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Physical training does not increase allergic inflammation in asthmatic children

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Abstract

We studied the effects of a 3-month physical training program on airway inflammation and clinical outcomes in school-aged children with asthma.

Thirty four subjects, 12.7±3.4 years, with persistent allergic asthma were randomly allocated into training and control groups. Exercise consisted of twice-weekly 50 minutes sessions for 12 weeks. Inflammation was assessed by exhaled nitric oxide, blood eosinophils, eosinophil cationic protein, C-reactive protein, total and mite specific IgE. Lung volumes and bronchial responsiveness to metacholine were determined. Paediatric Asthma -and Caregiver's- Quality of Life Questionnaires were used to evaluate activity restrictions, symptoms and emotional stress. Efficacy of the training was assessed by accelerometry.

After the program, exercise children had double daily minutes in moderate-to-vigorous activities compared to controls. No differences in changes were seen between groups for asthma outcomes. However, total IgE decreased more in the exercise group, as did mite specific IgE.

Training did not increase inflammation in children with persistent asthma, and may have decrease both total and allergen specific IgE levels. We conclude there is no reason to discourage asthmatic children with a controlled disease to exercise.

Keywords: asthma; exhaled nitric oxide; quality of life; physical activity; randomized controlled trial

Introduction

The increase in the prevalence of asthma observed in most developed countries has been accompanied by important changes in lifestyle [1]. Reduced physical activity has been associated with increased asthma prevalence [2-4], and high physical activity has been suggested to prevent disease progress [5]. Physical training may reduce breathlessness and asthma symptoms by strengthening respiratory muscles and by decreasing ventilation rate during exercise. Training programs in asthma have not, however, showed any improvement in lung function in controlled trials [6-13]. Effects on airway inflammation are largely unknown.

Heavy physical activity has also been related to asthma occurrence and exacerbation. In elite athletes asthma is diagnosed more frequently than in the general population [14]. This has been attributed to airway inflammation and increased bronchial responsiveness induced by high-intensity long-term exercise like competitive swimming or long-distance running. Asthma symptoms may attenuate after discontinuing training and competition [15,16]. Atopy and type of sports appear to be the two major risk factors with atopic long distance runners having the highest risk of asthma compared with non-atopic non-athletes [17].

We studied the effects of a 3-month physical training program on airway inflammation and clinical outcomes in school-aged children with persistent asthma. We wanted to find rationale for exercise and sporting guidance for children and their parents.

Methods

Patient Selection

Atopic school-aged children with controlled asthma, treated with small to moderate dose of inhaled corticosteroids (ICS) for a period of at least one year and followed in the outpatient clinic of a University Hospital were invited to participate. The study was explained to parents and patients with informed consent obtained from those willing to participate. After 131 telephone invitations, 34 children were included (Fig. 1). Atopy was defined by a positive skin prick test (wheal ≥3mm when the control solutions gave expected results) to at least one aeroallergen (house dust mites, pollens, animal dander, moulds). All subjects were sensitized to *Dermatophagoides pteronyssinus*.

All 34 children used ICS, 22 used long-acting β_2-agonists, 32 short-acting β_2-agonists, 9 leukotriene antagonists, and 19 were on specific immunotherapy to house mites for at least one year. Median (range) duration since diagnosis was 4 (2 to 10) years. Controlled disease was defined as: (1) no exacerbation during the preceding 4 weeks necessitating oral steroids or an increase in inhaled steroids, (2) no use of rescue short acting beta-2 agonists more than 3 times a week, and (3) no indication to change maintenance treatment.

Study Design

Patients were randomly allocated to a 12-week exercise training program or to a standard care by a blinded computer-generated randomization schedule with a blocking factor of four. Allocation numbers were encoded on labels placed in each case report form by an

outside researcher, and patients were assigned the next available allocation number in sequence. Baseline and final assessments included two hospital visits each, one week apart. Patient and research team became aware of the allocations after the second baseline visit.

