Non-pharmacological treatments in asthma patients with obesity

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Short-term and long-term effect of a high intensity pulmonary rehabilitation program in obese patients with asthma: a randomized controlled trial

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ABSTRACT

Objective: To determine the short-term and long-term effects of a high intensity pulmonary rehabilitation (PR) program on asthma control, body composition, lung function and exercise capacity in obese asthma patients.

Methods: Patients with obesity (BMI $\geq$ 30 kg/m^2) and suboptimal controlled asthma (Asthma Control Questionnaire (ACQ) $\geq$ 0.75) were randomly assigned to a 3-month pulmonary rehabilitation program (PR only), pulmonary rehabilitation program with the use of an internet based self-management support program (PR+SMS) or usual care. The PR program included high intensity interval training, nutritional intervention and psychological group sessions. Patients in the usual care group were advised to lose weight and to exercise. The primary outcome was the difference of change of ACQ between PR only and PR+SMS after 3 months. Total follow-up was 12 months.

Results: Thirty-four patients were included in the study (14 PR only, 9 PR+SMS, 11 control). Compared to patients in usual care, patients in the PR only group had a significant reduction in BMI and significant improvements in asthma control, exercise capacity and aerobic capacity after 3 months. These improvements persisted during 12 months of follow-up. No difference in ACQ between PR+SMS and PR only groups were observed. However, users of the SMS program had a significant lower BMI after 12 months compared to subjects in the PR only group.

Conclusion: A high intensity pulmonary rehabilitation program provides sustained improvements in asthma control, body composition and exercise capacity in obese asthmatics that are not optimally controlled and, therefore, should be considered in the treatment of these patients.

INTRODUCTION

Obesity is associated with an increased risk of asthma, and asthma in patients with obesity is difficult to control (1-3). Physical inactivity is an independent risk factor for severe asthma (4, 5). Both asthma and obesity are associated with a decreased level of physical activity (5, 6). In a previous study, we demonstrated that obese adults with asthma have a lower exercise capacity compared to normal weight adults with asthma. Nevertheless, obese asthmatics were able to show similar improvements in exercise capacity and asthma control compared to non-obese asthmatics after a 12-week pulmonary rehabilitation (PR) program. Still, a large group of obese asthmatics had no improvements from this PR program, which may indicate that there is need for a different approach in this group of patients (7). In recent years, there has been increasing attention for lifestyle interventions in asthmatics with obesity. Until now, the few published studies show that a weight loss program with exercise and dietary restriction improves asthma control and the quality of life of obese asthma patients at short term (8, 9). However, information on long-term results of such programs are still lacking. Studies in this field are urgently needed, not only to demonstrate feasibility and long-term effectiveness, but also to determine the effects of different exercise modalities. High intensity interval training (HIIT) is feasible in obese subjects and was found to be superior to medium intensity continuous training in improving cardiopulmonary fitness (VO_{2max}) and in decreasing % body fat (10). However, the feasibility and effectiveness of HIIT have not yet been investigated in obese subjects with suboptimal controlled asthma. In addition, data about the use of an e-health program as a part of PR programs to improve long-term effectiveness is lacking. Therefore, we designed a 3-month PR program consisting of a combination of HIIT, a dietary intervention and a psychological intervention. In this pragmatic randomized trial, we investigated both short-term and long-term effects of this integrated PR program with and without the use of an internet-based self-management program on body composition, aerobic capacity, lung function and asthma-related outcomes compared to usual asthma care in patients with obesity and suboptimal controlled asthma.

METHODS

Study design

This single-centre pragmatic randomized controlled trial was conducted at the Franciscus Gasthuis & Vlietland, Rotterdam, a non-academic teaching hospital, the Netherlands. Patients were recruited from the pulmonology outpatient clinic between January 2014 and December 2016. Eligible subjects were randomly assigned to one of the intervention groups or control group: 1) pulmonary rehabilitation only (PR only), 2) pulmonary

rehabilitation with online self-management support (PR+SMS), 3) usual care. There was no blinding. For randomization details, see supplemental file (S1). This study was approved by the local medical research ethics committee (Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o; NL46602.101.13) (Netherlands Trial Registry number NTR4322).

Study patients

Subjects between 18 and 55 years were included if they fulfilled the criteria for obesity (BMI $\geq$30 kg/m^2) and had a suboptimal controlled asthma (asthma control questionnaire score (ACQ) $\geq$ 0.75) despite optimal inhalation therapy (inhalation corticosteroid and a long-acting B-agonist). Asthma was diagnosed according to the GINA guidelines (11). Exclusion criteria are included in the supplemental file (S2)

Intervention

The PR groups (PR only and PR+SMS) participated in a 12-week PR intervention program including exercise training, nutritional intervention and psychological group sessions. The exercise training was a high-intensity interval training session of 40-60 minutes (intensity around 90% of VO_{2max}), 3 times a week under the supervision of a physiotherapist (Supplemental file S3). In addition, participants were prescribed a caloric diet of approximately 1500 kcal/day with a balanced intake of macronutrients. They were supervised by a dietician (3 clinical visits + 3 phone calls during 12 weeks). During these visits, a healthy lifestyle was promoted and patients were educated in a healthy diet. Psychological counseling took place during 4 group sessions (1 hour). These sessions focused on behavioral modification and motivational strategies. Subjects who were randomized to PR+SMS participated in the same program but additionally used the internet based self-management tool 'PatientCoach' (www.patientcoach.lumc.nl). For details about this program, see supplemental file S4. Subjects who were randomized to PR+SMS group used the PatientCoach program during 3 months of PR and 12 months of follow-up. Subjects in the usual care group were advised to lose weight and to exercise. Total follow-up time was 1 year and all study participants were regularly seen every 3 months for assessment.

Outcomes

The primary outcome parameter was the difference of change of ACQ between PR+SMS group and PR only group after 3 months of intervention. Secondary outcomes were ACQ at 3 months between both PR groups and the usual care group, ACQ at 12 months, asthma related quality of life (AQLQ), lung function, physical activity level, exercise capacity, body composition, airway and systemic inflammation and exacerbation rate

at 3 and 12 months of follow-up between the PR only and control groups and between the PR+SMS and PR groups.

