Systematic Review and Meta-Analysis

Medicine

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Efficacy of exercise in patients with pulmonary fibrosis

A systematic review and meta-analysis

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Abstract

Background: Pulmonary fibrosis (PF) is easily caused by a variety of factors, resulting in dyspnea, exertion and movement intolerance. This systematic review aims to synthesize evidence on exercise training during rehabilitation for PF in order to improve patients' exercise capacity, quality of life, and lung function.

Methods: Retrieved from the Cochrane Library, Web of Science, PubMed, Scopus and Embase from inception until April 2022. Participants: patients with PF; Intervention measures: exercise training; Results: exercise ability, quality of life, lung function and cardiopulmonary endurance. Two reviewers independently screen the title, abstract and full text. Finally, quality evaluation and meta-analysis were conducted.

Results: In this study, 13 randomized controlled studies from 1468 articles were selected. A total of 456 patients with PF were enrolled. Compared with usual care in the control group, the 6-minute walking distance, predicted forced vital capacity, predicted forced expiratory volume at 1 second and maximal rate of oxygen consumption were increased significantly after exercise training, while there was no significant change in quality of life and predicted diffusing capacity of the lung for carbon monoxide.

Conclusion: Exercise training can significantly improve the exercise capacity, lung function and cardiopulmonary endurance of patients with PF, but has no effect on the quality of life. Exercise training is an effective rehabilitation strategy for PF.

Abbreviations: 6MWD = 6 minutes walking distance, CF = cystic fibrosis, DLCO% pred = predicted diffusing capacity of the lung for carbon monoxide, FEV1% pred = predicted forced expiratory volume at 1 second, FVC% pred = predicted forced vital capacity, IPF = idiopathic PF, PF = pulmonary fibrosis, VO_2 peak = maximal rate of oxygen consumption.

Keywords: 6MWD, exercise training, lung function, pulmonary fibrosis, quality of life

1. Introduction

Pulmonary fibrosis (PF) is a chronic, progressive, fibrotic interstitial pneumonia disease which is usually caused by bacterial or viral infections, drugs, environment or disease.[1,2] PF usually occurs when alveolar tissue is gradually replaced by fibrotic scarring, which threatens alveolar gas exchange and reduces alveolar compliance.[3] These results in changes in respiratory function, hypoxemia, and reduce motor capacity, further leading to progressive respiratory failure and death.[4] Currently, there are limited therapeutic methods for PF, most of which can only delay the development of the disease and cannot cure it expect lung transplantation.[5,6] Drug therapy and surgical treatment pose a serious financial burden for patients with PF. In the United States, medical costs associated with idiopathic PF (IPF) are estimated at $2 billion.[7] Severe disease characteristics and heavy financial burden greatly affect the quality of life of patients. Therefore, it is very important to explore an efficient and costless rehabilitation training method for patients with PF.

In preventive and rehabilitation medicine, exercise training is regarded as a convenient and effective treatment.[8,9] Types of exercise include aerobic exercise, anaerobic exercise, resistance training, endurance training and so on.[10] The American College of Sports Medicine said exercise can be effective in limiting the development of chronic diseases in the elderly.[11] In healthy and chronically ill people, regular exercise improves cardiolung function, muscle endurance, reduces the risk of death from cardiovascular disease and cancer, and reduces anxiety and depression in cancer and diabetes patients.[12–15] Studies have found that exercise-based pulmonary rehabilitation improves motor function in patients with chronic obstructive pulmonary disease and IPF.[16,17] However, current studies have shown that the effect of exercise on PF is not entirely consistent. Most studies have proved that exercise improves the 6-minute walk distance (6MWD) results of patients with PF,

YG, LZ, and ZY contributed equally to this work.

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but the effects on lung function are different.[18,19] Some studies have shown no significant improvement in patients' quality of life.[17,20] Furthermore, the ATS/ERS/JRS/ALAT guidelines have not yet strongly recommended levels for exercise-based rehabilitation of PF.[21]

This study summarized the reported results of studies evaluating the efficacy of exercise training in patients with PF, and explored the characteristics of the impact of exercise training on patients' quality of life, lung function and exercise ability. The exercise training mentioned in this article includes aerobic, resistance, endurance and other forms, not limited to one. This article includes all types of PF patients currently reported in the literature. We aim to provide the latest evidence for the role of exercise training in rehabilitation of PF.

2. Methods

2.1. Registration

The design and Reporting of this review followed the "Preferred Reporting Items for Systematic Reviews and Meta-analyses" statement. The review protocol was registered on the PROSPERO International Prospective Register for Systematic Reviews website (Registration #: CRD42022323612) in April 2022. Since there were no direct interventions on human participants or animal subjects in this study, ethical approval was not required.

2.2. Literature search strategy

Following the guidelines of the Cochrane Collaboration, 2 reviewers (GY and ZY) independently searched 5 databases: Cochrane Library, Web of Science, PubMed, Scopus and Embase. The time limit was until April 1, 2022. No language restriction was applied. The keywords used in this review include: participants: "pulmonary fibrosis" OR "fibrosis pulmonary" OR "pulmonary fibroses" OR "fibroses, pulmonary" OR "alveolitis fibrosing" OR "alveolitides, fibrosing" OR "fibrosing alveolitides" OR "fibrosing alveolitis" OR "idiopathic diffuse interstitial pulmonary fibrosis"; intervention measures: "exercise" OR "exercises" OR "physical activity" OR "activities, physical" OR "activity, physical" OR "physical activities" OR "exercise, physical" OR "exercises, physical" OR "physical exercise" OR "physical exercises" OR "acute exercise" OR "acute exercises" OR "exercise, acute" OR "exercises, acute" OR "exercise, isometric" OR "exercises, isometric" OR "isometric exercises" OR "isometric exercise" OR "exercise, aerobic" OR "aerobic exercise" OR "aerobic exercises" OR "exercises, aerobic" OR "exercise training" OR "exercise trainings" OR "training, exercise" OR "trainings, exercise." The detailed search strategy was shown in Table S1, Supplemental Digital Content, http://links.lww.com/MD/H925. All literature was imported into Endnote X9 (Thomson Reuters, Carlsbad, CA), which also removed duplications.

2.3. Selection criteria

2.3.1. Inclusion criteria.

(1) The study included patients with PF as defined by the World Health Organization, including IPF and cystic fibrosis (CF).
(2) Physical exercise includes aerobic exercise, resistance exercise, endurance exercise and so on as intervention. The specific requirements are as follows: aerobic exercise is a kind of exercise that provides the energy required for exercise by aerobic metabolism. It involves the whole muscle group, and the exercise lasts for a long time and has rhythm.[17,22–27] Anaerobic exercise is a kind of exercise with high load intensity, strong instants, short duration, and faster metabolism to consume more energy.[28] Resistance training requires the body muscle to exert a force against some form of resistance, such as weight, stretch bands or immovable objects.[18,19,26] Endurance training of relatively long duration and moderate intensity, which enhance maximal oxygen uptake, increasing physical stamina.[29] Flexibility training is a process of static stretching which is performed at the point of mild discomfort with stretches hold for 15 to 60 seconds.[29,30] Strength training aims to increase or maintain a muscle or a muscle group's ability to generate maximum force.[20,27,29,31] For the control group, patients with PF received usual care or maintained their normal daily activities without any physical activity.
(3) Studies that include any of the following results: 6MWD, maximal rate of oxygen consumption (VO_2 peak), predicted forced vital capacity (FVC% pred), predicted diffusion capacity of the lung for carbon monoxide (DLCO% pred), predicted forced expiratory volume in 1 second (FEV_1% pred), health-related quality of life test results.
(4) Only randomized controlled trials were included.

2.3.2. Exclusion criteria.

(1) Case reports;
(2) Participants with an inventory of interpersonal problems, connective tissue disorders or extra parenchymal causes of restriction;
(3) Cross sectional, retrospective, systematic reviews, editorial letters or conference abstracts without the full text available.

