Lung function improvement and airways inflammation reduction in asthmatic children after a rehabilitation program at moderate altitude

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Abstract

Background: Rehabilitational programs at moderate altitude (1500-2500 m) showed improvement of lung function and reduction in airways inflammation in asthmatic adults. Allergen avoidance was postulated as the major cause of these improvements.

Methods: Spirometries of 344 and fractional exhaled nitric oxide measurements (FeNO) of 124 asthmatic children and adolescents, staying in a rehabilitation hospital in Davos (1590 m) with at least 14 days between admission and discharge, were analyzed in association with atopic sensitization (skin-prick testing and/or specific IgE), level of asthma control, and inhalative corticosteroid (ICS) dose.

Results: Pulmonary conditions improved significantly on average during the sojourn. Uncontrolled asthmatics benefited most with an absolute increase in predicted FEV_1, MEF_{25}, and MEF_{75} of 7.7%, 9.9%, and 12.7%, respectively ($P < .001$). FeNO decreased by 36.9 ppb for uncontrolled, by 26.9 ppb for partly controlled, and by 11.8 ppb for controlled asthmatics. In uncontrolled subjects, pulmonary improvement was comparable between patients with and without house dust mites (HDM) sensitization. Pulmonary improvements of pollen-sensitized patients were not dependent on the season of the sojourn. For the group with constant ICS level, the absolute increase in FEV_1 was 4.9% ($P < .001$) with a FeNO decreased by 32.7 ppb ($P < .001$). When the ICS dose was elevated by one GINA level, the absolute increase in FEV_1 was slightly higher (6.6%, $P < .001$), with a FeNO decrease of 31.4 ppb ($P < .001$).

Conclusion: Inpatient rehabilitation at moderate altitude improved pulmonary conditions in asthmatic children and adolescents independent of sensitization status to HDM or pollen. A positive effect was also observed in patients without change in medication.

KEYWORDS
adolescents, asthma, children, Davos, Forced expiratory volume in 1 second, Fractional exhaled nitric oxide, inflammation, pulmonary function, rehabilitation

Abbreviations: GINA, Global Initiative for Asthma; HDM, house dust mites; HGK, Hochgebirgsklinik; FEV_1, Forced expiratory volume in 1 second; MEF_{25}, maximum expiratory flow at 25%; MEF_{75}, maximum expiratory flow at 75%; FeNO, Fractional exhaled nitric oxide; ICS, inhaled corticosteroid; LABA, long-acting beta-agonists; %pred, Percent predicted; ppb, Particles per billion.

1 | INTRODUCTION

Asthma in children and adolescents is a serious health impairment.[1] Prevalence rates of asthma vary, according to countries[2]: due to differences in the definition of asthma,[3] due to inhomogeneous study populations, and most likely due to environmental factors. Asthma is frequently associated with comorbidities like obesity and atopic diseases such as atopic dermatitis.[4] In children and adolescents, asthma is often accompanied by psychosocial problems, poorer academic-, and professional performance and negatively affects the quality of life of the family.[5,6] The GINA guidelines are effective for most asthmatic patients.[7] However, in patients in which the controlled level of asthma is hard to maintain,[8-10] a broader approach is needed to address all interfering comorbidities and concomitants of the patient. A feasible option is a multidisciplinatory-rehabilitational, inpatient setting.[11] A previous study of an inpatient rehabilitation program showed improvements of mid-expiratory flow und airway inflammation of forty-eight asthmatic children sensitized to HDM at moderate altitude.[12]

In our study, we investigated the overall effect of an inpatient rehabilitation program at the Hochgebirgsklinik Davos on pulmonary function and airway inflammation of asthmatic children and adolescents. Allergic sensitization, level of asthma control, and level of ICS dosage were included in our association study.