Assessments

Asthma control and asthma related quality of life were assessed by the validated asthma control questionnaire (ACQ) and the asthma quality of life questionnaire (AQLQ) (12, 13). Pulmonary function was measured with standard spirometry (Vmax Encore 22D, Carefusion) and bodybox (Vmax encore 62j, Carefusion) according to the American Thoracic Society (ATS) / European Respiratory Society guidelines (ERS) (14). Aerobic capacity (VO_{2max}) was measured with a cardiopulmonary exercise test (CPET) according to the ATS/ACCP guidelines (15). For a detailed description of all assessments and blood/sputum analysis see supplemental file S5 (16-23).

Statistics

Assuming an mean±SD effect size (difference of ΔACQ at 3 months) between PR+SMS and PR only groups of 0.5 ± 0.35, randomization ratio 1:1:1, and adjustment for 20% drop out, at least 3x12 patients had to be included in the study. See supplemental file S6 for descriptives and statistical analysis within the groups. Effectiveness of the pulmonary rehabilitation program was studied by comparing outcome parameters of the PR only group versus control group. The added value of the online self-management program was studied by comparing the PR only and PR+SMS groups. The data of the randomized subjects were analysed according to the intention to treat principle. For the comparisons of the primary and secondary outcomes between groups at 3 months, linear regression models were used with the randomization group, gender and the baseline variable as independent variables. Long-term (12 months) effectiveness for continuous measures was evaluated with repeated measurements analyses, with the outcome measure of interest as dependent variable, and the baseline value, time, group and gender as covariables (linear mixed model, covariance structure: unstructured). To analyze the effect of BMI on asthma control (ACQ), asthma quality of life (AQLQ), functional residual capacity (FRC) and VO_{2max} at 3 months and 12 months, we included ΔBMI in the regression analysis and BMI in the linear mixed model. Exacerbations at three months were analyzed as proportions of at least one exacerbation per patient, and tested with the binomial test. Long-term (12 months) effectiveness for number of exacerbations was modeled with Generalized Estimation Equations, with the number of exacerbations as dependent variable and the baseline value, time and group as covariables (distribution: Poisson, link: Log). The beta coefficients of the poisson model were transformed in rate ratios by exponentiating the beta of the model and the confidence intervals. IBM SPSS version 22 was used for all statistical analysis. Given the exploratory character of the

study, p-values were not adjusted for multiple testing. A p-value (two-sided) < 0.05 was considered to indicate a statistically significant difference in all comparisons.

RESULTS

Participants

A total of 112 subjects were screened for eligibility and 34 patients were randomized. Twenty-three subjects were randomly allocated to the intervention groups (14 PR only and 9 PR+SMS) and 11 subjects in the control group. Three subjects withdrew informed consent: one control patient just after randomization, and two patients in the PR+SMS group during the PR program. Eventually 31 subjects were included in the intention-to-treat analysis (Figure 1). Baseline characteristics of the three groups are presented in table 1. Participants had a class II obesity (mean±SD BMI 36.24 ± 4.46 kg/m^2) and

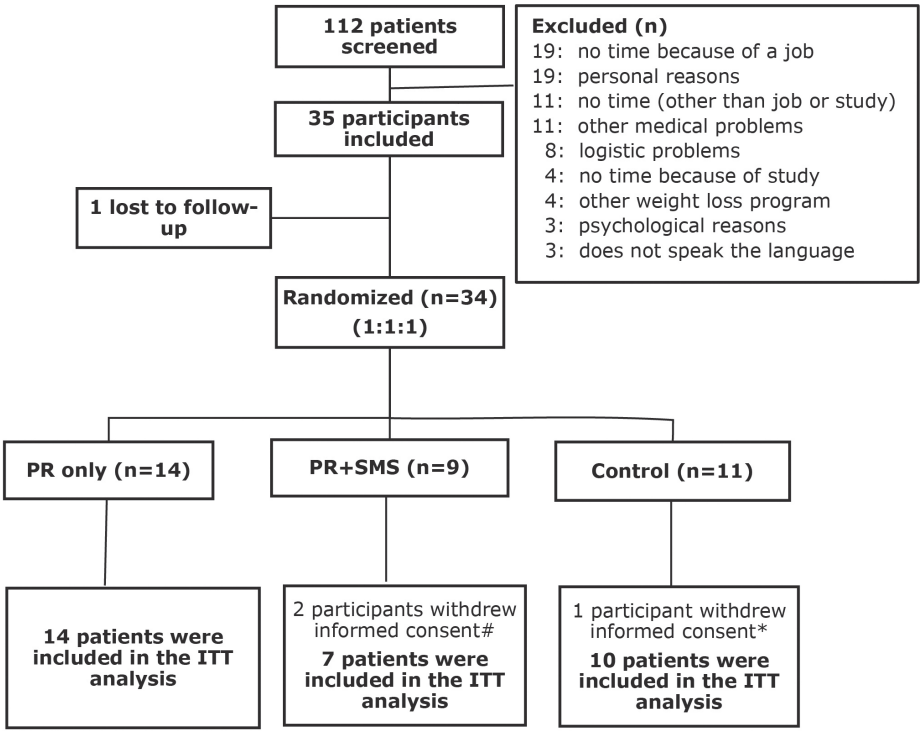

Figure 1: Diagram of inclusion and randomization of study participants. #: during the pulmonary rehabilitation program; *: after randomization.

a low physical fitness (VO_{2max} 18.25 ± 4.64 ml/kg/min). All patients were using inhaled corticosteroids (ICS) and a long-acting B_2 agonist (LABA). In addition, 39% of the patients were using a leukotriene receptor antagonist (LTRA) and 23% were using a long-acting muscarinic antagonist (LAMA). Based on the criteria of the GINA guidelines of 2019 (FeNO, serum and sputum eosinophils) the majority (77%) of the study participants had a type 2 asthma. Median ACQ was 2.0 [IQR 1.5-2.5] and 74% of the participants had an uncontrolled asthma (ACQ $\geq$ 1.5) at the time of randomization.

Table 1: baseline characteristics of study participants in three groups: pulmonary rehabilitation only (PR only), pulmonary rehabilitation + self-management support (PR+SMS) and control.

