Original Article

Constant-Load Exercise Versus High-Intensity Interval Training on Aerobic Fitness in Moderate-to-Severe Asthma: A Randomized Controlled Trial

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What is already known about this topic? High-intensity interval training (HIIT) and constant-load exercise (CLE) improve aerobic fitness.

What does this article add to our knowledge? HIIT induced a greater reduction in fatigue and dyspnea symptoms, and a similar improvement in physical fitness compared with CLE.

How does this study impact current management guidelines? This study shows the potential to include new models of physical training, such as HIIT, to the clinical treatment of asthma.

BACKGROUND: The effects of high-intensity interval training (HIIT) on dyspnea and aerobic fitness in adults with asthma are poorly understood.
OBJECTIVE: To compare constant-load exercise (CLE) versus HIIT for improvements in dyspnea symptoms and clinical control in adults with moderate-to-severe asthma.
METHODS: Participants were randomized into 2 groups: CLE (n = 27; started with 70% of maximal watts [Wmax] obtained during cardiopulmonary exercise testing [CPET]) and HIIT (n = 28; started with 80% and increased until 140% Wmax). Exercise training lasted 12 weeks (twice/week, 40 minutes/session on a cycle ergometer), and the intensity was based on CPET. Clinical asthma control (Asthma Control Questionnaire), aerobic fitness (the peak of oxygen uptake), health-related quality of life (Asthma Quality of Life Questionnaire), physical activity levels (PAL; accelerometer), symptoms of anxiety and depression (Hospital Anxiety and Depression Scale questionnaire), and dyspnea were evaluated before and after the intervention. Systemic and airway inflammation were also assessed. Two-way analysis of variance and χ^2 tests were used for comparisons. Sixteen participants dropped out during the interventions and returned for the final evaluations.
RESULTS: The CLE and HIIT groups showed similar improvements in aerobic fitness. The HIIT group had lower dyspnea and fatigue perception scores and higher PAL than the CLE group ($P < .05$) and clinical improvements in the psychosocial distress. In addition, only the HIIT group achieved a minimal clinically important difference in asthma symptoms. There was no change in the systemic and airway inflammation ($P > .05$).
CONCLUSION: Both interventions promoted similar improvements in aerobic fitness; however, HIIT induced a greater reduction in dyspnea and fatigue perception. Similar responses were observed for other variables. **(J Allergy Clin Immunol Pract 2022;10:2596-604)**

Key words: *Lung; Inflammation; Physical activity*

Asthma is defined as the presence of respiratory symptoms such as wheezing, shortness of breath, chest tightness, and cough, which vary over time in intensity, along with variable expiratory airflow limitation.[1] Adults with moderate-to-severe asthma often present high levels of anxiety and depression symptoms,[2] impairment in physical activity levels (PAL),[3] reduced health-related quality of life (HRQoL),[4] and low aerobic fitness.[2,5]

Asthma management requires both pharmacological and nonpharmacological treatments to improve symptom control. Pharmacological interventions are based on inhaled corticosteroids and bronchodilators.[1] Aerobic exercise is the

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Abbreviations used
ACQ- Asthma Control Questionnaire
AQLQ- Asthma Quality of Life Questionnaire
BMI- Body mass index
CLE- Constant-load exercise
COPD- Chronic obstructive pulmonary disease
CPET- Cardiopulmonary exercise testing
FeNO- Fractional exhaled nitric oxide
HIIT- High-intensity interval training
HRQoL- Health-related quality of life
MCID- Minimal clinically important difference
MCP-1- Monocyte chemoattractant protein 1
PAL- Physical activity levels
RANTES- Regulated on activation, normal T cell expressed and secreted
Tlim- Test limit
VE- Ventilation
VO_2peak- The peak of oxygen uptake
Wmax- Maximal exercise intensity

nonpharmacological intervention with the most substantial evidence-based benefits,[6,7] with increases in the physical activity, reducing asthma exacerbations.[5,8,9]

Studies have used constant-load exercise (CLE) to evaluate the effects of exercise in adults with asthma. These studies have demonstrated that CLE improves clinical control and HRQoL[7,8] and decreases airway hyperresponsiveness,[9] anxiety and depression levels,[7] and corticosteroid consumption[10] in adults with moderate-to-severe asthma. Other studies have also suggested that CLE reduces airway[11] and systemic inflammation.[12] However, the benefits of other training regimens, such as high-intensity interval training (HIIT), have been poorly investigated.

The benefits of HIIT have been investigated in healthy people,[13] individuals with cardiovascular[14] and chronic metabolic diseases,[15] and adults with chronic obstructive pulmonary disease (COPD); HIIT improves functional capacity and reduces dyspnea.[16] The benefits of HIIT in people with COPD have been related to the reduction in ventilatory limitation[17] and systemic inflammation.[18] Previous studies have investigated the impact of HIIT in adults with asthma, but were nonrandomized controlled trials or did not assess the maintenance effects of the intervention.[19,20] Further, few investigations on systemic inflammation have been conducted.[21] As a consequence, the effects of HIIT in adults with moderate or severe asthma remain unclear.

We hypothesized that HIIT can also improve aerobic fitness and clinical control in adults with moderate-to-severe asthma. The research question addressed in the present study was which model of physical training induces a greater benefit on dyspnea levels, clinical control, exercise capacity, psychosocial morbidity, and PAL in adults with moderate-to-severe asthma.

METHODS

Participants

Adults with asthma treated at a hospital with clinically stable (without exacerbations or changes in medication for at least 30 days), moderate or severe persistent asthma, who were aged between 20 and 59 years and had a body mass index (BMI) $\leq$35 kg/m^2 were included. Asthma was diagnosed as previously described,[1] and disease severity was determined by combining the current level of symptoms, pulmonary function, and maintenance treatment(s).[22]

Adults with asthma who were under optimal medical treatment and monitored by pulmonologists for at least 6 months were included. The Ethics Review Board approved the study (number 534,507), and informed consent was obtained from all participants. The study was also registered at ClinicalTrials.gov (NCT-02489383). The exclusion criteria were as follows: cardiovascular and musculoskeletal diseases or other chronic lung diseases, current participation in an exercise program, and current smokers or ex-smokers (>10 pack-years).

Experimental design

The study was performed between 2 medical consultations to avoid changes in medication (Figure 1). All participants were randomized into CLE or HIIT groups and participated in a 4-hour educational program before initiation of the exercise programs. Before and after the intervention, participants were evaluated for the following: clinical asthma control, HRQoL psychosocial morbidity, cardiopulmonary exercise testing (CPET), PAL, airway, and systemic inflammation. The participants were subjected to 24 sessions of either CLE or HIIT (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org).

Allocation and randomization

Eligible participants were randomly allocated to their respective intervention groups using a computer-generated randomization schedule completed by an investigator blinded to the participants' recruitment, evaluation, and treatment.[12]

Interventions

Educational program. Participants attended an educational program consisting of 2 sessions held twice a week before starting any exercise program (baseline). The educational sessions were divided into 2 days, duration of 2 hours in each class. On the first day, the participants received information on asthma physiopathology and medication skills. On the second day, the participants received information on self-monitoring techniques, environmental control, and the importance of keeping physically active.[9,11]

Exercise training programs. Exercise training was performed twice a week for 12 weeks for a total of 24 sessions (HIIT or CLE). HIIT sessions lasted 40 minutes (5 minutes of warm-up, 30 minutes of exercise, and 5 minutes of cool down) and were performed on a cycle ergometer (Bike 700; Technogym, Cesena, Itália). HIIT was performed in bouts, with the workload (maximal exercise intensity [Wmax]) based on the CPET.[17,23] In the first 2 weeks, the participants performed HIIT at 80% of Wmax; in weeks 3 to 4, 90% to 100% Wmax; in weeks 5 to 6, 110% to 120% Wmax; in weeks 7 to 8, 120% Wmax; in weeks 9 to 10, 130% Wmax; and in weeks 11 to 12, 140% Wmax. Each session was composed of rounds of 30 seconds of HIIT and 30 seconds of recovery (active exercise at 40% Wmax). For better physiological adaptation, the first 4 sessions had a duration of 20 minutes, with 5 minutes of warm-up, 10 minutes of the main exercise, and 5 minutes of cool down.[23]

