Original Article

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Effects of Different Modes of Upper Limb Training in Individuals With Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis

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Objective To determine effects of different modes of upper limb training on dyspnea and quality of life of individuals with chronic obstructive pulmonary disease (COPD) having different disease severity.

Methods Randomized clinical trials were retrieved from five electronic databases. Risk of bias and quality of evidence were assessed using the Cochrane Collaboration's tool and the GRADE approach, respectively. Effects of upper limb training compared to control were identified using standardized mean difference and 95% confidence interval.

Results Fifteen studies with 514 subjects were included. When compared to control, upper limb endurance and strength training with moderate quality of evidence resulted in significant improvement in dyspnea. However, quality of life was not significantly different between upper limb training of all modes of and the control. The upper limb training was more effective in reducing dyspnea in patients with severe COPD than in those with mild to moderate levels of COPD. Although quality of life was slightly improved by upper limb training for those with moderate or severe level of COPD, such improvement did not reach a significant level when compared to the control.

Conclusion Upper limb endurance and strength training could significantly improve dyspnea in individuals with chronic obstructive pulmonary disease. Thus, incorporating the upper limb training into pulmonary rehabilitation is recommended to reduce dyspnea, especially for those with severe patients. Further studies with larger sample size and standardized training protocol are needed to confirm these finding (Registration No. CRD42018102805).

Keywords Chronic obstructive pulmonary disease, Dyspnea, Meta-analysis, Quality of life, Upper limb training

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INTRODUCTION

Individuals with chronic obstructive pulmonary disease (COPD) experience a whole host of symptoms and activity limitations, including dyspnea, fatigue, exercise intolerance, and poor quality of life (QoL) [1,2]. Upper limb (UL) activities during activities of daily living (ADLs) often exacerbate dyspnea much sooner than lower limb (LL) activities [3]. To avoid dyspnea, individuals with COPD have to limit their UL activities [3]. Over time, overall reduction in UL activity can lead to UL muscle fatigue and exercise intolerance [4,5]. As individuals with COPD perform less UL activities, their poor UL muscle adaption can exacerbate dyspnea and fatigue [4]. The vicious cycle of activity limitation, muscle maladaptation, and dyspnea eventually results in poor QoL of individuals with COPD [4,6].

Although UL training has been recommended as an essential component of a pulmonary rehabilitation program, the effect of each mode of UL training on clinical outcomes relevant to individuals with COPD remains inconclusive [7-12]. UL endurance training (ULE) has been recommended to improve UL activity tolerance and endurance [7]. UL strength training (ULS) can increase UL muscle force in individuals with poor UL strength [8] and function [9]. Previously, four systematic reviews have summarized effects of UL training in individuals with COPD, highlighting controversies about beneficial effects of UL training on dyspnea, UL fatigue, UL function, UL exercise capacity, and QoL [10-13]. These conflicting results could not provide clinicians with a clear guideline for clinical decision-making. Moreover, only one review [13] has primarily identified the effect of different modes of UL training in individuals with COPD. McKeough et al. [13] have found that ULE can only lead to significantly greater improvement in UL endurance capacity than the control group. However, both ULE and ULS failed to show significantly greater improvement in dyspnea and QoL than the control. These non-significant results may be attributable to insufficient number of studies and sample size included in their meta-analysis [13]. Additionally, the quality of evidence was not systematically graded when the mode of exercise was analyzed separately. As a result, the level of confidence on the effect of UL training might have been overestimated. Therefore, further investigation related to the effect of different modes of UL training is warranted.

After the previous systematic review was published, several new studies related to UL training in individuals with COPD have been published. These additional studies provide us with a unique opportunity to update and strengthen the current evidence on the effect of different modes of UL training in individuals with COPD. Thus, the primary purpose of this study was to determine effects of different modes of UL training on dyspnea and QoL as primary outcomes in individuals with COPD. Secondary outcomes including UL fatigue, UL function, and UL exercise tolerance also have a significant impact on ADLs and prognosis of individuals with COPD [4,14]. Thus, effects of different modes of UL training on ULE, ULS, and combined endurance and strength training (ULC) were also analyzed. The second purpose of this study was to determine effects of UL training on patients with different disease severiteis by subroup analysis according to forced expiratory volume in one second (FEV_1) value. The quality of evidence specific to each mode and UL training (ULA) was systematically rated using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach to provide the most transparent results and their clinical utility.

MATERIALS AND METHODS

The methodology for this review was based on the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement [15]. This study was registered with the International Prospective Register of Systematic Reviews (PROSPERO; Registration No. CRD42018102805).

Eligibility criteria

Eligibility criteria of studies to be included in this research were as follows: (1) population, individuals with stable COPD of any age, disease severity, and being treated in any clinical settings; (2) study design, randomized controlled or clinical trials (RCTs) investigating effects of UL training compared to control conditions of no training, LL training, or other types of exercise; (3) outcomes, primary outcomes of interest were dyspnea and QOL using subjective scores (e.g., modified Borg Scale, total scores of QoL questionnaires) and secondary outcomes were UL fatigue, UL function, and UL exercise tolerance

using either subjective or objective scores (e.g., rating of perceived exertion scale, a total amount of time spent on UL activities); (4) intervention, ULE, ULS, and ULC were primary interventions. They were performed two to three times a week for a minimum of 16 sessions [9]. The classification of modes of UL training was based on exercise characteristics as clearly described by McKeough et al. [13]. ULE was defined as exercise aimed to improve aerobic capacity. ULE was further subdivided according to whether arms were supported (i.e., arm cycle ergometry) or unsupported (i.e., lifting free weights or weighted dowel). ULS was defined as an exercise modality that involved the application of external resistance to improve muscle strength such as exercise using weight machines and dumbbells. ULC was defined as a combination of ULE and ULS.

Studies were excluded if they included individuals with other respiratory diseases, if they were published in any language other than English, or if their publications were available in other forms such as books and conference proceedings.

Search strategy

Literature search was performed electronically through MEDLINE, ScienceDirect, Scopus, CINAHL, and Cochrane Library from the inception to December 11, 2018. Search terms and strategies used for all databases were as follows: ['COPD' or 'chronic obstructive pulmonary disease' or 'chronic obstructive airway disease' or 'chronic obstructive lung disease'] and ['upper limb' or 'upper extremity' or 'shoulder' or 'arm'] and ['exercise' or 'training' or 'movement' or 'pulmonary rehabilitation'].

Study selection

Two investigators (CK and NU) independently applied the eligibility criteria to assess titles and abstracts and identify full texts of studies to be included. A third investigator (AT) was consulted to resolve discrepancy observed between the two investigators.

Data collection process

Two investigators (CK and NU) independently extracted aggregated data from each study using a data extraction form based on the Cochrane guidelines. Data obtained by the two authors were reviewed for completeness and compared for consistency. Any inconsistency in the data was discussed and resolved through consultation with a third investigator (AT). Data were extracted from all included studies without requesting for more information from the original studies.

Risk of bias assessment

The Cochrane Collaboration's tool [16] was used to assess the risk of bias of included studies. Seven risks of bias (random sequence generation, allocation concealment, selective reporting, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and other bias) were assessed. One of three rating categories (low, high, or unclear risk of bias) was assigned to each criterion. A study having four or more high or unclear risk was categorized as high risk of bias. Otherwise, it was classified as low risk of bias. Results of risk of bias assessment by the two investigators (CK and NU) were compared for consistency and a third investigator (AT) was consulted to resolve any discrepancy.

Quality of evidence assessment

The GRADE approach was used to evaluate quality of evidence and provide recommendation strength of each outcome [17]. Quality of the evidence was categorized into high, moderate, low, and very low levels of quality. Initially, all outcomes were considered high-quality evidence. They were downgraded based on the accumulation of the following: (1) limitations of study design (>25% of subjects from studies with high risk of bias); (2) heterogeneity among studies ($I^2 \geq 50\%$ or only one study was available); (3) indirectness (the existence of indirectness of participants, interventions, outcome measures, or comparison of the study); (4) imprecision of treatment effects (<400 subjects); and (5) publication bias across studies (presence of an asymmetry funnel plot) [17,18].

Data analysis

Data analyses were performed using Review Manager (RevMan 5.3). For primary objective, data analyses were performed based on the mode of UL training. For secondary objective, data subgroup analyses were carried out according to patient severity. In this study, included studies were divided by patient severity according to GOLD classification of the severity of COPD by using the percentage of predicted FEV_1 or FEV_1 in liters [19]. Ef-

fects of the intervention compared to the control were assessed using standardized mean difference (SMD) and 95% confidence interval (CI). Based on Cohen's classification of effect size (Cohen's d), SMD of 0.2, 0.5, and 0.8 represented small, medium, and large effect sizes, respectively [20]. Heterogeneity across studies was evaluated by using I^2 statistics [21]. A fixed- or random-effect model of meta-analysis was used when the heterogeneity was low (I^2<50%) or high (I^2≥50%), respectively [21].

RESULTS

Study selection and characteristics

The initial search identified a total of 1,422 articles. After screening for duplications, titles, and abstracts, 1,201 articles were eliminated. Of 221 remaining articles, 15 RCTs met the criteria and were included in the meta-analysis (Fig. 1). Characteristics and results of each RCT are summarized in Table 1.

The total number of subjects included in this study was 514. Twelve studies reported no between-group differences in subject characteristics [22-33]. One study reported significantly lower mean body weight in the UL training group than that in the control group [34]. Two studies did not report statistical differences in subject characteristics. Their data appeared to be within the same range between groups [35,36].

According to the GOLD classification of the severity of COPD, included studies were divided as follows: (1) nine studies had individuals with severe COPD [22-29,34], (2) four studies had individuals with moderate COPD [30-33], and (3) two studies [35,36] did not describe the percentage of the predicted FEV_1 (Table 1).