	PR only (n=14)	PR+SMS (n=7)	Control (n=10)	p-value
Age (y)	41.57 ± 9.73	41.57 ± 12.54	41.90 ± 8.58	0.996
Gender (%female)	71.43	57.14	90.00	0.298
Weight (kg)	103.25 ± 17.76	106.33 ± 10.87	100.68 ± 17.56	0.786
BMI (kg/m^2)	36.72 ± 4.79	36.82 ± 4.96	35.16 ± 3.86	0.664
Fat mass (%)	44.67 ± 5.90	39.60 ± 11.80	44.1 ± 4.5	0.330
Waist (cm)	109.07 ± 13.75	114.29 ± 8.83	107.00 ± 10.51	0.458
Diabetes (%)	7.14	28.57	0.00	0.133
Hypertension (%)	14.29	0.00	30.00	0.246
PD_{20} (mg)	0.12 [0.06-1.59]	0.28 [0.07-0.28]	0.22 [0.04-0.47]	0.784
FEV_1 (%)	86.93 ± 9.35	95.86 ± 11.74	82.4 ± 16.17	0.105
FEV_1/FVC	76.86 ± 8.88	78.71 ± 6.79	74.30 ± 8.97	0.565
RV (%)	78.92 ± 15.47	85.43 ± 20.55	86.80 ± 17.86	0.528
TLC (%)	66.00 ± 14.30	68.29 ± 11.94	91.10± 8.57	0.262
RV/TLC (%)	27.00 ± 5.52	26.57 ± 4.93	30.60 ± 6.24	0.245
FRC (%)	66.0 ± 14.30	68.86 ± 11.94	72.30 ± 18.14	0.621
Fe_{NO} (ppb)	18.0 [10.5-25.0]	17.0 [16.0-25.0]	17.0 [8.5-26.0]	0.895
VO_{2max} (%)	51.07 ± 17.66	60.57 ± 16.46	56.50 ± 11.27	0.405
ACQ	2.17 [1.46-2.50]	1.67 [1.17-1.83]	2.09 [1.50-2.68]	0.333
AQLQ	4.77 [4.33-5.43]	4.40 [4.13-5.33]	4.47 [3.47-5.00]	0.668
6MWD (m)	578.17 ± 75.70	605.78 ± 55.95	587.30 ± 72.95	0.733
Steps	5997 [4024-8048]	5616 [4306-6080]	7413 [2962-8155]	0.421
PAL	1.48 ± 0.16	1.43 ± 0.09	1.47 ± 0.14	0.815

Data are presented as mean±SD or median [interquartile range], unless otherwise stated. BMI: body mass index; PD20: doses of methacholine (mg) leading 20% reduction in forced expiratory volume in 1 s (FEV1); FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; RV/TLC: ratio between residual volume and total lung capacity; FRC: functional residual capacity; FeNO: fractionated exhaled nitric oxide; VO2max: maximal oxygen uptake; ACQ: asthma control questionnaire; AQLQ: asthma quality of life questionnaire; 6MWD: 6-min walking distance; PAL: physical activity level.

Intervention

The median compliance rate to the PR (PR only and PR+SMS) program was 85.7% [IQR 72.0-94.4%]. Four patients had a compliance rate < 50%. Two of these patients withdrew from the physical training program because of knee problems originated during the training. One patient was diagnosed with a neurological disorder during the intervention period and one patient participated very irregularly to the program for unknown reasons. Generally, HIIT was well tolerated by the participants. The most frequent complaint of patients was muscle aches in the first weeks of the training.

Changes in outcomes at 3 months within groups

The outcomes in each group are presented in table 2. In both PR only and PR+SMS groups, there was a significant reduction in weight, BMI and %fat mass after 3 months of PR. Waist circumference only decreased significantly in the PR+SMS group. No reduction

Table 2: Parameters at baseline and changes within groups after 3 months.

	Baseline	**Change within groups after 3 months**	**p-value** PR vs control PR+SMS vs PR
ACQ			
Control	2.09 [1.50-2.68]	-0.25 [-0.66-0.63]	
PR only	2.17 [1.46-2.50]	-0.67 [-1.42-0.00]**	0.113
PR+SMS	1.67 [1.17-1.83]	-0.66 [-1.17,-0.33]**	0.620
AQLQ			
Control	4.47 [3.47-5.00]	0.12 [-0.26-0.62]	
PR only	4.77 [4.33-5.43]	0.20 [-0.33-0.84]	0.758
PR+SMS	4.40 [4.13-5.33]	1.47 [-0.40-1.74]	0.384
Weight (kg)			
Control	100.7 [17.56]	- 0.1 [1.7]	
PR only	103.3 [17.76]	- 4.9 [4.9]**	**0.028**
PR+SMS	106.3 [10.87]	-10.9 [8.4]**	0.091
BMI (kg/m^2)			
Control	35.2 [3.9]	0.25 [0.65]	
PR only	36.7 [4.8]	-1.81 [1.79]**	**0.010**
PR+SMS	36.8 [5.0]	-3.62 [2.73]**	0.152
Waist circumference (cm)			
Control	107.0 [10.5]	4.67 [11.96]	
PR only	109.1 [13.7]	- 3.68 [7.23]	0.173
PR+SMS	114.3 [8.8]	-12.14 [9.84]**	0.107
Fat mass (%)			
Control	44.1 [4.5]	-0.33 [1.75]	
PR only	44.7 [5.9]	-1.41 [1.36]**	**0.015**
PR+SMS	39.6 [11.8]	-2.01 [3.86]**	0.326
FEV$_1$ (%)			
Control	82.4 [16.2]	-0.22 [7.5]	
PR only	86.9 [9.4]	1.0 [6.2]	0.351
PR+SMS	95.9 [11.7]	2.5 [7.8]	0.808

Table 2: Parameters at baseline and changes within groups after 3 months. (*continued*)