2.4. Data collection and analysis

2.4.1. Selection of studies. Two reviewers (GY and ZY) independently checked the titles, abstracts, and keywords of the retrieved articles, leaving studies that fully met all the criteria and those that met some criteria but did not have enough information available to determine their relevance. Two reviewers (GY and ZY) then read the full text of the remaining studies and decided on the final study to be included. Differences were settled by consensus.

2.4.2. Data extraction and management. Data were extracted and recorded independently by 2 reviewers (GY and ZY), followed by random checks for accuracy by the lead reviewer (LJ). Differences were settled by consensus. The extracted data includes: author(s)' name, the publication year, study period, region, subject characteristics (including age, PF type, gender), intervention, treatment for control group, F/U period, the number of participants, PF related measures of lung function, exercise capacity, and health-related quality of life.

2.4.3. Assessment of risk of bias in included studies. Two review authors (GY and ZY) assessed the internal validity of included studies using the Cochrane Collaboration's Risk of Bias Assessment Tool (including sequence generation for randomization, allocation concealment, blinding of participants and assessors, loss to follow-up, completeness of outcome assessment and other possible bias prevention). Disagreements were resolved by consensus. Synthesis of ROB plots were done using software Revman. Egger regression test was used to assess the potential publication bias of the included studies by Stata 15.0.

2.4.4. Data processing and synthesis. For continuous variables, we recorded the mean and standard deviation of post-intervention changes from baseline for the experimental and control groups. Positive values are recorded when the recorded indicators improve and negative values are recorded when the recorded indicators deteriorate. Mean differences for outcomes measured with the same metrics or standardized mean differences (SMDs) for outcomes measured with different metrics were calculated using Stata 15. A fixed-effect model or a random-effects model was used, depending on assessment of heterogeneity.

2.4.5. Subgroup analysis and investigation of heterogeneity. Subgroup analyses were conducted to explore possible sources of heterogeneity. Three subgroup analyses were specified a priori. As follows: types of PF: through literature screening, it was found that there is a large age difference between IPF and CF, and exercise may have different effects on the 2 diseases. Timing of intervention: the duration of exercise training may affect the patient's tolerance and have long-term or short-term effects on the patient's lung function. Type of exercise training: different exercises have different effects on oxygen demand, muscle endurance, and respiratory function.

2.4.6. Sensitivity analysis. Sensitivity analysis was performed to explore the robustness of study quality and sample size results. The results were analyzed and compared by 1 exclusion study.

2.5. Classification of the outcome

The 6MWD was used to assess functional limitations and functional ability, the ability to reflect daily activities at a self-paced maximum. Health-related quality of life was measured by generic or disease-specific quality of life scale. All quality of life scale used were considered. VO_2 peak, FVC% pred, DLCO% pred, FEV1% pred were used to assess lung function in patients with PF.

2.6. Assessment of the certainty of evidence

The assessment of the certainty of the evidence found was carried out using the GRADE approach. The evidence found for each of the outcomes was rated considering the risk of bias, inconsistency, direct or indirect evidence and imprecision, the risk of selective outcome reporting, and the dose–response gradient.

3. Results

3.1. Results of the search

A total of 1468 studies were retrieved from 5 databases until April 2022. After the removal of duplicate publications, evaluation titles and abstracts, 48 studies remained. After reading the full text, 13 randomized controlled studies were obtained. The selection process is shown in Figure 1. Characteristics of

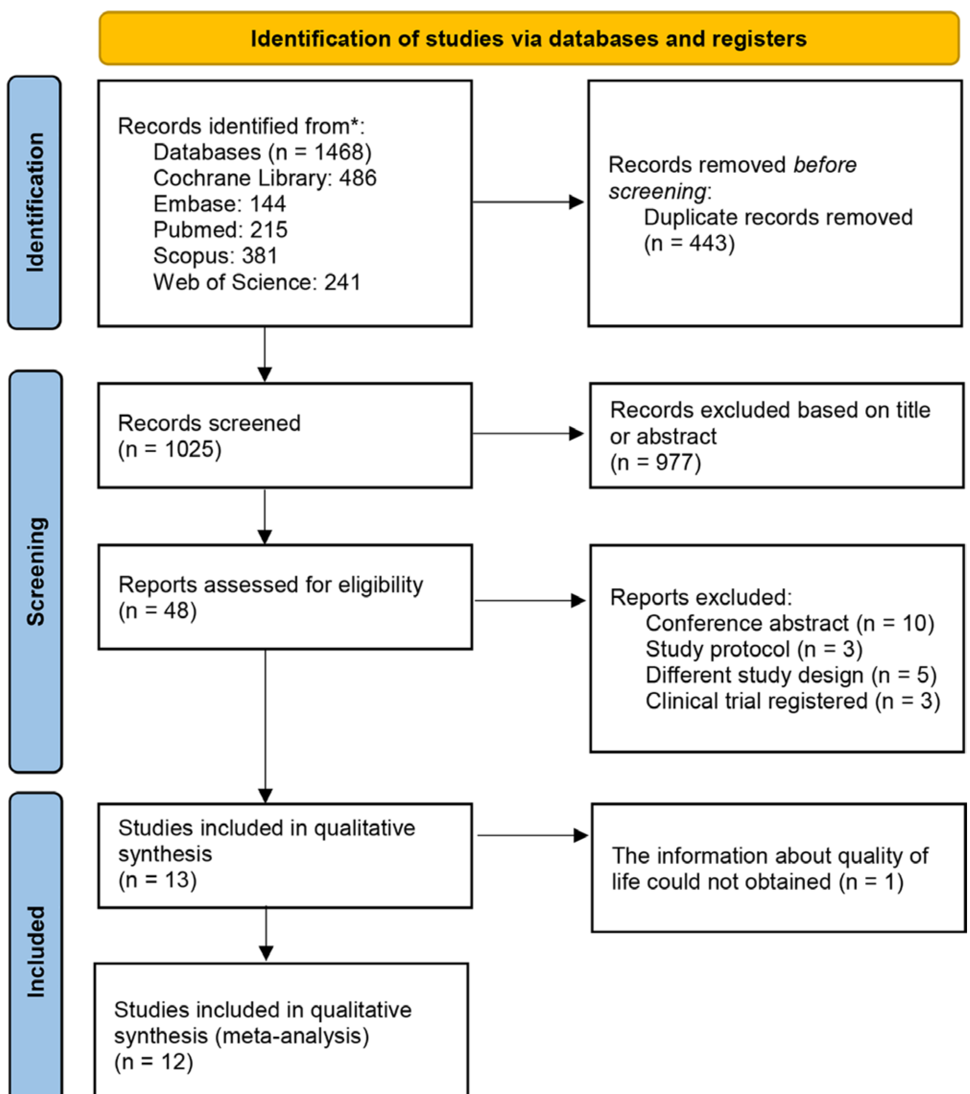

Figure 1. Flow chart of retrieval, screening and inclusion of articles in systematic review.

the 13 studies included types of PF, intervention time, outcome indicators, etc. (Table 1). A total of 456 patients with PF were enrolled. All studies compared exercise training with usual care or maintained their normal daily activities without any physical activity. There were 15 experimental groups and 13 control groups. Eight studies included patients with CF and 5 included patients with IPF. Exercise training lasted for 12 weeks (3 months) in 5 studies, 1 year or more in 3 studies, and less than 12 weeks in the rest. Based on the analysis of study results, 5 studies reported 6MWD results, 9 studies reported effects on health-related quality of life, 5 studies reported FVC% pred and FEV1% pred, 5 studies described VO_2 peak results, and 2 studies described DLCO% pred results.

