



Effect of pulmonary rehabilitation in an allergen safe outdoor environment on children and adolescents with mild to moderate persistent allergic asthma

M. Lipej, D. Plavec, J. Živković, O. Malev, B. Nogalo, R. Magdić, R. Lulić Jurjević & M. Turkalj

To cite this article: M. Lipej, D. Plavec, J. Živković, O. Malev, B. Nogalo, R. Magdić, R. Lulić Jurjević & M. Turkalj (2020): Effect of pulmonary rehabilitation in an allergen safe outdoor environment on children and adolescents with mild to moderate persistent allergic asthma, Journal of Asthma, DOI: [10.1080/02770903.2020.1784192](https://doi.org/10.1080/02770903.2020.1784192)

To link to this article: <https://doi.org/10.1080/02770903.2020.1784192>

 View supplementary material 

 Accepted author version posted online: 16 Jun 2020.
Published online: 30 Jun 2020.

 Submit your article to this journal 

 Article views: 14

 View related articles 

 View Crossmark data 



Effect of pulmonary rehabilitation in an allergen safe outdoor environment on children and adolescents with mild to moderate persistent allergic asthma

M. Lipej, MSc^a , D. Plavec, PhD^{a,b} , J. Živković, MSc^a, O. Malev, PhD^{a,c}, B. Nogalo, PhD^{a,d}, R. Magdić, MSc^e, R. Lulić Jurjević, PhD^{a,b}, and M. Turkalj, PhD^{a,b,f}

^aSrebrnjak Children's Hospital, Zagreb, Croatia; ^bFaculty of Medicine, J.J. Strossmayer University of Osijek, Osijek, Croatia; ^cDepartment of Biology, Faculty of Science, University of Zagreb, Zagreb, Croatia; ^dFaculty of Dental Medicine and Health Osijek, Osijek, Croatia; ^eHotel and tourism management high school, Zagreb, Croatia; ^fCatholic University of Croatia, Zagreb, Croatia

ABSTRACT

Background: Environmental interactions are very complex in childhood asthma, and we hypothesized that even a short-term exposure to an allergy safe outdoor environment (AllSOE) combined with pulmonary rehabilitation program (PRP) could exert significant beneficial effects. Our aim was to test the effects of 2-week PRP provided in an AllSOE in children with mild to moderate asthma.

Methods: 110 children (aged 7.5–17 years, 46% girls), with partially or totally controlled asthma, attended the PRP at the Island of Lošinj (Croatia) supervised by a multidisciplinary team (pediatric pulmonologist, sports medicine specialist, physiotherapist and kinesiologist). Each child had an adjusted intensity of physical activity with at least 2 h of exercise per day. Body height and weight, spirometry, fraction of exhaled nitric oxide (FeNO), running distance during free running test (FRT) and the decline in lung function after FRT (exercise-induced bronchoconstriction- EIB) were measured at baseline and after PRP.

Results: A significant improvement in running distance (from 903 ± 272 m to 968 ± 289 m; $p < 0.001$), a decrease of FeNO (from 37 ± 32 ppb to 25 ± 17 ppb; $p < 0.001$) were determined after PRP. There were no significant changes in lung function and EIB, except EIB in the fourth quartile (significant EIB at baseline) where EIB significantly decreased ($p < 0.001$) after PRP.

Conclusion: Two weeks of PRP in an AllSOE significantly improved exercise capacity and reduced airway inflammation and airway hyperreactivity showing that even a short-term PRP within a proper environment could be effective and affordable management strategy for children and adolescents with mild to moderate asthma.

Abbreviations: AllSOE: allergen safe outdoor environment; PRP: pulmonary rehabilitation program; HRQoL: health-related quality of life; BMI: body mass index; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; FeNO: fraction of exhaled nitric oxide; FRT: free running test

ARTICLE HISTORY

Received 13 November 2019
Revised 2 June 2020
Accepted 14 June 2020

KEYWORDS

Pulmonary rehabilitation;
allergen safe outdoor
environment; children;
allergic asthma;
asthma camp

Introduction

Asthma is one of the most common chronic diseases in the general population and among children with a predominant allergic phenotype (1,2). Currently, sensitization rates to one or more allergens among school children are approaching 40%-50% (3), and experts estimate that one in five infants will develop asthma (4,5). This disease has a significant impact on children's quality of life, especially on children with a poorly controlled and/or severe asthma (6). Physical exercise is a common trigger for asthma symptoms in 40–90% of children, provoking exercise-induced

bronchoconstriction (EIB) with shortness of breath, cough and wheeze (7).