	Baseline	Change within groups after 3 months	p-value PR vs control PR+SMS vs PR
FRC (%)			
Control	72.3 [18.1]	- 1.4 [8.8]	
PR only	66.0 [14.3]	9.2 [8.1]*	**0.017**
PR+SMS	68.3 [11.9]	10.2 [10.5]	0.943
ERV (l)			
Control	0.45 [0.22]	0.04 [0.16]	
PR only	0.42 [0.18]	0.22 [0.16]*	**0.033**
PR+SMS	0.53 [0.23]	0.31 [0.47]	0.783
FeNO (ppb)			
Control	17.0 [8.5-26.0]	-0.5 [-14.8-4.0]	
PR only	18.0 [10.5-25.0]	-0.5 [-3.3-3.3]	0.113
PR+SMS	17.0 [16.0-25.0]	0.5 [-7.3-6.5]	0.875
VO_{2max} (%)			
Control	56.5 [11.3]	- 0.1 [10.5]	
PR only	51.1 [17.7]	+13.2 [9.2]*	**0.029**
PR+SMS	60.6 [11.3]	+11.2 [13.5]	0.678
6MWD (m)			
Control	587 [73]	-14 [51]	
PR only	578 [76]	52 [40]*	0.080
PR+SMS	606 [56]	63 [40]**	0.627
Steps (n)			
Control	7413 [2962-8155]	1281 [-65-4036]	
PR only	5997 [4024-8048]	1008 [70-2994]	0.100
PR+SMS	5616 [4306-6080]	3097 [1785-4740]**	0.181
PAL			
Control	1.47 [0.14]	0.04 [0.08]	
PR only	1.48 [0.16]	0.00 [0.18]	0.429
PR+SMS	1.43 [0.09]	0.11 [0.08]**	0.367
Sputum eosinophills (%)			
Control	0.65 [0.50-2.90]	1.20 [0.25-3.05]	
PR only	0.65 [0.05-4.30]	-0.15 [-2.40-1.13]	0.270
PR+SMS	0.90 [0.23-4.05]	0.00 [-0.83-1.05]	0.680
Sputum neutrophills (%)			
Control	49.4 [39.6-57.2]	- 7.2 [-49.1- -7.2]	
PR only	37.2 [28.4-51.0]	- 3.6 [-33.5-35.9]	0.828
PR+SMS	29.6 [23.4-57.9]	15.1 [-9.8-22.4]	0.852

Data are presented as median [interquartile range] or mean±SD, unless otherwise stated. PR only: pulmonary rehabilitation only; PR+SMS: pulmonary rehabilitation+self-management support; ACQ: asthma control questionnaire; AQLQ: asthma quality of life questionnaire; BMI: body mass index; FEV1: forced expiratory volume in 1 s; FRC: functional residual capacity; ERV: expiratory reserve volume; FeNO: exhaled nitric oxide fraction; VO2max: maximal oxygen uptake; 6MWD: 6 min walking distance; PAL: physical activity level. Stated p-values are for difference between PR only versus control and PR+SMS versus PR only groups (ANOVA). Differences within groups tested with the paired samples Student's t-test or Wilcoxon matched pairs test. *: $p \leq 0.005$ versus baseline; **: $p \leq 0.05$ versus baseline.

was observed in any of these parameters in the usual care group. Significant improvements in asthma control was observed in both intervention groups after 3 months of PR (median ΔACQ -0.67 for PR only and -0.66 for PR+SMS), whereas no significant improvement was seen in the usual care group (median ΔACQ -0.25) (figure 2). The median improvements in both groups were above the minimal clinically important difference (MCID) of 0.5. There was an increase in functional residual capacity (FRC) in the PR only group, and a trend was observed in the PR+SMS group. There were no significant improvements in dynamic lung function parameters, such as FEV_1 and FVC. Aerobic capacity (VO_{2max}) improved only significantly in the PR only group and a trend was observed in the PR+SMS group. There was an improvement in 6MWD in both PR only and PR+SMS groups. The activity level only improved in the PR+SMS group (table 2).

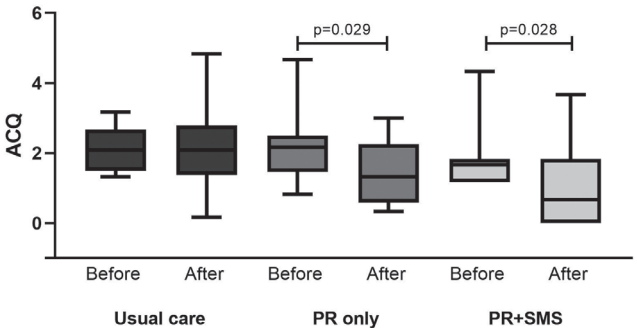

Figure 2: Changes in asthma control (Asthma Control Questionnaire (ACQ)) in each group after 3 months. Data are presented as median (interquartile ranges); p-value for ANOVA.

Outcomes in pulmonary rehabilitation (PR only) versus usual care groups

Subjects in the PR only group had a significantly greater reduction in weight (β=-2.193 CI [-4.116; -0.271], p=0.028), BMI (β=-0.986 CI [-1.70; 0.273], p=0.010) and %fat mass (β = -1.633 CI [-2.888; -0.377], p=0.015) compared to the usual care group at 3 months and these improvements in body composition persisted during 12 months of FU (table 2, 3 and figure 3). At 3 months, there were no differences in asthma control or asthma quality of life between the PR only and usual care group, but during 12 months of FU ACQ was significantly lower in the PR only group compared to the usual care group (β=-1.06 CI [-1.84; -0.27], p=0.011). In addition, there was a significant increase in function residual capacity (FRC) and expiratory reserve volume (ERV) in the PR only group compared to the usual care group at 3 months. However, these improvements were not significantly different after 12 months of FU. Exercise capacity (VO_{2max} and 6MWD) improved significantly in the PR only group after 3 months of PR and these improvements persisted during 12 months of FU. Delta BMI was only significantly associated with improvement in FRC (β=-4.13 CI [-6.24; -2,01], p=0.001), but not with ACQ (β=0.005 CI [-0.396; 0.406, p=0.979), ACLQ (β=-0.20 CI [-0.60; 0.19], p=0.288) and VO_{2max} (β=-1.00 CI [-6.25; 4.25],

