Effects of exercise on muscle fatigability in COPD: a systematic review and meta-analysis

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This systematic review on the effects of exercise training on peripheral muscle fatigability in people with COPD suggests a positive impact of exercise in improving fatigue resistance, particularly in the leg muscles. https://bit.ly/46eEeBA

Cite this article as: Pancera S, Buraschi R, Lazzarini SG, *et al*. Effects of exercise on muscle fatigability in COPD: a systematic review and meta-analysis. *Eur Respir Rev* 2025; 34: 250008 [DOI: 10.1183/16000617.0008-2025].

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Received: 13 Jan 2025
Accepted: 14 July 2025

Abstract

This systematic review aims to summarise the impact of exercise training on peripheral muscle fatigability in people with COPD, addressing different assessment methods and exercise interventions (*i.e.* endurance, resistance and combined training).

PubMed, CENTRAL, CINAHL and PEDro databases and trial registers were searched from inception to September 2024. We identified randomised and nonrandomised trials assessing pre-to-post-training changes in muscle fatigue resistance, assessed as a reduction in volitional or non-volitional measures of muscle strength or muscle total work output during standardised fatiguing protocols. The Cochrane Risk of Bias 2 (RoB 2) and Risk of Bias in Non-randomized Studies – of Interventions (ROBIN-I) tools were used for assessing risk of bias in randomised controlled trials and nonrandomised studies of interventions, respectively, and meta-analyses were performed.

A total of 20 studies (574 participants from 14 randomised controlled trials and 217 from six nonrandomised studies of interventions) were included. Overall, combined endurance and resistance training appeared to improve muscle fatigue resistance. While results varied by study design, type of training and fatiguing protocols, similar improvements were observed in quadriceps fatigue resistance regardless of the assessment method. In contrast, no significant improvements were observed in the fatigue resistance of the arm muscles. However, the presence of moderate to high risk of bias in several included studies may have influenced the results.

The findings of this systematic review suggest a positive effect of exercise training in improving muscle fatigue resistance, particularly in the leg muscles, in people with COPD. Future research should establish standardised protocols for assessing muscle fatigability and explore alternative tools to facilitate the clinical implementation of muscle fatigability outcomes into COPD rehabilitation.

Introduction

COPD affects more than 300 million people worldwide, causing a global health emergency and a growing burden on citizens and healthcare systems [1, 2]. Symptoms of dyspnoea frequently limit exercise capacity in individuals with COPD [3]; however, a considerable proportion of patients also experience persistent, moderate-to-severe fatigue that exacerbates inactivity and negatively impacts quality of life [4]. Although the development of fatigue is attributable to a variety of factors, these factors can be categorised into two interconnected domains: perceived fatigability and performance fatigability related to exercise [4, 5]. In COPD, performance fatigability may be amplified by the dysfunction of peripheral muscles [6]. Specifically, morphological and structural alterations in the peripheral muscles predispose patients with

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COPD to a more rapid onset of muscle fatigue compared with healthy individuals, under identical exercise conditions [7, 8].

The development of peripheral muscle fatigue during exercise depends on the ability of the peripheral muscles (*i.e.* contractile function) and the central nervous system (*i.e.* muscle activation) to meet the demands of a given task [9]. Accordingly, peripheral muscle fatigue refers to an acute exercise-induced reduction in the ability of the involved muscles to produce strength or power [10]. This reduction ultimately results in task failure, although muscle performance can be restored with rest. Additionally, muscle fatigue resistance can be characterised as the capacity of the muscle to sustain a predetermined amount of submaximal work over time [6, 11].

To date, these complementary measures have been quantified in patients with COPD using a variety of methods, mainly in the quadriceps muscle [6, 12]. Changes in peripheral muscle strength after exercise can be assessed either using volitional efforts or non-volitional techniques, in which twitch force is evoked by a single magnetic or electrical stimulus of the motor nerve, at rest or immediately after a maximal voluntary contraction (*i.e.* potentiated twitch force (Tw_P)) [13, 14]. Beyond providing reliable measures of quadriceps strength [15], non-volitional techniques have also been used to quantify peripheral muscle fatigability after whole-body exercises (*e.g.* cycling) in individuals with COPD [16, 17]. Typically, a ⩾15% acute reduction in Tw_P post-exercise is considered indicative of clinically meaningful fatigue [18]. However, given the limited clinical applicability of non-volitional techniques, muscle fatigue resistance is often alternatively estimated in COPD by quantifying the total work output (W_T) generated by a muscle during repeated isokinetic contractions [19, 20]. An additional approach to the assessment of muscle fatigability is the analysis of surface electromyographic (EMG) signals and their change during static or dynamic muscle contractions [16, 21].

While muscle fatigability contributes to exercise limitation in COPD, the development of clinically meaningful fatigue at a given percentage of maximal workload prior to pulmonary rehabilitation (PR) may be favourable. This is because it may indicate that training can be delivered with an adequate training stimulus and predict the patient's responsiveness to exercise throughout the training programme [5]. This hypothesis is supported by two studies showing that patients who exhibited acute clinically meaningful fatigability of the quadriceps at baseline, either following exhaustive submaximal cycling [22] or after a single exercise training session [23], experienced significantly greater improvements in PR outcomes compared to those who were less fatigable before PR.

The goal of the exercise-based component of a comprehensive PR programme is to improve exercise tolerance and peripheral muscle function in patients with COPD [6, 24]. In support of this evidence, the effect of exercise interventions on different muscle characteristics (*e.g.* maximal muscle strength, endurance and power) has been previously investigated through randomised controlled trials (RCTs) and systematic reviews [25–27]. However, peripheral muscle fatigability, as one of these key muscle characteristics, has not yet been reviewed in patients with COPD, except in a systematic review of cross-sectional studies [11]. Accordingly, expanding the scope of the review conducted by Evans *et al.* [11] to include clinical studies of intervention may provide valuable insights by 1) evaluating the efficacy of exercise training on peripheral muscle fatigability in people with COPD and 2) encouraging the implementation of the objective assessment of muscle fatigability as part of the outcomes used in PR [28].

Therefore, specifically focusing on muscle-related outcomes, the present systematic review aimed to assess the effectiveness of exercise training in reducing peripheral muscle fatigability (*i.e.* improving muscle fatigue resistance) in people with COPD. Furthermore, this systematic review provided a descriptive summary of the protocols for assessing peripheral muscle fatigability and examined the effects of different physical interventions on this outcome in patients with COPD.

Methods

This systematic review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [29], and the protocol was registered in PROSPERO (CRD42024480944).

Eligibility criteria

To conduct this systematic review, we identified and included RCTs, crossover trials (if pre-crossing data were available) and prospective nonrandomised studies of interventions (NRSIs), both controlled and uncontrolled [30]. Eligible studies had to involve an exercise-based intervention (*e.g.* endurance training (ET), resistance training (RT) or combined training (CT)), whether performed in isolation or included in a comprehensive PR programme, directed at single or groups of peripheral muscles in patients with COPD.