Fear from triggering EIB may keep children from engaging in physical activity or sports resulting in sedentary lifestyle (8). Less physical activity means less aerobic capacity that can aggravate dyspnea and asthma symptoms leading to complete exercise avoidance. On the other hand, it is proven that regular physical activity in asthmatics reduces corticosteroid consumption, improves aerobic capacity and asthma symptoms as well as health-related quality of life (HRQoL) and overall having beneficial anti-inflammatory effects which

CONTACT Marcel Lipej  lipej@bolnica-srebrnjak.hr  Srebrnjak Children's Hospital, Srebrnjak 100, Zagreb, Croatia.

 Supplemental data for this article can be accessed at [publisher's website](#).

© 2020 Taylor & Francis Group, LLC

makes it an add-on treatment for asthma (7,9). Therefore, pulmonary rehabilitation programs (PRPs) play a significant role in chronic respiratory disorders management and treatment. PRPs for children and adolescents focus at preventing exacerbations, improving HRQoL and overall health status (HS) or disease progression (10). Asthma camps gather children suffering from asthma and provide continuous health education combined with climate/balneotherapy which decreases symptoms, emergency department visits, hospitalizations, exacerbations and school absence (10–12).

Taking into consideration that environmental interactions for childhood asthma development are complex, we hypothesized that even a short time exposure to an allergen safe outdoor environment (AllSOE) combined with PRP can exert significant beneficial effects in asthmatic children. The aim of this study was to test the potential effects of 2 weeks PRP in an AllSOE in children with mild to moderate persistent allergic asthma.

Methods

Experimental design

In this work was performed an interventional single arm prospective study (quasi-experimental research design) that enrolled 110 children (51 girls and 59 boys), aged 7.5–17 years, body mass index (BMI) ranging from 13.7 to 27.2 kg/m² with mild to moderate persistent allergic asthma. All patients had allergic rhinitis (from mild to moderate persistent). They were all recruited from our outpatient clinic, regularly controlled and skin prick tested with a standard panel for inhalant and for nutritive allergens (Supplemental Table S1).

Inclusion criteria were as follows: diagnosed asthma for at least one year before the study, regular control visits at our outpatient clinic with lung function tests and fraction of exhaled nitric oxide (FeNO) measurements, mild to moderately severe asthma (partially or totally controlled according to GINA guidelines) (13). Exclusion criteria of the subjects were presence of any other significant pulmonary, cardiovascular or musculoskeletal disorder, severe and uncontrolled asthma, as well as hospitalization with an asthma exacerbation within the prior month. All parents/legal guardians signed and dated the informed consent form approved by the Institutional Ethics Committee before taking part in the PRP study. All participants attended two weeks of PRP at the Island of Lošinj (Croatia). This destination was selected due to its geographical position which is characterized by mild Mediterranean

climate with over 2500 sunny hours a year and natural healing aerosol with dissipated droplets of medicinal plant's essential oils and sea salt particles which gives asthmatic children the opportunity for high-quality climate/balneotherapy. Veli Lošinj is declared as Climatic Health Resort with long-lasting domestic and international reputation for treatment of respiratory diseases, asthma, allergies and psoriasis.

The PRP at Asthma camp was organized in mid-June after the end of school term. In that period average air temperature was 24.2° Celsius (28.2° daily maximum and 20.3° daily minimum), average value of air humidity was 61.4% and average value of air pressure was 1,00,803 Pa. At Asthma Camp children have the opportunity to interact with peers sharing the same health problems, learn more about their disease and how to better cope with it through sport activities and workshops which reduce anxiety and fear from physical exercise as an asthma trigger. Children were supervised by a multidisciplinary team consisting of pediatric pulmonologists, sports medicine specialists, kinesiologists, physiotherapists, and respiratory nurses from Srebrnjak Children's Hospital. The intensity of PRP was personally adjusted for each child according to its age and individual capacities. The training intensity was set from mild to vigorous and included morning stretching and exercise, swimming and sports games during the morning and afternoon, resulting in at least 2 h of active exercise per day (Table 1). Ninety percent of trainings were aerobic (mild to moderate intensity) with at least 10% of anaerobic training per day (14). Breathing exercises were also incorporated as the morning and evening routine.

All subjects used their regular antiasthma treatment with inhaled corticosteroids with or without long acting beta-2 agonist or leukotriene modifiers. Prior to testing (i.e. lung function and free running tests) an appropriate washout period of applied bronchodilators was performed. FeNO was measured in the morning at rest, at baseline and at the end of 2-week PRP. Spirometry was measured before the free running test (FRT) and within 10 and 20 min after the FRT) at baseline and after 2 weeks of PRP. Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) were recorded and expressed as the % of predicted values. The FEV1/FVC ratio was expressed as the absolute value. The maximal decline in lung function after FRT was calculated as the percentage of baseline FEV1 value (((lowest FEV1 after FRT – baseline FEV1)/baseline FEV1)*100%) for both the baseline FRT test and the FRT test performed after

Table 1. Daily training activities and intensities.