CLE sessions lasted 40 minutes (5 minutes of warm-up, 30 minutes of exercise, and 5 minutes of cool down) and were performed on a cycle ergometer. The intensity was initiated at 70% of the Wmax obtained in the CPET.[9-11] The exercise workload was increased by 5% every 2 weeks when supported by the participant based on dyspnea and fatigue symptoms.[11,24]

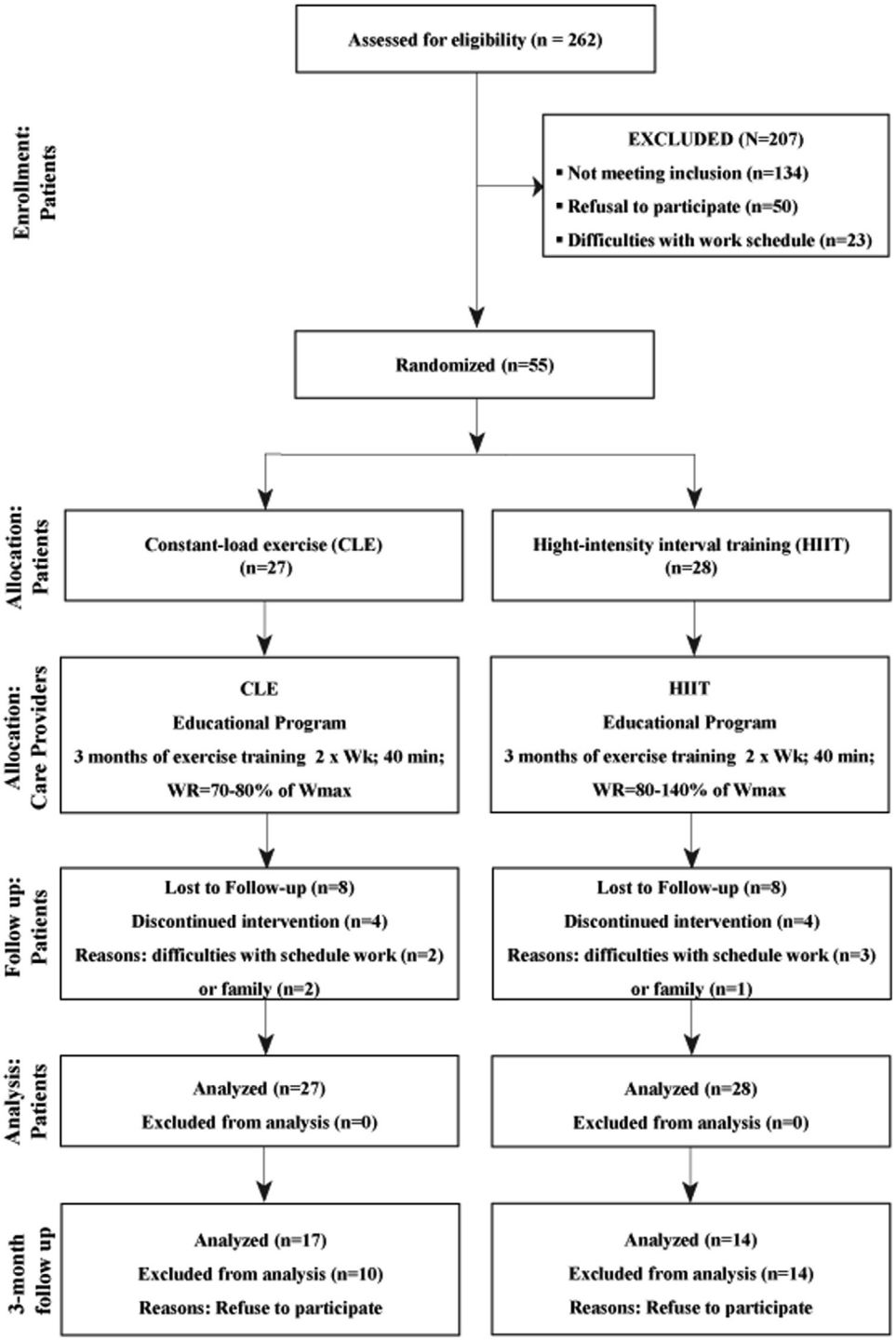

FIGURE 1. Flowchart of the participants throughout the study (CONSORT diagram). *Wk*, Week; *Wmax*, watts maximal obtained in the cardiopulmonary exercise testing, *WR*, work rate.

Outcome assessments

Cardiopulmonary exercise testing. CPET was performed using an electrical cycle ergometer[12] (Corival; Lode B.V. Medical Technology, the Netherlands) equipped with an electronic system (CPX System; CareFusion, Germany).[25] Aerobic fitness levels were classified in accordance with the Brazilian population.[26]

Submaximal exercise testing (isotime). After the intervention, the time limit (Tlim) test was assessed at 75% of the maximum wattage obtained in the CPET in an isotime test. The Tlim is a constant-power endurance test recommended in the evaluation of the effects of an intervention on exercise tolerance.[27,28] Dyspnea and fatigue levels were assessed using the Borg scale every 2

TABLE I. Baseline characteristics of subjects with asthma patients before the intervention

Characteristics	CLE (n = 27)	HIIT (n = 28)
Anthropometric data		
Sex (F/M)	23/4	23/5
Age (y)	48.0 (34.2, 52.7)	42.5 (33.5, 49.0)
BMI (kg/m^2)	30.4 (25.5, 31.6)	27.2 (24.8, 31.8)
Lung function		
FEV_1 (%)	68.0 (59.0, 80.0)	71.5 (63.0, 82.5)
FVC (%)	83.0 (71.2, 94.0)	86.5 (78.5, 89.0)
FEV_1/FVC (%)	80.0 (74.2, 85.7)	86.5 (78.5, 92.5)
Clinical control		
ACQ-6, score	1.83 (0.70, 2.33)	1.85 (1.33, 2.41)
CPET		
VO_2 peak (mL/kg/min))	19.3 (17.9, 23.7)	22.1 (19.7, 24.6)
% predicted	87.5 (78.8, 100.4)	87.9 (76.8, 109.1)
Workrate (W)	100 (100, 125)	125 (100, 137)
% predicted	107 (86.2, 133)	107.5 (86.2, 131)
HRQoL		
Physical limitation, score	3.90 (2.72, 5.06)	3.72 (2.90, 4.18)
Symptoms, score	4.41 (3.00, 5.89)	3.83 (3.20, 5.12)
Emotional function, score	4.00 (2.75, 5.40)	3.60 (2.30, 5.00)
Environmental stimuli, score	4.50 (1.75, 5.00)	3.00 (1.55, 4.50)
Total, score	3.78 (2.89, 5.40)	3.54 (2.76, 4.46)
Psychosocial morbidity		
Anxiety, score	9.00 (6.25, 12.0)	9.50 (7.00, 13.0)
Depression, score	7.00 (5.00, 11.7)	10.0 (6.50, 11.5)
Physical activity level		
Total steps, WK	9251 (7832, 12,653)	9994 (8548, 12,393)
Total steps, WKND	9453 (7256, 11,212)	8701 (4815, 12,061)
Moderate steps, WK	4337 (3511, 5267)	4604 (3481, 5775)
Moderate steps, WKND	3781 (2851, 4925)	4414 (2380, 5705)
Medication		
Budesonide (μg/d)	800 (500, 1200)	800 (800, 1500)

Data are presented as median and confidence interval (25%-75%). The "Total steps" parameter represents the amount of all steps walked at all intensities during 24 hours; "Moderate steps" represent only steps performed at a cadence ≥110 steps/min.
ACQ, Asthma Control Questionnaire; *BMI*, body mass index; *CLE*, constant-load exercise; *CPET*, cardiopulmonary exercise testing; *FEV_1*, forced expiratory volume in the first second; *FVC*, forced vital capacity; *HADS*, Hospital Anxiety And Depression Scale; *HIIT*, high-intensity interval training; *HRQoL*, health-related quality of life; *VO_2 peak*, peak oxygen consumption; *WK*, during the weekdays; *WKND*, during the weekend days.

minutes until exhaustion.[12,16] These assessments were conducted at 2, 4, 6, and 8 minutes.