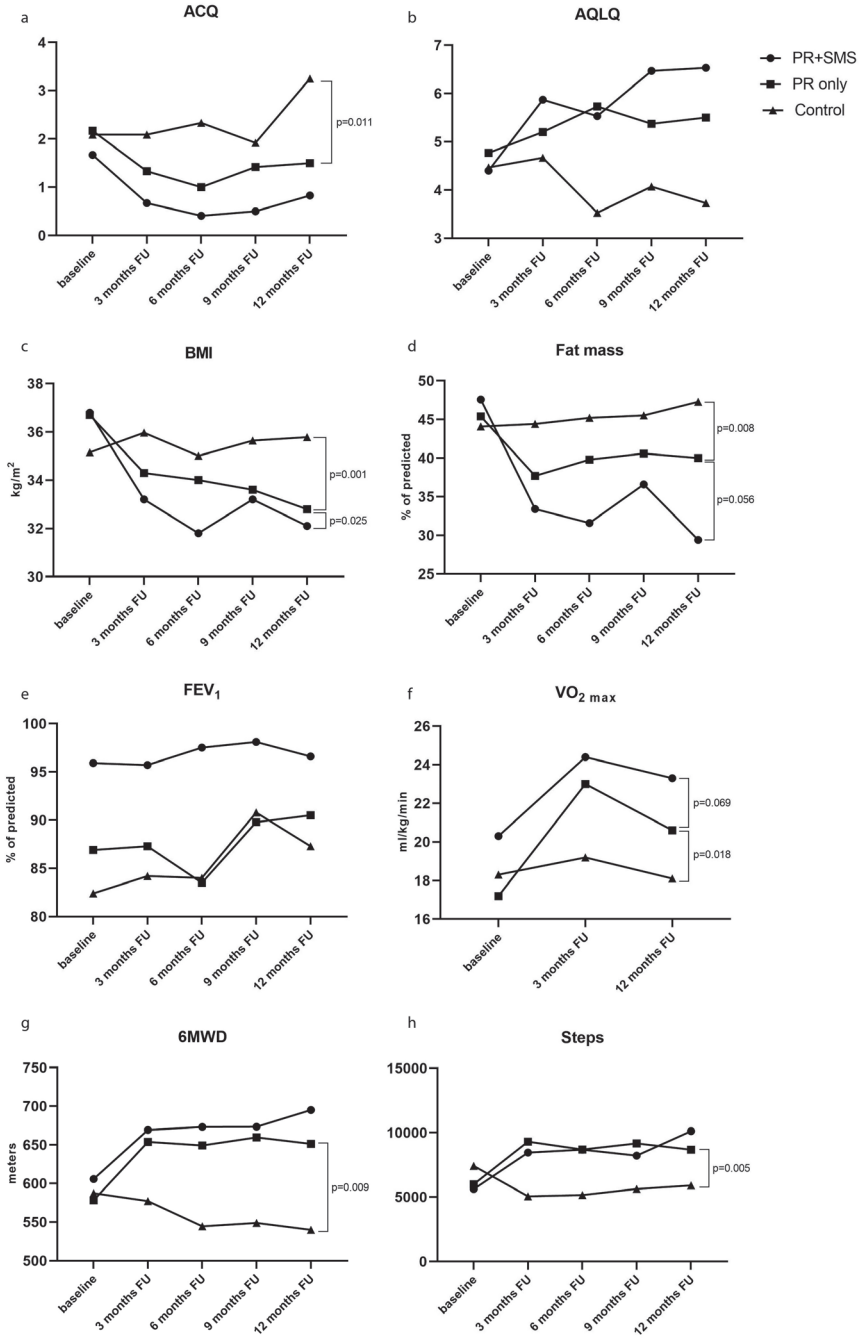

Figure 3: Changes over time in a) Asthma Control Questionnaire (ACQ), b) asthma-related quality of life (AQLQ), c) body mass index (BMI), d) fat mass, e) forced expiratory volume in 1 s (FEV_1), f) maximum exercise capacity (VO_{2max}), g) 6-min walk distance (6MWD), h) steps. Dots present mean or median values. p-value for difference between groups over time (repeated measurements (mixed model)).

Table 3: Change after 12 months.

	Change at 12 months vs baseline within groups	Mean difference between the groups over time* β-coefficient (95% CI)	p-value
ACQ			
Control	0.91 [-0.49-2.50]		
PR only	-0.59 [-1.62-0.22]	-1.06 [-1.84- -0.27]	**0.011**
PR+SMS	-1.05 [-0.84- -1.87]	-0.34 [-0.95-0.27]	0.252
AQLQ			
Control	-0.14 [-0.62-1.37]		
PR only	0.59 [-0.46-1.93]	0.28 [-0.65-1.22]	0.537
PR+SMS	0.60 [-0.44-2.50]	0.32 [-0.64-1.29]	0.483
BMI			
Control	0.78 [1.29]		
PR only	-2.15 [2.85]	-2.25 [-3.38- -1.11]	**0.001**
PR+SMS	-4.90 [6.11]	-2.27 [-4.20- -0.35]	**0.025**
Waist circumference (cm)			
Control	-0.33 [3.33]		
PR only	-4.88 [7.77]	-3.25 [-8.86-2.35]	0.239
PR+SMS	-12.5 [17.87]	-7.07 [-15.91-1.78]	0.109
Fat mass (%)			
Control	1.80 [1.11]		
PR only	-3.62 [4.41]	-2.63 [-4.42- -0.84]	**0.008**
PR+SMS	-6.30 [8.44]	-2.03 [-4.13-0.07]	0.056
FEV1 (%)			
Control	1.43 [6.32]		
PR only	4.50 [10.49]	0.24 [-5.40-5.87]	0.931
PR+SMS	0.00 [6.67]	3.37 [-4.41-11.14]	0.368
FRC (%)			
Control	8.83 [26.32]		
PR only	7.38 [13.50]	12.2 [7.91-16.5]	**<0.001**
PR+SMS	10.8 [5.89]	1.37 [-6.64-9.38]	0.702
VO_{2max} (%)			
Control	1.33 [14.07]		
PR only	11.7 [15.65]	12.04 [1.99-22.08]	**0.022**
PR+SMS	7.50 [3.70]	-7.83 [-19.58-3.92]	0.174
6MWD (m)			
Control	-40.38 [53.99]		
PR only	40.29 [53.52]	58.0 [16.9-99.1]	**0.009**
PR+SMS	81.40 [59.45]	10.5 [-25.98-46.91]	0.539
Steps			
Control	987 [-1621-5747]		
PR only	5591 [3480-4491]	3200 [1256-5144]	**0.005**
PR+SMS	902 [-282-2080]	740 [-1614-3095]	0.388

Data are presented as median [interquartile range] or mean±SD, unless otherwise stated. PR only: pulmonary rehabilitation only; PR+SMS: pulmonary rehabilitation+self-management support; ACQ: asthma control questionnaire; AQLQ: asthma quality of life questionnaire; BMI: body mass index; FEV1: forced expiratory volume in 1 s; FRC: functional residual capacity; VO2max: maximal oxygen uptake; 6MWD: 6 min walking distance. p-value for difference between PR only versus control and PR+SMS versus PR only groups over time (repeated measurements (mixed model)). *: effect sizes adjusted for time, parameter baseline value and gender.

p=0.685) at 3 months. However, we found a trend for significant association of BMI with FRC (β=-0.61 CI [-1.23; 0.01], p=0.054) and VO_{2max} (β=-1.17 [-2.38; 0.037], p=0.057) at 12 months, but no association with ACQ (β=-0.03 [-0.12; 0.05], p=0.412) and AQLQ (β=-0.01 [-0.09; 0.77], p=0.901) were found. We observed no significant changes in the amount of daily steps or physical activity level at 3 months, but subjects in the PR only group had significant higher amount of daily steps compared to the subjects in the usual care group after 12 months of FU (β= 3200 CI [1256; 5144], p=0.005) (table 2, 3 and figure 3). There were no differences observed in airway inflammation (FeNO, sputum eosinophils and sputum neutrophils) between PR only and usual care groups after 3 and during 12 months of FU. However, there was a significant decrease in serum leptin levels in the PR only group compared to the control group after 3 months and during 12 months of FU (table 4). This decrease in serum leptin was significantly associated with reduction in BMI (β= 9.37 CI [4.60; 14.12], p=0.001).

