Received: 24 February 2020 | Accepted: 21 April 2020
DOI: 10.1002/ppul.24798

ORIGINAL ARTICLE: ASTHMA

PEDIATRIC PULMONOLOGY WILEY

Effect of a combined exercise program on physical fitness, lung function, and quality of life in patients with controlled asthma and exercise symptoms: A randomized controlled trial

Verónica Sanz-Santiago MD[1] | Ignacio Diez-Vega PhD[2] | Elena Santana-Sosa PhD[2] | Carlos Lopez Nuevo PT[2] | Tamara Iturriaga Ramirez MSc[2] | Fernanda Maria Vendrusculo PhD[3] | Márcio Vinícius Fagundes Donadio PhD[3] | José Ramón Villa Asensi PhD[1] | Margarita Pérez-Ruiz PhD[2]

[1]Pulmonology Unit, Hospital Universitario Infantil Niño Jesús de Madrid, Madrid, Spain
[2]Faculty of Sport Sciences, Universidad Europea de Madrid, Madrid, Spain
[3]Laboratory of Pediatric Physical Activity, Infant Center, PUCRS, Porto Alegre, Brazil

Correspondence
Margarita Pérez-Ruiz, Facultad de Ciencias de la Actividad Fisica, Deporte y Fisioterapia, Universidad Europea de Madrid. Calle Tajo, s/n. Villaviciosa de Odón, 28670 Madrid, España.
Email: margarita.perez@universidadeuropea.es

Funding information
Conselho Nacional de Desenvolvimento Científico e Tecnológico; VII Convocatoria de Ayudas a la Investigación de la Cátedra Real Madrid Universidad Europea, Grant/Award Number: P2015/16RM; Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Grant/Award Number: 001; XV Premios Fundación Neumomadrid, Sociedad Española de Neumología Pediatrica (SENP 2015)

Abstract

Background: Asthmatic patients may benefit from exercise training, although the effects of a combined aerobic and resistance training program are still poorly investigated in children and adolescents.

Objective: To analyze the effects of a combined exercise training (resistance and aerobic) program on aerobic fitness, lung function, asthma control and quality of life in a group of mild-moderate asthmatic children with exercise symptoms.

Methods: This was a 12-week randomized controlled trial including children and adolescents diagnosed with mild-moderate asthma and presenting exercise-induced symptoms. The intervention group (IG) performed the exercise training (resistance and aerobic) 3 days/week, for 60 minutes. The control group (CG) followed routine clinical orientations. The main outcomes were cardiorespiratory fitness, muscle strength, lung function, quality of life, asthma control, and functional tests after 3 months of the intervention.

Results: Fifty-three patients (IG = 25 and CG = 28) with a mean age of 11.5 ± 2.6 years were included. No significant differences were found between groups regarding lung function, asthma control, quality of life, and functional tests. Ventilatory equivalent for oxygen consumption at ventilatory threshold ($P = .025$; $\eta_p^2 = 0.083$), peak oxygen consumption ($P = .008$; $\eta_p^2 = 0.116$) and test duration ($P = .014$; $\eta_p^2 = 0.1$) presented greater improvements in the IG. In addition, improvements were observed in leg press ($P < .001$; $\eta_p^2 = 0.36$), hamstring curl ($P = .001$; $\eta_p^2 = 0.217$), high row ($P = .003$; $\eta_p^2 = .167$), low row ($P = .009$; $\eta_p^2 = 0.128$) and quadriceps leg extension ($P = .015$; $\eta_p^2 = 0.108$) in the IG.

Conclusion: Combined exercise training (resistance and aerobic) improved cardiorespiratory fitness and muscle strength in children and adolescents with controlled asthma and exercise symptoms.

KEYWORDS
asthma, exercise, pediatrics, resistance training

1 | INTRODUCTION

Asthma is a chronic inflammatory disease characterized by respiratory symptoms, variable airway obstruction, airway hyperresponsiveness, and airway inflammation.[1,2] Exercise-induced bronchoconstriction (EIB) is present in 40% to 90% of children with asthma.[3] Asthmatics usually report symptoms to exercise and lower exercise tolerance, which is associated to several factors, including the degree of airway obstruction at rest, decreased ventilatory capacity, the greater sensation of dyspnea, and EIB. However, there is contradictory evidence regarding aerobic fitness levels of asthmatic children and adolescents, and it remains unclear whether significant differences exist between asthmatic children and their nonasthmatic counterparts.[4]

Research has also shown that inactivity, as a result of breathlessness, can lead to peripheral muscle deconditioning, which is an important factor limiting exercise capacity.[5] Furthermore, deconditioning may result in further breathlessness[6] requiring increased ventilation for exercise to be maintained. Thus, asthmatic patients may benefit from exercise training and available data confirm the positive effects of exercise programs on improving exercise capacity in asthmatics.[3]

Exercise has been shown to attenuate systemic inflammation,[7] which may potentially help in the control of asthma. In addition, systematic reviews have found positive effects of regular exercise training on quality of life and cardiovascular function,[8] although with minimal effects on bronchial hyperreactivity.[3] However, its effects on inflammatory parameters[9] and lung function[8] are still poorly understood and there are few studies measuring whether these improvements have an impact on decreasing medication use or altering peripheral muscle physiology.[10] A study in patients with cystic fibrosis has suggested that combined training of both aerobic and strength abilities may be better than either training type alone.[11] Moreover, both cardiorespiratory and muscular fitness are shown to be associated with cardiovascular disease risk factors in childhood and adolescence.[12,13] Thus, the optimal volume of training, as well as the use of different modalities, are still major relevant research questions for children with asthma.