Asthma Control Questionnaire. Clinical asthma control was evaluated using the Asthma Control Questionnaire (ACQ),[9,11] and a change of ≥0.50 point was considered the minimal clinically important difference (MCID).[29]

Heath-related quality of life. HRQoL was evaluated using the Asthma Quality of Life Questionnaire (AQLQ),[29] and the MCID ≥0.50 point was considered clinically significant.[29-31]

Psychosocial morbidity. Symptoms of anxiety and depression were evaluated using the Hospital Anxiety and Depression Scale.[12,32] An MCID was considered with a change of <1.32 points for anxiety and ≤1.40 points for depression.[33]

Lung function. Pulmonary function testing was performed according to the current guidelines[34] using a KoKo spirometer (Nspire Health Inc.).

Physical activity levels. PAL was evaluated before and after the interventions and during the follow-up assessment using an accelerometer (Power Walker PW610; Yamax, Japan).[35] The MCID was considered an increase of 500 steps/day.[36]

Airway inflammation. Airway inflammation was quantified using a portable analyzer device (NIOX-MINO; Aerocrine AB, Solna, Sweden) to measure the exhaled fraction of nitric oxide.[11,37]

Systemic inflammation. It was assessed using blood-based markers.[11,15] The cytometric bead array method (BD Biosciences, San Jose) was used to analyze the levels of IL-1β, IL-17, TNF-α, IL-2, IL-10, monocyte chemoattractant protein 1, and regulated on activation, normal T cell expressed and secreted (RANTES).[9,12] Cortisol was also quantified using a fluoroimmunoassay.[12] The measurements were performed using blood collected before and after the interventions.

Follow-up. Twelve weeks after the interventions, the participants' clinical control, HRQoL, PAL, psychosocial distress, and lung function were assessed (third and final evaluation).

Statistical analysis

The sample size was calculated, assuming a difference in Borg scale scores of 1.0 ± 1.3.[23] An 80% statistical power and a 5% significance level were considered. A total sample size of 55 participants was calculated, and the number was increased to 60, assuming a loss of 10% throughout the study. The sample calculation was performed using SigmaStat. The normality of the data was assessed using the Shapiro-Wilk test. Comparisons of the initial and final data were analyzed via 2-way repeated-measures analysis of variance, and the categorical outcomes were assessed via χ^2 tests. A P value of <.05 was deemed significant. The statistical analysis was blinded to the treatment regimen. An intention-to-treat analysis was used to preserve the effects of group allocation and assess the treatment's practical impact. Analyses were preceded by multiple imputation analyses based on 100 imputed versions obtained via predictive mean matching.[38] In addition, the effect size was calculated using the Cohen method and classified as small (0.21-0.49), medium (0.50-0.79), or large (>0.80).[34,36]

RESULTS

Baseline data and characterization of the adults with asthma

A total of 262 adults were evaluated; 134 did not meet the inclusion criteria, 50 were not enrolled because of the participants working hours that coincided with the schedule of the physical training sessions, and 23 were excluded because of other associated diseases. A total of 55 participants were randomized into 2 groups, either the CLE (n = 27) or HIIT (n = 28) (Figure 1). The participants of both groups were similar when comparing their gender, age, BMI, pulmonary function, ACQ, the peak of oxygen uptake (VO_2peak), HRQoL, psychosocial

TABLE II. Comparison of the aerobic fitness between CLE versus HIIT in patients with moderate-to-severe asthma

	CLE (n = 27)			HIIT (n = 28)			Interaction
CPET	Baseline	Change after intervention	*P* time	Baseline	Change after intervention	*P* time	Time × Group
Maximal							
VO_2 peak (mL/kg/min)	19.3 (17.9, 23.7)	1.50 (0.07, 4.77)	.003	22.1 (19.7, 24.6)	2.15 (0.35, 3.85)	.005	NS
Work rate (W)	100.0 (100.0, 125.0)	25.0 (0.0, 25.0)	.001	100.0 (100.0, 137.5)	25.0 (25.0, 25.0)	.001	NS
RCP							
VO_2 (mL/kg/min)	16.2 (15.2, 17.8)	2.90 (1.37, 5.47)	.003	17.4 (15.0, 19.7)	2.25 (0.77, 4.55)	.005	NS
Anaerobic threshold							
VO_2 (mL/kg/min)	12.6 (10.6, 13.6)	1.40 (0.65, 3.12)	.03	12.4 (10.0, 14.6)	1.75 (0.40, 3.80)	.05	NS

Data are presented as median and confidence interval (25%-75%). The comparisons are shown as the difference observed in relation to the baseline.
CLE, Constant-load exercise; *CPET*, cardiopulmonary exercise testing; *HIIT*, high-intensity interval training; *NS*, not significant; *RCP*, respiratory compensation point; *VO_2 peak*, peak oxygen uptake.

distress, medication use, and PAL ($P > .05$; Table I). Before the intervention, the number of adults classified as having uncontrolled asthma (ACQ score >1.5) was similar between the CLE and HIIT groups using the ACQ-6 (17 [62%] vs 22 participants [78%], respectively; $P > .05$).

Effects of CLE versus HIIT on aerobic fitness, dyspnea, and perception of fatigue during CPET

Results showed that both interventions increased the VO_2peak and the workload ($P < .05$; Table II), without differences between groups ($P > .05$). In addition, there were no differences between the groups in dyspnea levels and lower limb fatigue after the interventions ($P > .05$; Figure 2, *A-D*). However, the HIIT's participants experienced a reduction in dyspnea and lower limb fatigue during the CPET (from the 4th to 10th minute). In contrast, the adults who participated in CLE showed an improvement between 4 and 6 minutes compared with the baseline, and they reported no significant change in fatigue perception.

Improvements in PAL

After the intervention, the HIIT group achieved an MCID in total PAL during weekdays compared with the CLE group ($P < .05$); however, this improvement was abolished in the follow-up. Only the HIIT group exceeded the MCID (>500 steps/day) for total and moderate PAL (1149 and 825 steps, respectively), with an increase compared with the baseline ($P < .003$). There were no changes in PAL on the weekend days in either group ($P > .05$; Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

Effects of CLE versus HIIT at the Tlim

Dyspnea symptoms reached higher levels than limb fatigue at the end of the physical Tlim in both groups before and after the interventions (Figure 3). After the interventions, a reduction in dyspnea levels was observed during Tlim (2nd to 4th minute) in the participants who performed HIIT when compared with those who performed CLE ($P < .05$; Figure 3, *A*). However, there were no between-group differences in lower limb fatigue ($P > .05$; Figure 3, *B*).

Performance during CLE and HIIT exercise sessions

The first 2 weeks included a period of adaptation to exercise training (Figure E2, *A-D*, available in this article's Online Repository at www.jaci-inpractice.org), after which participants in both groups maintained dyspnea and fatigue levels between "somewhat hard" and "hard" (13-15). In addition, both groups presented similar dyspnea levels, lower limb fatigue, and heart rates when evaluated during the exercise sessions ($P > .05$; Figure E2, *A-C*, available in this article's Online Repository at www.jaci-inpractice.org). However, energy expenditure in the HIIT group was greater than that in the CLE group between the 10th and 24th sessions ($P < .05$; Figure E2, *D*, available in this article's Online Repository at www.jaci-inpractice.org).

Effects of CLE and HIIT on the clinical control of asthma and lung function

After the intervention, there was no clinically significant difference for both groups in the ACQ-6 (44% vs 35%, respectively; $P > .05$). However, the participants in the HIIT group reached an MCID difference in ACQ-6 scores after the intervention compared with baseline (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). Regardless of treatment group, ACQ-6 scores from baseline were linearly correlated after the intervention and 3 months after the intervention (Figure E3, *A* and *B*, available in this article's Online Repository at www.jaci-inpractice.org). No differences were observed in the 3-month follow-up period regarding clinical control or lung function in both groups ($P > .05$; Table E2, available in this article's Online Repository at www.jaci-inpractice.org).