The hospital has its expertise in a multidisciplinatory-rehabilitational treatment for chronic respiratory, skin, and allergic diseases and is located 1590 m above sea level in the Swiss Alps. In Davos, environmental investigations showed a very low indoor HDM concentration[13] combined with low outdoor pollen concentration,[14] especially when compared to lowland areas. Patients included in this investigation originated all from German lowlands. German pension insurance regulations entitle children and adolescents with asthma and/or atopic eczema for a minimum stay of 21 days in a specialized rehabilitation clinic every 5 years. The rehabilitation program provided by the hospital is based on the GINA guidelines and the Swiss recommendation for treatment of obstructive pulmonary diseases in childhood[15,16] and consists of multiple parts. The first part is the diagnosis confirmation within the first 2-3 days including differential blood, standard specific IgE panel, standard prick test, spirometry, exhaled NO test, and/or a methacholine challenge. If required, the patient will receive an adjustment of medication according to the clinical course in the last twelve months and during follow-up during the rehabilitation program. The second part of the rehabilitation program consists of patients and/or parents educational lessons about disease theory, management and prevention, breathing techniques, inhaler use, nutrition, etc. Thirdly, physical in- and outdoor activities are a daily routine for all patients to improve their overall fitness level. For selected patients, psychosocial therapy (psychotherapy, ergotherapy) is performed if necessary.

2 | METHODS

2.1 | Study population

Retrospective data analysis of 134 female and 210 male rehabilitation patients (4-19 years of age; mean 10.5 years) staying at the Hochgebirgsklinik Davos during January 2012 until October 2013 was performed. Inclusion criteria were a physician diagnosis of asthma or current asthma symptoms and two spirometries, with at least 14 days between admission and discharge.

2.2 | Questionnaire

Prior to admission, patients or their parents answered a questionnaire about their clinical history. Patients were classified into three asthma control level groups (controlled, partly controlled, and uncontrolled) according to GINA 2016 guidelines.

2.3 | Pulmonary function

Pulmonary function was assessed by spirometry (Master Screen Body, Jäger) for controlled (n = 61), partly controlled (n = 155), and uncontrolled asthma patients (n = 128). Outcome parameters were the forced expiratory volume in 1 second (FEV_1), maximum expiratory flow at 25% (MEF_{25}) and 75% (MEF_{75}) compared between admission and discharge. The differences between admission and discharge are reported as absolute changes from the percent predicted value.

2.4 | Airway inflammation

Measurement of fractional exhaled nitric oxide (FeNO) was assessed as airway inflammatory marker [15] for controlled (n = 24), partly controlled (n = 48), and uncontrolled asthma patients (n = 52). Values below 20 particles per billion (ppb) were defined as normal.[17] One test consisted of two FeNO measurements of which the average value was taken as the result.

2.5 | Sensitization status

Patients with a positive skin-prick test and/or specific serum IgE level of >0.35 kU/L to HDM or pollen (hazel, ash, alder, birch, common timothy, ragweed, mugwort) were defined as sensitized to HDM or, respectively, to pollen.

2.6 | Medication

Patients were separated into a group without ICS and into three groups (low, medium, or high dose) with ICS at admission according to GINA guidelines. Comparison between admission and discharge resulted in six groups: no ICS, ICS lowered 2 or more levels, ICS lowered 1 level, ICS level constant, ICS increased 1 level, and ICS increased 2 or more levels. Inhalative long-acting b2-agonists (LABA) are administered combined with corticosteroids; therefore, to assess the effect of an additional b2-agonist treatment, we split the group, in which the ICS level remained constant during the stay, into 4 subgroups: no additional LABA at admission and discharge (no LABA), LABA added shortly after admission (added LABA), LABA present prior to admission and present at discharge (constant LABA). LABA were stopped in only one patient within this group (stopped LABA).

2.7 | Statistics

Changes of pulmonary function and airway inflammation were analyzed by paired *t* test and Wilcoxon signed-rank test for paired samples. Differences between groups were analyzed with *t* tests and Mann-Whitney *U* tests. Stratification and sensitivity analyses were performed in order to take into account the following factors: level of asthma control, gender, age, sensitization, history of atopic dermatitis, duration of sojourn, season of the rehabilitation. *P* -values < .05 were considered statistically significant. Stata was used for analysis.