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Therefore, eligible studies could have control conditions such as no intervention, pharmacological therapy, education, respiratory muscle training in isolation or no comparators. Studies with designs other than RCTs and NRSIs were excluded. For RCTs comparing different exercise interventions, the training arms were combined, where feasible, to obtain the overall effect of exercise interventions on muscle fatigability. Only data related to patients with COPD were considered for studies involving healthy subjects or patients with conditions other than COPD as controls (*e.g.* people with other respiratory diseases or heart conditions). Studies that proposed passive or mixed interventions (*e.g.* neuromuscular electrical stimulation (NMES) or functional electrical stimulation) or respiratory muscle training as isolated physical intervention were excluded. Studies purposefully recruiting patients after an acute exacerbation of COPD or with overlapping respiratory conditions were also excluded.

The primary outcomes were pre-to-post-training change (Δ) in peripheral muscle fatigability and muscle fatigue resistance. The former was objectively quantified as a relative reduction in force, either volitional (*e.g.* maximal voluntary contraction) or non-volitional (*e.g.* Tw_P evoked by a standardised stimulation). The latter was assessed as the muscle's capacity to sustain a predetermined amount of submaximal work over time (*e.g.*W_T generated by a muscle). These measures were obtained during or after standardised protocols, such as repeated muscle contractions or cycling exercise. Secondary outcomes were Δ in the time domain (*e.g.* the root mean square) and frequency domain (*e.g.* mean or median frequency) of the surface EMG activity of peripheral muscles during a fatiguing exercise. We excluded studies that assessed respiratory muscle fatigability, studies not strictly related to muscle-related outcomes (*e.g.* time to task failure or total body power output) and studies that assessed perceived fatigue.

Search strategy

The complete search string (supplementary table 1S) included Medical Subject Headings (MeSH) and other subject terms and was reviewed by an author with experience in bibliographic searches (S.G. Lazzarini). The databases consulted for the search were PubMed, The Cochrane Library for clinical trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, Scopus and the Physiotherapy Evidence Database (PEDro), from inception to 20 February 2024. We also searched for conference abstracts and study protocols of ongoing studies as well as study records in non-commercial trial registries (*i.e.* the World Health Organization International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov). A backwards citation analysis of the included studies was also performed. The searches were re-run in September 2024.

Selection process

Screening by title and abstract of papers written in languages known by the authors was conducted by pairs of independent investigators (S. Pancera, R. Buraschi, S.G. Lazzarini, P. Mellaerts). A software system (Rayyan) was used to record decisions [31]. One review author (S. Pancera) retrieved the full text and two authors (S. Pancera, R. Buraschi) screened the full texts for inclusion. Discrepancies were resolved by referring to a third author (M. Gobbo).

Data extraction

We used a data extraction form for study characteristics and outcome data, which was piloted on three studies included in the review. Study authors (S. Pancera, R. Buraschi) extracted the following data from included studies: 1) study characteristics (*i.e.* authors, year, country, design, setting), 2) intervention(s) of interest (*i.e.* type of intervention, frequency, duration, volume, intensity), 3) characteristics of the participants (*i.e.* number, age, sex, pulmonary function, body composition), 4) details about the fatiguing protocol (*e.g.* tested muscle(s), type of contraction, technique, fatigability timepoints, measuring instrument) and 5) pre- and post-intervention numerical data (*e.g.* mean±SD) of any reported measure of interest for the primary and secondary outcomes. A third investigator (LNCB) resolved disagreements between individual judgements. Study authors were contacted for missing or additional data. WebPlotDigitizer software (Automeris LLC) was used to extract numerical data from figures when no data were available in the text.

Risk of bias and certainty of the evidence assessments

Risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2) [32] tool for RCTs and the Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I) [33] tool for NRSIs. The certainty of the evidence was rated using the Grading of Recommendations, Assessment, Development and Evaluation approach (GRADE) approach [34]. Two independent authors (S. Pancera, R. Buraschi) assessed risk of bias for included studies and certainty of the evidence limited to RCTs.

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Data synthesis

Meta-analyses of at least two studies using a random effects model and inverse variance method were performed with RevMan 5.4 software (revman.cochrane.org). Between-study variance (τ^2) was estimated using the DerSimonian and Laird method and 95% CIs were calculated using the Wald-type method. To verify robustness of results, we repeated the meta-analyses in JASP (https://jasp-stats.org/) using restricted maximum likelihood (REML) as τ^2 estimator and the Hartung Knapp Sidik Jonkman correction for CIs, in line with the most updated Cochrane guidelines (see supplementary material for additional details). Mean differences (MDs) or standardised mean differences (SMDs) for continuous outcomes were calculated. When available, mean Δs and ΔSDS were extracted and used for analysis. In addition, robust equations were used to impute SDS from CIs or SES, as well as to combine study arms [35]. When ΔSDS were unavailable, either as ΔCIs or ΔSES, post-intervention means and SDS were used. Meta-analyses were performed separately for studies with different design, with the exception of a caterpillar plot [36] used to graphically present the overall effect of exercise training on peripheral muscle fatigability, according to training characteristics. Heterogeneity between studies was assessed using the I^2 statistic. A sensitivity analysis was performed by excluding RCTs or NRSIs at high or serious risk of bias, respectively. Narrative descriptions were used to summarise data from the included studies that could not be pooled to perform an effective analysis.

Results

The systematic search identified 12 189 records, 7720 of which were screened by title and abstract after duplicate removal. A total of 102 reports were assessed for eligibility, with 20 studies (29 reports) finally included in the systematic review. The selection process is detailed in the PRISMA flow diagram (figure 1) and reasons for full-text exclusion are provided in supplementary table 2S. The authors of 15 reports, including study protocols and trial registry records, were contacted for additional information, but only four of them agreed or were able to share data [23, 27, 37, 38]. The authors of one of these studies provided pooled data for the two study groups because no differences were observed between groups [37]. The characteristics of the included RCTs and NRSIs are summarised in table 1 and table 2, respectively.

Study characteristics

Data from 574 and 217 participants were extracted from 14 RCTs and six NRSIs, respectively. Most of the studies were conducted in Europe and North America (*i.e.* the USA and Canada), except for one study from Brazil and one from China. The median (interquartile range (IQR)) age was 65 years (63–68 years), percentage of predicted forced expiratory volume in 1 s (FEV_1) was 45% (42–55%) and body mass index was 25 $kg \cdot m^{-2}$ (24–27 $kg \cdot m^{-2}$) for participants in the study arms. The percentage of women in the included studies ranged from 5% to 73%.

Most studies adopted outpatient PR programmes of eight to 36 sessions. Three out of 14 RCTs compared exercise training with no intervention. Two [40, 47] of these studies performed RT in the intervention group, and one RCT [49] performed traditional Chinese exercises (*i.e.* Liuzijue) that combined respiratory training with RT. Two RCTs investigated ET with supplemental O_2 or noninvasive ventilation [39], or CT with the adjunct of hyperpnoeic respiratory training [45]. Four RCTs [38, 41–43] administered different nutritional supplements (*i.e.* creatine, antioxidants or whey proteins) *versus* placebo as an adjunct to CT. Regarding exercise modalities, two RCTs [44, 46] by the same research group investigated CT *versus* ET and CT (with continuous ET) *versus* CT (with interval ET), respectively. One study compared conventional and downhill walking training [37]; however, we retrieved aggregated data from the study groups. In addition, one RCT [27] investigated single-limb *versus* two-limb RT and another RCT [48] compared lower limb RT with NMES. Regarding NRSIs, five studies [23, 51–54] adopted CT as an intervention, whereas one study [50] delivered RT in isolation.

