ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Comparative effects of aerobic, combined, and intermittent exercise in children and adolescents with asthma: a systematic review

Efeitos comparativos dos exercícios aeróbicos, combinados e intermitentes em crianças e adolescentes com asma: uma revisão sistemática

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ABSTRACT

Asthma is a chronic disease with a heterogeneous pathogenesis and etiology. Inflammation is considered one of the main triggers of bronchospasm and airway obstruction, which lead to clinical manifestations. Exercise is encouraged as a way to avoid cardiovascular, musculoskeletal, and psychosocial disorders and help control the disease. Our objective was to analyze the comparative effects of aerobic, combined (resistance and aerobic), and intermittent exercise on the functional capacity, lung function, and quality of life of children and adolescents with asthma, as well as to identify the relationship between exercise, other functional parameters, and inflammatory components characteristic of asthma. This was a systematic review of randomized clinical trials involving asthmatic populations aged between 6 and 17 years. PEDro, Lilacs, PubMed, and Cochrane Library/Central were searched for studies published in the last 10 years in English or Portuguese. We identified 8136 references, of which only 3 met the eligibility criteria. Considering the intervention time, aerobic exercise showed better functional capacity results. Regarding the common parameters used to assess lung function, intermittent exercise was the only type to result in significant change. Regarding quality of life, intermittent exercise had superior results, while combined exercise stood out for musculoskeletal improvement. Exercise can be a good non-pharmacological strategy for reducing the consequences of this pathology.

Keywords: Asthma, exercise, child, adolescent.

RESUMO

A asma é uma doença crônica, com patogênese e etiologia heterogêneas. Considera-se o quadro inflamatório como um dos principais desencadeantes do broncoespasmo e obstrução das vias aéreas, os quais levam às manifestações clínicas. Sugere-se que os exercícios físicos sejam uma terapêutica importante para evitar distúrbios cardiovasculares, musculoesqueléticos e psicossociais, e ajudar no controle da doença. O objetivo deste estudo é analisar os efeitos comparativos dos exercícios físicos aeróbicos, combinados (resistência e aeróbico) e intermitentes na capacidade funcional, função pulmonar e qualidade de vida das crianças e adolescentes com asma, identificando também as possíveis relações dos exercícios com outros parâmetros funcionais e componentes inflamatórios característicos da asma. As fontes de buscas utilizadas foram PEDro, LILACS, PubMed e Cochrane Library/Central, dos quais selecionou-se apenas ensaios clínicos randomizados, em crianças e adolescentes com o diagnóstico de asma, com idade entre 6 e 17 anos, publicados nos últimos dez anos, nas línguas inglesa e portuguesa. Foram identificadas 8.136 referências, sendo que destas, apenas três preencheram os critérios de inclusão. Considerando o tempo de intervenção, o exercício aeróbico apresentou melhores resultados referente à capacidade funcional. Em relação ao parâmetro comum utilizado para avaliar a função pulmonar, o exercício intermitente foi o único a obter alterações significativas. Quanto à qualidade de vida, o exercício intermitente obteve resultados superiores, e os exercícios combinados destacam-se pela melhora musculoesquelética. A prática de exercícios físicos pode ser uma boa estratégia, não farmacológica, para reduzir as consequências desta patologia.

Descritores: Asma, exercício físico, criança, adolescente.

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Introduction

Asthma, a chronic non-communicable disease, is common in children and adults. Its main manifestation is respiratory symptoms, such as wheezing, coughing, dyspnea, and chest tightness. These result from an inflammatory condition that leads to bronchospasm and airway obstruction.[1-4] Nevertheless, asthma has a heterogeneous pathogenesis and etiology that can result in different clinical presentations.[1,2,5]

The allergic (atopic) form is commonly diagnosed in childhood and may be associated with individual susceptibility or genetic or environmental factors. On the other hand, non-allergic (non-atopic) asthma is often associated with later diagnosis, generally after 40 years of age, and may be persistent or intermittent. Viral infections of the respiratory system, low temperatures, and physical activity can initiate both forms of crisis, but exposure to allergens is only associated with the allergic form.[6-10]