2.8 | Ethics

Informed consent for retrospective data analysis was waived by institutional and governmental ethics boards.

3 | RESULTS

3.1 | Patient data

Among the 344 asthmatic patients, 17.7% were defined as controlled, 45.1% as partly controlled, and 37.2% as uncontrolled (Table 1). About 60% of the patients had a history of atopic dermatitis. Sensitization to HDM was observed in 75.6%, to pollen in 78.8% of the patients.

3.2 | Impaired pulmonary function and present airway inflammation at admission

Pulmonary function parameters at admission were significantly below their predicted values on average. Pathologic FeNO (>20 ppb) was observed in 97 of 124 (78.2%) patients. Impaired pulmonary function and increased FeNO were even present in patients with the allegedly best condition—controlled asthma. Mean FEV_1 at admission ranged from 89.4% [95% confidence interval (CI):86.7%-92.2%] in patients with uncontrolled asthma to 96.8% [95% CI: 93.8%-99.9%] in patients with controlled asthma (Figure 1A). Mean MEF_{25} at admission ranged from 75.7% [69.9%-81.4%] in patients with uncontrolled asthma to 93.6% [95% CI: 86.0%-101.3%] in patients with controlled asthma (Figure 1B). Mean MEF_{75} at admission ranged from 76.5% [95% CI: 77.0%-84.5%] in patients with uncontrolled asthma to 93.1% [95% CI: 88.2%-98.1%] in patients with controlled asthma (Figure 1C). Median FeNO at admission ranged from 27.6 ppb in patients with controlled asthma to 49.9 ppb in patients with uncontrolled asthma (Figure 1D).

TABLE 1 Characteristics of the study population

	FEV_1, MEF_{75}, MEF_{25}, n = 344 (%)	FeNO, n = 124 (%)
Female	134 (39.0)	51 (41.1)
Age (y)		
4-6	78 (22.7)	
7-10	93 (28.5)	
11-15	118 (34.3)	
16-19	50 (14.5)	
Level of asthma control		
Controlled	61 (17.7)	24 (19.4)
Partly controlled	155 (45.1)	48 (38.7)
Uncontrolled	128 (37.2)	52 (41.9)
Sensitized to		
HDM	260 (75.6)	104 (83.9)
Pollen	271 (78.8)	109 (87.9)
Atopic dermatitis	200 (58.1)	71 (57.1)

3.3 | Improved lung function parameters at discharge

Forced expiratory volume in 1 second and MEF_{75} improved in all patients. The increase in MEF_{25} was statistically significant for uncontrolled, but not for controlled or partly controlled subjects. Controlled individuals showed FEV_1 and MEF_{75} values close to the 100% predicted benchmark at discharge. The improvement of all three outcome parameters was more distinct in the uncontrolled group, absolute difference of FEV_1: 7.7%, *P* < .001, MEF_{75}:12.7%, *P* < .001, and MEF_{25}:9.9%, *P* < .001 (Figure 1A-C).

3.4 | Reduced airway inflammation at discharge

Airway inflammation significantly reduced in all three asthma control groups. Reduced FeNO was observed in 114 of 124 patients. From 97 patients admitted with pathologic FeNO, 68 showed normalized values (<20 ppb) at discharge. Median FeNO reduced by almost 12 ppb, *P* < .001 for the controlled, by almost 27 ppb, *P* < .001 for the partly controlled and by almost 36 ppb, *P* < .001 for the uncontrolled group (Figure 1D).

3.5 | Similar rehabilitation effect among uncontrolled asthmatics with house dust mite or pollen sensitization

To evaluate a possible effect of the reduced allergen exposure due to the moderate altitude, first we stratified the patients in two groups, with HDM-sensitization and without HDM-sensitization. Uncontrolled and HDM-sensitized patients started rehabilitation with slightly less favorable pulmonary conditions (Figure 2). Their pulmonary improvements did not differ from those of non-HDM-sensitized patients and ranged at the same margin. A similar pattern was observed regarding airway inflammation. FeNO was reduced in patients with HDM-sensitization (−32.4 ppb, *P* < .001) as well as in non-HDM-sensitized patients (−42.4 ppb, *P* < .028). While non-HDM-sensitized patients started with slightly higher FeNO, the improvement between these groups did not differ significantly. Similarly, improvements were observed for uncontrolled and pollen-sensitized patients staying in autumn/winter and for those staying in the spring/summer. However, the difference of improvement between these two groups was not significant (data not shown).