The aim of the present study is to analyze the effects of a program of combined exercise training (resistance and aerobic) on aerobic fitness, lung function, asthma control, and quality of life in a group of mild-moderate asthmatic children with exercise symptoms. The hypothesis here is that the respiratory pattern of asthmatic children with exercise-induced symptoms is altered to different workloads, so that proper training, including peripheral muscles, may improve physical fitness and reduce disease symptoms, increasing quality of life.

2 | METHODS

2.1 | Study design

This is a randomized controlled trial following the recommendations of the Consolidated Standards of Reporting Trials statement of 2010.[14] It was carried out in a tertiary children's Hospital (Niño Jesus, Madrid, Spain) following all principles described in the Declaration of Helsinki. The study was approved by the Hospital Research Ethics Committee (R-0031/14), as well as registered on ClinicalTrials.gov (NCT02693301). All legal guardians and patients over 12 years signed informed consent to participate in the study.

After baseline measurements, subjects were randomly allocated to one of the two groups: control group (CG) or intervention group (IG). All participants were evaluated in two moments, at baseline (PRE) and at the end (POST) of the 12-week exercise program, by the same investigators. The study was performed between January 2016 and October 2018.

2.2 | Participants

Patients diagnosed with mild-moderate asthma and presenting exercise-induced symptoms were included. The following inclusion criteria were used (a) children and adolescents aged 7 to 17 years old; (b) asthma diagnosis with at least 6 months of evolution; (c) exercise-associated symptoms (a score 0-1 in the question 2 of the asthma control test [ACT] childhood questionnaire, validated in Spanish,[15] or 2-3 in the question 7 of the asthma control questionnaire for children-CAN[16]). The exclusion criteria used were (a) requirement of increase in the basal medication use, including an increase in the inhaled corticosteroid dose, long-acting β 2 agonist or leukotriene receptor antagonists or oral corticosteroids or omalizumab, as well as respiratory exacerbation that required systemic corticosteroids in the last 3 months or the presence of mild crisis in the last month; (b) locomotor system problems that interfere in the evaluation/intervention protocol; (c) irregular use of the medication prescribed by the physician; (d) another chronic respiratory or cardiac disease that cause symptoms during exercise.

2.3 | Randomization

Participants were randomly assigned to either the control or the training group by using individual codes and the Excel randomize function.

2.4 | Familiarization and reliability of outcome assessment

Before the start of the study, all participants underwent a familiarization period with all the tests for the outcome assessments.

2.5 | Exercise intervention

The exercise program was performed for 12 weeks, with a frequency of 3 days/week (36 sessions in total), from Monday to Friday. The type of exercise used was combined (resistance and aerobic) and the duration of each session was 60 minutes. The exercise plans were individualized and, during all sessions, children wore a portable HR monitor to assess exercise intensity. The training started with a 10-min warm-up period (cycle ergometer), followed by the 20- to 40-min aerobic cycle ergometer training. The workload was set for each session so that it corresponded to the HR eliciting the ventilatory threshold (VT_1) measured at baseline through cardiorespiratory exercise testing (CPET). Afterward, three circuits of the following 11 resistance exercises were performed: bench press, shoulder press, leg extension, leg press, leg curl, abdominal crunch, low back extension, arm curl, elbow extension, seated row, and lateral pulldown. For each exercise, the participants performed one set of 12 to 15 repetitions (total of approx. 20-s duration) with no rest period between exercises. The load was gradually increased as the strength of each child improved, that is, from 40% of five-repetition maximum (5RM) lifting ability at the start of the program to 60% of 5RM at the end of the program. All sessions were individually supervised by trained professionals.

2.6 | Outcomes

The outcomes of this study were the changes in cardiorespiratory fitness, muscle strength, lung function, quality of life, asthma control, and functional tests after 3 months of the intervention.

2.7 | Assessments

2.7.1 | Anthropometric data and body composition

Weight and height were measured with a mechanical scale (Asimed, Barys Plus C) and with a telescopic height gauge, respectively. The body mass index was calculated. The waist-height ratio was used as a variable of percentage of estimated intra-abdominal visceral fat and was calculated by measuring the waist circumference and dividing by the height in centimeters.[17]

2.7.2 | Asthma control

The ACT was used to evaluate the asthma control level of the children and adolescents.[15,18]

2.7.3 | Quality of life

The quality of life of the participants was evaluated using the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) validated in Spanish.[19]

2.7.4 | Lung function

Spirometry was performed with a Master Screen spirometer (Jaeger, Germany) following the American Thoracic Society-European Respiratory Society ATS/ERS guideline.[20]

2.7.5 | Exercise-induced bronchoconstriction

A bronchial challenge test was performed in a treadmill using an incremental load, following the ATS/ERS recommendations for the assessment of bronchial hyperresponsiveness. A positive EIB test was considered when there was a decrease in the forced expiratory volume in the first second (FEV_1) more than 10% in any of the postexercise measures.[21]

2.7.6 | Cardiorespiratory exercise testing

To evaluate cardiorespiratory fitness, a treadmill incremental maximum test was used. Gas exchange data were measured breath-by-breath using open-circuit spirometry along with electrocardiogram recording.[22,23]

2.7.7 | Muscle strength

After familiarization with the techniques of the movements involved (low paddle, pull ahead, chest press, leg press, knee extension, and knee flexion lying down), tests were performed for the direct calculation of 5RM.[24] As the age of the population studied is wide, we have decided to normalize data by calculating the relative strength, that is, the weight achieved in each muscle group by the weight of the subject (both variables in kg).