Characteristics of interventions

Eight of 15 included studies investigated the effect of ULE [22-25,28,30,34,35].The predominant unsupported exercises consisted of modified proprioceptive neuromuscular facilitation (PNF) [22,24], weight dowel lifts [25,34], and exercise with arm above the head at low resistance high repetition (e.g., throwing a ball and passing a beanbag) [23,28,35]. The supported ULE training utilized arm cycle ergometry [23,30]. For ULS training, free-weight [22,26,27,29,32,33,36] and weight machines [30,31] were used to target the major UL muscles involved in respiration and UL functions. Only one study that investigated the effect of ULC training included UL crank ergometry, unsupported UL training, and weight training

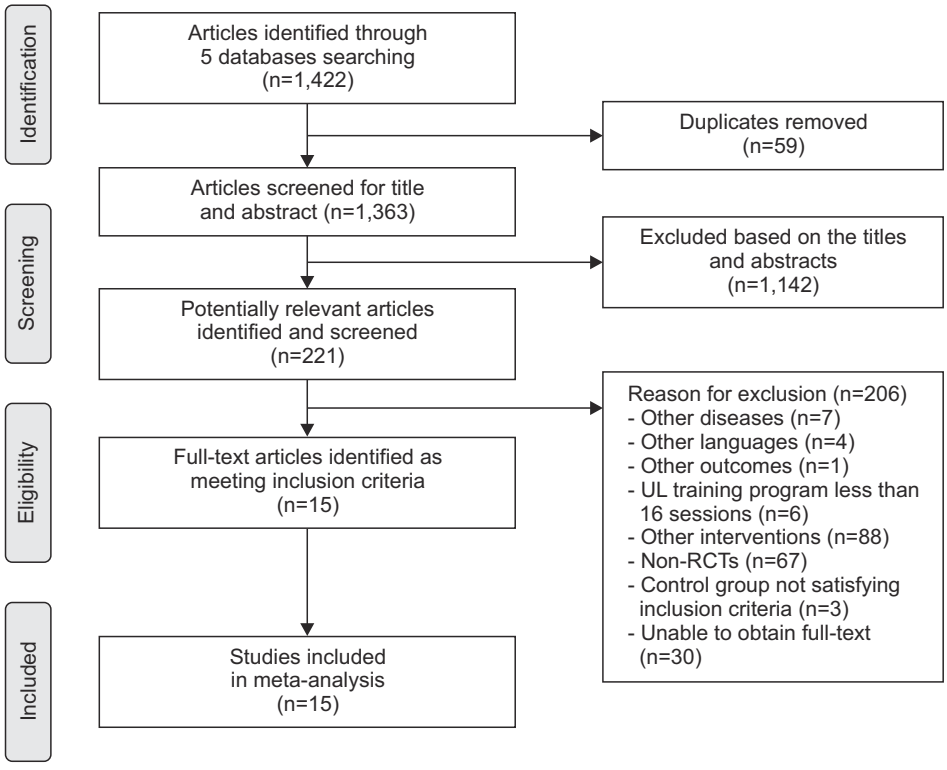

Fig. 1. Search strategy and flow diagram of article screening process.

Table 1. Characteristics of studies included in the meta-analysis

Study	No. of participants (male/female)	Participants	Severity	Intervention group	Control group	Exercise intensity	Exercise time and duration	Frequency (day/wk)	Exercise sessions	Outcomes measurement (tool)	Results
Ries et al., [22], 1988	28 (NA)	Age (yr): NA FEV_1 (% pred): 36±14.47	Severe	I1: Gravity resistance training I2: Modified PNF training	C: Walking training	I1: Five low-resistance and high-repetition exercises (level able achieve1 set of all exercises) and the load was increased by number of arm motions, number of sets, and hand weight I2: Three sets of 4 to 10 reps of each exercise/set (1–5 lb)	>15 min 6 wk	Every other day for 1 week and then once daily	38-39	UL exercise tolerance (unsupported UL exercise capacity test) Perceived breathlessness rating (modified Borg scale) Perceived exertion rating (modified Borg scale) UL function (ADL simulation test)	I1 vs I2=+ I1, I2 vs C=+ I1 vs I2=0 I1, I2 vs C=0 I1 vs I2=0 I1, I2 vs C=0 I1 vs I2=+ I1, I2 vs C=+
Lake et al., [23], 1990	26 (22/4)	Age (yr): 66.45±5.43 FEV_1 (% pred): 32(NA)	Severe	I: Arm cycle ergometry and unsupported UL training (throwing ball against wall, passing a bean bag, pulling on ropes and pulleys, and moving a ring)	C: No treatment	I: NA	40 min 8 wk	3	24	UL exercise tolerance (arm ergometer test) Dyspnea (NA)	I vs C=+ I vs C=+
Bauldoff et al. [24], 1996	20 (9/11)	Age (yr): 62±13.50 FEV_1 (% pred): 32±17.02	Severe	I: UL training modified from PNF program	C: Contacted weekly by telephone to equalize attention from health care providers	I: One to 3 set of 6 reps at 6RM and the weight increment increases from no weight to a total of 4 lb	NA 8 wk	5	40	UL exercise tolerance (6-PBRT) Perceptions of breathlessness (BFS) Perceptions of fatigue (BFS)	I vs C=0 I vs C=0 I vs C=+
Epstein et al. [34], 1997	23 (21/2)	Age (yr): 65±2 FEV_1 (L): 0.86±0.10	Severe	I: Unsupported UL training by weight dowel lifts	C: low intensity resistive breathing by using a threshold resistor device	I: 750 g dowel lifts and the weight was increased by 250 g every 3 sessions	30 min 7-8 wk	3	21-24	UL exercise tolerance (UAEX)	I vs C=+

Table 1. Continued 1

Study	No. of participants (male/female)	Participants	Severity	Intervention group	Control group	Exercise intensity	Exercise time and duration	Frequency (day/wk)	Exercise sessions	Outcomes measurement (tool)	Results
Holland et al. [25], 2004	38 (24/14)	Age (yr): 68±7.70 FEV_1 (% pred): 37±10.28	Severe	I: Incremental unsupported UL endurance training by weight dowel lifts	C: Sham training of a pegboard finger dexterity and LL endurance training	I: 500 g stick and the weight was increased by 0.5 kg increments to maintain RPE at 12-14 and dyspnea scores 3	>15 min 6 wk	7	42	UL exercise tolerance (UULEX) Dyspnea (modified Borg scale) UL Fatigue (RPE) QoL (CRQ)	I vs C=+ I vs C=0 I vs C=0 I vs C=0
Marrara et al. [26], 2008	14 (14/0)	Age (yr): 66.50±10.05 FEV_1 (% pred): 43.50±11.54	Severe	I: Six UL training by progressive training (elbow flexion-extension, shoulder abduction, horizontal shoulder adduction, primitive diagonal, functional diagonal)	C: Bronchial hygiene therapy along with diaphragmatic pattern breathing orientations and stretching of the cervical, UL and LL muscles	I: 10RM of 5 trials for each exercise and the load was increased 3 sets of 10 reps at 50%, 75%, and 100% of 10RM	~60 min 6 wk	3	18	Dyspnea (modified Borg scale)	I vs C=0
Costi et al. [27], 2009	50 (33/17)	Age (yr): 69.5±8.9 FEV_1 (% pred): 40.90±15.5	Severe	I: 15 sessions of resistance UL training by using dumbbells	C: PR program that consisted of a minimum of 15 consecutive sessions of specific training for the LL and general exercises	I: 50% of 1RM of 3 series of 10 reps for each exercise and increase number of reps from 10-12 and 12-15 reps, and increase load by 500 g	NA 3 wk	7	21	UL exercise tolerance (6-MRT) Dyspnea (modified Borg scale) UL Fatigue (modified Borg scale) UL function (ADL field test)	I vs C=+ I vs C=0 I vs C=+ I vs C=+

Table 1. Continued 2

Study	No. of participants (male/female)	Participants	Severity	Intervention group	Control group	Exercise intensity	Exercise time and duration	Frequency (day/wk)	Exercise sessions	Outcomes measurement (tool)	Results
Subin Rao et al. [28], 2010	18 (18/0)	Age (yr): 58±8 FEV_1 (% pred): 44.50±8.55	Severe	I: Unsupported UL training (throwing ball against wall, passing a bean bag, pulling on ropes and pulleys, and moving a ring)	C: LL training by walking training	NA	~15 min 4 wk	5	20	UL exercise tolerance (UULEX)	I vs C=0
Janaudis-Ferreira et al. [29], 2011	36 (21/15)	Age (yr): 67±11 FEV_1 (% pred): 35.15±15.12	Severe	I: Unsupported UL training by resistance training with free-weights	C: Sham training consisted of UL flexibility and stretching exercises	I: Loads equivalent to 10-12 reps maximum and the load was increased for both sets on 2 consecutive training sessions	NA 6 wk	3	18	UL exercise tolerance (UULEX) Dyspnea (modified Borg scale) UL Fatigue (modified Borg scale) QoL (CRQ)	I vs C=+ I vs C=0 I vs C=0 I vs C=0
Covey et al. [31], 2012	64 (52/12)	Age (yr): 70.76±8.35 FEV_1 (% pred): 57.83±17.88	Moderate	I: UL resistance training (by using a cable crossover system) with exercise-specific self-efficacy enhancing intervention/health education	C: Sham training (gentle chair exercise and stretching) with health education	I: eight lifts in shoulder shrug, modified latissimus dorsi pulldown overhead pulldown, front pulldown, front raise, upright row, biceps curl, and triceps extension of 2 set of 8-10 reps, at 70% of 1RM and intensity wa s increased at 80% of 1RM and the load was increased to 3 sets of 8-10 reps and maintain RPE at 12 for week 5-16	NA 16 wk	3	48	UL function (UB-FPT)	I vs C=0

Table 1. Continued 3

Study	No. of participants (male/female)	Participants	Severity	Intervention group	Control group	Exercise intensity	Exercise time and duration	Frequency (day/wk)	Exercise sessions	Outcomes measurement (tool)	Results
McKeough et al. [30], 2012	38 (23/15)	Age (yr): 65.50±7.60 FEV_1 (% pred): 57±15.71	Moderate	I1: UL endurance training (supported and unsupported UL exercises) I2: UL strength training by using weight machines I3: Combined UL endurance and strength training	C: Standard LL endurance and strength training	I1: At 60% of peak work rate and the load was increased according to dyspnea and arm perceived exertion in order to maintain at score 3 I2: Two sets of 10 reps at 60% of 1RM and the load was increased 3 sets at 80% of 1RM	~20 min 8 wk	3	24	UL exercise tolerance (UULEX) Dyspnea (modified Borg scale) UL Fatigue (RPE) QoL (SGRQ)	I1 vs I2 vs I3 vs C=0 I3 vs I1, I2, C=+ I3 vs I1, I2, C=+ I1 vs I2 vs I3 vs C=0
Rekha et al. [36], 2016	30 (NA)	Age (yr): NA FEV_1 (% pred): NA	Unknown	I: UL resistance training by using 1 liter water bottle	C: Thoracic mobility exercise	I: One liter water bottle 3 sets of 8-10 reps and the load was increased by increments to maintain RPE and dyspnea scores 12-14	30 min 4 wk	5	20	Dyspnea (modified Borg scale)	I vs C=+
Gadesha & Bhise [35], 2015	36 (34/2)	Age (yr): 58.05±NA FEV_1 (% pred): NA	Unknown	I: Unsupported UL training in shoulder flexion, abduction, horizontal adduction and abduction, elbow flexion and extension with PR program	C: PR program (treadmill, static cycling and stair climbing)	I: Three sets of 10 reps of each exercise and the load was increased by 10 to 12 to 15 reps, weight from 0.2 to 1.5 kg, and maintain RPE at 12 to 13	NA 8 wk	3	24	UL exercise tolerance (UULEX)	I vs C=+