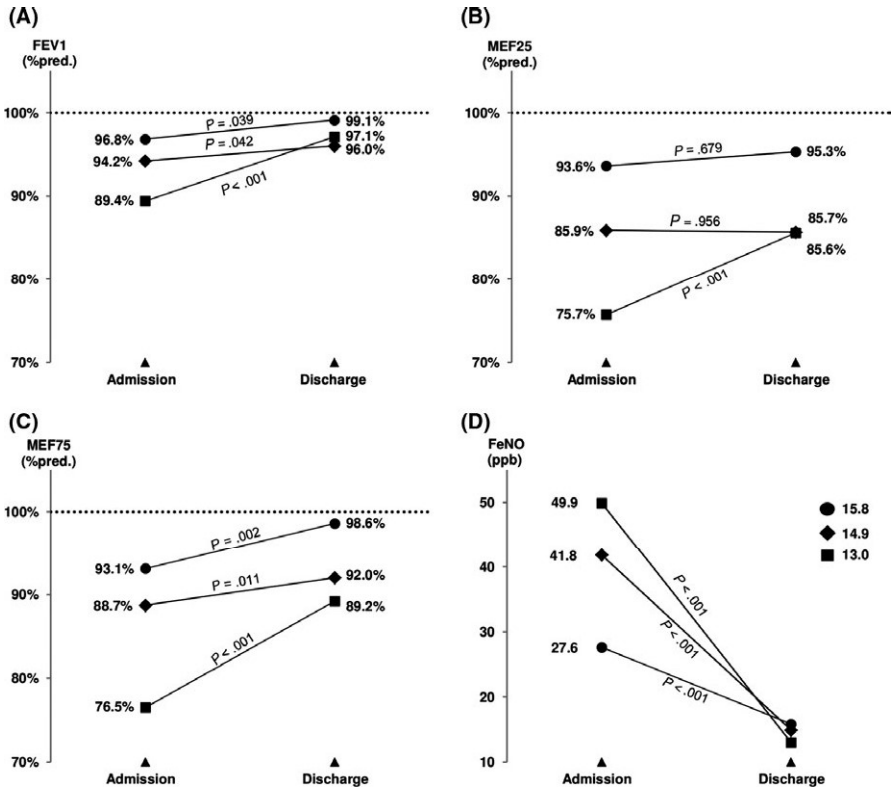

FIGURE 1 Pulmonary function and airway inflammation at admission and discharge—stratified for level of asthma control. A, B, C, Pulmonary function (n = 344) is reported by mean values. Circles show patients with controlled asthma (n = 61). *P* –value = comparison between discharge and admission, by *t* test for paired samples. Diamonds show patients with partly controlled asthma (n = 155). Squares show patients with uncontrolled asthma (n = 128). D, Airway inflammation (n = 124) is reported by median values. *P* –value = comparison between discharge and admission, by Wilcoxon signed-rank test. Circles show patients with controlled asthma (n = 24). Diamonds show patients with partly controlled asthma (n = 48). Squares show patients with uncontrolled asthma (n = 52)