Comparison between CLE and HIIT on psychosocial distress, HRQoL, and inflammation

After the interventions, clinical improvement was observed in anxiety and depression symptoms, and the proportions of participants who presented clinical reductions in anxiety (63% vs 53%) and depression levels (74% vs 71%) were similar between groups (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). However, these symptoms were improved only in the HIIT during the follow-up (3 months after the intervention). After the interventions and during the follow-up period, the CLE did not show clinical improvements in the total score or domain scores on the AQLQ (Figure 4, *A* and *B*). However, only the HIIT showed clinical improvements in the total score and in the symptoms related to the emotional function that lasted 3 months after the intervention (Figure 4, *A* and *B*). There were no changes in inflammatory markers ($P > .05$; Table E3, available in this article's Online Repository at www.jaci-inpractice.org).

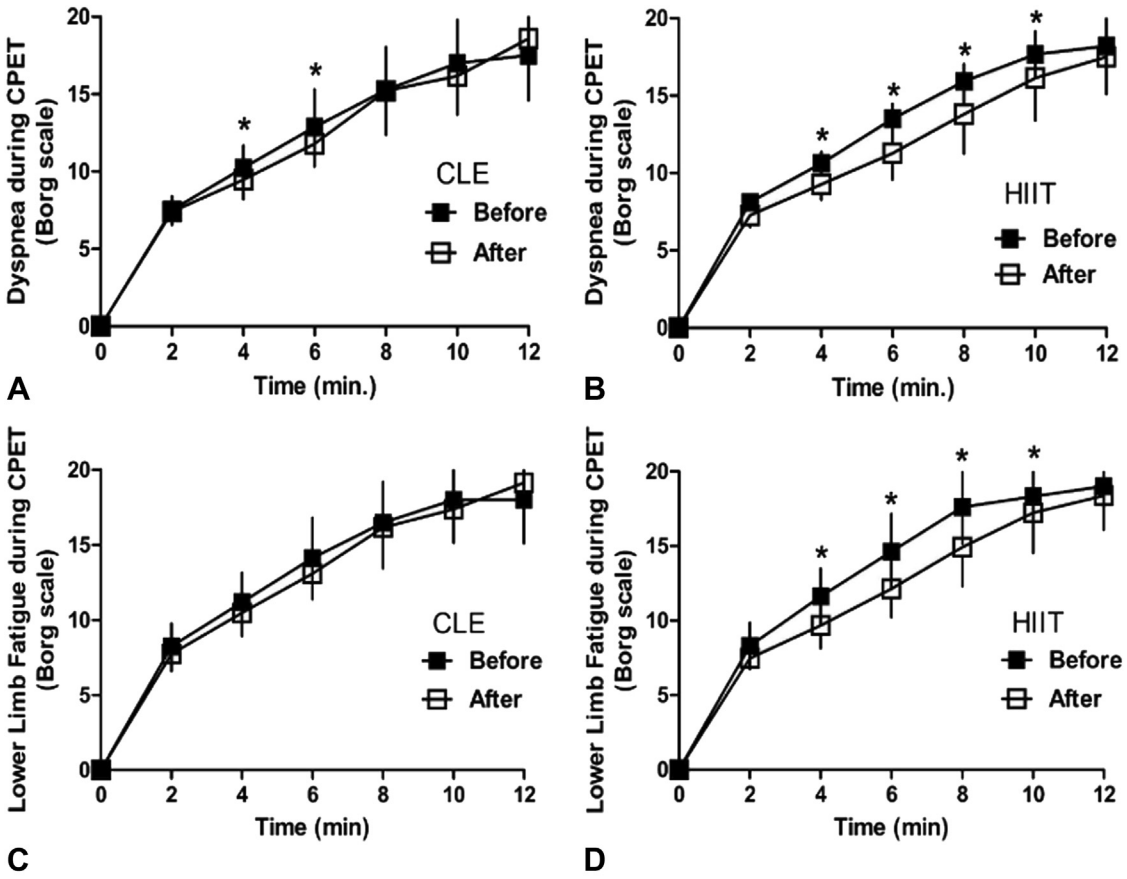

FIGURE 2. Comparison of dyspnea and lower limb fatigue levels. Levels of (**A** and **B**) dyspnea and (**C** and **D**) lower limb fatigue during the CPET before (closed square) and after (open square) the interventions. *CLE*, Constant-load exercise; *CPET*, cardiopulmonary exercise test; *HIIT*, high-intensity interval training. $*P < .05$ when compared with baseline.

Effect size

The results showed that the effect size ranged from small to large for all outcomes in both groups. In general, the effect size was greater with 7 of 9 outcomes in favor of the HIIT (Figure 5). The aerobic fitness outcomes (VO_2peak and work rate) reached higher values in the CLE. In contrast, improved outcomes related to anxiety/depression symptoms, HRQoL, and clinical control (ACQ-6) were higher in the HIIT group.

DISCUSSION

Our study demonstrated that adults with asthma who were subjected to either CLE or HIIT showed improved aerobic fitness; however, the HITT group presented a greater reduction in dyspnea and fatigue symptoms. In contrast, no changes were observed in systemic inflammation or psychosocial morbidity. Our results also demonstrated that only participants with asthma who underwent HIIT showed an improvement in moderate PAL and reached a clinical improvement for asthma control and HRQoL.

Physical exertion, dyspnea, or the fear of triggering other asthma symptoms are responsible for keeping adults with asthma away from participating.[12,24] This may explain why individuals with asthma are less physically active than those without asthma.[5,24] Previous studies have demonstrated that CLE training improves asthma symptoms;[9,11,12] however, the benefits of exercise training on fatigue and dyspnea symptoms are less understood. The effects of HIIT on dyspnea and fatigue have been extensively studied in individuals with other chronic pulmonary diseases,[16,39] but not in participants with asthma. Our study showed that HIIT reduced dyspnea and fatigue symptoms during maximum exercise (CPET). A possible explanation for these benefits may be the physiological adaptations that occur during HIIT, such as greater efficiency for lactate removal[40] and reducing stimulation of central fatigue.[41] The effect of HIIT on the reduction of dyspnea seems less pronounced in our participants with asthma than that previously observed in participants with COPD.[16,17] Although a direct comparison between adults with asthma and those with COPD is difficult, the greater benefit in participants with COPD could be explained by major musculoskeletal dysfunction.

In our study, no significant differences were observed in the clinical asthma control or HRQoL in both groups despite aggregate clinical improvements (Figure 4); however, only the HIIT reached the clinical improvement. Interestingly, these results are inconsistent with previous studies from our group that demonstrated that participants who perform CLE achieve clinically significant better asthma control.[7,8,12] We speculate that ACQ did not significantly improve in the CLE group because some participants had good asthma control (score <1.50) at

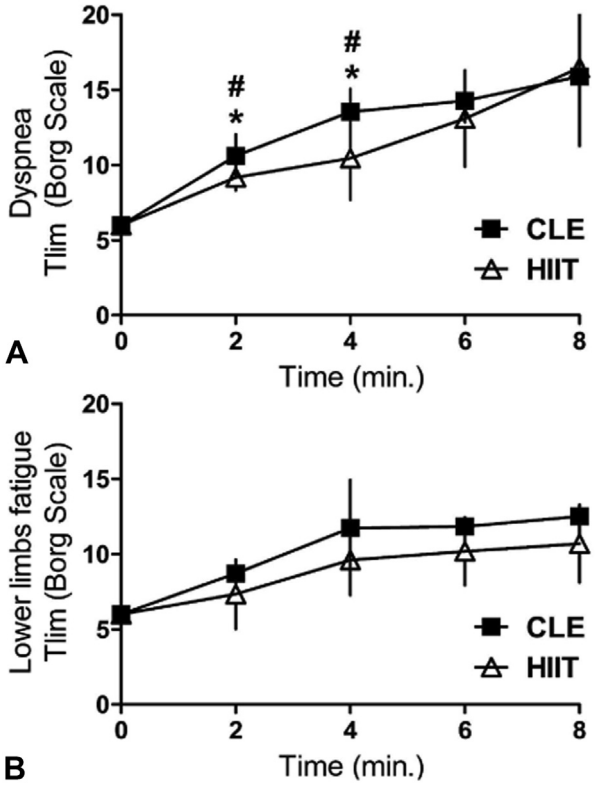

FIGURE 3. Evaluation of (**A**) dyspnea and (**B**) lower limb fatigue during the test limit (Tlim) performed after interventions. The symbol "*" represents the intragroup reduction in the dyspnea levels for both groups ($P < .05$). In contrast, the symbol "#" represents a significant decrease in the dyspnea levels comparing CLE versus HIIT ($P < .05$). *CLE*, Constant-load exercise; *HIIT*, high-intensity interval training.