Six [23, 39, 43–46] out of 12 studies set the initial ET intensity between 50% and 80% of the maximal workload (W_{max}) achieved by participants during an incremental exercise test. In the remaining studies the initial ET intensity was not reported or not based on W_{max}. Similarly, six studies set the initial RT load at 60% and 70% of one-repetition maximum [23, 39, 43, 44, 48, 50]. Three other studies prescribed the initial load between 6 and 30 maximum repetitions [27, 47, 53], with all training protocols performing three sets of 8–15 repetitions per session.

Characteristics of the fatiguing protocol

For fatiguing protocols, 12 studies [27, 38–43, 47–49, 51, 54] used repeated contractions, with a predetermined duration or until exhaustion, to fatigue the quadriceps muscle; five of these studies [27, 40, 47, 49, 51] also assessed shoulder and arm muscles. In addition, incremental [52] or constant work [44–46, 53] exercise tests on the cycle ergometer were used as fatiguing protocols in five studies, while one study [50] used a NMES protocol to fatigue the quadriceps. Two other studies [23, 37] assessed

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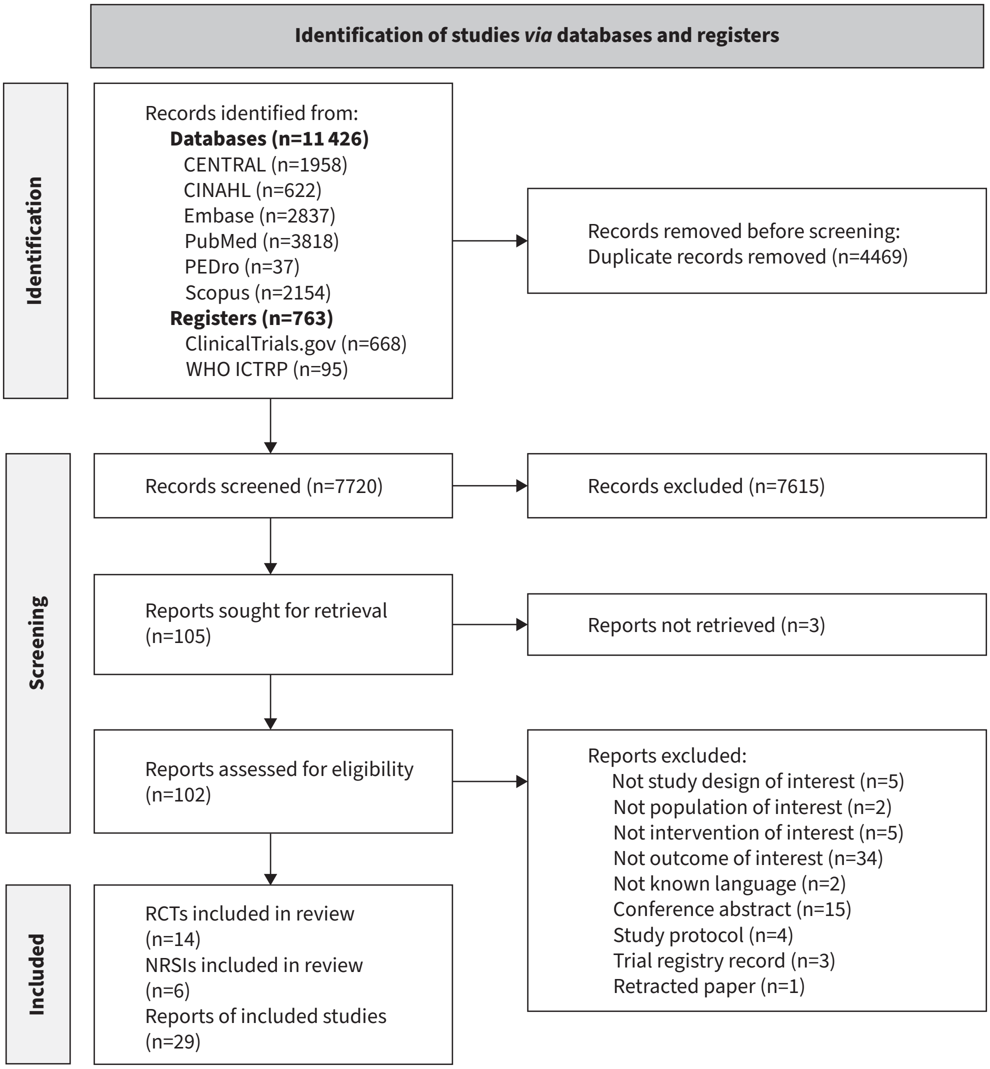

FIGURE 1 Flow diagram of the included reports. CINAHL: Cumulative Index to Nursing and Allied Health Literature; PEDro: Physiotherapy Evidence Database; RCT: randomised controlled trial; NRSI: nonrandomised study of intervention; WHO ICTRP: World Health Organization International Clinical Trials Registry Platform.

muscle fatigability after a complete exercise training session. Ten studies [27, 39–42, 47–49, 51, 54] assessed the W_T of a muscle (in J) with the isokinetic dynamometer at angular velocities between $60°\cdot s^{-1}$ and $180°\cdot s^{-1}$. In contrast, nine studies [23, 37, 43–46, 50, 52, 53] used a magnetic or electric stimulus to evoke quadriceps Tw_P. Among these, seven [23, 37, 43–46, 53] studies obtained the Tw_P before and 10–60 min after the fatiguing exercise or a complete training session. Of note, with the exception of one study [37], quadriceps Tw_P was evaluated at an identical absolute work load pre- and post-training. Moreover, there was only one study [52] that assessed muscle fatigability by analysing surface EMG amplitude and frequency parameters of the vastus lateralis during an incremental exercise test.

Risk of bias in included studies

Seven [41–45, 48, 49] RCTs (50%) were judged to have an overall high risk of bias (supplementary figure 1S). The most critical domain was bias due to deviations from the intended interventions, which was rated as high risk in five RCTs [41, 42, 44, 45, 48]. Two other RCTs [43, 44] were found to have a high risk of bias arising from the randomisation process and one trial [49] had a high risk of bias in the selection of reported results. Some concerns were found for the other RCTs [27, 37–40, 46], while one study was rated as low risk of bias [47]. Similarly, two NRSIs (33%) [53, 54] were rated with a serious overall risk of bias (supplementary figure 2S) due to confounding. The remaining NRSIs [23, 50–52] were rated at a moderate risk of bias.