Daily training activities	Activities	Intensity		
		Mild	Moderate	Vigorous
Athletic 7.15–8.00 h	Walking, breathing exercise, game of chase, aerobic running, stretching	x		
	Running school		x	
	Aerobic – anaerobic running		x	
	Relay race games			x
	Stretching	x		
Swimming 16.00–17.30 h	Stretching	x		
	Aerobic swimming	x		
	Swimming technique		x	
	Swimming races (relay)			x
	Soccer	x	x	
Sport of choice 18.00–19.30 h	Basketball	x	x	
	Table tennis	x	x	
	Badminton	x	x	
	Breathing exercise	x		

Table 2. Age and anthropometric parameters according to sex ($N = 110$).

Variable	All	Boys ($n = 59$)	Girls ($n = 51$)	p -value*
Age (year)	12.1 (± 2.1)	12.1 (± 2.1)	12.0 (± 2.1)	0.961
Body height (cm)	156.3 (± 13.2)	156.0 (± 14.6)	156.6 (± 11.3)	0.726
Body weight (kg)	48.7 (± 11.7)	49.6 (± 12.5)	47.6 (± 10.7)	0.541
BMI (kg/m^2) [†]	19.7 (± 2.9)	20.2 (± 3.0)	19.2 (± 2.7)	0.096

*Calculated using Mann-Whitney U-test.

[†]BMI – body mass index.

2 weeks of PRP. FRT was performed as a 3 min running test in children aged <10 years and as a 6 min running test in children aged ≥ 10 years. Heart rate, blood pressure and oxygen saturation were measured and recorded before and after the FRT together with the distance run.

Fraction of exhaled nitric oxide (FeNO) and spirometry were measured on site using a portable FeNO device (NIOX MINO, Aerocrine AB, Sweden) and MasterScreen spirometer (CareFusion, Germany) according to the ATS/ERS guidelines and standards (15,16). Blood pressure was measured using Welch Allyn (USA) device while heart rate and blood oxygen saturation were measured using a pulse oximeter (Nonin Onyx Vantage, USA).

Statistical analysis

All continuous variables are presented as mean $\pm$ standard deviations ($\pm$ SD). Differences between the tests at baseline and at the end of PRP (% of maximal decline of FEV1 from baseline after 3/6-FRT, FEV1 (%), Tiffeneau index (FEV1/FVC), FeNO and 3/6-FRT running distance) were tested using Wilcoxon Signed Ranks Test. Multiple regression models and canonical correlation were applied to assess the relative contribution of the independent variables (age, sex and BMI) to the total variance of the outcome measures. The threshold value of $p < 0.05$ was considered statistically significant for all performed tests. Statistical

analyses were performed using MedCalc statistical software for Windows, version 14.8.

Results

Children were aged from 7.5–17 years (mean age 12.1 years) with no significant difference in relation to sex ($p = 0.961$). Boys and girls also had comparable body height, body weight and body mass index – BMI (Table 2), and showed no significant differences for all outcome variables of lung function, FeNO and running distance in a free running test (Table 3).

Running distance (mean $\pm$ SD) improved significantly from 903 ± 272 m to 968 ± 289 m ($p < 0.001$) and FeNO (median) improved significantly from 27 ppb to 19 ppb ($p < 0.001$) after 2 weeks of PRP (Table 3, Figures 1 and 2). Although no significant difference in EIB after 2 weeks of PRP was found for the whole tested group ($p = 0.401$), the patients in the 4th quartile experienced significant and clinical improvement from $-12.4 \pm 8.6\%$ to $-2.8 \pm 5.3\%$ ($p < 0.001$, Cohen's $d = 1.33$). Those were the patients ($N = 27$) with the greatest max. FEV1 decline from baseline after FRT, representing patients with the greatest EIB level (Table 3 and Figure 3). As presented in Table 3, measured significant improvements vary from small to very large clinical improvement (Cohen's d from 0.23 to 1.33) except for FEV1 (%) that declined ($d = 0.18$, not clinically significant). Interaction of lung function parameters and FeNO

Table 3. Lung function and FeNO measurements and running distance in a free running test ($N = 110$).

