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Effectiveness of pulmonary rehabilitation at high-altitude compared to sea-level in adults with severe refractory asthma

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ABSTRACT

Background: Beneficial effects of pulmonary rehabilitation at high-altitude (HAPR) in patients with severe refractory asthma have been reported earlier, but evidence for the effectiveness is limited.
Aim: To investigate the effectiveness of high-altitude pulmonary rehabilitation to comparable treatment at sea-level (LAPR) on patient outcome parameters.
Methods: Adults with severe refractory asthma living in The Netherlands were included. Treatment consisted of a 12-week personalized multidisciplinary rehabilitation program either at high-altitude (Davos Switzerland) ($n = 93$) or in a tertiary lung center at sea-level in The Netherlands ($n = 45$). At baseline, after treatment, and during 12 months follow-up asthma related quality of life (AQLQ), asthma control (ACQ), pulmonary function and OCS-dose were assessed. Patients could not be randomized resulting in different asthma populations. Groups were compared using linear regression analysis (ANCOVA) adjusted for baseline values, in addition to age, atopy, smoking history, BMI and gender.
Results: After treatment, and at 12 months follow-up, improved AQLQ(0.92,$p < 0.001$ and 0.82,$p = 0.001$, respectively), ACQ(-0.87,$p < 0.001$ and -0.69,$p = 0.008$, respectively) and lower maintenance OCS dose (Unadjusted linear regression analysis-5.29 mg, $p = 0.003$ and Crude Odds Ratio-1.67, $p = 0.003$, respectively) were observed in the HAPR-group compared to the LAPR group. Patients receiving HAPR also had less asthma exacerbations (≥1 exacerbation: 20% *vs* 60%,$p < 0.001$) and showed improvement in lung function (%predFEV_1 3.4%,$p = 0.014$) compared to the LAPR group, but at 12 months no differences between groups were observed.
Conclusion: HAPR resulted in a larger improvement in patient outcome parameters compared to LAPR, on the long run the improvement in patient reported symptoms and lower maintenance OCS-dose persists. Underlying factors that explain this observed effect need to be investigated.

1. Introduction

Difficult-to-treat asthma is characterized by difficulty to achieve disease control despite high-dose inhaled corticosteroids (ICS), long-acting bronchodilators or adding oral corticosteroids (OCS). In patients with severe refractory asthma, the disease remains uncontrolled despite addressing and removing all possible factors that might aggravate the underlying disease [1]. Severe refractory asthma imposes a substantial burden due to symptoms, exacerbations and medication side-effects, which have profound consequences for mental and emotional health, relationships and careers [2]. It is estimated that 3.6% of the adults with asthma living in the Netherlands have severe

Abbreviations: ANCOVA, analysis of covariance; ACQ, Asthma control; AQLQ, Asthma related Quality of Life scores; BMI, Body Mass Index; FEV_1, forced expiratory volume in 1 s; LAPR, pulmonary rehabilitation at sea-level; HAPR, pulmonary rehabilitation at high-altitude; PR, Pulmonary rehabilitation; OCS, oral corticosteroids; SD, standard deviation.

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refractory asthma but their care is estimated to account for more than 60% of the costs associated with asthma [1,3].

Treatment of patients with severe refractory asthma is challenging. In the last decade several biologicals have been proven effective for this patient group, resulting in lower exacerbation frequency besides decrease of OCS-dependency [4]. Also non-pharmacological add-on interventions, such as pulmonary rehabilitation and allergen avoidance are recommended [5,6]. Pulmonary rehabilitation is defined as a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies, which include but are not limited to, exercise training, education and behavior change, designed to improve the physical and psychological condition of patients with chronic respiratory disease and to promote the long-term adherence of health-enhancing behaviors [7]. Beneficial effects of asthma rehabilitation at high-altitude (HAPR) in adults with severe refractory asthma have been observed. Of interest, several studies showed an improvement in asthma control, a decrease in corticosteroid use and an increase in pulmonary function after pulmonary rehabilitation at high-altitude [8–10]. The rationale behind this treatment lies in the unique climatic conditions at high-altitude that are supposed to be beneficial for patients with allergic asthma [11]. However, several studies suggest that avoidance or reduction of allergen exposure is not the only driver for a successful outcome of this treatment modality [12–15]. For example, less pollution at high altitude may also play an important role [29]. The improvement of asthma related quality of life after HAPR is independent of the asthma phenotype suggesting that non-specific aspects of this treatment, such as reduction of non-allergic inflammatory triggers could be responsible for a positive treatment effect [16]. Moreover, a decrease in the number of exacerbations and sustained improvement in asthma control up to 12 months after HAPR was found in a population of adults with severe refractory asthma [17]. The exact determinants associated with the observed effects of asthma rehabilitation in a high-altitude environment are unknown. To that end a comparison between an inpatient rehabilitation program at high-altitude and sea-level is needed.

The aim of this study was to investigate the effectiveness of a 12 week personalized pulmonary rehabilitation at high-altitude in comparison with a comparable personalized pulmonary rehabilitation program that is offered at sea-level in the Netherlands in a population of adults with severe refractory asthma on patient outcome parameters. After treatment disease outcomes were measured for an additional 12 months.

2. Methods

2.1. Study design

The study was initially set up as a parallel, clinical trial with random allocation to asthma rehabilitation in a high-altitude center or asthma rehabilitation center at sea-level.

However, randomization frequently turned out to be not feasible for several reasons. First, a number of patients had a decided preference for one one of the two locations. Second, some of the referring pulmonologists referred patients specifically for rehabilitation at high or low altitude. This resulted in a proportion of about 75% of all referred patients that could not be randomized. Because of this high proportion of patients that could not be randomized, we concluded that randomization had failed and considered that the study fell back to an observational design and was analyzed and interpreted accordingly. The small group of patients (~25%) which could be randomized was too small to obtain sufficient statistical power and this was a strong argument against an independent analysis for this part of the study. The treatment lasted for a total of 12 weeks. After treatment, patients were followed for an additional 12 months with a follow-up visit every 3 months at the sea-level treatment location in The Netherlands.

Patients were assessed and evaluated in accordance with a systematic protocol. Demographic and social characteristics, clinical history and medical consumption over the preceding 12 months were assessed at entry. Atopic asthma was defined as a positive serum IgE level to a mix of common aero-allergens (house dust mite, mixed grass and birch, pollen, cat and dog dander and cladosporium). Asthma related quality of life (AQLQ) and asthma control (ACQ) questionnaires were obtained at entry, every 3 weeks during the treatment period and during follow-up. Rhinosinusitis-related quality-of-life (SNOT), use of corticosteroids, pulmonary function and exercise tolerance were assessed at entry, after the 12-week asthma rehabilitation program and every follow-up visit. Exacerbations during the treatment period were prospectively assessed.

