

Effects of exercise-based pulmonary rehabilitation on children with asthma:a systematic review and network meta-analysis

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Abstract

Objective: This systematic review aimed to systematize different designs of exercise-based pulmonary rehabilitation (PR) for children with asthma and explore which designs are optimal. **Methods:** PubMed, EMBASE, Cochrane Library, Web of Science Core Collection and MEDLINE were searched up until April 01, 2021, which was conducted for any relevant randomized controlled trials (RCTs) of exercise-based PR in childhood asthma. Language is limited to English. Network meta-analyses and standard meta-analyses were performed using STATA (version 16.0), quality analyses were performed using RevMan (version 5.3). **Results:** A total of 24 RCTs involving 1031 patients were included. 14 studies were endurance training, which was the most commonly used form of exercise, and 7 studies rehabilitation sites were conducted in hospitals. A network meta-analysis showed that compared with other forms of exercise, interval training significantly improved the PAQLQ (Pediatric Asthma Quality of Life Questionnaire), including activity scores [MD=3.02, 95% CI (1.74,4.30)], symptom scores [MD=2.68, 95% CI (2.04,3.32)], emotional scores [MD=2.47, 95% CI (0.91,4.03)], and total scores [MD=2.68, 95% CI (1.79,3.57)]. Interval training [MD=188.97, 95% CI (-59.27, 437.21)] also had a more significant effect on the 6MWT (6-minute walk test). No adverse events were found in this study. Exercise training had no significant effect on FEV₁ (the forced expiratory volume at 1s to predicted value ratio) [WMD=0.59, 95% CI (-2.00, 3.19)], however, the combined of endurance training and respiratory training was found to significantly improve both FVC (the forced vital capacity to predicted value ratio) [MD=5.37, 95% CI (0.07,10.67)] and FEF_{25-75%} (the forced expiratory flow between 25% and 75% of vital capacity ratio) [WMD=11.31, 95% CI (2.13, 20.48)]. **Conclusions:** Exercise-based PR is a safe and effective for childhood asthma. Interval training may be a core component of improving quality of life and exercise capacity in childhood asthma, the combination of respiratory training and endurance training has significant effects on lung function. This result should be viewed with caution, and high-quality RCTs are still needed to confirm its clinical efficacy,

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Abstract

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Keyword: asthma, children, pulmonary rehabilitation, network meta-analysis, Systematic review

1. Background

Asthma in children is a common non-infectious chronic respiratory disease characterized by episodic and persistent airflow restriction, with symptoms of wheezing, coughing, chest tightness and shortness of breath [1,2]. Asthma has become more common globally in recent years, which is one of the most important global public health problems. It is estimated that around 300 million people suffer from asthma, and the incidence of asthma is likely to increase as the proportion of the urban population increases [3]. The prevalence of asthma in children (9.5%) is higher than adults (7.7%), and women (9.2%) higher than men (7.0%) [4]. Approximately 157,000 children hospitalized with asthma and 640,000 emergency room visits are recorded in the United States [5]. Asthma negatively affects children's quality of life, exercise capacity, and lung function, while increasing family stress and socioeconomic burden [6]. Treatment goals for childhood asthma are to minimize the negative impact of these events and prevent their recurrence.

Currently, β_2 -agonists and glucocorticoids, as the main drugs for childhood asthma, are widely used in clinical practice, but most of the drugs have side effects. Therefore, safer and more effective interventions are being explored. As a core component of non-drug therapy, PR is a comprehensive intervention that mainly includes exercise training, family education, and health education, aiming to improve the physical and mental health of patients and promote long-term health [7,8]. Exercise training as the cornerstone of PR, mainly including endurance training, resistance/strength training, inspiratory muscle training, interval training, and neuromuscular electrical stimulation [8], and has been shown to improve asthma symptoms and severity, quality of life, and lung function [9-11]. After a search we found that formal PR programs are very rare in a child environment, and there is a lack of data describing potential benefits for childhood

asthma, especially whether exercise-based PR can be used as an adjunctive treatment for childhood asthma. Thus, this systematic review aimed to systematize the different designs used to provide exercise-based PR designs for childhood asthma and explore which ones are the most effective.

METHODS

2.1 Search strategy

The International Register of Prospective Systematic Reviews (PROSPERO) and the Cochrane Library were searched for no similar studies. The systematic review protocol is registered on the PROSPERO website (www.crd.york.ac.uk/Prospero), number CRD42022326995. PubMed, EMBASE, Cochrane Library, Web of Science Core Collection and MEDLINE were searched up until April 01, 2021, which was conducted for any relevant randomized controlled trials (RCTs) of exercise-based PR in childhood asthma. The language restriction is English.

