



# Aerobic and breathing exercises improve dyspnea, exercise capacity and quality of life in idiopathic pulmonary fibrosis patients: systematic review and meta-analysis

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**Background:** Idiopathic pulmonary fibrosis (IPF) is a progressive disease associated with significant dyspnea and limited exercise capacity. This systematic review aimed to synthesize evidence of exercise interventions during pulmonary rehabilitation that aim to improve exercise capacity, dyspnea, and health-related quality of life (HRQL) in IPF patients.

**Methods:** Searches were performed in MEDLINE, Embase, CENTRAL, SPORTDiscus, PubMed and PEDro from inception to January 2019 using search terms for: (I) participants: 'IPF or interstitial lung disease'; (II) interventions: 'aerobic training or resistance training or respiratory muscle training'; and (III) outcomes: 'exercise capacity or dyspnea or health-related quality of life'. Two reviewers independently screened titles, abstracts and full texts to identify eligible studies. Methodological quality of studies was assessed using the Downs and Black checklist and meta-analyses were performed.

**Results:** Of 1,677 articles identified, 14 were included (four randomized controlled trials and 10 prospective pre-post design studies) that examined 362 patients receiving training and 95 control subjects. Exercise capacity was measured with the 6-minute walk distance, peak oxygen consumption, peak work rate, or endurance time for constant work rate cycling, which increased after exercise [aerobic exercise; aerobic and breathing exercises; aerobic and inspiratory muscle training (IMT) exercises] compared to the control groups. Dyspnea scores improved after aerobic and breathing exercises. HRQL also improved after aerobic exercise training alone or combined with breathing exercises. Aerobic training alone or combined with IMT or breathing exercises improved exercise capacity.

**Conclusions:** Breathing exercises appears to complement exercise training towards improved dyspnea and HRQL in patients with IPF.

**Keywords:** Dyspnea; interstitial lung diseases; rehabilitation; quality of life; exercise

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## Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common type out of the idiopathic interstitial pneumonias (IIPs) and also associated with the greatest mortality; it is characterized as a chronic disease with progressive parenchymal fibrosis of unknown etiology (1). The incidence of IPF is estimated at 3 to 9 cases per 100,000 per year in North America and Europe (2). IPF has a high mortality rate with a median survival ranging from 2 to 5 years after diagnosis (3). With disease progression, increased dyspnea and skeletal muscle dysfunction contribute to deterioration of exercise capacity, impairment in activities of daily living (ADL) and health-related quality of life (HRQL) (4).

The well-established clinical efficacy of pulmonary rehabilitation (PR) in patients with chronic obstructive pulmonary disease (COPD) provides some foundation that it may be beneficial for those with IPF (5,6). Based on guideline recommendations, both short and long-term benefits can be derived from a PR program (5,7). Similar to COPD, exercise capacity of individuals with IPF is significantly limited due to dyspnea. However, the pathophysiology of IPF may result in differences in PR outcomes. Ventilatory and circulatory impairments in IPF patients generally result in a higher prevalence of exercise-induced hypoxemia, and concomitant pulmonary hypertension compared to those with other chronic lung diseases, which may affect PR tolerance (8).

IPF patients derive gains in exercise capacity, dyspnea reduction, and ADL similar to COPD patients with PR (9). Most exercise programs for IPF patients have included aerobic exercise such as walking and cycling, while others have included a combination of resistance training, inspiratory muscle training (IMT) and breathing exercises (e.g., diaphragmatic breathing (10). To date, beneficial effects from exercise interventions in individuals with IPF have been comprised of various exercise programs, and thus the effectiveness of these training programs requires further verification (11).

Some reviews have provided support for the effectiveness of PR for patients with interstitial lung disease (ILD) (8,12). However, two systematic reviews with meta-analyses only included 5 RCTs; both demonstrated the effectiveness of exercise-centered PR on exercise tolerance [improved 6-minute walk distance (6MWD)] and improved HRQL in patients with IPF (13,14) but specific breathing exercises and IMT were not evaluated. Although, several reports describe the effects of breathing exercise and IMT in

COPD patients (14-16), parallel studies examining these interventions in IPF patients are scarce (17). Certainly, such interventions warrant synthesis in a systematic review because of their potential benefit to improve symptoms and daily function.

The purpose of this systematic review was to synthesize evidence from studies that evaluated the efficacy of different types of exercises, including breathing exercises and IMT, in patients with IPF. We evaluated the impact of aerobic exercise training alone and when paired with resistance training, breathing exercises or IMT and their effects on exercise capacity, dyspnea, and HRQL.

## Methods

### *Search strategy*

A search strategy was developed with the assistance of a reference librarian. Searches were performed from inception to January 22<sup>nd</sup>, 2019 in six databases including MEDLINE (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily), Embase, Cochrane Central Register of Controlled Trials (CENTRAL), SPORTDiscus and PubMed and Physiotherapy Evidence Database. Reference lists of the included papers were manually reviewed. Only studies published in English and Japanese were included. The review was registered with the PROSPERO database: CRD42018091411 and this study was reported in accordance with the PRISMA standards guidelines (18).

Scientific databases were searched using the Medical Subject Headings and keywords related to: (I) participants: 'ILD, IIPs or IPF or pulmonary fibrosis or interstitial fibrosis or nonspecific interstitial pneumonia or lung fibrosis'; (II) interventions: 'aerobic training or resistance training or respiratory muscle training'; and (III) outcomes: 'exercise capacity or dyspnea or ADL or HRQL' (Supplement A).

### *Study criteria*

Studies were included if: (I) the cohort included patients with IIPs; (II) an exercise program was the primary intervention that included a single intervention or a combination of aerobic, resistance, IMT or breathing exercise training (diaphragmatic or pursed lip); (III) they had any of the following outcomes—exercise capacity measured with 6MWD (19), maximal rate of oxygen consumption

(peak  $\dot{V}O_2$ ), peak work rate (peak WR), endurance time ( $t_{lim}$ ) from a constant work rate cycle ergometry test, dyspnea score (at rest and post exercise) measured with the modified Borg scale (20), Medical Research Council score (21), modified Medical Research Council (mMRC) score (22), Baseline Dyspnea Index (BDI) (23), visual analog scale that assessed dyspnea (VAS) (24); HRQL evaluated using St. George's Respiratory Questionnaire (SGRQ) (25), the SGRQ-I (IPF version) (26) or 36-Item Short-Form Health Survey (SF-36) (27); and (IV) the study design was either a randomized control trial (RCT) or prospective observational study with pre-post design.

Studies were excluded if they: (I) involved participants other than IIPs, connective tissue disorders and extra-parenchymal causes of restriction; or (II) were cross-sectional, retrospective, systematic reviews, editorial letters or conference abstracts without full-text.

### **Study selection and data extraction**

Two investigators (M.H and K.T.K) independently screened abstracts to be selected for full text review. The same two investigators performed full-text review independently to determine inclusion for data synthesis and meta-analyses. Data was independently extracted and confirmed by the two reviewers. Any disagreements regarding the selected articles were discussed between reviewers until consensus was achieved. A third person was not required to achieve agreement.

### **Methodological appraisal**

The methodological quality of each study was assessed independently by two investigators using the Downs and Black checklist (28) and scores were discussed until consensus was reached. Each study was assessed on items in the following categories: (I) reporting; (II) external validity; (III) internal validity (bias); (IV) internal validity (confounding); and (V) power. The quality of studies meeting >75% of the applicable criteria was considered high, 60–74% moderate, and <60% deemed low (29).