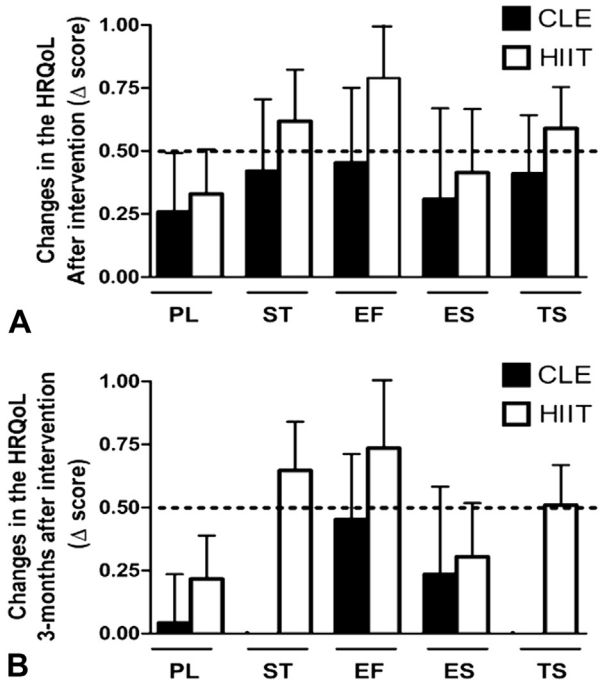

FIGURE 4. Change in health-related quality of life (HRQoL) after the (**A**) intervention and (**B**) follow-up. Data are shown as the mean ± standard deviation of delta scores (after intervention−baseline) (**A**) and follow-up (3 months after intervention−baseline) (**B**). The dashed line represents the minimal clinical important difference (change of at least >0.50 points). In panel **B**, values in the ST and TS domains of the CLE group are 0 ("zero"). *CLE*, Constant-load exercise; *EF*, emotional function; *ES*, environmental stimuli; *HIIT*, high-intensity interval training; *HRQoL*, health-related quality of life; *PL*, physical limitation; *ST*, symptoms; *TS*, total score.

baseline. This is reinforced by the lower ACQ score in this study than those in previous studies.[12,24] Another explanation for the lower benefit observed in the clinical control could be explained by the fact that exercise training in the present study was performed using a cycle ergometer instead of a treadmill, as was used in previous studies.[7,9,12] This explanation may also support the greater benefits observed in the HIIT because, in this exercise modality, people can reach greater exercise intensity[35] and energy expenditure than can be achieved with CLE (Figure E2, *A*, available in this article's Online Repository at www.jaci-inpractice.org). Other previous studies have demonstrated that clinical control improvements are dependent on an increase in aerobic fitness.[7,9,12] In the present study, HIIT and CLE induced similar aerobic fitness improvements (approximately 2.2 mL/kg/min), which were lower than previously observed values[7,9] and values reported by systematic reviews (4.9-5.5 mL/kg/min, respectively).[6,42]

Participants who performed HIIT showed an increase in moderate physical activity after the intervention; in contrast, a small reduction was observed in participants who performed CLE. Although speculative, our results suggest that the improvement in PAL may have occurred because participants experienced lower dyspnea and fatigue levels after exercise training (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). However, the improvement in PAL did not last through the follow-up period. The lack of difference in the after 3 months of the interventions may be underpowered due to the high dropout rate; despite that, our results may be considered a pilot study to assess PAL in future studies. The effect of exercise training on PAL in adults with asthma is poorly understood. To the best of our knowledge, only Freitas et al[24] demonstrated that exercise training improves PAL; however, they specifically evaluated obese individuals with asthma, and weight loss could explain this increase. The reduction in the PAL after CLE training observed in our study can be explained by a compensatory behavior effect after exercise training, as previously reported.[35] Contrary to the CLE, our results revealed improvements in PAL in the HIIT group, which could be important in reducing asthma exacerbation, as previously suggested.[24] On the basis of our findings, we suggest the need for future studies to evaluate whether HIIT can be used to improve PAL in association with behavior intervention.[43]

The participants who performed CLE or HIIT showed a clinical improvement reduction in the anxiety symptoms, and those who performed HIIT also showed a clinical improvement in the depressive symptoms. The effects of exercise training on reducing psychosocial distress have been previously demonstrated;[7,12] however, the effect of HIIT on psychosocial distress is

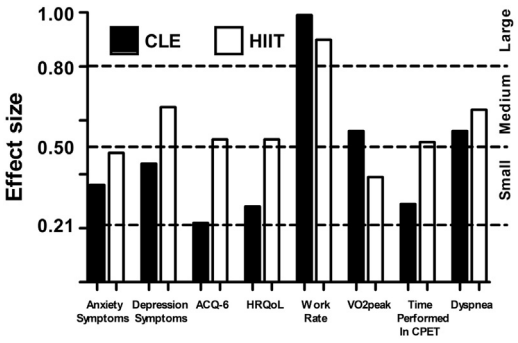

FIGURE 5. Comparison of effect sizes for psychosocial morbidity, clinical control, HRQoL, physical fitness, and dyspnea. The effect size was evaluated immediately after the interventions and calculated using the Cohen method and classified as small (0.21-0.49), medium (0.50-0.79), and large (>0.80). *ACQ*, Asthma Control Questionnaire; *CLE*, constant-load exercise; *CPET*, cardiopulmonary exercise test; *HIIT*, high-intensity interval training; *HRQoL*, health-related quality of life; VO_2, oxygen consumption.

poorly known. A recent study showed that HIIT reduces anxiety symptoms in individuals with athma.[20] We speculate that this improvement in distress symptoms may have occurred because of the reduction of dyspnea induced by HIIT (Figure 3). In addition, evidence demonstrates that the level of physical fitness is associated with psychosocial morbidity and HRQoL in adults with asthma.[7,24] Our findings support these results and indicate that HIIT can also reduce psychosocial symptoms reaching a clinical improvement in HRQoL.[7]

Although previous studies have suggested that CLE decreases airway and systemic inflammation,[11,12] our findings showed that neither CLE nor HIIT changed inflammatory asthma biomarkers (Table E3, available in this article's Online Repository at www.jaci-inpractice.org). Reinforcing our findings, Toennesen et al[44] showed that HIIT did not reduce the inflammatory profile in participants with asthma. Furthermore, the lack of consensus on the effects of exercise training on airway inflammation was verified in a systematic review[45] and a recent study.[46] These results may suggest that the impact of exercise on airway inflammation may depend on the disease severity or asthma phenotype.[45]The magnitude of the effects of CLE and HIIT was also compared using effect sizes (Figure 5), which ranged from small to large. We observed that HIIT resulted in greater benefits in 7 of 9 outcomes. Outcomes related to psychosocial distress, clinical control, and dyspnea showed greater benefits after HIIT training. On the other hand, outcomes related to physical fitness (VO_2peak and work rate) showed greater benefits after CLE training. In addition, the present study evaluated the possible maintenance of the effects of physical training in individuals with asthma 12 weeks after the end of the last exercise session (follow-up to medium term), as shown in a previous study.[47] HIIT showed that participants who maintained improvement did not reach statistical significance but reached MCID in HRQoL. These benefits may have occurred because of the physical fitness improvement obtained after the exercise training program.[21,45]

Limitations

The study has some limitations. First, 8 participants in each group dropped out during the interventions, but they returned for reassessment after the intervention period (n = 55). In addition, 17 participants in the CLE and 14 in the HIIT (n = 31) groups were evaluated in the short term at the third evaluation; nevertheless, we understand that this represents what occurs in real life. Second, we performed CLE using a cycle ergometer instead of a treadmill, which has been used in most previous studies.[7,9,12] However, it would be difficult to compare the 2 interventions if they were performed on different ergometers. In addition, HIIT has been mostly performed on cycle ergometers because it allows increases in the workload and quick interruptions during the training exercise.[16,17,30] The Tlim was performed only after the interventions, in contrast to the previous studies.[16,23,24] However, both groups performed CPET before physical training, and there was no difference in physical fitness.

