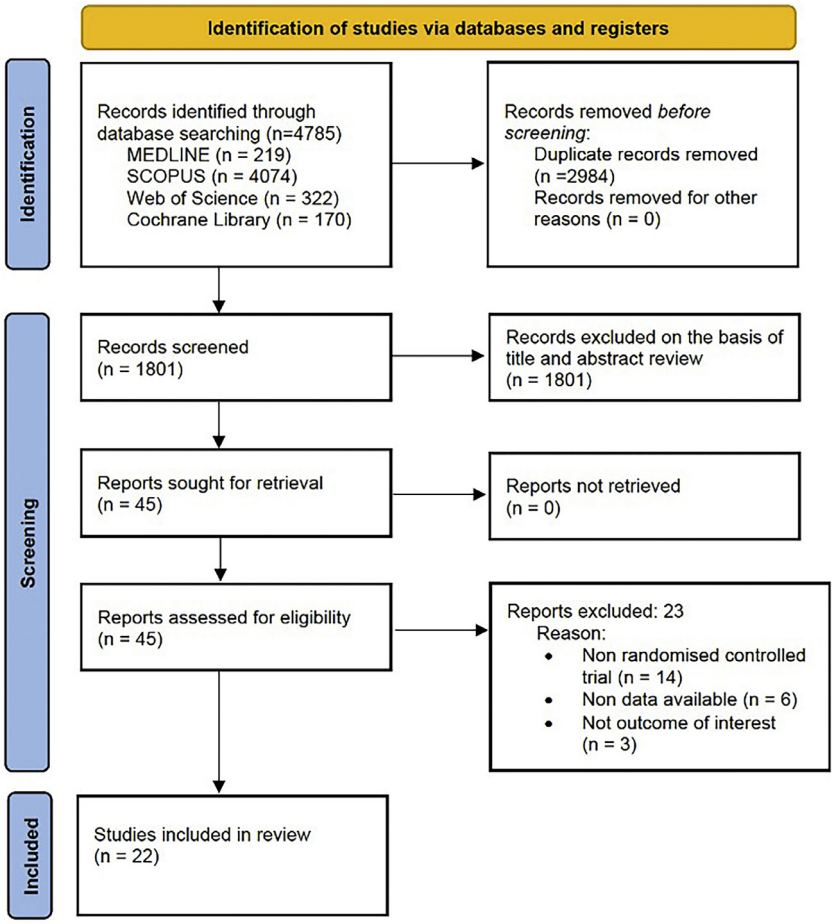

Fig. 1. Network meta-analysis flowchart of study inclusion.

Table 1
Characteristics of the samples described in the included studies.