2.7.8 | Functional tests (agility walking and in stairs)

To measure children's functional mobility, we have used the Timed Up and Go test of 3 m and the Timed Up and Down Stairs test.[25] Performance time in both tests was measured by the same investigator with the same stopwatch to the nearest 0.1 second.

2.8 | Methods online supporting information

The complete and detailed information on the following topics is presented in the Methods Online Supporting Information file: sample size calculation, randomization, familiarization, and reliability of outcome assessment, anthropometric data and body composition, asthma control, quality of life, lung function, exercise-induced bronchoconstriction, CPET, muscle strength, and functional tests (agility walking and in stairs).

2.9 | Statistical analysis

Although all the results were analyzed by protocol and intention-to-treat analysis (ITT), only the ITT results are presented. The distribution and normality of the data were analyzed with the

Shappiro-Wilk and Levene tests and with P-P and Q-Q plots. The data were expressed as means and standard deviation (mean ± SD) for parametric and as median and interquartile range for the nonparametric variables. Independent *t* test and the U-Mann Whitney were used to compare differences between both groups (CG and IG) before the exercise intervention, aiming to assess the homogeneity of groups. U-Mann Whitney test was also used to analyze the effect of training on variables that did not meet the parametric assumptions. The comparison of increases (deltas) produced between the initial and final assessments was calculated, adjusting the level of significance to $P = .025$. A multivariate variance test of repeated measures with two time and two group factors was used to assess the effect of training in parametric data. To assess the effects of the intervention and minimize the risk of type I error, only the time-group interactions were taken into account. The level of statistical significance was set at $P = .05$. Eta partial squared (η_p^2) was used as a measure of effect size. All statistical analysis was performed with SPSS 21.0 (IBM, Armonk, NY).

3 | RESULTS

A total of 275 asthmatic children and adolescents were eligible for the study. Sixty patients accepted to participate in the study, 35 were allocated to the intervention group, and 35 to the control group. However, seven participants did not complete all measurements in the CG and 10 in the IG. Figure 1 shows the flow diagram of the study.

No significant differences were found at baseline between groups regarding sociodemographic and clinical characteristics, cardiorespiratory fitness, muscle strength, quality of life and functional tests. As for lung function, only the absolute value of forced vital capacity (FVC) was significantly higher in the IG, although there was no difference in the normalized z-score value. The main baseline characteristics of the sample are presented in Tables 1 and 2.

When the delta (differences after-before the intervention) of lung function, asthma control, quality of life and functional tests were compared, no significant differences were found between the IG and CG (Table 3). Time×group interaction was significant for cardiorespiratory function ($F(8,51) = 2.5$; $P = .023$; $\eta_p^2 = 0.282$). Ventilatory equivalent for oxygen consumption (V_E/VO_2) at VT_1 ($P = .025$; $\eta_p^2 = 0.083$), VO_2peak ($P = .008$; $\eta_p^2 = 0.116$) and test time ($P = .014$; $\eta_p^2 = 0.1$) had greater improvements in the IG compared to the CG (Figure 2). Oxygen consumption ($P = .100$; $\eta_p^2 = 0.046$) and ventilatory equivalent for carbon dioxide production (V_E/VCO_2) ($P = .182$; $\eta_p^2 = 0.031$) at VT_1, as well as heart rate ($P = .087$; $\eta_p^2 = 0.05$), respiratory exchange ratio ($P = .942$; $\eta_p^2 < 0.001$) and ventilation ($P = .304$; $\eta_p^2 = 0.018$) at peak did not show significant differences.

All exercises, except bench press ($P = .067$; $\eta_p^2 = 0.062$), have shown a significant training effect on relative strength (Figure 3). The greatest improvements were observed in leg press ($P < .001$; $\eta_p^2 = 0.36$), hamstring