Variable	Patients	Baseline Mean $\pm$ SD	Final Mean $\pm$ SD	Mean difference $\pm$ SD difference	Baseline Median	Final Median	Cohen's d	p-value*
FVC [†] (%)	Boys (n = 59)	100.4 $\pm$ 16.6	98.8 $\pm$ 13.6	-1.6 $\pm$ 3.0	97.0	96.7		
	Girls (n = 51)	101.2 $\pm$ 13.7	98.3 $\pm$ 11.6	-2.9 $\pm$ 2.1	99.1	96.3		
	Boys vs. Girls:							0.068
	All	100.7 $\pm$ 15.3	98.5 $\pm$ 12.6	-2.2 $\pm$ 2.7	97.85	96.5	0.16	0.087
FEV1 [‡] (%)	Boys (n = 59)	105.9 $\pm$ 17.9	103.5 $\pm$ 14.8	-2.0 $\pm$ 3.1	105.6	101.3		
	Girls (n = 51)	107.6 $\pm$ 14.6	104.6 $\pm$ 12.0	-3.0 $\pm$ 2.6	108.1	104.4		
	Boys vs. Girls:							0.220
	All	106.7 $\pm$ 16.4	104.0 $\pm$ 13.5	-2.7 $\pm$ 2.9	105.8	103.35	0.18	0.033
FEV1/FVC	Boys (n = 59)	0.88 $\pm$ 0.05	0.87 $\pm$ 0.09	-0.01 $\pm$ 0.04	0.87	0.86		
	Girls (n = 51)	0.91 $\pm$ 0.06	0.91 $\pm$ 0.10	< -0.01 $\pm$ 0.04	0.91	0.87		
	Boys vs. Girls:							0.634
	All	0.89 $\pm$ 0.06	0.89 $\pm$ 0.10	< -0.01 $\pm$ 0.04	0.88	0.87	0.02	0.704
FeNO [§] (ppb)	Boys (n = 59)	37 $\pm$ 33	23 $\pm$ 16	-14 $\pm$ 17	25	19		
	Girls (n = 51)	37 $\pm$ 31	27 $\pm$ 18	-10 $\pm$ 13	29	19		
	Boys vs. Girls:							0.188
	All	37 $\pm$ 32	25 $\pm$ 17	-12 $\pm$ 15	27	19	0.48	<0.001
Running distance (m)	Boys (n = 59)	936 $\pm$ 294	1007 $\pm$ 314	70 $\pm$ 20	1035	1065		
	Girls (n = 51)	865 $\pm$ 241	924 $\pm$ 254	59 $\pm$ 13	924	980		
	Boys vs. Girls:							0.602
	All	903 $\pm$ 272	968 $\pm$ 289	66 $\pm$ 17	960	1025	0.23	<0.001
Max.FEV1 decline from baseline after FRT [¶] (%)	Boys (n = 59)	-3.0 $\pm$ 9.3	-2.3 $\pm$ 3.9	0.7 $\pm$ 5.4	-1.4	-2.0		
	Girls (n = 51)	-2.9 $\pm$ 6.9	-1.5 $\pm$ 4.1	1.4 $\pm$ 2.3	-2.5	-1.5		
	Boys vs. Girls:							0.336
	All	-3.0 $\pm$ 8.2	-1.9 $\pm$ 4.0	1.0 $\pm$ 4.2	-2.0	-1.8	0.16	0.401
Max.FEV1 decline from baseline after FRT [¶] (%) (4th quartile)	Boys (n = 14)	-13.6 $\pm$ 10.2	-3.0 $\pm$ 5.8	10.6 $\pm$ 4.4	-8.9	-2.4		
	Girls (n = 13)	-11.1 $\pm$ 6.7	-2.7 $\pm$ 5.0	8.4 $\pm$ 1.7	-7.4	-3.4		
	Boys vs. Girls:							0.923
	All (n = 27)	-12.4 $\pm$ 8.6	-2.8 $\pm$ 5.3	9.6 $\pm$ 3.3	-7.9	-2.6	1.33	<0.001

*Statistical analysis was done using a Wilcoxon Signed Ranks Test.

[†]FVC-forced vital capacity.[‡]FEV1-forced expiratory volume in 1 s.[§]FeNO- fraction of exhaled nitric oxide.[¶]FRT- free running test.

between anthropometric measures (age, sex and BMI) tested non-significant in the multiple regression with low coefficient of determination ($R^2 = 0.03$ – 0.06 ; $p > 0.05$ for all, [Supplemental Table S2](#)). Canonical correlation between all outcome variables and anthropometric variables (age, sex and BMI) was also not statistically significant ($p = 0.40$, [Supplemental Table S3](#)).

Discussion

In this study was found that in children and adolescents with asthma already after 2 weeks of aerobic exercise training (PRP) in an AllSOE, level of airway inflammation (FeNO) and hyper-reactivity (EIB) significantly decreased and running distance in FRT increased. Changes of EIB in the fourth quartile, where EIB significantly decreased ($p < 0.001$) after PRP, showed that even after a short PRP subjects with the lowest tolerance to physical activity experienced the largest (clinically significant) improvement of EIB, thus validating our initial hypothesis.

However, FVC and FEV1 have not changed significantly during the PRP, showing if anything a slight non-significant (clinical and/or statistical) decline after 2 weeks. There are two possible explanations for this finding: (1) The average FVC and FEV1 at baseline were already in the reference range because these children had partially or totally controlled asthma, or (2) the increased control, better physical fitness and improvement in diaphragm's strength could decreased expiratory time and increased starting expiratory flow thus seemingly changing these parameters. However, there was no evident change for Tiffeneau-Pinelli index (FEV1/FVC) that by some authors relates better to asthma symptoms than FEV1 (17). Similar results were also presented in the review by Wanrooij et al. (7) that compared intervention and control groups in all performed studies ($N = 9$).