2.2. Patients

Adults with severe refractory asthma who were referred by their pulmonologist in the Netherlands to a tertiary asthma clinic, either the Dutch Asthma Centre in Davos, Switzerland, or the Merem Asthma Center in Hilversum, The Netherlands, were recruited between October 1, 2015 and February 1, 2018. Patient's eligibility was discussed in a staff meeting with pulmonologists from both centers. If needed, the referring pulmonologist was asked for additional information. In case of doubt, an expert panel consisting of 3 pulmonologists from other asthma expert-centers in The Netherlands verified the eligibility criteria. Patients who met both the inclusion and exclusion criteria were asked to participate in the trial. Baseline measurements were performed at the site of treatment.

Adults (aged 18–75 years) were able to participate in the study if they had a diagnosis of severe refractory asthma according to the ERS/ATS criteria [1]. All patients used long-acting bronchodilators and high dose inhaled corticosteroids (ICS, $\geq$ 1000 μg fluticasone daily or equivalent) with or without oral corticosteroids (OCS, $\geq$ 6 months/-year). All patients were symptomatic and had uncontrolled asthma. Uncontrolled asthma was defined by the presence of at least two of the following criteria [1]: poor symptom control defined as an ACQ-score $\geq$ 1.5 or an ACT-score $<$ 20 [2], frequent severe exacerbations defined as 2 or more bursts of OCS (>3 days) in the previous year [3], serious exacerbations defined as at least one hospitalization or ICU stay or mechanical ventilation in the previous year because of an asthma exacerbation and/or [4] persistent airflow limitation (post-bronchodilator $FEV_1 < 80\%$ of predicted or a FEV_1/FVC z-score < 1.64).

All patients were either nonsmokers or ex-smokers for >6 months. Before being referred to a tertiary asthma clinic, inhalation technique, adherence to medication and optimal avoidance of exposure to allergens and cigarette smoke was checked using a questionnaire completed by the referring pulmonologist. In addition, treatment of comorbidity was optimized before taking part in the study. Exclusion criteria were alcohol abuse or a severe unstable psychiatric condition requiring treatment, participation in a clinical trial in the preceding three months, unstable cardiovascular status, pregnancy or planning to become pregnant, suffering from another lung disease that had impact on asthma symptoms and use of long-term oxygen therapy at sea-level.

The study was approved by the Ethics Committee of the Academic Medical Center of the University of Amsterdam (Amsterdam, the Netherlands) and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before taking part in the study. This study was registered at The Netherlands Trial Register, www.trialregister.nl under NTR 5182.

2.3. Treatment

All included patients were living in The Netherlands. Treatment consisted of a multidisciplinary pulmonary rehabilitation program with a duration of 12 weeks either in the high-altitude asthma center in Davos, Switzerland, or in the tertiary asthma clinic at sea-level in Hilversum, The Netherlands. The patients who were treated at sea-level

went home in the weekend while the patients who were treated in Davos stayed for the full 3 months period of the treatment. Both treatment options were fully covered by Dutch mandatory health insurance, except for costs to travel home in the weekends when attending the facility at sea-level.

The centers maintained their usual pretreatment assessment procedures. Before treatment started in Switzerland, patients had an intake interview with a specialized nurse in The Netherlands and an interview by video conference with the pulmonologist in Switzerland. The procedure of the center in The Netherlands consisted of a home visit by a specialized social worker followed by an intake interview with the pulmonologist and finally, a 3-day assessment in the treatment center, consisting of, but not limited to psychological assessment through intake by a psychologist, including a psychological questionnaire, lung function testing, cardio-pulmonary exercise testing, blood tests, including if needed allergy screen, and an interview by a pulmonary nurse. After this pretreatment assessment procedure 8 patients were referred for another treatment option.

Both centers supply structured, quality-controlled, personalized treatment for adults with severe asthma, which includes attempts to achieve optimal asthma control and to reduce (oral) corticosteroids to the lowest effective level, exercise training, asthma education including self-management and psychological support. Treatment in both centers was personalized by using a modular approach with standardized treatment modules. Standardized treatment included 9 basic modules (medication and inhalation; exacerbation; self-management; physical fitness; daily physical activity; functional-ADL-training, dyspnea management; food and diet; coping; psychological support). During follow-up, patients were treated by their referring pulmonologist in The Netherlands according to (international) guidelines.

2.4. Primary outcomes

2.4.1. Asthma related quality of life

The asthma related quality of life was measured by the *Juniper Asthma Quality of Life Questionnaire* (AQLQ), an asthma specific questionnaire that measures symptoms, activity limitations, emotional functioning and environmental stimuli [18]. The mean of the 32 items in the AQLQ between 1 (very poor asthma related quality of life) and 7 (best asthma related quality of life) was used. The minimally clinical important difference (MCID) for AQLQ is considered to be 0.5 [19].

2.5. Secondary outcomes

2.5.1. Patient reported symptoms

2.5.1.1. Asthma control. The level of asthma control was assessed using the *Juniper ACQ-6 score*, a 6-item version of the ACQ questionnaire with the FEV_1 question omitted [20]. In this questionnaire, patients recall their experiences over the past 7 days and respond to each question on a 7-point Likert scale, where 0 represents no impairment and 6 represents maximum impairment. The MCID for ACQ is considered to be 0.5 [20].

2.5.2. Rhinosinusitis-related quality of life

The *22-question Sino-Nasal Outcome test* (SNOT-22) was used to measure rhinosinusitis-related quality-of-life. The mean total score ranges from 0 (no symptoms) to 5 (severe symptoms) and is calculated by averaging an individual's responses to all questions [21]. The MCID for SNOT-22 is considered to be 0.4 [21].

2.6. Medical consumption

2.6.1. Exacerbations, hospitalizations and the use of corticosteroids

The number of exacerbations during 12-week treatment in the specialized third line asthma center was prospectively assessed and defined as the number of periods of deterioration of asthma symptoms which requires the use of oral corticosteroids for at least 5 days, or an increase from a stable maintenance dose for at least 5 days, the use of oral antibiotics or hospitalization. The number of exacerbations before treatment and during follow-up was based on self-report and defined by the number of oral corticosteroids bursts in the previous 3 months and the number of asthma-related hospitalizations.

The use of ICS was expressed as equivalent doses beclomethasone and the use of oral corticosteroids was expressed as equivalent doses prednisone. Steroid dependent asthma was defined as $\geq$ 6 months/year daily use of oral corticosteroids in the past 12 months prior to treatment. The OCS dose was recorded at entry and after a treatment period of 12 weeks. Every 3 months during follow up the OCS dose was recorded only in those who fulfill the criteria of OCS dependent asthma at entry.