Training program
Exercise group (EG) underwent a sub-maximal aerobic exercise designed as a moderately intensive training program including both lower and upper extremity activities. During the 12-week training program, between February and May 2005, the sessions were performed twice a week, for 50 minutes in each session. All sessions were carried out in an indoor gymnasium. Subjects were instructed to use β_2-agonists before the training or if necessary during the session. A typical session started with a warming-up period (10 min) with arm and leg exercise, followed by sub-maximal training (30 to 35 min) including aerobic exercises, strength training, some balance and coordination exercises, and cool-down (7 to 10 min). In order to offer an enjoyable training session varied recreational games were performed. Control group (CG) subjects continued their usual daily routine.

Measurements
Exhaled nitric oxide (eNO) was determined by chemiluminescence in accordance with recommendations of the American Thoracic Society, with an exhalation flow rate of 50 mL/s [18] (NIOX; Aerocrine; Stockholm, Sweden). Blood eosinophil numbers were counted.
Serum C reactive protein (CRP) levels were measured using a highly sensitive (hsCRP) assay (Dade Behring CardioPhase hsCRP using the Behring Nephelometer BN-100; Behring Diagnostics, Westwood, USA). The assay could detect a minimal CRP concentration of 0.175mg/L. Serum total and mite specific IgE, and eosinophil cationic protein (ECP) were measured by fluorometric enzyme immunoassay (FEIA) (Phadia, Uppsala, Sweden).

Accelerometry
Compliance with the program was assessed by an accelerometer. Physical activity (PA) was measured with the use of Actigraph monitor (model 7164; Computer Science and Applications, Shalimar, USA) between weeks 8 and 12. The Actigraph uses a uniaxial accelerometer that measures vertical acceleration and deceleration in 1-min epochs. This accelerometer can be used to discriminate among light, moderate, and vigorous levels of PA [19]. The monitor was affixed above the iliac crest of the right hip with an elastic belt and adjustable buckle. The subjects were instructed to wear the monitor for one week and to remove it for sleep. Data from day 1 to day 7 were downloaded into a computer. Movement counts were converted to average minutes per day spent in resting or light [<3 metabolic equivalents (METs)], moderate (3–6 METs), and vigorous (6–9 METs), and very vigorous (>9 METs) physical activity. The minutes per day spent doing moderate, vigorous and very vigorous levels were combined into one variable. The minutes per day spent doing moderate, vigorous and very vigorous levels were combined into moderate-to-vigorous physical activity category (MVPA).

Lung function tests and bronchial responsiveness
Spirometry was performed using a calibrated, computerized pneumotachograph spirometer (SensorMedics Vmax 22, SensorMedics, Yorba Linda, USA) according to ATS recommendations. Bronchial responsivenss (BHR) was assessed by metacholine challenge test performed according to recommendations [20].

Recording of peak expiratory flow (PEF) variability
PEF-values were measured by PIKO-1 (Ferraris Respiratory, Hertford, United Kingdom). The minimum morning PEF and the maximum evening PEF were determined, respectively as the lowest and highest PEF during the one week monitoring [21]. PEF variation was expressed according to the formula: highest amplitude percentage = (highest PEF-lowest PEF)/highest PEF of the day.

Paediatric Asthma Quality of Life Questionnaire (PAQLQ) and Paediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ)
PAQLQ is a disease-specific questionnaire to evaluate health-related quality of life of asthmatic children. The self-administered form of the questionnaire was used [22]. It includes 23 items in three domains; activity limitation (n=5), symptoms (n=10) and emotional function (n=8). Both the scores of the three domains and the overall score range from 1 (maximum impairment) to 7 (no impairment). Clinical changes in PAQLQ score were considered minimal or moderate if they were above 0.5 and 1.0 units, respectively [23]. The impact of the child´s asthma on the caregiver's normal daily activities and emotional functioning was assessed using the self-administered Paediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ) [24]. It is a 13-item questionnaire that assesses caregiver burden during a one week recall period. It contains four items in an activities domain and nine items in an emotional function domain. Individual items are weighted equally. Total and domain scores range from 1 to 7, with higher scores indicating a more positive response.

Statistical analysis
All analyses were conducted using the "intention to treat" approach, including all randomized patients who had at least one post-baseline efficacy variable measurement. Baseline characteristics were compared using Fisher exact test for categorical variables or Student's test for numeric variables; changes within groups were compared using paired *t*-test and differences between exercise and control groups were compared by analysis of covariance (ANCOVA) with baseline value as covariate. To detect a 25% effect of the intervention using exhaled NO as the main outcome the estimated sample size would be of 30 subjects [25]. Values of $p<0.05$ were regarded as significant.