CONCLUSION

Our study suggests that CLE and HIIT effectively improve aerobic fitness in adults with moderate-to-severe asthma. However, HIIT was more effective in reducing dyspnea levels and lower limb fatigue, and increasing PAL. As the effects of CLE and HIIT were similar in several outcomes, our findings suggest that HIIT may be an alternative exercise training model to be performed for participants with moderate-to-severe asthma.

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ONLINE REPOSITORY

METHOD

Allocation and randomization

Eligible participants were randomly allocated to their respective intervention groups using a computer-generated randomization schedule completed by an investigator blinded to the participants' recruitment, evaluation, and treatment. Each participant's allocation was concealed using sequentially numbered papers, sealed, and placed in opaque envelopes. The sealed envelopes were opened in front of the participants as they were informed of their group allocation. The researcher who provided the treatment was not involved in the data collection. Because of the nature of the interventions, it was not possible to blind the physiotherapist who provided the exercise training[E1] (Figure E1).

Cardiopulmonary exercise testing

The cardiopulmonary exercise testing (CPET) was performed using an electrical cycle ergometer (Corival; Lode B.V. Medical Technology, the Netherlands) digitally equipped with an exercise evaluation system (CPX System; CareFusion Corporation, Germany), in accordance with the European Respiratory Society statement.[E2] Peripheral oxygen saturation (SpO_2) and electrocardiography were continuously monitored during the tests. The following variables were recorded: work rate (W), oxygen consumption (VO_2), minute ventilation (VE), carbon dioxide production (VCO_2), respiratory exchange rate (RER), and heart rate (HR). Blood pressure, leg discomfort, and dyspnea[E3] were also monitored. Participants performed a symptom-limited CPET, consisting of 2 minutes of rest, 2 minutes of warm-up (unloaded pedaling), and a ramp work period (from 10 to 15 W), taking into account the participants' daily activity level. The predicted maximum oxygen consumption was obtained from the Brazilian population norms.[E4] The anaerobic threshold was identified as the VO_2 at which the change in slope of the relationship of VCO_2 to CO_2 occurs.[E2,E4] The respiratory compensation point was determined by increasing VE/VCO_2 values, accentuated tachypnea, and a progressive reduction in $P_{ET}CO_2$.[E2]

Submaximal exercise testing

A submaximal or limit test was also performed based on the workload obtained in the CPET. The load was progressively increased (using a ramp-up) for 2 minutes until the target workload was reached (75% of the maximum wattage, obtained during full CPET). The levels of dyspnea and fatigue were assessed using the Borg scale of perceived exertion every 2 minutes until exhaustion.[E5] The comparisons of high-intensity interval training (HIIT) and constant-load exercise (CLE) on dyspnea and fatigue levels were performed at 2, 4, 6, and 8 minutes.

Asthma Control Questionnaire

The Asthma Control Questionnaire (ACQ), a reliable and validated survey,[E6] consists of 5 questions related to asthma symptoms (daytime and nighttime symptoms, activity limitations, dyspnea, and wheezing) and 1 question related to rescue medication (eg, the use of short-acting β2 agonists). Scores lower than 0.75 are associated with good asthma control; scores greater than 1.5 indicate poor asthma control, and a change of $\geq$0.5 points in the ACQ score is considered clinically significant.[E7]

Heath-related quality of life

Heath-related quality of life was evaluated using the Asthma Quality of Life Questionnaire (AQLQ).[E6] The AQLQ consists of 32 questions rated on a 7-point scale (from 1 = a great deal to 7 = not at all), divided into the following 4 domains (activity limitations, symptoms, emotional function, and environmental stimuli). The AQLQ has been translated and validated for Portuguese. Higher AQLQ scores indicate a better quality of life; clinically effective treatment has shown to result in a $\geq$0.5-point increase in the score after the intervention.[E8]

Psychosocial morbidity

Symptoms of anxiety and depression were evaluated using the Hospital Anxiety and Depression Scale,[E9] which consists of 14 items divided into 2 subscales (7 for anxiety and 7 for depression). Each item is scored from 0 to 3, with a maximum score of 21 points for each subscale. A score greater than 9 for each subscale suggests a diagnosis of anxiety and/or depression.[E10] Clinical improvements were considered to be a $\geq$1.32-point decrease in anxiety scores and a $\geq$1.40-point decrease in depression scores, as previously described.[E11]

Physical activity levels

A triaxial accelerometer (Power Walker PW610; Yamax, Japan) was used to quantify the change in physical activity level (PAL)[E12] and has been used to assess PAL in participant with lung disease.[E13,E14] The equipment records the total daily steps and the number of daily steps in moderate to vigorous intensity ($\geq$110 steps/min). The Yamax accelerometer considers the interindividual variability of steps at $\geq$110 steps/min, a consistent value associated with absolutely defined moderate intensity (ie, 3 metabolic equivalents).[E15] The assessment was performed for 7 days before and after the interventions. The accelerometer recorded the total number of steps, and the moderate-intensity PAL was recorded for each participant daily. The average number of steps was used for 5 days (the first and last day were excluded).[E12,E15] In the present study, PAL assessment during weekdays was the main objective because it represents the participant's regular daily life. Weekend PAL was included as complementary information to identify whether the improvement in physical capacity could also modify physical activity behavior when the individual was more sedentary. At least 3 weekdays and 1 weekend day were considered the minimum number of days needed to validate the data analysis, as previously described,[E15] and the number of steps per day was averaged per week. A change of 500 steps/d was considered a minimal clinically important difference as previously described.[E16]

Airway inflammation

Airway inflammation was quantified using a portable analyzer device (NIOX MINO; Aerocrine AB, Solna, Sweden) to measure the exhaled fraction of nitric oxide (FeNO), in accordance with American Thoracic Society/European Respiratory Society guidelines.[E17] The participants with asthma were asked to perform a full inhalation through a NIOX filter until they reached near total lung capacity and then immediately exhale at a constant flow rate of 50 mL/s using a visual feedback system. The average levels of at least 3 acceptable measurements were used. The participants were instructed to avoid eating foods containing nitrates and caffeine, smoking, and exercise for 24 hours before testing and refrain from ingesting either food or water for at least 2 hours before testing. The same professional performed nitric oxide collection at the same time of day to maintain consistency. A cutoff point of 25 parts per

billion was used to confirm or exclude a diagnosis of eosinophilic airway inflammation.[E1,E18]

Systemic inflammation

Participants' inflammatory systemic profiles were assessed using blood-based markers. Venous blood samples were collected after at least 8 hours of overnight fasting, and the participants were advised to avoid exercise, alcohol, and caffeinated beverages for the 24 hours before testing. The cytometric bead array method (BD Biosciences, San Jose, CA) was used to analyze the levels of IL-1β, IL-17, TNF-α, IL-2, IL-10, monocyte chemoattractant protein 1 (MCP-1), and regulated on activation, normal T cell expressed and secreted (RANTES), as previously described.[E1,E18] Plasma levels of the hormone cortisol were also quantified using a fluoroimmunoassay.[E1]

RESULTS—FOLLOW-UP

PAL

Table E1 shows the results from 3 months after the end of the interventions. The follow-up results showed no changes in PAL after follow-up in the CLE group, but there was an increase in the total steps in the HIIT group ($P < .05$; Table E1). No differences in clinical control and lung function in either group were observed compared with baseline ($P > .05$). Clinical improvements in AQLQ symptoms were observed only in the HIIT group ($P < .05$; Table E2), whereas the environmental stimuli improved only in the CLE group. On the other hand, emotional function improved in both groups. Anxiety symptoms were reduced in both groups, and depression symptoms decreased only in the HIIT group ($P < .05$; Table E2).