3.2. Risk of bias in included studies

The risk of bias for the included studies is summarized in Figure 2. All of the studies were randomized, and 2 studies did not specify how random sequences were generated. Five studies did not provide enough information to determine allocation methods, and the rest were reported using sealed envelopes or independent researchers. Seven of the studies showed that the participants were non-blind, and the rest did not have enough data to show whether the participants were deluded. Seven studies reported using blinds for evaluators of measurement results. Five studies reported participant withdrawal and absence, and 8 studies reported no participant withdrawal or use of intentional analysis results. All studies reported all results at all points in time, with no other risk of bias.

3.3. Effects of exercise

3.3.1. 6-minute walk distance. The results of 6MWD were assessed by 5 studies.[17,20,22,23,32] There were 68 participants in the exercise group and 73 in the control group. The results of the meta-analysis are shown in Figure 3. The differences between the 2 groups in the figure support the effectiveness of exercise training (WMD: 54.144; 95% CI: 29.167–79.120; $I^2 = 0.0\%$; $Z = 4.25$, $P < .01$). The type of PF and duration of exercise training were analyzed by meta-regression, and the results showed that these factors had little effect on heterogeneity (Table S2, Supplemental Digital Content, http://links.lww.com/MD/H926). The results of sensitivity analysis were found to be robust (Figure S1, Supplemental Digital Content, http://links.lww.com/MD/H927).

3.3.2. Health-related quality of life. Health-related quality of life in patients with PF were reported by 10 studies,[17,18,20,22,24,26,28,32] and 2 studies had insufficient data for meta-analysis.[23,29] Significant differences in health-related quality of life after exercise training between the 2 groups were confirmed in 8 studies.[18,22–24,26,28,29,32] No immediate improvement in health-related quality of life after exercise training was identified in 2 studies..[17,20] Data were collected from 8 studies involving 130 participants in the exercise group and 120 in the control group. St. George's Respiratory Questionnaire was used by 4 studies,[17,20,22,32] the Spanish version of The Cystic Fibrosis Questionnaire-Revised was used by 3 studies,[18,24,28] another study used the Quality of Well Being Scale.[26] As shown in Figure 4, the overall analysis showed no significant improvement in health-related quality of

Table 1

Study design, characteristics of participants, characteristics of intervention and outcomes.

Study	Study period	Region	Age		Pulmonary fibrosis type	Gender		Intervention	Treatment for control group	F/U period	No. participants		Outcomes
			Exp.	Con.		Exp.	Con.				Exp.	Con	
Cerdan-de-Las-Heras, J. 2021	2017.9–2018.4	Denmark	70.1 ± 8.8	72.4 ± 7.6	IPF	M:13 F:2	M:8 F:6	AT	Usual care	12 wk	15	14	①②⑤⑧
Del Corral, T. 2018	2015.7–2016.7	Spain	12.6 ± 3.4	11 ± 3	CF	M:10 F:10	M:11 F:9	AT	Usual care	6 wk	20	20	①③
Donadio, M. V. F. 2022	2019.1–2020.3	Spain	12.8 ± 3.1	11.7 ± 3.5	CF	M:5 F:3	M:8 F:3	RT	Usual care	8 wk	11	11	⑦
Gaunaurd, I. A. 2014	2014	American	71 ± 6	66 ± 7	IPF	NC	NC	ET-FT-ST	Usual care	12 wk	11	10	②
Gupta, S. 2019	2013.3–2014.7	India	12.3 ± 2.8	12.7 ± 3.3	CF	M:15 F:10	M:15 F:12	RT	Usual care	1 yr	25	27	③⑤⑥
Klijn, P. H. 2004	2004	Netherlands	13.6 ± 1.3	14.2 ± 2.1	CF	NC	NC	AAT	Usual care	12 wk	11	9	③⑦
Nishiyama, O. 2008	2000–2004	Japan	68.1 ± 8.9	64.5 ± 9.1	IPF	M:12 F:1	M:9 F:6	ST	Usual care	10 wk	13	15	②⑤⑥
Santana Sosa, E. 2012	2010.1–2011.1	Spain	11 ± 3	10 ± 2	CF	M:6 F:5	M:7 F:4	AT	Usual care	8 wk	11	11	①③⑤⑥⑦
Schneiderman-Walker, J. 2000	2000	Canada	13.4 ± 3.9	13.3 ± 3.6	CF	M:18 F:12	M:20 F:15	AT	Usual care	3 yr	30	35	⑤⑥
Vainshelboim, B. 2014	2012.1–2012.12	Israel	68.8 ± 6	66 ± 9	IPF	M:10 F:5	M:11 F:6	AT	Usual care	12 wk	15	17	①②⑤⑥⑦⑧
Yuen, H. K. 2019	2019	American	67.4 ± 7.4	72.2 ± 8.4	IPF	M:5 F:5	M:8 F:2	AT	Usual care	12 wk	10	10	①②
Selvadurai, H. C. 2002	2002	Canada	13.2 ± 2.0	13.2 ± 2.0	CF	M:19 F:25	M:9 F:13	AT-RT	Usual care	1 wk	44	22	④⑤⑥
Kriemler, S. 2013	2000.12–2001.3	Switzerland	21.8 ± 5.3	20.3 ± 4.6	CF	M:20 F:9	M:5 F:5	AT-ST	Usual care	1 yr	29	10	⑤⑥⑦

Mean ± standard deviation unless otherwise specified.

① = 6 minutes walking distance, ② = St. George's Respiratory Questionnaire, ③ = the Spanish version of the Cystic Fibrosis Questionnaire-Revised, ④ = the Quality of Well Being Scale, ⑤ = predicted forced vital capacity, ⑥ = predicted forced expiratory volume at 1 second, ⑦ = maximal rate of oxygen consumption, ⑧ = predicted diffusing capacity of the lung for carbon monoxide, AAT = anaerobic training, AT = aerobic training, CF = cystic fibrosis, Con. = control group, ET = endurance training, Exp. = experimental group, F = female, FT = flexibility training, IPF = idiopathic pulmonary fibrosis, M = male, NC = unrecorded, RT = resistance training, ST = strength training.