### **Statistical analysis**

The Cochrane systematic review software Review Manager (version 5.3.5) was used to determine the mean differences, which is calculated as the absolute difference between the mean values of the exercise versus control groups; or

between the pre versus post exercise effects. In addition, the 95% confidence intervals were also calculated by this software. Meta-analyses were conducted to evaluate the effects of exercise training interventions on exercise capacity, dyspnea, and HRQL. The change in 6MWD, peak  $\dot{V}O_2$ , peak WR, and  $t_{lim}$  from a constant WR cycle ergometry test were analyzed as continuous outcomes and expressed as between-groups differences in means and 95% confidence intervals. Forest plots were constructed to display the effects of exercise in individual studies and evaluate statistical heterogeneity, where  $I^2$  values of <25%, 26–74% and >75% represented small, moderate and large levels of heterogeneity, respectively (30). Fixed-effects models were used for analyses.

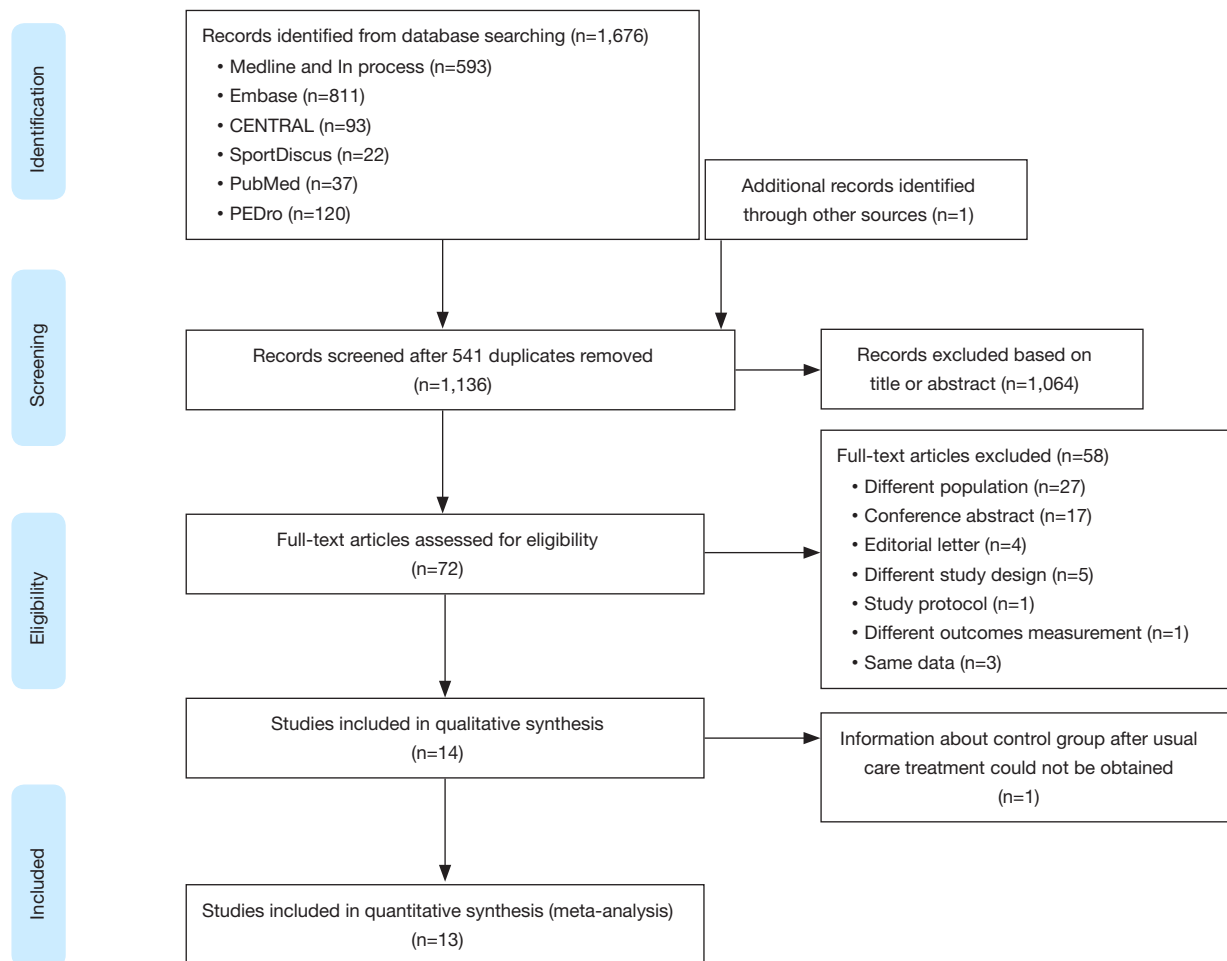
## **Results**

### **Study selection**

Fourteen full-text articles of the 1,677 reviewed abstracts were included in this review (*Figure 1*). In these reports, data from 362 IPF trained patients and 95 control subjects were reported. The authors of 4 papers were contacted for more information and 3 provided the required data for meta-analyses (31–34). Of this number, 4 RCTs included 71 patients in the treatment groups and 71 patients in the control groups (31,35–37). Ten prospective observational studies had a pre-post design that included 291 patients that received exercise training (9,32–34,38–42) and one of these reports had 24 patients assigned in a non-random fashion to a control group (43). The rehabilitation programs included aerobic training, resistance training, breathing exercises and IMT that were provided in 2–3 sessions per week for 8 to 12 weeks (*Table 1*).

### **Study quality**

The mean quality assessment score of the included studies was  $16 \pm 2$  out of 28, which equated to  $56\% \pm 7\%$  (range: 46–71%) (*Table 2*). Four RCTs and one pre-post study had moderate quality scores, while the other nine pre-post design studies had low quality scores. All studies received points in the external validity category for reporting a hypothesis, a clear description of methods and participant characteristics, use of appropriate statistics, and reliable and accurate outcome measures. The less commonly reported items were an *a priori* power calculation and whether the subject sample was representative of the general IPF population (*Table 2*).



**Figure 1** Flow chart of retrieval, screening and inclusion of articles in systematic review.

### Exercise capacity

The 6MWD, peak  $\text{VO}_2$ , peak WR, and  $t_{\text{lim}}$  on a constant WR cycle ergometer tests were used to evaluate exercise capacity in eleven, two, three and five studies, respectively. The mean difference of the 6MWD was significant and in favour of patients engaged in aerobic exercise training, aerobic training with breathing exercise, or aerobic exercise training with IMT compared to controls ( $P < 0.00001$ ) with no subgroup differences ( $P = 0.15$ ) (Figure 2A). Eight studies that examined 6MWD pre- and post-exercise found overall significant improvement in favour of individuals with exercise training ( $P < 0.00001$ ), but no significant subgroup differences ( $P = 0.79$ ) (Figure 2B).

Significant increases in peak WR were shown in RCTs that applied combinations of aerobic training with breathing exercises or IMT ( $P < 0.00001$ ) with greater improvement in

the subgroup that applied breathing exercises ( $P = 0.0003$ ) (Figure 3A). However, no significant improvements in peak WR were shown in favour of aerobic exercise training and IMT in one pre-post design study ( $P = 0.29$ ) (Figure 3B). Peak  $\text{VO}_2$  was greater in the exercise training compared to the control group in one study (37), while no significant pre- and post-effect was found in a study measuring the effect of aerobic training with IMT over 10 weeks.

The mean difference of constant work rate cycling  $t_{\text{lim}}$  was significant and in favour of individuals in the aerobic exercise training, or aerobic exercise training with IMT groups compared to controls ( $P < 0.00001$ ) with greater improvement in the latter ( $P < 0.00001$ ) (Figure 3C). Furthermore, significant differences in favour of aerobic exercise training, or aerobic exercise training and IMT were demonstrated in studies with pre- and post-design ( $P < 0.0001$ ) (Figure 3D).