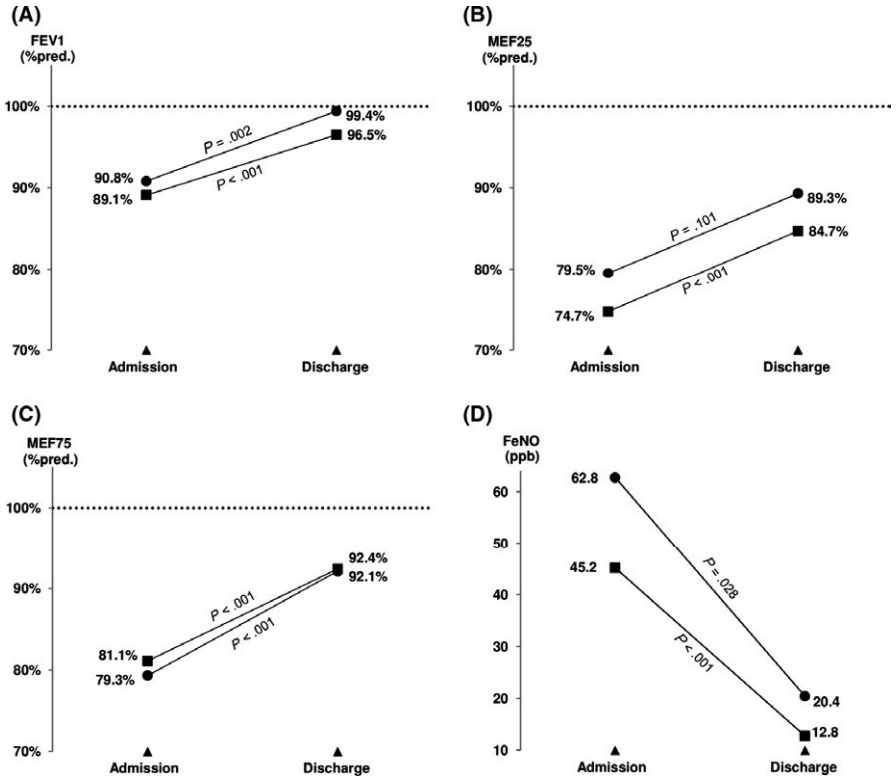

FIGURE 2 Pulmonary function and airway inflammation at admission and discharge of patients with uncontrolled asthma—stratified for house dust mite sensitization. A, B, C, Pulmonary function (n = 128) is reported by mean values. *P* -value = comparison between discharge and admission, by *t* test for paired samples. Circles show non-sensitized patients (n = 26). Squares show sensitized patients (n = 102). D, Airway inflammation (n = 52) is reported by median values. *P* -value = comparison between discharge and admission, by Wilcoxon signed-rank test. Circles show non-sensitized patients (n = 6). Squares show sensitized patients (n = 46)

3.6 | Atopic dermatitis does not influence the rehabilitation effect

Stratified analyses among patients with atopic dermatitis and among those without the disease showed that both groups benefited significantly from the sojourn. The difference was slightly bigger among patients with atopic dermatitis considering FEV_1 (patients with atopic dermatitis: +4.7%, $P < .001$ and patients without atopic dermatitis: +3.3%, $P = .003$) and slightly smaller considering FeNO (patients with atopic dermatitis: −17.6 ppb, $P < .001$ and patients without

atopic dermatitis: −29 ppb, $P < .001$) (Figure 3), even though the differences of improvement between patients with and without atopic dermatitis were not significant.

3.7 | Influence of the medication on the outcome

In the group whose inhaled corticosteroid dose was elevated by one GINA-ICS level, significant improvements (FEV_1:+6.6%, $P < .001$/FeNO:−31.4 ppb, $P < .001$) were observed (Table 2). Upon elevation of two or more GINA-ICS-levels, the lung function improvements were even higher (FEV_1:+7.2%, $P = .002$/FeNO:−38.5 ppb, $P = .002$). Patients with constant GINA-ICS level throughout the sojourn showed also increased FEV_1:+4.9%, $P < .001$ and reduced FeNO:−32.7 ppb, $P < .001$. Within this group, those whose initial, inhalative ICS treatment was supplemented with LABA (added LABA) showed the highest improvement of FEV_1: 12.5%, $P = .004$ and largest reduction in FeNO:−46.8 ppb, $P = .021$. In another subgroup, where LABA were already present at admission and remained at discharge, we observed a significant FEV_1 elevation of 4%, $P = .001$ and also a highly significant reduction in FeNO:−33.4 ppb, $P < .001$. Even in the group with no ICS, FeNO reduction was still −10.1 ppb, $P < .001$, while there was no significant change in FEV_1, which was already 96.9%pred. at admission. Interestingly, we observed a FeNO reduction −24.2 ppb, $P = .020$ for those whose dose was lowered by one GINA-ICS level. FEV_1 in this group was already 100.6%pred. at admission and did not show a significant improvement at discharge.