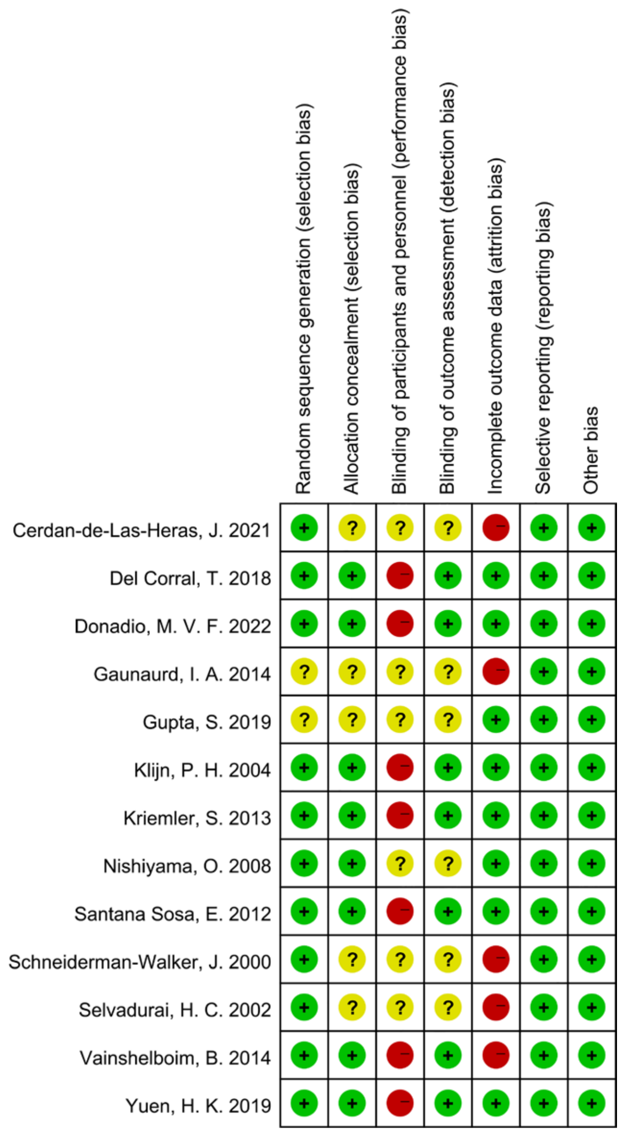

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

life with exercise training (SMD: 0.076; 95% CI: –0.54 to 6.55; I^2 = 79.1%; Z = 0.26, P = .798). Exercise training did not improve health-related quality of life in patients with IPF (SMD: –0.458; 95% CI: –1.513 to 0.598; I^2 = 84.4%; Z = 0.85, P = .396). For CF patients, exercise training significantly improved health-related quality of life (SMD: –0.458; 95% CI: –1.513 to 0.598; I^2 = 84.4%; Z = 0.85, P = .396). As shown in Table 2, aerobic resistance training and anaerobic training significantly improved health-related quality of life (Z = 2.10, P < .05; Z = 1.97, P < .05). Through subgroup analysis, we found that the duration of exercise training had a significant impact on heterogeneity, and the type of PF, exercise training and scale were not the source of heterogeneity (Table 2). Sensitivity analysis found that the effect of each study on heterogeneity was also small and the results were robust (Figure S2, Supplemental Digital Content, http://links.lww.com/MD/H928).

3.3.3. FVC% pred. The changes in FVC% pred after exercise training were reported by 6 studies.[17,18,25–27] The baseline values of a study were statistically different, so the data were not included.[22] Data from 5 studies were analyzed, involving 140 participants in the exercise group and 109 in the control group. As shown in Figure 5, differences between the 2 groups support the effectiveness of exercise training (WMD: 3.159; 95% CI: 0.008–6.311; I^2 = 69.3%; Z = 1.96, P < .05). Subgroup analysis in Table 2 showed that the change of FVC% pred in IPF patients after exercise training was significantly greater than that in the control group (Z = 2.11, P < .05). The duration of exercise training for more than 1 year was significant for the improvement of FVC% pred (Z = 2.50, P < .05), and aerobic strength training had a supportive effect on FVC% pred (Z = 3.18, P < .01). However, the type of PF, duration of exercise training, and type of exercise training were not source of heterogeneity (Table 2). Due to high heterogeneity, sensitivity analysis was conducted to exclude all studies, and heterogeneity change was not significant, and the results were robust (Figure S3, Supplemental Digital Content, http://links.lww.com/MD/H929). The results of meta-regression analysis showed that gender ratio had a significant influence on FVC% pred (Z = –2.27, P < .05) (Table S2, Supplemental Digital Content, http://links.lww.com/MD/H926).

3.3.4. FEV1% pred. The changes in FEV1% pred after exercise training were reported by 5 studies.[17,18,25–27] One study showed that exercise training did not improve FEV1% pred.[18] There were 140 participants in the exercise group and 109 in the control group. Data analysis of 5 studies showed that the differences between the 2 groups supported the effectiveness of exercise training (WMD: 4.266; 95% CI: 0.579–7.953; I^2 = 54.4%; Z = 2.27, P < .05), as shown in Figure 6. Subgroup analysis in Table 2 showed that exercise training duration less than 12 weeks supported the improvement of FEV1% pred (Z = 2.03, P < .05). Both aerobic strength training and aerobic resistance training can significantly increase FEV1% pred (Z = 2.93, P < .01; Z = 2.03, P < .05). The type of PF, duration of exercise training, and type of exercise training had little effect on heterogeneity. Sensitivity analyses were performed and found that heterogeneity was low for each study (Figure S4, Supplemental Digital Content, http://links.lww.com/MD/H930). The reasons for heterogeneity were explored through meta-regression analysis, and gender ratio also had no effect on heterogeneity (Table S2, Supplemental Digital Content, http://links.lww.com/MD/H926).

3.3.5. VO_2 peak. The effect of exercise training on VO_2 peak were reported by 5 studies.[17,19,24,27,28] Significant differences in VO_2 peak between groups after exercise training were demonstrated in 4 studies.[17,24,27,28] Another study found that exercise training had no effect on VO_2 peak.[19] Data came from 5 studies involving 66 participants in the exercise group and 57 in the control group. The analysis results are shown in Figure 7. Compared with the control group, VO_2 peak in the exercise group has a significant positive increase (WMD: 2.882; 95% CI: 1.838–3.927; I^2 = 43.1%; Z = 5.41, P < .01). As shown in Table 2, the results of subgroup analysis suggested that exercise training can significantly improve VO_2 peak in both IPF and CF (Z = 3.39, P < .01; Z = 4.25, P < .01). When the exercise training time was more than 12 weeks and less than 1 year, the influence on VO_2 peak is significant (Z = 4.44, P < .01). Aerobic training, anaerobic training and aerobic resistance training could effectively improve VO_2 peak (Z = 2.37, P < .05; Z = 2.13, P < .05; Z = 2.10, P < .05). The type of PF, duration of exercise training, and type of exercise training had a low effect on heterogeneity (Table 2). To find the source of heterogeneity, sensitivity analysis and meta-regression analysis were performed. The results showed that each influencing factor had a low impact on heterogeneity (Table S2, Supplemental Digital Content, http://links.lww.com/MD/H926 and Figure S5, Supplemental Digital Content, http://links.lww.com/MD/H931).

3.3.6. DLCO% pred. The effect of exercise training on DLCO% pred changes were reported by 2 studies.[17,22] There

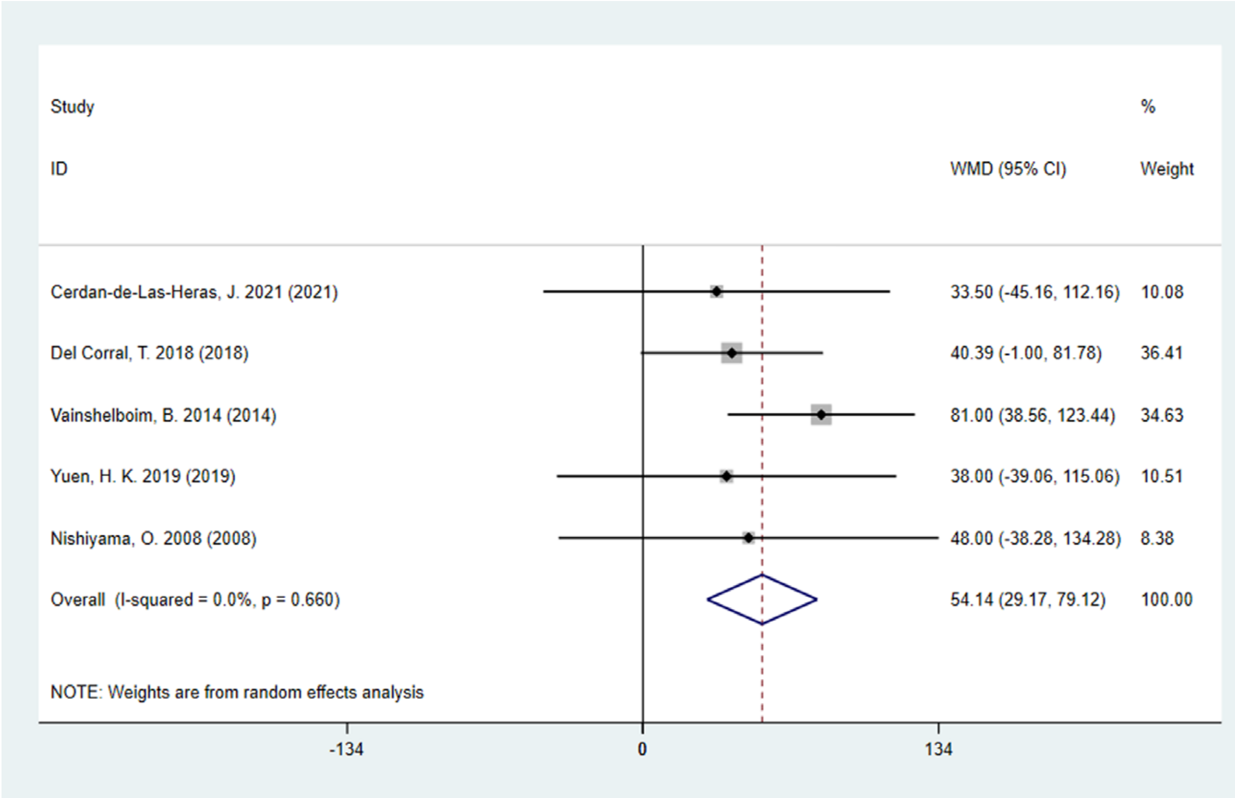

Figure 3. Forest plot of comparison: change in 6-minute walk distance.