Results
At baseline, with the exception of long acting beta-2 agonists use, no significant differences were observed between groups (Table 1). A few subjects used indifferently short acting beta-2 agonists twice a day or long-acting beta-2 agonist. However, no differences existed between groups considering the overall use of beta-2 agonists. The training program was completed by all except two children. In the control group one subject was lost to follow up because of non-adherence, and another child in the exercise group withdrew due to excess of extracurricular activities. Therefore, 32 children, 16 in both groups had the final examination at the end of the 12-week period. All children were able to maintain the intensity of training sessions without getting asthma exacerbations. No changes in medication occurred during the program. In the end, the exercise group, compared to the control, had almost double of daily minutes spent in moderate-to-vigorous activities assessed by accelerometry (30±13 *vs.* 16±11; p=0.027), but no differences in minutes spent resting (469±88 *vs.* 528±44; p=0.073) or in light physical activity (119±60 *vs.* 113±31; p=0.799).

Inflammation and other asthma outcomes
No differences in changes of eNO, blood eosinophil numbers, serum ECP, or serum C-reactive protein, were observed between groups (Table 2). However, in the exercise group, compared to the controls, there was a significant decrease in serum total and mite specific IgE. Changes in lung function, peak expiratory variability, airway responsiveness and quality of life scores were not significant between groups. The percentage of subjects achieving a clinically important improvement in the PAQLQ score from baseline was not different between groups. Individual variations for each outcome are illustrated in Figure 2 (*online depository*).

Discussion
Physical training programme of moderate intensity did not affect inflammatory or other clinical outcomes in children with good asthma control. Our results are valid for subjects allowed to use effective medication against exercise induced asthma symptoms.

A recent Cochrane review [26] pooled data from 13 studies and 455 subjects, and could not show physical training to improve lung function or decrease wheezy episodes. However, physical training improved cardiopulmonary fitness and maximum expiratory ventilation. In our program, children started their physical activity almost at a recreational level and a more intense and vigorous programme could have produced greater improvements. However, it has been shown that the best way to increase activity level is spending more time on moderate-intensity exercise and less on high-intensity activity [27]. Short periods of vigorous physical activity do not influence the overall activity probably due to a decreased compensatory activity outside the training sessions [28].

The intervention period was 12 weeks in the present study, which is the longest among published studies with a controlled randomized design [26]. It is possible that a longer intervention, or more frequent sessions, would have created differences between the groups. It could also be argued that children in the training program were supervised by health professionals, which could limit the possible negative effects of exercise. It is unlikely that an increase awareness of the disease have affected the outcomes, because no additional medical visits were paid by the intervention group. If any unlikely benefit existed with the use of long acting beta-2 agonist this would have been in favour of the control group. Other strengths of our study include the use of validated tools for the measurement of physical activity and quality of life, and the assessment of inflammation.

Regular exercise has induced a variable degree of airway inflammation depending on type of sports and medical history of the athlete [17]. In contrast with asthmatics, increased numbers of inflammatory cells in healthy athletes´ airways do not correlate with exercise-induced symptoms or bronchial responsiveness [29]. Recently, it has been observed that healthy children doing outdoor recreational activities have a significant increase in eNO, dependent on ambient ozone levels, but with no changes in lung function tests [30]. Neither of these effects was observed in our study with asthmatic subjects. Although the decrease in eNO was larger in the non-exercising group after the program, no significant differences between groups were observed. All our children were treated with inhaled corticosteroids, which may have suppressed the exercise effect.