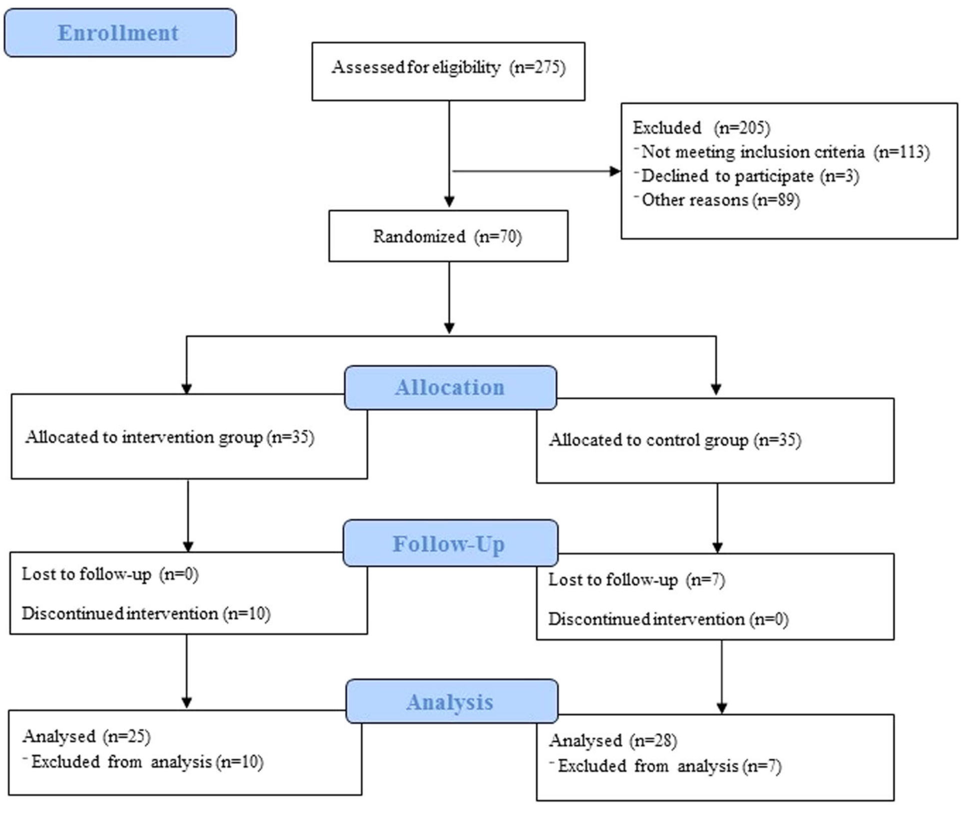

FIGURE 1 Flow diagram of the study [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Characteristics of the participants at baseline.

Variables evaluated	Total	IG	CG	*P*
Demographic				
Sex (% girls)	58.3	60	57.1	.825
Age (y)	11.5 ± 2.6	12.1 ± 2.1	11.1 ± 2.9	.119
Anthropometric				
Weight (z-score)	0.57 ± 1.1	.79 ± 0.90	.41 ± 1.21	.185
Height (z-score)	0.26 ± 1.02	.34 ± 1.02	.20 ± 1.03	.595
Body Mass Index (z-score)	0.64 ± 1.3	.95 ± 1.08	.42 ± 1.4	.119
Waist height ratio	0.48 ± 0.06	.49 ± 0.05	.47 ± 0.07	.418
Clinical				
EIB (%)	48.3	56.0	42.9	.315
Atopic dermatitis (%)	61.7	64	60	.753
Allergic reaction (%)	63.3	68	60	.526
Food allergy (%)	25	24	25.7	.880
Passive smoker (%)	45	52	40	.357
Hemoglobin (g/dL)	13.75 ± 0.92	13.83 ± 0.93	13.69 ± 0.93	.593
FeNO first visit (ppB)	31 (46.5)	21 (29.5)	17 (24)	.453
Total eosinophils (mcl)	335 (349)	280 (241)	420 (375)	.309
Tanner				.066
Stage 1 (%)	36.7	20	48.6	
Stage 2 (%)	26.7	36	20	
Stage 3 (%)	6.7	4	8.6	
Stage 4 (%)	3.3	8	0	
Stage 5 (%)	26.7	32	22.9	
Lung function				
FEV_1 (L)	2.29 (0.94)	2.44 (0.55)	1.91 (0.95)	.072
FEV_1 (z score)	−0.95 (1.38)	−0.94 (1.29)	−1.06 (1.29)	.759
FVC (L)	2.76 (0.91)	2.81 (0.55)	2.3 (0.86)	.019
FVC (z-score)	−0.47 (1.42)	-0.45 (1.37)	−0.5 (1.8)	.922
FEV_1/FVC (absolute)	.82 (0.1)	.82 (0.1)	.84 (0.12)	.534
FEV_1/FVC (z-score)	−0.9 (1.62)	−0.93 (1.53)	−0.88 (1.7)	.554
$FEF_{25\%-75\%}$ (L/min)	2.16 (1.51)	2.22 (1.35)	2.13 (1.76)	.414
$FEF_{25\%-75\%}$ (z-score)	−1.35 (1.73)	−1.7 (1.75)	−0.79 (1.67)	.440

Note: Values expressed as mean ± standard deviation or median (inter-quartile range).
Abbreviations: CG, control group; EIB, exercise-induced bronchoconstriction; IG, intervention group; FEV_1, forced expiratory volume in one second; $FEF_{25-75\%}$, forced expiratory flow between 25% and 75% of vital capacity, FVC, forced vital capacity.

curl (P = .001; η_p^2 = 0.217), high row (P = .003; η_p^2 = 0.167), low row (P = .009; η_p^2 = 0.128) and quadriceps leg extension (P = .015; η_p^2 = 0.108), respectively. In the IG, 80% to 92% of the participants improved strength, while in the CG only 41% to 62% of participants presented improvements. Adherence to the exercise program was 83.4%

4 | DISCUSSION

The results of the present study demonstrated that a 12-week program of combined exercise training (resistance and aerobic) improved cardiorespiratory fitness and muscle strength in children and adolescents with controlled asthma and exercise symptoms. However, no significant changes were found for quality of life and functional mobility after the 3 months of the intervention.