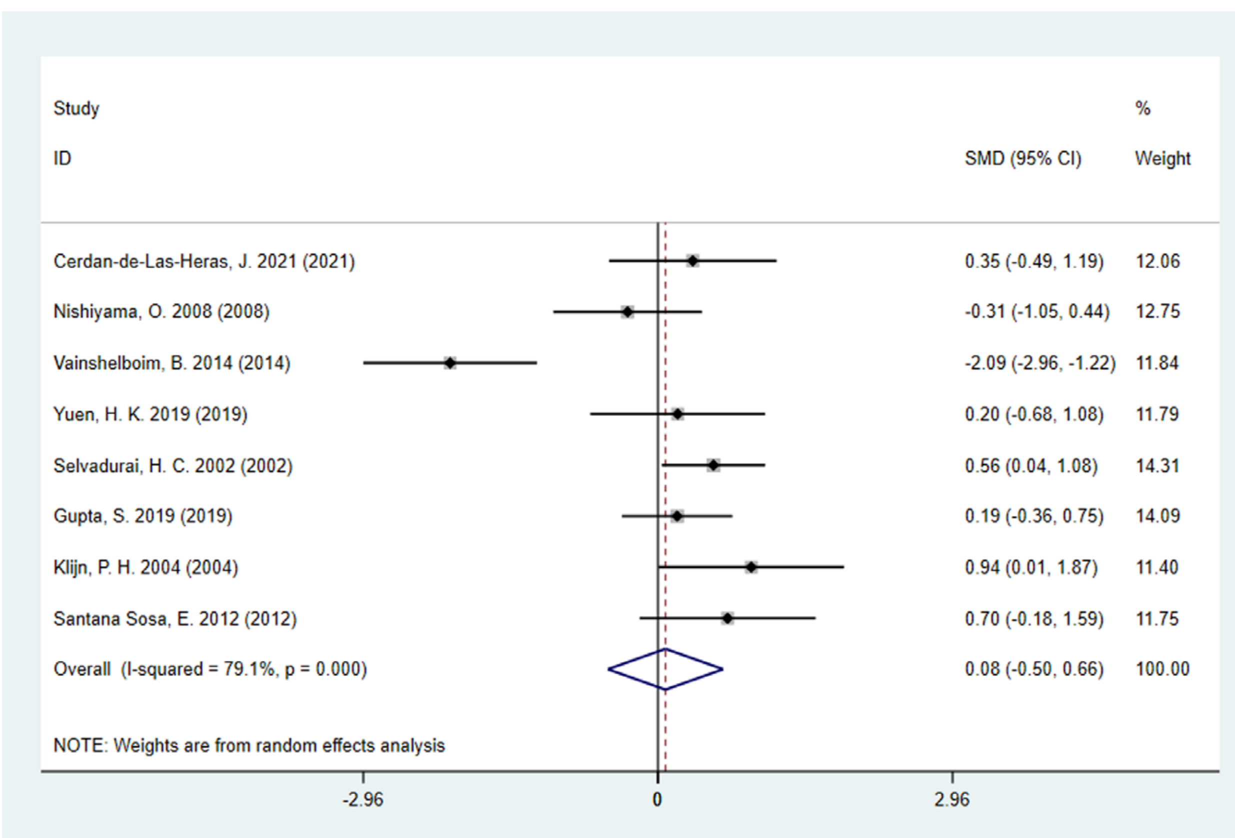

Figure 4. Forest plot of comparison: change in quality of life.

Table 2

Subgroup analysis results.

	Group standard	Sample size (n) (Exp/Con)	Mean difference (95% CI)	Z	I^2	P
Quality of life						
Pulmonary fibrosis type	IPF	49/53	−0.458 (−1.513, 0.598)	0.85	84.40%	.396
	CF	90/67	0.498 (0.171, 0.825)	2.98	0.00%	.003
Duration of exercise training	<12 wk	23/26	0.168 (−0.815, 1.152)	0.34	65.40%	.737
	12 wk ≤ × < 1 yr	116/94	0.039 (−0.701, 0.779)	0.10	83.70%	.917
Type of exercise training	AT	46/49	−0.210 (−1.450, 1.031)	0.33	87.70%	.74
	ST	13/15	−0.305 (−1.052, 0.442)	0.80	−%	.424
	AT-RT	44/22	0.558 (0.037, 1.079)	2.10	−%	.036
	RT	25/25	0.194 (−0.362, 0.749)	0.68	−%	.495
	AAT	11/9	0.938 (0.005, 1.871)	1.97	−%	.049
Types of scales	SGRQI	49/53	−0.458 (−1.513, 0.598)	0.85	84.4%	.396
	CFQ-R	46/45	0.474 (0.028, 0.919)	2.09	8.0%	.037
	QWBS	44/22	0.558 (0.037, 1.079)	2.10	−%	.036
FVC% pred						
Pulmonary fibrosis type	IPF	15/17	6.000 (0.421, 11.579)	2.11	−%	.035
	CF	125/92	2.553 (−0.907, 6.014)	1.45	71.20%	.148
Duration of exercise training	12 wk ≤ × < 1 yr	110/74	4.803 (−1.428, 11.034)	1.51	75.70%	.131
	>1 yr	30/35	2.170 (0.467, 3.873)	2.50	−%	.013
Type of exercise training	AT	45/52	3.126 (−0.123, 6.375)	1.89	39.60%	.059
	RT	25/27	0.130 (−10.785, 11.045)	0.02	−%	.981
	AT-RT	44/22	0.115 (−2.068, 2.298)	0.10	−%	.918
	AT-ST	26/8	15.558 (5.965, 25.251)	3.18	−%	.001
FEV1% pred						
Pulmonary fibrosis type	IPF	15/17	7.200 (−0.711, 15.111)	1.78	−%	.072
	CF	125/92	3.830 (−0.337, 7.998)	1.80	60.50%	.074
Duration of exercise training	<12 wk	44/22	3.805 (0.129, 7.481)	2.03	−%	.043
	12 wk ≤ × <1 yr	66/52	7.553 (−2.376, 17.483)	1.49	61.20%	.136
	>1 yr	30/35	2.010 (−0.059, 4.079)	1.90	−%	.057
Type of exercise training	RT	25/27	−2.840 (−15.913, 10.233)	0.43	−%	.67
	AT	45/52	3.143 (−1.059, 7.345)	1.47	35.40%	.143
	AT-ST	26/8	17.306 (5.738, 28.873)	2.93	−%	.003
	AT-RT	44/22	3.805 (0.129, 7.481)	2.03	−%	.043
VO_2 peak						
Pulmonary fibrosis type	IPF	15/17	2.600 (1.097, 4.103)	3.39	−%	.001
	CF	51/40	3.146 (1.694, 4.598)	4.25	55.70%	0
Duration of exercise training	<12 wk	18/22	2.988 (−4.171, 10.148)	0.82	75.40%	.413
	12 wk ≤ ×<1 yr	48/35	2.557 (1.427, 3.687)	4.44	0.00%	0
Type of exercise training	AT	25/28	4.095 (0.702, 7.489)	2.37	75.80%	.018
	RT	8/11	−1.300 (−7.824, 5.224)	0.39	−%	.696
	AAT	11/10	2.100 (0.164, 4.036)	2.13	−%	.033
	AT-ST	22/8	3.948 (0.271, 7.625)	2.10	−%	.035

AAT = anaerobic training, AT = aerobic training, CF = cystic fibrosis, CFQ-R = the Spanish version of the Cystic Fibrosis Questionnaire-Revised, FEV1% pred = predicted forced expiratory volume at 1 second, FVC% pred = predicted forced vital capacity, IPF = idiopathic pulmonary fibrosis, QWBS = the Quality of Well Being Scale, RT = resistance training, SGRQI = St. George's Respiratory Questionnaire, ST = strength training, VO_2 peak = maximal rate of oxygen consumption.

were 26 participants in the exercise group and 28 in the control group. As shown in Figure 8, there was no significant difference in DLCO% pred between groups after exercise training (WMD: 2.132; 95% CI: −3.256 to 7.519; I^2 = 0.0%; Z = 0.78, P = .438).

