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Effect of muscle training on dyspnea in patients with chronic obstructive pulmonary disease

A meta-analysis of randomized controlled trials

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Abstract

Background: Rehabilitation training is beneficial for patients with chronic obstructive pulmonary disease (COPD). This study was aimed at evaluating the efficacy of muscle training on dyspnea.

Methods: We used 5 common databases for conducting a meta-analysis included PubMed, the Cochrane Library, Science Direct, Web of Science and Clinical Trials.gov, and eligible randomized controlled trials (RCTs) were included. The main results of include studies were dyspnea of patients who had a clinical diagnosis of COPD measured using Borg score and Medical Research Council (MRC) or modified Medical Research Council (mMRC) scale as the criteria before and after intervention. The intervention measures included respiratory or expiratory muscles or upper limb (UL) or lower limb (LL) training. The mean differences (MD) with the 95% confidence interval (CI) were considered for summary statistics. We also assessed risk of bias using the Cochrane collaboration's tool, and the value of I^2 was applied to evaluate the heterogeneity of the trials.

Results: Fourteen RCTs with 18 interventions (n = 860 participants) were included. Muscle training significantly improved dyspnea during exercise and in the daily life of patients with COPD (MD, 95% CI: −0.58, −0.84 to −0.32, $P < .0001$ and −0.44, −0.65 to −0.24, $P < .0001$, respectively). In the subgroup analyses, the trials that used respiratory muscle and UL trainings significantly improved dyspnea during exercise (MD, 95% CI: −0.72, −1.13 to −0.31, $P = .0005$ and −0.53, −0.91 to −0.15, $P = .007$, respectively). The studies also showed that the participants in the rehabilitation group, who received respiratory muscle and UL trainings, had a significant improvement of dyspnea in daily life (MD, 95% CI: −0.38, −0.67 to −0.09, $P = .01$ and −0.51, −0.80 to −0.22, $P = .0007$, respectively).

Conclusion: There were some limitations that most of the subjects in this study were patients with moderate to severe COPD and were male, and the training period and duration were different. The analyses revealed that respiratory muscle and UL trainings can improve dyspnea in patients with COPD during exercise and in daily life.

Abbreviations: CI = confidence interval, COPD = chronic obstructive pulmonary disease, IMT = inspiratory muscle training, LL = lower limb, MD = mean difference, mMRC = modified Medical Research Council, MRC = Medical Research Council, PR = pulmonary rehabilitation, RCT = randomized controlled trial, UL = upper limb.

Keywords: chronic obstructive pulmonary disease, dyspnea, muscle training, rehabilitation

1. Introduction

Chronic obstructive pulmonary disease (COPD) increased from the 11th position in 2007 to the seventh position in 2017 (13.2%) in the list of the top causes of years of life lost among non-communicable diseases.[1] Many recent studies have focused on pulmonary rehabilitation (PR). The latest reports on PR published by the European Respiratory Society mentioned that exercise training during PR can reduce the burden of symptoms and improve cardiovascular function.[2] The discomfort associated with dyspnea has been shown to affect the quality of life and health status of patients.[3] Dyspnea has been shown to have a moderate to strong correlation with the impairment of health-related quality of life in patients with COPD, and the severity of dyspnea can affect rehabilitation outcomes.[4,5] As the intensity of exercise training is limited by dyspnea and abnormal ventilation, better training results could potentially be achieved if the intensity of dyspnea was reduced. Although the exercise capacity and quality of life of patients with COPD have greatly improved using the current rehabilitation techniques, still no breakthrough progress has occurred in improving breathing difficulties, and the mechanism of training to alleviate dyspnea has not been clearly defined.

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The datasets generated during and/or analyzed during the current study are publicly available.

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The aim of this study was to conduct a meta-analysis using the Borg scale and Medical Research Council (MRC) scores to assess the effects of different muscle trainings (respiratory muscle, upper limb (UL), and lower limb (LL) trainings) on dyspnea during exercise and in daily life in patients with COPD.

2. Methods

2.1. Literature search and retrieval

Current meta-analysis was based entirely on previous published studies which had declared ethical approvals and no original clinical raw data was collected or utilized, thereby ethical approval was not conducted for this study. The current meta-analysis of the published studies of dyspnea of patients in COPD before and after exercise rehabilitation was conducted following the principle of the PRISMA statement. However, there were no protocol or registration for the study.

