Original Article

Effects of continuous aerobic exercise on lung function and quality of life with asthma: a systematic review and meta-analysis

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Background: Despite the obvious benefits of aerobic exercise for asthmatic patients, controversies persist. The current study evaluated the effectiveness of continuous aerobic exercise on lung function and quality of life of asthmatic patients.

Methods: We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials databases up to May 2019 and included randomized controlled trials (RCTs) of asthmatic patients intervened with whole body continuous aerobic exercise (moderate intensity, at least 20 minutes and two times a week, over a minimum period of four weeks), in which the endpoint measures were lung function and asthma-related quality of life. A fixed-effects model ($I^2 \leq 50\%$) or random-effects model ($I^2 > 50\%$) was applied to calculate the pooled effects according to the I^2-and Chi-squared (χ^2) test, funnel plots were quantified to present publication bias, and a P value <0.05 was statistically significant.

Results: Eventually, 22 trials conformed to the selection criteria. In the aerobic exercise group, the forced expiratory volume improved in one second (FEV1) (I^2=10.2%, WMD: 0.12, P=0.011), peak expiratory flow (PEF) (I^2=87.3%, WMD: 0.66, P=0.002), forced vital capacity (FVC) (I^2=0.0%, WMD: 0.18, P<0.001), FVC/predict (I^2=3.9%, WMD: 4.3, P=0.014), forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25-75\%}$) (I^2=0.0%, WMD: 9.6, P=0.005), Asthma Quality of Life Questionnaire (AQLQ) (I^2=0.0%, WMD: 0.20, P=0.002), and Pediatric Asthma Quality of life Questionnaire (PAQLQ) (I^2=72.1%, WMD: 0.81, P<0.001), respectively, while no statistical significance existed in FEV1%predict (I^2=36.0%, WMD: 0.68, P=0.312) and FEV1/FVC ratio (I^2=0.0%, WMD: 0.27, P=0.443) compared with the control group. When the exercise mode was taken into account, we observed significant improvement in FEV1, PEF, and FVC in the swimming (P<0.05) or indoor treadmill (P<0.05) training group.

Conclusions: Our meta-analysis proved that regular continuous aerobic exercise benefits asthma patients on FEV1, PEF, FVC, FVC%pred, $FEF_{25-75\%}$, and quality of life, and was well tolerated, while there were no improvements in FEV1%pred and FEV1/FVC%. As such, swimming and treadmill training may be appropriate options.

Keywords: Asthma; aerobic exercise; pulmonary function; quality of life; meta-analysis

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Introduction

Asthma is a common chronic inflammatory pulmonary disorder resulting in a detrimental impact on the physical, emotional, and social daily life activity of patients (1). Asthmatics should have a reliever or controller medications. However, a variety of adverse events can occur, especially in children with asthma (2-4). To date, considerable research has been devoted to asthma's characteristics and non-pharmacologic interventions. Pulmonary rehabilitation, a reputed feasible method of exercise training, education, and behavioral change, is designed to improve the physical and psychological condition of those with chronic respiratory disease and promote long-term adherence to health-enhancing behaviors (5,6). As an essential component of pulmonary rehabilitation, physical exercise demonstrated improvement in cardiovascular function, physical activity levels, and sociological benefits in previous studies (7-9).

Reports of physical exercise interventions vary methodologically in terms of the mode, intensity, frequency, and duration (10). The Centers for Disease Control and Prevention and American College of Sports Medicine recommend at least 30 minutes of moderately intense physical activity five days per week or vigorously intense activity for a minimum of 20 minutes three days per week (11). Prior studies (12,13) reported that the best method of increasing activity levels was spending more time on moderate-intensity exercise and less time on high-intensity activity. Aerobic exercise is considered any form of physical activity that produces an increased heart rate and respiratory volume to meet the oxygen requirements of the activated muscles. Oxygen inhalation and demand are equal in the human body to achieve physiological equilibrium during training. In a mouse model of allergic asthma, moderately intense aerobic exercise attenuated lung inflammatory responses (14). Neder *et al.* (15) reported aerobic improvement and significant medication reduction with aerobic training in patients with moderate to severe asthma.

Systematic reviews have verified that physical training improved cardiopulmonary fitness, maximum oxygen uptake, asthma symptoms, and quality of life in asthmatic patients, with no adverse effects on lung function (16-19). Conversely, several emerging studies demonstrated improved asthma symptoms and lung function (20,21) after aerobic exercise. Despite obvious benefits of aerobic exercise for asthmatic patients, controversies persist. We performed a meta-analysis for an exhaustive review of the available evidence on pulmonary function and quality of life between asthma and continuous aerobic exercise.

We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/jtd-19-2813).

Methods

Search strategy

A comprehensive electronic search for aerobic exercise training trials in asthmatic patients was conducted in PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CINAHL) containing the following retrieval strategies: "asthma AND (train* OR exercise* OR physical activity* OR aerobic exercise* OR pulmonary rehabilitation*)". There were no age, language, or date of publication restrictions.

Selection criteria

The inclusion criteria are as follows: The clinical diagnosis of asthma according to the Global Initiative for Asthma (GINA) recommendations or made by a physician and/or using objective criteria such as bronchodilator reversibility or both; any type of whole aerobic exercise lasting at least 20 minutes and two times per week for a minimum duration of 4 weeks; original trials in which continuous aerobic training and asthma were involved and a control group consisting of no intervention or receiving the same level of education or medication; and outcomes of trials for quantitative synthesis including pulmonary function and quality of life (QoL). We excluded studies that did not conform to whole body continuous aerobic physical training in asthma patients and did not contain randomized controlled trial designs or valid data. Two reviewers independently assessed the rationality of the included articles. In cases of dispute, agreement was reached through consultation.