The improvement in cardiorespiratory fitness confirmed previously reported findings in children with asthma that demonstrated a significant increase in VO_2peak after exercise interventions.[26,27] In our study, the training program increased VO_2peak and the test duration on treadmill when compared to the CG. Moreover, data has shown a decrease in the V_E/VO_2 at VT_1, suggesting an improvement in the ventilatory efficiency of subjects, which may contribute to attenuate breathlessness, improve exercise capacity at submaximal levels and also contribute to the well-being of patients during their daily activities.[26] Among the main factors that seem to contribute to greater effectiveness of physical training protocols in cardiorespiratory fitness in asthmatic patients are the adequate intensity prescription (established at the ventilatory threshold), as well as the frequency and duration of training. To date, all studies showing increased

TABLE 2 Exercise capacity, muscle strength, quality of life, and functional tests at baseline

Variables evaluated	Total	IG	CG	*P*
Physical activity				
PAQ	2.39 (0.73)	2.22 (0.84)	2.5 (0.77)	.213
CPET				
Ventilatory threshold				
HR (bpm)	136.5 (19.25)	134 (18)	137 (21)	.600
VO_2 (mL.kg^{-1}.min^{-1})	2.1 (3.93)	20 (3.6)	2.1 (3.6)	.333
VO_2 (%VO_2peak)	57.4 (11.5)	56.2 (11.6)	58.2 (13.6)	.910
V_E (L.min^{-1})	22.15 (1.8)	23.9 (1.8)	2.6 (12.6)	.056
V_E/VO_2	27 (4)	27 (5.5)	27 (4)	.786
V_E/VCO_2	31 (5)	31 (5)	32 (5)	.465
Peak exercise				
HR (bpm)	190 (13.5)	190 (1.5)	188 (16)	.641
VO_2 (mL.kg^{-1}.min^{-1})	35.05 (7)	34.8 (8.35)	35.3 (11)	.154
V_E (L.min^{-1})	53.55 (32.5)	64.3 (27.85)	44.4 (2.7)	.073
V_E/VO_2	34 (6)	36 (6.5)	34 (5)	.088
V_E/VCO_2	32 (4.75)	31 (4.5)	32 (6)	.493
RER	1.09 (0.21)	1.11 (0.17)	1.05 (0.21)	.148
Time (min)	9.4 (2.6)	9.4 (2.2)	10 (2.6)	.470
Relative strength (kg/wt)				
Hamstring curl	.65 (0.4)	.74 (0.37)	.59 (0.33)	.391
Leg press	1.44 (0.75)	1.22 (0.69)	1.56 (0.93)	.256
High row	.66 (0.29)	.64 (0.27)	.7 (0.32)	.761
Low row	.63 (0.3)	.67 (0.25)	.63 (0.42)	.353
Leg extension	1.01 (0.49)	1.02 (0.39)	1 (0.6)	.573
Bench press	.7 (0.25)	.7 (0.19)	.7 (0.43)	.755
Quality of life-PAQLQ				
Global	6 (1.5)	6 (1.9)	6 (1.3)	.825
Emotional sphere	6 (2.2)	6 (2.2)	5.6 (1.8)	.494
Physical activity limitation	6.63 (0.94)	6.5 (1.69)	6.75 (0.63)	.308
Symptom	6.04 (0.78)	6.02 (1.21)	6.04 (0.65)	.787
Functional test (s)				
3 meter test	3.56 (0.62)	3.56 (0.56)	3.6 (0.71)	.714
12 stair test	6.62 (0.94)	6.62 (0.70)	6.62 (1.66)	.549

Note: Values expressed as mean ± standard deviation or median (inter-quartile range).
Abbreviations: CG, control group; CPET, cardiopulmonary exercise testing; HR, heart rate; IG, intervention group; PAQ: Physical activity questionnaire; PAQLQ, pediatric quality of life questionnaire in asthmatics; RER, respiratory exchange ratio; V_E, minute ventilation; V_E/VCO_2, ventilatory equivalent ratio for carbon dioxide production; V_E/VO_2, ventilatory equivalent ratio for oxygen uptake; VO_2, maximal oxygen uptake.

VO_2peak after an exercise program performed training with intensity at VT_1, three times per week, for at least 3 months.

Although there is variability in training programs for asthmatic patients, aerobic training is the most commonly used for children with asthma. To the best of our knowledge, this is the first study to use a combined exercise training (resistance and aerobic) to demonstrate improvement in muscle strength in children and adolescents with asthma. Studies have demonstrated that cardiorespiratory and muscular fitness are associated with cardiovascular disease risk factors in childhood and adolescence,[12,13] highlighting the importance of peripheral muscle function on these effects. Moreover, Castro-Piñero et al[13] found an association of muscle fitness with present and future cardiovascular health in youth, in an effect independent of cardiorespiratory fitness, reinforcing the importance of resistance training for this age group. The decrease in peripheral muscle strength has been observed in chronic lung diseases[27,28] and it is plausible to hypothesize that children with asthma would also develop similar impairments. Muscle impairments are usually associated with chronic use of corticosteroids, sedentary lifestyle, and reduction in aerobic capacity, although the literature on peripheral muscle function in asthmatic subjects is still scarce. Villa et al[10] described a reduction in skeletal muscle function and observed that endurance was lower in the quadriceps muscle of severe asthmatic patients compared to moderate and intermittent disease, although there was no difference in strength.

TABLE 3 Comparison of cardiopulmonary exercise variables, lung function, asthma control, quality of life and functional tests between the intervention and control group