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TABLE 1 Characteristics of randomised controlled trials included in the systematic review

Study, country	Subjects (n)	Age (years)	FEV_1 (% pred)	Interventions	Weeks (days)	Fatiguing protocol	Tested muscles	Fatigue outcomes	Baseline	Post-training
Borghi-Silva 2010 [39], Brazil	12	67±7	33±7	ET: 1-h treadmill Adjunct: supplemental O_2	6 (3)	1-min isokinetic contractions at an angular velocity of 60°·s^{-1}	Quadriceps	W_T Total power Fatigue index	1367±366 J 46±12 W 44±18%	1397±379 J 47±12 W 49±20%
	12	68±9	34±10	ET: 1-h treadmill Adjunct: NIV			Quadriceps	W_T Total power Fatigue index	1315±444 J 46±14 W 44±13%	1481±445 J 57±21 W 32±12%
Camillo 2020 [37], Belgium	20	62±9	54±20	ET: treadmill walking, stair climbing, cycling, arm cranking RT: upper and lower limb strength training	12 (3)	SMS of the femoral nerve pre- and post-training session	Quadriceps	n=35[#] Tw_P (rest) Tw_P (15 min)	 133.3±51 N 87.6±11.8%[¶]	 133±49.7 N 88.9±15.1%[¶]
	24	62±8	47±16	ET: downhill treadmill walking, stair climbing, cycling, arm cranking RT: upper and lower limb strength training						
Clark 2000 [40], UK	26	51±10	76±23	RT: bench press, body squat, squat calf, latissimus, arm curls, leg press, knee flexion and hamstrings	12 (2)	1-min isokinetic contractions at an angular velocity of 70°·s^{-1}	Quadriceps Triceps Deltoid	W_T W_T W_T	1000±498 J[+] NR NR	1320±661 J[+] NR NR
	17	46±11	79±23	No exercise intervention			Quadriceps Triceps Deltoid	W_T W_T W_T	951±399 J[+] NR NR	983±446 J[+] NR NR
Faager 2006 [41], Sweden	10	64±6	42±12	ET: ergometer cycling RT: upper and lower limb muscle training with dumbbells, elastic bands and weight cuffs Adjunct: placebo supplementation	8 (2)	3×30 isokinetic contractions at an angular velocity of 180°·s^{-1}	Quadriceps	n=5 Mean PT[¶]: Bout 1 Bout 2 Bout 3	 NR NR NR	 NR NR NR
	13	67±6	44±21	ET: ergometer cycling RT: upper and lower limb muscle training with dumbbells, elastic bands and weight cuffs Adjunct: creatine supplementation			Quadriceps	n=7 Mean PT: Bout 1 Bout 2 Bout 3	 −13.56%[¶+] −22.66%[¶+] −28.82%[¶+]	 −29.92%[¶+] −30.43%[¶+] −29.45%[¶+]

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TABLE 1 Continued

Study, country	Subjects (n)	Age (years)	FEV$_1$ (% pred)	Interventions	Weeks (days)	Fatiguing protocol	Tested muscles	Fatigue outcomes	Baseline	Post-training
Fuld 2005 [42], UK	11	64±10	45±16	ET: ergometer cycling (20 min) RT: circuit-based training of the upper and lower limbs Adjunct: placebo supplementation	4 (2)	5×15 isokinetic contractions at an angular velocity of 150°·s^{-1}	Quadriceps	n=11 W_T	 1648±881 J	 2010 J±NR
	14	62±8	45±14	ET: ergometer cycling (20 min) RT: circuit-based training of the upper and lower limbs Adjunct: creatine supplementation			Quadriceps	n=14 W_T	 1833±740 J	 3049 J ±NR
Gouzi 2019 [38], France	26	61±9	62±27	ET: cycling or walking (45 min) RT: 8–10 strength exercises (30 min) Adjunct: placebo supplementation	NR	6 isotonic contractions per min at 30% of MVC until exhaustion	Quadriceps	MVC (after test) ΔMVC (after test)	25.4±11.4 kg 25±8.1%	26.1±10.6 kg 23.4±8.7%
	31	62±7	57±17	ET: cycling or walking (45 min) RT: 8–10 strength exercises (30 min) Adjunct: antioxidant supplementation			Quadriceps	MVC (after test) ΔMVC (after test)	NR NR	NR NR
Laviolette 2010 [43], Canada	10	68±4	54±14	ET: ergometer cycling (30 min) RT: seated press, elbow flexion and shoulder adduction, leg press, and knee extension Adjunct: placebo supplementation	8 (3)	SMS of the femoral nerve before and after 5-s isometric contractions at 60% of MVC until exhaustion	Quadriceps	n=10 Tw_{P} (rest) Tw_{P} (10 min)	 8.5±0.8 kg[+] 75.3±6.2%[¶+]	 8.4±0.7 kg[+] 75.9±4.9%[¶+]
	12	63±10	47±14	ET: ergometer cycling (30 min) RT: seated press, elbow flexion and shoulder adduction, leg press, and knee extension Adjunct: whey supplementation			Quadriceps	n=10 Tw_{P} (rest) Tw_{P} (10 min)	 8.9±1 kg[+] 69.3±5.4%[¶+]	 8.3±1.1 kg[+] 76.7±5.5%[¶+]
Mador 2004 [44], USA	11	74±2	44±4	ET: cycle ergometer and treadmill training RT: knee flexion, knee extension, seated chest press and a combined movement of shoulder adduction and elbow flexion	8 (3)	SMS of the femoral nerve before and after CWRT (60% of W_{max})	Quadriceps	Tw_{P} (rest) Tw_{P} (10 min) Tw_{P} (30 min)	9.6±1.1 kg 79.5±3.1%[¶] 82.5±3.8%[¶+]	11.1±1.6 kg 80±3.7%[¶+] 81.8±2.8%[¶+]
	13	68±2	40±4	ET: cycle ergometer and treadmill training			Quadriceps	Tw_{P} (rest) Tw_{P} (10 min) Tw_{P} (30 min)	10.7±0.4 kg 76.4±4%[¶] 80.5±3.4%[¶+]	10.7±0.5 kg 92.3±3.5[¶+] 86.6±3.6%[¶+]

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TABLE 1 Continued

Study, country	Subjects (n)	Age (years)	FEV_1 (% pred)	Interventions	Weeks (days)	Fatiguing protocol	Tested muscles	Fatigue outcomes	Baseline	Post-training
Mador 2005 [45], USA	14	71±2	44±4	ET: cycle ergometer and treadmill training RT: calisthenic exercises with and without small weights	8 (3)	SMS of the femoral nerve before and after CWRT (60–70% of W_{max})	Quadriceps	Tw_P (rest) Tw_P (10 min) Tw_P (30 min)	NR (kg) 79.6±2.7%[¶+] 78±2.7%[¶]	NR (kg) 86±3.4%[¶+] 79.3±2.5%[¶+]
	15	70±2	45±6	ET: cycle ergometer and treadmill training RT: calisthenic exercises with and without small weights Adjunct: Hyperpnoeic training (15–20 min)			Quadriceps	Tw_P (rest) Tw_P (10 min) Tw_P (30 min)	NR (kg) 83.9±3.1%[¶+] 82.5±4.3%[¶]	NR (kg) 90.3±2.4%[¶+] 91.8±2.1%[¶+]
Mador 2009 [46], USA	20	72±8	42±13	ET: continuous cycle ergometer and treadmill training RT: calisthenic exercises with and without small weights	8 (3)	SMS of the femoral nerve before and after CWRT (60–70% of W_{max})	Quadriceps	n=17 Tw_P (10 min) Tw_P (30 min)	 71.9±2.6%[¶+] 69.8±2.2%[¶+]	 79.4±4%[¶+] 81.5±3.7%[¶+]
	21	72±7	45±14	ET: interval cycle ergometer and treadmill training RT: calisthenic exercises with and without small weights			Quadriceps	n=17 Tw_P (10 min) Tw_P (30 min)	 75.1±3.1%[¶+] 74.8±2.7%[¶+]	 86.5±3.9%[¶+] 83.3±3.5%[¶+]
Nyberg 2015 [47], Canada	22	69±5	59±11	RT: upper and lower limb muscle training (8 exercises) with elastic bands	8 (3)	30 isokinetic contractions at an angular velocity of 60°·s^{-1}	Quadriceps Shoulder flexion	W_T W_T	1936 J (95% CI 1.67–2.21 J) 474 J (95% CI 367–581 J)	2158 J (95% CI 1.89–2.43 J) 549 J (95% CI 441–657 J)
	22	68±6	55±15	Education			Quadriceps Shoulder flexion	W_T W_T	1942 J (95% CI 1.67–2.21 J) 476 J (95% CI 369–594 J)	1978 J (95% CI 1.71–2.25 J) 490 J (95% CI 382–598 J)
Nyberg 2021 [27], Canada	17	65±7	35±9	RT: two-limb exercises with elastic bands including knee extension, leg curl, latissimus row, chest press, elbow flexion, shoulder flexion and calf-raise	8 (3)	30 isokinetic contractions at an angular velocity of 60°·s^{-1}	Quadriceps Shoulder flexion	W_T W_T	3087±1.1 J 396±206 J	3484±1.11 J 496±227 J
	16	66±6	43±7	RT: single-limb exercises with elastic bands including knee extension, leg curl, latissimus row, chest press, elbow flexion, shoulder flexion and calf-raise			Quadriceps Shoulder flexion	W_T W_T	3336±1.54 J 394±304 J	3607±1.57 J 451±308 J

