Clinical effectiveness and safety of eccentric cycling for patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis

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Introduction. To assess the clinical effectiveness and safety of eccentric cycling in patients with chronic obstructive pulmonary disease (COPD) compared with concentric cycling.
Methods. We searched eight major electric databases and two ongoing trial registers before January 2023 for CCTs on patients with COPD. The main outcome measures were FEV1/FVC (% of predicted post-bronchodilator) and FEV1 (% of predicted post-bronchodilator). Two reviewers independently selected the trials and extracted data. The results were presented by RevMan 5.4. The risk of bias was assessed using the Cochrane Collaboration Bias Risk Assessment tool.
Results. Ten CCTs involving 136 participants were included in this review. All trials were poor in quality for blinding of participants and personnel. The pooled result showed a trend favouring the eccentric training group in MVC strength with no significant difference. Eccentric cycling showed more tolerance as dyspnoea was lower. Moreover, minute ventilation in comparable eccentric training vs. concentric training intensity favoured eccentric cycling.
Conclusions. This review indicates that eccentric cycling is considered a promising and feasible exercise approach on patients with COPD. However, larger clinical trials with more patients over a longer period are needed to determine these findings.

Keywords. Eccentric cycling; Chronic obstructive pulmonary disease; Meta-analysis; Review

INTRODUCTION

Chronic obstructive pulmonary ailment (COPD) has the frequent elements of persistent respiratory signs and symptoms as well as airflow obstruction precipitated with the aid of alveolar and/or airway abnormality, generally due to high toxic gas or particle exposure, which is under the influence of host factors (such as aberrant pulmonary development) [1].

In line with 2019 'Global Health Assessment' of the World Health Organization (WHO), COPD is one of those three major global causes of death. By 2060, it is estimated that COPD and its associated disorders will cause deaths in >5.4 million of the population annually. COPD will have an effect on lifestyles first-class of instances and increase annual oxygen treatment and medication expenses, thereby causing tremendous burden on the family as well as the society. According to reports, COPD is becoming one of those five most significant burden diseases by 2013 globally [1-3]. Consequently, it is of extreme importance to scientifically prevent and effectively treat the disease.

As mentioned in the 2022 gold COPD guidelines, pulmonary rehabilitation training is the critical adjuvant therapy for treating COPD, which indicates the individualised, integrative and multi-course interventions for decreasing symptom burdens whilst enhancing cardiovascular activity [1, 4]. Exercise training has been a major part in pulmonary rehabilitation programme [5], and it has an essential impact on the latter as the treatment approach for improving heath-related life quality and functional dyspnea whilst improving workout overall performance amongst COPD cases [6-8]. As suggested in international guidelines, exercise components in pulmonary rehabilitation are resistance and aerobic training [9-11]

Cycling represents endurance exercise in the healthy form, which does not significantly affect joints as the non-weight-bearing activity, and has low stress on the body compared with running sports like jogging [12]. Conventional cycling, a traditional cardio training, is a frequent exercising intervention method for patients with COPD, usually carried out on treadmill or cycle ergometer that involves concentric muscle contractions [13, 14], which improves muscle oxidative capacity, exercise tolerance, and life quality [15], reduces the scale of type IIx fibres and will increase CSA of all myofiber types [16]. However, there is also evidence that concentric cycling (CON cycling) cannot be tolerated by many patients with COPD, especially those with severe airflow obstruction, because of its high training intensities that cause muscle soreness, dyspnoea, wheezing and chest tightness [6, 17, 18].

Eccentric cycle training, belonging to eccentric training, is a novel exercising shape the place decrease limb muscle eccentric training is carried out to resist cranks' backward rotational movement resulting from the eccentric ergometer, while the hip and knee flexors and extensors absorb work via the eccentric contractions [13, 19].
Compared with CON cycling, eccentric cycling (ECC cycling) has been demonstrated as a valid and safe alternative. Firstly, as resistance training, ECC cycling exploits the specific muscle action lengthening property causing the increased force-generating ability in comparison with CON cycling [15, 20, 21]. Secondly, eccentric muscle actions are also advantageous in that the production of metabolites at the muscle level (i.e. creatine or lactate) following eccentric circulation decreases relative to CON cycling [8, 15, 22]. Thirdly, ECC biking may want to decorate ability for developing functions of functional muscles, balance and dynamic stability greater than CON cycling and concentric resistance training [15, 23]. As for time cost, the higher level of workload tolerated by way of sufferers with COPD means they can use less time to perform the same amount of exercise, thereby saving resources as well. Several trials showed that most patients managed to maintain the habit of an ECC cycling programme and the compliance of eccentric crew improved relative to concentric group [14, 21, 24, 25]. Moreover, eccentric exercise can improve life quality for COPD cases as it involves a less metabolically-demanding training [26].
Although some trials have reported that ECC cycling exerted beneficial effects on patients with COPD, ECC cycling must be selected cautiously among severe COPD cases, according to the result that the ECC cycling is associated with hypermnesic ventilatory pattern, decreased IC as well as reduced ventilatory efficiency [24]. Hence, there is a need to compare ECC and CON cycling.
To date, there have been some systematic reviews and meta-analyses on eccentric training. As reported by one meta-analysis published in 2015, eccentric exercise shows advantages and is comparable to conventional exercise with regard to enhancing walking and strength in COPD cases [27]. And a overview posted in 2021 described physiological responses to ECC cycling, according to the results, ECC biking may decorate workout tolerance, muscle mass and strength, and aerobic power/capacity [19]. Although these reviews and meta-analysis have conducted relevant evaluations and provided preliminary evidence, limitations include no special