Study Characteristics			Sample Characteristics				
Study	Country	n	Age (y), Mean (SD)	Disease Severity	FEV1 % pred	Groups by Intervention	n for each intervention
Ortega et al., 2002 [29]	Spain	72	60 (9)	Severe COPD	33(12)	**IG:** COMB	14
			66 (6)		40(14)	**IG:** ST	17
			66 (8)		41(11)	**IG:** CONT HIGH END	16
			NR			**CG:** CON	18
Simpson et al., 1992 [30]	Canada	34	73	Severe COPD	39.5 (18.96)	**IG:** COMB	14
			70		39.2 (21.39)	**CG:** CON	14
Bernard et al., 1999 [31]	Canada	45	64 (7)	Moderate to severe COPD	45 (15)	**IG:** COMB	21
			67 (9)		39 (12)	**IG:** CONT HIGH END	15
Clark et al., 2000 [32]	United Kingdom	43	51(10)	Moderate to severe COPD	76 (23)	**IG:** COMB	26
			46(11)		79 (23)	**CG:** CON	7
Tandon., 1978 [33]	Australia	24	60 (53–65)	Severe COPD	NA	**IG:** AMBMT	12
			60 (52–64)			**CG:** CON	12
Ye et al., 2010 [34]	USA	10	65 (6)	Moderate to severe COPD	53 (7)	**IG:** AMBMT	5
			66 (6)		47 (7)	**CG:** CON	5
Borghi-Silva et al.,2009 [35]	USA	34	67 (10)	Severe COPD	33 (9)	**IG:** COMB	20
			67 (10)		35 (11)	**CG:** CON	14
Skulmlien et al., 2007 [36]	Norway	60	63 (8)	Moderate to severe COPD	45 (11)	**IG:** COMB	40
			65 (7)		46 (10)	**CG:** CON	20
Coppoolse et al., 1999 [37]	Netherland	21	67 (3)	Moderate to severe COPD	37.4 (18.2)	**IG:** END INT	11
			63 (8)		36.2 (10.3)	**IG:** CONT MOD END	10
Bronstad et al., 2012 [38]	Norway	24	64.8 (7.7)	Moderate to severe COPD	54.8 (8.7)	**IG:** END INT	10
			64.9 (5.3)		49.9 (14.5)	**IG:** CONT HIGH END	7
			64.5 (6.4)		NA	**CG:** CON	17
Baumann et al., 2012 [39]	Germany	100	63 (11)	Moderate to severe COPD	47 (13)	**IG:** COMB	37
			65 (8)		45 (13)	**CG:** CON	44
Varga et al., 2007 [40]	USA	71	67 (10)	Moderate COPD	64 (29)	**IG:** END INT	17
			61 (12)		51 (16)	**IG:** CONT HIGH END	22
			60 (12)		52 (16)	**CG:** CON	32
Arnardóttir et al., 2006 [41]	Sweden	60	65 (7)	Severe COPD	35 (13)	**IG:** END INT	28
			64 (8)		32 (10)	**IG:** CONT HIGH END	32
Mehri et al.,2007 [42]	Iran	38	52.1 (10.7)	Severe COPD	NA	**IG:** END MODE	20
			52.17 (11.6)			**CG:** CON	18
Ries et al., 1995 [43]	USA	119	61.5 (8.0)	Mild to severe COPD	NA	**IG:** COMB	57
			63.6 (6.3)			**CG:** CON	62
Duruturk et al., 2015 [44]	Turkey	47	61.2 (5.1)	Moderate to severe	57.2 (10.5)	**IG:** ST	14
			61.2 (5.0)	COPD	58.4 (14.4)	**IG:** CONT MOD END	15
			63.8 (5.7)		63.6 (10.8)	**CG:** CON	13
Larson et al., 1999 [45]	USA	53	68 (6)	Moderate to severe	46 (17)	**IG:** CONT MOD END	14
			66 (6)	COPD	46 (17)	**IG:** CONT MOD END	14
			66 (5)		55 (17)	**CG:** CON	13
			62 (7)		55 (18)	**CG:** CON	12
Borghi-Silva et al., 2015 [46]	Brazil	20	67 (7)	Severe COPD	32 (11)	**IG:** CONT HIGH END	10
			66 (10)		35 (12)	**CG:** CON	10
Wijkstra et al., 1996 [47]	Netherland	43	64 (5)		44 (11)	**IG:** COMB	28
			62 (5)		45 (9)	**CG:** CON	15
Emery et al., 1998 [48]	USA	79	65.4 (6.4)	Moderate to severe COPD	43 (18)	**IG:** COMB	29
			67.4 (5.9)		43 (18)	**CG:** CON	25
			67.4 (7.1)		39 (16)	**CG:** CON	25
Göhl et al., 2005 [49]	German	34	62.5 (7)	Moderate to severe	53.4 (10.7)	**IG:** COMB	10
			63.2 (8.5)	COPD	53.7 (58)	**CG:** CON	9
Reardon et al., 1994 [50]	United Kingdom	20	66.3	Moderate to severe COPD	35	**IG:** COMB	10
			66.1		33	**CG:** CON	10

COMB: Combined; CON: Control; END: endurance; CONT HIGH END: continuous, high intensity endurance exercise; CONT MOD END: continuous, moderate intensity endurance exercise; END INT: endurance interval training; FEV1%: Forced expiratory volume in the first second as a percentage of the predicted value; IG: Intervention Group; n: sample size; NA: Not available; ST: strength; y: year.

sample of 1051 participants fulfilled the inclusion criteria and were included in the analyses. Of the included studies, 16 had 2 arms (1 intervention and 1 control or 2 interventions), and 6 had 3 arms (2 interventions and 1 control or 1 intervention and 2 controls). Regarding the interventions included in each study, continuous, moderate-intensity endurance exercise was evaluated in 4 studies with 73 participants, continuous, high-intensity endurance exercise in 6 studies with 102 participants, combined exercise in 12 studies with 306 participants, endurance interval training in 4 studies with 66 participants, and strength and AMBMT were studied in 2 studies including 31 and 17 participants respectively (Table 1). The ages of the participants in the studies ranged from 46 to 73 years. The characteristics of the included studies are detailed in Table 1, and the characteristics of the interventions are specified in Table 2.

Risk of bias

Twelve studies were assessed as at a low risk of bias, 3 with some concerns, and 7 at a high risk of bias. Regarding each specific domain, the randomization process was classified at a low risk of bias in 64% of the studies; the deviations from the intended interventions were classified at a low risk of bias (91%); the missing outcome data was classified at a low risk of bias (96%); the measurement of the outcome was classified at a low risk of bias (68%); and the selection of the

Table 2
Characteristics of the interventions described in the included studies.