Table 1. Continued 4

Study	No. of participants (male/female)	Participants	Severity	Intervention group	Control group	Exercise intensity	Exercise time and duration	Frequency (day/wk)	Exercise sessions	Outcomes measurement (tool)	Results
Calik-Kutukcu et al. [32], 2017	42 (27/15)	Age (yr): 59.04±9.30 FEV_1 (% pred): 51.85±15.73	Moderate	I: Unsupported UL training by strength training with free-weights and breathing exercises	C: Breathing exercises	I: At 40-50% of 1RM 3 sets of 8-12 reps and increase number of reps in 2 consecutive training sessions and the load was increased by 250 or 500 g per week	NA 8 wk	3	24	UL exercise tolerance (arm ergometer test) Dyspnea (modified Borg scale) UL Fatigue (modified Borg scale) UL function (ADL simulation test)	I vs C=0 I vs C=+ I vs C=0 I vs C=0
Silva et al. [33], 2018	51 (21/30)	Age (yr): 67.5±7.87 FEV_1 (% pred): 56±21.71	Moderate	I: UL resistance training with free-weight by using dumbbells in arm flexion-abduction and elbow flexion-extension, and physical exercise routine (aerobic exercises, inspiratory muscle training, and stretching, followed by massage therapy)	C: Physical exercise routine (diagonal functional movements for UL and LL, inspiratory muscle training, UL stretching, and massage)	I: At 50% of maximum load 3 sets of 10 reps	30-60 min 6 wk	3	18	Dyspnea (mMRC) QoL (SGRQ)	I vs C=+ I vs C=+

M/F, male/female; NA, not available; FEV_1; forced expiratory volume in one second; UL, upper limb; LL, lower limb; PNF, proprioceptive neuromuscular facilitation; reps, repetitions; RM, repetition maximum; ADL, activities of daily living; PR, pulmonary rehabilitation; 6-PBRT, 6-minute pegboard and ring test; BFS, breathlessness and fatigue scale; UAEX, unsupported arm exercise test; UULEX, unsupported upper limb exercise test; RPE, rating of perceived exertion scale; 6-MRT, 6-minute ring test; QoL, quality of life; CRQ, Chronic Respiratory Disease Questionnaire; SGRQ, St. George's Respiratory Questionnaire; UB-FPT, upper-body functional performance test; mMRC, modified Medical Research Council dyspnea scale; I, intervention group; I1, intervention group 1; I2, intervention group 2; I3, intervention group 3; C, control group; positive (+), if the UL training was demonstrated to be statistically more effective than a control group; negative (-), if the UL training was demonstrated to be statistically less effective than a control group; neutral (0), if the UL training did not statistically differ from a control group.

[30].

ULE training was performed for 15–40 minutes per session. Its training frequency varied from 3 to 7 days per week for 4–8 weeks (Table 1). ULS training ranged from 15–60 minutes per session. Its training frequency varied from 3 to 7 days per week for 3–16 weeks (Table 1). ULC was performed approximately 20 minutes per session, 3 sessions per week for 8 weeks (Table 1). UL exercise progression was done by increasing resistance [22,24-27,29-32,34,35], the number of repetitions per set [22,27,32,35], the number of sets per session [22,24,29-32], and maintaining the perceived exertion rating of 12 to 14 [25,31,35,36] or dyspnea scores of three on the Borg scale [25,30]. Three studies did not specify the exercise progression method [23,28,33]. A few studies reported that ULE and ULS were safe [22,29], practical [22,29,31,32], and cost-effective [22]. Excellent patient's compliance and adherence to the program were observed [22,23,29,31,32]. Four patients reported adverse events such as back pain, muscle soreness, tendinitis of the elbow, and exacerbation of an old shoulder injury associated with ULS training [22,31].

In the included studies, the sensation of dyspnea was measured using a variety of scale including the breathlessness and fatigue scale (BFS) [24], modified Borg scale [22,25-27,29,30,32,36], and modified Medical Research Council dyspnea (mMRC) scale [33]. QoL-related outcome was measured using total score of Chronic Respiratory Disease Questionnaire (CRQ) [25,29] and St. George's Respiratory Questionnaire (SGRQ) [30,33]. For secondary outcomes, UL fatigue related outcome measures were BFS [24], modified Borg scale [22,27,29,32], and rating of perceived exertion (RPE) scale [25,30]. UL function related outcome measures included ADL simulation test [22,32], ADL field test [27], and upper-body functional performance test (UB-FPT) [31]. Lastly, UL exercise tolerance related measures were unsupported UL exercise capacity test [22], arm ergometer test [23,32], 6-minute pegboard and ring test (6-PBRT) [24], unsupported arm exercise test (UAEX) [34], unsupported upper limb exercise test (UULEX) [25,28-30,35], and 6-minute ring test (6-MRT) [27]. The wide variety of outcome measures among included studies required the use of SMD to summary results.

Risk of bias across studies

Of 15 studies, 10 (67%) [23-25,27,29-34] and 5 (33%) studies [22,26,28,35,36] were classified as having low and high risk of bias, respectively (Fig. 2). Eleven studies (73%) had a high or unclear risk of bias due to non-blinding of subjects and research personnel [22,23,26-28,30-32,34-36]. Outcome assessors were blinded to the intervention group in 8 (53%) studies [25,27,29-34]. Allocation concealment was not described in 8 (53%) studies [22,23,25,26,28,34-36].

Analysis of results

The effect of each mode of UL training (ULE, ULS, ULC) and all UL training (ULA) was compared to the control group. Quality of evidence is summarized in Tables 2–5. The quality of evidence was very low to moderate for all

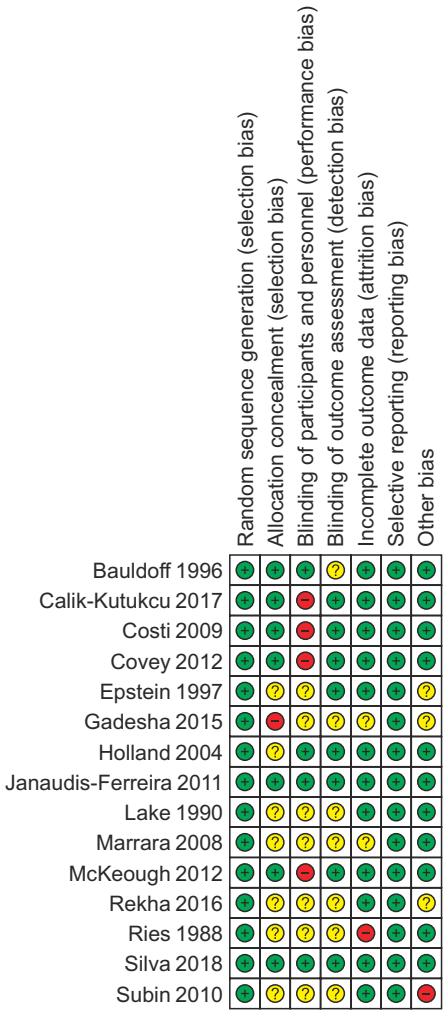

Fig. 2. The risk of bias assessment of included studies by the Cochrane Collaboration's tool.

Table 2. Summary of findings for the effectiveness of ULE training in individuals with COPD

Outcomes	Illustrative mean (95% CI)		No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Control group	ULE group			
Dyspnea	Mean dyspnea ranged across control group from 2.00–16.40 units	SMD dyspnea in the ULE group was -0.56 units (-0.95 to -0.16)	107 (5 RCTs)	⊕⊕⊕◯ Moderate[4]	Significant
Quality of life by using CRQ	Mean CRQ score was 98.95 units	SMD CRQ score in the ULE group was 0.18 units (-0.47 to 0.82)	38 (1 RCT)	⊕⊕◯◯ Low[2,4]	Not significant
Quality of life by using SGRQ	Mean SGRQ score was 35 units	SMD SGRQ score in the ULE group was 0.12 units (-0.81 to 1.05)	18 (1 RCT)	⊕⊕◯◯ Low[2,4]	Not significant
UL fatigue	Mean UL fatigue ranged across control group from 2.40–15.90 units	SMD UL fatigue in the ULE group was -0.41 units (-0.83 to -0.00)	95 (4 RCTs)	⊕⊕⊕◯ Moderate[4]	Significant
UL function	Mean UL function was 548 units	SMD UL function in the ULE group was 1.01 units (0.03 to 1.99)	19 (1 RCT)	⊕◯◯◯ Very low[1,2,4]	Significant
UL exercise tolerance	Mean UL exercise tolerance ranged across control group from 10.20–480.27 units	SMD UL exercise tolerance in the ULE group was 0.78 units (0.16 to 1.40)	184 (8 RCTs)	⊕◯◯◯ Very low[1,2,4]	Significant

ULE, upper limb endurance training; COPD, chronic obstructive pulmonary disease; CI, confidence interval; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; SMD, standardized mean difference; RCT, randomized clinical trial; CRQ, Chronic Respiratory Disease Questionnaire; SGRQ, St. George's Respiratory Questionnaire; UL, upper limb.

The risk in the intervention group (and 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and 95% CI).

GRADE Working Group grades of evidence: High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality (We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different), Low quality (Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect), Very low quality (We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect).

[1]Limitations of study design (>25% of the participants were from studies with a high risk of bias); [2]Inconsistency ($I^2 \geq$ 50% or only one RCT was available); [3]Indirectness (e.g., existence of indirect of interventions or outcome measurement); [4]Imprecision (<400 participants were included); [5]Publication bias (asymmetry of funnel plot was present).

five outcomes due to limitations of study design, heterogeneity across studies, and imprecision.

Effect of UL training on dyspnea

Effect of UL training on dyspnea by comparing each mode of UL training to control condition is summarized in Fig. 3A. Five studies compared the effect of ULE on dyspnea to the control [22-25,30]. The quality of evidence was moderate (Table 2). ULE demonstrated a significantly greater improvement in dyspnea than the control (SMD=-0.56; 95% CI, -0.95 to -0.16; p=0.006).

Eight studies compared the effect of ULS on dyspnea to the control [22,26,27,29,30,32,33,36]. There was a moderate-quality evidence of significant difference (SMD=-0.36; 95% CI, -0.61 to -0.11; p=0.004) in dyspnea between groups, favoring the ULS (Table 3).

Only one study investigated the effect of ULC on dyspnea [30]. There was a trend of significant difference in dyspnea between groups (SMD=-1.05; 95% CI, -2.15 to 0.06; p=0.06), favoring the ULC. However, the quality of evidence was low (Table 4).