**Table 1** Study design, characteristics of participants, characteristics of intervention and outcomes

Author, year, country, study design	Patient characteristics [group, n, age (year), % of male, BMI (kg/m <sup>2</sup> )]	Lung function (expressed as predicted)	% on LT O <sub>2</sub>	Type & intensity of exercise	Frequency and duration	Supervised	Outcomes measurements
Nishiyama <i>et al.</i> 2008 (35), Japan, RCT	PR, 13, 68±9, 92%, 23; C, 15, 65±9, 60%, 23	FVC: 66%±13%, DLco: 59%±17%; FVC: 69%±20%, DLco: 49%±17%	No	TM at 80% of 6MWD; L/E cycling at 80% of peak WR; and RT	2x/week x 10 week outpatient	Yes	At 10 wk: 6MWD 42 m*, BDI 0 point, SGRQ -2.9 point* improved
Jackson <i>et al.</i> 2014 (36), USA, RCT	PR, 11, 71±6; C, 10, 66±7	FVC: 60%±11%, DLco: 44%±11%; FVC: 61%±14%, DLco: 43%±11%	NR	TM and L/E cycling at 60-80% of HRmax; RT and flexibility	120 min 2x/week x 12 week outpatient	Yes	At 3 months: 6MWD: -7 m
Vainshelboim <i>et al.</i> 2014 (37), Israel, RCT	PR, 15, 69±6, 67%, 28; C, 17, 66±9, 65%, 29	FVC: 66%±15%, DLco: 49%±17%; FVC: 70%±17%, DLco: 53%±12%	38	Walking at 70-80% of 6MWD; L/E cycling at 50-60% of peak WR; stairs climbing; RT; flexibility; Br Ex	60 min 2x/week x for 12 week outpatient	Yes	At 12 week: 6MWD: 70 m**, 30 s chair stand +3.7 step**, mMRC -0.7**, SGRQ: -7 point**, peak V O <sub>2</sub> : 2.1 mL/min, peak WR: 15.4 watt improved
Downman <i>et al.</i> 2017 (31), Australia, RCT	PR, 32, 70±10, 66%; C, 29, 73±9, 69%	FVC: 74%±18%, DLco: 50%±17%; FVC: 78%±19%, DLco: 49%±11%	10	Walking at 80% of 6MWD; L/E cycling at 70% of peak WR; RT; and education	2x/week x 9 week outpatient	Yes	At 9 weeks: 6MWD: 31 m**, SGRQ -5.7*, mMRC 0.009*; at 6 months: 6MWD: 0.9 m**, SGRQ -0.8*, mMRC -0.3* improved
Ozalevli <i>et al.</i> 2010 (34), Turkey, pre-post	15, 63±9, 67%, 26	FVC: 72%±8%, DLco: 68%±32%	No	Walking 15-30 min; RT; and Br Ex	Daily home-based sessions x 12 week; phone call once/wk	No	At 12 weeks: 6MWD: 41 m*, QF: 9.8%, mMRC: -0.9**, post exercise dyspnea (Borg scale): -2.2 point* improved
Swigris <i>et al.</i> 2011 (38), USA, pre-post	21, 72±7, 86%	FVC: 73%±22%, DLco: 38%±13%	33	TM and L/E cycling at 60% of HRmax for at least 30 min; RT; Br Ex	2-3x/week x 6-8 week outpatient	Yes	At 8 weeks: 6MWD: 62 m, Fatigue Severity Scale score -1.5 points*, SF-36: PCS 3.3 point improved
Kozu <i>et al.</i> 2011 (33), Japan, pre-post	65, 67±7, 71%	FVC: 69%±20%, DLco: 47%±17%	66	L/E cycling at 50% WR; interval walking at 100% 6MWD; RT for U/E and L/E; walking; Br Ex; education	90 min 2x/week x 8 week, outpatients/home-based	Yes (MRC grade 5 unsupervised)	At 8 weeks: 6MWD: MRC grade 2/3; 31 m**/19 m*, ADL score: each MRC grade improved
Kozu <i>et al.</i> 2011 (9), Japan, pre-post	45, 68±8, 82%, 21	FVC: 69%±16%, DLco: 39%±20%	58	L/E cycling at 50% peak WR for 20 min; RT- 1-3 sets of 10 RM; Br Ex; education	2x/week of 90 min duration, for 8 week, outpatients/home-based	Yes	At 8 weeks: 6MWD: 16 m**, MRC: -0.4*, ADL score: 1.1 point* improved; at 6 months: 6MWD: -3 m decreased, MRC: -0.1**, ADL score: 0.5 point** improved

**Table 1** (continued)

Table 1 (continued)

Author, year, country, study design	Patient characteristics [group, n, age (year), % of male, BMI (kg/m <sup>2</sup> )]	Lung function (expressed as predicted)	% on LTO <sub>2</sub>	Type & intensity of exercise	Frequency and duration	Supervised	Outcomes measurements
Rammaert et al. 2011 (39), France, pre-post	13, 67±13, 62%, 29	FVC: 67%±14%, DLco: 32%±13%	100	L/E cycling at ventilatory threshold HR; RT; walking; stair climbing	Daily home-based for 8 weeks	No (home visit by PT 1/wk)	At 8 weeks: 6MWD: -8 m decreased, stepper: 134 step, cycle endurance time: 6.7 min, dyspnea: VAS -0.7 cm** improved
Holland et al. 2012 (41), Australia, pre-post	25, 73±7	FVC: 75%±17%, DLco: 49%±19%	40	Walking at 80% of 6MWD and cycling for 30 min; RT; education.	2x/week for 8 weeks outpatients	Yes	At 8 weeks: mean differences 6MWD: 21 m*, CRDQ dyspnea 2.7 point* improved
Arizono et al. 2014 (43), Japan pre-post	PR, 24, 69±7, 67%; C, 24, 69±6, 67%	VC: 71%±18%, DLco: 50%±16%; VC: 76%±1%, DLco: 48%±17%	No	L/E cycling at 80% peak WR; U/E & L/E RT; Br Ex; IMT at 30% MIP x 15min	2x/week of 90 min duration, outpatient for 10 weeks	Yes	At 10 weeks: peak VO <sub>2</sub> : 42.8 mL/min, peak WR: 5.9 watt, 6MWD: 26 m, ISWT: 28m improved
Rifaat et al. 2014 (42), Egypt, pre-post	30, 54±6, 27%	FVC: 52%±15%, DLco: 62%±14%	No	L/E cycling; RT; stair climbing; and Br Ex	3x/week, outpatient for 8 weeks	Yes	At 4 weeks: 6MWD: 31 m**, modified Borg scale: -0.6 point**, SGRQ: -20.6 point** improved; at 8 weeks: 6MWD: 61 m**, modified Borg scale: -1.3 point**, SGRQ: -34.8 point** improved
Arizono et al. 2017 (40), Japan, pre-post	22, 57±10, 58%	FVC: 72%±18%, DLco: 50%±17%	No	L/E cycling; U/E & L/E endurance and RT; Br Exs; IMT, education	2x/week of 90 min duration, outpatient for 10 weeks	Yes	At 10 weeks: 6MWD: 27 m*, ISWT: 30 m*, BDI 0.5 point*, SGRQ -3.8 point*, peak VO <sub>2</sub> : 11.6 mL/min, peak WR: 67.2 watt improved
de Fontoura et al. 2018 (32), Brazil, pre-post	31, 54±6, 27%, 27	FVC: 49%±14%, DLco: 47%±16%	58	TM for 20-30 min at 3/10 of modified Borg scale; U/E & L/E RT; education	3x/week of 60 min duration, outpatient for 12 weeks	Yes	At 12 weeks: 6MWD: 58 m**, mMRC -1*, SF-36: PCS 3.3 point* improved