In our study, performed between late winter and early spring, significant differences between groups were observed in changes of total and mite-specific IgE. Seasonal variations in mite allergen exposure may account for changes in total and specific IgE in mite-sensitive asthmatics [31], but exercise seemed to boost this effect. This has been observed in mouse model of allergic asthma, where moderate intensity aerobic exercise attenuated lung inflammatory responses [32,33]. In OVA-sensitized mouse, exercise reduced mucus production, lung epithelial cell hypertrophy, secretion of the Th2 type cytokines, expression of adhesion molecules, and production of OVA-specific IgE [32]. In other recent animal study, moderate training decreased bronchoalveolar eosinophil and peribronchial cells expressing IL-4 and IL-5 but had no effect in total IgE levels [33]. In our study, the lack of effect on other outcomes besides IgE may suggest the balance between the pro- and the anti-inflammatory effects of exercise in asthma would be null in respect to markers of airway inflammation, such as eNO. However, because we have not addressed physiological changes during the training, this may represent a random effect. This can only be clarified in further studies. Seasonal variations in mite allergen load may also account for the eNO changes in both groups. In children who are sensitized to indoor allergens, higher dust mite allergen exposure has been associated with increased eNO levels [34].

Exercise group significantly improved in all domains of asthma related quality of life, even with a moderate increase in the activities, while changes in control children were only significant for the activities domain. Failure to achieve statistical difference between groups could be due the inclusion of already well controlled subjects, leaving little room for improvement, and to a type II error due to small sample size. This is in contrast with the trial of Basaran et al. [35], where a significant improvement occurred in the exercise group compared to control group. However, in that study a significant baseline difference in symptom scores was observed between groups.

In a physical intervention program for school-aged children an extra burden is put into the family. Additionally to medication administration, ongoing care and disease monitoring, the caregiver is required to drive the child several times per week for a couple of months to a sports training centre and stay there until the session ends. Nevertheless, the additional burden introduced to the family did not have a negative impact in caretakers' quality of life.

Currently, the Global Initiative for Asthma Guidelines does not include recommendations for exercise as part of the treatment for patients with asthma [36]. Exercise is a powerful trigger for asthma symptoms. For this reason, caretakers may be reluctant to allow their asthmatic children to engage in sports practice, fearing an exacerbation of the disease. Every child with asthma should be questioned about exercise performance, tolerance and symptoms. We conclude there is no reason to discourage asthmatic children with a controlled disease to exercise.

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Table 1. Baseline characteristics in randomized patients by intervention group

	Exercise n=17	Control n=17	Total n=34	p value
Age, yr	12.9 (3.4)	12.5 (3.5)	12.7 (3.4)	.695
Sex (female:male)	6:11	8:9	14:20	.486
Height, cm	152 (12)	152 (13)	152 (13)	.947
Weight, kg	46.8 (13.4)	46.3 (13.0)	46.6 (13.0)	.928
Allergic rhino-conjunctivitis, n (%)	17 (100)	17 (100)	34 (100)	-
Duration of disease (years)	4.4 (2.2)	4.9 (1.8)	4.7 (2.0)	.507
Inhaled short acting beta2 agonists, n (%)	16 (94)	17 (100)	33 (97)	.310
Inhaled long acting beta2 agonists, n (%)	7 (41)	15 (88)	22 (65)	.004
Inhaled corticosteroid dosage, µg	402 (117)	400 (61)	17 (100)	-
Leucotriene antagonist, n(%)	3 (18)	6 (35)	9 (27)	.244
Immunotherapy, n (%)	12 (71)	8 (47)	20 (59)	.163

Data are presented as mean±sd unless otherwise indicated.