Study	Groups by Intervention	Intervention	Time (min)/ rep	Intensity	Duration (wk)	Frequency (x/wk)
Ortega et al., 2002 [29]	**IG: COMB**	6-8 rep of the five weight-lifting procedures + 20 min CYC	2 series of 6-8 rep + 20 CYC	70-85% of 1RM +Work rate: 70% of peak work rate.	12	3
	IG: ST	ET: "chest pull" (latissimus dorsi), "butterfly" (pectoralis major), "neck press" (triceps brachii and deltoid), "leg flexion" (biceps femoris and gastrocnemius), "leg extension" (quadriceps femoris)	4 series of 6-8 rep /e/e	70-85% of 1RM		
	IG: CONT HIGH END	40 min leg ex on ergocycle.		Work rate: 70% of peak work rate.		
Simpson et al., 1992 [30]	**IG: COMB**	5 min Warm up of low resistance **CYC**+ 2 min of low resistance arm ex on **AC** + **WLE** single arm curl, single leg extension, single leg press ex. Normal breathing during the lifting phase of ex.	3 series of 10 rep	50% (1 week)- 85% 1RM final	8	3
	CG: CON	Usual medical care				
Bernard et al., 1999 [31]	**IG: COMB**	Aerobic training + WLE: pectoralis major, elbow flexion, shoulder adduction (latissimus dorsi), leg press, and bilateral knee extension.	30 min aerobic + 45 ST 2 series of 8/10 rep. Thereafter, it increased by more than 10 rep	Work rate 80% of peak work in incremental ex test + 60% 1RM	12	3
	CG: CONT HIGH END	Leg ex on ergocycle + relaxation and breathing ex.	30 min + 45 relax and breathing	Work rate 80% of peak work in incremental ex test	12	3
Clark et al., 2000 [32]	**IG: COMB**	Warm-up+ CYC or treadmill walking+ 3 sets of 10 rep of eight individual weight ex (triceps, quadriceps, gastrocnemius, soleus, latissimus dorsi, bieps, gluteals,hamstrings)+ cool down using CYC or treadmill.		Each of 8 ex was set at a load 70% of the subject´s max. Sixth week a new max value was determined. Last 6 weeks was undertaken at this new workload.	12	Twice weekly
	CG: CON	Were advised to continue their usual daily activities.				
Tandon et al., 1978 [33]	**IG: AMBMT**	Ten yogic postures+ practice all breathing manoeuvres at home			4 +4+28	Both groups: 1 hour, 3 times/week (first 4 weeks), twice a week (next 4 weeks), once a week (thereafter for a total of 9 months)
	CG: CON	Relaxation ex (accessory respiratory muscles, lateral costal and diaphragmatic breathing ex and general leg and trunk ex				
Yeh et al., 2010 [34]	**IG: AMBMT**	Warm up ex (WLE+ arm swinging+ gentle stretchs of the neck, shoulders, spine, arms, legs, visualization techniques and traditional breathing methods) + 5 Tai chi movements + 35 min instructional videotape with ex to practise at home at least 3 times/week	1h		12	2+ 3 at home
	CG: CON	Usual medical care				
Borghi-Silva et al., 2009 [35]	**IG: COMB**	Aerobic training (ST lower and upper limbs+ TMW) + STCH ex + DB (hamstrings, quadriceps, calves, shoulders, neck, and lower back)	30 min aerobic+ 10 min STCH	Training intensity in TMW: 70% max speed achieved during the ex test	6	3
	CG: CON	Vibration and clapping associated with postural drainage for 10 min with supported cough	10 min			
Skulmlien et al., 2007 [36]	**IG: COMB**	Three to four 45-min educational sessions all weekdays+ Resistance and endurance training. Treadmill endurance training: 4-5 times a week. Resistance training: 3-4 times a week.	Endurance: From 18 to 21 minutes during the four weeks.	Endurance: Training intensity increased form 64%- 83% of initial peak work rate.	4	Endurance: 4-5
	CG: CON	Usual medical care	Resistance: 2-3 series of 10 rep.	Resistance: Intensity, from 62% to 70% of 15 RM for legs and 82%-86% of 15 RM for arms.		Resistance: 3-4
Coppoolse et al., 1999 [37]	**IG: END INT**	3 days of interval training: nine blocks including 3 min of alternated 90% (1 min) + 45% (2 min) of the peak work rate. The other 2 days: continuous training at 60% of the peak work rate.		90% /45% of the peak work rate	8	3+ 2 (5)
	CG: CONT MOD END	5 days of cycle ergometer at 60% of the peak work rate.	30 min	60% of the peak work rate		5
Bronstad et al., 2012 [38]	**IG: END INT**	Uphill treadmill walking.10 min warm up at 50% to 60% of $VO_{2\text{-peak}}$ (60%-70% of peak HR) before exercising. 4 intervals of 4 min at 90%-95% of peak HR. Each interval was separated by 3 min active pauses, walking at 50%-70% of peak HR+ 3 min cool-down at 50%-70% of peak HR.	38 min	Warm up: 50% to 60% of $VO_{2\text{-peak}}$ (60%-70% of peak HR).	10	3
	IG: CONT HIGH END	Ex continuously at 70% of peak HR.	47 min	Intervals: 90%-95% of peak HR.		
	CG: CON			Pauses: 50%-70% of peak HR.		
				Cool-down: 50%-70% of peak HR.		