Mean ± standard deviation (SD) unless otherwise specified. P<0.05\*, <0.01\*\*. Minimal clinically important differences (MCID) for outcomes are as follows: 6-minutes walking distance: 26±2 m; St George's Respiratory Questionnaire (SGRQ): 4 points; modified Borg scale: 1 unit; CRDQ: 0.5 units; SF-36: 2.0 to 7.8 points; mMRC: 1; peak VO<sub>2</sub>: 2 mL/kg/min. 6MWD, 6-minutes walking distance; ADL, activities of daily living; BDI, Baseline Dyspnea Index; BMI, body mass index; Br Ex, breathing exercises; C, control group; CRDQ, Chronic Respiratory Disease Questionnaire; DLco, diffusing capacity of carbon-monoxide; FVC, forced vital capacity; HR, heart rate; IPF, idiopathic pulmonary fibrosis; IMT, inspiratory muscle training; ISWT, Incremental Shuttle Walking Test; IPF, idiopathic pulmonary fibrosis; LT O<sub>2</sub>, long-term oxygen; L/E, lower extremity; MIP, maximum inspiratory pressure; MRC, Medical Research Council Dyspnea Scale; mMRC, Modified Medical Research Council Dyspnea Scale; NR, not reported; PCS, physical component summary scores; PR, pulmonary rehabilitation; RCT, randomized control trial; RM, repetition maximum; RT, resistance training; SF-36, 36-item Short-Form Health Survey; SGRQ, St George's Respiratory Questionnaire; TM, treadmill; peak VO<sub>2</sub>, maximal oxygen consumption; peak WR, peak work rate; U/E, upper extremity.

**Table 2** Quality assessment scores based on the modified Downs and Black Checklist

Study (year published)	Reporting	External validity	Internal validity (bias)	Internal validity (confounding)	Power	Total score	
						Out of 28	%
Nishiyama <i>et al.</i> 2008	8	0	6	3	0	17	61
Jackson <i>et al.</i> 2014	7	0	5	1	0	13	46
Vainshelboim <i>et al.</i> 2014	8	0	6	4	0	18	64
Dowman <i>et al.</i> 2017	9	1	6	4	0	20	71
Ozalevli <i>et al.</i> 2010	8	0	5	1	0	14	50
Swigris <i>et al.</i> 2011	8	0	5	2	0	15	54
Kozu <i>et al.</i> 2011	9	0	5	1	0	15	54
Kozu <i>et al.</i> 2011	10	0	5	1	0	16	57
Rammaert <i>et al.</i> 2011	8	0	5	2	0	15	54
Holland <i>et al.</i> 2012	10	0	5	2	1	18	64
Arizono <i>et al.</i> 2013	7	0	5	2	0	14	50
Rifaat <i>et al.</i> 2014	7	0	5	1	0	13	46
Arizono <i>et al.</i> 2017	7	0	5	2	0	14	50
Fontoura <i>et al.</i> 2018	7	1	5	3	0	16	57
Total for each item	113	2	73	29	1		
% for each item	81	5	74	35	7		
Average	8.1	0.1	5.2	2.1	0.1	15.6	56

All questions were scored on the following scale: yes—1, unable to determine—0, no—0.

### Dyspnea

Dyspnea was evaluated in twelve studies, while data from seven were pooled for meta-analyses. Five studies were excluded because data was not similar enough to be combined in the meta-analysis. Five studies used the modified Medical Research Council scale (9,32-34,37), while the others used the BDI (35), Chronic Respiratory Disease Questionnaire (CRDQ) (41) and VAS (39). The RCTs showed a significant reduction in dyspnea for the overall effect ( $P=0.01$ ) and subgroup analyses demonstrated a greater improvement when exercise training was combined with breathing exercise versus control groups ( $P=0.0002$ ) (Figure 4A). A significant decrease in dyspnea was found between pre- and post-intervention studies ( $P=0.0008$ ) but no subgroup differences were shown ( $P=0.69$ ) (Figure 4B).

### HRQL

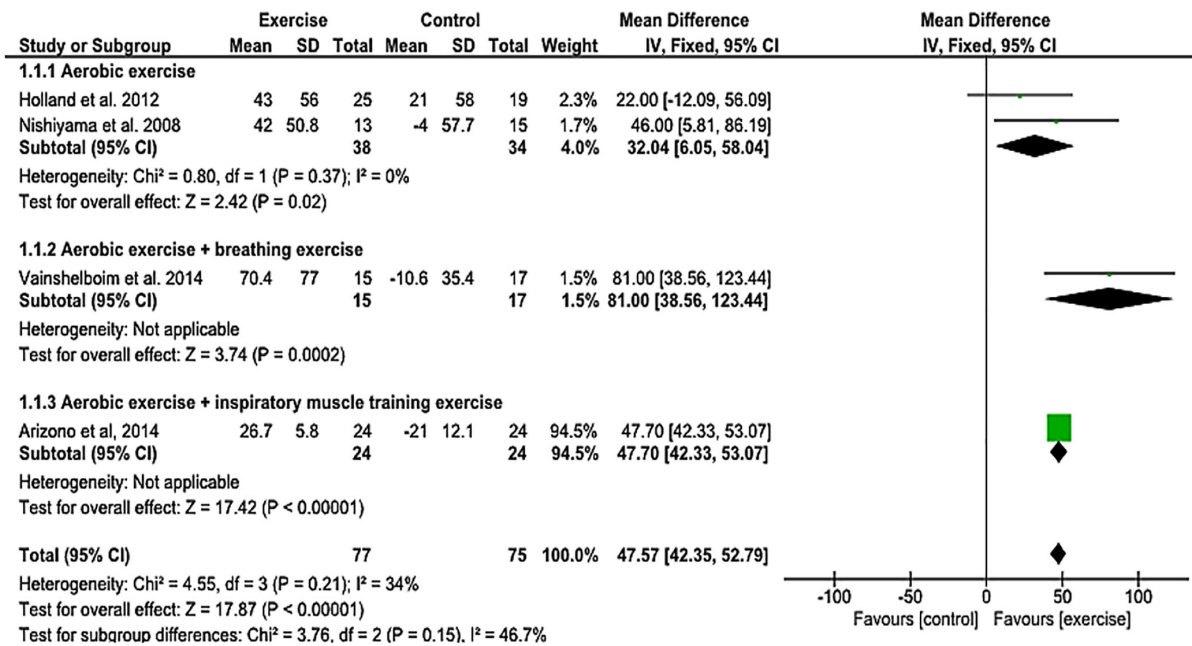
The HRQL was evaluated in nine studies: four studies used

SGRQ (35,37,42,43), (Figure 5) and five studies used SF-36 (Figure 6) (9,32-34,38). Compared to the control groups, the mean difference in SGRQ showed a significant overall effect in favour of the aerobic exercise training, and the aerobic exercise training with breathing exercise groups ( $P<0.00001$ ) with only a tendency of greater improvement in the latter ( $P=0.06$ ) (Figure 5A). In a parallel fashion, SGRQ score showed a significant improvement post-training in the aerobic exercise training with breathing exercise group ( $P=0.006$ ) (Figure 5B). In five studies that evaluated HRQL using the SF-36 (10,28-30,40), the mean difference in all domains significantly increased after the exercise training regimens (Figure 6).