When all modes of UL training (14 RCTs) were analyzed

Table 3. Summary of findings for the effectiveness of ULS training in individuals with COPD

Outcomes	Illustrative mean (95% CI)		No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Control group	ULS group			
Dyspnea	Mean dyspnea ranged across control group from 1.10-3.60 units	SMD dyspnea in the ULS group was -0.36 units (-0.61 to -0.11)	259 (8 RCTs)	⊕⊕⊕○ Moderate[4]	Significant
Quality of life by using CRQ	Mean CRQ score was 5.30 units	SMD CRQ score in the ULE group was 0.15 units (-0.51 to 0.80)	36 (1 RCT)	⊕⊕○○ Low[2,4]	Not significant
Quality of life by using SGRQ	Mean SGRQ score ranged across control group from 27.40–35.00 units	SMD SGRQ score in the ULS group was -0.44 units (-0.92 to 0.05)	67 (2 RCTs)	⊕⊕⊕○ Moderate[4]	Not significant
UL fatigue	Mean UL fatigue ranged across control group from 1.60–6.60 units	SMD UL fatigue in the ULS group was -0.22 units (-0.53 to 0.09)	164 (5 RCTs)	⊕⊕⊕○ Moderate[4]	Not significant
UL function	Mean UL function ranged across control group from 6.32–548.00 units	SMD UL function in the ULS group was 0.39 units (-0.10 to 0.87)	176 (4 RCTs)	⊕⊕○○ Low[2,4]	Not significant
UL exercise tolerance	Mean UL exercise tolerance ranged across control group from 10.20–566.00 units	SMD UL exercise tolerance in the ULS group was 0.55 units (0.23 to 0.86)	164 (5 RCTs)	⊕⊕⊕○ Moderate[4]	Significant

ULS, upper limb strength training; COPD, chronic obstructive pulmonary disease; CI, confidence interval; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; SMD, standardized mean difference; RCT, randomized clinical trial; CRQ, Chronic Respiratory Disease Questionnaire; SGRQ, St. George's Respiratory Questionnaire; UL, upper limb.
The risk in the intervention group (and 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and 95% CI).
GRADE Working Group grades of evidence: High quality (We are very confident that the true effect lies close to that of the estimate of the effect), Moderate quality (We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different), Low quality (Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect), Very low quality (We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect).
[1]Limitations of study design (>25% of the participants were from studies with a high risk of bias); [2]Inconsistency ($I^2 \geq$ 50% or only one RCT was available); [3]Indirectness (e.g., existence of indirect of interventions or outcome measurement); [4]Imprecision (<400 participants were included); [5]Publication bias (asymmetry of funnel plot was present).

together to determine the effect of ULA on dyspnea, the quality of evidence was moderate (Table 5). ULA demonstrated a significantly greater improvement in dyspnea than the control (SMD=-0.44; 95% CI, -0.64 to -0.23; p<0.001). When data were analyzed based on disease severity, ULA demonstrated a significantly greater improvement in dyspnea in patients with severe COPD than the control (SMD=-0.54; 95% CI, -0.82 to -0.25; p<0.001) (Fig. 3B).

Effect of UL training on QoL

The quality of evidence of effect of UL training on QoL compared to the control is summarized in Tables 2–5. One study examined the effect of ULE [25] and ULS [29] on QoL by using CRQ. There was low-quality evidence of no significant difference in CRQ score in both ULE (SMD=0.18; 95% CI, -0.47 to 0.82; p=0.59) and ULS (SMD=0.15; 95% CI, -0.51 to 0.80; p=0.66) compared to the control (Fig. 4A).

Two studies used SGRQ to assess QoL [30,33]. Only one study compared the effect of ULE on QoL using the

Table 4. Summary of findings for the effectiveness of ULC training in individuals with COPD

Outcomes	Illustrative mean (95% CI)		No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Control group	ULC group			
Dyspnea	Mean dyspnea was 3.60 units	SMD dyspnea in the ULC group was -1.05 units (-2.15 to 0.06)	15 (1 RCT)	⊕⊕◯◯ Low[2,4]	Not significant
UL fatigue	Mean UL fatigue was 6.60 units	SMD UL fatigue in the ULC group was -1.18 units (-2.31 to -0.06)	15 (1 RCT)	⊕⊕◯◯ Low[2,4]	Significant
UL exercise tolerance	Mean UL exercise tolerance was 10.20 units	SMD UL exercise tolerance in the ULC group was 0.04 units (-0.97 to 1.05)	15 (1 RCT)	⊕⊕◯◯ Low[2,4]	Not significant

ULC, combined upper limb endurance and strength training; COPD, chronic obstructive pulmonary disease; CI, confidence interval; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; SMD, standardized mean difference; RCT, randomized clinical trial; CRQ, Chronic Respiratory Disease Questionnaire; SGRQ, St. George's Respiratory Questionnaire; UL, upper limb.
The risk in the intervention group (and 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and 95% CI).
GRADE Working Group grades of evidence: High quality (We are very confident that the true effect lies close to that of the estimate of the effect), Moderate quality (We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different), Low quality (Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect), Very low quality (We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect).
[1]Limitations of study design (>25% of the participants were from studies with a high risk of bias); [2]Inconsistency ($I^2 \geq$ 50% or only one RCT was available); [3]Indirectness (e.g., existence of indirect of interventions or outcome measurement); [4]Imprecision (<400 participants were included); [5]Publication bias (asymmetry of funnel plot was present).

SGRQ score to the control [30]. There was a low-quality evidence of a non-significant difference (SMD=0.12; 95% CI, -0.81 to 1.05; p=0.79) in SGRQ score between groups (Fig. 5A). Two studies compared the effect of ULS on SGRQ score to the control. The quality of evidence was moderate [30,33]. There was a trend of significant difference between groups (SMD=-0.44; 95% CI, -0.92 to 0.05; p=0.08) in SGRQ score, favoring the ULS (Fig. 5A).

When all modes of UL training were analyzed together to determine the effect of ULA on CRQ score and SGRQ score, the quality of evidence was moderate (Table 5). There was no significant difference between ULA and the control in CRQ (SMD=0.16; 95% CI, -0.30 to 0.62; p=0.49) (Fig. 4A) or SGRQ score (SMD=-0.32; 95% CI, -0.75 to 0.11; p=0.15) (Fig. 5A). Regarding subgroup analysis by patient severity, there was no significant difference in CRQ score between ULA training in individuals with severe COPD and the control (SMD=0.16; 95% CI, -0.30 to 0.62; p=0.49) (Fig. 4B). Similarly, individuals with moderate COPD showed no significant difference in SGRQ score between ULA and control groups (SMD=-0.33; 95% CI, -0.79 to 0.13; p=0.16) (Fig. 5B). For the effect of ULC on QoL, meta-analysis was not conducted due to insufficient data.

Effect of UL training on UL fatigue

Effect of UL training on UL fatigue is presented in Fig. 6. Four RCTs compared the effect of ULE on UL fatigue to the control [22,24,25,30]. The quality of evidence was moderate (Table 2). ULE group demonstrated a significantly greater improvement in UL fatigue than the control group (SMD=-0.41; 95% CI, -0.83 to -0.00; p=0.05).

Five RCTs compared effect of ULS on UL fatigue to the control [22,27,29,30,32]. There was moderate-quality evidence of no significant difference in UL fatigue between groups (SMD=-0.22; 95% CI, -0.53 to 0.09; p=0.17) (Table 3).

Only one study compared the effect of ULC on UL fatigue to the control [30]. There was low-quality evidence of a significant difference (SMD=-1.18; 95% CI, -2.31 to -0.06; p=0.04) in UL fatigue between ULC training and control groups, favoring the ULC (Table 4).

Table 5. Summary of findings for the effectiveness of UL training in individuals with COPD

Outcomes	Illustrative mean (95% CI)		No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Control group	UL training group			
Dyspnea	Mean dyspnea ranged across control group from 1.10–16.40 units	SMD dyspnea in the UL training group was -0.44 units (-0.64 to -0.23)	381 (14 RCTs)	⊕⊕◯◯ Moderate[4]	Significant
Quality of life by using CRQ	Mean CRQ score ranged across control group from 5.30–98.95 scores	SMD CRQ score in the UL training group was 0.16 scores (-0.30 to 0.62)	74 (2 RCTs)	⊕⊕⊕◯ Moderate[4]	Not significant
Quality of life by using SGRQ	Mean SGRQ score ranged across control group from 27.40–35.00 units	SMD SGRQ score in the UL training group was -0.32 units (-0.75 to 0.11)	85 (3 RCTs)	⊕⊕⊕◯ Moderate[4]	Not significant
UL fatigue	Mean UL fatigue ranged across control group from 1.60–15.90 units	SMD UL fatigue in the UL training group was -0.33 units (-0.57 to -0.09)	274 (10 RCTs)	⊕⊕⊕◯ Moderate[4]	Significant
UL function	Mean UL function ranged across control group from 6.32–548.00 units	SMD UL function in the UL training group was 0.47 units (0.03 to 0.92)	195 (5 RCTs)	⊕⊕◯ Low[2,4]	Significant
UL exercise tolerance	Mean UL exercise tolerance ranged across control group from 10.20–566.00 units	SMD UL exercise tolerance in the UL training group was 0.60 units (0.26 to 0.94)	363 (14 RCTs)	⊕◯◯◯ Very low[1,2,4]	Significant

UL, upper limb; COPD, chronic obstructive pulmonary disease; CI, confidence interval; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; SMD, standardized mean difference; RCT, randomized clinical trial; CRQ, Chronic Respiratory Disease Questionnaire; SGRQ, St. George's Respiratory Questionnaire.
The risk in the intervention group (and 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and 95% CI).
GRADE Working Group grades of evidence: High quality (We are very confident that the true effect lies close to that of the estimate of the effect), Moderate quality (We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different), Low quality (Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect), Very low quality (We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect).
[1]Limitations of study design (>25% of the participants were from studies with a high risk of bias); [2]Inconsistency ($I^2 \geq$ 50% or only one RCT was available); [3]Indirectness (e.g., existence of indirect of interventions or outcome measurement); [4]Imprecision (<400 participants were included); [5]Publication bias (asymmetry of funnel plot was present).

When all modes of UL training were combined (10 RCTs) to identify the effect of ULA on UL fatigue, the quality of evidence was moderate (Table 5). A significant between-group difference (SMD=-0.33; 95% CI, -0.57 to -0.09; p=0.008) in UL fatigue, favoring the ULA, was observed.

Effect of UL training on UL function

Fig. 7 summarizes the effect of UL training on UL function. Only one study compared the effect of ULE on UL function to the control [22]. The ULE group demonstrated a significant improvement in UL function than the control group (SMD=1.01; 95% CI, 0.03 to 1.99; p=0.04). However, the quality of evidence was very low (Table 2).