Taking into account the possible differences between different databases, the retrieval strategy was adjusted accordingly. Detailed search strategy and steps can be found in Appendix 1 of the Supplementary Material. Additionally, we also read citations to relevant articles retrieved to ensure inclusion.

2.2 Inclusion criteria

Inclusion criteria include the following: (a) Research subjects: childhood asthma who were under 18 years old. All meet the diagnostic standard of GINA childhood asthma [12], and the sex, race were not restricted. (b) Intervention: Any exercise-based PR technique, such as endurance exercise (cycling, running, yoga, basketball, Tai Chi, etc.), strength training, interval training, etc. (c) Control: conventional treatment includes medication, standard care, or routine activities without exercise. (d) Outcome: exercise capacity (measured by 6MWT), Quality of life indicators (measured by PAQLQ: total score, activity scores, symptom scores, emotional scores). Lung function (measured by FEF_{25-75%} pred, FEV_{1%} pred and FVC% pred). (e) Type of study: randomized controlled trial. (f) Language: English only.

2.3 Exclusion criteria

The exclusion criteria include any of the following: (a) Non-English language studies; (b) Full-text literature that cannot be obtained through various channels; (c) Participants with pulmonary disease other than asthma; (d) Conferences, guidelines, reviews, animal experiments; (e) Non-randomized controlled trials with study designs that were, retrospective, observational, cohort, and case-control studies.

2.4 Study selection

NoteExpress software was used for research screening. First, two researchers (J Jiang and ZG Wu) independently screened and checked the titles and abstracts of articles to exclude duplicate and irrelevant studies. Second, the full text of potentially eligible studies was downloaded and reviewed according to the inclusion and exclusion criteria stated above. Finally, when inconsistencies or disagreements arose, a third author (W Zhang) assisted in resolving the issue.

2.5 Data extraction

Two authors (J Jiang and D Zhang) independently extracted data and cross-checked, disagreements were resolved with the help of W Zhang. The extracted contents included: (a) Basic research information: first author and publication year; (b) Study characteristics: patient age, sample size, intervention measures, intervention site, treatment frequency and treatment time. (c) Outcome measures were as follows: 6MWT, PAQLQ, FEF_{25-75%} pred, FEV_{1%} pred and FVC% pred.

2.6 Quality assessment

Risk of bias was used the Cochrane Collaboration's risk of bias assessment tool [13]. Two authors (J Jiang and YP Huang) independently rated each study as "high", "low", "unclear" for risk of bias assessment, W Zhang helped resolve when disagreements were reached. The evaluation tools mainly include the method of random

allocation sequence, blinding of subjects or trial personnel, blinding of outcome assessors, completeness of outcome data, selective reporting, allocation concealment, and other sources of bias.

2.7 Data analysis

All network meta-analyses and standard meta-analyses were performed using the STATA (16.0 version). Continuous variables were expressed as weighted MD (WMD) or mean difference (MD), and 95% confidence intervals (95% CI) were calculated. The adjusted indirect comparisons were performed with MD and 95% CI to assess the indirect comparisons different types of exercise PR on childhood asthma quality of life, lung function and exercise capacity. We conducted a subgroup analysis of FEV₁ and FEF_{25-75%} based on different interventions to reduce heterogeneity and address potential confounding.

Results

Search results

A total of 10208 studies were retrieved, of which 1877 studies were replicated. By screening titles and abstracts, 55 studies were considered potentially eligible. After reading the full text, 24 studies [14-37] were finally included (Fig1).

3.2 Study characteristics

The characteristics of the 24 studies are summarized in Table 1. (a) Study characteristics: A total of 7 interventions are endurance training; endurance and respiratory training; endurance, resistance and respiratory training; endurance and strength training; respiratory and strength training; respiratory training; interval training. A single training modality included 14 studies [15,17,18,21,23,25,26,28,29, 31-33,36,37] of endurance training, 2 studies [27,35] of interval training, and 1 study [24] of respiratory muscle training; (b) The treatment time of the study is different, ranging from the time of up to 4-52 weeks. Most frequent timings to begin intervention were 12 W (n=9) [16,18,23,25,27,29,33,34,37], 6 W(n=6) [15,21,22,28,32,36]; (c) Most of the studies treatments frequency are different, from 1 to 6 times per week. Most of the study treatment frequency were 3 times per week (n=12) [14-17,22, 25-27,29,32,36,37]. 2 times per week (n=6) [20,21,23,30,31,34]. (d) Most studies were conducted in hospital settings (n=7) [14,16-18,23,26,32], followed by patients' home (n=2) [19,33], school (n=2) [24,35]. Some studies did not mention the specific location of children's exercise (Table.1).