quantitative study comparing ECC and CON cycling in patients with COPD [19, 28, 29], no cost-effectiveness evaluation of eccentric exercise, no focus of outcome measures of clinical important interest (leg fatigue, breathing frequency, etc.) as well as no up-to-date quantitative research [27, 28].

This review aimed to qualitatively and quantitatively analyze existing studies for assessing ECC cycling's safety and efficacy for COPD cases.

METHODS

Our study protocols were registered at INPLASY (doi: 10.37766/inplasy2023.1.0048) on 17 January 2023, which can be obtained from https://inplasy.com/inplasy-2023-1-0048/. The present work was performed in line with PRISMA guidelines (see Supplementary Table 2) [30].

Literature Searching Strategy

Literature research was conducted from inception up to August 2022 based on PubMed, The Cochrane Library, Web of Science, EMBASE, CNKI, VIP, CBM and Wanfang databases. The following terms were used 'Chronic Obstructive Lung Disease', 'COPD', 'Chronic Obstructive Pulmonary Disease', 'COAD', 'Chronic Obstructive Airway Disease', 'Chronic Obstructive Airway Disease' and 'eccentric/concentric cycle protocol', 'eccentric bicycle ergometer', 'eccentric bicycle exercise', 'eccentric concentric cycle protocol', 'ECC', and 'ECC bout'. The search was without language restriction. Supplementary Table 1 shows personalized search strategies of all English databases as well as the detailed search criteria. In addition, the World Health Organization trials portal (WHO ICTRP) and Clinical Trials.gov were searched to identify uninterrupted trials, and a manual search of reference lists inassociated research used to be additionally conducted.

Inclusion and Exclusion Criteria

Participants: patients aged ≥18 years who had moderate-evere COPD, with no restriction of sex. Patients have been chosen primarily based on criteria below, 1. the ratio of forced expiratory volume in 1 s [FEV1] to compelled quintessential ability [FVC] was < 70%, with FEV1 < 80% of the estimated daa in line with criteria in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [1]. 2. stable COPD cases of levels B/C/D based on the complete assessment system. Patients conforming to standards under have been excluded, those with severe arrhythmia; unstable angina pectoris; uncontrolled hypertension; cardiac insufficiency; arthropathies, peripheral vascular diseases or neuromuscular disorders affecting exercise; as well as those suffering from severe psychiatric or cognitive impairments.

Interventions: ECC cycling with/without usual care (such as medical treatment and/or respiratory rehabilitation training). In this study, usual exercises included non-resistance together with resistance exercises. ECC cycling interventions should be performed onto the cycle ergometer with backward movement of motor powered pedals for identifying execution and exercise and for comparing eccentric loading with control.

Comparisons: CON cycling with/without usual care (such as medical treatment and/or respiratory rehabilitation training). In tihs study, usual care for both intervention and control groups was identical.

Outcome measures: the fundamental consequence measures are FEV1/FVC (percent of estimated post-bronchodilator) as well as FEV1 (percent of estimated post-bronchodilator). We included the following secondary outcome measures: coronary heart rate, minute ventilation, dyspnoea, muscle strength, MVC strength, 6-min walk test, quadriceps muscle isometric peak torque, muscle soreness, plasma CK activity, oxygen consumption, perceived exertion rating, breathing frequency and leg fatigue.

Study design: controlled clinical trial (CCT), which included non-randomized and randomized controlled trials (RCTs). In this study, the arallel, before-after and cross-over controlled trial was included.

Study Selection

Duplicates were removed, afterwards, two researchers were responsible for independent title, abstract as well as full-text screening. Disagreements between them were solved by mutual negotiation of both researchers (Zhou MC and Zhou MQ). In full-text screening, the causes of excluded studies were recorded.

Data Collection

Two researchers (Zhou MC and Zhou MQ) had been accountable for unbiased statistics series the use of a standardised form, with disagreement solved by discussion. The following information was extracted: the characteristic of the trials, intervention, outcomes measures and results. Any disagreement between them was solved by the opinion of a third author (Li X).