3.8 | Uncontrolled asthmatics benefit from a stay longer than 35 days

Among all groups, our findings showed best results for uncontrolled subjects if their stay was longer than 35 days. An increase in FEV_1:+7.6%, $P < .001$, MEF_{25}:+7%, $P = .003$, and MEF_{75}:+12.5%, $P = .002$ accompanied by a reduction in FeNO: −40.6 ppb, $P < .001$ was observed (Figure 4). This group showed also benefits for sojourns between 14 and 35 days, but to a lesser extent.

Moreover, stratification and sensitivity analyses concerning the factors gender and age did not show a significant difference of improvement in favor for any analyzed group (data not shown).

4 | DISCUSSION

In this study, we showed a significant improvement of pulmonary function and a reduction in airway inflammation of children and adolescents after an inpatient rehabilitation of at least 14 days. Particularly, the pulmonary conditions of uncontrolled asthmatic patients improved considerably. Sensitization status to pollen or house dust mites did not influence the effect of rehabilitation significantly, nor did a concomitant diagnosis of atopic dermatitis. As also the groups with constant ICS and without ICS showed pulmonary improvements, an increase in ICS was most likely not the only reason for the positive effect of the rehabilitation program. An increase in duration of the stay was especially beneficial to uncontrolled asthmatics.

Previously, numerous studies have shown multiple benefits of sojourns at moderate or high altitude, especially for dust mite allergic asthmatics.[11,17-20] Allergen reduction was discussed as the major contributing factor. A recent cohort study of the Dutch Asthma Centre in Davos showed improved pulmonary conditions of adult asthmatics irrespective of sensitization status.[21] In our study, uncontrolled asthmatic children and adolescents with HDM-sensitization showed similar FEV_1 at admission and discharge compared to the Dutch patients. However, our non-HDM-sensitized patients had a greater improvement of FEV_1. Also, FeNO of our uncontrolled patients was higher at admission, while the reduction at discharge was considerably higher after a much shorter time period.

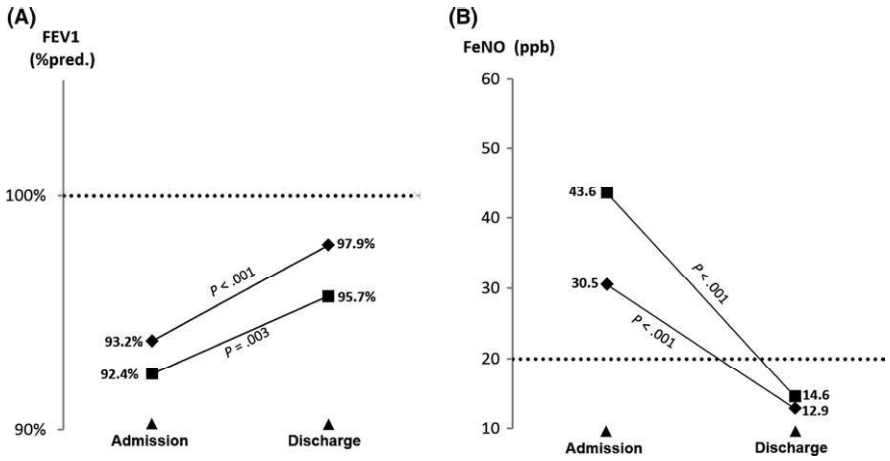

FIGURE 3 Pulmonary function and airway inflammation at admission and discharge of patients with asthma—stratified for atopic dermatitis. A, Pulmonary function (n = 343) is reported by mean values. *P* -value = comparison between discharge and admission, by *t* test for paired samples. Diamonds show patients with atopic dermatitis (n = 200). Squares show patients without atopic dermatitis (n = 143). B, Airway inflammation (n = 124) is reported by median values. *P* -value = comparison between discharge and admission, by Wilcoxon signed-rank test. Diamonds show patients with atopic dermatitis (n = 71). Squares show patients without atopic dermatitis (n = 53)