Changes in clinical control

Our findings showed that CLE or HIIT induced similar benefits regarding clinical control (Figure E2). Nevertheless, no changes were observed compared with the values obtained in either group after the interventions ($P > .05$).

Airway and systemic inflammation

The participants in both groups had similar baseline levels of FeNO, cytokines (IL-1β, IL-17, and IL-10), and the chemokines MCP-1 and RANTES ($P > .05$; Table E3). Neither CLE nor HIIT reduced systemic and airway inflammation ($P > .05$). The markers IL-2, IL-4, IL-5, IL-6, IL-8, IL-12, IL-17, IFN-γ, TNF-α, MIG, IP-10, TGF-β, and cortisol presented at values below the level of detection by flow cytometry (data not shown).

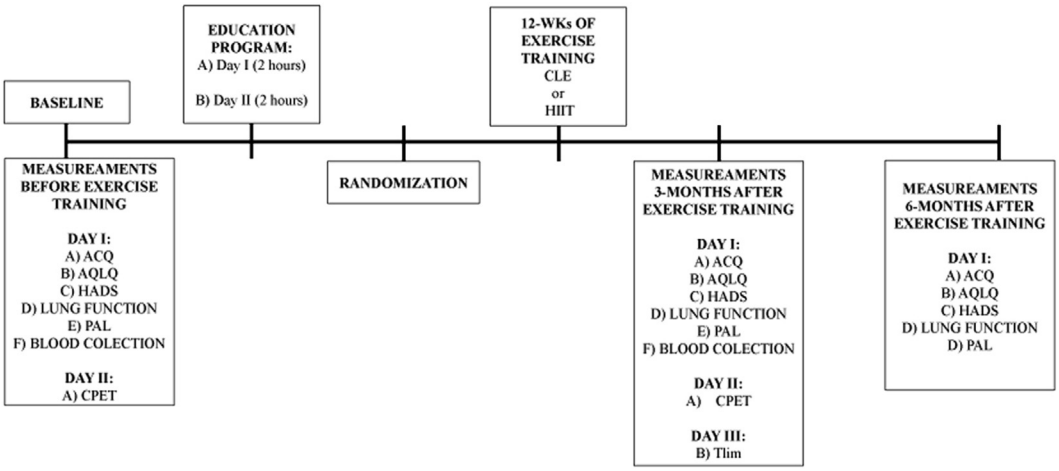

FIGURE E1. Timeline of the study. The baseline consisted of evaluations made before the beginning of educational actions and exercise programs. *ACQ*, Asthma Control Questionnaire; *AQLQ*, Asthma Quality of Life Questionnaire; *CLE*, constant-load exercise; *CPET*, cardiopulmonary exercise testing; *HADS*, Hospital Anxiety and Depression Scale; *HIIT*, high-intensity interval training; *PAL*, physical activity level; *Tlim*, time limit test.

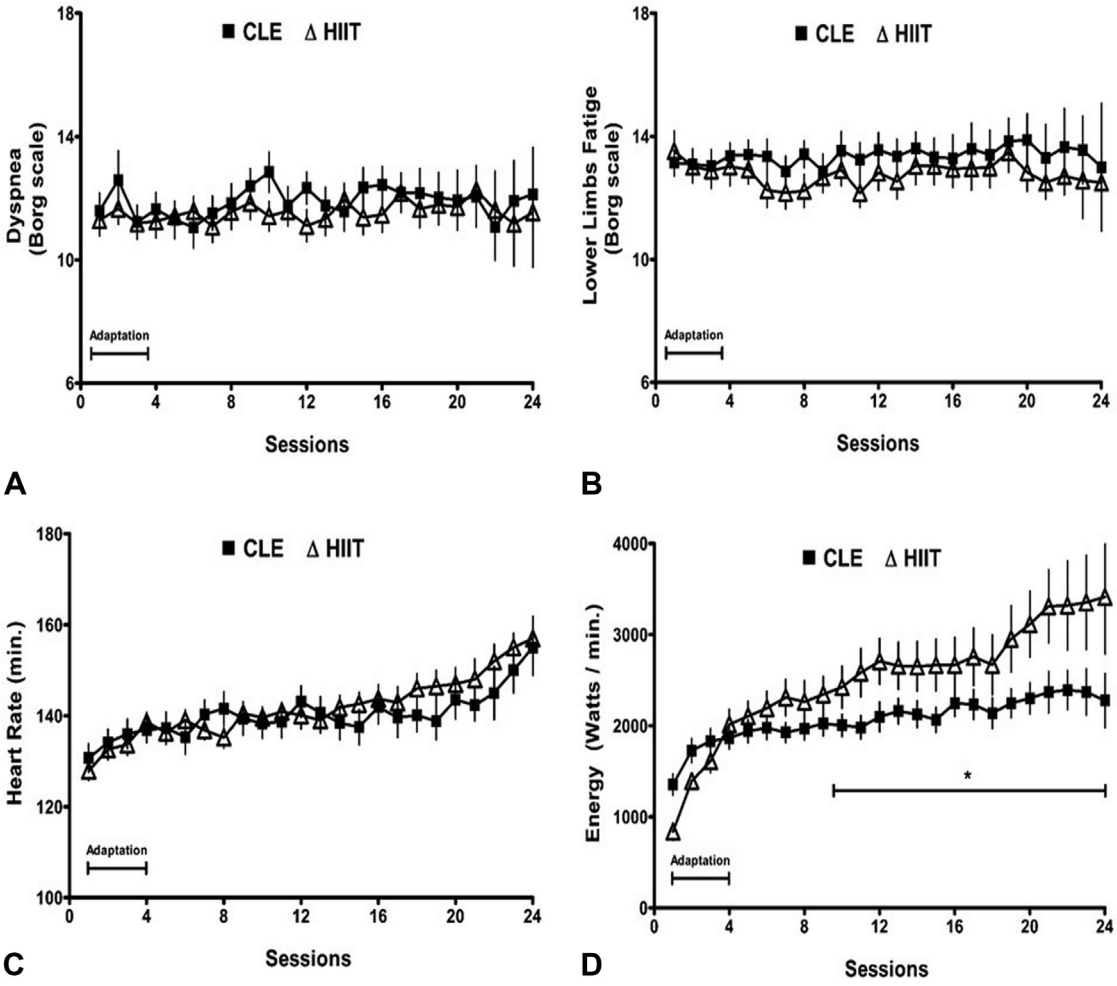

FIGURE E2. Features assessed during the exercise sessions. (**A**) Dyspnea, (**B**) lower limb fatigue, (**C**) heart rate, and (**D**) energy expenditure. Data are presented as the mean ± standard deviation. The adaptation period for HIIT was performed in the first 4 sessions. *CLE*, Constant-load exercise; *HIIT*, high-intensity interval training. # $P < .05$ when compared with CLE versus HIIT.