Mainly, in asthmatic children aerobic exercise may trigger asthma attacks, and because of that they usually avoid to actively exercise, their fitness deteriorates, and dyspnea may occur even with lower levels of physical activity. However, exercise can decrease the

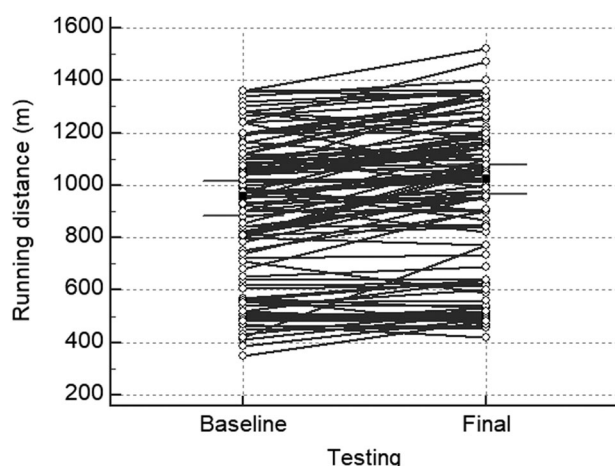


Figure 1. Running distance (in meters) during the free running test at baseline and final measurements after two week-program; black dots represent median and horizontal lines represent 95% confidence interval, $p < 0.001$, Wilcoxon Signed Rank Test.

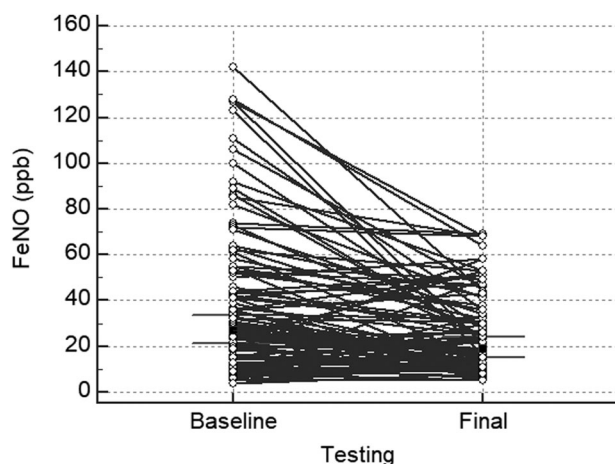


Figure 2. Fraction of exhaled nitric oxide (FeNO) in parts per billion (ppb) at baseline and final measurements after two week-program; black dots represent median and horizontal lines represent 95% confidence interval, $p < 0.001$, Wilcoxon Signed Rank Test.

frequency and severity of asthma attacks, but mostly in patients who are well controlled and regularly use anti-inflammatory therapy, and also exercising for at least an hour per day has many other health benefits for asthmatic children and adolescents (1,13). Different studies investigated potential effects of regular exercise in asthmatic children with different exercise modes, e.g. swimming, running or cycling and all showed significant improvement in maximum oxygen uptake, though no effects were observed in other measures of pulmonary function (7,18,19). Abdelbaset et al. investigated the effects of moderate-intensity exercise training in 38 asthmatic school-aged children and found that ten weeks of physical exercise had

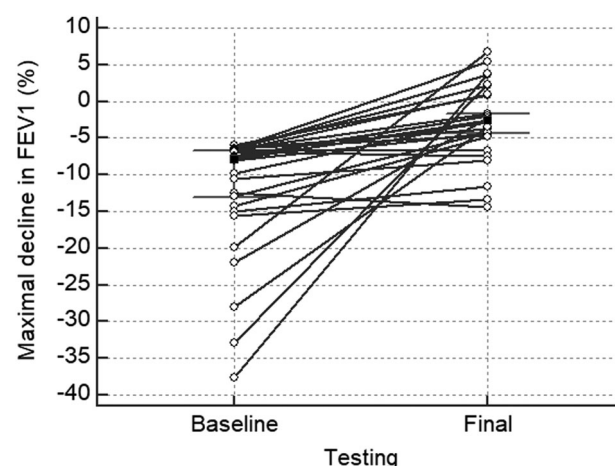


Figure 3. Maximal decline in forced expiratory volume in 1 s (FEV1) after the free running test (FRT) in the fourth quartile subgroup at baseline and final measurements after two week-program; black dots represent median and horizontal lines represent 95% confidence interval, $p < 0.001$, Wilcoxon Signed Rank Test.

beneficial effects on pulmonary functions and aerobic capacity (20).