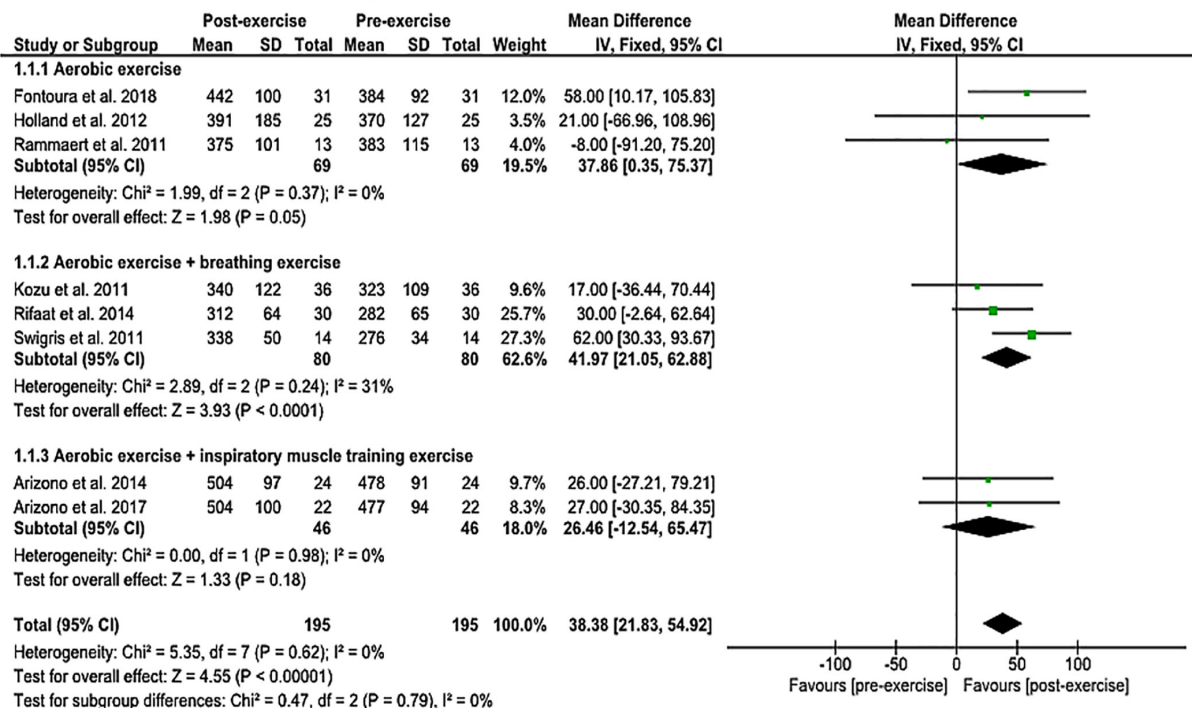
### Discussion

This systematic review with meta-analyses demonstrated that PR utilizing aerobic training alone or combined with breathing exercises or IMT led to significant improvements in exercise capacity, dyspnea and HRQL. Improvement in

**A Exercise versus Control Group**



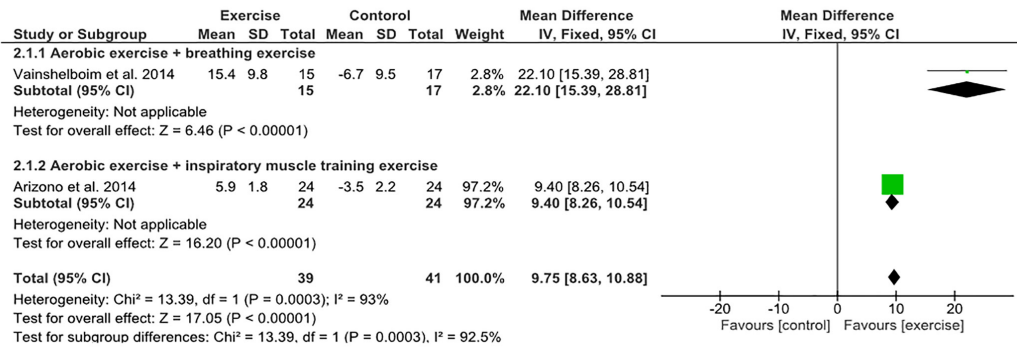
**B Pre versus post exercise training**



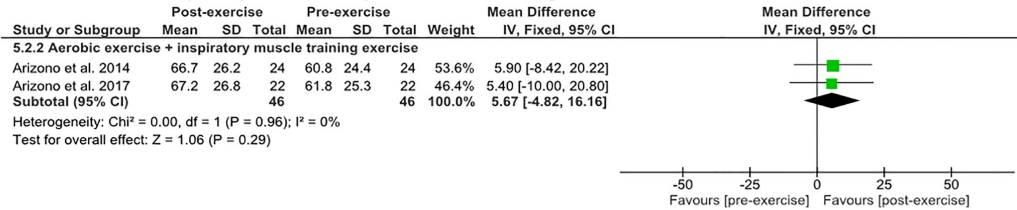
**Figure 2** Change in 6-minute walk distance (m). (A) Exercise versus control; (B) pre and post exercise. Symbols: for single studies, the squares indicate the mean difference and the relative size of the square is an indication of the weighting of this study towards the overall effect. The endpoints of the horizontal lines are the upper and lower 95% confidence interval. The large diamonds represent the summed data for the subgroups and all studies included in the meta-analysis; the midpoint of the diamond indicates the mean difference whereas the endpoints are the upper and lower 95% confidence interval. 95% CI, 95-percent confidence interval; IV, inverse variance; SD, standard deviation.



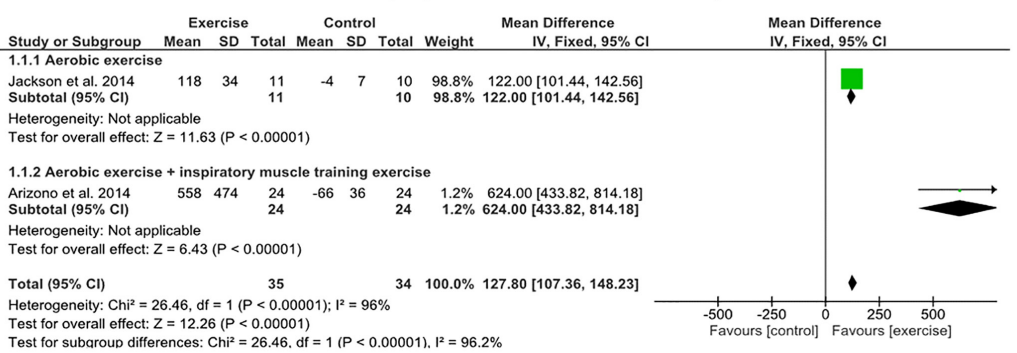
**A Peak Work Rate (watts) - Exercise versus Control Group**



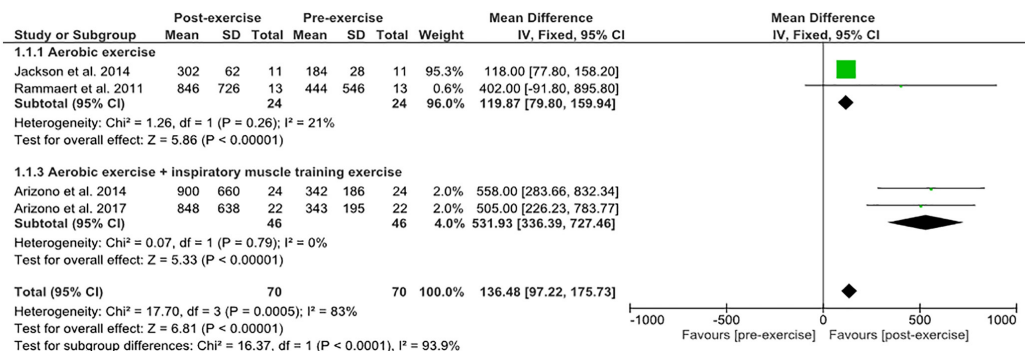
**B Peak Work Rate (watts) - Pre versus post exercise training**