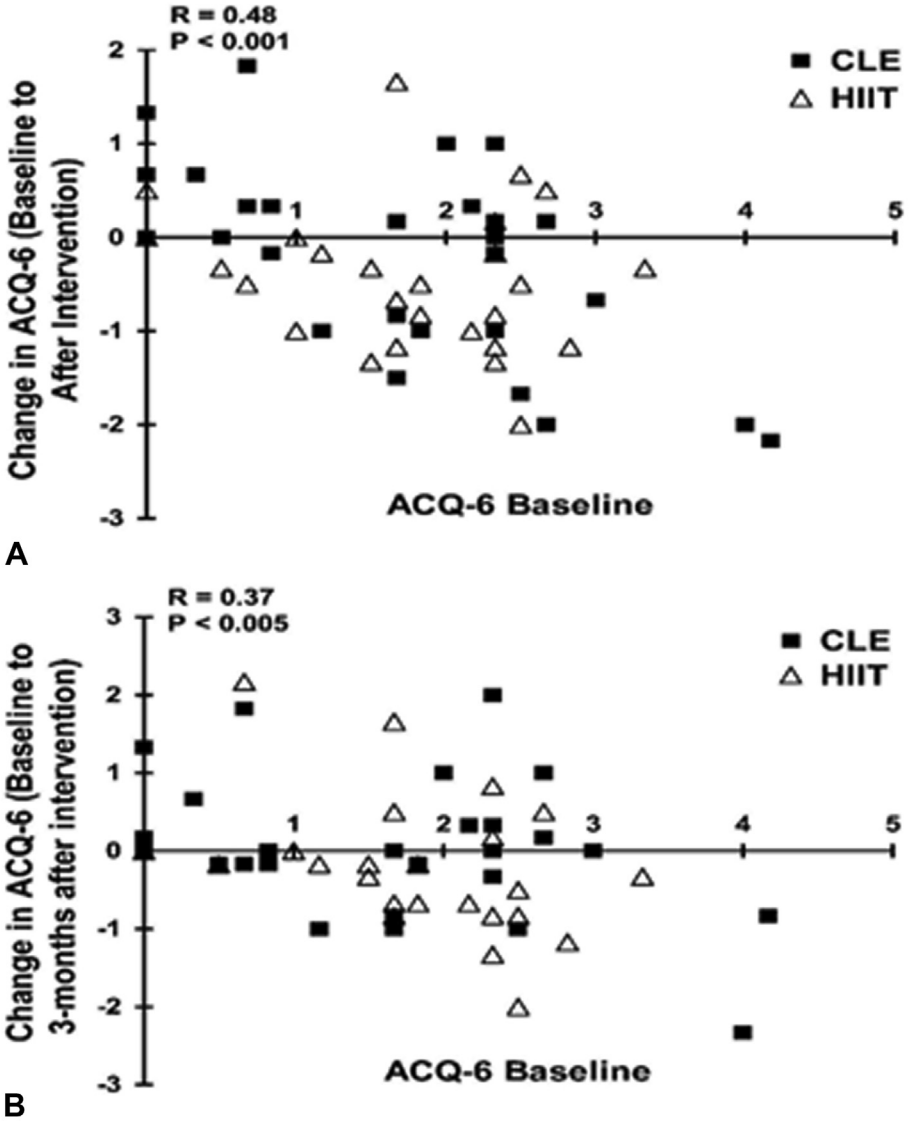

FIGURE E3. Changes in clinical control. Improvements after the interventions and 3 months after the interventions. Associations between changes in the ACQ-6 (**A**) after the intervention and (**B**) 3 months after the intervention, with delta improvement (final − initial) for each outcome in adults with asthma submitted to constant-load exercise (CLE; dark squares) and high-intensity interval training (HIIT; white triangles). *ACQ*, Asthma Control Questionnaire.

TABLE E1. Comparison of the daily life physical activity level between CLE versus HIIT in patients with moderate-to-severe asthma

		Time period		*P* value		
	Groups	Change after intervention	Change 3 mo after intervention	Group × Time	Time	Group
Physical activity (WK), steps						
Total	CLE	−138.4 (−2327, 1165)	−599.0 (−2130, 839.9)	NS	NS	NS
	HIIT	1149 (−1032, 3299)	−179.0 (−1334, 2935)	NS	NS	NS
Moderate	CLE	−386.0 (−1586, 1021)	−687.8 (−1243, 587.0)	NS	NS	NS
	HIIT	825.1 (−560.3, 1249)	645.8 (−1171, 1158)	.003	NS	NS
Physical activity (WKND), steps						
Total	CLE	−777.5 (−3581, 1223)	−1778 (−4460, 858.3)	NS	NS	NS
	HIIT	−486.7 (−1951, 2659)	−300.6 (−3052, 3306)	NS	NS	NS
Moderate	CLE	−482.5 (−1688, 390.1)	−771.0 (−2183, 591.7)	NS	NS	NS
	HIIT	−159.1 (−1514, 1792)	−359.5 (−2415, 1337)	NS	NS	NS

Data are presented as median and confidence interval (25%-75%). The HIIT presented a minimal clinical significant change of 500 steps/d; change after intervention: CLE n = 27 and HIIT n = 28; change 3 months after intervention: CLE n = 17 and HIIT n = 14.
CLE, Constant-load exercise; *HIIT*, high-intensity interval training; *NS*, not significant; *PAL*, physical activity level; *WK*, during the week; *WKND*, during the weekend.

TABLE E2. Comparison at baseline and after interventions following the period and at the 3-month follow-up assessment

		Time period		*P* value		
	Groups	Change after intervention	Change 3 mo after intervention	Group × Time	Time	Group
ACQ-6, score	CLE	−0.23 (−1.00, 0.33)	0.04 (−0.29, 0.33)	NS	NS	NS
	HIIT	−0.50 (−1.08, 0.33)	−0.25 (−0.83, 0.00)	NS	NS	NS
Psychosocial morbidity, score						
Anxiety	CLE	−1.63 (−1.50, 4.00)	−0.70 (−3.00, 2.00)	NS	NS	NS
	HIIT	−2.14 (−4.00, 0.00)	−2.68 (−6.00, 0.00)	NS	NS	NS
Depression	CLE	−1.85 (−2.75, 0.00)	−0.85 (−2.00, 0.00)	NS	NS	NS
	HIIT	−2.86 (−7.50, 0.00)	−2.68 (−5.00, 0.50)	NS	NS	NS
Lung function						
FEV_1 (%)	CLE	−0.70 (−4.50, 6.75)	0.85 (−6.75, 8.75)	NS	NS	NS
	HIIT	0.00 (−6.00, 4.50)	0.50 (−6.50, 7.00)	NS	NS	NS
FVC (%)	CLE	2.67 (−7.75, 9.75)	3.89 (−7.00, 9.75)	NS	NS	NS
	HIIT	3.00 (−5.00, 6.00)	3.50 (−9.50, 5.00)	NS	NS	NS
FEV_1/FVC ratio	CLE	−0.22 (−6.00, 5.00)	0.59 (−2.75, 3.00)	NS	NS	NS
	HIIT	7.00 (−4.00, 2.50)	7.00 (−4.50, 2.50)	NS	NS	NS

Data are presented as median and confidence interval (25%-75%). After the intervention, the number of participants in each group was CLE n = 27 and HIIT n = 28. Three months after the intervention (follow-up), the number of participants was CLE n = 17 and HIIT n = 14.
ACQ, Asthma Control Questionnaire; *CLE*, constant-load exercise; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *HIIT*, high-intensity interval training; *NS*, not significant.

TABLE E3. Comparison of the inflammatory and anti-inflammatory mediators between CLE versus HIIT in patients with moderate-to-severe asthma

	CLE (n = 27)			HIIT (n = 28)			Interaction
	Baseline	Change after intervention	*P* time	Baseline	Change after intervention	*P* time	Time × Group
FeNO (ppb)	30.0 (14.5, 42.2)	2.0 (−11.6, 9.10)	NS	25.7 (16.1, 38.8)	0.68 (12.5, 39.9)	NS	NS
Chemokines (pg/mL)							
MCP-1	37.6 (28.1, 51.8)	−3.07 (−13.1, 4.18)	NS	46.3 (25.2, 83.9)	−1.17 (11.0, 10.8)	NS	NS
RANTES	633.5 (512.9, 1272)	352.0 (203.0, 617.5)	NS	783.4 (506.4, 1130)	155.0 (52.0, 397.0)	NS	NS
Inflammatory cytokine (pg/mL)							
IL-1β	11.3 (0.00, 105.4)	0.00 (−90.9, 42.1)	NS	0.00 (0.00, 175.8)	0.00 (0.00, 66.0)	NS	NS
IL-17	80.0 (70.7, 85.2)	101.0 (7.50, 497.5)	NS	86.5 (78.7, 92.5)	0.00 (0.00, 225.7)	NS	NS
Anti-inflammatory cytokine (pg/mL)							
IL-10	278.0 (67.7, 422.2)	−1.00 (−139.0, 276.3)	NS	203.0 (106.7, 502.7)	4.00 (−120.0, 311.7)	NS	NS

Data are presented as median and confidence interval (25%-75%).
CLE, Constant-load exercise; *HIIT*, high-intensity interval training; *FeNO*, fractional exhaled nitric oxide; *MCP-1*, monocyte chemoattractant protein 1; *NS*, not significant; *ppb*, particles per billion; *RANTES*, regulated on activation, normal T cell expressed and secreted.

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