(*continued on next page*)

Table 2 (*Continued*)

Study	Groups by Intervention	Intervention	Time (min)/ rep	Intensity	Duration (wk)	Frequency (x/wk)
Baumann et al., 2012 [39]	**IG: COMB**	Training sessions with chairs, elastic bands, sticks and hand weights+ breathing techniques (PLB, DB, cough technique, muscle relaxation) + ST + END (interval training)+ coordination training+ education sessions.	During first 9 sessions: 10-20 min breathing technique + 15 min END+ 10 min ST+ 10 min coordination+ 5 min home ex instructions	Self- assessment using the Borg scale (4-6)	26	1
	CG: CON	Standard care	Remaining sessions: 10 min breathing technique + 20 min END+ 15 min ST+ 15 min coordination+ 5 min home ex instructions			
Varga et al., 2007 [40]	**IG:** END INT	Warm up (7,5 min at 50%) peak work rate+ 30 min period of CYC for 2 min at 90% followed by 1 min at 50% peak work rate+ cool-down phase.	45 min	Target protocol: 90% peak work rate/ 50%.	8	3
	IG: CONT HIGH END	Supervised continuous training	45 min	Some participants: 9 first sessions: 70% peak work rate achieved in an incremental ex test, in the high intensity phase/ 40% in the low intensity phase. Next sessions the target protocol.		
	CG: CON	Were instructed to cycle, climb stairs and walk in their natural environment.	30 min-45 min	80% peak wort rate.		
Arnadóttir et al., 2006 [41]	**IG:** END INT	Ergometer CYC: 6 min warm up (30-40% W peak) + interval training (all intervals were 3 min. High and low intensity intervals were equally long) + 6 min cool down (30-40% W peak) + PLB during ex. Once a week Callisthenics and relaxation (Jacobson) and once a week resistance training (upper and lower limbs+ abdominal muscles (2 sets of 10 rep at 70% 1RM)	39 min	Some participants: 9 first sessions: 65% 5 Uphill intervals: 80% W peak	16	2
	IG: CONT HIGH END	Ergometer CYC: 6 min warm up (30-40% W peak) + continuous training at 65% W peak + 6 min cool down (30-40% W peak)+ PLB during ex. Once a week Callisthenics and relaxation (Jacobson) and once a week resistance training (upper and lower limbs+ abdominal muscles (2 sets of 10 rep at 70% 1RM)		4 Downhill intervals: 30-40% W peak		
Mehri et al., 2007 [42]	**IG:** CONT MOD END	5 min Warm up (stretched ex) + Treadmill (the speed was gradually increased from minimum speed and 0° elevation)			4	2
	CG: CON					
Ries et al., 1995 [43]	**IG:** COMB	**Two phases. Phase I** (core program). Education+ physical and respiratory care instruction+ psychosocial support+ supervised ET (30 min continuous walking at the highest tolerated symptom-limited level). Were asked to walk at home at least twice daily and also instructed and trained in upper-extremity ex with ergometer and a progressive program of arm lifts with weights for home training. **Phase II:** monthly follow-up visits for 1year.	Twelve 4-hour sessions	At the highest tolerated symptom-limited level	8	3
	CG: CON					
Duruturk et al., 2015 [44]	**IG:** ST	Education session on thoracic expansion ex and bronchial hygiene techniques, lasting about 30 min+ warm up (lower and upper extremity joint movements- 10 rep e/e) + 16 different strengthening and STCH ex of lower and upper extremity muscles.	First and second weeks: 10-15 times e/e per session.	4 to 7 Modified Borg scale	6	3
			Third and fourth weeks: 15-20 times per session. Fifth and sixth weeks: 25-30 per session.	4 to 7 Modified Borg scale		

(*continued on next page*)

Table 2 (*Continued*)

Study	Groups by Intervention	Intervention	Time (min)/ rep	Intensity	Duration (wk)	Frequency (x/wk)
	IG: CONT MOD END	Education session on thoracic expansion ex and bronchial hygiene techniques, lasting about 30 min+ 3 min warm-up consisting of pedaling at a low work rate (20-30% of VO_{2max}) 20-30 min of continuous CYC at 50-70% of VO_{2max} + 3 min cool-down (pedaling at 20-30% of VO_{2max})	20-45 min			
	CG: CON					
Larson et al.,1999 [45]	**IG:** END INT	CET: Interval training protocol, four work sets, 5 min in duration separated by rest intervals (2-4 min) of unloaded CYC	20 min/d	50% of the peak work rate	4 months	5
	IG: END INT	CET + IMT	20 min/d CET+ 30 min/d IMT	30% - 60% PI_{max}		5
	CG: CON	IMT: Six work sets, 5 min duration, separated by rest intervals lasting 1-3 min	30 min/d			5
	CG: CON	Health education	1 hour			1
Borghi-Silva et al., 2015 [46]	**IG:** CONT HIGH END	5 min of warm up (walking) at 2 km/h+ 30 min at an intensity of 70% of peak speed+ cool down (STCH lower and upper limbs in seated and supine positions)		ET intensity was increased 0,5 km/h when Borg score was less than 4.	12	3
	CG: CON	Respiratory therapy				1
Wijkstra et al., 1996 [47]	**IG:** COMB	Relaxation ex (Jacobson technique) + PLB+ DB+ upper limb training (PNF) (two ex for each arm with the same weight+ + IMT+ CYC (4 min at 60% of W_{max} - 12 min at 75% of W_{max})	IMT: 3 seg with pressure+ 4 s unloaded expiration. 15 min twice a day	IMT: 70% of PI_{max}	12	Relax ex + breathing on alternating days.
	CG: CON		30 min			IMT+ Upper limb training + ET every day.
Emery et al., 1998 [48]	**IG:** COMB	5 weeks intensive: 10 min warm-up+ 45 min aero (stationary bicycle, arm ergometry and walking) + ST + cool-down period of STCH+ 4 h educational lectures per week+ stress management and psychosocial support.	60-90 min		10	3
	CG: CON	5 more weeks: ex sessions for 60-90 min+ one hour-long weekly stress management class.				
	CG: CON	Stress management education				
Göhl et al., 2005 [49]	**IG:** COMB	ST (ex with free weights, Theraband or ex on strength machines, ex without equipment in different modalities (dynamic, isometric) + Aero (Walk, ergometer cycle, stair climbing, stepper)+ STCH+ coordination (ex with breathing)+ education session	90 min		12 months	2-3
	CG: CON					
Reardon et al., 1994 [50]	**IG:** COMB	Upper extremity training with therabands and light weight lifting stair climbing treadmill and stationary bicycle ex+ IMT+ educational session	3 h	70-80% max ex testing	6	3
	CG: CON					