The databases of PubMed, the Cochrane library, Science direct, Web of Science, and Clinical Trials.gov were searched to March 1st, 2019. And the last search date was November 28th, 2019. There were no limitations according to full-text language or publication date. The search strategy was as follows: ("exercise" OR "training") AND ("pulmonary disease" OR "chronic obstructive lung disease" OR "chronic obstructive pulmonary disease" OR "COPD"). More articles were obtained by manually searching the list of references included in the available studies, and by searching the cited references on the "Web of Science" database. The selection of the articles was conducted independently by 2 authors using the eligibility criteria, and differences were resolved through discussion.

2.2. Eligibility criteria

The inclusion criteria were as follows:

1. population: patients who had a clinical diagnosis of COPD;
2. intervention: endurance and strength training of respiratory or expiratory muscles or UL or LL training;
3. comparative interventions: non-exercise interventions such as health education and sham training;
4. duration: patients who underwent any training program for a minimum duration of 3 weeks;
5. result measurement: the main results were dyspnea measured using the Borg scale score and MRC or modified Medical Research Council (mMRC) scale score as the criteria before and after intervention; and
6. study design: randomized controlled trial (RCT).

The exclusion criteria were as follows:

1. abstracts, letters, editorials, expert opinions, reviews, and case reports;
2. studies without sufficient data or that did not meet the inclusion criteria;
3. unclear training methods used in the study; and
4. patients who had an acute exacerbation before intervention.

2.3. Data selection and extraction

We extracted the following items from the included studies and itemized in a predesigned table: the first author, year of publication, COPD stage, research design, intervention measures (including the intervention mode, intensity and duration of the intervention), sample size (intervention/control), patients' characteristics, results summary. The extraction of data was accomplished by 2 investigators who reviewed the full texts independently. A third investigator checked all of the data, and resolved disagreements. For studies that met the inclusion criteria, full papers were obtained for further analysis.

2.4. Quality assessment

The internal effectiveness of the study was assessed using the Cochrane collaboration's tool for assessing risk of bias. Freedom from bias was evaluated for each study in accordance with the basis of methodological domains as follows: adequacy of random-sequence generation and allocation concealment, attrition bias, reporting bias, and other biases. Two authors reviewed all the studies and assigned a "high," "low," or "unclear" quality grade to each study. For the purpose of assessing the reliability of the grade, the quality grades of the selected articles were independently assessed by 2 investigators and divergences were resolved by a third investigator.

2.5. Statistical analyses

The results of the studies selected by the above-mentioned processes were separated, and the meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[6] We used the Revman version 5.3 software (the Cochrane Collaboration, Oxford, United Kingdom) for all the data and statistical analyses. Data were expressed as mean with standard deviation. The mean differences (MD) with the 95% CI were considered for summary statistics. The heterogeneity of each comparison was assessed using I^2 statistics.[7,8] In the case of heterogeneity ($I^2 \geq 50\%$), the random-effect model was used; otherwise, the fixed-effect model was used. For all the comparisons, a P value $<.05$ was considered statistically significant. A subgroup analysis using MD with 95% CI was also performed in this study to identify which subgroup was more effective for patients with COPD who had dyspnea.

3. Results

3.1. Bibliographic search

Figure 1 shows the study search process. A total of 1377 potential related studies were identified. After eliminating duplicated and inadequate studies on the basis of titles and abstracts, 14 RCTs met the criteria for inclusion in the meta-analysis.[9–22] Four studies included multiple independent interventions (with 2 different intervention groups, which were all compared with the same control group). Two of the 4 studies were divided into upper limb endurance and strength training groups, 1 study was divided into inspiratory muscle and cycle ergometry training groups, and 1 study was divided into upper and LL training groups. In total, 18 interventions were included in this meta-analysis.

3.2. Characteristics of the included studies

The main characteristics are shown in Table 1. Of the 860 participants, 448 were in the training group and 412 were in the control group. The largest sample size was 149 participants,[20]