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TABLE 1 Continued

Study, country	Subjects (n)	Age (years)	FEV_1 (% pred)	Interventions	Weeks (days)	Fatiguing protocol	Tested muscles	Fatigue outcomes	Baseline	Post-training
Sillen 2014 [48], The Netherlands	40	64±1	33±2	RT: bilateral leg extension and bilateral leg press exercises	8 (5)	30 isokinetic contractions at an angular velocity of 90°·s^{-1}	Quadriceps	W_T	1175±76 J	1367 J±NR
	41	64±1	33±2	RT: high-frequency NMES of the quadriceps and calf muscles at 75 Hz			Quadriceps	W_T	1189±87 J	1474 J±NR
	39	66±1	35±2	RT: low-frequency NMES of the quadriceps and calf muscles at 15 Hz			Quadriceps	W_T	1164±67 J	1265 J±NR
Wu 2018 [49], China	15	65±8	55±17	40 min Liuzijue Qigong exercises on land	12 (2)	30 isokinetic contractions at an angular velocity of 180°·s^{-1}	Quadriceps	W_T	705.9±308 J	746±284 J
								MER	0.6±0	0.6±0
							Triceps	W_T	365.5±105 J	403.6±76 J
								MER	0.7±0	0.7±0
	14	65±11	59±22	40 min Liuzijue Qigong exercises in water			Quadriceps	W_T	712.1±517 J	983.6±563 J
								MER[#]	0.6±0	0.6±0
							Triceps	W_T	328±108 J	400.5±169 J
								MER[#]	0.7±0	0.7±0
	16	66±8	59±17	No exercise intervention			Quadriceps	W_T	816.5±326 J	817.6±306 J
								MER[#]	0.6±0	0.6±0
							Triceps	W_T	378.6±89 J	381.1±93 J
								MER[#]	0.7±0	0.6±0

Data are presented as mean±SD, unless otherwise indicated. [#]: means of merged groups; [¶]: recorded as % of baseline; [+]: derived from graphic data. CWRT: constant workload exercise test; ET: endurance training; FEV_1: forced expiratory volume in 1 s; MER: muscle endurance ratio; MVC: maximal voluntary contraction; NIV: noninvasive ventilation; NMES: neuromuscular electrical stimulation; NR: not reported; PT: peak torque; RT: resistance training; SMS: supramaximal magnetic stimulation; Tw_P: potentiated twitch force; W_{max}: maximal workload; W_T: muscle total work output.

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TABLE 2 Characteristics of nonrandomised studies of interventions included in the systematic review

Study, country	Subjects (n)	Age (years)	FEV$_1$ (% pred)	Interventions	Weeks (days)	Fatiguing protocol	Tested muscles	Fatigue outcomes	Baseline	Post-training
Brunton 2023 [50], Canada	14	73±6	61±19	RT: squats, lunges, deadlifts, leg press, forward and lateral step-ups, standing hamstring curls, modified trunk extensions and standing hip flexion	4 (3)	NMES of the quadriceps for 3 min at 25% of the MVC	Quadriceps	n=12		
								Absolute force	3.4±1.3 kg	4±1.2 kg
								% force	46.8±11.9%¶	53.2±9.1%¶
								Absolute RFD	29.3±16.3 kg·s^{-1}	31.3±14.5 kg·s^{-1}
								% RFD	36±14%¶	43±21%¶
Burtin 2012 [23], Belgium, Canada	46	64±8	42±13	ET: cycle ergometer, treadmill and stair climbing training RT: leg press	12 (3)	SMS of the femoral nerve pre- and post-training session	Quadriceps	n=42		
								Tw_P (rest)	113.9±37.8 N	117.4±36.3 N
								Tw_P (15 min)	78.8±10.5%¶	84.1±9.3%¶
								Tw_P (40 min)	75.4±12.5%¶	83.3±10.6%¶
Franssen 2005 [51], The Netherlands	87	63±9	35±16	ET: cycle ergometer (2×20 min) and treadmill (20 min) RT: strength exercises for upper and lower limbs	8 (5)	15 isokinetic contractions at an angular velocity of 90°·s^{-1}	Quadriceps	ΔPT/contraction	98±1.1%#	98.5±1.4%#
							Biceps	ΔPT/contraction	97.2±1.4%#	97.1±1.4%#
Gosselin 2003 [52], France	7	61±3	62±6	ET: cycle ergometer (45 min) and country walking (2 h) RT: 1-h weight-training, including abdominal exercises	3 (5)	EMG of the vastus lateralis during IET	Vastus lateralis	RMS (% reference value)	229.9±48.5%#	275.2±32.6%#
								Median frequency	103.8±10.7 Hz#	84.6±7.5 Hz#
Mador 2001 [53], USA	21	70±2	45±4	ET: cycle ergometer and treadmill training RT: upper limb exercises with free weights	8 (3)	SMS of the femoral nerve before and after CWRT (60–70% of W_{max})	Quadriceps	Tw_P (rest)	12.7±0.7 kg	13.8±0.7 kg
								Tw_P (10 min)	73.9±3.9%¶	85±4%¶
								Tw_P (30 min)	80.5±3.4%#¶	89.4±3.5%#¶
Wadell 2005 [54], Sweden	15	64±16	55±34	Land or water-based ET: 3×4-min repetitive large-muscle exercises intending to increase heart rate RT: 3-min strength exercises for upper and lower limbs and torso	12 (3)	Isokinetic contractions until exhaustion or 100 repetitions at an angular velocity of 90°·s^{-1}	Quadriceps	Mean PT/100	84.3±29.8 N	94.8±34.5 N
	15	64±12	56±27				Quadriceps	Mean PT/100	81.7±29.6 N	85.4±31 N
	12	60±21	50±31	No exercise intervention			Quadriceps	Mean PT/100	107.8±28.5 N	91.9±22.2 N

Data are presented as mean±SD, unless otherwise indicated. #: derived from graphic data; ¶: recorded as % of baseline. CWRT: constant workload exercise test; EMG: surface electromyography; ET: endurance training; FEV$_1$: forced expiratory volume in 1 s; IET: incremental exercise test; MVC: maximal voluntary contraction; NMES: neuromuscular electrical stimulation; NR: not reported; PT: peak torque; RFD: rate of force development; RMS: root mean square; RT: resistance training; SMS: supramaximal magnetic stimulation; Tw_P: potentiated twitch force; W_{max}: maximal workload.