TABLE 2 Pulmonary function and airway inflammation at admission and discharge—stratified for change in level of inhalative corticosteroid dosage

	FEV_1 (%pred.)				FeNO (PPb)			
	n (344)	Admission	Discharge	*P* -Value	n (124)	Admission	Discharge	*P* -Value
Change of GINA ICS level								
No ICS	71	96.9	97	.923	22	30.5	20.4	<.001
ICS−1	23	100.6	102.1	.380	8	41.4	17.2	.020
ICS−2	6	109.2	106.7	.770	0	-	-	-
ICS level constant	147	92.6	97.5	<.001	52	48.1	15.4	<.001
No LABA	29	95.8	98.4	.450	6	23.1	12.5	.095
Added LABA	17	90.8	103.3	.004	7	63.2	16.4	.021
Constant LABA	100	92.2	96.2	.001	38	49.3	15.9	<.001
Stopped LABA	1	-	-	-	1	-	-	-
ICS + 1	66	88.9	95.5	<.001	31	46.5	15.1	<.001
ICS + 2	31	84.5	91.7	.002	11	51.7	13.2	.002

No ICS, patients without inhalative corticosteroid; ICS−1, inhalative corticosteroid reduced by one GINA level; ICS−2, inhalative corticosteroid reduced by two GINA levels; ICS level constant, inhalative corticosteroid level not changed; ICS + 1, inhalative corticosteroid elevated by one GINA level; ICS + 2, elevated by two GINA levels; No LABA, no additional LABA at admission and discharge; added LABA, LABA added shortly after admission; constant LABA, LABA present prior to admission and present at discharge; stopped LABA, LABA were stopped shortly after admission.