In the allergic form, dendritic cells can initiate an immune response, processing and presenting an antigen to type 2 helper T cells, which induces production of interleukins (IL-4, IL-5, IL-13).[2,5,10-12] These cytokines regulate other receptors and stimulate the production of eosinophils, mast cells, and basophils. The inflammatory condition can be mediated by histamines, prostaglandins, and leukotrienes, which trigger greater smooth muscle contractility, vascular congestion, and infiltration, obstructing the airflow.[4] In the non-allergic form, innate lymphoid cells stimulate the production of interleukins, and the process results from epithelial damage by pollutants or microorganisms, such as viruses.[5,9]

The relationship between a persistent inflammatory condition, oxidative stress, and reactive oxygen species is an important pathophysiological component, whose role in the activation of inflammatory mediators of the immune system produces greater reactivity of the respiratory system, lipid peroxidation, and increased vascular permeability.[10,15-18]

Among children, asthma is more prevalent in boys, but this changes in adolescence, with an increasing prevalence in girls.[7,19] Disease severity can be classified as persistent (41%), periodic (38%), or in remission (21%).[5] In 2015 the asthma prevalence in Brazil among 5- to 19-year-olds was 16%, while in 2020 there were an estimated 15,406 hospitalizations due to crises, costing a total of BRL 9,385,208.68.[20] Thus, asthma must be considered a public health problem, since it is responsible for many hospitalizations each year, whose expense impacts the health care system.[7,19,21,22]

Diagnosis should be based on clinical findings. Symptoms and their inflammatory characteristics should be correlated with their frequency, as well as symptomatic response to specific medications. Lung function testing contributes to diagnosis, verifying limitations in expiratory airflow. These limitations are associated with a lower than expected ratio between forced expiratory volume in one second (FEV_1) and forced vital capacity according to sex, age, race, and height.[22-24]

For preschool-aged children, diagnostic confirmation can involve greater challenges due to heterogeneous inflammatory conditions associated with other pathologies and difficulty performing the lung function test. In this age group, it is still common to find an absence of symptoms for 1 year (remission), 5 years, or normal spirometry values.[25-27]

Exercise-induced bronchoconstriction due to bronchial hyperresponsiveness may be the only symptom in some individuals.[28-30] An increased sensation of dyspnea during exercise may be one reason why asthma patients avoid it, which could also be associated with the patient's condition at rest. However, a sedentary lifestyle can trigger a vicious cycle in which cardiovascular and musculoskeletal disorders are associated with lung impairment. Thus, prolonged inactivity can aggravate the patient's baseline condition.[31-33]

In the pediatric population, asthma can lead to functional and social impairment, which, when persistent, affect their adult lives. Exercise has been suggested as an important non-pharmacological therapy for controlling the disease, improving functional capacity, lung function, and quality of life. Correct prescription of exercise intensity, frequency, and duration can directly influence the results.[34-38] One study demonstrated that an exercise program reduces bronchial hyperresponsiveness and the concentration of some pro-inflammatory biomarkers, contributing to lower exacerbation and improved quality of life through better clinical control.[39] The changes triggered by this pathology and its prevalence make the topic relevant.

The present study aimed to analyze the comparative effects of aerobic, combined (resistance and aerobic), and intermittent exercise on functional capacity, lung function, and quality of life in children and adolescents, in addition to identifying relationships between exercise

and other functional parameters and inflammatory components characteristic of asthma.

Methods

Protocol and registration

This systematic review was registered in the international prospective register of systematic reviews (number CRD42021252567) and was conducted according to Preferred Reporting Items for Systematic reviews and Meta-Analyses[40] and Cochrane Handbook for Systematic Reviews of Interventions[41] guidelines.

Eligibility criteria

The inclusion criteria were randomized clinical trials of children and adolescents (aged 6 to 17 years) diagnosed with asthma that were published in in English or Portuguese the last 10 years. The exclusion criteria were protocols for randomized clinical trials, trials without a control group or a control group who did not receive usual care, trials with adults, exclusive comparisons between medication types, comparisons between medication and exercise-induced bronchoconstriction, and duplicate publications.

Searches were performed in the Physiotherapy Evidence Database (PEDro), Lilacs (Bireme/BVS), PubMed (MEDLINE), and Cochrane Library/Central, with the final search occurring on May 15, 2021. To guide the searches, a PICO question was developed: population (children and adolescents diagnosed with asthma), intervention (aerobic, combined, and intermittent physical exercise), comparisons (control group), and outcomes (functional capacity, lung function, quality of life). The search strategy for PubMed (MEDLINE) was as follows:

Population: "Asthma" [Mesh] OR "Asthmas" OR "Bronchial Asthma" OR "Asthma, Bronchial".