Outcome measures

The primary endpoints were pulmonary function (FEV1, FEV1%pred, FVC, FVC%pred, PEF, $FEF_{25-75\%}$, and FEV1/FVC%) and the secondary outcome was quality of life (QoL).

Quality assessment and data extraction

Two investigators evaluated the quality of the trials and the risk of bias using the Jadad Scale score (22) and the Cochrane Handbook for Systematic Reviews of Intervention Criteria (23), respectively. The characteristics of eligible articles were stated with the first author, publication, year, country, age, interventions, patients, and outcomes (*Tables 1,2*). Two pursuers independently extracted the sample size, mean value, and standard deviation of the outcome indicators. In cases of inconsistency, the results were discussed with a third researcher.

Statistical analysis

For the continuous variables, the standardized mean difference (SMD) or weighted mean difference (WMD) were calculated according to the uniformity of the measuring unit. The pooled effect size was described using forest plots, and a P value <0.05 was statistically significant. The heterogeneity of the studies was assessed via I^2-and Chi-squared (χ^2) statistics, and a fixed-effects model was used to amalgamate the effect size when $I^2 \leq 50\%$ or P>0.1 in the χ^2 statistics. We also attempted to find potential sources of heterogeneity through subgroup analysis or sensitivity analysis if significant heterogeneity ($I^2 > 50\%$) emerged or incorporated heterogeneity using a random-effects model (23). Funnel plots were quantified to detect any publication bias (P value <0.05) if there were sufficient articles (10 or more studies). All of the data analyses were completed using Stata 14.0 software.

Results

We identified 2,379 manuscripts from an initial search of the databases, and 1,517 citations remained after duplicates were removed. Of these, 1,359 were excluded after appraising the titles/abstracts. Based on full-text screening, we agreed on 25 articles for qualitative synthesis. Finally, 22 studies were incorporated into the meta-analysis due to insufficient data in 3 articles (*Figure 1*).

Characteristics of eligible studies

Twenty-two trials (24-45) involving the randomization of 874 participants assessing the effect of aerobic exercise on lung function or quality of life in asthmatic patients were published between 1990 and 2019. Of these, the patients in 12 articles (25-27,29-32,34,36,41,44,45) were children. Six studies involved individuals with moderate or severe persistent asthma, and others had mild to moderate persistent asthma. The measurements of outcomes were recorded after a 6- to 16-week training run, and spirometric variables and quality of life of post-exercise intervention were compared between the exercise group and control group. In most of the studies, the training modes were cycling, treadmill walking, and swimming. One involved submaximal basketball, two included multiple aerobic exercises, and four trials did not refer to a specific form of exercise. The frequency of aerobic exercise training in 12 studies involved two sessions per week, while others studies mandated exercise 3 times a week. The exercise training sessions ranged from 20 to 90 minutes, and moderate exercise intensity was controlled by maintaining the heart rate between 50% and 80% of the maximum heart rate (46,47) (HRmax) during exercise in the majority of the included trials (*Tables 1,2*).

Methodologic quality assessment of the included trials

All of the trials mentioned randomization, but many did not provide detailed information. In the Jadad Scale score, six studies were marked by four scores, eight studies were given three marks, and others scored two (*Tables 1,2*). The risk of bias is summarized in *Figure 2*. Low means that there was a plausible bias unlikely to seriously alter the results. High means that plausible bias occurred that can seriously weaken confidence in the results. Uncertain was stated if there were unclear risks of bias or if plausible bias could raise some doubts about the results (23). However, blinding of the participants and personnel was not regarded as a possible bias because the design of the study itself (exercise *vs.* no exercise) precluded blinding.

Results of the meta-analysis

We excluded several studies by Mendes *et al.* (in 2010, 2011) (35,39) and Gonçalves *et al.* (33) from the current meta-analysis because of the presentation of medians and interquartile ranges in the relevant parameters. We were unable to clarify whether the participants enrolled in three studies would overlap because the subjects were recruited by the same researchers. A study by Farid *et al.* (28) could not be pooled due to the imprecise description of the variables. A study by Wicher *et al.* (36) was excluded due to obvious differences in the pre-study FEV1% and FVC%pred parameters between the exercise and control groups. A study by Andrade *et al.* (41) was removed because no valid data could be pooled.