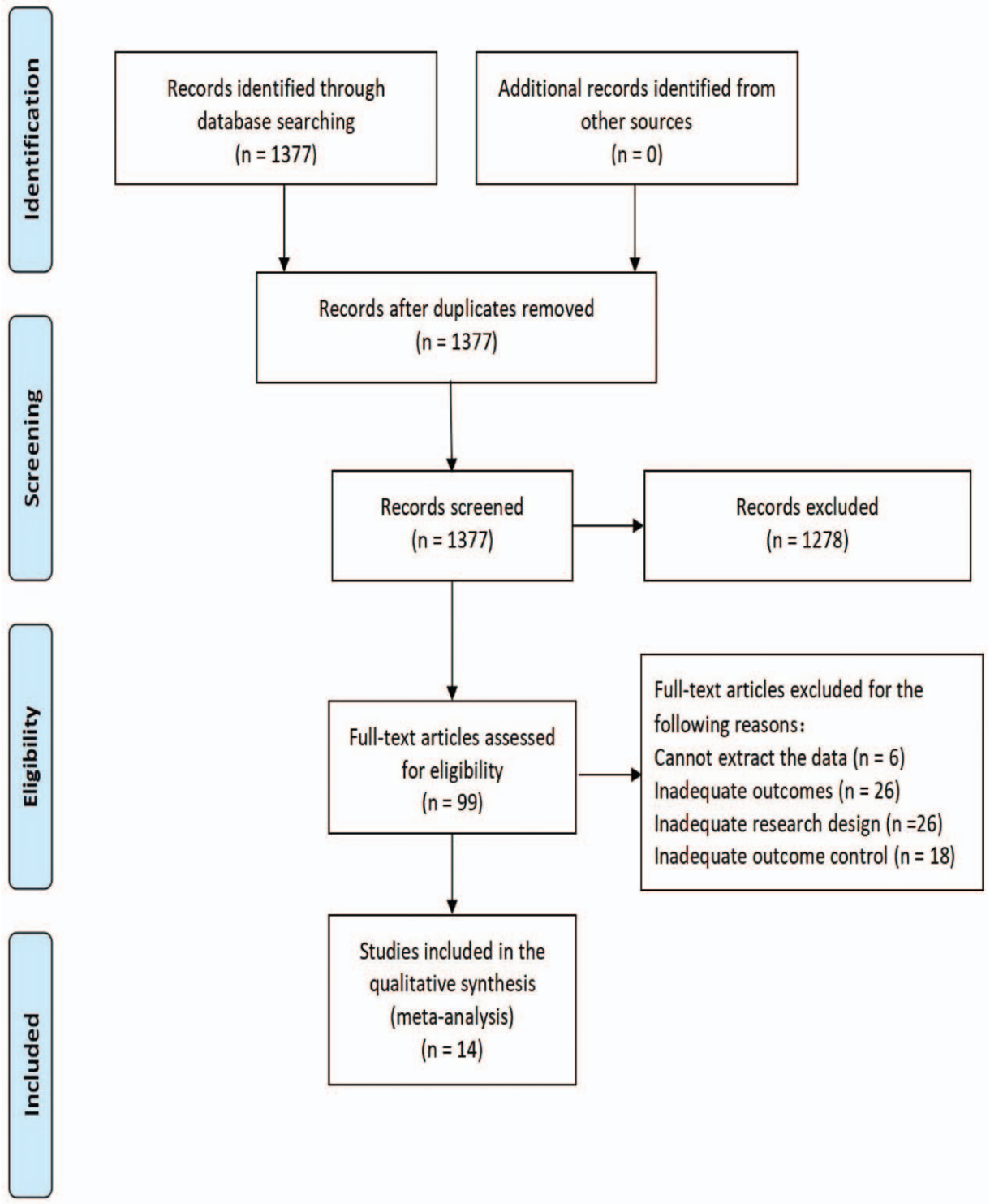

Figure 1. Flow diagram of the study selection process.

and the smallest sample was 14 participants.[14] In these studies, patients underwent training for at least 3 weeks and at most 6 months, mostly between 4 and 8 weeks. Among 18 eligible studies, 17 used the Borg scale[9–17] and 5 used the MRC or mMRC scale[10,15–18] to estimate dyspnea. Among the studies that used the Borg scale, 7 were respiratory muscle training studies,[10–13,19–21] 8 were UL training studies,[9,14–17] and 2 were LL studies.[10,14] The studies that used the MRC or mMRC scale included 3 respiratory muscle training studies[19–21] and 2 UL training studies.[10,22]

Table 1

Characteristics of the include studies.