AC: arm crank ergometer; AERO: aerobic exercises; AMBMT: active mind-body movement therapies; CET: cycle ergometry training; CG: control group; COMB: combined: strength + endurance; CON: control; CONT HIGH END: continuous, high-intensity endurance exercise; CONT MOD END: continuous, moderate-intensity endurance exercise; CYC: cycling; DB: diaphragmatic breathing; e/e: each exercise; END INT: endurance interval training ET: exercise training; EX: exercise; HR: heart rate; IG: intervention group; IMT: inspiratory muscle training; min: minutes; max: maximal; PI_{max}: Maximal inspiratory pressure; PLB: pursed-lip breathing; PNF: proprioceptive neuromuscular facilitation; ST: strength training; STCH: stretching; TMW: treadmill walking; WLE: weight lifting exercise; W: work; 1RM: one repetition maximum; 6MWT: 6-minute walking test.

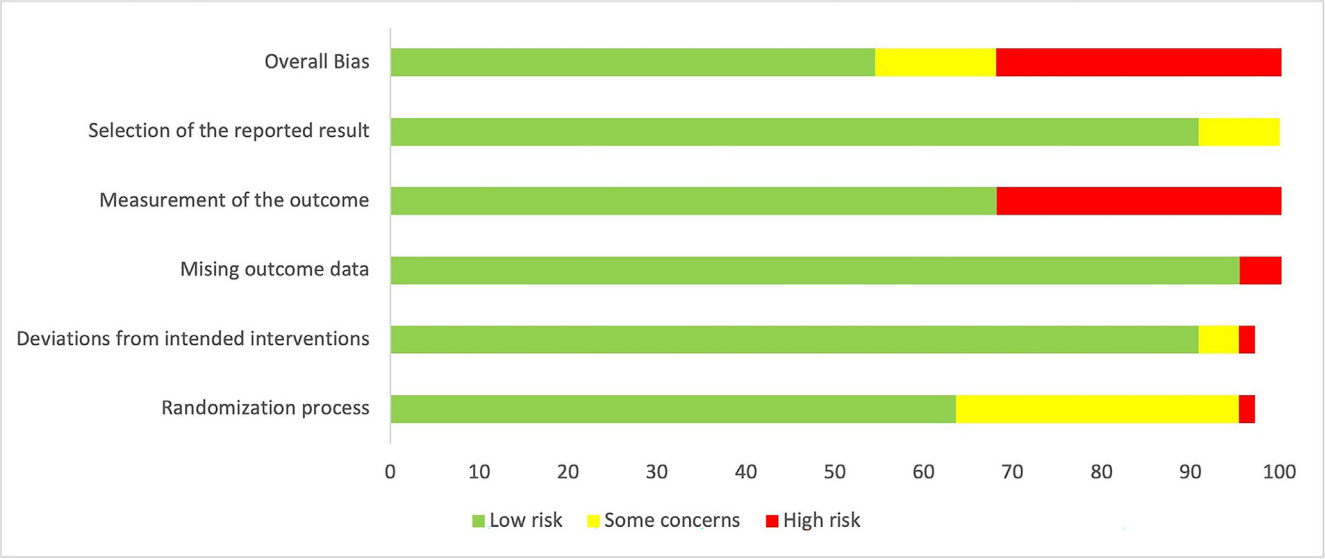

Fig. 2. Percentage risk of bias of included studies assessed with the Risk of Bias tool (RoB2).

reported result outcome was classified at a low risk of bias (91%) (Figs. 2 and S.1).

The GRADE results are shown in Table S.3.

Network meta-analysis

Network diagrams showed the relative amount of evidence available for the different exercise interventions for maximal oxygen uptake in people with COPD. The NMA involved 12 direct comparisons for variable maximal oxygen uptake (Fig. 3). Most of the interventions were directly compared with at least 1 control.