Variables evaluated	IG	CG	*P*	η_p^2
CPET				
Δ Ventilatory threshold				
HR, bpm	4.32 ± 15.47	−1.54 ± 10.06	.080	.052
VO_2, mL·kg^{-1}·min^{-1}	1.58 ± 3.39	−0.21 ± 4.48	.100	.046
VO_2, %VO_2peak	−0.88 ± 10.18	−1.09 ± 9.94	.936	<.001
V_E, L·min^{-1}	1.61 ± 5.33	.99 ± 5.7	.672	.003
V_E/VO_2	−1.2 ± 3.73	.8 ± 3.04	.025	.083
V_E/VCO_2	−1.16 ± 3.17	.14 ± 4	.182	.031
Δ Peak exercise				
HR, bpm	2.6 ± 17.14	−3.46 ± 9.67	.087	.050
VO_2, mL·kg^{-1}·min^{-1}	3.61 ± 4.03	.59 ± 4.29	.008	.116
V_E, L·min^{-1}	5.89 ± 11.18	3.44 ± 7.14	.304	.018
V_E/VO_2	−0.92 ± 6.11	1.14 ± 3.37	.099	.046
V_E/VCO_2	−0.24 ± 4.03	.23 ± 4.09	.661	.003
RER	0 ± 0.17	0 ± 0.14	.942	.001
Test time, min	.96 ± 2.09	−0.11 ± 1.17	.014	.100
Δ Lung function (z-score)				
FEV_1	−0.05 (0.93)	−0.15 (1.88)	.412	.013
FVC	−0.19 (0.85)	−0.10 (1.31)	.722	.002
FEV_1/FVC	.32 (0.73)	−0.03 (1.05)	.066	.064
$FEF_{25\%-75\%}$	.31 (1.06)	−0.01 (1.38)	.245	.016
Δ Asthma control				
ACT	1 (4)	.5 (5.75)	.430	.012
Δ Quality of life-PAQLQ				
Global	.61 (1.2)	.22 (1.05)	.327	.02
Emotional sphere	.25 (1.16)	0 (0.69)	.888	.047
Physical activity limitation	.1 (1.55)	.2 (1)	.127	<.001
Symptom	.45 (1.6)	.3 (1.25)	.327	.02
Δ Functional test (s)				
3 Meter test	−0.18 (0.62)	−0.14 (0.33)	.712	.003
12 Stair test	−0.36 (0.82)	−0.1 (0.89)	.061	.066

Note: Values expressed as mean ± standard deviation or median (inter-quartile range); Δ, increment after-before intervention.
Abbreviations: ACT, asthma control test; CG, control group; CPET, cardiopulmonary exercise testing; $FEF_{25\%-75\%}$, forced expiratory flow between 25% and 75% of vital capacity; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; HR, heart rate; IG, intervention group; PAQLQ, pediatric quality of life questionnaire in asthmatics; RER, respiratory exchange ratio; V_E, minute ventilation; V_E/VCO_2, ventilatory equivalent ratio for carbon dioxide production; V_E/VO_2, ventilatory equivalent ratio for oxygen uptake; VO_2, maximal oxygen uptake.

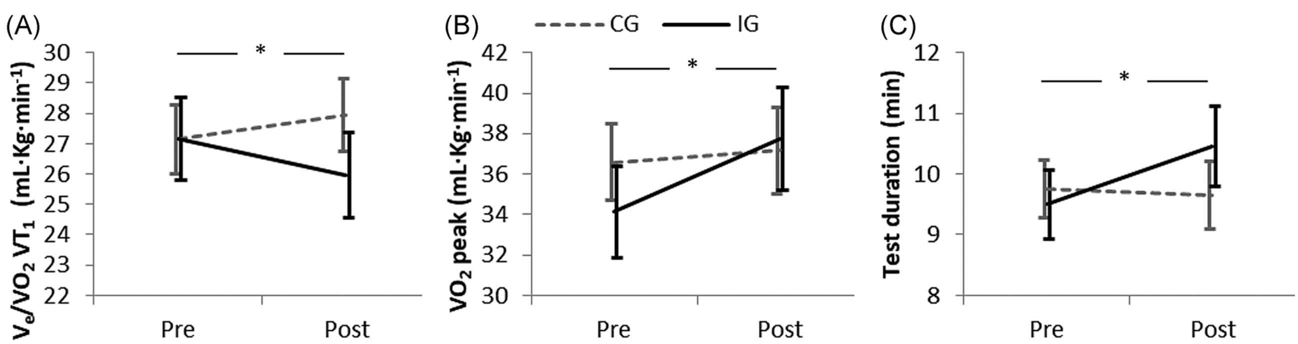

FIGURE 2 Effects of combined aerobic and resistance training on cardiopulmonary exercise testing in variables. A, Ventilatory equivalent for oxygen consumption (V_E/VO_2) at ventilatory threshold (VT_1). B, Peak oxygen consumption (VO_2peak). C, Test duration. *indicates significant differences at *P* < .05. CG, control group; IG, intervention group

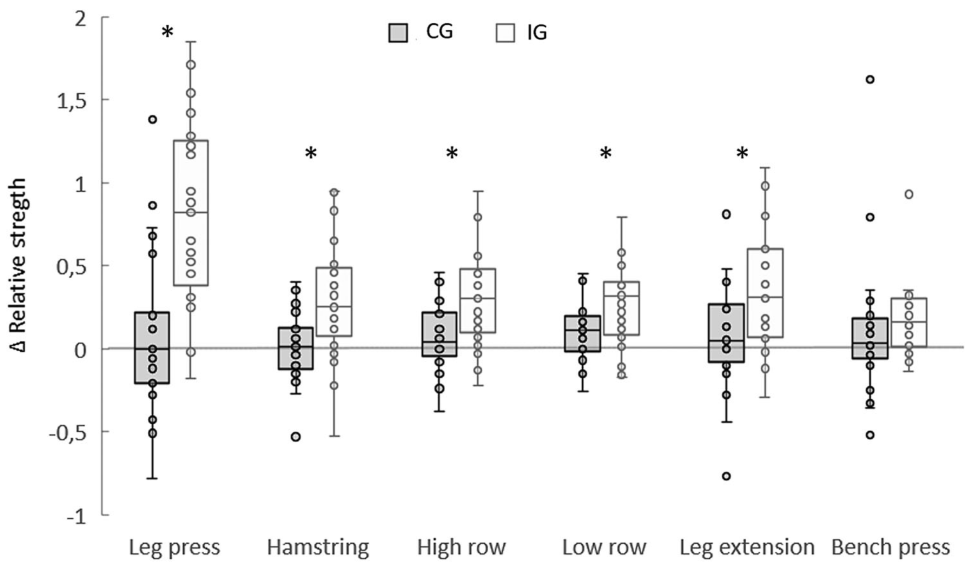

FIGURE 3 Effects of combined aerobic and resistance training on relative muscle strength. CG, control group; IG, intervention group. *indicates significant differences at $P < .05$