	Author, year	N, male (I/C)	Age (years) (mean, I/C)	Patients grade, staging	Intervention group (modalities: duration, frequency, intensity)	Control group	Measurement scale	Study design
1	Ries, 1988 [9]	8/11, Unreported gender	NR	Severe	UL endurance training: 6w, 2 times/d, 7d/w	Walking training	Borg	RCT
2	Ries, 1988 [9]	9/11, Unreported gender	NR	Severe	UL strength training: 6w, every other day for 1 week and then once daily	Walking training	Borg	RCT
3	Janet, 1999 [10]	13/12, Unreported gender	66.0/ 62.0	FEV1: < 65%, FEV1/FVC < 70%, Moderate to severe	IMT: 4 months, 5d/w, 30min/d, 60% of PImax	Health education	Borg	RCT
4	Janet, 1999 [10]	14/12, Unreported gender	66.0/ 62.0	FEV1: < 65%, FEV1/FVC < 70%, Moderate to severe	CET: leg training 4 months, 5d/w, 20min/d	Health education	Borg	RCT
5	Riera, 2001 [11]	10/10, 9/9	67.0/ 67.6	NR	IMT: 6 months, 6 d/w, 15 min/d, 60–70% of PImax	No-load IMT	Borg	RCT
6	K. Hill, 2006 [12]	16/17, 11/11	69.4/ 66.6	FEV1: 15–70%	H- IMT: 8 w, 3 times/w, 21 min at a time -103 cm H_2O	Sham IMT	,Borg	RCT
7	Koppers, 2006 [13]	18/18, 8/9	54.4/57.0	GOLD II, III	RMET: 5 w, 7 d/w, 15min/d, twice daily	Sham RMET	Borg	RCT
8	Marrara, 2008 [14]	8/6, 8/6	65.0/68	GOLD II	ULTG: 6w, 3 times/w, 1.5 hours at a time, 10 RM	Bronchial hygiene therapy	Borg	RCT
9	Marrara, 2008 [14]	8/6, 8/6	73.0/68.0	GOLD II	LLTG: 6w, 3 times/w, 1 hour at a time, treadmill exercise	Bronchial hygiene therapy	Borg	RCT
10	Costi, 2009 [15]	25/25, 18/15	68.6/70.4	GOLD II, III, IV	Unsupported UEET + PR: 3w, 15 sessions of resistance exercise to 5 different muscular groups	PR	Borg, MRC	RCT
11	Janaudis, 2011 [16]	17/19, 12/9	67.0/67.0	Stable COPD, FEV1 < 80%	ATP: 6 w, 3 times a week	Sham training	Borg	RCT
12	Mckeough, 2012 [17]	9/9, 4/4	66.0/65	GOLD I, II, III, IV	UL strength training + standard leg endurance and strength training: 8 w, 3 times a week	Standard leg endurance and strength training	Borg	RCT
13	Mckeough, 2012 [17]	11/9, 9/4	65.0/65.0	GOLD I, II, III, IV	Arm endurance training + standard leg endurance and strength training: 8 w, 3 times a week, arm cranking and unsupported arm exercise	Standard leg endurance and strength training	Borg	RCT
14	Calik, 2017 [18]	21/21, 16/11	58.4/59.7	GOLD II, III	Arm strength training + breathing exercise: 8 w, 3 d/w, 3 times/d, free weights at 40% to 50% of 1RM	Breathing exercise	Borg	RCT
15	Kaminsky, 2017 [19]	21/22, 7/10	68.0/68.0	GOLD II, III, IV	Breathing + education and usual care: 12 w, every day, 30 min per day	Education and usual care	Borg, mMRC	RCT
16	Beaumont 2018[20]	74/75, 44/50	62.2/65.9	FEV1 < 50%, GOLD III, IV	IMT: 4 w, 5 d/w, 2 sessions of 15 min per day, the cycle of 10 inspirations was repeated 15 times, 50% of PImax, 60% of PImax after 10 days	Treadmill, educational program	Borg, mMRC	RCT
17	Langer, 2018 [21]	10/10, 4/3	73.0/67.0	PImax < 70cmH_2O, stable	IMT: 8 w, 7 d/w, 2 to 3 daily sessions of 30 breaths, 4 to 5 min per session, 40 to 50% PImax	Sham IMT	Borg, MRC	RCT
18	Silva, 2018 [22]	26/25, 10/11	68.1/67.0	GOLD I, II, III, IV	Upper limb resistance exercise + the same physical exercise as the control group: 8 w, 3 sessions per week, 30 to 60 min per session	Warm-up, aerobic exercise, IMT, session stretching, msa asge therapy	mMRC	RCT

10RM = 10-repetition maximum test, ADL = activities of daily life, ATP = arm training program, CET = cycle ergometry training, EMT = expiratory muscle training, GOLD = global initiative for chronic obstructive lung disease criteria, H-IMT = high-intensity inspiratory muscle training, I/C = intervention/control, IMT = inspiratory muscle training, LLTG = lower limb training group, mMRC = modified Medical Research Council dyspnea scale, MRC = the Medical Research Council, NR = not reported, PR = pulmonary rehabilitation, PRP = pulmonary rehabilitation programme, RMET = respiratory muscle endurance training, UEET = the upper extremity exercise training, UL = upper limb, ULTG = upper limb training group.

3.3. Methodological quality assessment

Figure 2 presents the risk of bias analysis results. The methodological quality scores of the eligible studies ranged from 4 to 8, as shown in Table 2. All the studies were RCTs and performed with similar baselines, between-group comparisons, point measures, and measures of variability description.