Table 1 Basic characteristics of the eligible studies

Author	Year	Country	Simple size		Age (years)		Characteristics of participants	Duration (weeks)	Jadad score*
			E	C	E	C			
Clark	1990	England	18	18	27±7	28±8	Adults with mild to moderate asthma	6	2
Varray	1991	France	7	7	11.4±1.8	11.4±1.5	Children with atopic asthma	12	2
Van Veldhoven	2001	Netherland	23	24	10.5±1.2	10.7±1.2	Children with light to moderate asthma	12	3
Weisgerber	2003	USA	5	3	7–12	7–12	Children with moderate asthma	6	3
Farid	2005	Iran	18	18	27	29	Adults with allergic asthma	8	2
Silva	2006	Brazil	23	23	9.2±0.2	9.5±0.2	Children with moderate asthma	16	2
Basaran	2006	Turkey	30	28	10.3±2.2	10.5±2.1	Children with mild to moderate asthma	8	4
Fanslli	2007	Brazil	21	17	11±2	10±2	Children with moderate to severe asthma	16	3
Moreira	2008	Portugal	16	16	12.7±3.4	12.7±3.4	Children with allergic asthma	12	4
Gonçalves	2008	Brazil	11	12	34.6±18.2	34.6±18.2	Adults with persistent asthma	12	3
Wang	2009	China	15	15	9–11	9–11	Children with mild asthma	6	2
Mendes	2010	Brazil	44	45	20–50	20–50	Adults with moderate or severe asthma	12	3
Wicher	2010	Brazil	30	31	10.3±3.1	10.9±2	Children with moderate allergic asthma	12	2
Shaw	2011	South Africa	22	22	21±3.8	21±3.89	Adults with moderate asthma	8	2
Ece Onur	2011	Turkey	15	15	8–13	8–13	Children with persistent asthma	8	2
Mendes	2011	Brazil	27	24	20–50	20–50	Adults with moderate or severe asthma	12	3
Turner	2011	Australia	20	15	65.3±10.8	71.0±9.7	Adults with moderate or severe asthma	6	3
Andrade	2014	Brazil	14	19	6–17	6–17	Children with moderate asthma	6	4
França-Pinto	2015	Brazil	22	21	40±11	44±9	Adults with moderate or severe asthma	12	4
Refaat	2015	Egypt	38	30	35.8±1.7	38±5.3	Adults with moderate to severe asthma	12	3
Abdelbasset	2018	Egypt	19	19	9±1.76	10±1.52	Children with moderate asthma	10	4
Zhang	2019	China	36	36	6.9±2.3	7.1±2.7	Children with mild asthma	6	4

*, Jadad score: a widely applied and validated system to evaluate the methodological quality of RCTs, with a total of 5 scores including the generation of randomized sequences, double-blind methods and losses or withdrawals. E: exercise group; C: control group.

Table 2 Basic characteristics of the eligible studies

Author	Year	Aerobic exercise training				Outcomes
		Mode of train	Frequency	Session	Intensity	
Clark	1990	Cycling and jogging	Three times a week	30 minutes	75% HRmax	FEV1, FEV1%pred
Varray	1991	Swimming	Twice a week	60 minutes	Submaximal intensity	FEV1, FVC
Van Veldhoven	2001	Physical activities	Twice a week	60 minutes	Submaximum heart	FEV1, FEV1%pred, FVC, FVC%pred, PEF, FEVI/FVC%
Weisgerber	2003	Swimming	Twice a week	45 minutes	Unclear	FEV1, FEV1%pred, FVC, FVC%pred, PEF, PEF%pred, $FEF_{25–75\%}$
Farid	2005	Unclear	Three times a week	35 minutes	Unclear	FEV1, FVC, PEF%pred, $FEF_{25–75\%}$, FEVI/FVC%
Silva	2006	Multiple aerobic exercises	Twice a week	90 minutes	75–80% HRmax	FEV1, FEV1%
Basaran	2006	Basketball	Three times a week	60 minutes	moderate	FEV1, FVC, FEV1%, FEVI/FVC%, PAQLQ
Fanslli	2007	Cycling or treadmill	Twice a week	90 minutes	2/3 HRmax	PAQLQ
Moreira	2008	Extreme activities	Twice a week	50 minutes	Moderately	FEV1%pred, $FEF_{25–75\%}$, PAQLQ
Gonçalves	2008	Treadmill	Twice a week	30 minutes	70% HRmax	HRQoL
Wang	2009	Swimming	Three times a week	30 minutes	66% HRmax	FEV, FVC, FEV/FVC%, $FEF_{25–75\%}$, PEF
Mendes	2010	Unclear	Twice a week	30 minutes	Unclear	HRQoL, FEV1%pred, $FEF_{25–75\%}$, FEVI/FVC%, FVC%pred
Wicher	2010	Swimming	Twice a week	60 minutes	Unclear	FEV1, FEV1%, FVC, FVC%, FEV/FVC%, $FEF_{25–75\%}$
Shaw BS	2011	Walking and jogging	Three times a week	30 minutes	60% HRmax	FVC, FEV1, PEF
Ece Onur	2011	Bicycling	Twice a week	60 minutes	50–80% HRmax	FEV1%pred, FVC%pred
Mendes	2011	Indoor treadmill	Twice a week	30 minutes	80% HRmax	FEV1%pred, $FEF_{25–75\%}$, FEVI/FVC%, FVC%pred
Turner	2011	Multiple aerobic exercise	Three times a week	80 minutes	Unclear	AQLQ
Andrade	2014	Electric treadmill	Three times a week	30 minutes	70–80% HRmax	FVC%pred, FEV1%pred, PEF, PAQLQ
França-Pinto	2015	Indoor treadmill	twice a week	35 minutes	Unclear	AQLQ, FEV1, FEV1%pred
Refaat	2015	Treadmill walking	Three times a week	25 minutes	60–80% HRmax	AQLQ, FEV1, PEF, FVC
Abdelbasset	2018	Treadmill walking	Three times a week	40 minutes	50–75% HRmax	FEV1%pred, FVC%pred, PAQLQ
Zhang	2019	Aerobic circuit training	Three times a week	40 minutes	Unclear	PADQLQ, FEV1%, FEVI/FVC%

FEV1, forced expiratory volume in one second; PEF, Peak expiratory flow; FVC, forced vital capacity; FEV1%pred, forced expiatory volume in the first second of the expected value; FVC%pred, forced vital capacity of the expected value; FEV1/FVC%, ratio of the forced expiratory volume in 1 second to the forced vital capacity; $FEF_{25–75\%}$, forced expiratory flow between 25% and 75% of vital capacity; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; HRQoL, Paediatric Allergic Disease Quality of Life Questionnaire; HRmax, optimum maximal heart rate in exercise.