Four studies compared the effect of ULS on UL function to that of the control [22,27,31,32]. There was low-quality evidence of no significant difference (SMD=0.39; 95% CI, -0.10 to 0.87; p=0.12) in UL function between the two groups (Table 3).

Five RCTs compared effects of ULA on UL function. The quality of evidence was low (Table 5). The ULA demonstrated a significant greater improvement (SMD=0.47; 95% CI, 0.03 to 0.92; p=0.04) in UL function than the control.

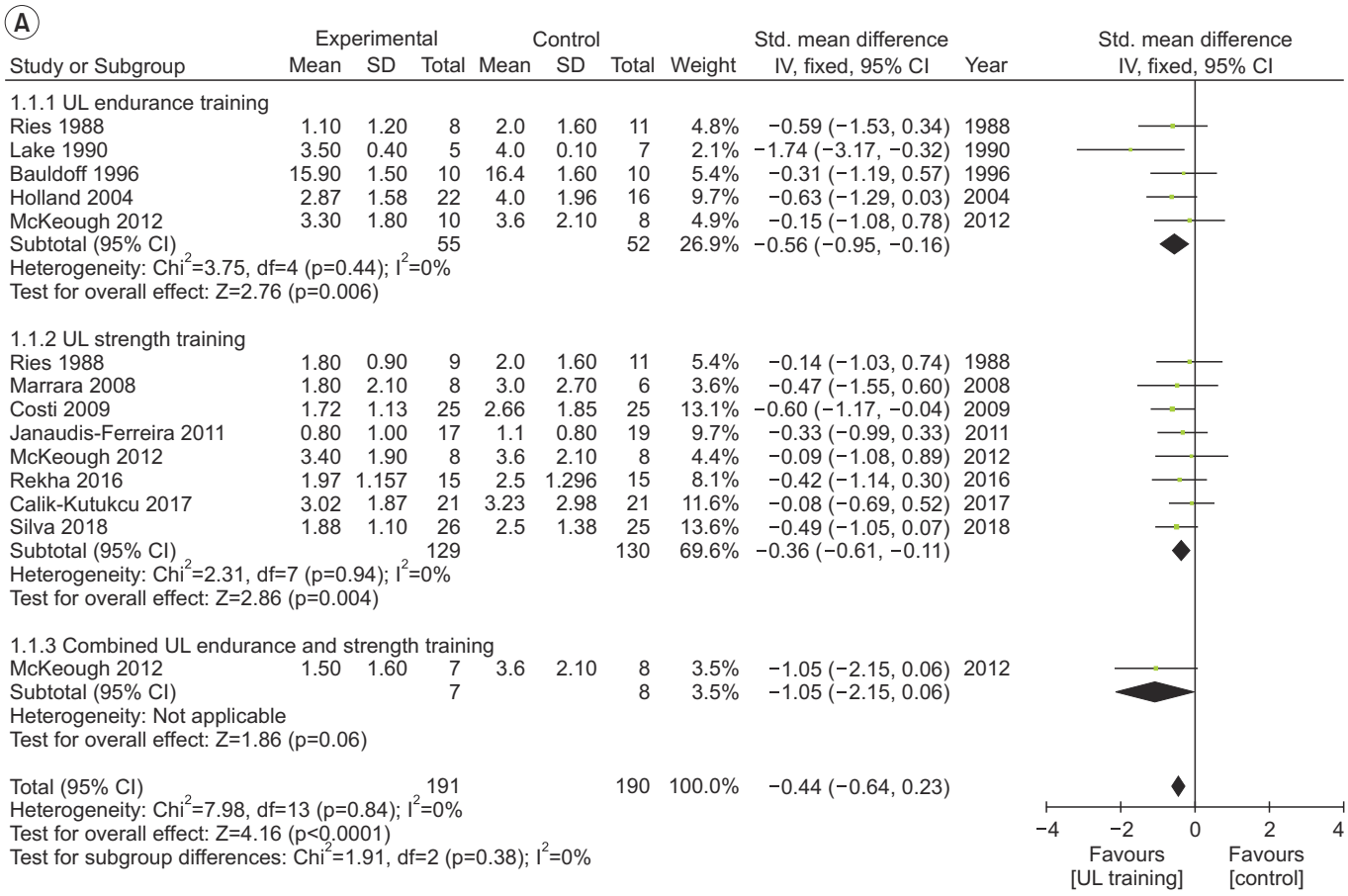

Fig. 3. Forest plot showing difference in dyspnea by comparing modes of upper limb (UL) training with control condition (A) and by patient severity (B).

Effect of UL training on UL exercise tolerance

Fig. 8 summarizes the effect of UL training on UL exercise tolerance. Eight RCTs compared the effect of ULE on UL exercise tolerance to the control [22-25,28,30,34,35]. There was very low-quality evidence of a significant difference (SMD=0.78; 95% CI, 0.16 to 1.40; p=0.01) in UL exercise tolerance between ULE and control groups, favoring ULE (Table 2).

Five RCTs compared effect of ULS to various control conditions on UL exercise tolerance [22,27,29,30,32]. There was moderate-quality evidence of a significant greater improvement (SMD=0.55; 95% CI, 0.23 to 0.86; p<0.001) in UL exercise tolerance in the ULS group than the control group (Table 3).

One study investigated the effect of ULC on UL exercise tolerance [30]. There was low-quality evidence of no significant difference (SMD=0.04; 95% CI, -0.97 to 1.05; p=0.94) in UL exercise tolerance observed between ULC and control groups (Table 4).

Fourteen RCTs were included in the meta-analysis to identify the effect of ULA on UL exercise tolerance. The quality of evidence was very low (Table 5). There was a significant difference in UL exercise tolerance between ULA and control (SMD=0.60; 95% CI, 0.26 to 0.94; p<0.001).

DISCUSSION

The primary goal of this study was to delineate effects of ULE, ULS, and ULC on dyspnea, QoL, UL fatigue, UL function, and UL exercise tolerance in individuals with COPD compared to control conditions. This systematic review was the most updated and comprehensive one as it systematically rated the quality of evidence specific to each mode of UL training according to the GRADE approach to provide transparency of recommenda-

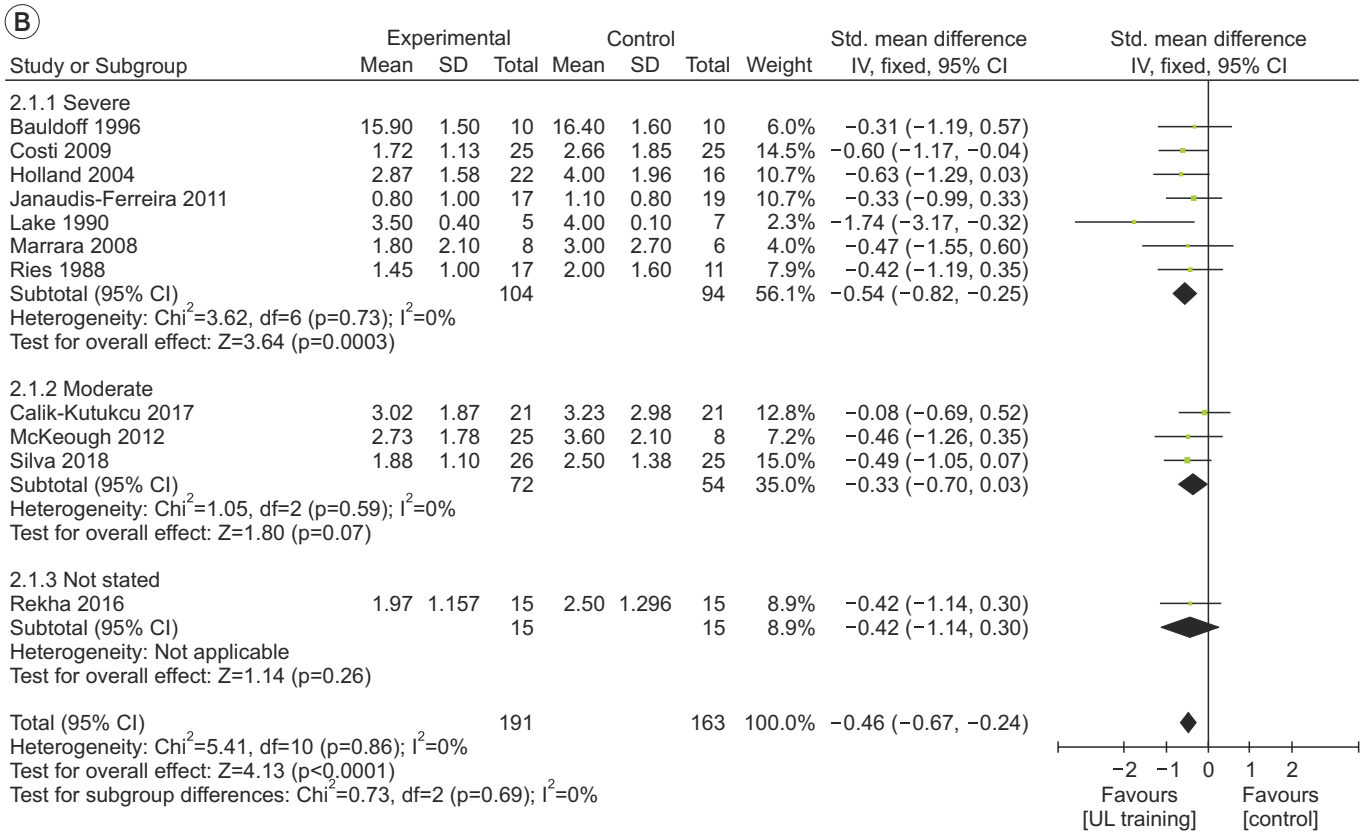

Fig. 3. Continued.

tions. Our findings showed that ULE could be effective in improving dyspnea, UL fatigue, UL function, and UL exercise tolerance. ULS resulted in significantly greater improvement on dyspnea and UL exercise tolerance than the control. ULC was significantly more effective in improving UL fatigue than the control. Therefore, ULE deems superior to ULS and ULC in improving clinically relevant outcomes in individuals with COPD. When all modes of UL training were analyzed together, UL training demonstrated positive effects similar to those of ULE. Additionally, UL training was found to be effective in improving dyspnea in patients with severe COPD level, but not in those with mild to moderate severity level of COPD. Unfortunately, all modes of UL training failed to significantly improve QoL compared to the control. Since the quality of evidence was very low to moderate, recommendation for each mode of UL training on the above outcomes is currently conditional. Further research with better quality of study design and larger sample size will most likely to have a substantial impact on results and conclusions of this study.