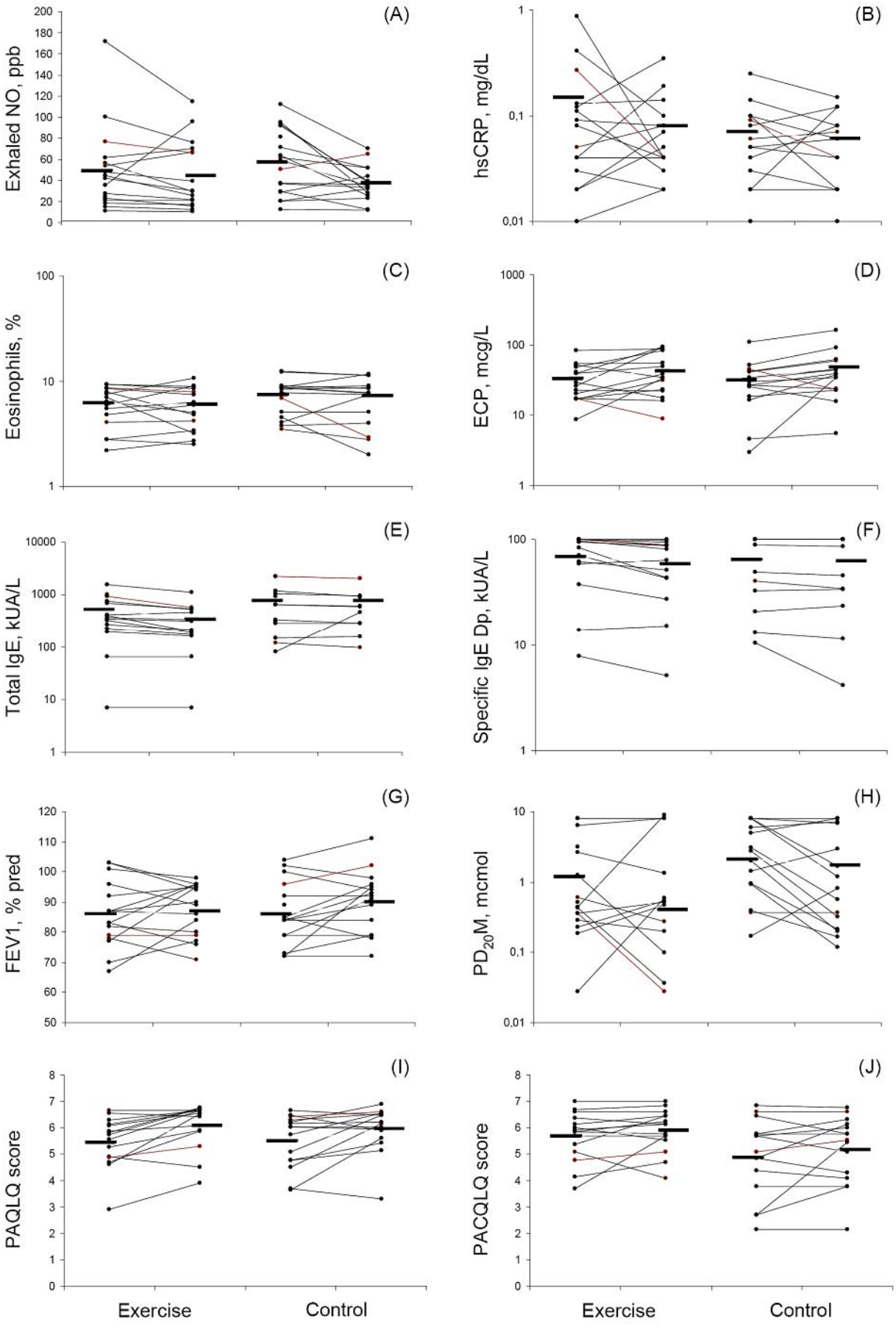
Table 2. Changes of biomarkers, lung function, bronchial responsiveness, body mass index, and quality of life related to asthma at baseline and after 12 weeks