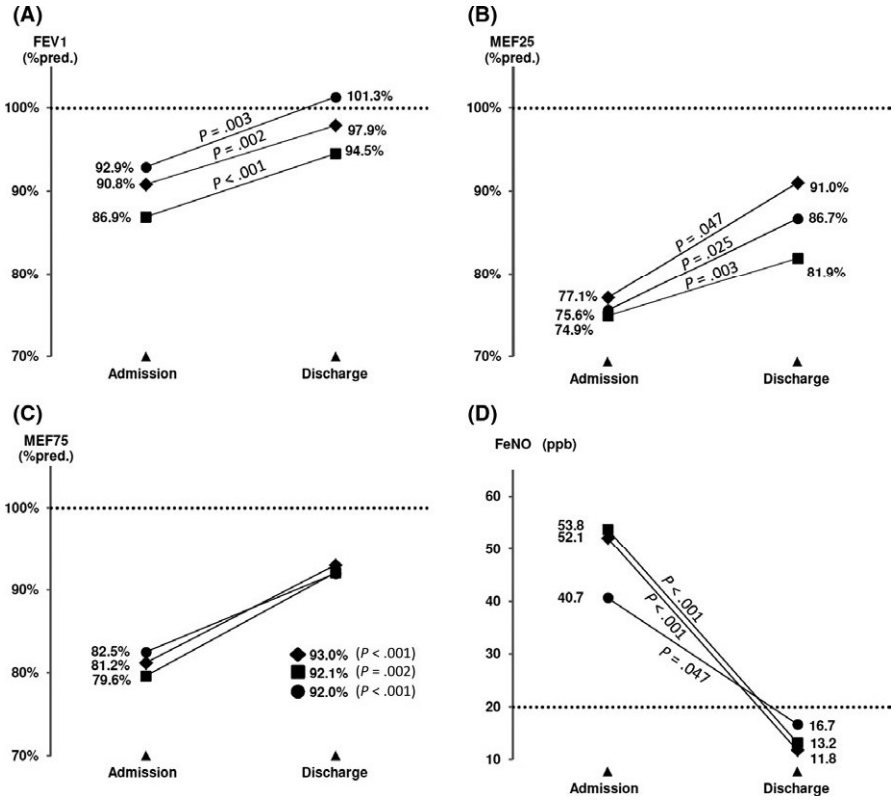

FIGURE 4 Pulmonary function and airway inflammation at admission and discharge of patients with uncontrolled asthma—stratified for duration of the sojourn. A, B, C, Pulmonary function (n = 128) is reported by mean values. *P* -value = comparison between discharge and admission, by *t* test for paired samples. Circles show patients with a stay of 14-21 d (n = 30). Diamonds show patients with a stay of 22-35 d (n = 61). Squares show patients with a stay of >35 d (n = 37). D, Airway inflammation (n = 52) is reported by median values. *P* -value = comparison between discharge and admission, by Wilcoxon signed-rank test. Circles show patients with a stay of 14-21 d (n = 10). Diamonds show patients with a stay of 22-35 d (n = 25). Squares show patients with a stay of >35 d (n = 17)

Our finding, that non-HDM-sensitized benefit to a similar extent as HDM-sensitized, is consistent with finding of the Dutch cohort. As pollen-sensitized and non-pollen-sensitized, uncontrolled asthmatics responded within the same range in our study, the reduction in exposure to pollen allergens does not fully explain the benefit of the stay.

Thus, we further assessed whether the adjustment with asthma medication, as it is often inadequate,[13,22] was responsible for the beneficial effect. Indeed, our data showed strong effects on lung function and airway inflammation for those whose ICS dose was increased. However, the striking finding was the reduced airway inflammation in patients with no, constant or even decreased ICS. For patients with

constant ICS, lung function also improved significantly, suggesting other beneficial factors than the medication adjustment.

Interestingly, there was already a benefit for uncontrolled patients after a short term stay of 2-3 weeks, while with prolonged duration of the stay, the benefits accumulated and showed best results for this group at 36+ days. This finding underlines the importance of time in a given inpatient setting in order for the intervention to be successful and provides a reasonable explanation to health insurances regarding the minimum length of stay for an uncontrolled asthmatic patient.

Our findings suggest that the impact of allergen reduction may be overrated, but may still remain a beneficial factor among others such as asthma education, corrected inhalation technique, physical activity, physiotherapy, and improved adherence leading to optimal disease management.[15,23-25] In addition, noteworthy are the specific climate factors present in moderate altitude, which independently have shown positive effects on lung function and airway inflammation and therefore, especially in combination, might also contribute to the observed effect. Among those factors are a low air pollution,[26] high number of sunshine days, which leads to increased vitamin D levels,[27] and a reduced gas/air density, which leads to a decrease in lung resistances and to an increase in respiratory and expiratory flows.[28,29]

We consider the individualized treatment approach to be a limitation of our study. As due to the personalized rehabilitation schedule and a missing control group, we could not investigate individual effects of particular treatment approaches. Moreover, there is no assessment time period after discharge in our patients. A previous study assessed long-term effects of inpatient rehabilitation in Germany in children with severe forms of asthma.[30] Pulmonary function was still on a high level in a 12-month follow-up, as well as other outcome parameters such as school absence, disease management, and quality of life improved in the long term.

Thus, further research is needed to evaluate whether the effects of rehabilitation programs at moderate altitude can be preserved over a longer time period. Also, for a better evaluation of the climate effect, a moderate altitude rehabilitation program should be compared to a comparable program of a clinic at lower altitude.

In conclusion, we showed that an inpatient rehabilitation program at moderate altitude is eligible for improving pulmonary function and reducing airway inflammation of children and adolescents, regardless their sensitization status to pollen or house dust mites. An inpatient rehabilitation program is especially beneficial to patients who are classified as “uncontrolled” according to the GINA guidelines.

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