3.3 Risk of bias evaluation

24 RCTs were evaluated for literature quality. Ten studies reported a generation of random sequences, one study was a random draw [20], six for random number table [15,16,18,21,23,34], two for randomized envelope [17,32], one for random sampling [33]. Of note, four studies [14,15,17,32] reported using the allocation concealment and one study [19] mentioned double-blinding, the risk of bias evaluation is summarized in (Fig. 2, 3)

3.4. Standard meta-analysis

3.4.1. FEV₁%

15 studies [14,17-19,21-23,25,26,30-34,36,37] provided numerical data for the FEV₁, five comparisons against control were performed (Fig. 4a). Compared with the conventional treatment, there was no significant difference: endurance training [WMD=-0.05, 95% CI (-4.75, 3.66)], endurance and strength training [WMD=1.00, 95% CI (-8.80, 10.80)], endurance and respiratory training [WMD=0.35, 95% CI (-7.32, 8.02)], endurance, resistance and respiratory training [WMD=5.19, 95% CI (-2.38, 12.75)], respiratory and strength training [WMD=-2.45, 95% CI (-8.38, 3.48)], endurance and respiratory training [WMD=4.23, 95% CI (-2.68, 11.14)]. After combined analysis, there was no statistical significance between exercise PR and lung function FEV₁ [WMD=0.59, 95% CI (-2.0,3.19)] (Fig. 4b).

3.4.2. FEF_{25-75%}

7 studies [19,21-24,36,37] were included in the analysis and three comparisons with the control group (Fig. 5a). Compared with conventional treatment, endurance and respiratory training [WMD=11.31, 95% CI (2.13,20.48)], endurance training [WMD=0.74, 95% CI (-4.11, 5.58)], respiratory and strength training [WMD=1.29, 95% CI (-13.39,15.97)]. After combined analysis, FEF25-75% [WMD=4.07, 95% CI (-0.62, 8.77)], the difference was not statistically significant (Fig. 5b).

3.5. Network meta-analysis

3.5.1. FVC%

9 studies [18-23,26,31,37] were included in the analysis and two comparisons with the control group (Fig. 6a). 9 pairwise comparison was included. Endurance training [MD=2.93, 95% CI (0.73, 5.14)], endurance and respiratory training [MD=5.37, 95% CI (0.07, 10.67)]. The ranking probability of SUCRA sorting chart is from high to low: endurance and respiratory training, endurance training, conventional treatment (88.8%, 59.8%, 1.4%), endurance and respiratory training was superior to endurance training in lung function FVC(Fig. 6b-d).

3.5.2 6MWT

3 studies [17,26,27] provided 6WMT data for analysis, two comparisons were made with the control group (Fig. 7a). Compared with conventional treatment, endurance training [MD=2.93, 95% CI (0.73,5.14)], interval training [MD=188.97, 95% CI (-59.27, 437.21)]. The ranking probability of SUCRA sorting chart is from high to low: Interval Training, Endurance Training, Conventional treatment (82.4%, 56.9%, 10.7%). The results show interval training has a significant effect on exercise capacity (Fig. 7b-d).

3.5.3 PAQLQ

6 studies [15-17,26,27,34] provided PAQLQ data for meta-analysis, four comparisons with the control group (fig. 8a). The four parts of the PAQLQ: activity scores, symptoms scores, emotional scores, and total scores were analyzed. Compared with conventional treatment, both endurance training and interval training improved PAQLQ. Endurance training was in the activity scores [MD=1.32, 95% CI (0.60,2.03)], symptoms scores [MD=1.15, 95% CI (0.78,1.52)], emotional scores [MD=1.25, 95% CI (0.39,2.12)], total scores [MD=1.16,95% CI (0.66,1.66)]. Interval training was in the activity scores [MD=3.02, 95% CI (1.74, 4.30)], symptoms scores [MD=2.68, 95% CI (2.04, 3.32)], emotional scores [MD=2.47, 95% CI (0.91 ,4.03)], total scores [MD=2.68, 95% CI (1.79,3.57)] (fig. 8b-e). The ranking probability of the SUCRA ranking chart from high to low, activities scores: endurance training + resistance training + respiratory training, interval training, endurance training, respiratory training + strength training, conventional treatment (89.1%, 79.2%, 50.1%, 22.8%, 8.7%). Emotional scores: interval training, endurance training, respiratory training + strength training, conventional treatment, endurance training + resistance training + respiratory training (96.9%, 72.8%, 31.7%, 24.9%, 23.8%). Symptoms scores: interval training, endurance training, respiratory training + strength training, endurance training + resistance training + respiratory training, conventional treatment (100%, 74.5%, 30.9%, 29.7%, 14.9%). Total scores: interval training, endurance training, endurance training + resistance training + respiratory training, respiratory training + strength training, conventional treatment (99.9%, 71.7%, 36.9%, 26.5%, 14.9%). Comprehensive analysis of PAQLQ interval training superior to endurance training(8i-m).