Risk of Bias In Individual Trials

Two researchers (Zhou MC and Zhou MQ) were in charge of evaluating bias risk with Cochrane Collaboration Bias Risk Assessment approach [31]. Disagreements between them were solved based on the opinion of the third author (Chen X). Studies were rated high-, low or unclear-risk with regard to allocation concealment, random sequence generation, participant/personnel blinding, outcome assessment blinding, insufficient outcome information, selective reporting or additional bias. Any disagreement between them was solved by the opinion of a third author (Li X).

Meta-analysis

The present work was carried out with Review Manager Software 5.4. For continuous data, weighted imply variations had been adopted to be effect size. For data with inconsistent units, standardized imply distinction ought to be applied. Binary variables were represented by risk ratios. For effect sizes, we determined their 95% CIs along with p-values. The random-effect mannequin need to be used in the presence of significant methodological or clinical heterogeneity; or else, the fixed-effect model should be used for $I^2 < 50\%$. Moreover, sensitivity analysis was conducted for assessing result robustness. Possible publication bias was assessed by Funnel plots when over ten have been blanketed into one meta-analysis.

RESULTS

Selected Trials

We initially included altogether 1584 trials. Then, 507 trials were removed, including 486 duplicates, and titles and abstracts in 1054 trials were read, as a result, 44 trials were selected in subsequent analysis.Later, 34 trials were excluded, while the rest 10 trials were enrolled for further analysis (Fig.1 displays the exclusion causes).

Study Characteristics

Three RCTs, four cross-over controlled trials, three before–after controlled trials were included, in whom all 136 participants had COPD defined as a clinical diagnosis of COPD and compelled critical potential (% of envisioned (% of predicted post-bronchodilator) < 80% for man or woman contributors (Table 1). The included trials were published in 1997, 2011, 2017, 2020, 2021 and 2022. Three trials only enrolled male patients with COPD. All trials used a cycle ergometer allowing for ECC and CON exercises. Further, all trials used a backward direction for ECC and a forward direction for CON. The maximal duration of the programme was 10 months.

The duration of each bout ranged from 4 to 30 min in six trials. There were no dropouts in the seven trials. Ten trials remained in regular exercising depth at some point of the programme while one increased in intensity. All trials performed the familiarisation sessions before the first formal training session.

Quality assessment

Figure 2 displays risk of bias determined by Cochrane Collaboration approach. Those 10 trials were CCTs with comparable basic features. Among them, eight trials had random sequence generation and two trials failed to clearly describe it. Five trials reported allocation concealment. Due to cycling feature, it was once no longer convenient for participant/personnel blinding in all trials as dyspnoea, leg fatigue, and muscle soreness may be subjective. No result assessment techniques have been furnished in nine included trials, and just one article described those two blinded evaluators responsible for evaluation before and after training. No trials confirmed inadequate effect information. One trial showed a high selective reporting risk owing to technical failure in metabolic cart, which avoided measuring peak VO_2 post-training. Two studies reported having low quality of other biases owing to unbalanced sample size between groups (Figs. 2 and 3).

Outcome Effects

Primary outcomes. The momentous diagnostic criteria of patients with COPD are mainly based on lung function examination, showing concretely in FEV1/FVC (percent of estimated post-bronchodilator) < 70% or FEV1 (percent of estimated post-bronchodilator) < 80%. Only one trial [15] reported FEV1 (F = 0.58, P = 0.45), FVC (F = 0.46, P = 0.50) together with FEV1/FVC (F = 0.29, P = 0.59) ratios, which remained unchanged in each group following training.

Secondary outcomes.

Effectiveness. Quadriceps muscle isometric peak torque (N)

Two trials [4, 21] involving 39 subjects reported, with 18 subjects from CON group together with 21 people from ECC group (39 subjects; MD = －14. 57, 95%CI = －39.58–10.44, P = 0.25, I^2 = 0%). Both trials reported that EEC cycling significantly enhanced isometric peak strength compared with CON cycling alone, however, inter-group difference was of no significance.

MVC strength (N)

Two trials reported MVC strength. The pooled result favoured the ECC training group

(30 participants; MD = 57, 95%CI = −49.41–164.41, I^2 = 0%, P = 0.29). Results have been now not notably exceptional of both groups. One trial [15] found that eccentric exercise led to little change after ECC and CONC as a group, indicating that some participants showed >20% increase in MVC strength. One trial [25] reported a decrease immediately and 24 h from the baseline after ECC training in high workload, respectively.

Six-minute walk test (metres) and life quality

Two trials involving 44 participants with COPD assessed the effect of ECC cycling versus CON cycling (44 participants; MD = 8.77, 95%CI = −43.67–61.21, I^2 = 39%, P = 0.74). One trial [15] reported significant improvements in the ECC group but was unchanged for the CON group, which was also the unique study investigating the life quality.