FEV1

Twelve studies (24-27,29,32,36,37,41-43) with 455 patients reporting forced expiratory volume in one second at the endpoint of exercise were meta-analyzed. No heterogeneity existed among trials (I^2=10.2%, P=0.345), and a fixed-effects model of the pooled effect showed adequate efficiency (WMD: 0.12, 95% CI: 0.05–0.20, P=0.011) (*Figure 3*) in adults and children trained with aerobic exercise. The forest plot diagrammed in *Figure 3* and Egger's test demonstrated no evidence of publication bias (P=0.663).

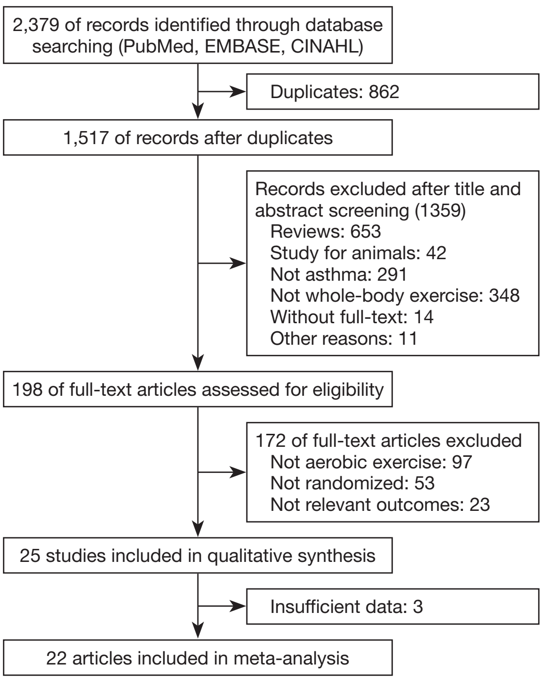

Figure 1 Diagram illustrating the study retrieval and selection.

FEV1%pred

We assessed the pooled fixed-effect model of 11 studies (24,26,27,29,30,32,33,38,42,44,45) with 439 participants. There was no difference between two groups after aerobic training (I^2=36.0%, WMD: 0.68, 95% CI: −0.64 to 2.01, P=0.312) whether in adults (P=0.808) or children (P=0.325) as participants. Egger's test displayed no publication bias (P=0.413) from the forest plot (*Figure 3*). We conducted a subgroup analysis with different modes of training. Swimming (P=0.015) and indoor treadmill (P=0.006) improved significantly (*Table 3*).

FVC

Ten trials (25-27,32,34,36,37,41-43) involving 373 subjects provided data on the forced vital capacity index that could be pooled with a fixed model (I^2=0.0%, P=0.817). The meta-analysis demonstrated a significant difference in favor of aerobic exercise compared with the controls (WMD: 0.18, 95% CI: 0.09–0.27, P=0.0001) in swimming (P=0.003) and indoor treadmill (P=0.005) exercise programs (*Table 3*) and no publication bias using Egger's test (P=0.546) (*Figure 3*).

PEF

In six studies (26,27,34,37,41,43) with 113 patients in exercise groups and 111 in control groups focused on peak expiratory flow levels of the subjects during follow up. A random-effects model (I^2=87.30%, P=0.001) indicated that aerobic exercise improved predominantly more than the control groups (WMD: 0.66, 95% CI: 0.24–1.09, P=0.002)

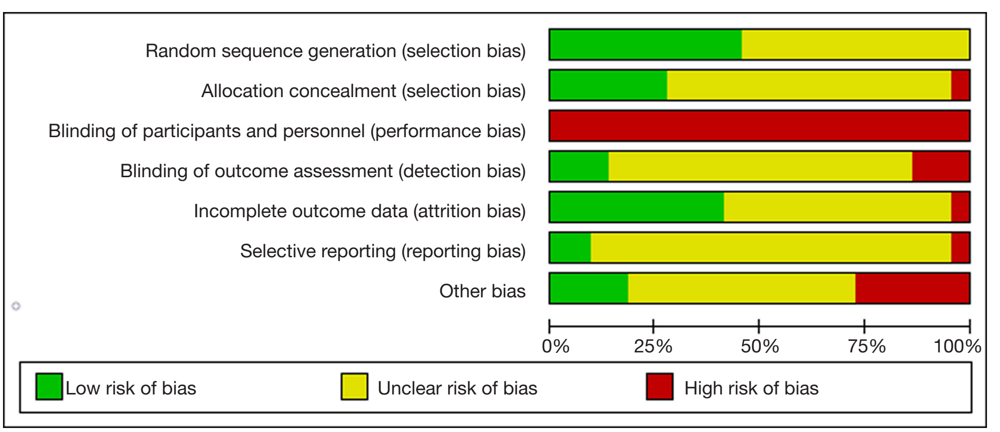

Figure 2 Risk of bias graph reviewing the authors' judgments regarding each methodological quality item presented as percentages across all of the included studies.