In our study patients with the lowest tolerance to physical activity (patients with the greatest EIB level) had the greatest benefit from the PR program. Zampogna et al. (21) conducted a retrospective study in 515 subjects (mean age = 64 yrs.) with moderate to severe asthma who underwent 3 weeks of PRP. The subjects who benefited more from PRP were patients with worse lung function impairment and with lower baseline 6-min walk distance. These results support the expectations that PRP benefits are more pronounced in patients who were more disabled.

Several studies applied climate therapy for asthmatic patients in low-trigger environments (22–24) but there was no record of organized physical or PR activities while in our study subjects had daily organized training activities with intensities set from mild to vigorous. Hashimoto et al. (23) conducted a 12-week study in severe asthma patients in a low-trigger environment (1600 meters altitude in Davos, Switzerland). Intervention was done in 136 patients (mean age 46 yrs.) and found improved quality of life and lung function in all patients with severe asthma. Mallett et al. (24) presented results of a 5 day stay at asthma camp in 34 children (mean age = 11 yrs, 56% boys) with diagnosed asthma. Asthma camp was based on regular summer camp activities and daily asthma education. After the participation in camp subjects had increased their lung function variables, improved attitudes and knowledge, had better ACT scores and decreased visits in emergency department and hospitalizations.

However, our study is specific because the PRP we conducted is combined with climate/balneotherapy. We believe that the improvement after just 2 weeks represents a combined effect of regular training activities and exposure to characteristic Mediterranean environmental factors in a clean (allergen safe) outdoor environment. This combined effect is also supported by a significant reduction of FeNO values measured on site in our patients. Our result is supported by the study done by Kaminsky et al. showing a significant reduction of FeNO after a week of asthma camp, without significant changes in lung function or asthma control. In the same study, the anti-inflammatory therapy during asthma camp was not modified and the authors concluded that airway inflammation was reduced because of improved adherence to therapy and/or reduced exposure to pro-inflammatory stimuli when residing out of the home environment (22). FeNO is also involved in nonallergic inflammatory and pulmonary vascular mechanisms or responses to environmental stimuli. Elevated FeNO is found in people with nonatopic chronic conditions including diabetes and chronic obstructive pulmonary disease (COPD) exposed to higher levels of air pollution (25). In our study FeNO levels after the 2-weeks of PRP tested at rest showed a significant decrease of airway inflammation supporting the hypothesis that even a short PRP with the combined effect of regular exercise and allergy safe outdoor environment can be effective. This effect however is not comparable to what Evjenth et al. reported in non-asthmatics after acute exposure to exercise. Even though FeNO levels improved significantly, the result was clinically marginal and as it was not tested at rest which can lead to erroneous (lower) FeNO readings (26).

To our notion, such a particular combination of PRP with climate/balneotherapy was not studied thoroughly by other researchers. Few studies investigated the effects of pulmonary rehabilitation but without the concomitant climate therapy (20,21), while others only investigated the effects of a climate therapy without PRP (22–24). The single study that combined organized PRP and climate therapy was done by Muller et al. (27), but in elderly patients (mean age 61 yrs, $n=678$). They were mostly patients with asthma (77%), but also patients with and/or COPD and/or allergic rhinitis. After 3 weeks of combined therapy, significant improvements were found for 6-min walk test, and for several lung function parameters (i.e. FEV1, FEV1/FVC). Current recommendations suggest that a pulmonary rehabilitation program should last for 6 to 12 weeks to produce benefits that gradually

decline over 12 to 18 months (28). On the other hand, our PRP lasted only two weeks, but demonstrated statistically and clinically significant benefits on important outcomes (i.e. airway inflammation and hyperreactivity, and physical fitness). Our findings represent an added value which can steer the pulmonary rehabilitation to a shorter 2-week programs in a specified environment allowing school children and their parents/legal guardians less absence from school and work, respectively with consequent lower direct and indirect costs.

The uniqueness of our study is the combined approach of pulmonary rehabilitation in allergen free outdoor environment with specific climate/balneology properties which potentially facilitate the effectiveness and benefits of the applied PRP. However, it is also important to consider the limitations of this interventional single arm prospective study (quasi-experimental research design) such as: short period of PRP, no randomized control group and the lack of follow-up period. All these aspects should be considered in future similar studies. On the other hand, even though the study was done in a group of children with well or partially controlled mild to moderate asthma the significant benefits were clearly evident.

Conclusion

The results of this study showed that even a short-term pulmonary rehabilitation program (PRP) provided in an AllSOE in children with mild to moderate persistent asthma could produce a significantly beneficial clinical effect. Children and adolescents who attended such PRPs significantly improved their exercise capacity and demonstrated improvement in both airway inflammation and bronchial hyperreactivity levels.

Disclosure statement

The authors report no conflict of interest.