3.4. Dyspnea during exercise

Seventeen articles compared the difference of dyspnea between the exercise and control groups before and after the intervention exercise. The Borg scale was used to evaluate dyspnea at the end of the 6-minute walk test, at the end of the incremental or constant load test or during the inspiratory muscle training (IMT) sessions. As shown in Figure 3, a significant result was obtained with the pooled MD of −0.58 (95% CI, −0.84 to −0.32) when comparing the effects of the different training methods and non-training on dyspnea in patients with COPD (using the change in Borg score, $P < .0001$).

We further performed subgroup analyses to investigate the impact of the different muscle training groups on dyspnea during exercise. The subgroup analysis revealed that respiratory muscle and UL trainings can improve dyspnea in patients with COPD (MD, 95% CI: −0.72, −1.13 to −0.31, $P = .0005$ and −0.53, −0.91 to −0.15, $P = .007$, respectively). A fixed-effect model was used in the pooled analysis, and no significant heterogeneity was found between the studies ($P = .66$, $I^2 = 0\%$).

3.5. Dyspnea in activities of daily living

In 5 studies, MRC or mMRC was used to measure dyspnea in activities of daily living in the intervention and control groups (Fig. 4). Muscle training significantly improved dyspnea in daily life (MD, −0.44; 95% CI, −0.65 to −0.24, $P < .0001$).

The subgroup analysis also revealed that respiratory muscle and UL training can improve dyspnea (MD, 95% CI: −0.38, −0.67 to −0.09, $P = .01$ and −0.51, −0.80 to −0.22, $P = .0007$, respectively). A fixed-effect model showed that the heterogeneity test was not significant ($P = .16$, $I^2 = 39\%$).

4. Discussion and conclusion

The pooled analysis of data from the 18 RCTs had several meaningful findings indicating that muscle training had beneficial effects in COPD patients. The main findings of the meta-analysis were that respiratory muscle and UL training can improve the dyspnea induced by exercise and activities of daily living in COPD patients; meanwhile, LL training does not significantly improve dyspnea.

In the meta-analysis, dyspnea was divided into 2 different groups, dyspnea during exercise and dyspnea during daily life, to study the effect of exercise training. Dyspnea during exercise testing was measured at high workloads under controlled conditions. By contrast, dyspnea during activities of daily living was measured at much lower workloads. For example, the exercise test induced dyspnea during bicycle exercise or 6-minute walk, and the degree of dyspnea was measured.[23] However, patients with severe COPD cannot withstand any form of exercise testing. At this point, the patient's daily activities must be used as reference to induce stimulation and measure the degree of dyspnea.[24] Different dyspnea scales have different areas of application; for example, the MRC scale is suitable for measuring the degree of dyspnea in daily life; meanwhile, the Borg and visual analog scales are used to measure dyspnea during exercise.[25,26] The lack of critical comparisons between those different tools has been a widespread problem. Owing to the complexity of the dyspnea scale to maintain the reliability of the research results, we only selected a single scale to evaluate the effect of training on dyspnea during exercise or daily life. By using the Borg scale and MRC or mMRC scales, this study demonstrated that respiratory