2.7. Functional characteristics

2.7.1. Pulmonary function and exercise tolerance

Pulmonary function was measured according to international recommendations using the Masterscreen PFT (Jaeger Viasys, Germany) [22]. Forced vital capacity (FVC) and Forced expiratory volume in 1 s (FEV_1) was assessed after inhaled administration of 400 μg salbutamol and expressed as percentage of predicted value [23].

Exercise tolerance was measured with the incremental shuttle walk test (ISWT) [24]. The walking distance is recorded. At entry, patients were asked to complete the test twice with the best result recorded. At sea-level, patients performed the test in groups, while at high-altitude the patients did an individual test. The MCID for the ISWT is considered to be 47.5 m [25].

2.8. Sample size calculation

The sample size was estimated using a covariance analytic model for the AQLQ. Assumptions on the variability of AQLQ scores were made based on a previous study [8]. The minimal clinical important AQLQ difference (MCID) was assumed to be 0.5 point [19]. In the estimation process we let the SD vary between 1 and 1.3 by 0.1 steps and the R^2 value between 0.1 and 0.4 by 0.1 steps. Allocation ratio was 1:1, α was set at 5% and 1-ß at 80%. These calculations indicated that 160 subjects (80 per group) would be sufficient. Post hoc analyses indicate that achieved sample size reached a power of 86% to detect a difference in AQLQ of 0.5 point.

2.9. Statistical analysis

Differences between groups were tested using an unpaired *t*-test or Mann-Whitney *U* test and within groups using a paired *t*-test. For comparison of proportion between groups, chi-square test was used. Changes from baseline were analyzed using an unpaired *t*-test or Wilcoxon signed rank test, depending on the distribution of the variable. Linear regression analysis was performed using analysis of covariance (ANCOVA). The structural part of the regression model can be described as follows:

$$E(AQLQ_{fu}) = b_0 + b_1 * AQLQ_0 + b_2 * I$$

In this model, the dependent variable is the AQLQ score at t = 12 (post treatment) or t = 64 (post follow-up) while the covariates are the baseline AQLQ (t = 0) and the intervention status I (0 = sea-level, 1 = high mountain) (plus any confounders). The same structure was used for the ACQ data. Both ACQ and AQLQ were approximately normally distributed. Sensitivity analyses were performed using a repeated linear mixed model analysis using the three-week interval AQLQ and ACQ-scores. These analyses resulted in comparable results. In addition, subgroup analysis was performed in the group in which treatment allocation was randomized. In this group differences in baseline AQLQ and ACQ scores between the HAPR and LAPR-group were found. We

concluded that randomization failed and the study should be considered as an observational study.

All secondary outcome measures (with repeated measurements before and after treatment) were analyzed by analysis of covariance. Missing data or in case of re-admission to an inpatient asthma rehabilitation program values were imputed by the most recent previous data (Last Observation Carried Forward).

3. Results

3.1. Flow chart and baseline characteristics

One hundred and seventy-three patients were enrolled in this study. Thirty patients dropped out prior to the treatment for several reasons (Fig. 1). There were no differences in demographic characteristics between the patients who dropped out and the patients who were enrolled. Treatment was started in 143 patients ($n = 97$ HAPR *vs* $n = 46$ LAPR). After admission, 5 patients were incorrectly included ($n = 4$ HAPR *vs* $n = 1$ LAPR). In these 5 patients, it appeared that the criteria described in the study protocol were not met. A total of 138 patients ($n = 93$ HAPR *vs* $n = 45$ LAPR) completed the treatment period. In both groups the median treatment time was 11 weeks with a IQR of 11–12 weeks in the high-altitude group versus 9–12 weeks in the sea-level group.

One hundred and twenty-seven patients participated in the follow-up part of the study ($n = 88$ HAPR vs $n = 39$ LAPR). During follow-up 9 patients were lost to follow-up and 1 patient was excluded due to co-morbidity unrelated to the study. There were no differences in demographic or clinical characteristics between those who dropped out and those who completed follow-up. A total of 117 patients ($n = 79$ HAPR and $n = 38$ LAPR) completed follow-up.

The baseline characteristics are described in Table 1. Patients in the high-altitude group were younger, were less often an ex-smoker, were more often atopic and had more frequent chronic rhinosinusitis or eczema comorbidity as compared to patients in the sea-level group. At entry the high-altitude group used higher dosages of ICS and demonstrated a lower AQLQ and higher ACQ as compared to the sea-level group. Biologicals were more often used in the high-altitude group and were temporally stopped during HAPR. During follow-up 9 patients started with a biological treatment ($n = 5$ HAPR versus $n = 4$ LAPR). Five of those patients had oral corticosteroid (OCS)-dependent asthma at entry ($n = 2$ HAPR and $n = 3$ LAPR) and were excluded from analyses with respect to OCS use on the long run. There were no differences between the groups with respect to the season in which the treatment was started. In the high-altitude group 50% of the population underwent previous treatment at high-altitude in the preceding 6 years while none of the patients treated at sea-level underwent previous treatment at sea-level in the preceding 6 years.

3.2. High-altitude pulmonary rehabilitation

Changes in patient reported outcomes within the high-altitude group are shown in Table 2. After 12 weeks of HAPR, significant improvements in AQLQ, ACQ and SNOT were observed. A part of these effects was still present twelve months after treatment (= 64 weeks after entry). No differences in the dose of ICS was found after treatment at high-altitude. Within the group of patients with OCS dependent asthma ($n = 46$) there was a significant reduction in OCS dose after HAPR, which was still present after twelve months. After treatment at high-altitude there was an improvement in FEV_1 and ISWT-distance, which sustained during the follow-up period. Furthermore, a reduction in the number of OCS bursts was found twelve months after treatment at high altitude as compared to before treatment. No significant difference in the number of hospitalizations before and 12 months after treatment at high altitude was found. The results of AQLQ, ACQ, SNOT, FEV_1 and ISWT distance within the high-altitude group are visualized in Figs. 2 and 3. During the 12 months follow-up, three patients were re-admitted to HAPR.