Intervention: "Exercise" [Mesh] OR "Exercises" OR "Physical Activity" OR "Activities, Physical" OR "Activity, Physical" OR "Physical Activities" OR "Exercise, Physical" OR "Exercises, Physical" OR "Physical Exercise" OR "Physical Exercises" OR "Acute Exercise" OR "Acute Exercises" OR "Exercise, Acute" OR "Exercises, Acute" OR "Exercise, Isometric" OR "Exercises, Isometric" OR "Isometric Exercises" OR "Isometric Exercise" OR "Exercise, Aerobic" OR "Aerobic Exercise" OR "Aerobic Exercises" OR "Exercises, Aerobic" OR "Exercise Trainings" OR "Training, Exercise" OR "Trainings, Exercise" OR "Circuit-Based Exercise" [Mesh] OR "Circuit Based Exercise" OR "Circuit-Based Exercises" OR "Exercise, Circuit-Based" OR "Exercises, Circuit-Based" OR "Circuit Training" OR "Training, Circuit" OR "Resistance Training"[Mesh] OR "Training, Resistance" OR "Strength Training" OR "Training, Strength" OR "Weight-Lifting Strengthening Program" OR "Strengthening Program, Weight-Lifting" OR "Strengthening Programs, Weight-Lifting" OR "Weight Lifting Strengthening Program" OR "Weight-Lifting Strengthening Programs" OR "Weight-Lifting Exercise Program" OR "Exercise Program, Weight-Lifting" OR "Exercise Programs, Weight-Lifting" OR "Weight Lifting Exercise Program" OR "Weight-Lifting Exercise Programs" OR "Weight-Bearing Strengthening Program" OR "Weight-Bearing Strengthening Program" OR "Strengthening Program, Weight-Bearing" OR "Strengthening Programs, Weight-Bearing" OR "Weight Bearing Strengthening Program" OR "Weight-Bearing Strengthening Programs" OR "Weight-Bearing Exercise Program" OR "Exercise Program, Weight-Bearing" OR "Exercise Programs, Weight-Bearing" OR "Weight Bearing Exercise Program" OR "Weight-Bearing Exercise Programs" OR "High-Intensity Interval Training" [Mesh] OR "High Intensity Interval Training" OR "High-Intensity Interval Trainings" OR "Interval Training, High-Intensity" OR "Interval Training, High-Intensity" OR "Training, High-Intensity Interval" OR "Trainings, High-Intensity Interval" OR "High-Intensity Intermittent Exercise" OR "Exercise, High-Intensity Intermittent" OR "Exercises, High-Intensity Intermittent" OR "High-Intensity Intermittent Exercises" OR "Sprint Interval Training" OR "Sprint Interval Trainings"

Comparisons: randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [pt] OR evaluation studies as topic [mh] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospective* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT humans [mh])

Outcomes: outcomes were not included in the searches to expand the findings.

In the other databases, terms corresponding to the MeSH terms were used: "Asthma", "Aerobic Exercise",

"Circuit Training", "Resistance Training" and "High-Intensity Intermittent Exercise".

Data analysis and extraction

The articles were initially analyzed in EndNote to exclude duplicate references. Language, year, and study type filters were then applied. The titles and abstracts of the remaining articles were read, and those meeting the eligibility criteria were analyzed in full. The process was performed by 2 independent and blinded reviewers. Disagreements were resolved by consensus, or when necessary, a third reviewer. The data were extracted using a form filled out by independent and blinded reviewers. Data synthesis was performed qualitatively, using a comparative table for the results.

Risk of bias

Methodological quality was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions[41]: random sequence generation, allocation concealment, participant and personnel blinding, outcome evaluation blinding, incomplete outcome data, selective reporting, and others sources of bias. Studies were classified as high, unclear, or low risk of bias. Study quality was assessed independently by 2 blinded reviewers.

Results

Study selection

The electronic database search identified 8,136 records, of which only 3 met the inclusion criteria. The search method is shown in the inclusion flowchart (Figure 1), as are the methodological criteria used to exclude certain studies.

Study characteristics

The aggregate sample of the included articles was 185 participants (93 interventions and 92 controls). The mean age in the control and intervention groups was 11 years. The sample sizes ranged from 27 to 105 individuals. In all 3 studies, the control group received usual care. Two of the studies scored 642.43 and the other scored 544 on the PEDro scale (Table 1).