Our study began to substantiate the effect of each mode of UL training on clinical outcomes relevant to individuals with COPD. Positive results observed in our study were attributable to an increase in the number of RCTs as well as the number of subjects included in our meta-analysis compared to those used in a previous study [13]. In the present study, five additional RCTs with a total of 223 individuals with COPD afford us with a relatively higher statistical power, leading to significant and positive results on dyspnea, UL function, and UL exercise tolerance compared to the previous study [13].

ULE showed a significant effect on four of five outcomes of interest. These effects were similar to those of ULA when all modes of exercise were analyzed together. As hypothesized, ULE showed its specificity of training effect on dyspnea, UL fatigue, UL function, and UL exercise tolerance in individuals with COPD. These findings are consistent with results of a previous meta-analysis by McKeough et al. [13], where ULE was found to be more effective in improving unsupported UL endurance capacity compared to control condition. The low-intensity and

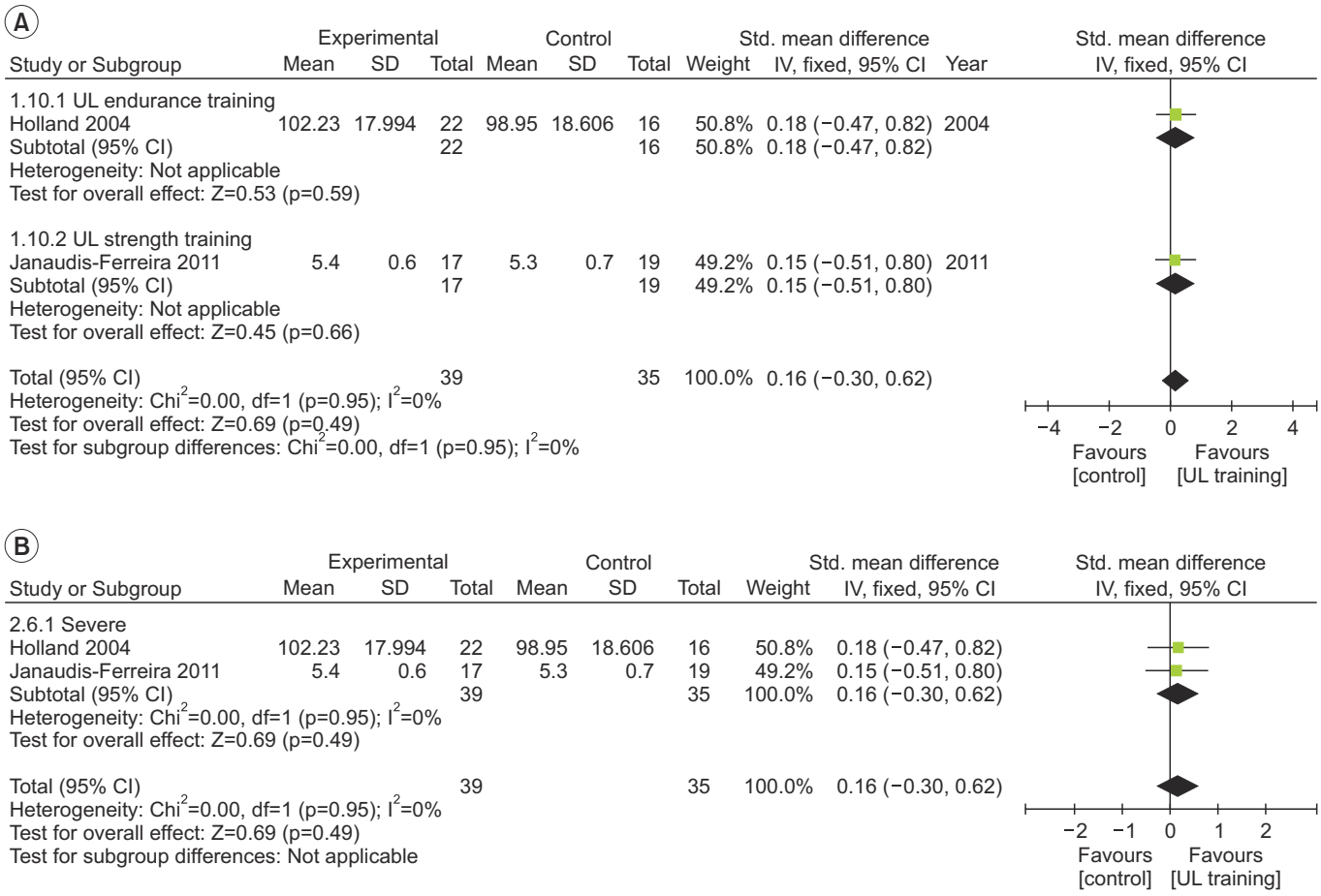

Fig. 4. Forest plot showing difference in quality of life from Chronic Respiratory Disease Questionnaire (CRQ) score by comparing modes of upper limb (UL) training with control condition (A) and by patient severity (B).

long-duration characteristics of ULE are similar to those of UL functional activities and ADLs. Adaptations associated with endurance training such an increase in type I fibers [37,38], oxidative enzyme activity [39], mitochondria density [37,38], and capillary within muscles [37,38] might have contributed to an increase in UL muscle endurance and function during ADLs. ULE has also been shown to be able to improve endurance capacity of respiratory muscles and coordination between muscles of the chest wall and the UL, leading to a reduction in respiratory load and dyspnea during UL activities [12]. Increased UL muscle capacity after ULE was also significantly associated with a decrease in symptom of fatigue [37]. These results support the effect of ULE on these outcomes.

In our study, ULS demonstrated a significant effect on dyspnea and UL exercise tolerance in individuals with COPD compared to the control. These new findings were in contrast with the non-significant effect of ULS in improving dyspnea noted in a previously systematic review [13]. Such discrepancy is most likely due to additional RCTs and number of subjects included in our meta-analysis. ULS has been shown to be able to improve strength of inspiratory accessory muscles [32,34] that can promote subjects' participation during breathing, leading to an increase in ventilatory capacity and a decrease in respiratory demand on the diaphragm [34]. As a result, the sensation of dyspnea decreased [26,32,34]. Unexpectedly, results also revealed positive effect of ULS on UL endurance. This might be explained by reducing the load imposed on the muscles relative to its force generation capacity [11,32]. Enhanced oxygen transport system associated with muscle adaptation to strength training [11,40] might have led to greater improvement in force generation, endurance, and exercise capacity of UL muscles [11,32,40]. Taken together, these results support the effect of ULS on dyspnea and UL exercise tolerance.

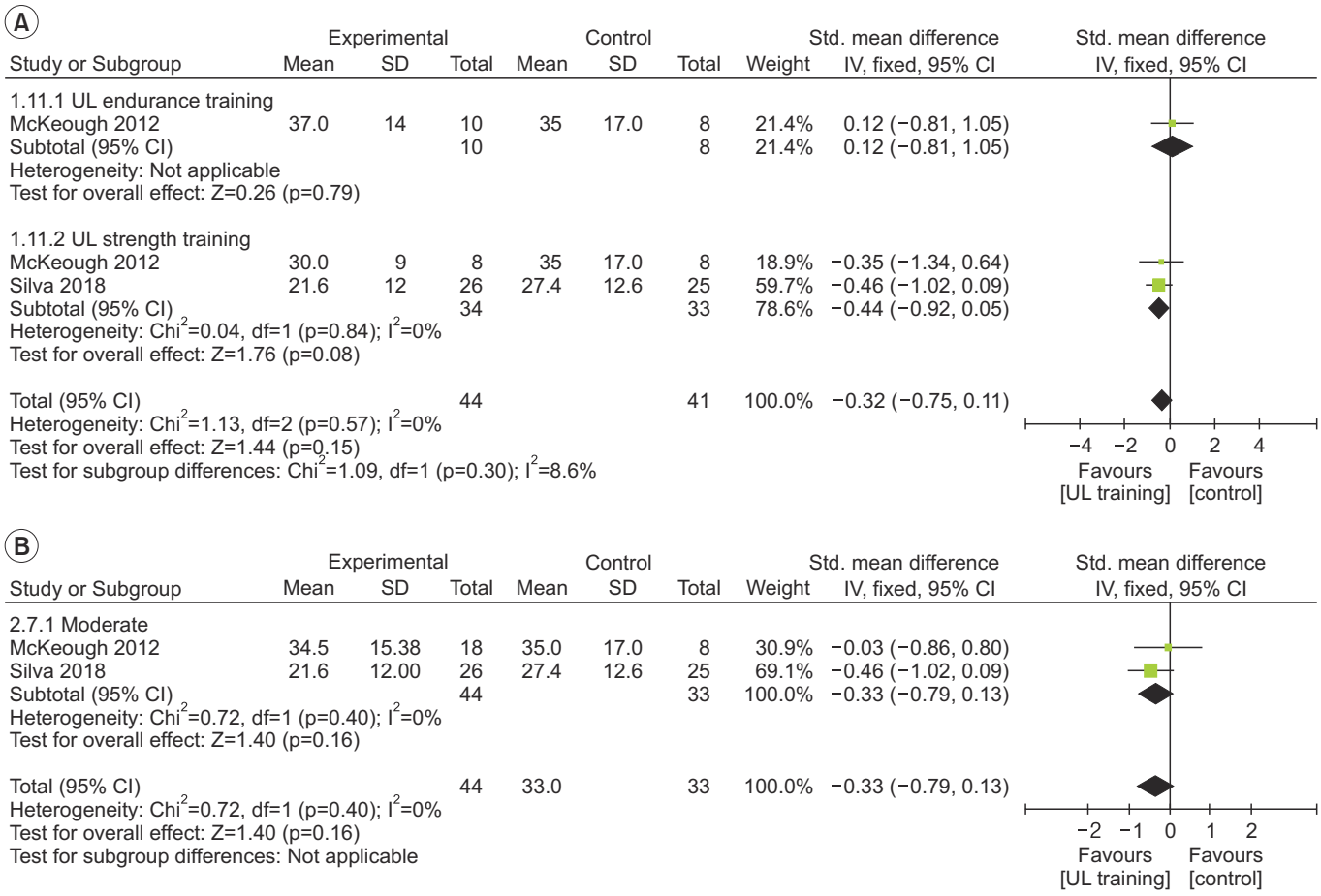

Fig. 5. Forest plot showing difference in quality of life from St. George's Respiratory Questionnaire (SGRQ) by comparing modes of upper limb (UL) training with control condition (A) and by patient severity (B).