3.3. Pulmonary rehabilitation at sea-level

Changes in patient reported outcomes within the sea-level group are shown in Table 3. After twelve weeks of LAPR, significant improvements were found in AQLQ, ACQ, SNOT and ISWT distance. After 12 months follow-up, these effects could no longer be demonstrated. No difference in the dose of ICS or FEV_1 was found after LAPR. Within the group of patients with OCS dependent asthma ($n = 17$) there was a significant reduction in OCS dose after treatment at sea-level, but there was no such effect during follow-up. In addition, no significant differences were found in the number of OCS bursts or hospitalizations before and 12 months after treatment at sea-level. The results of AQLQ, ACQ, SNOT, FEV_1 and ISWT distance within sea-level group are visualized in Figs. 2

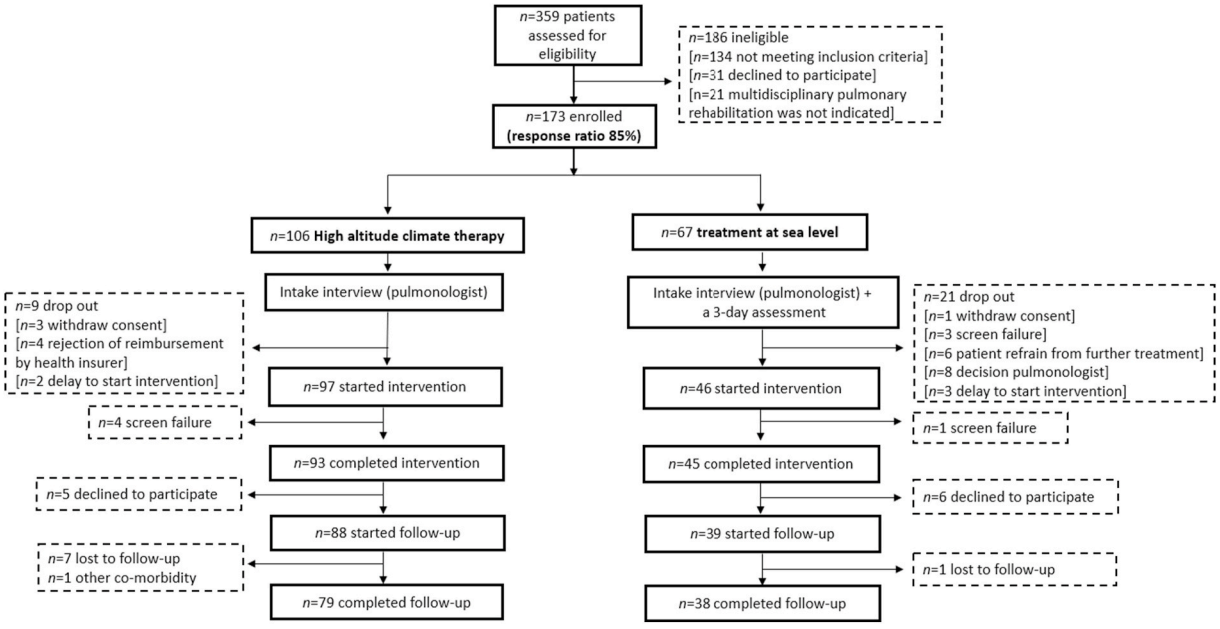

Fig. 1. Number of patients who were screened, enrolled and completed the study.

Table 1
Baseline characteristic of the study population.

	High-altitude	Sea-level	p-value
Patients (*n*)	93	45	
Age (years)*	44 ± 14.1	51 ± 14.2	***0.003***
Gender (% female)	76	62	0.08
Adult-onset asthma (%)	36	47	0.21
BMI*	29.6 ± 5.6	31.2 ± 5.3	0.10
Ex-smoker (%)	14	53	***<0.001***
Social-economic status			
Single house holding (%)	24	24	0.99
Payed job (%)	24	27	0.68
Welfare benefit (%)	15	15	0.99
Unemployment benefit (%)	47	49	0.81
Atopic			
Atopic asthma (%)	72	53	***0.03***
IgE#	176 (47–526)	112 (28–426)	0.12
Comorbidities			
Fear/depression (%)	12	18	0.34
Chronic rhinosinusitis (%)	72	53	***0.03***
Diabetes mellitus (%)	12	7	0.35
Eczema (%)	41	7	***<0.001***
Sleep apnea (%)	14	20	0.37
Thyroid problems (%)	11	7	0.44
Diseases of the musculoskeletal (%)	29	36	0.44
Use of medication			
Chronic use of Oral corticosteroids (*n*/%)	48/52%	17/38%	0.13
Dose of Oral corticosteroids (mg)#[1]	10 (9.3–23.8)	10 (7.5–17.5)	0.63
Dose of inhaled corticosteroids (μg/day)#	1600 (1200–3200)	1600 (800–2400)	***0.03***
Use of biologicals (%)	22[2]	7	***0.03***
Nasal corticosteroids (%)	58	53	0.60
Reflux medication (%)	57	58	0.93
Asthma exacerbations < 12 mths			
Number of OCS bursts (%)			0.10
- 0–2	17	18	
- 3–4	20	37	
- ≥ 5	63	45	
Number of hospitalizations (%)			0.98
- 0	42	40	
- 1–2	35	35	
- ≥ 3	24	25	
Patient reported symptoms			
AQLQ-score*	3.9 ± 0.9	4.5 ± 0.9	***0.001***
ACQ-score*	3.1 ± 0.9	2.4 ± 0.9	***<0.001***
SNOT-score*	2.3 ± 0.8	2.0 ± 0.8	0.10
Functional characteristics			
FEV_1 (% pred)*	86 ± 20.3	84 ± 25.4[1]	0.74
FVC (% pred)*	89 ± 14.8	92 ± 20.0	0.28
distance ISWT (m) #	390 (250–560)	450 (260–680)	0.32
Inflammatory markers			
FeNO (ppb)#	20 [12–40]	17 [11–38]	0.71
Blood eosinophils (10^9/l)	0.2 (0.1–0.3)	0.2 (0.1–0.2)	0.67

* Mean/SD.
\# Median/interquartile range (IQR).
[1] Dose within the group of patients with OCS dependent asthma.
[2] Biologicals stopped during treatment at high-altitude. **Abbreviations:** ACQ, Asthma Control Questionnaire scores; AQLQ, Asthma related Quality of Life scores; BMI, Body Mass Index; FeNO, fraction of exhaled Nitric oxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ISWT, incremental shuttle walk test; OCS, oral corticosteroids; SABA, short-acting beta agonist; SD, standard deviation; SNOT-22, Sino-Nasal Outcome Test.

and 3. During the 12 months follow-up, three patients were admitted to HAPR.

3.4. Pulmonary rehabilitation at high-altitude versus sea-level

Patients receiving HAPR had higher improvement in AQLQ (0.92, $p < 0.001$), ACQ (−0.87, $p < 0.001$), SNOT (−0.86, $p < 0.001$) and lung function (%pred FEV_1 3.4, $p = 0.014$) compared to the LAPR group (Table 4), adjusted for potential baseline confounders. One year after treatment there was still a higher improvement in AQLQ (−0.82, $p = 0.001$) and ACQ (−0.69, $p = 0.008$) in the HAPR group compared to the LAPR group. Fewer asthma exacerbations occurred during treatment at high-altitude compared to sea-level (OR = −1.45, $P < 0.001$) although no difference were observed between the groups in the number of OCS bursts or hospitalizations during follow-up. Repeating the analyses taking into account the number of OCS burst or hospitalization in the previous year leads to comparable results. No differences could be observed between treatment groups with respect to ICS-dose or walking distance during the ISWT.

