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ORIGINAL RESEARCH

Immediate and One-Year Outcomes of an Asthma-Tailored Pulmonary Rehabilitation Programme in Overweight and Obese People with Difficult-to-Treat Asthma

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Introduction: Management of difficult-to-treat asthma is particularly challenging in people with elevated body mass index (BMI). Our randomised controlled trial of pulmonary rehabilitation (PR) showed improved outcomes at 8 weeks. Here we assess immediate and one-year effects of asthma-tailored PR in participants with difficult-to-treat asthma and BMI ≥25 kg/m^2, and identify response predictors.

Methods: A prospective observational study of PR, tailored to asthma, comparing outcomes at baseline (V1), immediately after 8 weeks of PR (V2), and at 1 year (V3). Baseline characteristics were compared in responders/non-responders defined by achievement of minimum clinically important difference (MCID) for asthma control questionnaire (ACQ6) (0.5) at 8 weeks and 1 year.

Results: Of 92 participants, 56 attended V2 and 45 attended V3. Mean age was 60 (SD 13) years, 60% were female, and median (IQR) BMI was 33.8 (29.5–38.7) kg/m^2. At V1, V2, and V3, respectively, there were significant differences in ACQ6 (mean (95% CI): 2.5 (2.1–2.9), 2.2 (1.8–2.5), and 2.3 (1.9–2.7), $p<0.003$), Borg breathlessness score post-6-minute walk test (median (IQR): 2 (0.5–3), 1 (0–2), and 1 (0.5–2), $p<0.035$), and annualised exacerbations requiring prednisolone (median (IQR): 3 (2–5), 0 (0–4.7), and 1.5 (0–4.2), $p<0.003$). A total of 27/56 (48%) had improvements >MCID for ACQ6 at V2 and 16 (33%) at V3. Participants with higher ACQ6 scores at baseline (suggesting poorer asthma control) were more likely to achieve MCID. Baseline BMI, within the range studied, was not predictive.

Conclusion: Pulmonary rehabilitation induced improvements in asthma-related outcomes including perception of breathlessness, asthma control, and exacerbation frequency at 1 year. Those with poorer baseline asthma control were more likely to benefit.

Keywords: asthma, difficult-to-treat asthma, obesity, pulmonary rehabilitation

Introduction

Asthma is a heterogeneous condition associated with variable features of cough, wheeze, shortness of breath, and chest tightness, along with variable inflammation of the airways and airway hyper-reactivity.[1] Difficult-to-treat asthma describes asthma with persistent symptoms and/or frequent asthma attacks despite treatment with high-dose inhaled corticosteroids (ICS) plus a long-acting beta$_2$ agonist (LABA) or leukotriene receptor antagonist (LRTA); or medium-dose ICS plus a LABA or LRTA and an appropriate additional therapy; or continuous or frequent use of oral steroids; and other factors may contribute, eg poor treatment adherence, psychosocial factors, allergy, dysfunctional breathing, and other co-morbidities such as gastro-oesophageal reflux.[2] Obesity is associated with poorer outcomes in asthma,[3–5] and resistance to steroids,[6] the mainstay of asthma treatment. The links between obesity and asthma are complex, multifaceted, and bidirectional, involving changes in chest wall mechanics, airflow

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limitation, and hyper-responsiveness, as well as increases in inflammation, both systemically and within the airways.[7] Recently there has been a shift towards personalisation of treatment of airways disease by focusing intervention on treatable traits.[8,9] Type 2 inflammation (T2-high asthma) is the treatable trait in asthma with the widest range of treatment options including the biologic treatments targeting IgE, IL-5, and IL-4/13. Obese asthma is a recognised phenotype but with limited treatment options. It is more often associated with T2-low disease,[10–13] and patients may not be eligible for, or respond to, IgE, IL-5, or IL-4/13 targeted therapies; there is a recognition of an obese non-eosinophilic/non-atopic phenotype with late onset, female preponderance, and high symptom expression,[14,15] in particular, for which there is an unmet need.