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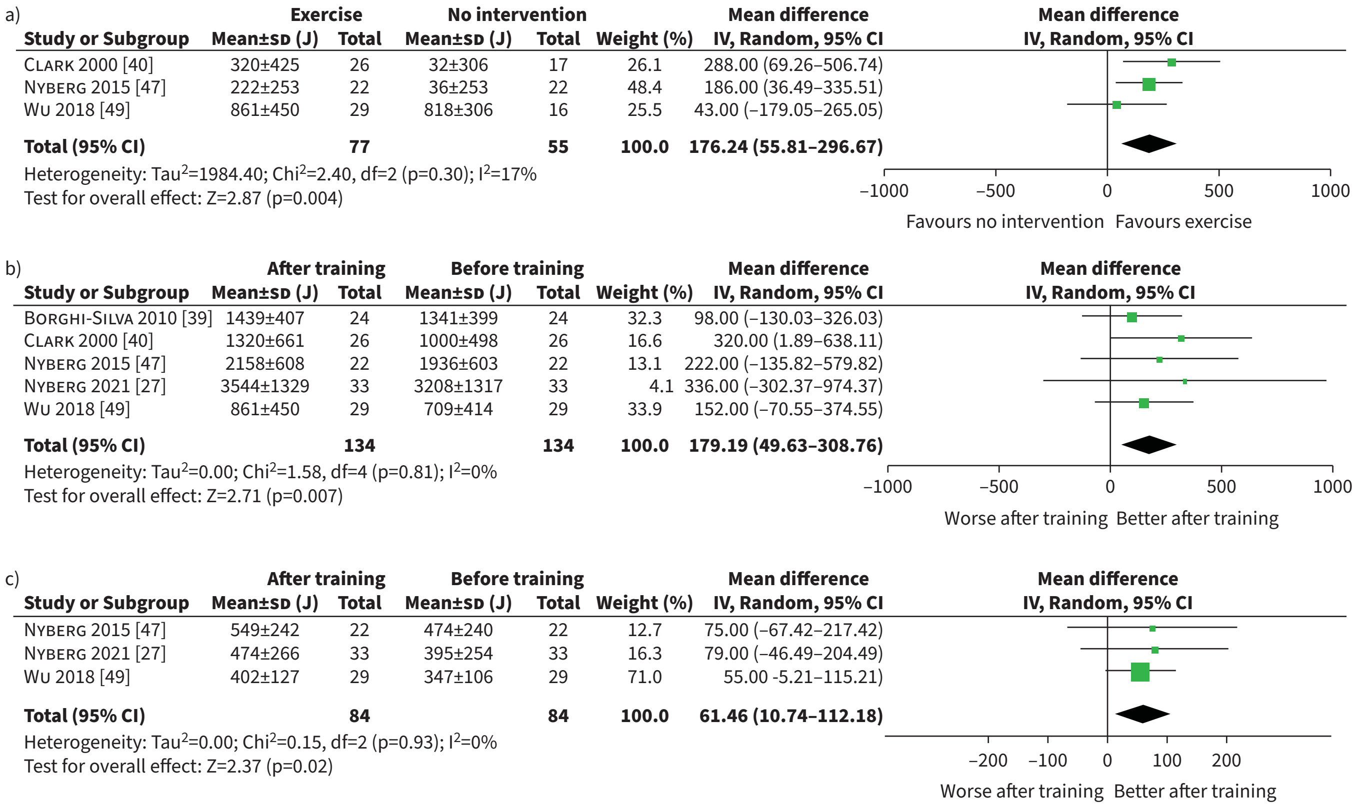
Effects of exercise on peripheral muscle fatigability in RCTs

Considering the training arms of the 11 RCTs [27, 37–40, 43–47, 49] and six NRSIs [23, 50–54] with complete data, the graphical analysis (supplementary figure 3S) suggested a potential positive effect of CT [23, 37, 38, 43–46, 51–54] on muscle fatigue resistance. This positive effect appeared less clear for RT [27, 40, 47, 49, 50] and ET, the latter supported by only one study [39]. Based on low certainty of the evidence (supplementary table 3S), three RCTs [40, 47, 49] comparing RT with no intervention showed a significant effect on quadriceps ΔW_T (MD 176.24 J, 95% CI 55.81–296.67 J, $I^2=17\%$), with negligible heterogeneity (figure 2a). With similar certainty of evidence, we observed a significant effect of exercise training on quadriceps ΔW_T (MD 179.19 J, 95% CI 49.63–308.76 J, $I^2=0\%$) when considering only the training arms of five RCTs (figure 2b) [27, 39, 40, 47, 49]. After removing one study [49] with high risk of bias, significant baseline differences between groups and which focused on a less conventional form of training (*i.e.* Liuzijue exercise), there was a significant effect favouring exercise on the previously mentioned outcome measures (supplementary figure 4SA, B). Based on low certainty of the evidence, three studies [27, 47, 49] reported significant improvements in ΔW_T of the arm muscles after RT (MD 61.46 J, 95% CI 10.74–112.18 J, $I^2=0\%$; figure 2c). However, the pooled effect was nonsignificant after the sensitivity analysis (supplementary figure 4SC). Based on a very low certainty of the evidence, four RCTs [43–46] showed a significant relative percentage increase in ΔTw_P of the quadriceps 10 min after the fatiguing exercise (MD 7.36%, 95% CI 5.10–9.61%, p<0.001; figure 3) when this was performed at identical absolute workloads pre- and post-PR. Of note, heterogeneity was substantial ($I^2=67\%$) and three studies [43–45] had a high risk of bias. The pooled effect size was calculated excluding one study [37] for methodological differences on the fatigability assessment with the other studies.

A descriptive analysis of two RCTs [41, 43] that compared CT and nutritional supplementation with CT and placebo supplementation revealed no effect of combining CT and supplements on peripheral muscle fatigue resistance. In contrast, one RCT [42] reported a significant effect of creatine supplementation *versus* placebo on quadriceps ΔW_T. In addition, two RCTs compared CT with ET [44] and continuous ET with interval ET [46], respectively. The authors reported no significant differences between exercise



a)

	Exercise		No intervention			Mean difference
Study or Subgroup	Mean±SD (J)	Total	Mean±SD (J)	Total	Weight (%)	IV, Random, 95% CI
Clark 2000 [40]	320±425	26	32±306	17	26.1	288.00 (69.26–506.74)
Nyberg 2015 [47]	222±253	22	36±253	22	48.4	186.00 (36.49–335.51)
Wu 2018 [49]	861±450	29	818±306	16	25.5	43.00 (−179.05–265.05)
Total (95% CI)		**77**		**55**	**100.0**	**176.24 (55.81–296.67)**

Heterogeneity: $Tau^2=1984.40$; $Chi^2=2.40$, df=2 (p=0.30); $I^2=17\%$
Test for overall effect: Z=2.87 (p=0.004)

b)