Outcomes in pulmonary rehabilitation group *with* versus *without* the use of the online self-management support (PR only vs PR+SMS)

No differences were found in weight or body composition between PR only and PR+SMS groups at 3 months (table 2). However, during 12 months of FU, patients in the PR+SMS group had a significant lower weight (β=-6.23 CI [-11.3; -1.12;], p=0.021) and BMI (β=-2.27 CI [-4.20; 0.35], p=0.025) compared to subjects in the PR only group. In addition, there was a trend for a lower %fat mass in the PR+SMS group (β=-2.03 CI [-4.13; 0.07], p=0.056) (table 3, figure 3). No statistically significant differences were observed in changes of ACQ, AQLQ, lung function, exercise capacity (VO_{2max} and 6MWD) or activity level (PAL or daily steps) between PR+SMS and PR only group at 3 months and during 12 months of FU. We did not find any difference in FeNO, sputum eosinophils or neutrophils between these groups at 3 months and during 12 month of FU. Serum leptin levels decreased significantly more in the PR only group compared to the PR+SMS group at 3 months (β= 19.5 CI [5.65; 33.35], p=0.009) and this difference persisted during 12 months of FU (β= 20.66 CI [7.10; 34.21], p=0.006). However, we observed no differences in any of other inflammatory markers at 3 months or 12 months of follow-up (table 4).

Exacerbations

No difference in the proportion of patients with an asthma exacerbation during the 3 months intervention period were found between the PR only group and the control group (16.7% vs. 55.6%, p=0.16). In addition, no difference in the proportion of patients with an exacerbation was observed in PR+SMS vs PR only group. During the 12 months of follow-up, a higher rate of exacerbations was observed in the control group compared to the PR only group (β (poisson rate)=0.839 CI [0.116; 1.563], p=0.023; RR 2.314 CI [1.123; 4.773]) whereas no significant difference in exacerbation rate was seen between

PR+SMS group and the PR only group (β (poisson rate)=0.319 CI [-0.811; 1.449], p=0.580; RR 1.376 CI [0.444; 4.259]).

Table 4: Change of systemic inflammatory markers after 3 months and 12 months.

	Baseline	Change within groups after 3 months	P-value (1)	Mean difference between the groups over time* β-coefficient (95% CI)	p-value (2)
Leptin (ng/ml)					
Control	71.0 [49.0-103.0]	-3.0 [-10.5-3.3]		0.0 [-16.0-15.0]	
PR only	77.5 [47.3- 98.3]	-27 [-37- -16]‡	**0.001**	-7.0 [-42.0-20.0]	**0.018**
PR+SMS	17.5 [8.5-100.0]	-2.5 [-6.5-2.3]	**0.009**	-5.0 [-11.0-1.5]	**0.006**
Adiponectin (µg/ml)					
Control	39.0 [18.5-53.0]	-9.0 [-28.8-9.8]		-4.0 [-27.0-7.0]	
PR only	34.0 [17.8-103.8]	-6.0 [-15.0-22.0]	0.228	0.0 [-22.0-37.0]	0.384
PR+SMS	41.5 [22.8-102.8]	-14.0 [-37.8-21.3]	0.541	-13.0 [-56.0- -14.5]	0.361
hsCRP (ng/ml)					
Control	8672 [1653-27145]	6.0 [-1351-542]		-301 [10911-313]	
PR only	3209 [1657-8069]	-222 [-1136-1699]	0.802	-899 [-1947- -260]	0.462
PR+SMS	7837 [1070-22397]	-1800 [-11597- -569]‡	0.758	-1677 [-4760-3322]	0.415
Pentraxin (pg/ml)					
Control	361.9 [297.1-424.2]	30.1 [2.3-104.4]		78.1 [52.9-376.4]	
PR only	431.7 [364.3-514.5]	25.4 [-54.3-223.1]	0.645	23.2 [-126.5-218.1]	0.830
PR+SMS	378.8 [226.2-579.1]	90.6 [-0.33-300]	0.249	121.4 [121.4-336.7]	0.149
Eosinophills (10^9 cells/l)					
Control	0.20 [0.10-0.25]	0.0 [-0.10-0.00]		0.0 [-0.08-0.00]	
PR only	0.30 [0.10-0.50]	0.0 [-0.20-0.04]	0.987	-0.01 [-0.06-0.12]	0.636
PR+SMS	0.20 [0.10-0.40]	-0.05 [-0.13-0.10]	0.465	-0.07 [-0.15-0.00]	0.684
Leucocytes (10^9 cells/l)					
Control	6.95 [5.83-8.10]	0.5 [-1.3-1.7]		0.3 [-1.0-1.8]	
PR only	6.15 [5.40-8.05]	0.3 [-0.6-1.5]	0.722	0.1 [-1.4-0.4]	0.126
PR+SMS	8.70 [6.60-9.70]	0.3 [-1.7-1.1]	0.955	-0.3 [-0.9-0.6]	0.544

Data are presented as median [interquartile range], unless otherwise stated. hsCRP: high sensitivity C-reactive protein. p-value(1) for difference between PR only vs control or PR+SMS vs. PR only groups at 3 months (ANOVA); *) effect sizes adjusted for time, parameter baseline value and gender. p-value(2) for difference between PR only vs control and PR+SMS vs PR only groups at 12 months (Repeated measurements); ‡ $p \leq 0.05$ vs. baseline (Significance estimated by regression analysis of log-transformed inflammatory markers

DISCUSSION

In this pragmatic study, we investigated the short and long-term effects of a 3-months high intensity pulmonary rehabilitation program in obese patients with suboptimal controlled asthma. The majority of the patients had an uncontrolled type 2 asthma (GINA 4) and a low aerobic capacity at the time of inclusion. Nevertheless, high intensity interval training in this group of patients was found to be feasible. Moreover, this short-term PR-program resulted in a clinically relevant improvement of asthma control and marked

improvements in body composition, aerobic capacity, and lung function in a short period of three months. More importantly, the positive effects on asthma control (ACQ), BMI, exercise capacity and physical activity persisted during the 12 months of follow-up period. Although, we did not find any difference in the primary outcome: asthma control, between the PR only and PR+SMS groups at 3 months, we demonstrated that adding an internet-based self-management program on top of the PR program results in better weight management over time. The outcomes of this study emphasize the feasibility and the importance of lifestyle modification in this particular group of patients.