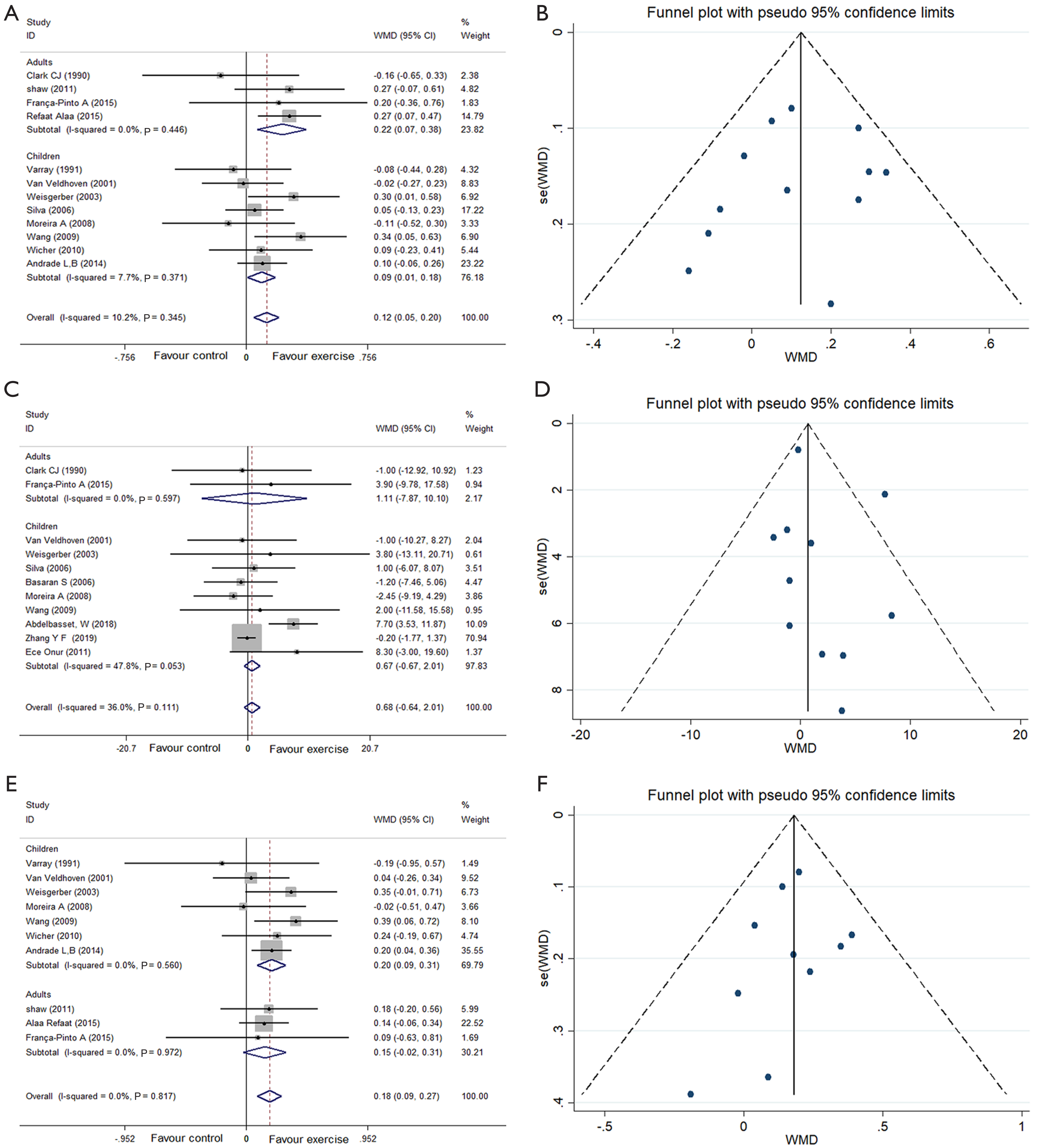

Figure 3 Meta-analysis of lung function parameters. (A) Effect of aerobic exercise on FEV1. (B) Funnel plot of FEV1 of the studies included in the meta-analysis. (C) Effect of aerobic exercise on FEV1%pred. (D) Funnel plot of FEV1%pred of the studies included in meta-analysis. (E) Effect of aerobic exercise on FVC. (F) Funnel plot of FVC of the studies included in the meta-analysis.

Table 3 Subgroup analyses of the effect of aerobic exercise on pulmonary function in different training modes

Parameters	Mode of exercise	Number of studies	P value	Chi-squared (I^2)
FEV1	Swimming	4	0.015*	26.50%
	Indoor treadmill	3	0.006*	0.00%
PEF	Swimming	2	0.001*	52.20%
	Indoor treadmill	2	0.001*	91.90%
FVC	Swimming	4	0.003*	0.00%
	Indoor treadmill	3	0.005*	0.00%

*, P value <0.05 is statistically significant. Chi-squared (I^2): I^2>50% indicates heterogeneity. FEV1, forced expiratory volume in one second; PEF, peak expiratory flow; FVC, forced vital capacity.

(*Figure 4*), and a subgroup analysis proved the same advantage in swimming (P=0.001) and indoor treadmill (P=0.001) groups (*Table 3*).

FVC%pred

We used a fixed-effects model for the pooled effect of FVC as a percentage of the predicted value in 6 studies (27,31,34,28,42,44) including 207 participators. Aerobic exercise increased FVC%pred compared with control groups (I^2=3.9%, WMD: 4.30, 95% CI: 0.88–7.72, P=0.014) (*Figure 4*).