The majority of studies evaluating the effects of exercise training in asthmatic subjects demonstrated improvements in quality of life,[29-32] evidenced by both overall PAQLQ scores, as well as specific scores of the activity limitation domain, symptoms, and emotional function. In our study, no significant differences in quality of life were found between groups, although the variation (delta) in the quality of life questionnaire scores was higher in the intervention group. Moreira et al[33] that also evaluated a 12-week exercise training program, did not find differences between exercise and control groups, which may be related to a good quality of life at baseline, with little possibilities of improvement.

Several studies,[3,31,32,34] as well as data presented here, have shown that exercise training has no relevant impact on lung function in asthmatic children. These findings are also in agreement with a study in adults, suggesting that lung volumes and lung function do not appear to be improved with the practice of regular exercise.[35] In contradiction, Abdelbasset et al[29] demonstrated a significant increase in both FEV_1 and FVC following a 10-week exercise training intervention. On the other hand, studies[3,32] have shown that only peak expiratory flow seems to slightly improve after exercise training, probably due to an increase in respiratory muscle strength, although this variable was not evaluated in the present study.

The study has also some limitations, including the mild to moderate severity of the disease. The effects of a combined exercise training program in severe or therapy-resistant patients are still to be addressed. In addition, evaluation of respiratory muscle strength would have provided further insights into the mechanisms involved in the effects of the exercise intervention.

In conclusion, the present study shows that a combined exercise training program (resistance and aerobic) may improve cardiorespiratory fitness and muscle strength in children and adolescents with controlled asthma and exercise symptoms. The incorporation of controlled exercise training including resistance exercises as part of the treatment may benefit children and adolescents with asthma.

ACKNOWLEDGMENTS

Márcio Vinícius Fagundes Donadio and Fernanda Maria Vendrusculo would like to thank Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)-finance code 001, and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). This work was supported by VIII Convocatoria de Ayudas a la Investigación de la Cátedra Real Madrid, Escuela Universitaria Real Madrid-Universidad Europea (P2015/16RM) and XV Premios Fundación Neumomadrid, Sociedad Española de Neumología Pediatrica (SENP 2015).

ORCID

Ignacio Diez-Vega http://orcid.org/0000-0002-5398-8951
Fernanda Maria Vendrusculo http://orcid.org/0000-0001-8208-3476
Márcio Vinícius Fagundes Donadio http://orcid.org/0000-0001-8836-9109
Margarita Pérez-Ruiz http://orcid.org/0000-0001-7240-2082

REFERENCES

1. Côté A, Turmel J, Boulet LP. Exercise and asthma. *Semin Respir Crit Care Med*. 2018;39:19-28.
2. Papadopoulos NG, Arakawa H, Carlsen K-H, et al. International consensus on (ICON) pediatric asthma. *Allergy*. 2012;67:976-997.
3. Wanrooij VHM, Willeboordse M, Dompeling E, van de Kant KDG. Exercise training in children with asthma: a systematic review. *Br J Sports Med*. 2014;48:1024-1031.
4. Welsh L, Roberts RGKJ. Fitness and physical activity in children with asthma. *Sports Med*. 2004;34:861-870.
5. Laveneziana P, Lotti P, Coli C, et al. Mechanisms of dyspnoea and its language in patients with asthma. *Eur Respir J*. 2006;27:742-747.

