



Intensity of physical exercise and its effect on functional capacity in COPD: systematic review and meta-analysis

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INTRODUCTION

Because COPD has systemic involvement and is an important risk factor for other comorbidities, it has a growing impact worldwide,⁽¹⁾ and chronic airflow limitation due to abnormality in the alveolar airways is its most striking characteristic, the major symptom of which is dyspnea,⁽²⁾ resulting from genetic deficiency (alpha-1 antitrypsin deficiency), outdoor or indoor air pollution (related to firewood burning), significant exposure to noxious particles or gases (such as cigarette smoke), etc. However, COPD can no longer be considered a disease presenting with pulmonary involvement alone.⁽³⁾

Exercise intolerance is a consequence of COPD, leading the patient to a sedentary lifestyle to avoid exercise-induced dyspnea. The association of physical inactivity with the metabolic disorders and structural changes caused by the disease, as well as the fact that smoking is also a primary cause, results in there being multiple risk factors for cardiovascular disease in this population.⁽⁴⁾ In addition, COPD is a powerful independent risk factor for cardiovascular morbidity and mortality,⁽⁵⁾ since the major risk factors for cardiovascular disease are also present in these patients.⁽⁶⁾

Physical exercise is an integral part of pulmonary rehabilitation programs. The principles of training are exercise duration, frequency, progression, modality, individualization, and, especially, intensity, which is recognized as the key determinant of the physiological benefits gained from rehabilitation.⁽⁷⁾ According to the

ABSTRACT

Objective: To evaluate the effects of high-intensity interval training (HIIT), in comparison with those of continuous exercise, on functional capacity and cardiovascular variables in patients with COPD, through a systematic review and meta-analysis of randomized controlled trials. **Methods:** We searched PubMed, the Physiotherapy Evidence Database, the Cochrane Central Register of Controlled Trials, and EMBASE, as well as performing hand searches, for articles published up through January of 2017. We included studies comparing exercise regimens of different intensities, in terms of their effects on functional capacity and cardiovascular variables in patients with COPD. **Results:** Of the 78 articles identified, 6 were included in the systematic review and meta-analysis. Maximal oxygen consumption (VO_{2max}) did not differ significantly between HIIT and control interventions. That was true for relative VO_{2max} (0.03 mL/kg/min; 95% CI: -3.05 to 3.10) and absolute VO_{2max} (0.03 L/min, 95% CI: -0.02 to 0.08). **Conclusions:** The effects of HIIT appear to be comparable to those of continuous exercise in relation to functional and cardiovascular responses. However, our findings should be interpreted with caution because the studies evaluated present a high risk of bias, which could have a direct influence on the results.

Keywords: Pulmonary disease, chronic obstructive; Exercise; Oxygen consumption.

American College of Sports Medicine,⁽⁸⁾ moderate-intensity continuous aerobic exercise for 20 to 60 min per session brings physiological benefits, whether on a treadmill or a cycle ergometer, the latter resulting in lower exercise-induced oxygen desaturation in the training of patients with COPD. High-intensity interval training (HIIT) can be an alternative to continuous exercise training for individuals with COPD who have difficulty reaching the target duration because of dyspnea, fatigue, or any other symptom.⁽⁹⁾

To date, there have been few studies correlating COPD and the effects of HIIT in pulmonary rehabilitation in terms of cardiovascular variables and functional capacity. One study describing the effects of two training programs in patients with COPD indicated improvement in functional capacity after 12 weeks of high-intensity training.⁽¹⁰⁾ One study evaluating improvement in systolic function in patients with COPD reported that the effects of HIIT and of moderate exercise result in positive changes in cardiovascular values.⁽¹¹⁾ A study analyzing heart rate variability after HIIT in patients with COPD reported improvement in autonomic cardiac function after three months of HIIT.⁽¹²⁾ In addition, a systematic review of studies on changes in ventilatory parameters in patients with moderate to severe COPD, who participated in pulmonary rehabilitation programs, evaluated exercise mode, frequency, duration, and intensity. Patients were shown to be able to perform HIIT, which resulted in positive changes in ventilatory parameters and in reduced exercise-related dyspnea.⁽¹³⁾

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Therefore, the present study plays an important role in improving scientific knowledge on the contributions of different intensities of aerobic exercise to cardiovascular health in individuals with COPD, given that the most recent systematic review on the subject was published in 2014 and evaluated only ventilatory outcomes. The objective of the present study was to systematically review the effects of HIIT, in comparison with those of continuous aerobic exercise or any other control intervention, on functional capacity and cardiovascular variables in patients with COPD.