FEV1/FVC%

FEV1/FVC% was included in 7 articles (26,30,34,36,37,42,45) at the end of training programs, and a fixed-effects model revealed no effectiveness of aerobic exercise (I^2=0.0%, WMD: 0.27, 95% CI: −0.43 to 0.98, P=0.443) (*Figure 4*).

$FEF_{25–75\%}$

Five studies (27,32,34,36,42) referred to forced expiratory flow between 25% and 75% of vital capacity at the end of exercise. A pooled fixed-effects model demonstrated a significant improvement in aerobic exercise groups (I^2=0.0%, WMD: 9.65, 95% CI: 2.84–16.46, P=0.005) (*Figure 4*).

QoL

Four of seven studies incorporated the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) (30-32,41,44) with children and the others reported the Asthma Quality of Life Questionnaire (AQLQ) (42,43) with adults. They demonstrated that aerobic exercise groups had significantly improved quality of life among children (I^2=72.1%, WMD: 0.81, 95% CI: 0.32–1.30, P<0.001) and adults (I^2=0.0%, WMD: 0.20, 95% CI: 0.07–0.32, P=0.002) (*Figure 5*).

Discussion

This meta-analysis confirmed the effectiveness of aerobic exercise training for ameliorating partial spirometry parameters (PEF, FEV1, FVC, FVC%pred, and $FEF_{25–75\%}$) and quality of life associated with asthma. Asthmatic patients should participate in mild to moderate continuous aerobic exercise programs.

The BTS Guideline on Pulmonary Rehabilitation in Adults (48) proposed that those with chronic respiratory disease should be referred to pulmonary rehabilitation, and the routine referral of patients with asthma to pulmonary rehabilitation is not recommended based on inadequate clinical evidence. Asthmatics can be anxious about exercise-induced bronchoconstriction (EIB) (49-52), which is why some prefer a sedentary lifestyle and avoid physical activity to deter asthmatic exacerbation (53,54). Nevertheless, the increasing amount of published research proved that asthmatic patients could benefit from regular exercise training (18); the same effectiveness emerged in patients with exercise-induced asthma (55-57).

However, viewpoints concerning which exercise programs are the most beneficial did not achieve a consensus. Regarding the training modality, aerobic training is exercise that can be performed for at least 20 minutes with mild or moderate fatigue (58,59). Most clinical trials designed to research chronic respiratory disease with exercise usually focus on regular aerobic training programs rather than high-intensity anaerobic exercise that can trigger exercise-induced asthma (EIA) (51,60). A review by Crosbie *et al.* (57) reported that training intensity was the most prominent factor for increasing aerobic capacity.