Pulmonary rehabilitation (PR) is a standard component of treatment for chronic lung diseases including COPD, bronchiectasis, and interstitial lung disease.[16,17] There have been a small number of trials assessing the role of PR in asthma with some promising findings,[18–21] but the benefits are uncertain. A Cochrane review of studies comparing PR to usual care in adults with asthma concluded that 'pulmonary rehabilitation is probably associated with clinically meaningful improvements in functional exercise capacity and quality of life upon programme completion' but that "there remains considerable scope for future research".[22] We recently published immediate outcomes from a randomised controlled trial of an 8-week course of asthma-tailored pulmonary rehabilitation in participants with difficult-to-control asthma associated with elevated BMI.[23] We demonstrated statistically significant improvements in 6-point asthma-control questionnaire (ACQ6), Medical Research Council (MRC) dyspnoea scale, six-minute walk distance (6MWD), and Borg breathlessness score following 6-minute walk test (6MWT). The evidence regarding longer-term outcomes from pulmonary rehabilitation in asthma is sparse, but some studies have suggested benefits may be maintained up to one year.[20,24] The design of our original study (see Clinicaltrials.gov - ID NCT03630432) included an 8-week randomised trial, to provide evidence for proof of concept for a novel intervention (already published),[23] and also allowed us to evaluate in a prospective, observational manner, the longer-term outcomes of PR in overweight and obese patients with difficult-to-treat asthma, with adequate study power in a larger patient group, and to identify any factors which could predict response to PR. We hypothesised that early benefits would be maintained at one year.

Methods

Study Design

The original study comprised two parts: a randomised controlled trial of PR and longer-term follow-up of all patients (including those randomised initially to PR and those that were switched to PR after 8 weeks). It was registered at Clinicaltrials.gov (ID NCT03630432), approved by the West of Scotland Regional Ethics Committee (reference 16/WS/0200), and complied with the Declaration of Helsinki. It took place between May 2017 and December 2020. All participants enrolled in the study were randomised 1:1 to PR or usual care (UC) for an eight-week period. Subsequently, the UC participants were offered the PR intervention and had further study visits at programme completion and after 1 year. In this paper we present one-year results for all participants who underwent pulmonary rehabilitation, with study visits at baseline before PR (V1), immediately after completion of PR (V2), and 1 year after the first visit (V3).

Study Participants

For a full description of study participants, see Ricketts et al.[23] In brief, participants, aged 18–80 years, with BMI of $\geq$25 kg/m^2 were recruited from tertiary asthma clinics and ward admissions throughout NHS Greater Glasgow and Clyde. Participants had confirmed uncontrolled asthma despite treatment with high-dose ICS-LABA. Exclusion criteria were initiation of biologic therapy or admission to intensive care unit within the last six months, exacerbation requiring OCS or antibiotics within four weeks, significant co-morbidity or mobility problem likely to influence study conduct, pregnancy, or breast-feeding. Written informed consent was obtained from all participants prior to any study activity.

PR Programme

For a full description of the pulmonary rehabilitation programme, see Ricketts et al.[23] In brief, the programme was based on items recommended by the British Thoracic Society Guidelines,[16] focusing on muscle resistance and aerobic training,

but tailored specifically for asthma, lasting eight weeks, and consisting of one in-hospital session per week (one hour education, one hour exercise).

The exercise classes were delivered in a hospital gymnasium by the PR team (consisting of appropriately trained physiotherapists and nurses) with medical supervision. Class size depended on rate of recruitment and was generally 4 to 8 participants on a given day. Classes began with a warm-up, then a series of strength and aerobic exercises as listed in Box 1; see online supplement for additional details regarding the exercise intervention. The difficulty was tailored to each individual, with the starting point based on distance covered during six-minute walk test (6MWT) during V1, and repetitions or intensity increased each week as tolerated. Participants were encouraged to repeat the exercises at least twice weekly at home to achieve the three exercise sessions recommended in PR guidelines.[16,25] On completion of the programme, participants were encouraged to continue regular exercise by referral to community-based facilities. See online supplement for additional details regarding the exercise intervention.

Study Measurements

During V1, baseline medical history and electronic medical record assessment was undertaken. Participants completed ACQ6, asthma-related quality of life questionnaire (AQLQ), hospital anxiety and depression scale (HADS), and Medical Research Council (MRC) Dyspnoea Score. Height and weight were measured and BMI calculated. A blood sample was taken for eosinophil count. Participants performed peak expiratory flow rate and then spirometry as per ATS/ERS guidelines,[26] using an electronic desktop spirometer (Vitalograph, Maids Moreton, U.K). Fraction of exhaled nitric oxide (FeNO)[27] was performed using NIOX VERO machine (Circassia Pharmaceuticals, Morrisville, USA). Two 6MWTs were completed as per American Thoracic Society Guidelines,[28] and Borg score for breathlessness was documented at completion of each, with the longest distance and corresponding Borg score used for analysis. During the visit, participants were provided with a personalised asthma management plan and symptom diary. Inhaler technique was checked and corrected if necessary.