METHODS

The study was conducted in accordance with the PRISMA Statement⁽¹⁴⁾ and was registered with the International Prospective Register of Systematic Reviews (PROSPERO; Protocol no. 42017056753).

Eligibility criteria and search strategy

We included randomized controlled trials that addressed the use of HIIT in patients with COPD, in comparison with the use of moderate-intensity continuous aerobic exercise or any other control intervention, on functional capacity, as measured by maximal oxygen consumption (VO_{2max}), six-minute walk distance (6MWD), and Borg dyspnea and leg fatigue scores, as well as on cardiovascular variables, such as endothelial function, ankle-brachial index, systolic blood pressure, diastolic blood pressure, HR, RR, and SpO_2 . We included studies that used different HIIT modalities, such as treadmill or cycle ergometer training. We excluded articles that evaluated patients with an exercise-limiting disease or medical condition.

We searched the following electronic databases (from inception through January of 2017): PubMed; Physiotherapy Evidence Database; Cochrane Central Register of Controlled Trials; and EMBASE. In addition, we hand searched the references in published studies on the subject. Our search was performed on January

27, 2017 and included the keywords "high intensity interval training" and "pulmonary disease, chronic obstructive", as well as the corresponding keywords in Portuguese "treinamento intervalado de alta intensidade" and "doença pulmonar obstrutiva crônica". The keywords were combined with a sensitive list of terms for searching for randomized controlled trials that was compiled by Robinson & Dickersin.⁽¹⁵⁾ Our search had no language restriction and was performed after the study had been registered with PROSPERO. Full articles published in journals and accepted papers were taken into account. The full search strategy used in PubMed is shown in Chart S1.

STUDY SELECTION AND DATA EXTRACTION

The titles and abstracts of all articles identified by the search strategy were evaluated independently and in duplicate by two reviewers. All abstracts that did not provide sufficient information about the inclusion and exclusion criteria were selected for full-text evaluation. In this second phase, the same reviewers independently evaluated the full texts and made their selections based on the pre-specified eligibility criteria. Disagreements between reviewers were resolved by consensus.

Using standardized electronic forms, the same two reviewers independently extracted data on the methodological characteristics of the studies, interventions, and results. Differences were again resolved by consensus.

Initially, the studies were assessed for the following: authors; year of publication; sample (total number of subjects); methodology; HIIT intervention protocol; control group; comparator protocol (if any); evaluated outcomes; results; and conclusions. The primary outcome extracted was VO_{2max} (in mL/kg/min and L/min). The secondary outcomes evaluated in the present study were 6MWD and the aforementioned cardiovascular variables.

Chart S1. Search strategy.

#1	"Pulmonary Disease, Chronic Obstructive"[Mesh] OR "Pulmonary Disease, Chronic Obstructive" OR "COPD, Severe Early-Onset" OR "COPD" OR "Chronic Obstructive Pulmonary Disease" OR "COAD" OR "Chronic Obstructive Airway Disease" OR "Chronic Obstructive Lung Disease" OR "Airflow Obstruction, Chronic" OR "Airflow Obstructions, Chronic" OR "Chronic Airflow Obstructions" OR "Chronic Airflow Obstruction"
#2	"High-Intensity Interval training"[Mesh] OR "High-Intensity Interval Training" OR "High Intensity Interval Training" OR "High-Intensity Interval Trainings" OR "Interval Training, High-Intensity" OR "Interval Trainings, High-Intensity" OR "Training, High-Intensity Interval" OR "Trainings, High-Intensity Interval" OR "High-Intensity Intermittent Exercise" OR "Exercise, High-Intensity Intermittent" OR "Exercises, High-Intensity Intermittent" OR "High-Intensity Intermittent Exercises" OR "Sprint Interval Training" OR "Sprint Interval Trainings" OR "Interval Training" OR "Interval Exercise" OR "Intermittent Exercise" OR "High Intensity Interval Exercise" OR "High Intensity Exercise" OR "High Intensity Training" OR "High Intensity Intermittent Exercises" OR "High-Intensity Exercise"
#3	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh])
#4	#1 AND #2 AND #3