Outcomes	Exercise			Control			Exercise *vs.* Control
	n	Baseline	Change*	n	Baseline	Change*	p-value**
Inflammatory							
Exhaled NO, ppb	16	48.9 (39.5)	-5.8 (-18.5 to 6.9)	16	56.8 (30.5)	**-17.9 (-31.8 to -4.0); p=0.015**	Ns
hsCRP, mg/dL	15	0.15 (0.23)	-0.06 (-0.20 to 0.07)	15	0.07 (0.06)	-0.01 (-0.04 to 0.02)	Ns
Eos, %	15	6.2 (2.4)	-0.2 (-1.2 to 0.9)	15	7.5 (2.8)	-0.3 (-1.3 to 0.7)	Ns
ECP, mcg/L	15	34.0 (19.6)	8.9 (-3.2 to 21.1)	15	33.6 (27.7)	11.5 (-5.9 to 28.9)	Ns
IgE, kUA/L	15	498.2 (411.6)	**-120.7 (-198.5 to -42.9); p=0.005**	15	898.8 (789.8)	-75.1 (-168.4 to 18.1)	**0.003**
IgE-Dp, kUA/L	15	68.6 (37.2)	**-9.5 (-16.0 to -3.0); p=0.007**	15	64.1 (40.9)	-1.2 (-2.6 to 0.3)	**0.014**
Functional							
FEV_1, % pred	16	86.0 (10.9)	1.68 (-3.02 to 6.40)	15	86.0 (10.7)	4.13 (-0.22 to 8.48)	Ns
FEF_{25-75}, % pred	16	82.9 (30.1)	0.87 (-10.03 to 11.78)	15	79.0 (29.2)	-0.42 (-12.00 to 11.10)	Ns
Highest PEF amplitude, %	11	20.6 (13.0)	-2.8 (-6.2 to 0.5)	13	18.0 (9.7)	-5.0 (-10.4 to 0.3)	Ns
Hyperreactivity							
$PD_{20}M$	14	1.20 (1.76)	-0.23 (-0.67 to 0.21)	13	2.08 (1.93)	-0.51 (-1.53 to 0.49)	Ns
Body mass index	16	20.0 (3.2)	-0.2 (-0.6 to 0.2)	16	20.8 (3.6)	-0.23 (-0.6 to 0.2)	Ns
Quality of life							
PAQLQ Activity	16	4.56 (1.14)	**1.16 (0.58 to 1.73); p=0.001**	15	4.92 (1.02)	**0.77 (0.28 to 1.26); p=0.004**	Ns
PAQLQ Symptom	16	5.50 (0.99)	**0.48 (0.19 to 0.78); p=0.003**	15	5.46 (1.33)	0.40 (-0.13 to 0.93); p=0.133	Ns
PAQLQ Emotion	16	5.98 (1.16)	**0.44 (0.12 to 0.77); p=0.011**	15	5.93 (0.94)	0.30 (-0.13 to 0.75); p=0.160	Ns
PAQLQ Total	16	5.46 (0.96)	**0.61 (0.29 to 0.95); p=0.001**	15	5.50 (1.00)	**0.45 (0.03 to 0.86); p=0.035**	Ns
PACQLQ Total	16	5.69 (0.93)	0.21 (-0.16 to 0.59)	15	4.89 (1.48)	0.28 (-0.21 to 0.77)	ns

Values are shown as mean (sd) or mean differences (IC95 %) were appropriate; * paired samples t-test; **Analysis of covariance, baseline value as covariate; NO: Nitric oxide; hsCRP: High sensitivity C-reactive protein; Eos: blood eosinophils; ECP: eosinophil cationic protein; IgE: Immunoglobulin E; IgE-Dp: Specific IgE to *Dermatophagoides pteronyssinus;* FEV_1: forced expiratory volume in the first second; FEF_{25-75} : Forced expiratory flow in the middle portion of FVC; PEF: Peak expiratory flow; $PD_{20}M$: Dose of methacholine causing a 20% decrease in FEV_1; BMI: body mass index; PAQLQ: Paediatric Asthma Quality of Life Questionnaire; PACQLQ: Paediatric Asthma Caregiver's Quality of Life Questionnaire; ns: non-significant

Figure 1. Flow chart of the participants during the study

Online depository. Outcome changes from baseline to the end of 12-week intervention in the exercise and the control group. Exhaled nitric oxide (A), high sensitivity C-reactive protein (B), blood eosinophils(C), eosinophil cationic protein (D), total IgE (E), specific IgE to *Dermatophagoides pteronyssinus* (F), FEV1 % predicted (G), airway responsiveness by metacholine (PD20M) (H), Paediatric Asthma Quality of Life Questionnaire (PAQLQ) score (I), and Paediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ) score (J). Horizontal bars and dots represent mean group and individual values, respectively.


(A)
Exhaled NO, ppb
200
180
160
140
120
100
80
60
40
20
0
(B)
hsCRP, mg/dL
1
0,1
0,01
(C)
Eosinophils, %
100
10
1
(D)
ECP, mcg/L
1000
100
10
1
(E)
Total IgE, kUA/L
10000
1000
100
10
1
(F)
Specific IgE Dp, kUA/L
100
10
1
(G)
FEV1, % pred
120
110
100
90
80
70
60
50
(H)
PD20M, mcmol
10
1
0,1
0,01
(I)
PAQLQ score
8
7
6
5
4
3
2
1
0
(J)
PACQLQ score
8
7
6
5
4
3
2
1
0
Exercise
Control
Exercise
Control