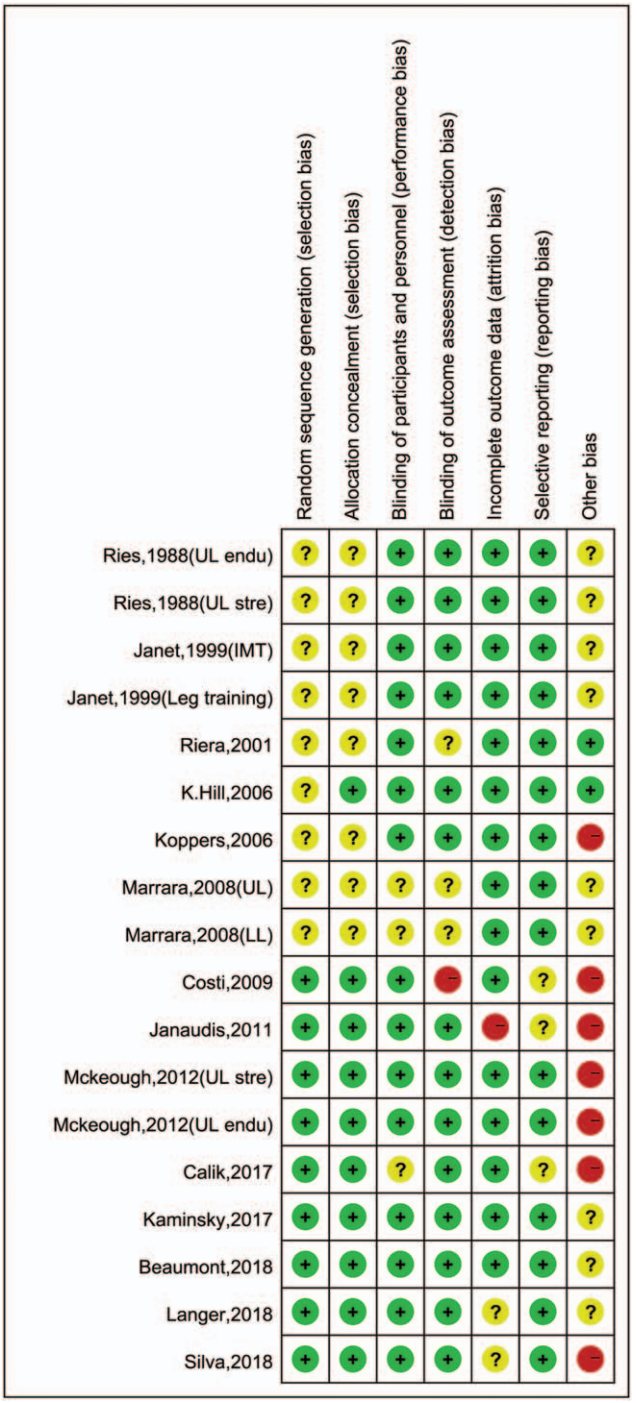

Figure 2. Assessment of risk of bias.

Table 2

Study quality assessment for eligible randomized controlled trails.

Author	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Score
Ries et al [9]	1	0	1	1	0	0	1	1	1	6
Janet et al [10]	1	0	1	1	0	0	1	1	1	6
Riera et al [11]	1	0	1	0	1	0	1	1	1	6
K. Hill et al [12]	1	1	1	1	1	0	1	1	1	8
Koppers et al [13]	1	0	1	1	1	0	1	1	1	7
Marrara et al[14]	1	0	1	0	0	0	1	1	0	4
Costi et al[15]	1	1	1	0	1	0	1	1	0	6
Janaudis et al[16]	1	1	1	1	1	0	1	1	1	8
Mckeough et al [17]	1	1	1	1	0	0	1	1	0	6
Calik et al[18]	1	1	1	1	1	0	1	1	0	7
Kaminsky et al[19]	1	1	1	1	1	0	1	1	0	7
Beaumont et al[20]	1	1	1	1	1	0	1	1	1	8
Langer et al[21]	1	1	1	1	0	0	1	1	1	7
Silva et al[22]	1	1	1	1	1	0	1	1	0	7

Item 1 = randomization; Item 2 = concealed allocation, Item 3 = similar baseline, Item 4 = blinding of assessors, Item 5 = more than 85% retention; Item 6 = missing data management (intention-to-treat analysis), Item 7 = between-group comparison, Item 8 = point measure and measures of variability, Item 9 = isolate exercise intervention, 1 = explicitly described and present in details, 0 = absent, inadequately described, or unclear.

muscle and UL training can improve dyspnea in patients with COPD during exercise and in daily life.

IMT has been used for a long time, and its benefits to quality of life, dyspnea, and exercise capacity were demonstrated.[27,28] We found that IMT can reduce the severity of dyspnea in patients with COPD by increasing inspiratory muscle strength and endurance, and these results are consistent with those of other studies.[29,30] However, the other benefits of IMT for dyspnea in patients with inspiratory muscle weakness (maximal inspiratory pressure $\leq$ 60 cm H_2O) were not verified.[31]