Tolerability. Muscle soreness

Based on pooled results from two clinical trials [15, 25], muscle soreness was not significantly different between the ECC and CON groups (30 participants; MD = 14.69, 95%CI = 0.18–29.19, I^2 = 23%, P = 0.05). Both trials found that muscle soreness in ECC group increased compared with CON group.

Leg fatigue Borg scale

Five trials reported the leg fatigue Borg scale [4, 8, 21, 24, 32]. Considering that the intensity in different trials varies a lot, we compared the effects of leg fatigue Borg scale in higher workload in the ECC than the CON group and comparable workload group (HIGH: MD = 0.51, 95%CI = −1.06–2.07, I^2 = 90%, P = 0.53; COMP: MD = −1.43, 95%CI = −2.37–−0.49, I^2 = 60%, P = 0.003). Great heterogeneities between agencies have been determined for the duration of meta-analyses, perchance due to the fact of various coaching depth and subjective sensation amongst participants.

Rating of perceived exertion

Only one study [33] reported the decreased RPE in ECC-M relative to CONC-M and ECC-H with no significant different.

Dyspnoea

Dyspnoea was reported in seven trials [4, 8, 21, 24, 25, 33, 34] including 98 subjects (see Fig. 4). Given the great heterogeneities across seven trials ($I^2 = 75\%$), trials were eliminated one by one when conducting sensitivity analysis. When the trial by

Nahmias et al. [24] was eliminated, a pooled SMD of −0. 69 (95% CI = −1.05– −0.32, I^2 = 48%, P = 0.0002) was obtained, which favoured ECC cycling. Considering the insignificant heterogeneity across trials (I^2 = 48%), we chose fixed-effects model.

Safety. Oxygen consumption—VO^2 (L/min)

Six trials [8, 15, 24, 25, 33, 34] reported oxygen consumption. The pooled impact measurement used to be substantially distinctive of each organizations (MD = −0.26, 95% CI = − 0.36– − 0.17, P < 0.0001) based on the random-effects model; nonetheless, significant heterogeneity (I^2 = 92.4%) was detected. Subgroup evaluation was once additionally carried out based totally on the greater or lower workload in ECC cycling than CON cycling, apart from sensitivity analysis. The heterogeneity of a subgroup (higher ECC vs. CON cycling intensity: four trials) was greatly reduced (I^2 = 8%). However, another subgroup (comparable ECC vs. CON training intensity: three trials) maintained high heterogeneity (I^2 = 88%)

Minute ventilation—VE (L/min)

Seven trials [4, 8, 25, 24, 33, 34, 35] provided data from 89 participants on the number of COPD. Pooling the results (greater/similar ECC vs. CON training intensity: N = 139 and 135 separately) from seven trials yielded a statistically significant mean difference in minute ventilation favouring ECC cycling with high heterogeneity (MD = 14.69, 95%CI = −1.66–−10.16, I^2 = 95.4%; P < 0.00001). Hence, we conducted subgroup analysis based on cycling intensity: greater/similar ECC vs. CON training intensity.

The consequences indicated that minute ventilation in higher ECC vs. CON training intensity (MD = −7.70, 95%CI = −9. 25–−6.15, I^2 = 0%, P < 0. 00001) and comparable ECC vs. CON training intensity (MD = −11.89, 95%CI = −12.94–−11.03, I^2 = 0%, P < 0. 00001) favoured ECC cycling with low heterogeneity.

Heart rate (beats/min)

The pooled analysis showed that when the workload of ECC cycling was higher than CON cycling, the former was smaller than the latter in heart rate (35 participants: MD = −9.10, 95%CI = −14.74–−3.45) with low heterogeneity (I^2 = 29%). Moreover, when the intensity was comparable between the two groups, the result was the same, but heterogeneity was high (39 participants; MD = −14.84, 95%CI = −23.33–−

6.36, I^2 = 80%). Upon sensitivity analysis, when Rooyackers et al.'s study [34] was excluded, solid result (MD = －19.46, 95%CI = －22.63–－16.28) with low heterogeneity(I^2 = 0%) was obtained.

Breathing frequency

Only one study [33] reported the RPE, which showed not statistically different at 60% peak VO_2.

CK level (U/L)

Two trials [21, 25] involving 35 people reported ECC, with 17 from CON group whereas 18 people from ECC group. Difference of both groups was of no significance (MD = 10.01, 95%CI = －17.57–37.60, I^2 = 0%, P = 0.48).