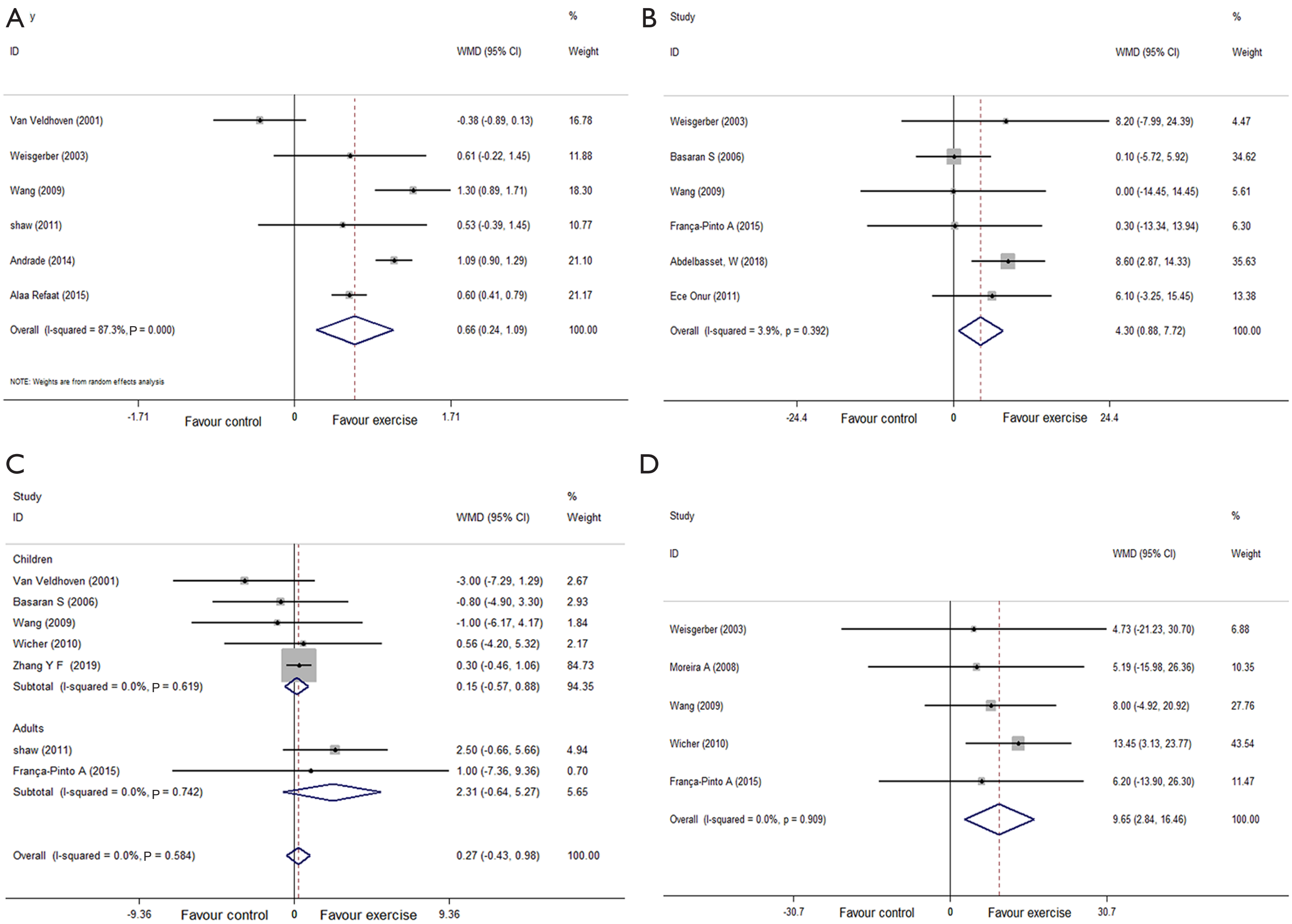

Figure 4 Meta-analysis of lung function parameters. (A) Effect of aerobic exercise on PEF. (B) Effect of aerobic exercise on FVC%pred. (C) Effect of aerobic exercise on the ratio of the FEV1/FVC%. (D) Effect of aerobic exercise on forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25-75\%}$).

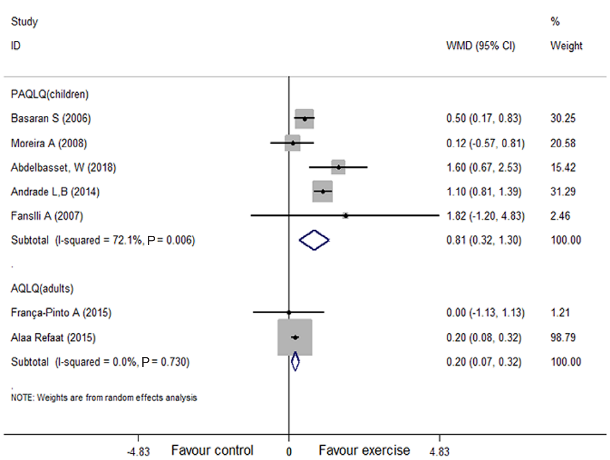

Figure 5 Effects of aerobic exercise on the PAQLQ and AQLQ.

A third session of prescribed exercise for 30 minutes each time was recommended by the American Thoracic Society/European Respiratory Society Official Policy (61). Hence, asthmatics should participate in appropriate whole-body aerobic exercise with a moderate intensity to provide evidence-based support for clinical practice.

Spirometry parameters play an essential role in the diagnosis, severity, and prognosis of asthma and are relevant to cardiorespiratory fitness (62,63). Previous studies of exercise training rarely considered lung function as the main outcome indicator and thus were insufficient to assess the effectiveness of interventions for chronic respiratory diseases (such as asthma and COPD). Accordingly, our research concentrated on lung function. In contrast to the

Cochrane meta-analysis of Carson *et al.* (18), we included five additional recent studies from our search strategy and eliminated the literature with overlapping trials, unclear outcome indicators, and interventions of high-intensity volume or frequency, resulting in differences in literature inclusion. In addition, Carson *et al.* analyzed limited indicators of lung function (FEVI, FVC), on the basis of which we added other variables and obtained valuable results.

Forced expiratory volume in one second (FEV1) and peak expiratory flow (PEF) are the two most common indicators of the objective evaluation of asthma. The Global Initiative for Asthma (GINA) guidelines recommend spirometry to manage exacerbations of asthma that require emergency treatment or hospitalization, including specific FEV1 and PEF values as indications for admission and response to treatment (64,65). Both parameters reflect airway patency and are used to measure airway function and respiratory muscle strength to indicate the degrees of airway obstructions and lesions (63,66). Our meta-analysis showed noteworthy improvements in FEV1 and PEF in contrast with a review by Philipp *et al.* (67) that reported amelioration of FEV1 rather than PEF. This discrepancy may be due to the cooptation of newly published reports (41,43) and normative difference with intervention. However, there were unexplained sources of heterogeneity with PEF, even if age, exercise patterns, follow-up time, and asthma severity were taken into account, which may be related to the time variability of the PEF measurement (66,68).

Our meta-analysis observed amelioration of FVC, FVC%pred, and $FEF_{25-75\%}$ after aerobic training programs, and no significant heterogeneity or selective was reported.

Both FVC and FVC%pred are indicators of force dependence and are considerably affected by respiratory muscle function, lung compliance airway resistance, and the patient's overall health. These conditions significantly improve after using bronchodilators (63,65,66). Improved in FVC, FVC%pred and FEV1, no significantly change was observed in FEV1/FVC% and FEV_1%pred, which are mainly affected by airway resistance. This confirms that the FEV_1/FVC ratio is not a reliable index of reversibility as FVC can increase more than FEV1, causing FEV1/FVC to decrease in the presence of a useful degree of bronchodilation (65). $FEF_{25-75\%}$, a non-force dependent part of FVC that's flow value is mainly affected by a small airway diameter with less variability, may be useful for pediatric patients as it has greater elasticity and empties more rapidly (69,70). Of the five studies included in the meta-analysis, four involved patients with children, and credible improvement was demonstrated by the pooled effect.

For further insight into the involvement of aerobic exercise in the qualified articles, age and mode of exercise were considered. There was credible improvement in FEV1, PEF, and FVC in swimming or indoor treadmill training groups. Moreover, most eligible patients had mild to moderate asthma, so regular sustained aerobic exercise for both adults and children with mild to moderate asthma is recommended, and swimming or treadmill training is a suitable choice.