3.4. Publication bias

Egger regression test was used to assess the potential publication bias of the included studies. We examined 6MWD, quality of life, FVC% pred, FEV1% pred and VO_2 peak. The results showed P > .05 without publication bias (Table 3).

3.5. Assessment of the certainty of the evidence identified

The certainty of the evidence for the outcomes of exercise were high, moderate and low, respectively (Table 4).

4. Discussion

Unlike the effect of exercise training on interstitial lung disease or the effect of exercise combined with respiratory training on PF, the aim of this study was to explore the effect of exercise training on PF. The results of the present study suggest that exercise training can improve exercise capacity, lung function, and cardiopulmonary endurance. For patients with moderate to severe lung disease, the 6MWD is a commonly used test to objectively assess functional motor capacity.[33] Our results show that exercise training significantly increases walking distance in patients with PF. The mean between-group difference in 6MWD after exercise training was 54 m, which is above the threshold for a clinically meaningful difference in 6MWD in IPF (i.e., 24–45 m).[34] In addition, despite the wide age span of our study, there was no effect on 6MWD, which is consistent with previous findings. Therefore, different age groups of patients with PF had similar benefits from exercise training.[35,36] A previous study showed that exercise training was effective in short-term improvement of 6MWD in patients with PF, which supported our analysis results.[37] Therefore, the current synthesis of evidence supports the idea that exercise training can increase the 6-minute walking distance in patients with PF.

Exercise intolerance, often seen in patients with PF, is characterized by dyspnea and fatigue, with a significant impact on health-related quality of life. Our analysis showed no significant

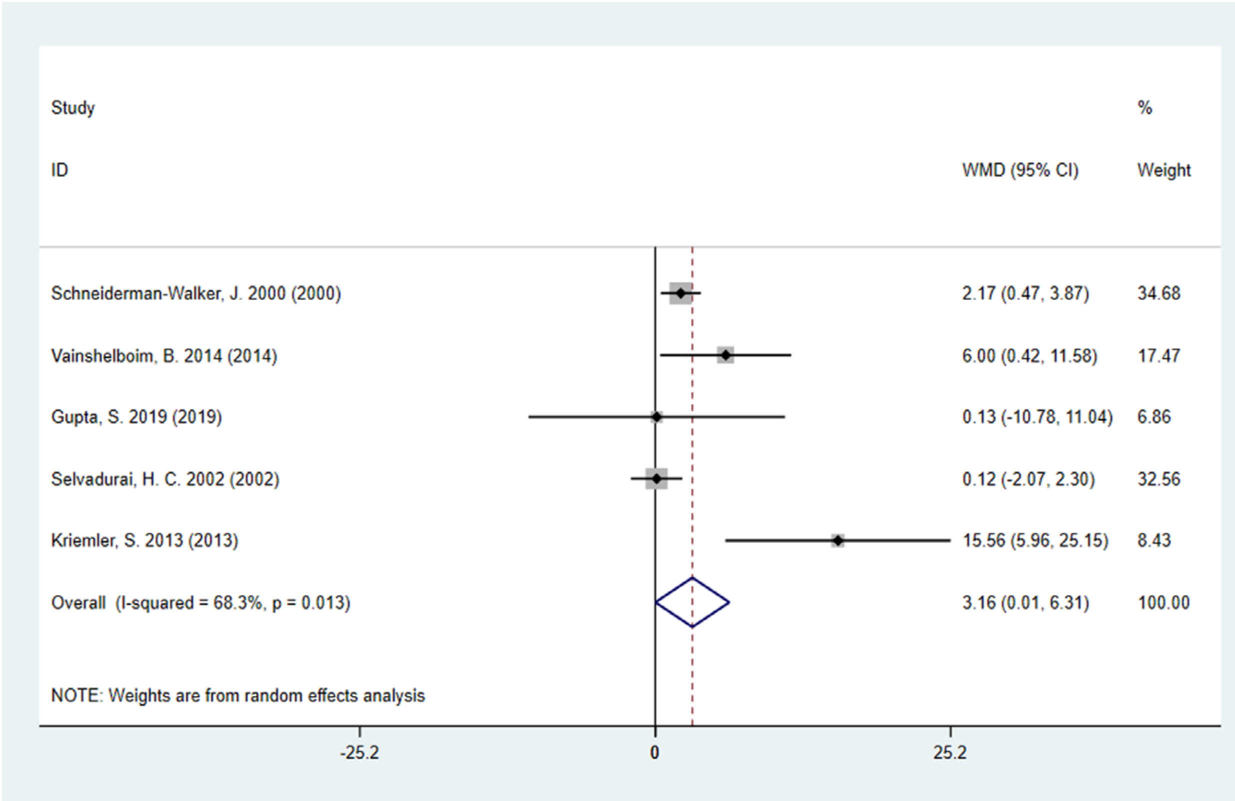

Figure 5. Forest plot of comparison: change in predicted forced vital capacity (FVC% pred).