	After training		Before training			Mean difference
Study or Subgroup	Mean±SD (J)	Total	Mean±SD (J)	Total	Weight (%)	IV, Random, 95% CI
Borghi-Silva 2010 [39]	1439±407	24	1341±399	24	32.3	98.00 (−130.03–326.03)
Clark 2000 [40]	1320±661	26	1000±498	26	16.6	320.00 (1.89–638.11)
Nyberg 2015 [47]	2158±608	22	1936±603	22	13.1	222.00 (−135.82–579.82)
Nyberg 2021 [27]	3544±1329	33	3208±1317	33	4.1	336.00 (−302.37–974.37)
Wu 2018 [49]	861±450	29	709±414	29	33.9	152.00 (−70.55–374.55)
Total (95% CI)		**134**		**134**	**100.0**	**179.19 (49.63–308.76)**

Heterogeneity: $Tau^2=0.00$; $Chi^2=1.58$, df=4 (p=0.81); $I^2=0\%$
Test for overall effect: Z=2.71 (p=0.007)

c)

	After training		Before training			Mean difference
Study or Subgroup	Mean±SD (J)	Total	Mean±SD (J)	Total	Weight (%)	IV, Random, 95% CI
Nyberg 2015 [47]	549±242	22	474±240	22	12.7	75.00 (−67.42–217.42)
Nyberg 2021 [27]	474±266	33	395±254	33	16.3	79.00 (−46.49–204.49)
Wu 2018 [49]	402±127	29	347±106	29	71.0	55.00 -5.21–115.21)
Total (95% CI)		**84**		**84**	**100.0**	**61.46 (10.74–112.18)**

Heterogeneity: $Tau^2=0.00$; $Chi^2=0.15$, df=2 (p=0.93); $I^2=0\%$
Test for overall effect: Z=2.37 (p=0.02)

FIGURE 2 Forest plots of the effect of exercise training a) *versus* no intervention on changes in quadriceps total work output in randomised controlled trials (RCTs); b) on changes in quadriceps total work output in the intervention group of RCTs; c) on changes in arms total work output.

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Study or Subgroup	After training Mean±SD (% baseline)	Total	Before training Mean±SD (% baseline)	Total	Weight (%)	Mean difference IV, Random, 95% CI
Fatiguing test performed at higher % of W_{max} post PR						
Camillo 2020 [37]	88.9±15.1	35	87.6±11.8	35	100.0	1.30 (−5.05–7.65)
Fatiguing test performed at identical % of W_{max} pre and post PR						
Laviolette 2010 [43]	76.3±5.1	20	72.3±6.4	20	19.5	4.00 (0.41–7.59)
Mador 2004 [44]	86.7±7.2	24	77.8±3.9	24	21.2	8.90 (5.62–12.18)
Mador 2005 [45]	88.2±3.6	29	81.8±3.6	29	30.5	6.40 (4.55–8.25)
Mador 2009 [46]	83±5.3	34	73.5±3.3	34	28.8	9.50 (7.40–11.60)
Subtotal (95% CI)		**107**		**107**	**100.0**	**7.36 (5.10–9.61)**

Heterogeneity: Tau^2=3.44; Chi^2=9.20, df=3 (p=0.03); I^2=67%
Test for overall effect: Z=6.40 (p<0.00001)

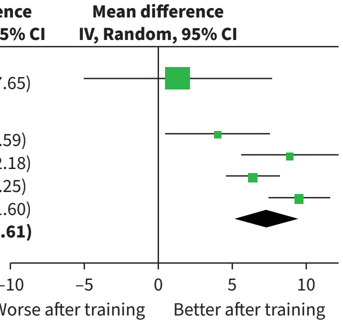

FIGURE 3 Forest plots of the intervention group of randomised controlled trials showing the effect of exercise training on changes in quadriceps potentiated twitch force following pulmonary rehabilitation (PR), 10 min after the fatigue protocol. Pooled effect size is showed only for studies performing the fatiguing test at identical percentage of maximal workload (W_{max}) pre- and post-training.

modalities on ΔTw_P of the quadriceps. The robustness of findings was confirmed by meta-analyses using REML, which had no impact on results (supplementary table 4S).

Effects of exercise on peripheral muscle fatigability in NRSIs

A meta-analysis of three NRSIs showed a significant improvement in ΔTw_P of the quadriceps after RT [50] or CT [23, 53] (MD 8.17%, 95% CI 3.69–12.64%, p=0.0003, I^2=67%), with substantial heterogeneity (supplementary figure 5SA). A sensitivity analysis, after removing one study [53] with serious risk of bias, resulted in a significant improvement (supplementary figure 5SB).

Two NRSIs analysed descriptively reported either a significant [51] or nonsignificant [54] improvement in quadriceps fatigue resistance, calculated as the ratio of mean force values and number of contractions. Another NRSI [52] reported changes in the EMG signal after PR, with an increase in the root mean square amplitude and a decrease in median frequency values during exercise.

Discussion

This systematic review provided a comprehensive summary of the impact of exercise training on quantitative outcome measures of peripheral muscle fatigability and muscle fatigue resistance in people with COPD. Overall, the included studies support a possible positive effect of exercise-based interventions on these outcomes, particularly when a CT approach is adopted. Variations in the duration and design of training programmes as well as differences in assessment procedures may have contributed to the heterogeneity observed. Small sample sizes and high risk of bias may have also influenced the results. However, after conducting sensitivity analyses, a positive effect of training on quadriceps Tw_P and W_T, though not on arms fatigue resistance, remained evident.

The evidence of a reduction in quadriceps fatigue resistance in individuals with COPD compared with healthy control subjects has been established in a previous review [11]. In this regard, we found that the quadriceps W_T was often assessed during repeated isokinetic contractions to measure changes in muscle fatigue resistance after PR. However, no standardised protocols for this outcome measure have been established in COPD [55]. Of note, impaired muscle fatigue resistance has been reported in 26–43% of patients with COPD, depending on the outcome used [56], and is independently associated with physical activity levels and functional exercise capacity [56, 57]. Based on three RCTs [40, 47, 49] included in this systematic review, exercise training may be superior to no intervention in improving quadriceps fatigue resistance. Similarly, we observed a positive effect of exercise on quadriceps ΔW_T [27, 39, 40, 47], but not on arms ΔW_T [27, 47], considering the intervention group of RCTs. The lack of improvement in fatigue resistance of the arm muscles may be partially explained by a preserved muscle function of the upper body in patients with COPD, even in those with reduced fat-free mass [51, 58]. It is worth noting that two RCTs [27, 47] adopted an endurance-oriented RT programme and found significant improvements in arm and leg muscle fatigue resistance after PR. This reinforces the idea that specific muscle characteristics, such as fatigue resistance, require specific training prescriptions, even in older adult and chronic disease populations [59].

Considering the training modality proposed by the various studies, we can only speculate that CT may be more effective than isolated RT or ET programmes in improving muscle fatigue resistance in patients with

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COPD. It is reasonable to assume, however, that heterogeneity in initial training intensity and load progression among the included studies may have influenced the results [60]. In addition, other factors may have further contributed to these diverging results, including the design of the PR programme, the characteristics of the fatiguing protocol and assessment procedures, the severity and duration of the disease in the study participants, and baseline skeletal muscle impairment.