ORCID

M. Lipej  <http://orcid.org/0000-0001-6284-053X>

D. Plavec  <http://orcid.org/0000-0003-2020-8119>

References

1. World Health Organization: bronchial asthma, Fact sheet no. 206. <https://www.who.int/mediacentre/factsheets/fs206/en/> [last accessed 21 October 2018].
2. Pearce N, Ait-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, Robertson C, ISAAC Phase Three Study Group. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of

- Asthma and Allergies in Childhood (ISAAC). *Thorax*. 2007;62(9):758–766. doi:10.1136/thx.2006.070169.
3. Haahtela T, von Hertzen L, Custovic A. Prevention of allergic diseases. In: Pawankar R, Canonica GW, Holgate ST, Lockey RF, Blaiss MS, eds. *White book on allergy*. WI, USA: World Allergy Organization; 2011: 133.
 4. Zuberbier T, Lötvald J, Simoons S, Subramanian SV, Church MK. Economic burden of inadequate management of allergic diseases in the European Union: a GA(2) LEN review. *Allergy*. 2014;69(10):1275–1279. doi:10.1111/all.12470.
 5. Gibson GJ, Loddikenkemper R, Lundbäck B, Sibille Y. Respiratory health and disease in Europe: the new European Lung White Book. *Eur Respir J*. 2013;42:559–563. doi:10.1183/09031936.00105513.
 6. Westergren T, Fegran L, Nilsen T, Haraldstad K, Kittang OB, Berntsen S. Active play exercise intervention in children with asthma: a PILOT STUDY. *BMJ Open*. 2016;6(1):e009721. doi:10.1136/bmjopen-2015-009721.
 7. Wanrooij VHM, Willeboordse M, Dompeling E, van de Kant KDG. Exercise training in children with asthma: a systematic review. *Br J Sports Med*. 2014;48(13):1024–1231. doi:10.1136/bjsports-2012-091347.
 8. Neder AJ, Nery LE, Silva AC, Cabral ALB, Fernandes A. Short term effects of aerobic training in the clinical management of moderate to severe asthma in children. *Thorax*. 1999;54(3):202–206. doi:10.1136/thx.54.3.202.
 9. França-Pinto A, Mendes FAR, de Carvalho-Pinto RM, Agondi RC, Cukier A, Stelmach R, Saraiva-Romanholo BM, Kalil J, Martins MA, Giavina-Bianchi P, et al. Aerobic training decreases bronchial hyper-responsiveness and systemic inflammation in patients with moderate or severe asthma: a randomised controlled trial. *Thorax*. 2015;70(8):732–739. doi:10.1136/thoraxjnl-2014-206070.
 10. Jung A, Heinrichs I, Geidel C, Lauener R. Inpatient paediatric rehabilitation in chronic respiratory disorders. *Paediatr Respir Rev*. 2012;13(2):123–129. doi:10.1016/j.prrv.2011.08.001.
 11. Nesvold JH, Gottier Fena P, Herman J, and the consortium on children's asthma camps board of directors. Assessing the value of children's asthma camps. *J Asthma*. 2006;43(4):273–277. doi:10.1080/02770900600622794.
 12. Buckner EB, Simmons S, Brakefield JA, Hawkins AK, Feeley C, Kilgore LA, Holmes S, Bibb M, Gibson L. Maturing responsibility in young teens participating in an asthma camp: adaptive mechanisms and outcomes. *J Spec Pediatr Nurs*. 2007;12(1):24–36. doi:10.1111/j.1744-6155.2007.00086.x.
 13. Global Initiative for Asthma. Global strategy for asthma management and prevention, 2018. <https://ginasthma.org/> [last accessed 12 December 2018].
 14. Višekruna I, Gospić AM, Plavec D, Lipej M, Nogalo B. The impact of moderate physical activity on the resting metabolic rate (RMR) in children with asthma. *Central Eur J Paed*. 2018;14(2):183–189.
 15. Dweik AR, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, Olin AC, Plummer AL, Taylor DR, on behalf of the American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (Fe) for Clinical Applications. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med*. 2011;184(5):602–615. doi:10.1164/rccm.9120-11ST.
 16. Miller MR, Hankinson J, Brusasco V. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319–338. doi:10.1183/09031936.05.00034805.
 17. Bacharier LB, Strunk RC, Mauger D, White D, Lemanske RF, Sorkness CA. Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. *Am J Respir Crit Care Med*. 2004;170(4):426–432. doi:10.1164/rccm.200308-1178OC.
 18. Counil FP, Varray A, Matecki S, Beurey A, Marchal P, Voisin M, Préfaut C. Training of aerobic and anaerobic fitness in children with asthma. *J Pediatr*. 2003;142(2):179–184. doi:10.1067/mpd.2003.83.
 19. Carson KV, Chandratilleke MG, Picot J, Brinn MP, Esterman AJ, Smith PJ. Physical training for asthma. *Cochrane Database Syst Rev*. 2013;9:1–71.
 20. Abdelbasset WK, Alsubaie SF, Tantawy SW, Elyazed TIA, Kamel DM. Evaluating pulmonary function, aerobic capacity, and pediatric quality of life following a 10-week aerobic exercise training in school-aged asthmatics: a randomized controlled trial. *Patient Prefer Adherence*. 2018;12:1015–1023. doi:10.2147/PPA.S159622.
 21. Zampogna E, Paneroni M, Cherubino F, Pignatti P, Rudi M, Casu G, Vitacca M, Spanevello A, Visca D. Effectiveness of a pulmonary rehabilitation program on persistent asthma stratified for severity. *Respir Care*. 2019; 64(12):1523–1530. doi:10.4187/respcare.06761.
 22. Kaminsky DA, Rice AA, Bissonette M, Larose T, Phillips L, Cohen L, Lahiri T, Frankowski B. Exhaled nitric oxide decreases in association with attendance at an asthma summer camp. *J Asthma*. 2008;45(5):415–419. doi:10.1080/02770900801971842.
 23. Hashimoto S, Rijssenbeek-Nouwens LH, Fieten KB, Weersink EJ, Bel EH. Predictors of benefit from high-altitude climate therapy in adults with severe asthma. *Neth J Med*. 2018;76(5):218–225.
 24. Mallett LH, Soto A, Govande J, Ogborn C, Sagar M. Role of asthma camp in improving the overall health of children with asthma. *Proc (Bayl Univ Med Cent)*. 2019;32(1):54–57. doi:10.1080/08998280.2018.1533309.
 25. Flashner BM, Rifas-Shiman SL, Oken E, Camargo CA, Platts-Mills TJ, Workman L, Litonjua AA, Gold DR, Rice MB. Obesity, sedentary lifestyle, and exhaled nitric oxide in an early adolescent cohort. *Pediatr Pulmonol*. 2019;55(2):503–507. doi:10.1002/ppul.24597.
 26. Evjenth B, Hansen TE, Holt J. Exhaled nitric oxide decreases during exercise in non-asthmatic children. *Clin Respir J*. 2013;7(2):121–127. doi:10.1111/j.1752-699X.2012.00292.x.
 27. Müller A, Ráthonyi G, Bíró M, Ráthonyi-Ódor K, Bács Z, Ács P, Hegyi G, Bácsné E. The effect of complex climate therapy on rehabilitation results of elderly asthmatic and chronic obstructive airways disease (COPD) patients. *Eur J Integrate Med*. 2018;20:106–114. doi:10.1016/j.eujim.2018.04.007.
 28. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, Make B, Rochester CL, ZuWallack R, Herrerias C. Pulmonary rehabilitation executive summary. *Chest*. 2007;131(5):1S–3S. doi:10.1378/chest.07-0892.