Discussion

As a comprehensive intervention measure, PR has good advantages in relieving patients' clinical symptoms, increasing exercise endurance and improving quality of life. It is considered as the first-line non drug therapy for chronic respiratory diseases, and widely used in the clinical practice of childhood asthma [38,39]. Exercise training, the cornerstone of PR, comes in a variety of forms, and it is unclear which form will have the best effect on childhood asthma. This systematic review provides a comprehensive overview of the design of PR-based programs implemented during asthmatic children and explores which types of exercise are most effective.

Our systematic review was based on 24 RCTs involving 1031 patients with asthmatic children. The Standard meta-analysis was based on 16 RCTs with 691 patients, and network meta-analysis was based on 13 RCTs with 433 patients. Most studies were conducted in an inpatient setting (29%) and the total duration of the intervention ranging from 4-52 weeks. Endurance training was the most used components, and most of the interventions included in the studies were combined with endurance training. Interval training may be a core component of improving quality of life and exercise capacity in childhood asthma, the combination of respiratory training and endurance training has significant effects on lung function. Exercise-based PR is a safe and effective for asthmatic children. Moreover, exercise-based PR is safe for asthmatic children, and no serious adverse events have been found.

Lung function, as an important adjustment index for the evaluation, treatment, and severity monitoring of bronchial asthma, has always been used for patient-level diagnosis and detection [40], and attracted more attention in the treatment of pediatric. The results showed that endurance training combine with respiratory training was significantly better than other forms of exercise in increasing FVC% pred and FEF25-75% pred, but no significant difference were found in FEV1% pred. This result may be due to the lack of exercise-based PR studies on childhood asthma and different degree of asthma, as well as the total duration of the intervention, the intensity and frequency of exercise training, etc.

It is reported that exercise can improve cardiorespiratory fitness, muscle strength, to relieve or control asthma [41]. Therefore, improving exercise capacity has a positive effect on children's quality of life and asthma symptom control. 6MWT is an effective and reliable method for measuring children's motor ability, which is safe, simple, and easy to operate [42]. Study results show that both endurance training and interval training improve 6MWT in childhood asthma, but interval training is better. These results support that exercise-based PR can improve exercise tolerance, which should be treated with caution because there are few studies included.

Symptoms and quality of life evaluation are important aspects of asthma control in children. The Children's Asthma Quality of Life Questionnaire (PAQLQ) has high reliability and can more accurately reflect the quality of life in children with asthma [43]. The higher the score, the higher the quality of life. Six studies were included in the meta-analysis, exercise-based PR had a positive effect on the PAQLQ activity domain, emotional domain, symptom domain and total score. It is worth noting that interval training and endurance training are better than other forms of exercise, and interval training is the best. The results show that exercise-based PR can improve the PAQLQ score and improve the quality of life on childhood asthma.

Methodological considerations

What needs to be affirmed is that this systematic review and meta-analysis has certain advantages and limitations. So far, this is the only Network meta-analysis evaluate the effect of exercise-based PR on childhood asthma, and exercise-based PR includes a larger and richer literature. Network meta-analysis makes a direct and indirect comparison of various types of exercise interventions to determine the best type of exercise. At the same time, our study has some limitations. First, some studies have small sample size and poor representativeness, which may lead to inaccurate results. Second, some studies have not clearly stated the exercise intensity and frequency, which may lead to some differences in the results. In addition, it is very difficult to use exercise as an intervention and blind method, which may affect the authenticity of the results.

Conclusions

Exercise-based PR may be a safe and effective measure for childhood asthma to improve children's lung function, exercise capacity, and quality of life. The combination of endurance and respiratory training seems to be the most effective for improvements on lung function. Interval training was more effective in improving quality of life and exercise capacity. Therefore, the effectiveness of exercise-based PR on childhood asthma control can provide a reference for children's clinical treatment. However, the site, intensity, duration, and frequency of exercise interventions varied among included studies, so results may be controversial. In conclusion, it is necessary to validate large-scale, higher-quality RCTs in the future.

Authors' Contributions

W Zhang and D Zhang were responsible for conception and design; J Jiang and ZG Wu were responsible for research screening; J Jiang and D Zhang were responsible for collection and assembly of data; J Jiang and YP Huang were responsible for study quality assessment; W Zhang and D Zhang were responsible for data analysis and interpretation; all authors were responsible for manuscript writing and final approval of manuscript. J Jiang and D Zhang contributed equally to this work and should be cofirst authors.

Conflict of interest

None declared.

Data availability statement

The data that supports the findings of this study are available in the supplementary material (References) of this article

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