Evaluation of risk of bias and data analysis

The evaluation of study quality was performed descriptively and included the following characteristics: adequate generation of randomization sequences; concealment of allocation; blinding; blinding of outcome assessors; intention-to-treat analysis; and reporting of losses and exclusions. All characteristics that were not clearly reported were classified as “no data”.

The use of intention-to-treat analysis in a study was considered as confirmation that the number of randomized participants was the same as the number of analyzed participants. Studies without this characteristic were considered not to meet this criterion. Study quality was evaluated independently by the same two reviewers.

Meta-analysis was performed using the random-effects model, and effect measures were calculated as the mean difference between baseline and follow-up values. An α value = 0.05 was considered statistically significant. Statistical heterogeneity of treatment effect across studies was assessed using the inconsistency I^2 test, in which values above 25% and 50% were considered to be indicative of moderate and high heterogeneity, respectively. All analyses were conducted with the software Review Manager, version 5.3 (RevMan 5; Cochrane Collaboration, Oxford, UK).

RESULTS

The initial search identified 78 articles, of which 49 were retrieved for detailed analysis. Of those, 17 were considered potentially relevant. However, 11 studies were excluded: those by Nasis et al.,⁽¹⁶⁾ Hsieh et al.,⁽¹⁷⁾ Pitta et al.,⁽¹⁸⁾ Rodríguez et al.,⁽¹⁹⁾ and Varga et al.,⁽²⁰⁾ because they were quasi-experimental studies; that by Camilo et al.,⁽¹⁰⁾ because the outcomes of interest were not reported; those by Probst et al.,⁽¹¹⁾ Puhan et al.,⁽¹²⁾ and Pomidori et al.,⁽²¹⁾ because the training performed was not consistent with the definition of HIIT; that by Mador et al.,⁽²²⁾ because the training did not fit within the upper limits defining HIIT; and that by Coppoolse et al.,⁽²³⁾ because HIIT was combined with another intervention. Therefore, 6 studies investigating a total of 295 patients were included in the systematic review and meta-analysis. Figure 1 provides a study inclusion flow chart, and Table 1 summarizes the characteristics of the included studies.

According to the inclusion criteria in the studies, the selected COPD patients were staged based on the presence of a post-bronchodilator $FEV_1 \geq 30\%$ and $< 80\%$ of predicted and an FEV_1/FVC ratio $< 70\%$, as per the Global Initiative for Chronic Obstructive Lung Disease,⁽¹⁾ as having grade II or III disease (moderate or severe disease, respectively).⁽²⁴⁻²⁹⁾

Four studies compared HIIT with a rehabilitation program that included psychological support, endurance training, breathing exercises, COPD education, and relaxation (total sample of 238 individuals, of whom 140 were in the HIIT group).⁽²⁴⁻²⁷⁾ One study compared HIIT with low-intensity continuous exercise,⁽²⁸⁾ whereas

another 1 compared HIIT with moderate-intensity continuous exercise.⁽²⁹⁾

Of the studies included in this systematic review, 4 (67%) had adequate randomization or reported randomization, having a low risk of bias; only 1 reported allocation concealment, and 1 reported blinding of outcome assessors, but only for one variable, having a high risk of bias; 5 described losses to follow-up and exclusions, having a low risk of bias; and none performed or reported intention-to-treat analysis, having a high risk of bias (Table 2).