**C Constant Work Rate Endurance Time (sec) - Exercise versus Control Group**

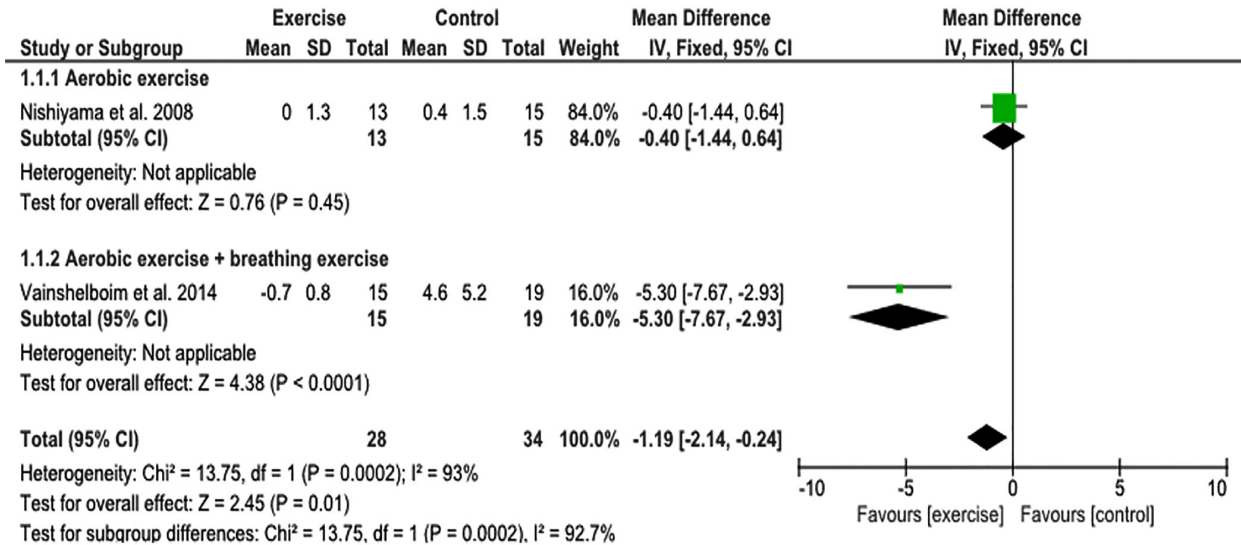


**D Constant Work Rate Endurance Time(sec) – Pre versus post exercise training**

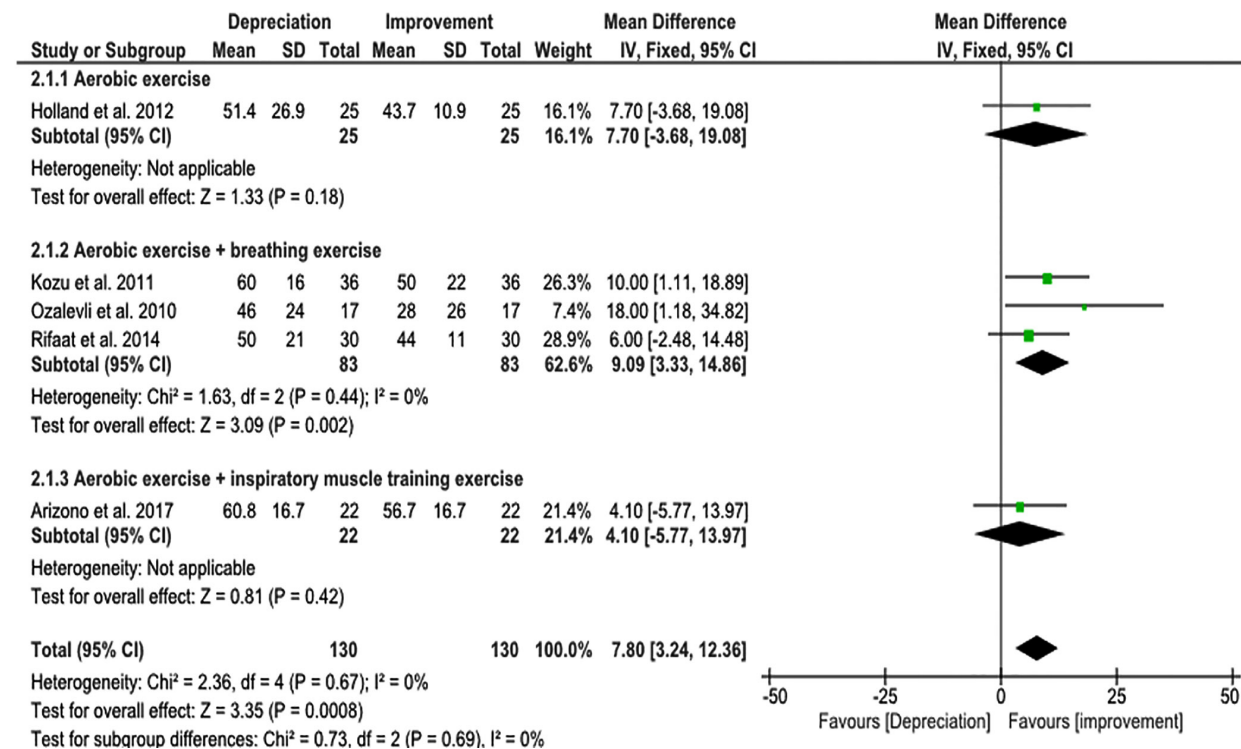


**Figure 3** Change in cycle ergometry outcome. (A) Peak work rate (watt)—exercise versus control; (B) peak work rate (watt)—pre and post exercise; (C) constant work rate endurance time (s)—exercise versus control; (D) Constant work rate endurance time (s)—pre and post exercise. Symbols: for single studies, the squares indicate the mean difference and the relative size of the square is an indication of the weighting of this study towards the overall effect. The endpoints of the horizontal lines are the upper and lower 95% confidence interval. The large diamonds represent the summed data for the subgroups and all studies included in the meta-analysis; the midpoint of the diamond indicates the mean difference whereas the endpoints are the upper and lower 95% confidence interval. 95% CI, 95-percent confidence interval; IV, inverse variance; SD, standard deviation.