The effect of ULC on outcomes relevant to individuals with COPD is quite limited. In our study, the effect of ULC was gathered from one study [29], which reported only three of five outcomes of interest: dyspnea, UL fatigue, and UL exercise tolerance. The ULC was found to be significantly effective in improving UL fatigue with a trend to improve dyspnea when compared to the control. The positive effect of ULC on UL fatigue might be due to increased endurance and strength of UL muscles [32,37]. Additionally, ULC might have increased the capacity of respiratory muscles, leading to a decrease in the sensation of dyspnea [12]. The ULC can elicit positive physiological adaptations such as improved muscle strength, muscle capillarization, and aerobic capacity of UL needed to sustain routine daily activities [30]. An improvement in UL fatigue may further improve dyspnea, UL function, and exercise tolerance in individuals with COPD [37]. However, larger studies with high quality and greater numbers of participants are needed to further identify the effect of ULC on clinical outcomes relevant to individuals with COPD.

The present study demonstrated a significant difference in dyspnea, UL fatigue, UL function, and UL exercise tolerance between ULA and control groups. These findings are consistent with those reported by McKeough et al. [13] showing that UL training demonstrates a significantly greater improvement in dyspnea and unsupported endurance UL exercise capacity than the control. Additionally, results of the present study are in line with the current guideline suggesting that UL training can increase UL function in individuals with COPD, emphasizing the importance of UL training in pulmonary rehabilitation program regardless of the mode of training [9]. However, when data were stratified into different modes of exercise, not all modes of exercise demonstrated the same effects as those of ULA. Only ULE demonstrated positive

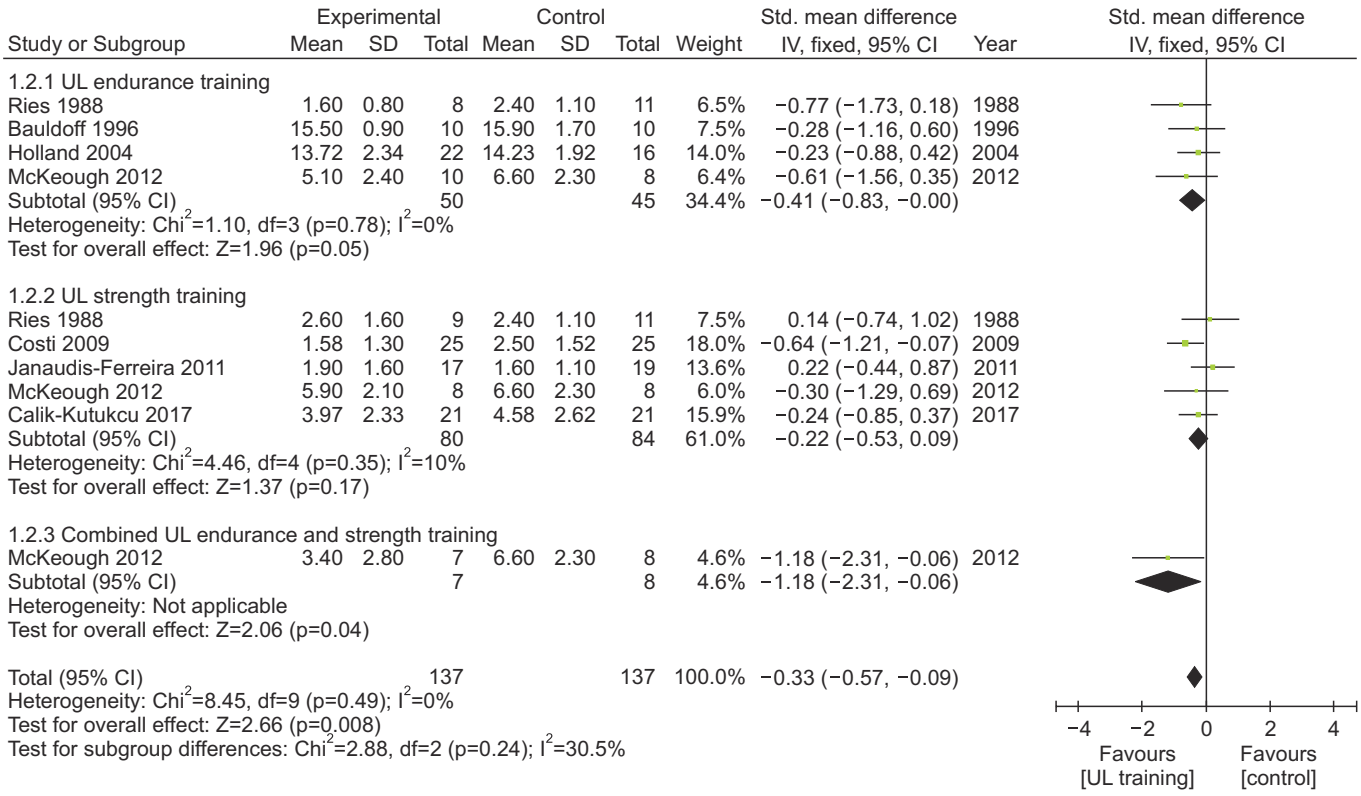

Fig. 6. Forest plot showing difference in upper limb (UL) fatigue by comparing modes of UL training with control condition.

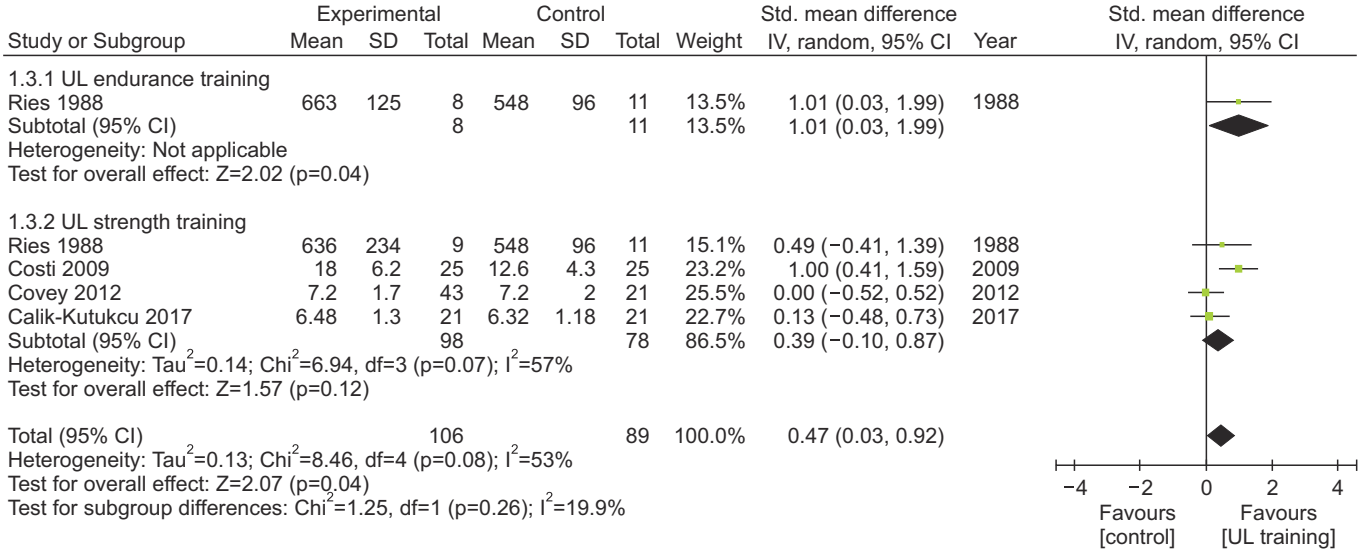

Fig. 7. Forest plot showing difference in upper limb (UL) function by comparing modes of UL training with control condition.

and significant effects similar to those of ULA. Additionally, when considering the effect size of each mode of UL training, ULE training had a relatively larger effect size than the other two modes on the same outcomes. Hence, ULE seems to be the largest contributor to the effect of UL training.

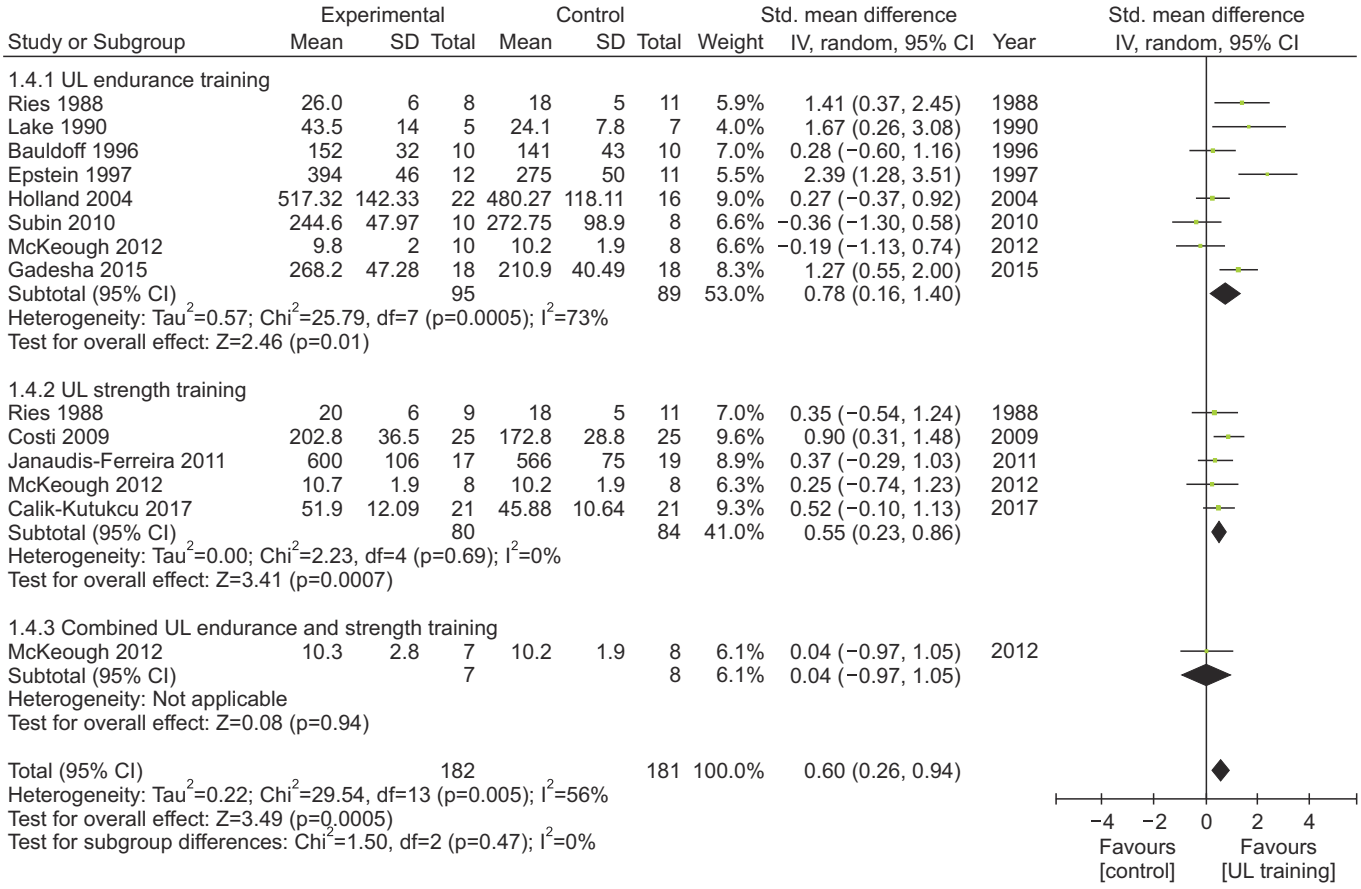

Fig. 8. Forest plot showing difference in upper limb (UL) exercise tolerance by comparing modes of UL training with control condition.