Two studies[42,44] used Global Initiative for Asthma criteria to classify asthma, while the other did not specify which criteria were used.[43] Two studies classified disease severity from mild to severe[42,43] and the other as controlled to uncontrolled.[44] The participants showed moderate and severe,[42] controlled and partially controlled,[44] and mild and moderate asthma.[43] The baseline FEV_1 obtained through spirometry in 1 study[42] was 1.81 (SD, 0.58) in the control group and 1.96 (SD, 0.62) in the intervention group (p = 0.546). In another study,[43] the control group value was 1.91 (0.95), while the intervention group value was 2.44 (0.55) (p = 0.072). FEV_1 in the third study 44 was 1.53 (0.79) in the control group and 1.33 (0.54) in the intervention group (p = not significant). Lack of exacerbation or change in medication was a criterion in all 3 studies, and 2 (66.7%) specified which medications were used (Table 2).

The applied techniques included aerobic training (n = 1), intermittent training (n = 1), and a combined exercise program (n = 1). All of the studies evaluated functional capacity, lung function, and quality of life outcomes in children and adolescents with asthma. In addition to these outcomes, 1 study assessed inflammatory component and respiratory muscle strength,[42] 1 study assessed body composition,[44] and 2 studies assessed the control and perception of asthma[42,43] (Table 3).

Synthesis of the results

In the study involving aerobic training,[42] no significant differences were found in spirometric variables, such as FEV_1 and forced vital capacity. Increased peak expiratory flow (PEF), improved functional capacity, and improved quality of life were found in the exercise group. Since there were no changes in plasma cytokines produced by Th1, Th2 and Th17, there was no improvement in inflammatory component. The sensation of dyspnea at the end of the protocol was significantly better in the intervention group (0.7 [SD, 0.3]; p < 0.01) than the control group (3.2 [SD, 0.3]; p < 0.01).

Significant changes were found in all analyzed parameters in the intermittent training intervention protocol.[44] Unlike the study that used aerobic intervention,[42] the one involving intermittent exercise[44] found increased FEV_1. BMI in the intervention group reduced from 19.69 kg/m² (p = 0.049) to 17.49 kg/m² (p < 0.001) after the program, while that of the control group did not improve. Another significant result that demonstrates the influence of exercise on the cardiorespiratory system was heart rate, which reduced from 141.26 bpm to 115.16 bpm (p < 0.001)

after the program in the intervention group. Perceived exertion (Borg scale) reduced from 5.15 to 0.73 ($p < 0.001$) after the program in the intervention group.

Using combined exercise, one study found improved lung function, ie, decreased ventilatory equivalent for oxygen (VE/VO_2 ratio) and an increase in peak oxygen consumption (VO_2 peak)[43] . Regarding resistance exercise, muscle strength improved from 80% to 92% in the intervention group and from 41% to 62% in the control group. The results are shown in Table 4.