The current mechanisms pertaining to improving lung function of asthmatic patients participating in aerobic exercise remain unclear. One pathophysiological study verified an increase in residual air flow and a decrease in reinforced bronchial expansion ventilation in asthmatic patients during physical exercise (71). Bronchial hyperresponsiveness (BHR) is a basic characteristic of asthma. Asthmatic animal models have systematically demonstrated that aerobic exercise reduced BHR (72,73). Three studies in our meta-analysis compared BHR with the control group post-intervention and shown a trend for lower, respectively. Moreover, a literatures review of Eichelberger *et al.* (67). reported the same argument. Additional research observed that regular moderate aerobic training prior to allergic asthma reduced airway inflammation and remodeling (74), similar to Qin *et al.*, who reported that low-intensity aerobic exercise training attenuated airway hyperresponsiveness, inflammation, and remodeling in a rat model of steroid-resistant asthma (75). Recent research confirmed the various molecular biological mechanisms of this effect (76). A randomized controlled trial demonstrated that supervised aerobic physical exercise for 8 weeks (2 times per week) could reduce asthma's pulmonary inflammation (77). According to those mechanism studies, aerobic exercise ameliorates airway inflammation, airflow obstruction, airway hyperresponsiveness, and remodeling in asthma. However, whether these effects improve lung function has not yet been determined considering that not all parameters of airway obstruction improved from our meta-analysis. Welsh *et al.* reported that physical activity increased expiratory reserve capacity (78). Shaw *et al.* (37) observed a reduction in airway obstruction and an increase in inspiratory force after aerobic training in asthmatics. Alberta *et al.* reported that aerobic exercise training alone increased abdominal muscular endurance (79).

The inconsistent conclusions of pulmonary function parameters may not only be related to the duration of aerobic training and airway variability, but also to amelioration of general health conditions, respiratory motivation, and lung compliance caused by continuous aerobic training.

Ten studies in the literature assessed quality of life associated with asthma. One (40) reported no overall scores, and another (33) presented median and quartile intervals that could not be pooled together. Routine activity, asthma symptoms, emotion, and the total quality of life score improved overall in eight trials (30,31,33,35,39,41,43,44). Because different types of questionnaires were utilized, we conducted a subgroup analysis according to the PAQLQ (children) and AQLQ (adults), and higher scores indicated better quality of life. Conversely, one study that evaluated quality of life (QoL) (45) using PADQLQ scores found that higher scores indicated worse quality of life. Our meta-analysis indicated that aerobic training improved asthma-related quality of life in both adults and children. The same conclusions were summarized in three studies (33,35,39) that could not be meta-analyzed, which is consistent with other research (67,80). Basaran *et al.* (30) indicated that changes in symptom scores significantly correlated with changes in total QoL scores, which was also reported by França-Pinto*et al.* (42). Zhang *et al.* (45) observed that asthmatics' wheezing, coughing, and sleep improved significantly in an exercise group. These reports found that regular aerobic exercise promotes the overall quality of life of asthmatic patients as demonstrated by physical fitness, asthma symptoms, and psychosocial factors (18,19). This advantageous effect may also ameliorate airway hyperreactivity and pulmonary function (67).

Aerobic exercise benefits many factors related to asthma. A recent longitudinal and multi-country study reported that the advantages of physical activity may differ according to body mass index (BMI) (81). A prospective trial by Torii *et al.* compared morning, afternoon, and evening exercise times over a 4-week period suggested that aerobic training was most effective in the afternoon (82). van Veldhoven *et al.* (26) conducted a multivariate analysis of variance (MANOVA) on sex factors and confirmed that boys in an experimental group benefited more from aerobic exercise than girls. Our meta-analysis found that some parameters improved more notably in children with asthma. Relatively few studies reported the effects of aerobic exercise on adult asthma. Different responses to aerobic exercise between adults and children must be further confirmed.

None of the qualified research articles reported adverse events during aerobic exercise training except two trials. Mendes *et al.* (35) observed that five patients (control group: 4; training group: 1) visited the emergency department, and eight (control group: 7; training group: 1) had asthma exacerbations. Turner *et al.* found that four patients (control group: 2; training group: 2) had asthma exacerbation during exercise (40). These studies also reported that severe asthma was associated with a higher risk of acute attacks (83). However, there was no increased risk of acute episodes due to exercise training, and aerobic exercise was well tolerated, as reported by Russell *et al.* (81), who found no association between physical activity and asthma incidents over 10 years, and lighter physical activity reduced asthma in middle-aged adults over time. Medication may be an important protective mechanism; the usage of prophylactic bronchodilators before each training session was mentioned in many of the eligible studies.

There are limitations to this study that merit mention. First, some relevant trials were excluded due to lack of outcomes of lung function and quality of life, or insufficient data were analyzed that could have potentially been a source of risk of bias. Second, most of the included articles had a small number of participants and evaluated only the short-term benefits of physical training, and some studies were low quality. Finally, there was indecipherable heterogeneity among some studies although the random-effects model was used.

Conclusions

Overall, our research demonstrated that regular continuous moderate intensity aerobic exercise at least 20 minutes two or three times per week over at least four weeks improved lung function and quality of life and would be a non-pharmacological benefit for asthmatic patients. Regarding the mode of exercise, swimming or treadmill training are appropriate options.

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Footnote

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