In this systematic review, peripheral muscle fatigability was mainly assessed as a decline in quadriceps Tw_P evoked by magnetic or electrical stimulation immediately after a maximal voluntary contraction [8, 61]. Although this technique allows assessment of the peripheral and central components of neuromuscular fatigue, regardless of the cooperation of the individuals, it is challenging to implement in clinical studies. In patients with COPD, an acute reduction $\geqslant$15% in Tw_P assessed following a cycling exercise to exhaustion is considered indicative of clinically meaningful muscle fatigue [18, 61]. This review found that PR elicited a significant improvement in ΔTw_P (*i.e.* less drop in twitch force) of the quadriceps, assessed 10 min after a fatiguing exercise performed at identical absolute workloads (*i.e.* the same percentage of baseline W_max). While most included studies were characterised by a high risk of bias and the evidence was very uncertain, this finding was corroborated by NRSIs, which also demonstrated significant improvements in ΔTw_P under identical absolute workloads. By contrast, at comparable relative workloads, the improvements in ΔTw_P were not consistently observed. Indeed, one RCT [37] reported no significant changes in ΔTw_P when quadriceps fatigability was assessed after a complete training session at a higher absolute workload after training. Together, these results suggest that muscle fatigue occurs later and at higher work rates after PR.

In recent years, there has been growing interest in identifying patients with COPD who have low resistance to muscle fatigue before the start of PR. Indeed, several authors have hypothesised that patients with COPD who develop clinically meaningful fatigue more rapidly at baseline show more favourable outcomes after PR than those who do not [22, 23, 37]. Among the studies included in this systematic review, 53–63% of patients showed low fatigue resistance after a submaximal cycling test or training session at baseline [23, 37, 46]. This is in line with the 50–60% reported by previous authors [16, 62]. The only exception was a NRSI [53] reporting 81% of patients with low fatigue resistance at baseline. However, the population's characteristics of 95% male, poor baseline functional status (6-min walk distance <350 m) and high proportion of patients with severe COPD may have influenced this outcome. The authors speculated that patients with more severe and complex disease experienced greater muscle deconditioning and, thus, were more fatigable. They reported a favourable response to PR, with significant improvements in maximal and submaximal exercise tolerance and functional exercise capacity. This partially aligns with other studies showing greater improvements in functional capacity and dyspnoea among patients with less fatigue resistance at baseline [22, 23]. The cause of the heterogeneous fatigability in individuals with COPD, unlike in healthy older adult subjects [63], remains unclear. Ventilatory constraints may accelerate the occurrence of muscle fatigue [46, 64]. Other authors have suggested a role for COPD-related muscle changes (*e.g.* capillarisation, oxidative enzyme activity and early rise in arterial lactate levels) in reducing fatigue resistance [7, 65].

Beyond the factor of patient cooperation, most studies in this systematic review assessed either W_T or Tw_P of the quadriceps using distinct fatiguing protocols. Quadriceps W_T was typically measured through repeated isokinetic contractions; nevertheless, angular velocities and test duration (time or number of repetitions) could vary. In contrast, Tw_P was usually assessed before and after a whole-body cycling exercise to exhaustion. This test involves multiple muscle groups and generates substantial cardiovascular and respiratory load, typical of whole-body exertion. One study concurrently assessed ΔW_T and ΔTw_P of the quadriceps; however, it did not explore their correlation [43]. Conversely, a recent study suggested no relationship between these measures in COPD [66]. Therefore, the effort required by the fatiguing exercise and the involvement of different limiting factors (*e.g.* central or peripheral factors, oxygen delivery or ultrastructural damage) should be considered when choosing the fatigability assessment procedure in COPD, particularly in patients with ventilatory limitations [6, 11].

Finally, it is also worth mentioning surface EMG to characterise peripheral muscle fatigability noninvasively in patients with COPD [16, 67]. However, we retrieved only one NRSI [52] that used this technique, confirming the underutilisation of surface EMG as a PR outcome, so far. Despite GOSSELIN *et al.* [52] reporting altered surface EMG parameters after 3 weeks of an inpatient CT programme, the interpretation of EMG results remains controversial because of low reliability between subjects and during dynamic exercises [68]. Nonetheless, the potential use of surface EMG for providing real-time data on muscle fatigability deserves further investigation.

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Strength and limitations

A notable strength of this systematic review was the inclusion of both RCTs and NRSIs, enabling a more comprehensive picture of the effect of exercise training on peripheral muscle fatigability in COPD. A further strength is the inclusion of both ΔW_T and ΔTw_P as outcome measures, consistent with previous reviews [11, 12]. Indeed, despite different underlying mechanisms, these outcomes are complementary in the objective quantification of muscle fatigability in COPD [6, 20]. We acknowledge certain limitations of this systematic review. The quality of the included studies posed a challenge, because nearly 50% were assessed to have a high or serious risk of bias, which may have influenced our findings. To mitigate this, we conducted sensitivity analyses and provided narrative descriptions when studies could not be pooled for meta-analysis. Finally, the small number of studies included in each meta-analysis precluded a robust assessment of publication bias.

Clinical implications

There is a crucial need to investigate peripheral muscle fatigability in people with COPD, because it remains an underutilised but clinically relevant outcome of PR. Accordingly, this systematic review is timely in addressing a gap in the literature regarding the effects of exercise training on this outcome in COPD. Overall, we observed an improvement in muscle fatigue resistance after PR programmes in patients with COPD; nonetheless, peculiarity exists in clinical applications. For instance, several studies reported improvements in fatigue resistance after CT, while endurance-oriented RT may also be effective [27, 47]. Determining the optimal training prescription to improve muscle fatigue resistance remains challenging. This may be due to the influence of the training specificity and the inability to develop clinically significant muscle fatigue after standardised exercises, indicative of a less favourable PR outcome, observed in a proportion of patients before training.

To date, the main limitation to implementing peripheral muscle fatigability assessments in the context of PR is the complexity of testing procedures. In this review we observed a widespread assessment of ΔW_T, which is better suited to clinical settings, as an alternative to the more complex assessment of ΔTw_P. However, we are confident that the dissemination of alternative tools (*e.g.* surface EMG) for assessing peripheral muscle fatigability, with potential applications in clinical practice, will gain momentum in the coming years. As a future direction, we advocate the identification of a reliable clinical measure of peripheral muscle fatigability, along with the determination of a minimal clinically important difference for improvements in muscle fatigue resistance.

Conclusions

This systematic review is the first to summarise the impact of exercise training on objective, exercise-induced peripheral muscle fatigability in people with COPD. Overall, we observed a potential improvement in the fatigue resistance of leg muscles after exercise training. These positive effects were equally evident regardless of the technique used to assess muscle fatigue resistance. To overcome the limitations of objectively assessing peripheral muscle fatigability in clinical settings, we advocate for the integration of portable and wearable instruments in COPD research in the coming years, as well as for the determination of a minimal clinically important difference for use in PR practice.

Points for clinical practice

- Combined endurance and resistance training may improve muscle fatigue resistance in leg muscles, but not in arm muscles, in patients with COPD.
- Standardised protocols and alternative tools to facilitate the assessment of muscle fatigability outcomes in clinical practice should be established.
- Individual susceptibility to peripheral muscle fatigue may guide the prescription of training intensity and predict responsiveness to training programmes.
- In the future, the determination of a minimal clinically important difference for improvements in muscle fatigue resistance in COPD is recommended.

Provenance: Submitted article, peer reviewed.

Conflict of interest: All authors have nothing to disclose.

Support statement: This project is supported by a C2 grant of KU Leuven (Belgium), reference number C2M/24/075.

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