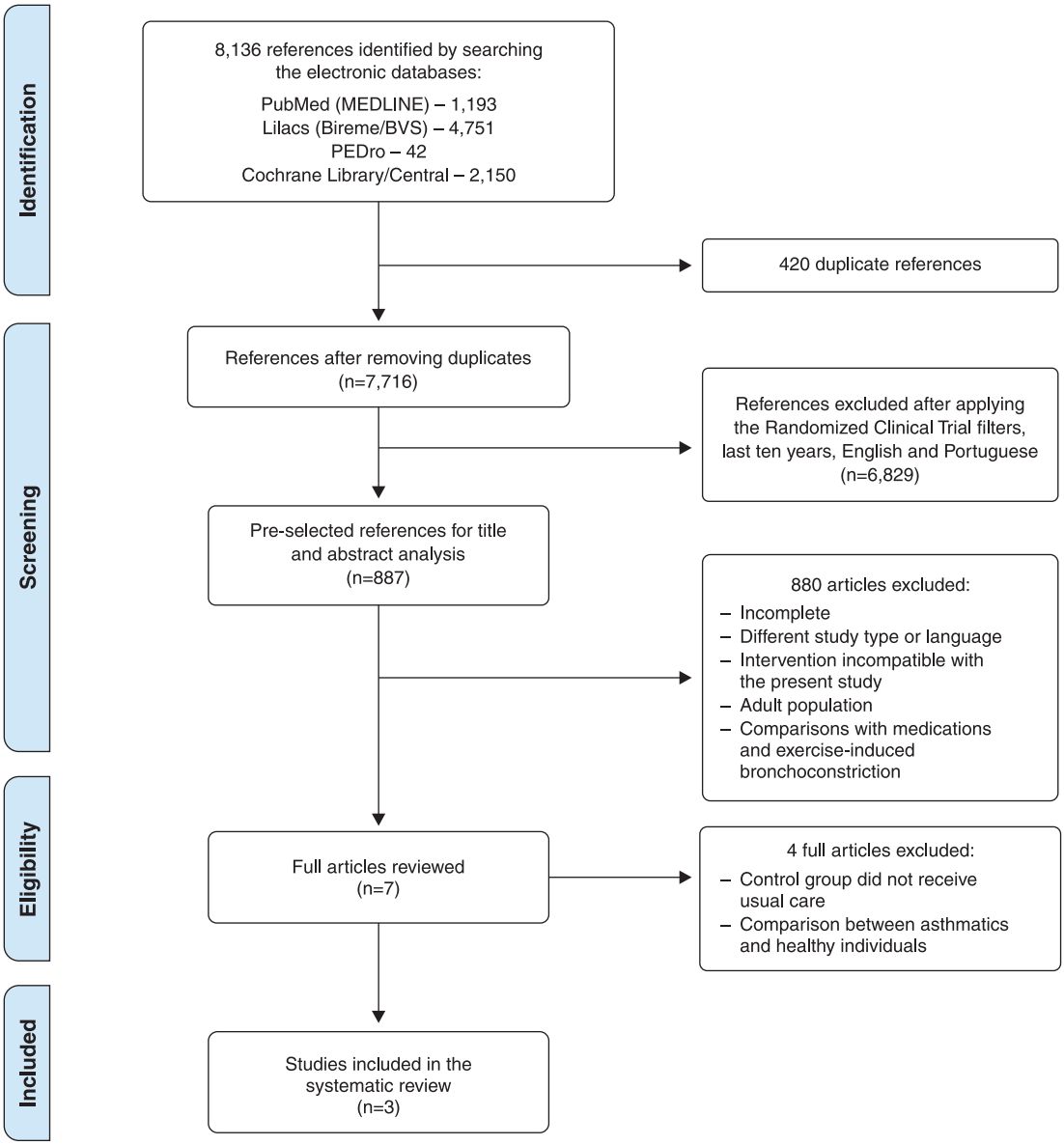

Figure 1
Flowchart of studies

Table 1
Characteristics of the included studies

Author/year	Number of participants	Mean age	Control group Characteristics	Clinical Trial Registration	PEDro score
Andrade et al., 2014	CG (n=17) IG (n=10)	CG (11.4 ± 2.3) IG (11.7 ± 2.3)	Usual routine	NCT0192052	6/10
Latorre-Román et al., 2014	CG (n=47) IG (n=58)	CG (11.51 ± 1.42) IG (11.55 ± 1.01)	Usual care	X	5/10
Sanz-Santiago et al., 2020	CG (n=28) IG (n=25)	CG (11.1 ± 2.9) IG (12.1 ± 2.1)	Clinical guideline routine	NCT02693301	6/10

CG = Control Group, IG = Intervention Group.

Table 2
Classification of disease and medications used in the included studies

Study	Classification	Severity	Pulmonary function	Medications
Andrade et al., 2014	GINA	Moderate GC: 16 GI: 9 Severe GC: 1 GI: 1	FEV_1 (l) CG: 1.81 (0.58) IG: 1.96 (0.62)	Inhaled corticosteroids Long-acting beta-2 agonist
Latorre-Román et al., 2014	GINA	Controlled GC: 57,4% GI: 58,6% Partial controlled GC: 42,6% GI: 41,4,6%	FEV_1 (l) CG: 1.53 (0.79) IG: 1.33 (0.54)	X
Sanz-Santiago et al., 2020	X	Mild to moderate	FEV_1 (l) CG: 1.91 (0.95) IG: 2.44 (0.55)	Inhaled corticosteroids Long-acting beta-2 agonist Leukotriene receptor antagonists Oral corticosteroids Omalizumab

CG = Control Group, IG = Intervention Group, FEV_1(l) = Forced expiratory volume in one second (liters).