Despite the relevance of weight loss in asthmatics with obesity, there are only few randomized controlled trials available about weight loss interventions in these patients (24, 25). The first studies included only dietary interventions (26) or diet combined with weight loss medication (27). Although these interventions resulted in a significant weight loss and improvements in asthma symptoms at short-term, information on the persistence of these effects over a long period was lacking. The study of Scott et al. (8) was the first randomized study comparing a combined dietary and exercise intervention with diet or exercise alone. This study demonstrated that exercise alone had no effect on weight loss or asthma symptoms, and that a combined diet/exercise intervention should be the choice in obese asthmatics (8). However, in this study, not only obese, but also overweight subjects were included and the level of asthma control was better compared to that in the present study (ACQ 1.36 vs 2.0). The mean weight loss was 8.3% after 10 weeks of intervention, including a very strict caloric restriction of 885-1170 kcal/day and an exercise program with aerobic and resistance training. In contrast, Ma et al. (28) found modest weight loss (5% and 4%) after 6 and 12 months of lifestyle intervention, including a dietary restriction of 1200 kcal/day and at least 150 min of moderate intensity physical activity/week in 330 obese adults with uncontrolled asthma. The effects on asthma control were disappointing. The authors concluded that a weight loss of 10% or greater may be required for a clinically significant improvement in asthma outcomes (28). More recently, Freitas et al. demonstrated that a 3-month weight loss program with caloric restriction of approximately 1300 kcal/day, aerobic and resistance training results in significant improvements in body composition, asthma control, aerobic capacity, lung function, airway and systemic inflammation in obese adults with asthma (9). In the present study, a less strict caloric restriction of 1500 kcal/day combined with high intensity interval training (intensity ±90% of VO_{2max}) resulted in a mean weight loss of 5% in the PR only group and 12% in the PR+SMS group at 3 months, with persistent improvements in asthma control, BMI and exercise capacity in the majority of patients at 12 months.

Obesity is characterized by low-grade systemic inflammation with increased production of pro-inflammatory cytokines. In this study, we did not find any reduction in pro-

inflammatory cytokines, like Hs-CRP or Pentraxin, but we have demonstrated that there was a decrease in serum leptin levels in participants immediately after the PR program and during 12 months of FU. This decrease in serum leptin appeared strongly associated with the persistent decrease of BMI during 12 months of follow-up in the PR only group.

Although an intervention period of 3 months may appear short to achieve a lifestyle change, we have demonstrated that a short-term well-designed multidisciplinary PR program could result in long-term benefits. The positive effects on weight, aerobic capacity and symptoms could encourage patients to maintain their diet and exercise for a longer period. In addition, the use of an internet-based self-management program during and after the PR-program could be supportive for long-term adherence. As we have showed in the present study, compared to non-users, users of the SMS program on average had a significant lower BMI after 12 months of FU. The role of such innovative approaches in the management of asthma and obesity should be further explored (29-31).

The implementation of the new HIIT exercise program was well tolerated and successful in this group of patients who are limited by their weight as well as by their asthma. In addition, the rate of exacerbations was not higher in the intervention group, indicating that HIIT did not negatively affect asthma control. To our knowledge, this is the first study showing that HIIT is feasible in obese persons with suboptimal controlled asthma. Furthermore, it has been shown that HIIT is perceived to be more pleasant than moderate intensity continuous exercise (32). This may improve the adherence to exercise and promote health benefit over a longer period.

Another important issue is the cost-effectiveness of such rehabilitation programs. The cost of a 3-month rehabilitation program is approximately €3000,- p.p. The costs of an exacerbation varies between €500-3000,- depending on the extra visits, ER visits and the requirement of a clinical admission. So depending on the severity of the exacerbations and the long-lasting effect of the program, PR could ultimately be cost-effective. In the Netherlands this program is therefore only available for more severe, uncontrolled patients. However, the present study was not designed or powered to calculate cost-effectiveness.

Our study has some limitations. Firstly, this study comprises a relatively small sample (figure 1). It was very difficult to recruit suitable candidates for this study. Most eligible patients were unable to participate because of work or other reasons. Despite small group-sizes, our explorative study suggests that PR is effective and that SMS contributes to maintaining long-term effects. A larger study is needed to corroborate these results

with sufficient power. Our study participants were predominantly female, and able and motivated to participate in this program which could have resulted in a selection bias. However, in this kind of studies, motivation for participation is an important requirement for success. In addition, diets were not tailored to each patients, which could be a pitfall. This could explain the differences in weight loss between the patients, especially male patients could have lost much more weight with this amount of caloric restriction. However, our diet was less strict compared with other studies (8, 9). Finally, we have used an integrated pulmonary rehabilitation program, and were unable to determine the contribution of the four individual components of this program to the outcome. We have shown that the reduction of BMI is especially associated with improvements in lung function, but not with the improvement of asthma control. This indicates that it is not "just a matter of weight loss", but that the other components of the PR program, like exercise and psychological intervention are probably at least equally important to achieve improvements in asthma control.

The present study, despite its limitations, is the first demonstrating that a short-term multidisciplinary PR program with HIIT and the use of an internet based self-management program is feasible and effective at both short and long term, in suboptimal controlled asthmatics with obesity. Such well-designed PR programs should be considered in the treatment of obese asthmatics.

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SUPPLEMENT

S1 Randomization

For randomization, a research randomization program was used (http://www.randomizer.org/form.htm). Randomisation was not stratified. Patients were randomly assigned in a 1:1:1 ratio using a computer-generated permuted-block scheme. Allocation took place by an independent researcher after written consent had been obtained from all subjects and baseline data were collected, ensuring concealment of allocation.