6. Swallow EB, Gosker HR, Ward KA, et al. A novel technique for nonvolitional assessment of quadriceps muscle endurance in humans. *J Appl Physiol*. 2007;103:739-746.
7. Wrnberg J, Cunningham K, Romeo J, Marcos A. Physical activity, exercise and low-grade systemic inflammation. *Proc Nutr Soc*. 2010;69:400-406.
8. Carson KV, Chandratilleke MG, Picot J, Brinn MP, Esterman AJ, Smith BJ. Physical training for asthma. *Cochrane Libr*. 2013;30:1-73.
9. França-Pinto A, Mendes FAR, De Carvalho-Pinto RM, et al. Aerobic training decreases bronchial hyperresponsiveness and systemic inflammation in patients with moderate or severe asthma: a randomised controlled trial. *Thorax*. 2015;70:732-739.
10. Villa F, Castro APBM, Pastorino AC, et al. Aerobic capacity and skeletal muscle function in children with asthma. *Arch Dis Child*. 2011;96:554-559.
11. Sosa ES, Groeneveld IF, Gonzalez-Saiz L, et al. Intrahospital weight and aerobic training in children with cystic fibrosis: a randomized controlled trial. *Med Sci Sports Exerc*. 2012;44:2-11.
12. Ruiz JR, Cavero-Redondo I, Ortega FB, Welk GJ, Andersen LB, Martinez-Vizcaino V. Cardiorespiratory fitness cut points to avoid cardiovascular disease risk in children and adolescents: what level of fitness should raise a red flag? A systematic review and meta-analysis. *Br J Sports Med*. 2016;50:1451-1458.
13. Castro-Piñero J, Perez-Bey A, Cuenga-Garcia M, et al. Muscle fitness cut points for early assessment of cardiovascular risk in children and adolescents. *J Pediatr*. 2019;206:134-141.
14. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *Int J Surg*. 2012;10:28-55.
15. Pérez-Yarza EG, Castro-Rodriguez JA, Villa Asensi JR, Garde Garde J, Hidalgo Bermejo FJ. Validación de la versión en español de la prueba de control del asma infantil (ACT) para su uso en España. *An Pediatría*. 2015;83:94-103.
16. Pérez-Yarza EG, Badía X, Badiola C, et al. Development and validation of a questionnaire to assess asthma control in pediatrics. *Pediatr Pulmonol*. 2009;44:54-63.
17. Marrodán MD, Martínez-Álvarez JR, De Espinosa MGM, López-Ejeda N, Cabañas MD, Prado C. Precisión diagnóstica del índice cintura-talla para la identificación del sobrepeso y de la obesidad infantil. *Med Clin (Barc)*. 2013;140:296-301.
18. Jia CE, Zhang HP, Lv Y, et al. The asthma control test and asthma control questionnaire for assessing asthma control: systematic review and meta-analysis. *J Allergy Clin Immunol*. 2013;131:695-703.
19. Badia X, García-Hernández G, Cobos N, López-David C, Nocea G, Roset M. Validación de la versión española del Pediatric Quality of Life Questionnaire en la valoración de la calidad de vida del niño asmático. *Med Clin (Barc)*. 2001;116:565-572.
20. Pellegrino R. Interpretative strategies for lung function tests. *Eur Respir J*. 2005;26:948-968.
21. Parsons JP, Hallstrand TS, Mastronarde JG, et al. An official American thoracic society clinical practice guideline: exercise-induced bronchoconstriction. *Am J Respir Crit Care Med*. 2013;187:1016-1027.
22. San Juan AF, Fleck SJ, Chamorro-Viña C, et al. Effects of an intrahospital exercise program intervention for children with leukemia. *Med Sci Sports Exerc*. 2007;39:13-21.
23. Gulmans VAM, De Meer K, Brackel HJL, Helders PJM. Maximal work capacity in relation to nutritional status in children with cystic fibrosis. *Eur Respir J*. 1997;10:2014-2017.
24. Kraemer W, Fry A. Physiological Assessment of Human Fitness. In: Mauch PJ, Foster C, eds. *Strength Testing Development and Evaluation of Methodology*. Champaign, IL: Human Kinetics; 1995.
25. Marchese VG, Chiarello LA, Lange BJ. Strength and functional mobility in children with acute lymphoblastic leukemia. *Med Pediatr Oncol*. 2003;40:230-232.
26. Meyer T, Lucía A, Earnest CP, Kindermann W. A conceptual framework for performance diagnosis and training prescription from submaximal gas exchange parameters - theory and application. *Int J Sport Med Suppl*. 2005;26:S38-S48.
27. Hussey J, Gormley J, Leen G, Greally P. Peripheral muscle strength in young males with cystic fibrosis. *J Cyst Fibros*. 2002;1:116-121.
28. Maltais F, Decramer M, Casaburi R, et al. An official American thoracic society/european respiratory society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2014;189:15-62.
29. Abdelbasset WK, Alsubaie SF, Tantawy SA, Abo Elyazed TI, Kamel DM. Evaluating pulmonary function, aerobic capacity, and pediatric quality of life following a 10-week aerobic exercise training in school-aged asthmatics: a randomized controlled trial. *Patient Prefer Adherence*. 2018;12:1015-1023.
30. eLin H-C, Lin H-P, Yu H-H, et al. Tai-Chi-Chuan exercise improves pulmonary function and decreases exhaled nitric oxide level in both asthmatic and nonasthmatic children and improves quality of life in children with asthma. *Evid Based Complement Alternat Med*. 2017; 2017:6287642.
31. Basaran S, Guler-Uysal F, Ergen N, Seydaoglu G, Bingol-Karakoç G, Ufuk Altintas D. Effects of physical exercise on quality of life, exercise capacity and pulmonary function in children with asthma. *J Rehabil Med*. 2006;38:130-135.
32. De Andrade LB, Britto MCA, Lucena-Silva N, Gomes RG, Figueroa JN. The efficacy of aerobic training in improving the inflammatory component of asthmatic children. *Randomized Trial. Respir Med*. 2014;108: 1438-1445.
33. Moreira A, Delgado L, Haahtela T, et al. Physical training does not increase allergic inflammation in asthmatic children. *Eur Respir J*. 2008;32:1570-1575.
34. Lu KD, Cooper DM, Haddad F, Radom-Aizik S. Four months of a school-based exercise program improved aerobic fitness and clinical outcomes in a low-SES population of normal weight and overweight/obese children with asthma. *Front Pediatr*. 2018; 6:380.
35. Satta A. Exercise training in asthma. *J Sport Med Phys Fitness*. 2000;40: 277-283.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Sanz-Santiago V, Diez-Vega I, Santana-Sosa E, et al. Effect of a combined exercise program on physical fitness, lung function, and quality of life in patients with controlled asthma and exercise symptoms: A randomized controlled trial. *Pediatric Pulmonology*. 2020;55:1608–1616. https://doi.org/10.1002/ppul.24798