DISCUSSION

4.1 Major outcome summarization

To our knowledge, the existing find out about is the first meta-analysis and systemic review that compares eccentric training with concentric training in patients with COPD. Altogether 10 CCTs involving 136 topics had been enrolled into the present work. According to the present work, eccentric exercise exhibited high tolerance, safety and efficacy in COPD patients. The mean ECC training workload increased by 3 or 4 times compared with CON for an identical RPE, but HR, VO_2, VE and muscle discomfort had been decrease and dyspnoea was less. Moreover, in patients with COPD, beneath same coaching workload conditions, VO_2, VE, dyspnoea, heart rate, leg fatigue and coronary heart fee had been decrease for the duration of ECC compared with CON. Our hypotheses were supported by these findings that ECC cycling resulted in lower cardio-respiratory, perceptual and metabolic responses relative to CON cycling among COPD cases. For the outcomes of quadriceps muscle isometric peak torque, MVC strength, 6-min walk test along with life quality, eccentric exercise achieved comparable effect on enhancing outcomes relative to baseline, although not statistically better than CON cycling.

4.2 Similarities and differences relative to additional trials or reviews

Consistently, as indicated in some systematic reviews, ECC cycling can be used effectively and safely as a rehabilitative tool, which achieves higher muscle tissue loads at lower metabolic expenses, respiratory demand and similar coronary heart charges [27, 28, 36, 37, 38]. Our reviews sustains the systematic evaluations stated in 2015 [27] and 2016 [28] regarding the safety of ECC cycling, in early and end stages in which management has become more and more crucial due to the increasing disability and healthcare utilization rate. Although two reviews were published in 2021 [38] and 2022 [37], these reviews neither included trials conducted on a cycle ergometer nor target populations with COPD; therefore, they may want to now not reply the query involving the efficacy and safety in patients with COPD using an eccentric bicycle ergometer. On the contrary, this work adopted the rigorous search strategy: to be specific, we compared the impact between CON and ECC cycling in patients with COPD using a bicycle ergometer. We also take FEV1/FVC (percent of estimated post-bronchodilator) or FEV1 (percent of estimated post-bronchodilator) as our primary outcomes, which are frequent symptoms for detecting lung function.

4.3 Clinical implications

According to our results, ECC cycling is well tolerated, safe and effective for patients with COPD. There was low side effect rate, and patients of ECC biking team have been all able to implement the programme. Collectively, our results lay solid scientific foundation for applying ECC cycling as the adjuvant and/or choice workout coaching approach in patients with low/moderate COPD conducted under the guidance of the professional doctors.

4.4 Implications for future research

Follow-up was once now not carried out for measuring long-time efficacy of ECC cycling. The present trials lack data on the cost-effectiveness and FEV1/FVC (percent of estimated post-bronchodilator) or FEV1 (percent of estimated post-bronchodilator), which have been outstanding indexes of patients with COPD. Moreover, while ECC biking may additionally want a decrease quantity of oxygen consumption for the higher strength output, effect of such training method on altering patients' health status, morbidity and mortality remains unclear, and health economics indicators, such as patient satisfaction, adherence and cost-effectiveness, have evidence gaps in existing studies. Hence, more future large-scale RCTs with the population should be performed to scientifically and objectively observe the effects of ECC biking amongst COPD cases, focusing on core patient and clinical outcomes.

4.5 Strength and limitations

This research is the first to focus on eccentric training with regard to its efficacy and feasibility among COPD cases. Our consequences have been mixed the use of the random-effects model if $I^2 > 50\%$, for this reason supplying the conservative prediction of the treatment. Two reviewers worked independently in pairs and assured that all texts were screened in duplicate, and disagreements were resolved in discussion with three people.

The current meta-analysis has several limitations. Firstly, our effects recommend that ECC cycling is applied in COPD cases as an option. Nonetheless, evidence is lacking: 10 trials including 136 participants with small sample sizes; three of the 10 trials recruited male patients alone, while in four trials, percentage of women was small (20%–27%). Secondly, of the enrolled trials, cases with COPD at a range of historical past and training degrees were enrolled. Consequently, great heterogeneities could be detected in some secondary outcomes because of diverse diseases, variables and sample sizes in those enrolled trials.

CONCLUSION

In conclusion, this find out about carried out a cutting-edge systematic review and meta-analysis for evaluating eccentric training with regard to its efficacy and safety in COPD cases. It was found that ECC workout used to be the candidate and suitable exercise approach with low cardio-respiratory and metabolic demands on patients with COPD. However, in-depth medical research with more cases in the extended period are needed for determining if a high workload is sustainable and translatable in functional, biological, and physiological improvements and whether it will adversely affect patients with severe COPD.

Our results lay solid scientific foundation for applying ECC cycling as the adjuvant and/or choice workout coaching technique in patients with low/moderate COPD conducted under the guidance of the professional doctors.