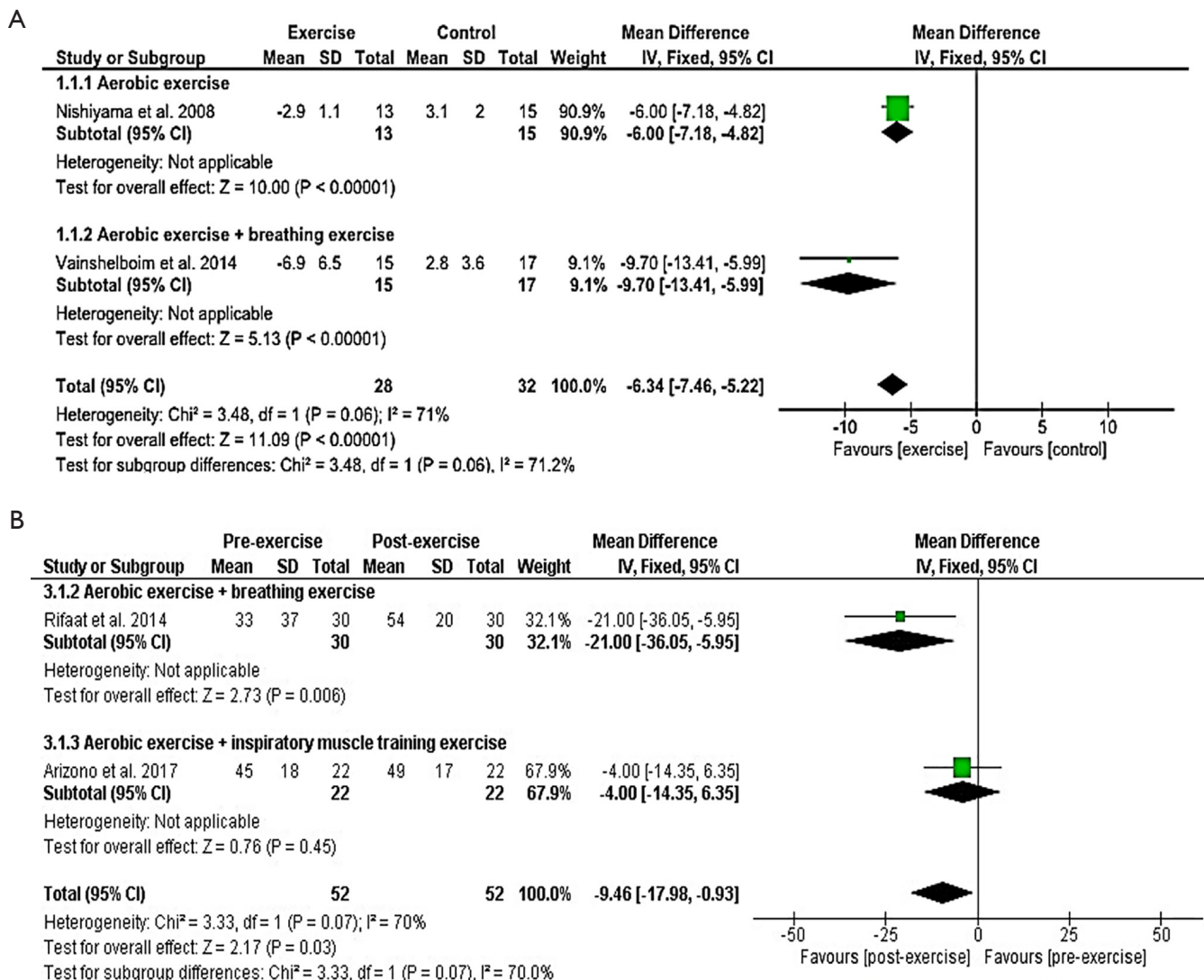
**A Exercise versus Control Group**



**B Pre versus post exercise training - % change**



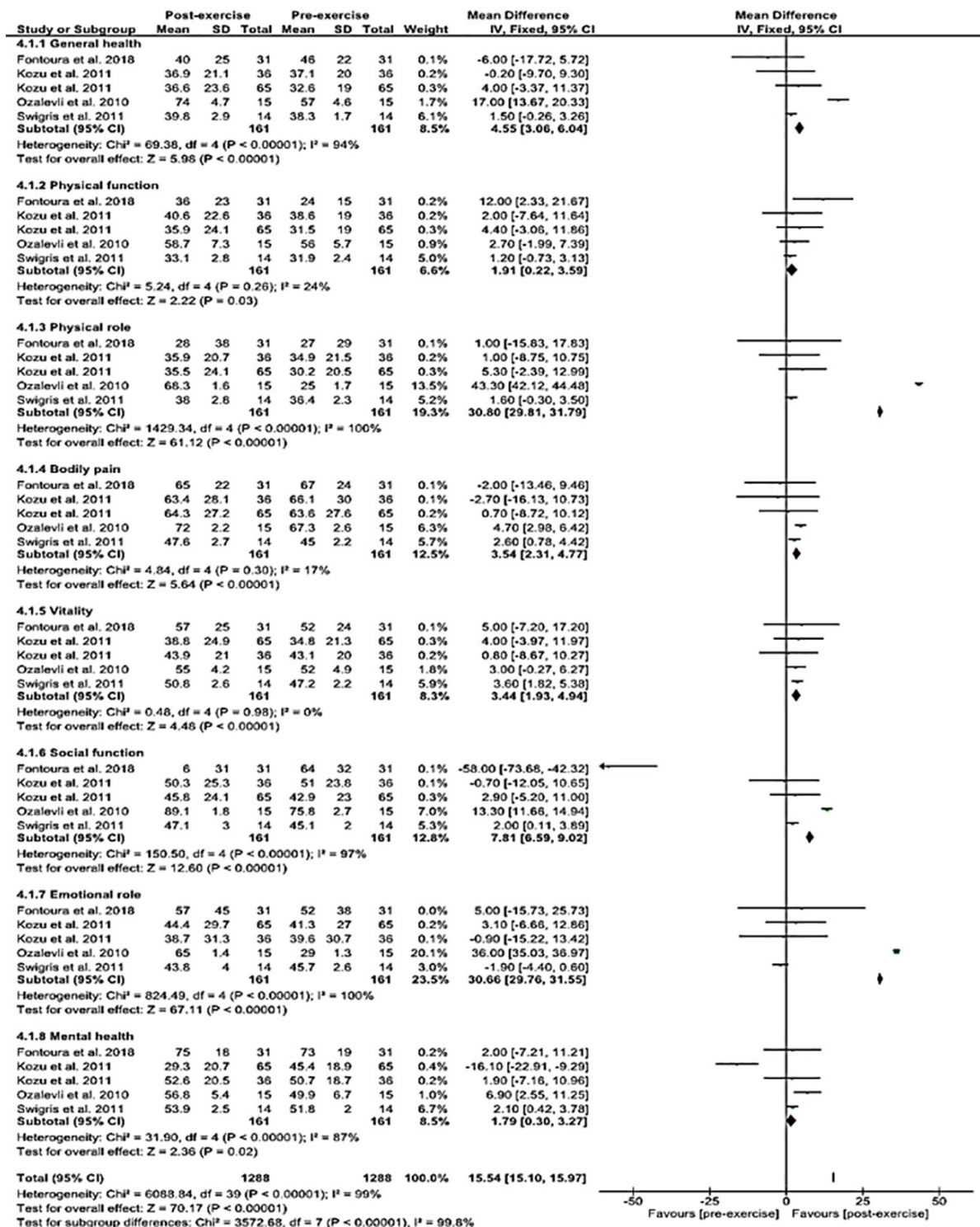
**Figure 4** Change in dyspnea score. (A) Exercise versus control; (B) % improvement of pre and post exercise. Symbols: for single studies, the squares indicate the mean difference and the relative size of the square is an indication of the weighting of this study towards the overall effect. The endpoints of the horizontal lines are the upper and lower 95% confidence interval. The large diamonds represent the summed data for the subgroups and all studies included in the meta-analysis; the midpoint of the diamond indicates the mean difference whereas the endpoints are the upper and lower 95% confidence interval. 95% CI, 95-percent confidence interval; IV, inverse variance; SD, standard deviation.



**Figure 5** Change in St. George’s Respiratory Questionnaire (point). (A) Exercise versus control; (B) Pre and post exercise. Symbols: for single studies, the squares indicate the mean difference and the relative size of the square is an indication of the weighting of this study towards the overall effect. The endpoints of the horizontal lines are the upper and lower 95% confidence interval. The large diamonds represent the summed data for the subgroups and all studies included in the meta-analysis; the midpoint of the diamond indicates the mean difference whereas the endpoints are the upper and lower 95% confidence interval. 95% CI, 95-percent confidence interval; IV, inverse variance; SD, standard deviation.

exercise capacity was shown in the 6MWD, peak WR and most consistently in the  $t_{lim}$  of constant WR cycle ergometry. Aerobic training combined with breathing exercises not only improved exercise capacity but appeared to have a complementary effect on improving dyspnea scores. To the best of our knowledge, this is the first systematic review to examine PR interventions that included breathing exercises or IMT combined with exercise training.

In this meta-analysis, exercise training showed a significant improvement in the 6MWD. Aerobic training combined with breathing exercises appeared to show a complementary effect. Our meta-analysis of RCTs showed an overall significant mean difference of 48 m in the 6MWD and the one RCT that utilized breathing exercises showed a mean difference of 81 m. An increase of 24 to 45 m in 6MWD has been reported as the minimal clinically



**Figure 6** The 36-item Short-Form Health Survey (SF-36) pre versus post-exercise. Symbols: for single studies, the squares indicate the mean difference and the relative size of the square is an indication of the weighting of this study towards the overall effect. The endpoints of the horizontal lines are the upper and lower 95% confidence interval. The large diamonds represent the summed data for the subgroups and all studies included in the meta-analysis; the midpoint of the diamond indicates the mean difference whereas the endpoints are the upper and lower 95% confidence interval. 95% CI, 95-percent confidence interval; IV, inverse variance; SD, standard deviation.

important difference in patients with IPF (44). These data suggest that breathing exercise with aerobic training may provide added benefit for patients with IPF. These findings are consistent with previously reported improvements in exercise tolerance with PR in individuals with ILD (8,12,13).