Box 1 A Chart Describing Both Educational Topics and Exercises Which Made Up the PR Programme

Educational Topics Covered (rolling programme delivered over 8 weeks)
What is asthma? Diagnosis and co-morbidities
Asthma treatments
Asthma management, inhaler technique, personalised asthma management plans
Breathing control and chest clearance
Health promotion including healthy eating
Asthma, general health, and physical activity
Asthma, mental health, and well-being
Benefits of exercise, anxiety management, and relaxation
Exercises performed
Leg extensions
Bicep curls
Sit-to-stand
Step ups
Pole raises
Knee lifts
Walking on flat or incline
Cycling on exercise bike

At completion of each visit, participants were given an ActiGraph wGTX3-BT (ActiGraph, Pensacola, USA) accelerometer and asked to wear it on their non-dominant wrist constantly for seven days, only removing it for water-based activities. After accelerometer return the data were downloaded and processed as detailed in the online supplement (see 3. Details of accelerometry recording and data processing).

The PR course began the following week, and V2 was scheduled for eight weeks later after course completion. V2 was postponed if appropriate depending on the time taken for each participant to complete all eight sessions. V3 was scheduled 1 year after V1. The format for visits 2 and 3 was similar to V1, but with any intervening changes in health or medications since the previous visit noted.

From the onset of the Covid pandemic, research activity continued in line with local lockdown rules. When face-to-face study visits were not permitted, but research staff were available, remote visits were performed by telephone call. This allowed for collection of data including questionnaires and exacerbation history to be collected.

Primary and Secondary Outcomes

The primary outcome of the original study was difference in change in AQLQ between visits immediately before and after pulmonary rehabilitation versus usual care.[23] Secondary outcomes included changes in ACQ, AQLQ (including separate domains), treatment burden (maintenance prednisolone use, asthma exacerbations requiring prednisolone boosts), healthcare usage (unscheduled GP and ED attendances, hospital admissions), MRC dyspnoea score, HADS, BMI, FeNO, spirometry, 6MWT distance, and Borg score, for all participants between baseline, immediately after PR, and at 1 year.

Statistical Analysis

Baseline characteristics are expressed as mean with standard deviation (SD), median and interquartile range (IQR), or numbers and proportions as appropriate. Results are expressed as mean with 95% confidence intervals or median and interquartile range. Normality testing was performed using D'Agostino–Pearson test. A p value of <0.05 was considered significant.

Statistical methodology was selected to achieve intention-to-treat analysis, but there were a number of missing values due to cancellation of face-to-face visits because of the Covid-19 pandemic. Outcomes analysis for normally distributed variables used mixed effects models (where missing values, $n=54$) or repeated measures analysis of variance (where no missing values); variables with non-parametric distribution were analysed using the Friedman test. The Friedman test could not compute with missing data so $n=45$ for variables with no missing data that could be collected virtually and $n\leq37$ where data collection required face-to-face visits.

A responder analysis was subsequently performed to identify factors associated with achievement of the minimum clinically important difference (MCID) for ACQ6 between V1 and V2, and V1 and V3. Difference between visits 1 and 2, and 1 and 3 were calculated, and any participant demonstrating improvement of at least the MCID (≥0.5 points[29]) was defined a responder. For each factor, comparisons between responder and non-responder group were made using Fisher's exact test for proportions, unpaired t test, or Mann–Whitney U as appropriate. Factors identified as significantly different between responders and non-responders were then analysed further using simple logistic regression analysis.

Results

A total of 101 participants provided written informed consent and were recruited into the original trial (see Figure 1). Of 95 randomised participants, 92 commenced pulmonary rehabilitation, and 56 completed V2 after PR; 2 of 56 completing V2 did so by telephone and were not included in the outcome analysis (n=54).

Baseline Characteristics (See Table 1)

For the 92 patients commencing PR, mean age was 60 years (±13), 60% were female, 41% were ex-, 51% never-, and 8% current smokers, and median BMI was 33.8 kg/m^2 (29.5–38.7). Median (IQR) age at diagnosis was 30 (6–45) and asthma duration 22 (10–40) years. Commonest co-morbidities included gastro-oesophageal reflux disease (80%), allergic rhinitis (73%), and psychological illness (63%). Median daily beclometasone diproprionate (BDP) dose was 1700 mcg (IQR

Figure 1 Flowchart of recruitment.