The similarity assumption was met for all comparisons by including participants with similar baseline characteristics (ie, age, percentage of women in the sample, and baseline values of FEV1% and maximal oxygen uptake) (Table S.4). The transitivity analyses did not show any relevant discrepancy between direct and indirect evidence,

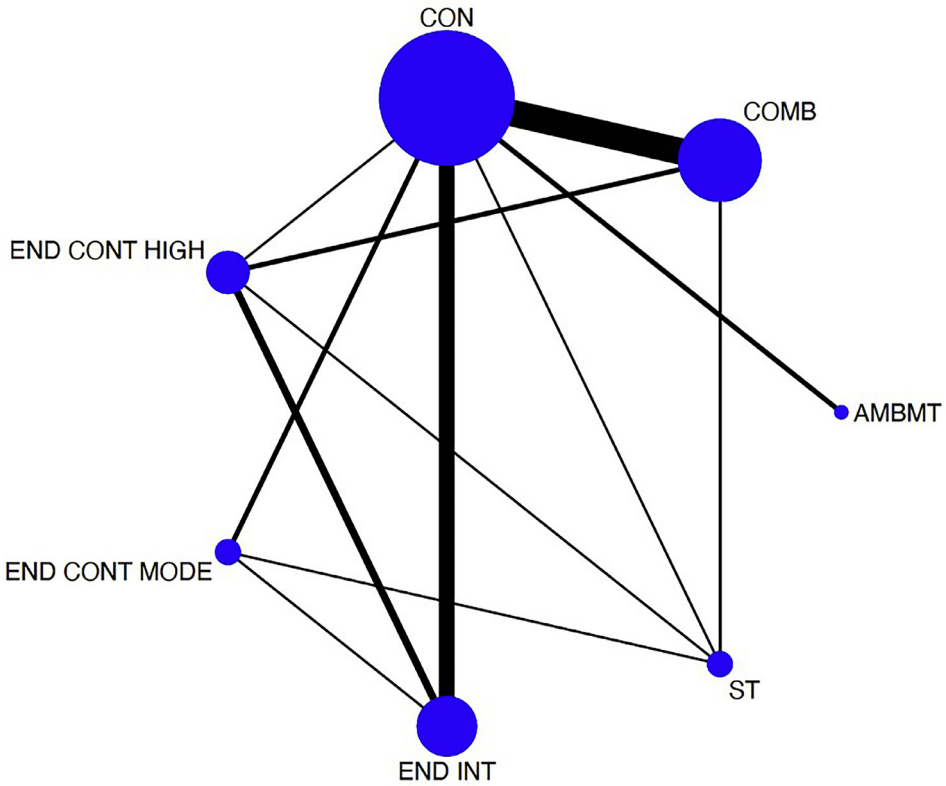

Fig. 3. Network of available comparisons between physical activity interventions on oxygen uptake. The size of the node is proportional to the number of trial participants, and the thickness of the continuous line connecting nodes is proportional to the number of participants randomized in trials directly comparing the 2 treatments. AMBMT: active mind-body movement therapies; COMB: combined; CON: control; CONT HIGH END: continuous, high-intensity endurance exercise; CONT MOD END: continuous, moderate-intensity endurance exercise; END INT: endurance interval training; ST: strength.

except for the comparisons involving control-continuous, moderate-intensity endurance interval training (Table S.5). The comparison of continuous, moderate-intensity endurance exercise with a control showed substantial statistical and clinical heterogeneity (I^2 = 69.4, τ^2 = 0.3324), all other head-to-head comparisons showed no significant heterogeneity ($P > .05$) (Tables S.6).

The highest effects for pairwise comparisons for maximal oxygen uptake scores were for continuous, moderate-intensity endurance exercise versus a control (ES 1.17; 95% CI 0.59 to 1.74), followed by continuous, high-intensity endurance exercise versus a control (ES 0.47; 95% CI 0.08 to 0.85), and combined exercise versus a control (ES 0.41; 95% CI 0.18 to 0.64) (Table 3).

Best treatment probabilities

The cumulative rankogram showed that continuous, moderate-intensity endurance exercise had the highest probability of being classified as the first treatment (Fig. 4). In addition, continuous, moderate-intensity endurance exercise had the highest probability of being the best treatment estimated by the SUCRA (98%) (Table S.7).

Analysis of sensitivity, heterogeneity, and publication bias

In the sensitivity analyses, the ES was not substantially modified after excluding any study from the analyses (Table S.8). The funnel plot of publication bias is shown in Figure S.2.

Discussion

The aim of this NMA was to compare the effect of each exercise training modality on oxygen uptake in people with COPD and to determine which type of intervention is most effective in improving it. This NMA, which included 22 RCTs and data from 1051 participants, provides evidence supporting exercise as an effective therapeutic strategy to improve oxygen uptake in people with COPD. In addition, the analysis of the available evidence indicates that continuous, moderate-intensity endurance exercise is the most effective approach for the improvement of oxygen uptake. Likewise, continuous, high-intensity endurance exercise and combined exercise are also effective modalities for improving oxygen uptake.

Until now, studies of the effects of different exercise modalities, such as endurance interval training versus a control, did not find statistically significant differences in the improvement of VO_2 [51]. In a meta-analysis that compared endurance interval training with continuous endurance training, only 9 studies included evaluated VO_2, showing no significant effect in the primary meta-analysis and leading the authors to conclude that there was no significant difference in either training group [22]. Another review expanded on previous contradictory observations and found that moderate physiological improvements, measured by the most relevant response, VO_2 peak, are achieved with conventional (continuous) endurance aerobic training in people with COPD [21].