·In-depth medical research with greater instances in the prolonged duration are wished for figuring out if a high workload is sustainable and translatable in functional, biological, and physiological improvements and whether it will adversely have an effect on sufferers with severe COPD.

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Table 1 Characteristics of included trials.

Study	Types of study	Sample	Age	Gender Male/Female	Severity of COPD	Intervention	Study period	Frequency	Intensity	Outcomes
Bourbeau 2020	RCT	N = 24 11 CON 13 ECC	CON 65.2 ± 5.0 ECC 68.5 ± 5.6	CON 11/0 ECC 13/0	FEV1%pred CON 38.9 ± 9.6 ECC 35.0 ± 11.8	ECC vs. CON exercise Custom-built semi-recumbent cycle ergometer	10 weeks	30 min exercise 3 times per week	CON: 60%–80% of the power peak output ECC: 4 times than CON	1–5
Inostroza 2022	RCT	N = 20 10 CON 10 ECC	CON 71.1 ± 10.3 ECC 68.2 ± 10.0	CON 4/6 ECC 6/4	FEV1%pred:73.2 % ± 11.4%	ECC vs. CON cycling Recumbent eccentric cycle ergometer	12 weeks	15 min cycling Same time of the day(±1 h)	At an RPE of 13	1, 6–10
MacMillan 2017	RCT	N=15 7 CON 8 ECC	CON 63 ± 2 ECC 68 ± 2	EET 8/0 CET 7/0	FEV1%pred ECC 36.2% ± 3.7% CON 45.8% ± 5.0%	EEC vs. CON cycling Custom-built recumbent cycle ergometer	10 weeks	30 min cycling Three sessions per week	CON:60%–80% of the peak power output ECC: 4 times than CON	3, 4, 11
Nahmias 2021	Cross-over controlled trial	N = 14	65.4 ± 5.6	N 11/3	FEV1%pred < 50% FEV1/FEV%pred < 70%	ECC vs. CON exercise Semi-recumbent ergometers	From June 2019 to March 2020	Same time (4 h) of the day after meal	Iso-VO_2 Iso-VE Iso-workload	3, 4, 6, 10
Nickel 2020	Before–after controlled trial	N = 10	68.3 ± 9.1	Nil	FEV1%pred: 68.6% ± 20.4% FEV1/FVC%pred : 75% ± 15.%3	CON (50% of Wmax) vs. ECC (50% of Wmax) vs. ECC (100% of Wmax) cycling Electromagnetic-resistant recumbent bicycle	Three exercise sessions	30 min cycling	CONC-M 50% of Wmax ECC-M 50% of Wmax ECC-H 100% of Wmax	4–6, 10, 12, 13
Rooyackers 1997	Cross-over controlled trial	N = 12	56 ± 12	N 10/2	FEV1%pred: 46% ± 16%	Positive work vs. negative work Electric brake cycle ergometer	2 consecutive days	6 min cycling 4 single-stage exercise test (2 on each	At constant workload of 25% and 50% max Wpos	3–6, 10

								day)		
Rooyackers 1997	Cross-over controlled trial	N = 12	56 ± 12	N 10/2	FEV1%pred: 46% ±16%	Positive work vs. negative work Electric brake cycle ergometer	2 consecutive days	6 min cycling 4 single-stage exercise test	At constant workload of 25% and 50% max Wpos	5, 6
Valladares-Ide 2021	Cross-over controlled trial	N = 10	68.3 ± 9.1	N 8/2	FEV1%pred: 68.6% ± 20.4%	CON (50% of Wmax) vs. ECC(50% of Wmax) vs. ECC (100% of Wmax)	To the laboratory: 13 times	30 min With 2 weeks washout period between bouts	CONC-M 50% of Wmax ECC-M 50% of Wmax ECC-H 100% of Wmax	4–6, 8, 9, 11
Vieira 2011	Before–after controlled trial	N = 6	63 (range 54–7)	N 6/0	FEV1%pred: 35% (range 17%–49%)	CON vs. ECC pedalling Custom-built, recumbent cycle ergometer	15 sessions	20 min pedalling 3 times per week	A target intensity of 60% CON peak VO_2	5
Ward 2020	Before–after controlled trial	N = 13	64 ± 9.4	N 8/5	FEV1%pred: 45% ± 19%	CON vs. ECC modes Commercially available upright ergometer	5 visits	4-min bouts Six bouts with a 4-min rest between bouts	At matched mechanical loads of increasing intensity	3–6, 10

1. 6-min walking test; 2. quadriceps muscle isometric peak torque; 3. leg fatigue Borg scale; 4. dyspnoea; 5. minute ventilation (VE); 6. oxygen consumption (VO_2); 7. FEV1/FVC ratio; 8. MVC strength; 9. muscle soreness; 10. heart rate; 11. CK level; 12. RPE; 13. breathing frequency