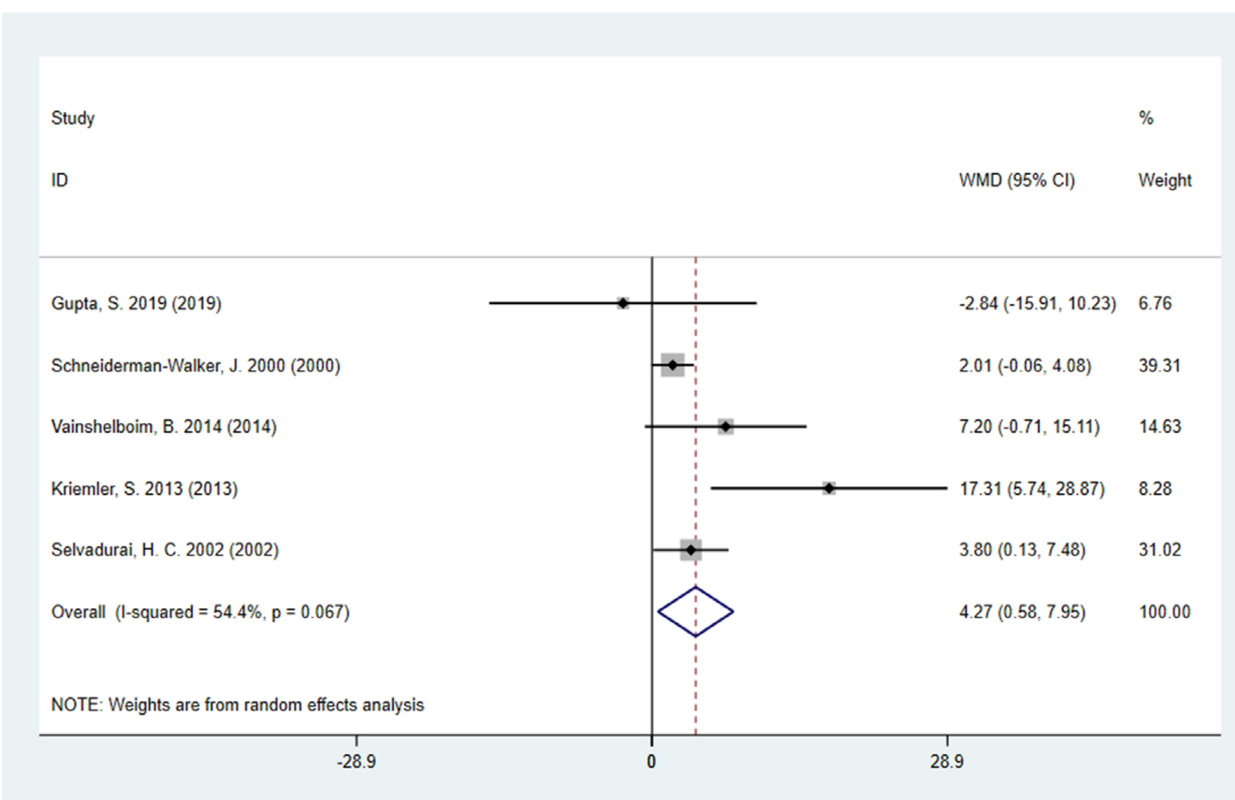

Figure 6. Forest plot of comparison: change in predicted forced expiratory volume at 1 second (FEV1% pred).

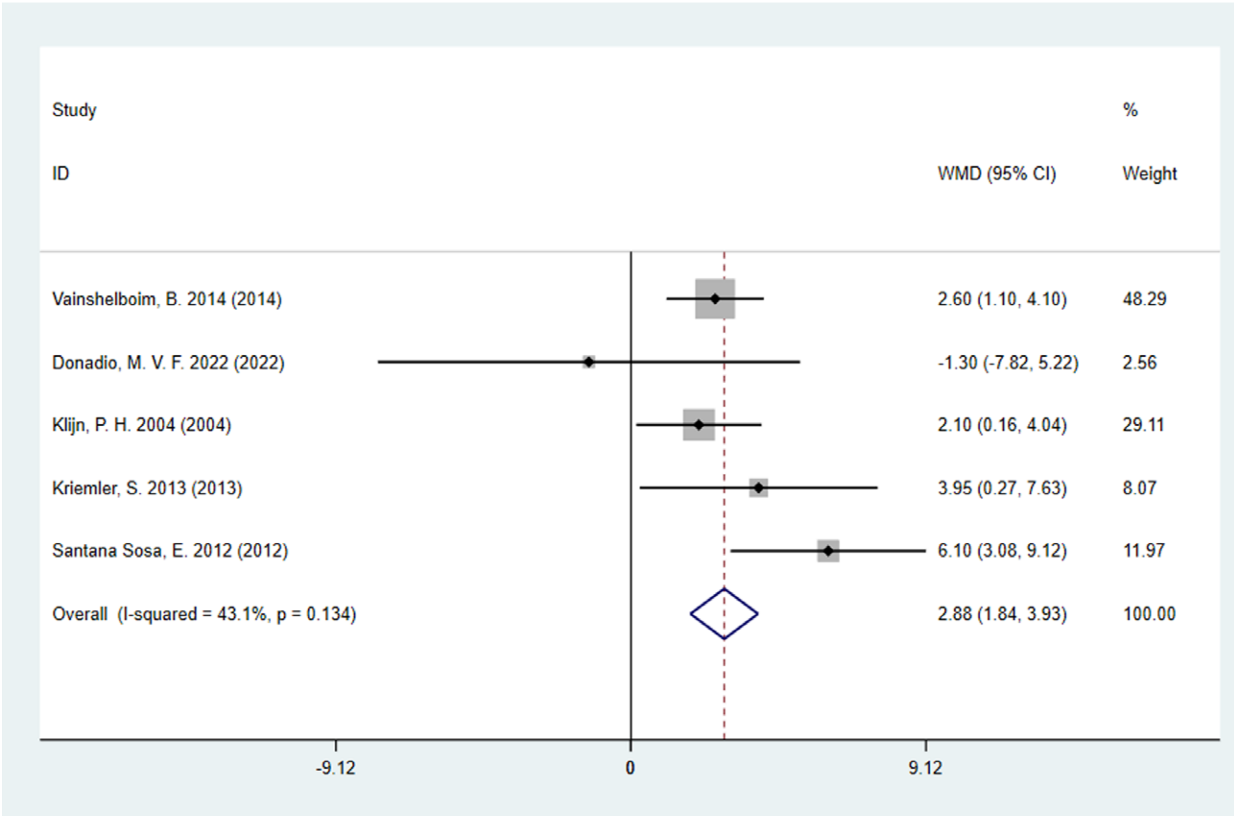

Figure 7. Forest plot of comparison: change in maximal rate of oxygen consumption (VO_2 peak).

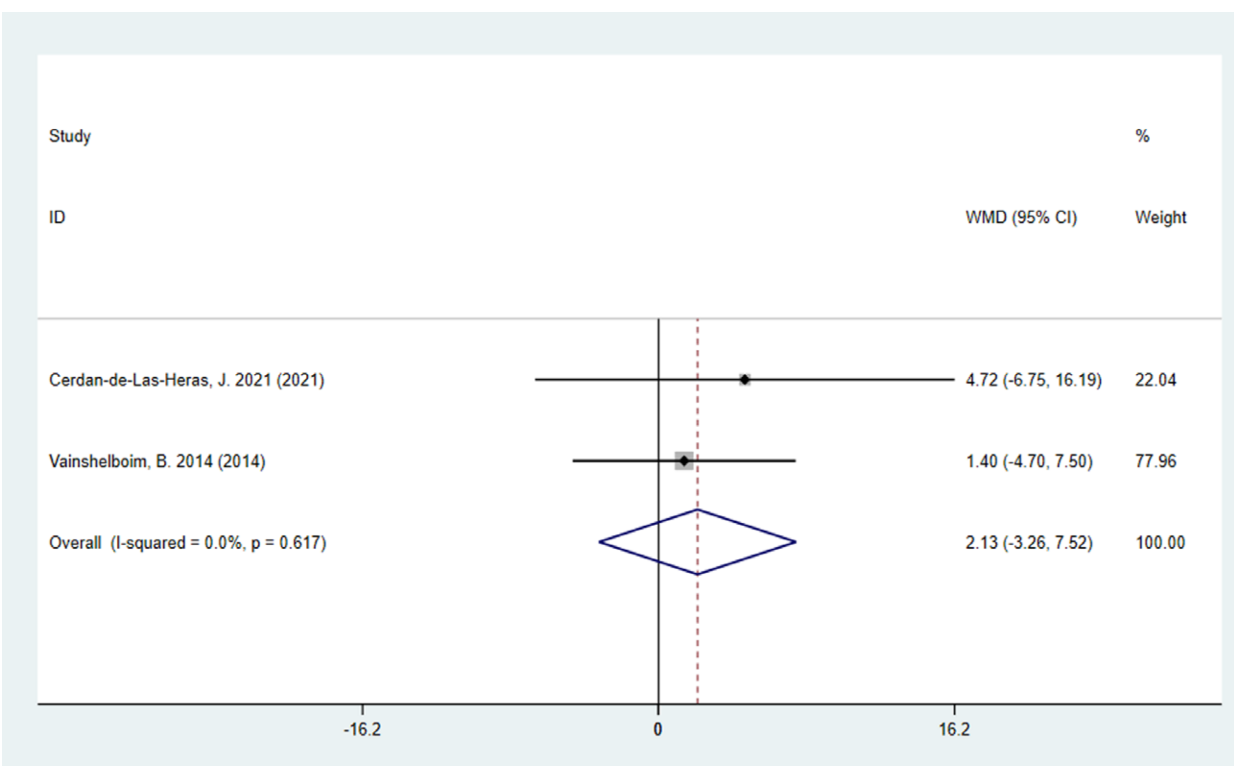

Figure 8. Forest plot of comparison: change in predicted diffusing capacity of the lung for carbon monoxide (DLCO% pred).

difference in changes in quality of life scores after exercise. However, exercise training significantly improved the quality of life of CF patients. The heterogeneity of the assessment for IPF patients was large, which was consistent with the findings of Vainshelboim et al.[12] This may be related to the disease severity of IPF. IPF is a progressive PF disease with different degrees and

Table 3

Egger regression test.

	t	*P* > |*t*|	95% CI	
6MWD	−0.84	0.463	−4.623855	2.694772
Quality of life	−0.59	0.574	−10.99513	6.699801
FVC% pred	1.26	0.298	−2.475985	5.702927
FEV1% pred	1.23	0.307	−2.054953	4.638131
VO_2 peak	0.17	0.878	−4.84086	5.375305

6MWD = 6 minutes walking distance, CI = confidence interval, FEV1% pred = predicted forced expiratory volume at 1 second, FVC% pred = predicted forced vital capacity, VO_2 peak = maximal rate of oxygen consumption.