Risk of bias

The risk of bias in each study (Table 5) and the risk of bias across studies (Figure 2) were determined according to the Cochrane Handbook for Systematic Reviews of Interventions.[41]

Discussion

The consensus of the included studies was that asthma symptoms and fear of shortness of breath in asthmatic children, in addition to related psychosocial aspects, can lead to low exercise tolerance and result in sedentarism, which directly influences cardiorespiratory fitness and peripheral muscle.

Hence, exercise has the potential to improve symptoms and exacerbation, lung and cardiovascular function, and quality of life. However, 2 studies[42,43] reported difficulties correlating the influence of exercise on inflammatory parameters, peripheral muscle strength, and lung function, and determining whether the results occurred in isolation or were associated, in a cause-consequence relationship.

In 1 study,[44] the authors stated that exercises which help cardiopulmonary function and lower limb muscle strength should be prioritized in training protocols. High-intensity exercise resulted in greater gains than low-intensity exercises, but a combination of these (intermittent) was recommended because

Table 3
Intervention protocols and main outcomes

Study	Intervention	Duration	Frequency	Intensity	Session time	Outcomes
Andrade et al., 2014	Supervised aerobic training on an electric treadmill	6 weeks	3 times a week	Warm up and cool down (40%-50% of maximum heart rate) Exercise (70%-80%)	10 min of warm up, 20 min of training (first and second week), 30 min of training (third to sixth week), 5 min of cool down	Inflammatory component, functional capacity, respiratory muscle strength, quality of life, and symptom perception
Latorre-Román et al., 2014	Supervised intermittent exercise (alternating low and high intensity)	12 weeks	3 times a week	Borg scale 0 to 10 (low intensity to high intensity)	10 min of warm up, 40 min of exercise alternating strength, aerobic and anaerobic, 10 min of cool down	Lung function, functional capacity, body composition, and quality of life
Sanz-Santiago et al., 2020	Supervised combined exercise (resistance and aerobic)	12 weeks	3 times a week	The workload for each session corresponded to HR at the first ventilatory threshold. For resistance exercises, initially 40% of 5-RM was performed, progressing to 60%	10 min of warm up on a cycle ergometer, 20 to 40 min training on a cycle ergometer, resistance exercise (approximately 20 s each set)	Cardiorespiratory capacity, muscle strength, lung function, of aerobic quality of life, asthma control, and functional capacity

HR = Heart rate, 5-RM = 5-repetition maximum.

Table 4
Comparisons of lung function, functional capacity and quality of life variables

Study	Lung function	Functional capacity	Quality of life
Andrade et al., 2014	PEF reduced by 20.6 L/min in the CG and increased by 34.5 L/min in the IG	6MWT: 99.7 m increase in the IG; no change in the CG	PAQLQ: IG increased 1.2 (p<0.001); CG decreased 0.1 (p=0.642)
	Increased respiratory muscle strength only in the IG (22.6 cmH_2O MIP and 21 cmH_2O MEP)		
	No significant differences in FEV_1 or FVC between groups		
Latorre-Román et al., 2014	PEF: mean pre-intervention value 0.84 L/s increased to 1.56 L/s post-intervention in IG	6MWT: 176.49 m increase in the IG	PAQLQ: IG increased 2.51 (p<0.001)
	FEV_1 increased by 1.22 L in the IG		
Sanz-Santiago et al., 2020	Increased VO_2 peak and reduced VE/VO_2	Treadmill test: IG duration increased compared to the CG	No significant differences were found in either group
	No significant differences in FEV_1 or FVC between groups	No significant differences were found in the functional tests (agility walking and in stairs)	

CG = Control Group, IG = Intervention Group, FEV_1 = Forced expiratory volume in one second, PEF = peak expiratory flow, VE/VO_2 = Ventilatory Equivalents for Oxygen, VO_2 peak = peak oxygen consumption, HR = heart rate, 6MWT = 6 Minute Walk Test, FVC = Forced vital capacity, PAQLQ = Pediatric Asthma Quality of Life Questionnaire, MIP = Maximal inspiratory pressure, MEP = Maximal expiratory pressure.

it provides a tolerable training load for beginners. Another study[43] suggested that associating aerobic and resistance exercises would be the best treatment strategy for improving cardiorespiratory and muscle function. However, adequate volume and different exercise modalities are necessary. One study[42] found that aerobic exercise alone led to improved functional capacity, but presented variable results in terms of quality of life and inflammatory component.