3.5. Sub-group analysis in patients with OCS-dependent asthma

Within the group of patients with OCS- dependent asthma at entry ($n = 65$), a higher reduction in OCS dose was found in the HAPR compared to the LAPR group (Unadjusted linear regression analysis ($n = 65$):-5.29 mg, $p = 0.003$). Five patients with OCS-dependent asthma at entry started mepolizumab during follow-up and were excluded from further analysis regarding reduction of OCS dose. One year after treatment a significant lower OCS dose was found in the HAPR group compared to the LAPR group (Unadjusted Odds Ratio ($n = 60$): −1.67, $p = 0.003$) (Table 5).

4. Discussion

In this longitudinal observational study we compared the results of a multidisciplinary pulmonary rehabilitation program at high-altitude (HAPR) to a comparable treatment program at sea-level (LAPR) in adults with severe refractory asthma. Randomization was not feasible leading to two different study populations. The HAPR-group was more often atopic and characterized by younger age, lower percentage ex-smoker, higher symptom expression, poor quality of life and higher medication requirement compared to the LAPR-group. After adjustment for differences in baseline characteristics, HAPR showed larger effects in asthma outcome parameters compared to LAPR and on the long run the improvement of patient reported symptoms and a reduction in chronic OCS-use sustained longer in the HAPR group. One year after HAPR clinical relevant improvements could still be demonstrated for patient reported outcomes compared to baseline. This could not be demonstrated in the LAPR-group.

Our study was based on the Dutch situation in which two regular treatment options for patients with severe refractory asthma were compared. Randomization failed and patients treated at high-altitude were significantly younger and had a higher ACQ at entry. These are all characteristics that are known predictors of a higher beneficial treatment effect at high-altitude as shown by Hashimoto et al. [16]. The majority of the patients with OCS-dependent asthma treated at high-altitude were able to reduce their OCS-dose even 1 year after treatment while maintaining the level of asthma control. Our study shows that pulmonary rehabilitation is effective extending previous studies in patients with asthma [6,26–30]. There is only one study comparing HAPR to LAPR in a RCT investigating the effects of a short (3-week) HAPR (3100 m) vs. LAPR (710 m). There were similar improvements in asthma control at both low and high altitude. Greater improvements of exercise capacity and airway inflammation were found in the HAPR-group and, after controlling for relevant confounders, it was suggested that patients with higher baseline PEF-variability values benefit more from HAPR [16]. This study was performed in Kyrgyzstan at very different "low"- and "high" altitudes and the PR-period was only 3 weeks, so comparison to our results is hampered. We also found an improvement in FEV_1 after HAPR which was not present in the sea-level group which is in concordance with a previous meta-analysis [9]. Interestingly, HAPR leads to an increase in patient reported asthma related quality of life and asthma control, which effects were still present 12 months after treatment extending two previous studies in a

Table 2
Clinical and functional changes within the **high-altitude group**.

	Number (*n*)	Baseline	12 weeks	Difference (SE)	p-value
Patient reported symptoms					
AQLQ-score	93	3.9 ± 0.9	5.8 ± 0.9	1.96 (0.11)	***<0.001***
ACQ-score	93	3.1 ± 0.9	1.2 ± 1.0	−1.91 (0.12)	***<0.001***
SNOT-22 score	91	2.3 ± 0.8	1.2 ± 0.9	−1.07 (0.11)	***<0.001***
Medical consumption					
Chronic use of OCS (*n*)		48 out of 93	20 out of 93		***<0.001***
OCS dose (mg)[1]	48	17.9 ± 15.7	5.4 ± 7.1	−12.58 (1.75)	***<0.001***
ICS dose (μg/day)	93	1600 (1200–3200)	800 (800–2800)	−116.1 (122.7)	0.35
Functional characteristics					
FEV_1 (% pred)	93	86 ± 20	90 ± 20	3.98 (0.70)	***<0.001***
distance ISWT (m)	91	418 ± 224	575 ± 261	156.9 (20.1)	***<0.001***
	Number (*n*)	**Baseline**	**64 weeks**	**Difference (SE)**	**p-value**
Patient reported symptoms					
AQLQ-score	79	3.9 ± 1.0	4.9 ± 1.2	1.02 (0.12)	***<0.001***
ACQ-score	79	3.1 ± 0.9	2.2 ± 1.3	−0.91 (0.14)	***<0.001***
SNOT-22 score	78	2.3 ± 0.8	1.9 ± 1.0	−0.39 (0.10)	***<0.001***
Medical consumption					
Chronic use of OCS (*n*)		46 out of 86	25 out of 86		***<0.001***
OCS dose (mg)[1]	46	18.3 ± 16.0	7.5 ± 10.1	−10.80 (1.89)	***<0.001***
OCS bursts <3 months[#]	70	2 [1–3]	0 (0–2)	−0.49 (0.16)	***0.003***
Asthma related hospitalizations < 3 months[#]	78	0 (0–1)	0 (0–0)	−0.13 (0.09)	0.17
Functional characteristics					
FEV_1 (% pred)	79	86 ± 21	89 ± 22	3.2 (1.1)	***0.003***
distance ISWT (m)	79	425 ± 214	561 ± 263	135.7 (24.5)	**<0.001**
	Number (*n*)	**12 weeks**	**64 weeks**	**Difference (SE)**	**p-value**
Patient reported symptoms					
AQLQ-score	79	5.8 ± 0.9	4.9 ± 1.2	−0.87 (0.11)	***<0.001***
ACQ-score	79	1.3 ± 1.0	2.2 ± 1.3	0.90 (0.15)	***<0.001***
SNOT-22 score	78	1.2 ± 0.9	1.9 ± 1.0	0.73 (0.12)	***<0.001***
Medical consumption					
Chronic use of OCS (*n*)		20 out of 86	25 out of 86		0.06
OCS dose (mg)[1]	46	5.0 ± 7.1	7.5 ± 10.1	2.54 (1.01)	***0.01***
Functional characteristics					
FEV_1 (% pred)	79	90 ± 21	89 ± 22	−1.1 (1.0)	0.27
distance ISWT (m)	79	578 ± 259	561 ± 263	−16.9 (16.7)	0.31

Data expressed as mean/SD.
[#] Median/interquartile range (IQR).
[1] Mean dose within the group of patients with OCS dependent asthma at entry.

comparable population [8,17].

The strength of our study is that it is the first study comparing short and long-term effects of HAPR with a comparable treatment at sea-level. Only patients with severe refractory asthma were included. These patients were referred by their pulmonologist for treatment in a tertiary asthma clinic since they did not sufficiently respond to regular maximal medical and non-medical treatment (GINA step 4).