In relation to the effects of the interventions, 3 studies^(24,25,29) determined relative VO_{2max} ($n = 200$) and 3 studies⁽²⁶⁻²⁸⁾ determined absolute VO_{2max} ($n = 95$). In both analyses, there was no significant difference between the HIIT groups and the control groups (relative $VO_{2max} = 0.03$ mL/kg/min; 95% CI: -3.05 to 3.10 ; $I^2: 92\%$; and absolute $VO_{2max} = 0.03$ L/min; 95% CI: -0.02 to 0.08 ; $I^2: 34\%$; Figures 2A and 2B).

On the basis of relative VO_{2max} , it is possible to identify similarities across studies,^(24,25,29) especially in relation to the duration of each session (40, 39, and 38 min, respectively). Intervention duration ranged from 22 to 28 sessions. The type of training in the intervention group was similar across studies: aerobic cycling exercise⁽²⁵⁾; aerobic exercise on a treadmill⁽²⁹⁾; and aerobic exercise on a cycle ergometer.⁽²⁴⁾ However, the control groups are noteworthy: 2 studies^(25,29) used a similar moderate-intensity intervention in the control group and reported no differences between the intervention and control groups; and 1 study⁽²⁴⁾ used a mix of interventions in the control group—patient education, drug therapy, breathing exercises, physical therapy, and nutrition—showing that the HIIT group was superior to the control group.

The studies⁽²⁶⁻²⁸⁾ that determined absolute VO_{2max} reported a total training session duration of 30-45 min and an intervention duration of 16-30 sessions. In 1 of those studies,⁽²⁸⁾ the control group performed low-intensity continuous exercise, whereas in 2,^(26,27) the control group underwent cycle ergometer training using parameters that were very close to those used in the intervention group. Although those studies found no differences between the intervention and control groups, 1 of the studies⁽²⁶⁾ reported a trend toward the superiority of the HIIT group over the control group (low-intensity exercise).

None of the included studies evaluated 6MWD, ankle-brachial index, Borg dyspnea scores, or SpO_2 . Only 1 study⁽²⁹⁾ evaluated endothelial function, and the authors found that there were no intragroup or intergroup differences in this variable.

Only 1 study⁽²⁹⁾ evaluated systolic and diastolic blood pressures and found that there were no pre- or post-intervention differences within the groups and no differences between the groups. Two studies^(24,29) evaluated HR, and 1 of the studies⁽²⁹⁾ found significantly reduced resting HR in both groups ($p < 0.05$); however, there were no differences between the groups. In 1