1600–2000), and 27% took maintenance OCS. Median (IQR) number of annual exacerbations requiring prednisolone was 4 (2–5), with 2 (0–4) annual unscheduled GP visits.

Baseline mean (SD) ACQ6 score was 2.7 (±1.3) and asthma-related quality of life score mean 4.0 (±1.2). Pre-bronchodilator $FEV_{1\%}$ predicted was 73.1 (±16.8), and FEV_1/FVC (forced vital capacity) ratio 65.9 (±10.0)%. Median

Table 1 Characteristics of the Population Commencing PR in This Study, Prior to the Intervention. Results Expressed as Median (Interquartile Range) or Number and % Unless Otherwise Specified

	n = 92
Age, years – mean (±SD)	60 (13)
Male sex	37 (40%)
BMI, kilogram/metre^2	33.8 (29.5–38.7)
Smoking status: Ex-smoker Lifelong non-smoker Current smoker	38 (41%) 47 (51%) 7 (8%)
Pack years	20 (9–35)
Age at diagnosis, years	30 (6–45)

(*Continued*)

Table 1 (Continued).

	n = 92
Disease duration, years	22 (10–40)
Atopy	61 (66%)
Allergic rhinitis	67 (73%)
Nasal polyps	14 (15%)
Nasal surgery	19 (21%)
Eczema	20 (22%)
GORD	74 (80%)
DFB/VCD	17 (19%)
Psychological illness	58 (63%)
Emphysema	7 (8%)
Bronchiectasis	14 (15%)
SAFS/ABPA	18 (20%)
LAMA	76 (83%)
BDP equivalent dose micrograms	1700 (1600–2000)
Maintenance prednisolone	25 (27%)
Biologic therapy	19 (21%)
Asthma exacerbations in last year	4 (2–5)
GP attendances in last year	2 (0–4)
ED attendances in last year	0 (0–1)
Hospital admissions in last year	0 (0–1)
MRC dyspnoea score	3 (2–4)
ACQ6 – mean (±SD)	2.7 (±1.3)
AQLQ: overall – mean (±SD) Symptom domain – mean (±SD) Activity domain – mean (±SD) Emotional domain – mean (±SD) Environmental domain – mean (±SD)	4.0 (±1.2) 4.0 (±1.3) 3.9 (±1.2) 4.1 (±1.6) 4.2 (±1.6)
HAD Anxiety score – mean (±SD) HAD Depression score – mean (±SD)	9.0 (±4.9) 8.2 (±4.5)
Blood eosinophil count ($\times 10^9$/litre)	0.3 (0.01–0.4)
FeNO (parts per billion)	23 (12–46)
Pre-BD FEV_1 (% predicted) mean (±SD)	73.1 (±16.8)
Pre-BD FEV_1/FVC % mean (±SD)	65.9 (±10.0)
% change in FEV_1 with BD	4.4 (−1.3 to 9.5)
6MWD, meters	390 (335–450)

(*Continued*)

Table 1 (Continued).

	n = 92
Borg score post- 6MWT	2 (0.5–3)
Inactive time, minutes/day	1176 (1107–1239)
Light PA, minutes/day	215.4 (168.4–268.8)
Moderate-vigorous PA, minutes/day	47.7 (25.2–66.8)

Abbreviations: SD, standard deviation; GORD, gastro-oesophageal reflux disease; DFB, dysfunctional breathing; VCD, vocal cord dysfunction; SAFS, severe asthma with fungal sensitisation; ABPA, allergic bronchopulmonary aspergillosis; LAMA, long-acting anti-muscarinic; ICS, inhaled corticosteroid; LABA, long-acting beta2-agonist; BDP, beclomethasone diproprionate equivalent dose; GP, general practitioner; ED, emergency department; BMI, body mass index; MRC, Medical Research Council; ACQ6, 6-point asthma control questionnaire; AQLQ, asthma-related quality of life questionnaire; HADS, hospital anxiety and depression scale; FeNO, fraction exhaled nitric oxide; pre-BD FEV1, pre-bronchodilator forced expiratory volume in 1 second; FVC, forced vital capacity; BD, bronchodilator; 6MWD, six-minute walk distance; 6MWT, six-minute walk test; PA, physical activity.