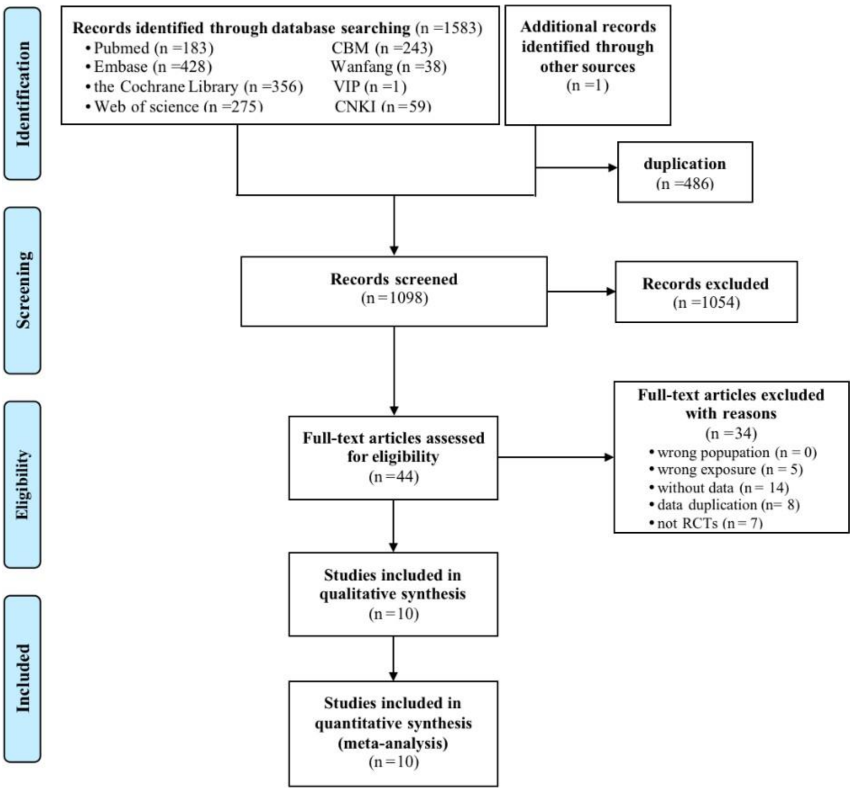


Figure 1 PRISMA flowchart

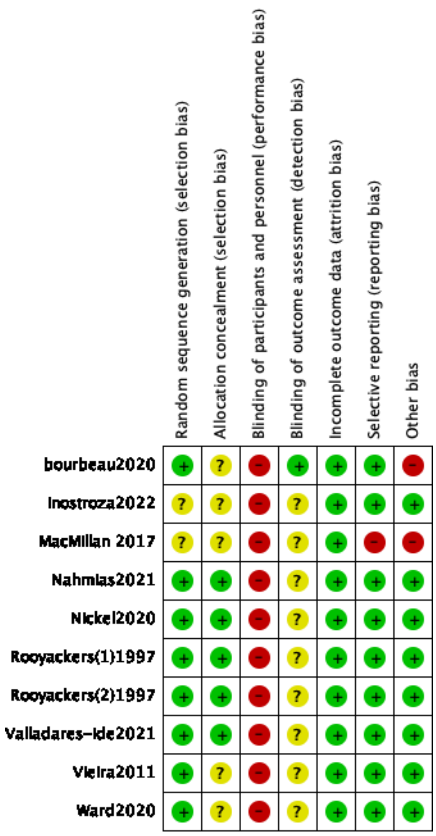
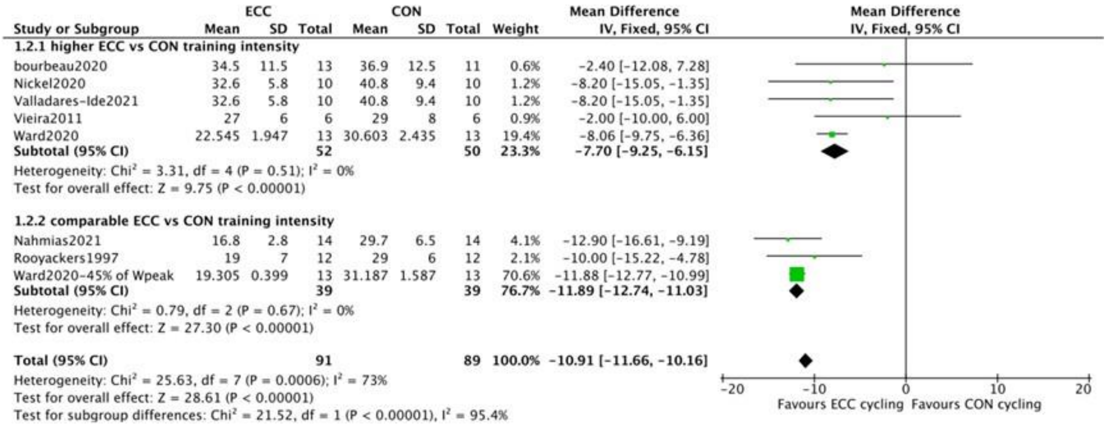
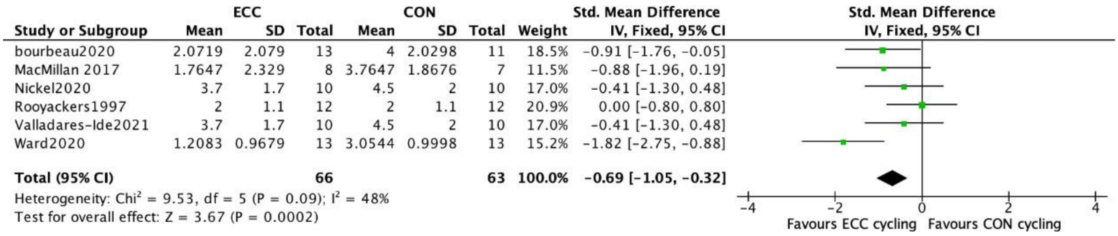