Supplemental Table 1

Standard SPT panel for inhalant allergens	Standard SPT panel for nutritive allergens
- Hazel (<i>Corylus avellana</i>) - Birch (<i>Betula alba</i>) - Grass mix - Mugwort (<i>Artemisia vulgaris</i>) - Ragweed (<i>Ambrosia artemisiifolia</i>) - <i>Alternaria alternata</i> (<i>tenuis</i>) - <i>Cladosporium herbarum</i> - <i>Parietaria</i> - Cat dander - Dog dander - <i>Dermatophagoides pteronyssinus</i> - <i>Dermatophagoides farinae</i>	- Sesame seed - Soybean - Peanut - Wheat flour - Corn flour - Egg - Milk - Hake - Trout - Tuna - Almond - Walnut - Hazelnut
SPT- Skin Prick Test	

Supplemental Table 2

Results of a multiple regression analysis for the outcomes (dependent variables) regarding age, sex and BMI (independent variables)

	Age		Sex		BMI		R ²	P-value
	Stand. Coeff. Beta	P-value	Stand. Coeff. Beta	P-value	Stand. Coeff. Beta	P-value		
Δ FVC (%)	-0.17	0.07	-0.09	0.32	-0.13	0.19	0.06	0.09
Δ FEV1 (%)	-0.18	0.06	-0.05	0.63	-0.12	0.21	0.03	0.10
Δ FeNO (ppb)	0.08	0.32	0.04	0.53	0.04	0.27	0.06	0.82
Δ Max.FEV1 decline from baseline after FRT (%)	-0.10	0.32	-0.06	0.53	-0.11	0.27	0.03	0.40

Supplemental Table 3

Correlations between Set-1 and Set-2

	Age	Sex	BMI
Δ FeNO (ppb)	0.043	0.072	0.032
Δ FEV1 (%)	-0.205	-0.023	-0.150
Δ FVC (%)	-0.198	-0.072	-0.144
Δ max. FEV1 decline from baseline after FRT (%)	-0.118	-0.041	-0.118

Canonical Correlations

$X^2(12) = 9.36$, $p=0.40$, $r=0.27$

$X^2(4) = 1.62$, $p=0.80$, $r=0.13$

$X^2(1) = 0.00$, $p=0.99$, $r=0.03$