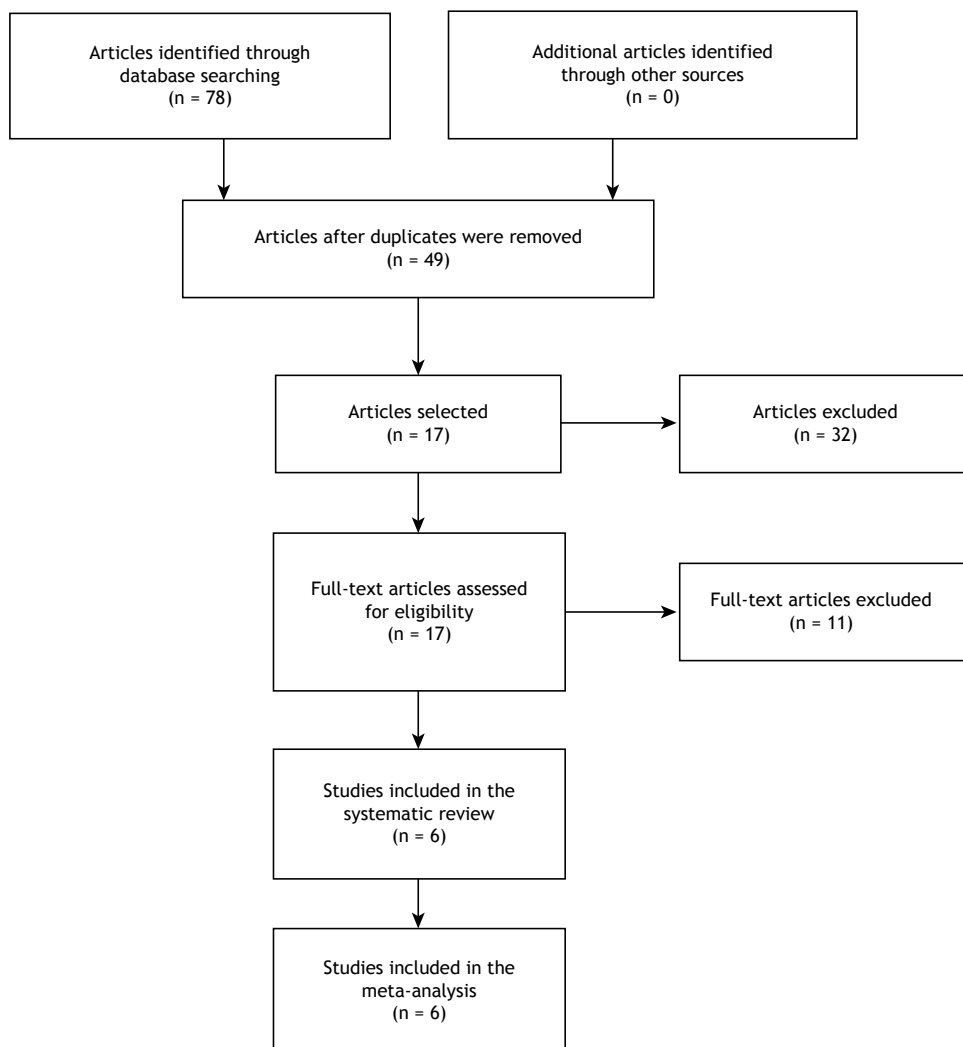


Figure 1. Study inclusion flow chart. RCT: randomized controlled trial; and HIIT: high-intensity interval training.

study,⁽²⁴⁾ there was an increase in HR in the intervention group ($p < 0.01$), but there were no differences between the groups.

One of the studies⁽²⁴⁾ evaluated RR and found that there was an increase in RR in the intervention group ($p < 0.05$); however, there was no difference between the groups. The same study⁽²⁴⁾ evaluated Borg leg fatigue scores and found a decrease in scores in the intervention group ($p < 0.01$), but there were no differences between the groups.

DISCUSSION

The findings of the present study indicate that the effects of HIIT are comparable to those of continuous exercise or any other control intervention regarding relative VO_{2max} , absolute VO_{2max} , and cardiovascular variables in patients with COPD.

In relation to the type and intensity of exercise that should be included in a pulmonary rehabilitation program, studies have shown positive effects of both

HIIT and moderate-intensity continuous exercise in patients with COPD.^(30,31) In addition, one study⁽²⁰⁾ comparing continuous and interval training in patients with COPD indicated that the physiological effects of the two types of training are similar in these patients.

A clinical trial⁽³²⁾ showed a reduction in perceived dyspnea, an increase in exercise capacity as measured by VO_{2max} , and an improvement in quality of life in patients with COPD who underwent both low- and high-intensity exercise training. One systematic review⁽³³⁾ showed that interval and continuous exercise both resulted in improved exercise capacity as measured by 6MWD and in improved quality of life. One study⁽³⁴⁾ comparing different intensities of exercise showed that continuous and interval exercise both appear to be equally effective in improving 6MWD, symptoms, and quality of life in patients with COPD.

In contrast to the results obtained here, studies^(17,35,36) evaluating the physiological effects of exercise training appear to indicate that these effects are more beneficial in patients who are able to perform higher-intensity