Regarding intervention time, the aerobic training protocol[42] showed better PEF results, with a mean difference of 0.575 liters/second, compared to the intermittent training study,[44] whose mean difference was 0.72 liters/second. The aerobic exercise group[42] also had better results in the 6-minute walk test than the intermittent intervention group.[44] Considering quality of life, intermittent training[44] led to better results than aerobic[42] or combined exercise.[43] The intermittent training protocol[44] was the only one that led to a significant change in FEV_1, an outcome common to all studies. Other parameters could not be compared, due to measurement differences or lack of certain outcomes.

One limitation of this review was the fact that only 3 studies were included, resulting in a small sample size. We also point out the scarcity of studies

Table 5
Risk of bias in each included study

Study	Random sequence generation	Allocation sequence concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Andrade et al., 2014	Low	Low	Low	High	Low	Low	Low
Latorre-Román et al., 2014	Low	Unclear	Unclear	High	Low	Low	Low
Sanz-Santiago et al., 2020	Low	Low	Unclear	High	Low	Low	Low

Low = study has the least bias, and results are considered valid.
Unclear = study may be missing information, making it difficult to assess limitations and potential problems.
High = rating indicates significant bias that may invalidate the results (at least one-half of the individual quality items are rated high risk or unclear risk).

on asthmatic individuals in this age group that involve aerobic, intermittent, or combined exercise interventions. Our search for adequate methodological quality can partially explain the limitation. The results of the included studies may have been influenced by small samples,[42] outcome measurement methods,[42] intervention duration,[42] disease severity,[43] and lack of certain outcomes.[43,44]

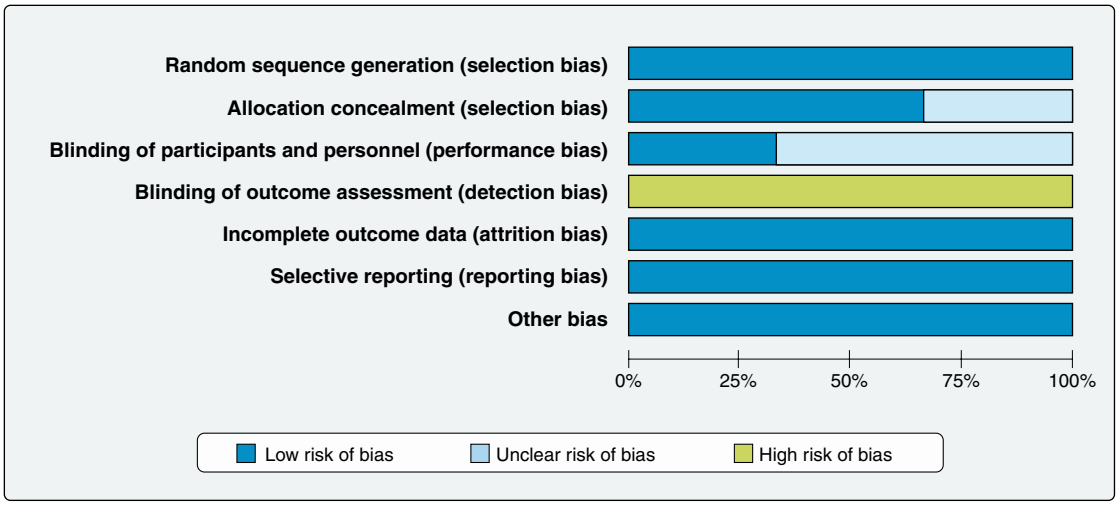

Figure 2
Risk of bias across studies

Conclusion

Asthma leads to biopsychosocial damage. However, exercise can be a good non-pharmacological strategy for reducing the consequences of this pathology. Aerobic exercise led to better PEF and respiratory muscle strength, intermittent exercise led to better FEV_1 and PEF, and both improved functional capacity and quality of life. Combined exercise improved musculoskeletal, VO_2 peak, and cardiopulmonary exercise test results.

Increased methodological rigor and standardized outcome analysis is necessary to increase reproducibility for comparing different types of exercise. New studies are needed to correlate PEF with respiratory muscle strength in intermittent and combined exercise. Further research can help clarify the relationship between exercise and the inflammatory component of asthma, as well as its influence on lung function, functional capacity, quality of life, and reported symptoms.

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