Randomization of the study population was not sufficiently possible, potentially leading in baseline differences in population characteristics. As a result, differences in change in outcome may be influenced by differences at baseline. Treatment allocation was based on the preference of the referring pulmonologist and the patients preference. Within the HAPR group 50% of the population underwent previous treatment at high-altitude while none of the patients treated at sea-level underwent previous treatment at sea-level in the 6 year prior to the study. It is unknown to what extent patient experiences from previous treatment leads to selection bias and have influenced our results. Although treatment was standardized using the same protocol, both centers used a different pre-assessment procedure leading to a higher drop out in the sea-level group and possibly to selection bias.

Furthermore, follow-up treatment was standard care by their referring pulmonologist, indicated by (inter) national asthma guidelines, which implies no differences in treatment during follow-up between the two treatment groups. Finally, biologicals were more frequently used in the high-altitude group and mepolizumab became available during the study which may have influenced our results, especially when analyzing the long-term effect in patients with OCS-dependent asthma. Repeating the primary analysis (patient reported outcomes) without patients using a biological did not lead to other results (data not shown).

There are several potential explanations for the observed effect of HAPR. First, environmental trigger of asthma may differ between regions. All included patients were living in The Netherlands and moved to the Alps, an area with considerably less air pollution [31], which can ameliorate the bronchial hyperresponsiveness and type 2 inflammation and therefore asthma control. It has also been hypothesized that a high-altitude environment is characterized by lower concentrations of house dust mite, molds and tree/grass pollen due to decreased humidity and climatic differences compared to sea-level. However, Grafetstatter et al. [32] did not find lower house dust mite allergens levels with rising altitude in alpine regions suggesting that differences in house dust mite exposure between study groups cannot explain the results of our study. Rijssenbeek et al. [8] showed that the benefit of HAPR was comparable between patients with and without house dust mite sensitization, in a population of adults with severe refractory asthma. Second, psychological factors may play a role. The high-altitude group is away from worries and work or family-related conflicts leading to a reduced psychological stress level [33]. Psychological stress factors have been shown to increase maladaptive coping styles in patients with severe asthma [34]. Finally, patients receiving HAPR had a larger improvement in lung function, less asthma exacerbation and they were able to lower

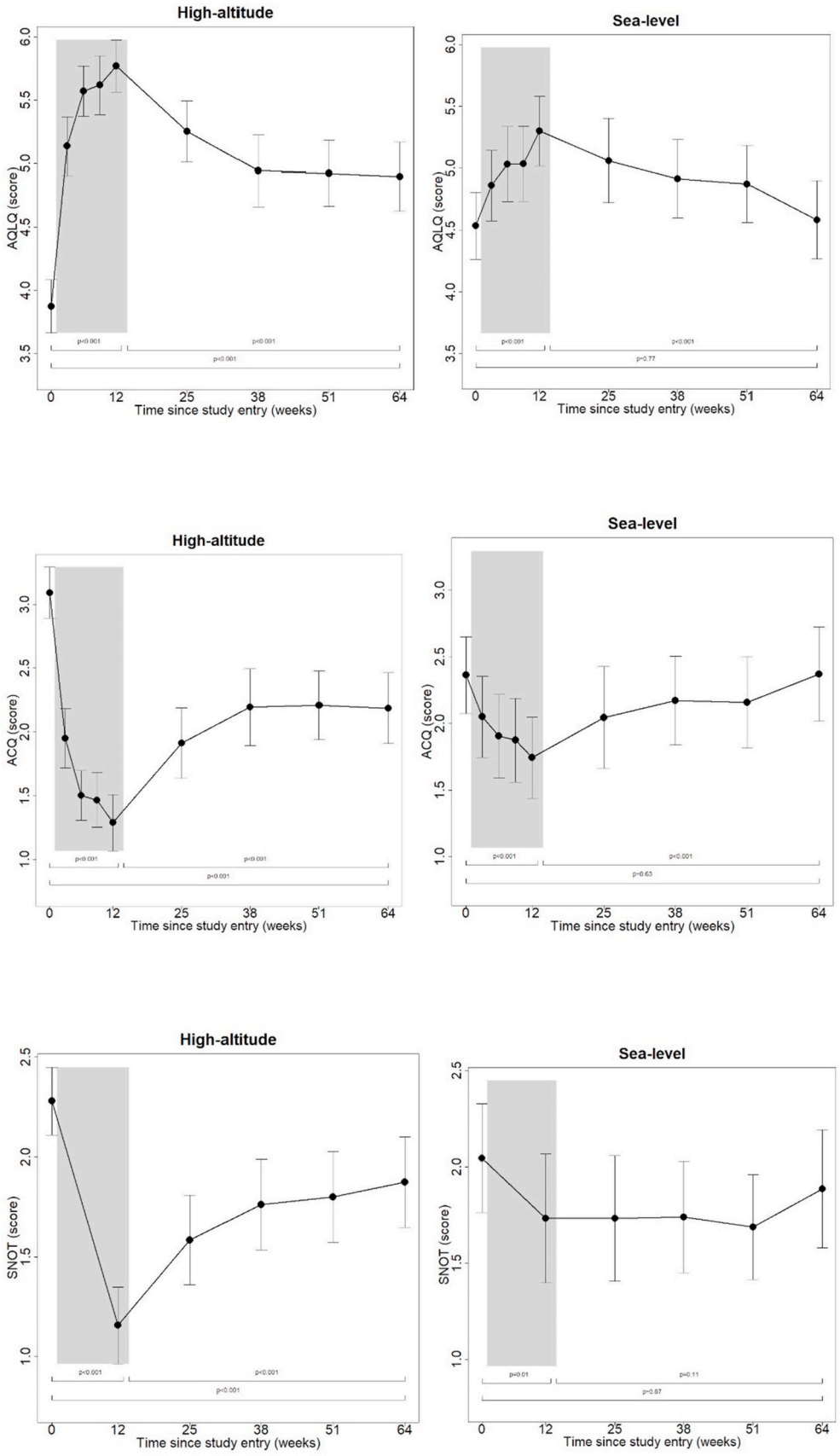

Fig. 2. AQLQ-score (a), ACQ- (b) and SNOT (c) presented as mean/standard deviation during asthma rehabilitation (gray) up to 12 months after for high altitude (left) and sea-level (right) populations.