S2 Exclusion criteria

Exclusion criteria were: current smoking or a smoking history of $\geq$ 10 pack years; asthma exacerbation (need of antibiotics/oral corticosteroids) in 6 weeks before inclusion; COPD or other pulmonary pathology apart from asthma, except for adequately treated OSAS with a Apnea Hypopnea Index < 5.0; and any significant orthopaedic of neurologic problems that reduce mobility or cooperation with physical training.

S3 Exercise training program

Training was performed three times per week for twelve weeks. Each training session was divided into four parts: the warming-up, stretching, the exercises and the cooling down. Between each part, the patients had thirty seconds rest and were allowed to drink some water. The warming up consisted of a seven-exercises routine, each exercise was thirty seconds. The routine was repeated 3 times. The intensity was progressive and patients were asked to reach a seven at the 10-grade Borg scale. The stretching consisted of ten minutes full-body stretching exercises, and aimed to improve the range of motion of joints, to prepare the body for the training and to prevent injuries. The number of sets completed in the exercises was increased during the first seven weeks. The patients started with three sets of four exercises. Each exercise was a bodyweight exercise and lasted 45 seconds. Between each series the patients had thirty seconds rest and they were allowed to drink some water. At the end of week seven (training 21 sessions) patients reached six set training session of four exercises. In each training session the patients were asked to maintain the intensity during the workout close to 90% of their VO_{2max} or to reach at least a seven at the 10-grade Borg scale.

The cooling down was also five minutes at the end of the training session. It consisted of full body exercises to return vital parameters to resting rate such as heart rate and breath before leaving the facility. During the cooling down there was no intensity target.

S4 Internet based self-management program "PatientCoach"

This program offers components for goal setting, tailored information, social forum and an e-consult option with health care professionals. In addition, the PatientCoach system includes modules for self-monitoring asthma control (ACQ), weight, lung function, feedback, medication plan, reminders and alerts. Furthermore, physical activity was monitored by an automated internet-based accelerometer (Fitbit, www.fitbit.com).

S5 Assessments

Body composition

Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters (kg/m^2). Obesity was defined as a BMI equal or greater to 30 kg/m^2. Fat mass (FM) and fat free mass (FFM) was measured with a bioelectrical impedance meter (Bodystat 1500, Bodystat Limited) and expressed as % of predicted. Metabolic syndrome was diagnosed according to the National Cholesterol Education Program's Adult treatment Panel III report (NCEP ATP-III) criteria (18).

Asthma control and asthma quality of life

Asthma control was assessed by the validated asthma control questionnaire (ACQ). It comprises 6 questions with different components of daytime symptoms and night time symptoms (14). Asthma related quality of life was measured with the validated asthma quality of life questionnaire (AQLQ) (15). For both questionnaires, a change of > 0.5 is considered as clinically relevant (14,15). An asthma exacerbation was defined as worsening of symptoms with need for oral corticosteroids and/or antibiotics)

Lung function

Pulmonary function was measured with standard spirometry (Vmax Encore 22D, Carefusion) and bodybox (Vmax encore 62j, Carefusion) according to the American Thoracic Society (ATS) / European Respiratory Society guidelines (ERS). Post-bronchodilator values were expressed as a percentage of predicted (16) . Methacholine challenge test was used to measure bronchial hyperresponsiveness (PD20). Fractional exhaled nitric oxide (Fe_{NO}) was measured with the Niox-Flex (Aerocrine AB, Sweden) at a constant flow rate of 50 ml/s and expressed as parts per billion in accordance with the guidelines of the American Thoracic Society and European Respiratory Society (19).

Exercise capacity

Aerobic capacity (VO_{2max}) was measured with a cardiopulmonary exercise test (CPET) performed on an Ergoselect cyclometer (Ergoline, Bitz, Germany) using a maximal symptom limited cardiopulmonary incremental protocol according to the recommendations

of the ATS/ACCP guidelines (17). The six-minute walking distance (6MWD) was measured by the six-minute walking test (6MWT), performed indoor using a 30 m walking course . Patient instruction and measurements were performed according to the ATS/ERS statement (25).

Daily activity

Daily activity such as daily steps and physical activity level (PAL) was measured with a portable movemonitor (DynaPort MoveMonitor, McRoberts, The Hague, The Netherlands), attached to the lower back by a belt. Participants were instructed to wear the movemonitor during 7 days at all times, except during water-related activities (20).

Blood sampling and analysis

Blood samples were obtained by venapuncture, and laboratory measurements were performed according to standard procedures by the department of Clinical Chemistry. For the analysis of serum markers of systemic inflammation, serum aliquots were frozen at -80°C and analysed in bulk. The Meso Scale Discovery Platform (Meso Scale Discovery, Gaitherburg, MD) was used to detect leptin, adiponectin and high sensitivity (hs)-CRP. Serum Pentraxin was analyzed using a commercial ELISA (Hycult Biotech (HBT)).

Sputum induction and analysis

Sputum induction with hypertonic saline (4.5%) and processing was performed by a validated method according to the guidelines (21-23). An ultrasonic nebulizer (Klava) with a two-way non-rebreathing valve (Hans Rudolph) and an output of 2 ml/min was used for induction. Before start and during the procedure, spirometry (Vmax Encore 22D, Carefusion) was performed to assess the lung function at baseline and during sputum induction. Pre-treatment with salbutamol 400 µg was given in order to prevent excessive bronchoconstriction. The expectorated sputum was kept at 4°C and processed immediately after collection to obtain cells and supernatant. For sputum processing, the whole sample was mixed with the same volume of sputolysin reagent (DTT), then placed in a shaking water bath of 37°C for 15 minutes for homogenization. After this, the sample was filtered through a 100 µm filter and centrifuged (1500 rpm;10 min). The supernatant was removed and was stored at -80°C. The cell pellet was resuspended in PBS/1% (w/v) human serum albumin (HSA). Total cell counts were determined with a Bürker Haemocytometer and cell viability was assessed using the by trypan blue exclusion method. Cytospins were made and stained with May-Grünwald-Giemsa. Differential cell counts were performed by counting at least 400 non-squamous sputum cells. Samples with more than 80% squamous cells were excluded from analysis (21-24).

S6 Statistical analysis

Baseline variables were summarized as mean±SD for continuous variables with normal distributions, median (interquartile range) for continuous variables with skewed distributions, and n (%) for categorical variables. The 3 and 12 months differences within groups were summarized as mean±SD or median (IQR) depending on the shape of the distribution and tested with the paired Student's t-test or the nonparametric Wilcoxon matched pairs test, respectively.