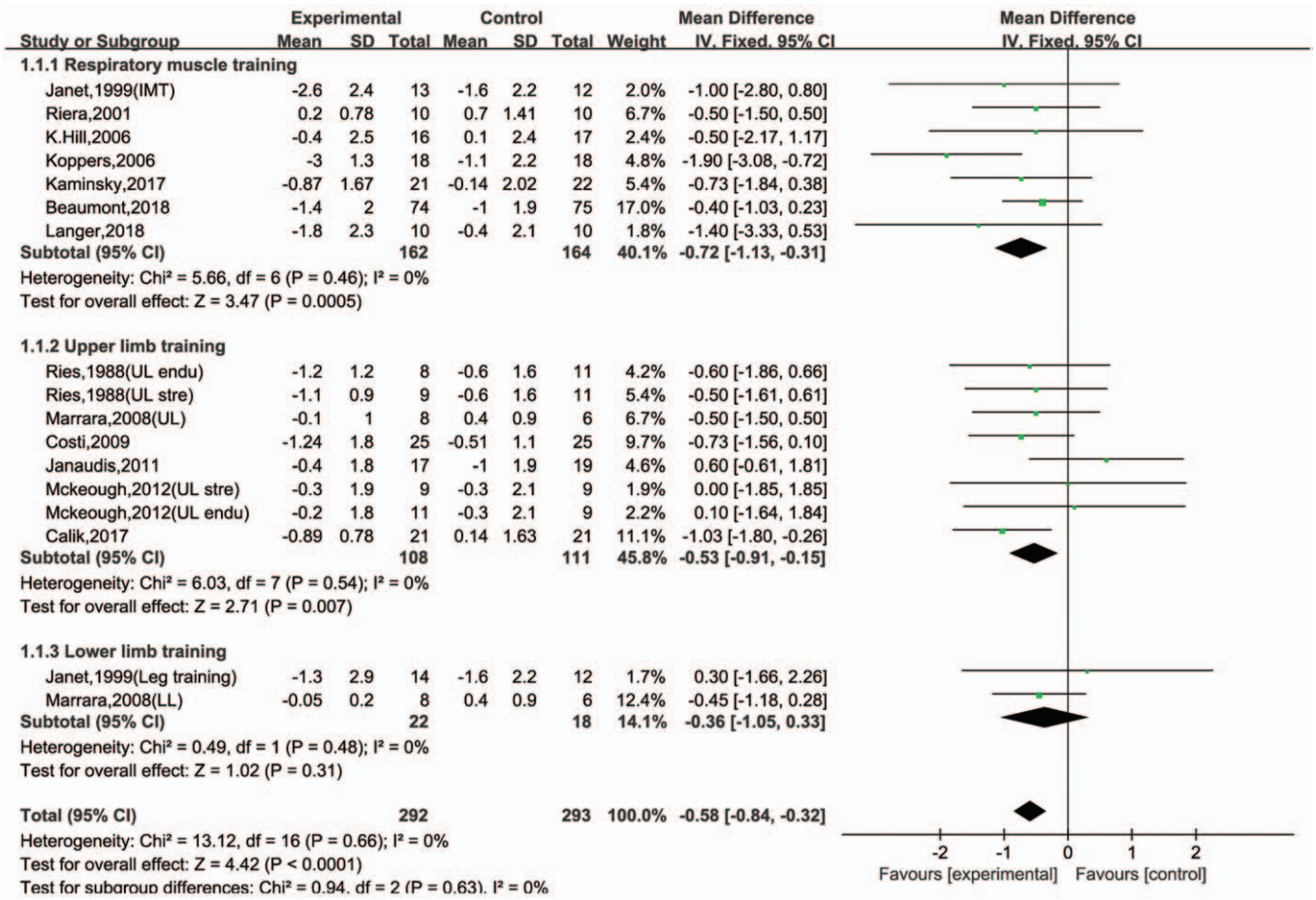

Figure 3. Effect of training on dyspnea during exercise (Borg scale).