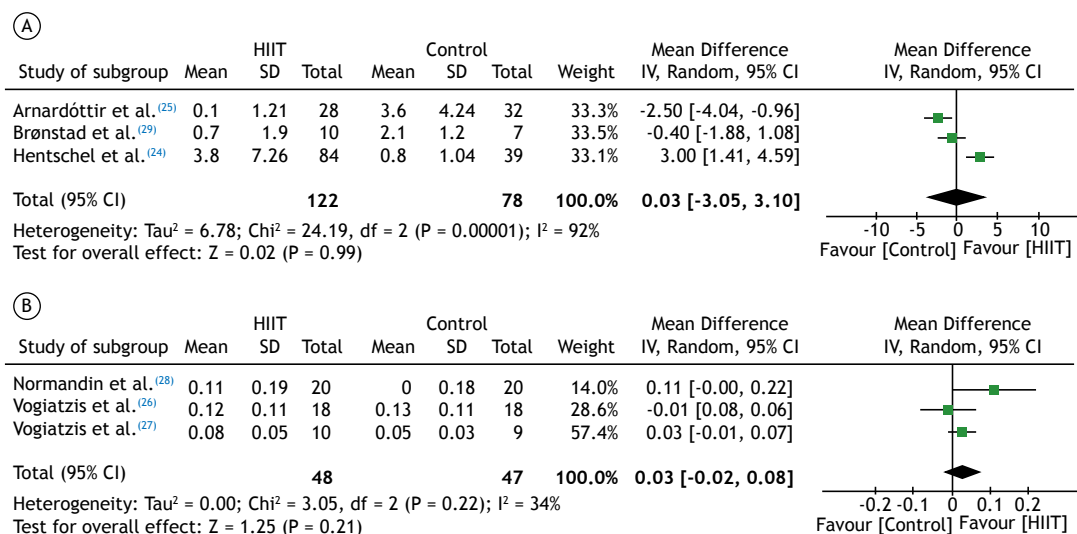
Table 1. Characteristics of the included studies.

Authors	Intervention group parameters	Intervention duration	Control group parameters	I/C patients, n	I/C patient age, years; mean \pm SD
Arnardóttir et al. ⁽²⁵⁾	Type of training: cycling; exercise intensity: 3-min intervals at $\geq 80\%$ of baseline peak exercise capacity and 3-min intervals at 30-40% of baseline peak exercise capacity; total time: 39 min	16 weeks (2 times a week)	Type of training: cycling (endurance training at $\geq 65\%$ of baseline peak exercise capacity) + breathing and relaxation exercises	28/32	65 \pm 7/64 \pm 8
Brønstad et al. ⁽²⁶⁾	Type of training: treadmill; intensity: 4 \times 4-min intervals at 90-95% of HR_{max} (10-min warm-up at 50%-60% of VO_{2max} and at 60-70% of HR_{max}); each interval was separated by 3 min of active rest at 50-70% of HR_{max} ; total exercise time: 38 min	10 weeks (3 times a week); at least 26 of 32 sessions	Type of training: treadmill; intensity: 70% of HR_{max} (moderate-intensity continuous exercise); total exercise time: 47 min	10/7	65 \pm 7/65 \pm 5
Hentschel et al. ⁽²⁴⁾	Type of training: cycle ergometer; intensity: training load = power at the anaerobic threshold + 40% of the difference to peak exercise; total exercise time: 40 min	4 weeks (at least 22 sessions)	Type of training: rehabilitation, education, medications, nutrition, physical therapy, and breathing exercises	84/39	48 \pm 10/49 \pm 12
Normandin et al. ⁽²⁸⁾	Type of training: treadmill and cycle ergometer; intensity: 80% of maximum workload (2 min of warm-up and cool-down time not counted); total exercise time: 30 min; intensity increased if Borg = 4 and intensity decreased if Borg = 7 or if HR close to maximum	8 weeks (2 times a week); 16 sessions	Type of training: classroom exercises/calisthenics with 8-10 repetitions (45-60 s; low-intensity continuous exercise); total exercise time: 40 min; total class time: 45 min	20/20	69 \pm 7/67 \pm 9
Vogiatzis et al. ⁽²⁶⁾	Type of training: cycling; intensity: 100% of baseline peak work rate (30 s) and 45% of baseline peak work rate (30 s) in weeks 1-4; 120% of baseline peak work rate in weeks 5-8; and 140% of baseline peak work rate in weeks 9-12; total exercise time: 40 min	12 weeks (2 times a week)	Type of training: cycle ergometer exercise at 50%, 60%, and 70% of baseline peak work rate + education, breathing exercises, psychological support, and relaxation	18/18	67 \pm 2/69 \pm 2
Vogiatzis et al. ⁽²⁷⁾	Type of training: cycling; intensity: 100% of baseline peak work rate (30 s) and 45% of baseline peak work rate (30 s); total exercise time: 45 min	10 weeks (3 times a week)	Type of training: cycle ergometer exercise at 60%, 70%, and 80% of baseline peak work rate + education, breathing exercises, psychological support, and relaxation	10/9	64 \pm 3/67 \pm 2

I/C: intervention/control; and VO_{2max} : maximal oxygen consumption.