Aerobic exercise combined with IMT was more beneficial in improving constant  $WR_{t_{lim}}$  compared to aerobic exercise training alone. Nykvist *et al.* performed IMT with aerobic exercise in patients with IPF for 8 weeks and reported a significant increase in exercise capacity and decrease in dyspnea symptoms compared to the control group (45). Aerobic exercise plus IMT may be beneficial because increased inspiratory muscle strength can improve the efficiency of the respiratory muscles required for ventilation (46). Furthermore, improved exercise endurance may result in improved aerobic capacity, and hence reduced ventilatory load during exercise.

The meta-analysis of RCTs indicated that dyspnea scores improved to a greater extent when breathing exercises were combined with aerobic exercise training (33,34,42) than aerobic exercise training alone (37) or when combined with IMT (40,41). Vainshelboim *et al.* (37) proposed several potential benefits from the repetitive stimuli of high ventilatory demands during exercise sessions, chest expansion during deep breathing exercises and stretching of the thoracic muscles. They postulated that these stimuli may contribute to a more efficient breathing pattern, improved strength of respiratory muscles, enhanced pleural elasticity and pulmonary compliance within the lung tissue, and decreased dyspnea perception following the exercise training program (4,10,37). These mechanisms that are possibly induced by aerobic and breathing exercises require further investigation.

Aerobic training plus breathing exercises showed greater benefits compared to aerobic exercise training alone or aerobic exercise training plus IMT in improving HRQL scores. These findings are consistent with other studies that used the SGRQ in ILD patients (47,48). Using the disease specific SGRQ, the two RCTs in this review showed a combined mean difference of 6.3 favoring improvement (35,37), which exceeded the minimal clinically important difference of 4 (49). Our results reinforce that aerobic training combined with breathing exercises is a critical component of PR for improving functional capacity and HRQL in ILD.

The mean quality assessment score of 16 out of 28 was low, likely due to inclusion of prospective studies with pre- and post-intervention designs. Furthermore, internal

validity might have been compromised due to selection bias of subjects included in the PR exercise program as they may have been relatively more stable. Moreover, many studies did not comment on the power, external or internal validity, which may limit the generalizability of the results.

This systematic review with meta-analysis has some limitations. Firstly, the independent impact of each exercise intervention could not be ascertained as several studies provided combinations of exercise training modalities in either a supervised or home-based setting. Secondly, disease severity, variability and progression may have influenced the impact of PR, but the majority of studies were in patients with mild-moderate disease and about one-third of patients were using supplemental oxygen.

In summary, this review showed significant improvements in exercise capacity, dyspnea and HRQL with the greater benefits derived from the combination of breathing and aerobic exercises for dyspnea and HRQL. Future studies should focus on examining the benefits and mechanisms of improvement from individual exercises, so interventions providing optimal results may be combined to maximize benefits for IPF patients.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## Supplement A Details of Medline search strategy

1. Idiopathic Pulmonary Fibrosis/
2. Idiopathic Interstitial Pneumonias/
3. Lung Diseases, Interstitial/
4. exp Pulmonary Fibrosis/
5. (idiopathic pulmonary adj (fibros\* or pneumon\*)).tw,kf.
6. ipf.tw,kf.
7. (idiopathic lung adj (fibros\* or pneumon\*)).tw,kf.
8. (idiopathic interstitial adj (fibros\* or pneumon\*)).tw,kf.
9. idiopathic fibros\*.tw,kf.
10. fibrosing alveolit\*.tw,kf.
11. interstitial lung disease?.tw,kf.
12. ((chronic or usual or fibrosing) adj interstitial pneumon\*).tw,kf.
13. UIP.tw,kf.
14. ((interstitial fibros\* or alveolar fibros\*) adj5 (lung? or pulmonary)).tw,kf.
15. (diffuse adj5 (lung? or pulmonary) adj5 fibros\*).tw,kf.
16. ((parenchymal or fibrotic or restrictive) adj lung disease\*).tw,kf.
17. ((non-specific or nonspecific) adj interstitial pneumon\*).tw,kf.
18. ((non-specific or nonspecific) adj interstitial fibros\*).tw,kf.
19. NSIP.tw,kf.
20. ((lung? or pulmonary or interstitial) adj fibros\*).tw,kf.
21. or/1-20
22. exp Exercise/
23. exp Exercise Therapy/
24. exp Exercise Movement Techniques/
25. Physical Fitness/
26. exp "Physical Education and Training"/
27. (exercise\* or exercising).tw,kf.
28. (gi gong or gigong).tw,kf.
29. ((tai adj ji) or ((tai or thai) adj chi) or taiji or taijiquan or taichi).tw,kf.
30. walking.tw,kf.
31. yoga.tw,kf.
32. (physical adj (fitness or condition\* or education or training or mobility or activit\* or exertion or effort)).tw,kf.
33. gymnastic\*1.tw,kf.
34. calisthenics.tw,kf.
35. aerobic\*1.tw,kf.
36. danc\*.tw,kf.
37. (jumping or hopping).tw,kf.
38. (running or jogging).tw,kf.
39. ambulat\*.tw,kf.
40. muscle strengthening.tw,kf.
41. ((strength or resistance) adj training).tw,kf.
42. ((weight\*1 adj2 lifting) or weightlifting or power lifting or weight training).tw,kf.
43. pilates.tw,kf.
44. stretching.tw,kf.
45. plyometric\*.tw,kf.
46. (cardio\* adj conditioning).tw,kf.
47. ((physical or motion or movement or recreation or activity or pulmonar\*) adj (rehab\* or therap\*)).tw,kf.
48. isometric training.tw,kf.
49. climbing.tw,kf.
50. cycling.tw,kf.
51. (swim or swimming).tw,kf.
52. (training adj (course\* or program\*)).tw,kf.
53. kinesi?therap\*.tw,kf.
54. exp Sports/
55. Rehabilitation/
56. Physical Therapy Modalities/
57. "Physical Education and Training"/
58. ((interval or endurance) adj train\*).tw,kf.
59. dance therapy/
60. or/22-59
61. Breathing Exercises/
62. exp Respiratory Muscles/ph
63. ((inspirator\* or expirator\* or respirator\* or ventilator\*) adj3 train\*).tw,kf.
64. (isocapn\* adj3 (hyperpn\* or hyperventila\*)).tw,kw.
65. (PFlex or powerlung).tw,kf.
66. PImax.tw,kf.
67. PEmax.tw,kf.
68. (Max\* inspirator\* adj2 Pressure\*).tw,kf.
69. (Max\* expirator\* adj2 Pressure\*).tw,kf.
70. (Max\* respirator\* adj2 Pressure\*).tw,kf.
71. (breath\* adj3 exercis\*).tw,kf.
72. ((inspirator\* or expirator\* or respirator\* or threshold\*) adj3 load\*).tw,kf.
73. ((inspirator\* or expirator\* or respirator\* or threshold\*) adj3 device?).tw,kf.
74. Maximal Respiratory Pressures/
75. exp Inspiratory Capacity/
76. or/61-75
77. exp Dyspnea/
78. dyspn?ea?.tw,kf.
79. breathlessness\*.tw,kf.
80. breathless-ness\*.tw,kf.
81. (breath adj2 short\*).tw,kf.
82. or/77-81
83. exp physical endurance/ or exercise tolerance/
84. (exercis\* adj2 (toleran\* or capacit\*)).tw,kf.
85. (aerobic\* adj2 (toleran\* or capacit\*)).tw,kf.
86. (function\* adj2 capacit\*).tw,kf.
87. or/83-86
88. 21 and (60 or 76) and (82 or 87)
89. limit 88 to english
90. limit 88 to japanese
91. 89 or 90
92. 91 not (exp animals/ not exp humans/)
93. 92 not ((exp children/ or exp infant/ or exp adolescent/) not (exp adults/ or exp aged/))