The endurance interventions consisted of programs whose objective was to increase heart rate and energy expenditure to cover the oxygen requirements necessary to keep the muscles activated. The time that people can maintain this load depends directly on their resistance capacity, closely linked to muscle fatigue; with a tolerance to effort that is decreased in people with COPD [52,53] who present a loss of resistance capacity and a rapid onset of muscle fatigue. This type of intervention allows an increase in the resistance to exercise, which helps people reach maximum oxygen consumption in the incremental test. These interventions included treadmill or cycle training at different intensities, which enabled us to classify studies into continuous, high-intensity resistance exercise, and continuous, moderate-intensity resistance exercise.

Table 3
Pooled mean differences of physical activity on oxygen uptake.

CONTROL	0.18 (−0.50; 0.85)	0.29 (0.11; 0.46)	0.22 (−0.24; 0.68)	1.17 (0.21; 2.13)	0.17 (−0.15; 0.50)	0.26 (−0.50; 1.02)
0.24 (−0.71; 1.19)	**AMBMT**	–	–	–	–	–
0.41 (0.18; 0.64)	0.17 (−0.81; 1.15)	**COMBINED**	−0.11 (−0.60; 0.38)	–	–	−0.09 (−0.80; 0.62)
0.47 (0.08; 0.85)	0.23 (−0.80; 1.26)	0.06 (−0.35; 0.47)	**ENDURANCE CONTINUOS HIGH**	–	−0.14 (−0.51; 0.23)	−0.05 (−0.73; 0.63)
1.17 (0.59; 1.74)	0.93 (−0.18; 2.04)	**0.76 (0.15; 1.36)**	**0.70 (0.05; 1.35)**	**ENDURANCE CONTINUOS MODE**	0.35 (−0.52; 1.21)	−0.57 (−1.31; 0.17)
0.37 (0.02; 0.72)	0.13 (−0.88; 1.15)	−0.04 (−0.44; 0.36)	−0.10 (−0.48; 0.28)	**−0.80 (−1.42; −0.18)**	**ENDURANCE INTERVAL TRAINING**	–
0.47 (−0.08; 1.02)	0.23 (−0.87; 1.33)	0.06 (−0.50; 0.62)	0.00 (−0.59; 0.59)	**−0.70 (−1.38; −0.02)**	0.10 (−0.51; 0.71)	**STRENGTH**

AMBMT: Active mind-body movement therapies. Effect size (ES) estimates and (95% CI). Data in bold indicated statistically significant. Upper right triangle gives the pooled mean differences from pairwise comparisons (column intervention relative to row), lower left triangle pooled mean differences from the network meta-analysis (row intervention relative to column).

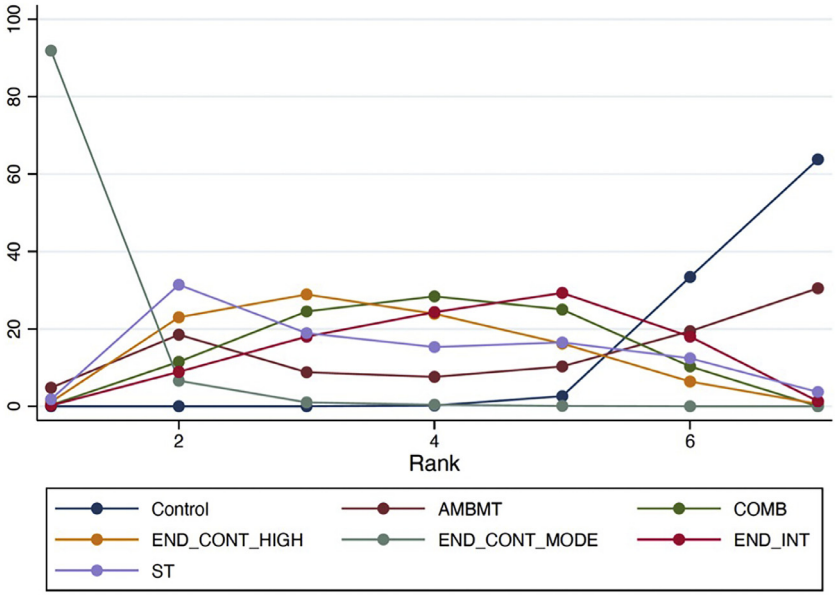

Fig. 4. Cumulative rankogram for each physical activity intervention on Oxygen intake. AMBMT: Active mind-body movement therapies; COMB: Combined; CON: Control; CONT HIGH END: continuous, high-intensity endurance exercise; CONT MOD END: continuous, moderate-intensity endurance exercise; END INT: endurance interval training; ST: strength.