Table 4

Assessing the certainty of the evidence presented for each outcome.

No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Exercise	Usual care	Absolute (95% CI)	Certainty
6MWD										
5	Randomized trials	Not serious	Not serious	Not serious	Not serious	No effect was observed	68	73	MD 54.14 higher (29.17 higher than 79.12 higher)	⨁⨁⨁⨁ HIGH
Quality of life										
8	Randomized trials	Serious*	Serious†	Not serious	Not serious	No effect was observed	139	120	SMD 0.08 higher (−0.50 lower than 0.66 higher)	⨁⨁○○ LOW
FVC% pred										
5	Randomized trials	Serious*	Not serious	Not serious	Not serious	No effect was observed	140	109	MD 3.16 higher (0.01 higher than 6.31 higher)	⨁⨁⨁⨁ HIGH
FEV1% pred										
5	Randomized trials	Serious*	Not serious	Not serious	Not serious	No effect was observed	140	109	MD 4.27 higher (0.58 higher than 7.95 higher)	⨁⨁⨁○ MODERATE
VO_2 peak										
5	Randomized trials	Not serious	Not serious	Not serious	Not serious	No effect was observed	66	57	MD 2.88 higher (1.84 higher than 3.93 higher)	⨁⨁⨁○ MODERATE
DLCO% pred										
2	Randomized trials	Not serious	Serious†	Not serious	Not serious	No effect was observed	26	28	MD 2.13 higher (−3.26 lower 到 7.52 higher)	⨁⨁○○ LOW

6MWD = 6 minutes walking distance, CI = confidence interval, FEV1% pred = predicted forced expiratory volume at 1 second, FVC% pred = predicted forced vital capacity, MD = mean difference, SMD = standardised mean difference, VO_2 peak = maximal rate of oxygen consumption.
*The random sequence generation not clear in one research.
†CIs are wide; they cross the line of no effect.

speeds of progression.[38] Our study did not define the severity of PF, so some patients may develop rapidly, while others will develop slowly or even enter a stable stage. Therefore, this progressive effect can affect the function of IPF patients, and thus affect the quality of life of patients. Another study showed that patients with PF had certain differences in response and adaptation to exercise training, so the duration of exercise training would affect patients' evaluation of quality of life.[8] The present study also found that the duration of exercise training has a significant impact on heterogeneity. However, changes in the duration of exercise training did not have a positive effect on patients' quality of life, probably due to the small sample size in this study, and the time didn't perform as a main effect. Therefore, larger randomized controlled trials are needed to explore the effects of the formulation of exercise prescription (the duration, intensity, and frequency of exercise training) on the quality of life of patients with PF at different stages.

Our analysis supported that exercise training increased FVC% pred and FEV1% pred, but had no effect on DLCO% pred. FVC and DLCO are the best lung function parameters to reflect the overall degree of parenchymal abnormalities in PF.[39] Patients with PF typically experience a decline in FVC, worsening dyspnea, and declined cardiopulmonary endurance. When FVC decreased by more than 10%, patients had twice the risk of death as those with an FVC decrease of less than 5%.[40] Meanwhile, a decrease in DLCO greater than 15% was a strong predictor of mortality.[41] But only 2 studies have reported changes in DLCO% pred, so the results need to be treated with caution. The positive effects of exercise training on FVC% pred and FEV1%pred reflect that exercise training improves exercise tolerance and increases airway ventilation in patients with PF, and this effective exercise breathing pattern has been demonstrated in patients with chronic obstructive pulmonary disease.[42] In addition, the type and duration of exercise training varied among the included trials. Combined exercise training may be an effective way to improve respiratory function. Subgroup analyses showed that combined aerobic and strength training and combined aerobic and resistance training had positive effects on respiratory function improvement. However, the mechanism of combined exercise training improves PF remains unclear. The underlying reason may be that combined training can improve the exercise endurance of patients to a greater extent than a single type of training, increase the frequency of air exchange during exercise, and then improve the ventilation level. Although subgroup analysis showed that training duration of less than 12 weeks or more than 1 year was effective in improving patients' respiratory capacity, due to the limited data, it is difficult to determine the optimal duration of exercise training.

PF often leads to impaired pulmonary gas exchange, leading to hypoxemia, hence increased pulmonary vasoconstrictor resistance, and ultimately to increased right ventricular afterload and left ventricular preload.[43] We investigated the effect of exercise training on cardiopulmonary endurance in patients with PF and found that VO_2 peak was improved by exercise. This may be due to the increased sympathetic excitability induced by exercise training, which induces a faster heart rate and increases cardiac output. Secondly, exercise training can reduce the contractility of smooth muscle cells, reduce the resistance of pulmonary vascular contraction, and further relieve the load of heart and lung. In a case report, VO_2 peak increased at 1.5 years after a supervised combined exercise training program in a man with IPF, remaining above the level of poor prognosis at 2 years.[44] However, due to limited data, we could not explore the long-term effects of exercise training on VO_2 peak. Vainshelboim's study suggested that the influence of supervised exercise training on VO_2 peak was different from that of unsupervised exercise training.[45] Our study did not examine cardiopulmonary endurance adaptations induced by supervised exercise training, a factor that might bias our findings. Therefore, the main mechanism of exercise training affecting cardiopulmonary endurance needs to be further discussed.

We need to acknowledge that this study has some limitations. First, the focus of our study was on exercise training in a population with PF; however, the reason that may be detrimental to our results is that PF is a progressive disease, and its severity has an important effect on the exercise capacity of the patient. Exercise training programs should therefore be individualized to the individual patient. Second, we included 2 types of PF, including IPF and CF. However, IPF patients are elderly people, and CF patients are adolescents, and their exercise tolerance is not consistent. Therefore, it is not possible to conduct a specific association study according to the patient's exercise prescription (exercise intensity, duration and frequency). Also, although most studies showed the same exercise training patterns, this meta-analysis included resistance, endurance, and strength training in addition to aerobic training. It was therefore not possible to examine the effect of training type on PF. Third, to assess the effect of exercise training on patients' health-related quality of life, we analyzed only changes in the total score on the scale. However, scores in other domains included in the scale may have potentially influenced our findings. More and more studies have shown that supervised exercise training has a better effect on PF. This review does not limit training compliance, and future studies could look at the role of supervised training.

5. Conclusion

Exercise training can improve the exercise capacity, lung function and cardiopulmonary endurance of patients with PF, and significantly improve the quality of life of CF patients, but the impact on the quality of life of IPF patients is not significant.

Author contributions

Conceptualization: Yan Gao, Zhaoyun Yang, Jiang Yi, Lijing Zhao.
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Software: Kang He.
Supervision: Lijing Zhao.
Writing – original draft: Yan Gao, Zhaoyun Yang.
Writing – review & editing: Yan Gao, Jiang Yi, Lijing Zhao.

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