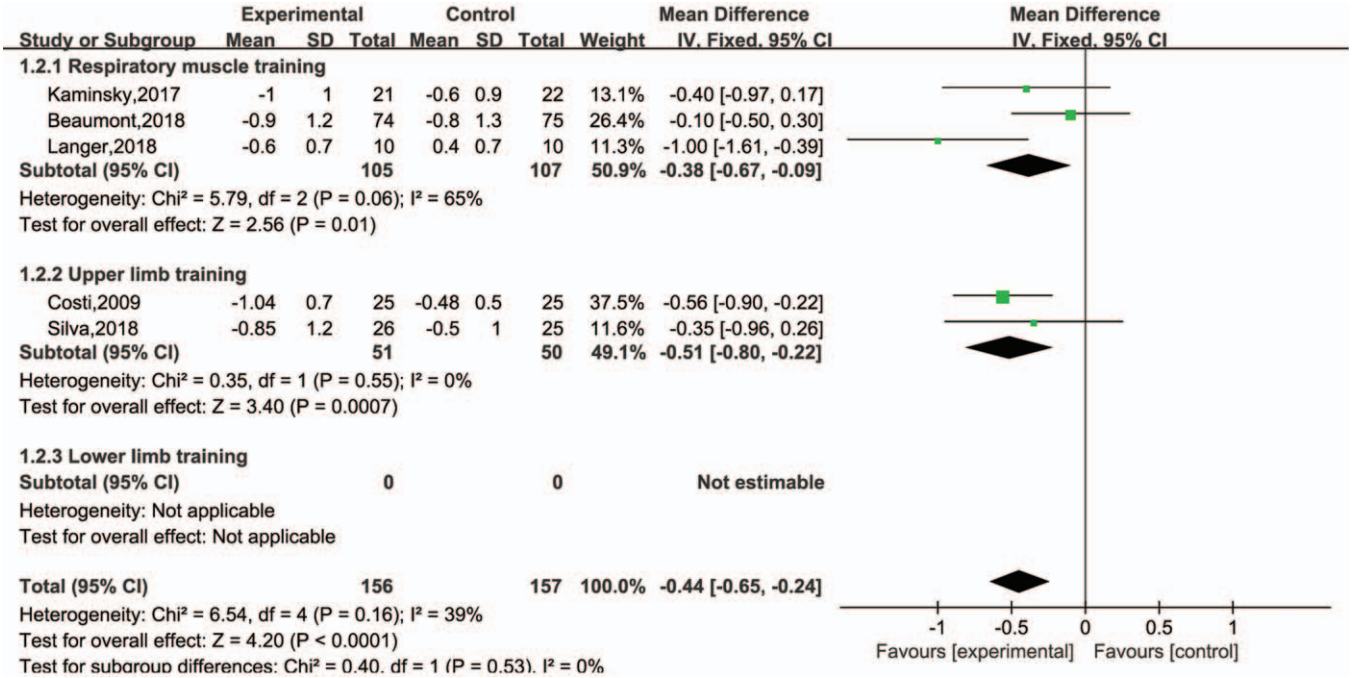

Figure 4. Effect of training on dyspnea in daily life (Medical Research Council or modified MRC).

UL activities during activities of daily living often exacerbate dyspnea much sooner than LL activities. To avoid dyspnea, individuals with COPD have to limit their UL activities.[32] Studies have shown that activities using the UL were performed at a lower intensity in patients with COPD as compared with healthy subjects.[33] As individuals with COPD perform less UL activities, their poor UL muscle adaptation can exacerbate dyspnea and fatigue.[34] Therefore, UL training has been recommended as an essential component of the PR program. Our results are consistent with those of another meta-analysis study that found that UL endurance and strength training could significantly improve dyspnea in individuals with COPD.[35] Some authors attributed relief of breathlessness to a corresponding decrease in ventilatory demand during exercise due to enhanced mechanical efficiency.[36,37]

The total daily activities in patients with COPD are largely related to leg activity, which were reduced when compared with those in controls of similar age.[38] A study showed that LL endurance training twice a week for 1 month improved dyspnea and pulmonary function test results safely and effectively in patients with COPD.[39] However, a meta-analysis confirmed that a combination of resistance and endurance trainings increases leg muscle strength, health-related quality of life, walking distance, and exercise capacity in patients with COPD, but none of the included studies investigated their combined effect on the level of dyspnea.[40] The results of LL training mainly showed its influence on muscle strength and endurance, and most studies have not reported on the effects of the training on dyspnea. Owing to the lack of research on LL training, we failed to understand its impact on dyspnea.

We found some limitations in our research. First, most of the subjects in this study were patients with moderate to severe COPD and were male. We failed to grade the severity of COPD and to clarify whether muscle training can improve dyspnea in female patients. Second, our study was also limited because of the many different dyspnea scales available. As mentioned earlier, different dyspnea scales have different areas of application.[25,28] A strict comparison between the different tools was lacking, and few studies have been conducted using the same scale (owing to the fact that numerous dyspnea scales exist), making it more difficult to evaluate the results of dyspnea. Third, in some research studies, the training lasted up to 6 months, whereas in some, it only lasted 3 weeks. The training period and duration will also affect the impact of the training on dyspnea. Thus, the implementation of these training methods in the different patient populations was quite different, and the smaller sample sizes may have led to bias.

The main strength of this study is that it analyzed the effectiveness of different types of muscle training programs on dyspnea (in different states of activity). Comparing the effects of various types of programs can provide useful information for the development and implementation of programs according to the needs of patients and type of institution. The search strategy used in this meta-analysis was comprehensive, broad, and systematic. Given that many of the studies had a small sample size, further studies with sufficiently larger sample sizes should be conducted to prove the efficacy of the different training programs on dyspnea, so as to provide clinically meaningful results.

The analysis indicated that respiratory muscle and UL trainings can improve dyspnea in patients with COPD during exercise and in daily life. However, considering the limitations of our study, the benefits of training in patients with COPD in large-scale, well-designed, multicenter RCTs must still be evaluated.

Author contributions

Conceptualization: Fang Zhang, Wei Wang.
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Formal analysis: Fang Zhang, Yaping Zhong.
Investigation: Yaping Zhong, Zheng Qin.
Methodology: Fang Zhang, Zheng Qin, Xiao-Meng Li.
Project administration: Fang Zhang, Wei Wang.
Software: Fang Zhang, Yaping Zhong.
Supervision: Fang Zhang.
Writing – original draft: Fang Zhang, Yaping Zhong.
Writing – review & editing: Fang Zhang, Wei Wang.

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