Figure 2 Risk of bias summary



Study or Subgroup	ECC Mean	ECC SD	ECC Total	CON Mean	CON SD	CON Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 higher ECC vs CON training intensity								
bourbeau2020	34.5	11.5	13	36.9	12.5	11	0.6%	-2.40 [-12.08, 7.28]
Nickel2020	32.6	5.8	10	40.8	9.4	10	1.2%	-8.20 [-15.05, -1.35]
Valladares-Ide2021	32.6	5.8	10	40.8	9.4	10	1.2%	-8.20 [-15.05, -1.35]
Vieira2011	27	6	6	29	8	6	0.9%	-2.00 [-10.00, 6.00]
Ward2020	22.545	1.947	13	30.603	2.435	13	19.4%	-8.06 [-9.75, -6.36]
Subtotal (95% CI)			**52**			**50**	**23.3%**	**-7.70 [-9.25, -6.15]**
Heterogeneity: Chi² = 3.31, df = 4 (P = 0.51); I² = 0%								
Test for overall effect: Z = 9.75 (P < 0.00001)								
1.2.2 comparable ECC vs CON training intensity								
Nahmias2021	16.8	2.8	14	29.7	6.5	14	4.1%	-12.90 [-16.61, -9.19]
Rooyackers1997	19	7	12	29	6	12	2.1%	-10.00 [-15.22, -4.78]
Ward2020-45% of Wpeak	19.305	0.399	13	31.187	1.587	13	70.6%	-11.88 [-12.77, -10.99]
Subtotal (95% CI)			**39**			**39**	**76.7%**	**-11.89 [-12.74, -11.03]**
Heterogeneity: Chi² = 0.79, df = 2 (P = 0.67); I² = 0%								
Test for overall effect: Z = 27.30 (P < 0.00001)								
Total (95% CI)			**91**			**89**	**100.0%**	**-10.91 [-11.66, -10.16]**
Heterogeneity: Chi² = 25.63, df = 7 (P = 0.0006); I² = 73%								
Test for overall effect: Z = 28.61 (P < 0.00001)								
Test for subgroup differences: Chi² = 21.52, df = 1 (P < 0.00001), I² = 95.4%								

Figure 3 Meta-analysis of minute ventilation (VE) comparing ECC and CON cycling in patients with COPD



Study or Subgroup	ECC Mean	ECC SD	ECC Total	CON Mean	CON SD	CON Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
bourbeau2020	2.0719	2.079	13	4	2.0298	11	18.5%	-0.91 [-1.76, -0.05]
MacMillan 2017	1.7647	2.329	8	3.7647	1.8676	7	11.5%	-0.88 [-1.96, 0.19]
Nickel2020	3.7	1.7	10	4.5	2	10	17.0%	-0.41 [-1.30, 0.48]
Rooyackers1997	2	1.1	12	2	1.1	12	20.9%	0.00 [-0.80, 0.80]
Valladares-Ide2021	3.7	1.7	10	4.5	2	10	17.0%	-0.41 [-1.30, 0.48]
Ward2020	1.2083	0.9679	13	3.0544	0.9998	13	15.2%	-1.82 [-2.75, -0.88]
Total (95% CI)			**66**			**63**	**100.0%**	**-0.69 [-1.05, -0.32]**
Heterogeneity: Chi² = 9.53, df = 5 (P = 0.09); I² = 48%								
Test for overall effect: Z = 3.67 (P = 0.0002)								

Figure 4 Meta-analysis of the Borg CR10 scale for dyspnoea comparing ECC and CON cycling in patients with COPD