The combined exercise consisted of combined strength exercises for the large upper and lower limb muscle groups, with part of the session dedicated to resistance or aerobic exercises. Current evidence affirms that to improve aerobic capacity, a sufficient volume of exercise, such as that obtained in endurance training, is necessary to overload the skeletal muscle metabolism, enhance oxidation capacity, and enable the cardiovascular system to achieve an improved oxygen supply [54]. In the particular case of people with COPD, it is difficult to achieve this volume of training. Sometimes it is not possible for people with COPD to achieve the necessary combination of exercise intensity and duration to meet these objectives [55] because of their exercise limitations, with hyperinflation and air trapping with expiratory flow limitation. In addition, these people have hypoxia, reduced diffusing capacity, a decrease in the strength of the peripheral musculature, and morphological abnormalities of the skeletal muscle that have been shown to contribute to exercise limitations in COPD [10,56-61].

People with COPD present a reduction in the mitochondrial density [62] of the muscle fiber [63,64], alterations in their function, and changes in bioenergetics, with an imbalance between oxidative and glycolytic metabolism [65]. Oxidative muscle metabolism during exercise is impaired in these people, leading to an increase in blood lactate levels when faced with a low workload [66,67]. It is suggested that this increase in lactate production is caused by an intrinsic muscle abnormality (reduced oxidative capacity) resulting in early activation of anaerobic glycolysis [68]. According to the available evidence, exercise favors mitochondrial biogenesis. This is indirectly evaluated by the expression level of a gene called PGC-1α, which is the main regulator of mitochondrial biogenesis [69,70]. By increasing mitochondrial biogenesis, the mitochondria will be better prepared to sustain a greater volume of exercise with a greater capacity. It seems that the highest levels of PGC-1α expression are found at an intensity of approximately 70–100% of peak work, however, it seems that higher levels fail to further increase the expression levels of PGC-1α, being close to 70% [71]. Other studies show an increase in PGC-1α during exercise at an intensity between 50% and 75% of peak work [72,73], which could be one of the causes of the results of our study, with better results in terms of improvement in VO_2 for continuous, moderate-intensity (50–60% of peak work), followed by continuous, high-intensity (70–80% of peak work) endurance exercise.

Data from this NMA indicate that the most effective type of physical exercise intervention to improve oxygen uptake in people with COPD is continuous, moderate-intensity endurance exercise. In this exercise training modality, the participant must maintain the load constantly, which is directly related to their resistance capacity and closely linked to muscle fatigue [54]. People with COPD present a decrease in exercise tolerance and rapid onset of muscle fatigue, observing the need for more time to reach the plateau of maximum oxygen consumption, requiring a greater ventilatory demand. That is why the continuous, moderate-intensity endurance exercise modality improves cardiorespiratory resistance, which is closely related to VO2 max.

Therefore, it is necessary to evaluate maximum oxygen uptake in people with COPD, as well as to determine if exercise programs improve their VO2 max, and to determine which type of exercise is most effective and at what intensity to improve oxygen consumption in this specific group. Many authors agree that maximal oxygen uptake is a better predictor of health-related quality of life and mortality than FEV1, which is more commonly studied in people with COPD [13]. Few studies have measured this parameter, probably because not all health centers have the required equipment or professionals trained in its measurement.

Study limitations

This study has some limitations. First, we were unable to consider exercise intensity in our analysis for all types of interventions as this information was not available. Second, we could not determine the appropriateness of each type of exercise based on the duration of the disease. Third, the moderate risk of bias in some of the included studies was mainly caused by the difficulty of blinding the interventions; however, the risk of bias in the included trials was generally acceptable for the other domains of the RoB2 tool. Fourth, the findings must be interpreted with caution because of the limited number of studies for some types of interventions. Finally, we analyzed peak and maximal oxygen uptake under the same concept, which could provoke some kind of bias in the results.

Conclusions

In summary, continuous, moderate-intensity endurance exercise appears to be the most effective type of exercise for improving oxygen uptake in people with COPD, followed by continuous, high-intensity endurance exercise and combined exercise. Endurance interval training also improved VO_2. Exercise should be considered as a fundamental therapeutic strategy to improve oxygen uptake in people with COPD. Because of the importance of VO_2 as a predictor of both quality of life and mortality in people with COPD, it is essential to include its measurement in future studies to estimate the effect of different types of exercise and continue to deepen understanding of the effect of different types of exercise in people with COPD. We recognize limitations relating to its measurement because of the still limited accessibility and difficulty in carrying out specific tests for the direct measurement of peak VO_2, the high cost they present, and the need for professionals trained in the use of these tests.

Ethical approval

Not applicable.

Consent for publication

The authors declare consent for publication.

Availability of data and materials

Data are available upon request. The data tables used to run the analyses are available upon request to the first author of this study.

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Authors' contributions

Conceptualization, S.P.-J., and C.Á.-B.; methodology, S.P.-J., M.I.L.-L-T and M.J.G-P.; formal analysis, P.L.-G., M.C.R.-G. and S.P.-J.; data curation, S.P.-J and C.Á.-B.; writing original draft preparation, S.P.-J. and F.A.-Q; writing review and editing, C.Á.-B. and P.L.-G. All authors have read and agreed to the published version of the manuscript

Declaration of competing interest

The authors declare no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rehab.2024.101875.

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