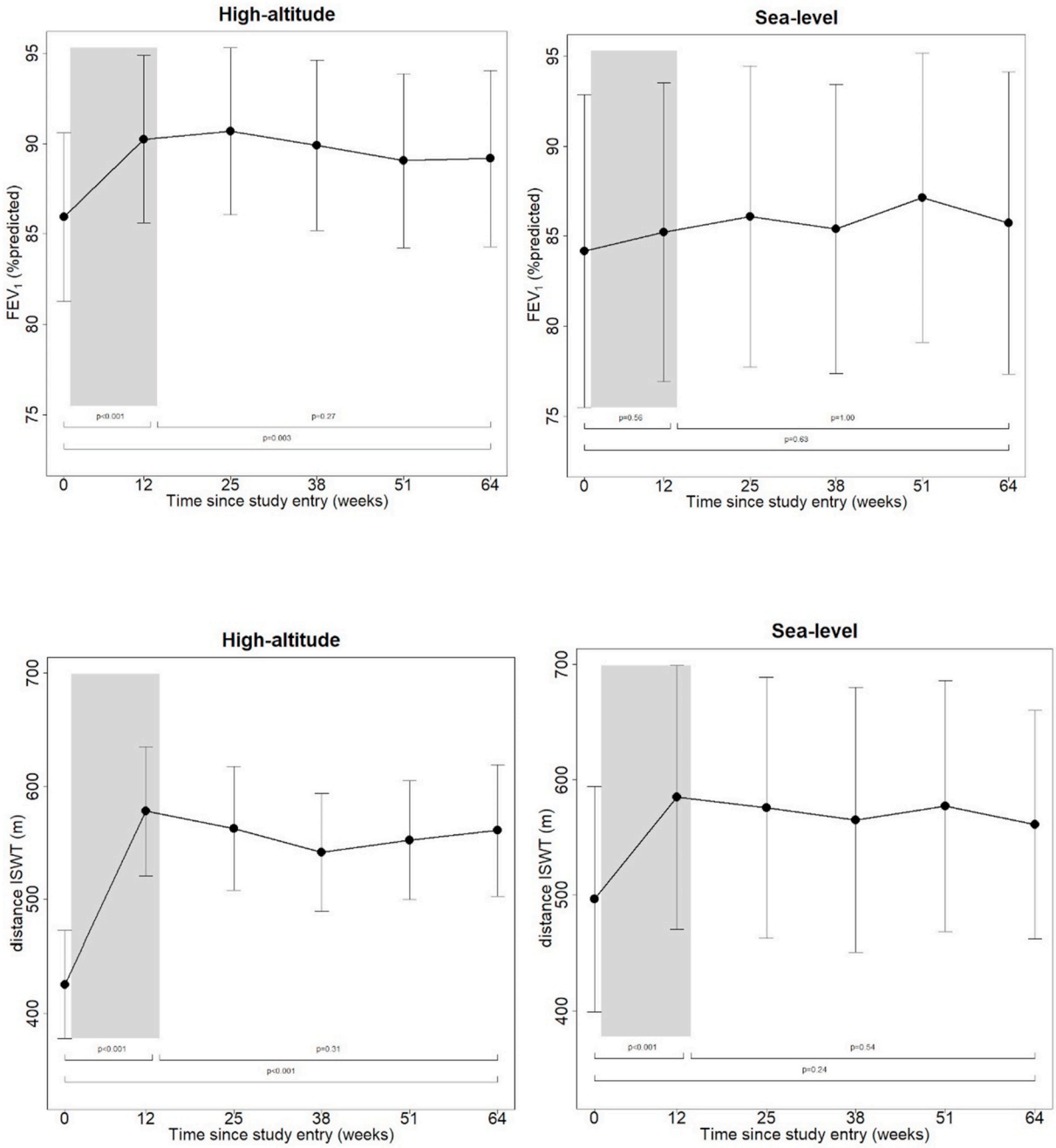

Fig. 3. FEV1 (% predicted) (a) and distance ISWT (m) (b) presented as mean/standard deviation before and after asthma rehabilitation (gray) up to 12 months after for high-altitude (left) and sea-level (right) populations.

the OCS dose compared to the sea-level group suggesting that the high-altitude climate may have a direct physiological and anti-inflammatory effect. This has been also observed in previous studies, treatment at high altitude resulted in reduced bronchial hyperresponsiveness, lower total blood eosinophils and lower eosinophilic cation protein [8,12,13,35,36]. Recently, during HAPR a reduction in systemic activation of T cell, ILC2 and monocytes was found suggesting that type 2 inflammation in patients with asthma was reduced [37].

What are the clinical implications of our study? Our study indicates that adults with asthma benefit from an individual personalized pulmonary rehabilitation program extending previous studies [38,39]. Despite new treatment options such as biologicals, there is still a group of severe asthma patients who do not sufficiently respond to treatment with medication including biologicals [40]. In patients with OCS-dependent asthma sustained effects in OCS-dose were found 1 year after HAPR compared to LAPR. Despite our data must be interpreted with caution since the low number of patients with OCS-dependent asthma in the sea-level group, it might be speculated that HAPR has comparable effects on OCS use as biologicals. However, for the individual patient the best treatment option needs to be determined based on future studies investigating the underlying mechanisms for improvement.

In conclusion, a 12-week inpatient pulmonary rehabilitation program is followed by improvement in patient reported parameters at both high-altitude and sea-level. HAPR showed a higher degree of improvement in asthma outcome parameters after a 12-week rehabilitation program compared to LAPR, after 12 months the improvement in

Table 3
Clinical and functional changes within the **sea-level group**.