Table 2. Evaluation of risk of bias.

Study, year	Random sequence generation	Allocation concealment	Blinding of outcome assessors	Reporting of losses and exclusions	Intention-to-treat analysis
Arnardóttir et al. ⁽²⁵⁾	Yes	No data	No data	Yes	No
Brønstad et al. ⁽²⁹⁾	Yes	Yes	No data	Yes	No data
Hentschel et al. ⁽²⁴⁾	No data	No data	No data	Yes	No data
Normandin et al. ⁽²⁸⁾	No data	No data	No data	Yes	No
Vogiatzis et al. ⁽²⁶⁾	Yes	No data	No data	No	No data
Vogiatzis et al. ⁽²⁷⁾	Yes	No data	Yes ^a	Yes	No

^aYes for threshold setting.

Figure 2. Comparison between the effects of HIIT and those of continuous exercise and rehabilitation on relative VO_{2max} (in A) and absolute VO_{2max} (in B). HIIT: high-intensity interval training; and VO_{2max} : maximal oxygen consumption.

exercise than in those who perform lower-intensity exercise. In addition, a systematic review⁽³⁷⁾ found a significant increase in maximal exercise capacity as measured by 6MWD and a reduction in leg pain only during interval exercise in patients with COPD. Furthermore, a study⁽³⁰⁾ evaluating VO_{2max} at different intensities of exercise showed that the response to HIIT was two to three times greater than the response to low-intensity training (85%-95% and 70% of maximal HR, respectively) in healthy individuals.

Hsieh et al.⁽¹⁷⁾ reported that only the patients who were able to perform high-intensity exercise training showed improvements in maximal exercise capacity as measured by VO_{2max} and by 6MWD, in FVC, and in work efficiency. Another study⁽¹¹⁾ concluded that high-intensity programs tend to result in significant physiological improvements, being especially efficient in increasing exercise capacity and muscle strength.

In general, the optimal intensity of exercise training depends on the individual goals of each patient, and, if the goal is to increase the ability to perform tasks that are above the current level of tolerance, HIIT appears to elicit greater performance increases because it involves significant anaerobic energy utilization and, therefore, can better mimic the physiological requirements of activities of daily living, is tolerable to patients, and

can indeed reduce the degree of dyspnea and dynamic hyperinflation through a reduced ventilatory demand.⁽³⁸⁾

The formulation of the research problem and the development of eligibility criteria were methodologically rigorous. Study selection was performed by two independent reviewers, who also assessed study methodological quality and agreed on the inclusion and exclusion of studies. The use of meta-analysis increases the robustness of evidence on the influence of HIIT on functional and cardiovascular variables.

We found that most of the studies included in the present review had a high or low risk of bias and that none included all items evaluated. For example, only 1 study reported concealment of allocation and blinding of outcome assessors, characteristics that could have a direct influence on the results. Therefore, it is possible that further studies with higher methodological quality in terms of the variables studied will change current findings. Nevertheless, few randomized controlled trials were found, and most of the studies involving HIIT and patients with COPD are quasi-experimental.

Although we found moderate and high heterogeneity in the meta-analyses of VO_{2max} , probably because of the intervention protocols and the control groups (different intensities of continuous exercise), it was not possible to perform sensitivity analyses because of

the small number of studies included in each analysis, which makes further analyses difficult.

In conclusion, our findings should be interpreted with caution because the included studies have a high risk of

bias, especially in terms of concealment of allocation, blinding of outcome assessors, and intention-to-treat analysis. The lack of these methodological characteristics could have a direct influence on the study results.

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