Patient's QoL is an important outcome measure to demonstrate whether or not an intervention will essentially have a significant impact on the patient [9]. Unfortunately, the present study did not demonstrate a significant effect of UL training on QoL compared to the control. This finding is consistent with results of the previous report [13]. It might be attributable to a limited number of studies and small sample size. In this study, the control group received either LL training [25,28,30,33], gentle chair exercises and incorporated stretching of all major joints [31], inspiratory muscle training [33], or UL flexibility and stretching exercises [29,33]. These exercises can significantly improve muscle capacity [7] and reduce dyspnea [7,9], both of which can lead to improved QoL in individuals with COPD [7,9]. As a result, no significant between-group difference was observed. However, the small effect size of the total score of QoL favoring the ULA may suggest an added value of both ULE and ULS for improving QoL of individuals with COPD.

Clinical implications

Findings of this systematic review indicate that the mode of UL training can significantly and differently impact clinical outcomes relevant to individuals with COPD. There was a significant improvement in dyspnea, UL fatigue, UL function, and UL exercise tolerance following ULE. ULS improved dyspnea and UL exercise tolerance. ULC was also useful to reduce UL fatigue. Nonetheless, ULE deemed to be superior to ULS and ULC. It should be an essential part of a pulmonary rehabilitation program for individuals with COPD. Considering the application of integrated UL training, individuals with severe COPD would benefit from it the most.

Limitations

This study has several limitations. First, a relatively small number of subjects (ranging from 74 to 381 subjects per meta-analysis) were included in each meta-analysis, which might have led to imprecision of results. Second,

a direct comparison between UL training and the control was difficult to make due to considerable variability within UL training and control groups. Finally, results were limited to an immediate effect after treatment without providing any information on the long-term effect. Further studies with larger sample size, standardized training protocol, and with a long-term follow-up are needed to minimize these limitations and improve the accuracy of the effect of each mode of UL training on these outcomes.

Conclusion

ULE is more effective in improving dyspnea, UL fatigue, UL function, and UL exercise tolerance than the control. ULS is effective in decreasing dyspnea and increasing UL exercise tolerance than the control. ULC is also useful in relieving UL fatigue in individuals with COPD. The application of integrated UL training is more useful for patients with severe COPD than in those with mild to moderate severity of COPD. However, all modes of UL training failed to show significantly greater effect on QoL than the control. Since the quality of evidence ranged from very low to moderate, the above recommendations for effects of UL training were conditional. Future research is needed to confirm results of the current meta-analysis.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTION

Conceptualization: Kruapanich C, Tantisuwat A, Mathiyakom W. Methodology: Kruapanich C, Ubolnuar N, Tantisuwat A. Formal analysis: Kruapanich C, Lertmaharit S. Funding acquisition: Tantisuwat A. Project administration: Tantisuwat A. Writing – original draft: Kruapanich C. Writing – review and editing: Kruapanich C, Tantisuwat A, Mathiyakom W, Thaveeratitham P. Approval of final manuscript: all authors.

REFERENCES

1. Wouters EF. Chronic obstructive pulmonary disease. 5: systemic effects of COPD. Thorax 2002;57:1067-70.
2. Pitta F, Troosters T, Spruit MA, Probst VS, Decramer M, Gosselink R. Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005;171:972-7.
3. Sclauser Pessoa IM, Parreira VF, Lorenzo VA, Reis MA, Costa D. Analysis of dynamic pulmonary hyperinflation (DH) following activities of daily living in patients with chronic obstructive pulmonary disease. Braz J Phys Ther 2007;11:469-74.
4. Panagiotou M, Kastanakis E, Vogiatzis I. Exercise limitation in COPD. Pneumon 2013;26:245-56.
5. Rabinovich RA, Vilaro J. Structural and functional changes of peripheral muscles in chronic obstructive pulmonary disease patients. Curr Opin Pulm Med 2010;16:123-33.
6. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T, Mishima M. Exercise capacity deterioration in patients with COPD: longitudinal evaluation over 5 years. Chest 2005;128:62-9.
7. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, et al. Pulmonary rehabilitation: Joint ACCP/AACVPR evidence-based clinical practice guidelines. Chest 2007;131(5 Suppl):4S-42S.
8. Langer D, Hendriks E, Burtin C, Probst V, van der Schans C, Paterson W, et al. A clinical practice guideline for physiotherapists treating patients with chronic obstructive pulmonary disease based on a systematic review of available evidence. Clin Rehabil 2009;23:445-62.
9. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med 2013;188:e13-64.
10. Costi S, Di Bari M, Pillastrini P, D'Amico R, Crisafulli E, Arletti C, et al. Short-term efficacy of upper-extremity exercise training in patients with chronic airway obstruction: a systematic review. Phys Ther 2009;89:443-55.
11. Janaudis-Ferreira T, Hill K, Goldstein R, Wadell K, Brooks D. Arm exercise training in patients with chronic obstructive pulmonary disease: a systematic

review. J Cardiopulm Rehabil Prev 2009;29:277-83.
12. Pan L, Guo YZ, Yan JH, Zhang WX, Sun J, Li BW. Does upper extremity exercise improve dyspnea in patients with COPD? A meta-analysis. Respir Med 2012;106: 1517-25.
13. McKeough ZJ, Velloso M, Lima VP, Alison JA. Upper limb exercise training for COPD. Cochrane Database Syst Rev 2016;11:CD011434.
14. Breslin EH. Dyspnea-limited response in chronic obstructive pulmonary disease: reduced unsupported arm activities. Rehabil Nurs 1992;17:12-20.
15. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264-9.
16. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
17. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.
18. Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401-6.
19. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global Strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD Executive Summary. Am J Respir Crit Care Med 2017;195:557-82.
20. Cohen J. A power primer. Psychol Bull 1992;112:155-9.
21. Melsen WG, Bootsma MC, Rovers MM, Bonten MJ. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. Clin Microbiol Infect 2014;20:123-9.
22. Ries AL, Ellis B, Hawkins RW. Upper extremity exercise training in chronic obstructive pulmonary disease. Chest 1988;93:688-92.
23. Lake FR, Henderson K, Briffa T, Openshaw J, Musk AW. Upper-limb and lower-limb exercise training in patients with chronic airflow obstruction. Chest 1990; 97:1077-82.
24. Bauldoff GS, Hoffman LA, Sciurba F, Zullo TG. Home-based, upper-arm exercise training for patients with chronic obstructive pulmonary disease. Heart Lung 1996;25:288-94.
25. Holland AE, Hill CJ, Nehez E, Ntoumenopoulos G. Does unsupported upper limb exercise training improve symptoms and quality of life for patients with chronic obstructive pulmonary disease? J Cardiopulm Rehabil 2004;24:422-7.
26. Marrara KT, Marino DM, de Held PA, de Oliveira Junior AD, Jamami M, Di Lorenzo VA. Different physical therapy interventions on daily physical activities in chronic obstructive pulmonary disease. Respir Med 2008;102:505-11.
27. Costi S, Crisafulli E, Degli Antoni F, Beneventi C, Fabbri LM, Clini EM. Effects of unsupported upper extremity exercise training in patients with COPD: a randomized clinical trial. Chest 2009;136:387-95.
28. Subin, Rao V, Prem V, Sahoo. Effect of upper limb, lower limb and combined training on health-related quality of life in COPD. Lung India 2010;27:4-7.
29. Janaudis-Ferreira T, Hill K, Goldstein RS, Robles-Ribeiro P, Beauchamp MK, et al. Resistance arm training in patients with COPD: a randomized controlled trial. Chest 2011;139:151-8.
30. McKeough ZJ, Bye PT, Alison JA. Arm exercise training in chronic obstructive pulmonary disease: a randomised controlled trial. Chron Respir Dis 2012;9:153-62.
31. Covey MK, McAuley E, Kapella MC, Collins EG, Alex CG, Berbaum ML, et al. Upper-body resistance training and self-efficacy enhancement in COPD. J Pulm Respir Med 2012;Suppl 9:001.
32. Calik-Kutukcu E, Arikan H, Saglam M, Vardar-Yagli N, Oksuz C, Inal-Ince D, et al. Arm strength training improves activities of daily living and occupational performance in patients with COPD. Clin Respir J 2017; 11:820-32.
33. Silva CMDSE, Gomes Neto M, Saquetto MB, Conceicao CSD, Souza-Machado A. Effects of upper limb resistance exercise on aerobic capacity, muscle strength, and quality of life in COPD patients: a randomized controlled trial. Clin Rehabil 2018;32:1636-44.
34. Epstein SK, Celli BR, Martinez FJ, Couser JI, Roa J, Pollock M, et al. Arm training reduces the VO2 and VE cost of unsupported arm exercise and elevation in chronic obstructive pulmonary disease. J Cardiopulm Rehabil 1997;17:171-7.

35. Gadesha A, Bhise A. Effect of unsupported upper extremity exercise training on symptoms & quality of life in patients with COPD. Indian J Physiother Occup Ther 2015;9:146-51.
36. Rekha K, Vijayalakshmi A, Samuel Sundar Doss D, Anandh V. Effects of home based upper extremity exercise in chronic obstructive pulmonary disease. Int J Pharmaceutial Clin Res 2016;8:1351-5.
37. Bogdanis GC. Effects of physical activity and inactivity on muscle fatigue. Front Physiol 2012;3:142.
38. Fitts RH. Effects of regular exercise training on skeletal muscle contractile function. Am J Phys Med Rehabil 2003;82:320-31.
39. Maltais F, Simard AA, Simard C, Jobin J, Desgagnes P, LeBlanc P. Oxidative capacity of the skeletal muscle and lactic acid kinetics during exercise in normal subjects and in patients with COPD. Am J Respir Crit Care Med 1996;153:288-93.
40. Daabis R, Hassan M, Zidan M. Endurance and strength training in pulmonary rehabilitation for COPD patients. Egypt J Chest Dis Tuberc 2017;66:231-6.