	Number (*n*)	Baseline	12 weeks	Difference (SE)	p-value
Patient reported symptoms					
AQLQ-score	44	4.5 ± 0.9	5.3 ± 0.9	0.82 (0.10)	***<0.001***
ACQ-score	42	2.4 ± 0.9	1.8 ± 0.9	−0.60 (0.11)	***<0.001***
SNOT-22 score	33	2.0 ± 0.8	1.8 ± 0.9	−0.24 (0.09)	***0.01***
Medical consumption					
Chronic use of OCS (*n*)		17 out of 45	14 out of 45		0.25
OCS dose (mg)[1]	17	12.4 ± 8.0	8.5 ± 5.4	−3.92 (1.63)	***0.02***
ICS dose (μg/day)	45	1600 (800–2400)	1600 (1200–2500)	71 (139)	0.61
Functional characteristic					
FEV_1 (% pred)	44	81 ± 26	81 ± 21	0.49 (0.84)	0.56
distance ISWT (m)	41	492 ± 305	549 ± 324	57.6 (16.0)	***<0.001***
	Number (*n*)	**Baseline**	**64 weeks**	**Difference (SE)**	**p-value**
Patient reported symptoms					
AQLQ-score	35	4.5 ± 0.8	4.6 ± 1.0	0.05 (0.16)	0.77
ACQ-score	35	2.4 ± 0.9	2.4 ± 1.0	0.08 (0.17)	0.63
SNOT-22 score	27	2.0 ± 0.7	2.0 ± 1.0	−0.03 (0.17)	0.87
Medical consumption					
Chronic use of OCS (n/%)		14 out of 36	12 out of 36		0.50
OCS dose (mg)[1]	14	13.9 ± 8.4	12.7 ± 9.4	−1.25 (1.75)	0.48
OCS bursts <3 months[#]	33	1 (0–2)	0 (0–2)	−0.16 (0.18)	0.37
Asthma related hospitalizations < 3 months[#]	35	0 (0–1)	0 (0–0)	0.04 (0.09)	0.62
Functional characteristics					
FEV_1 (% pred)	37	84 ± 26	85 ± 26	1.0 (2.1)	0.63
distance ISWT (m)	34	496 ± 290	539 ± 282	42.4 (35.6)	0.24
	Number (*n*)	**12 weeks**	**64 weeks**	**Difference (SE)**	
Patient reported symptoms					
AQLQ-score	37	5.3 ± 0.9	4.6 ± 1.0	−0.72 (0.13)	***<0.001***
ACQ-score	35	1.8 ± 0.9	2.4 ± 1.0	0.62 (0.14)	***<0.001***
SNOT-22 score	27	1.8 ± 0.9	2.0 ± 1.0	0.24 (0.15)	0.11
Medical consumption					
Chronic use of OCS (n/%)		12 out of 36	12 out of 36		1.00
OCS dose (mg)[1]	14	9.1 ± 5.2	12.7 ± 9.4	3.57 (1.77)	0.05
Functional characteristics					
FEV_1 (% pred)	37	85 ± 25	85 ± 26	0.0 (2.2)	1.00
distance ISWT (m)	34	559 ± 314	539 ± 282	−20.0 (32.9)	0.54

Data expressed as mean/SD.
[#] Median/interquartile range (IQR).
[1] Mean dose within the group of patients with OCS dependent asthma at entry.

Table 4
Comparison short and long-term effectiveness between pulmonary rehabilitation at high-altitude and pulmonary rehabilitation at sea-level.

Treatment effect (12 weeks after entry)		UNADJUSTED			ADJUSTED VALUES		
	Number (*n*)	**Coefficient**	**SE**	**p-value**	**Coefficient**	**SE**	**p-value**
Patient reported symptoms							
AQLQ-score	137	0.81	0.16	<0.001	0.92	0.18	***<0.001***
ACQ-score	135	−0.83	0.16	<0.001	−0.87	0.20	***<0.001***
SNOT-22 score	124	−0.70	0.17	<0.001	−0.86	0.19	***<0.001***
Medical consumption							
ICS dose (μg/day)	138	4.47	182	0.979	13.14	206.79	0.95
Number of asthma exacerbations during treatment[1]	138	−1.16	0.30	<0.001	−1.45	0.35	**<0.001**
Functional characteristics							
FEV_1 (% pred)	137	3.70	1.17	0.002	3.35	1.35	***0.014***
distance ISWT (m)	132	91.95	31.86	0.005	46.01	36.37	0.21
Long-term effect (64 weeks after entry)							
Patient reported symptoms							
AQLQ-score	116	0.79	0.20	<0.001	0.82	0.23	***0.001***
ACQ-score	114	−0.68	0.24	0.005	−0.69	0.26	***0.008***
SNOT-22 score	105	−0.29	0.20	0.14	−0.30	0.22	0.18
Medical consumption							
Number of OCS bursts < 3 months	91	−0.15	0.23	0.52	−0.08	0.28	0.77
Number of asthma related hospitalizations < 3 months	97	−0.13	0.40	0.74	−0.17	0.46	0.71
Functional characteristics							
FEV_1 (% pred)	114	2.30	2.15	0.288	1.46	2.40	0.54
distance ISWT (m)	106	76	43.6	0.084	42.0	49.6	0.40

Footnote Table 4: Values from linear regression analysis (ANCOVA) between pulmonary rehabilitation at high-altitude and treatment at level in each outcome. The unadjusted model included the baseline value at 12 weeks or at 64 weeks as covariate. The adjusted model included the outcome at 12 weeks or 64 weeks and as covariate the baseline value, corrected for age, atopy, smoking history, BMI and gender.[1] Results from linear regression analysis using an ordinal model.
[1] Calculated using an ordinal multivariable model.

Table 5
Subgroup analysis. Comparison of short (12-weeks after entry) and long-term effectiveness (64-weeks after entry) between pulmonary rehabilitation at high-altitude and sea-level in patients with OCS-dependent asthma.

Treatment effect		UNADJUSTED		
	Number (*n*)	Coefficient	SE	p-value
OCS-dose (mg)	65	−5.29	1.73	0.003
Long-term effect				
OCS-dose (mg)[1]	60	−1.67	0.57	0.003

Footnote Table 4: values form unadjusted linear regression.
[1] Calculated using a crude odds ratio model.

chronic OCS-use and patient reported symptoms sustained. Which factors are associated with this observed effect still needs to be elucidated. To that end, further studies should focus on understanding which mechanisms could explain the effect of pulmonary rehabilitation at high-altitude in a population of adults with severe asthma.

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Author contributions

LR, DV, EW, JL conceived and designed the study. LR, DV, SN recruited the subjects and/or collected the data. SN, EK, LP, HH, DH, JL analyzed and interpreted the data. SN drafted the manuscript. All authors were responsible for writing the manuscript and final approval of the version to be published.

CRediT authorship contribution statement

S.B. de Nijs: recruited the subjects and/or collected the data, analyzed and interpreted the data, Formal analysis, All authors were responsible for writing the manuscript and final approval of the version to be published. **E.J.M. Krop:** analyzed and interpreted the data. , Formal analysis, All authors were responsible for writing the manuscript and final approval of the version to be published. **L.H. Rijssenbeek-Nouwens:** conceived and designed the study. recruited the subjects and/or collected the data. All authors were responsible for writing the manuscript and final approval of the version to be published. **D. de Vries:** conceived and designed the study. recruited the subjects and/or collected the data. All authors were responsible for writing the manuscript and final approval of the version to be published. **E.J.M. Weersink:** conceived and designed the study. All authors were responsible for writing the manuscript and final approval of the version to be published. **H.G.M. Heijerman:** analyzed and interpreted the data, Formal analysis, All authors were responsible for writing the manuscript and final approval of the version to be published.All authors were responsible for writing the manuscript and final approval of the version to be published. **D.J.J. Heederik:** analyzed and interpreted the data, Formal analysis, Writing - original draft, drafted the manuscript, All authors were responsible for writing the manuscript and final approval of the version to be published. **J.-W.J. Lammers:** conceived and designed the study. analyzed and interpreted the data. , Formal analysis, All authors were responsible for writing the manuscript and final approval of the version to be published.

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