(IQR) distance for six-minute walk test was 390 (335–450) meters. Median daily minutes spent inactive was 1176 (1107–1239) and in moderate-vigorous physical activity was 47.7 (25.2–66.8).

Patients completing V2 (n=56) were older (56 (11) versus 48 (14) years, p=0.003), were diagnosed with asthma at older age (34 (22–48) versus 12 (3–38) years, p=0.006), had fewer GP (2 (0–3) versus 3 (0–7), p=0.039) and ED (0 (0–1) versus 0 (0–2), p=0.049) attendances, and had higher AQLQ (4.1 (1.3) versus 3.7 (0.9), p=0.044), than those that did not complete V2 (n=36); see Table S1. Patients completing 8 PR sessions (n=48) were older (58 (11) versus 48 (13) years, p<0.001), were diagnosed with asthma at older age (40 (22–49) versus 16 (3–36) years, p<0.001), and had fewer ED attendances (0 (0–0) versus 0 (0–1), p=0.017), than those that completed <8 PR sessions (n=44); see Table S2.

Immediate and One-Year Outcomes Following PR (See Table 2 and Figure 2)

Comparing V1, V2, and V3, respectively, significant differences were seen for ACQ6 (mean (95% CI) 2.5 (2.1–2.9), 2.2 (1.8–2.5), and 2.3 (1.9–2.7); p=0.003). Significant differences were also demonstrated for MRC dyspnoea score (median (IQR) at V1, 3 (2–4); V2, 3 (2–3); and V3, 3 (2–4); p=0.010) and Borg score at completion of longest 6MWT (median (IQR) 2 (0.5–3), 1 (0–2), and 1 (0.5–2), p=0.035). No significant differences were found for AQLQ (mean (95% CI) 4.2 (3.8–4.5), 4.3 (4.0–4.7), and 4.2 (3.9–4.6); p=0.325), separate AQLQ domains, Hospital Anxiety Depression Scale, or other variables.

Table 2 Table Comparing Results for Relevant Asthma Outcomes Between Visit 1 (V1), Visit 2 (V2), and Visit 3 (V3). Results Shown as Median (Interquartile Range) Unless Otherwise Specified. N= Column Displays Number of Participants Included in That Analysis and Statistical Test Used (See methods, Statistical Analysis for Details of Variation)

Asthma Measure	n=; Test Used	V1	V2	V3	P value
BMI, kilogram/metre^2	37; Friedman	32.8 (29.7–36.0)	32.1 (29.4–35.5)	32.5 (28.9–34.8)	0.009
Asthma exacerbations	45; Friedman	3 (2–5)	0 (0–4.7)	1.5 (0–4.2)	0.003
GP visits	45; Friedman	2 (0–3.5)	0 (0–5.1)	0 (0–2.9)	0.025
ED visits	45; Friedman	0 (0–0.5)	0 (0)	0 (0)	0.262
Hospital admissions for asthma	45; Friedman	0 (0–1)	0 (0)	0 (0)	0.104
MRC dyspnoea score	45; Friedman	3 (2–4)	3 (2–3)	3 (2–4)	0.010
ACQ6, mean (95% CI)	54; MEM	2.5 (2.1–2.9)	2.2 (1.8–2.5)	2.3 (1.9–2.7)	0.003

(*Continued*)

Table 2 (Continued).

Asthma Measure	n=; Test Used	V1	V2	V3	P value
AQLQ total, mean (95% CI)	54; MEM	4.2 (3.8–4.5)	4.3 (4.0–4.7)	4.2 (3.9–4.6)	0.325
AQLQ Symptoms	54; MEM	4.2 (3.8–4.6)	4.3 (4.0–4.7)	4.3 (3.9–4.7)	0.467
AQLQ Activity	54; MEM	4.0 (3.6–4.3)	4.2 (3.9–4.6)	4.1 (3.7–4.6)	0.139
AQLQ Emotional	54; MEM	4.4 (3.9–4.8)	4.5 (4.1–5.0)	4.4 (3.9–4.9)	0.208
AQLQ Environmental	54; MEM	4.3 (3.9–4.7)	4.3 (3.9–4.7)	4.4 (3.9–4.9)	0.824
HADS: Anxiety	45; Friedman	7 (5.5–11)	8 (4–13)	7 (3–11.5)	0.228
HADS Depression, mean (95% CI)	54; MEM	8.2 (6.9–9.5)	8.0 (6.6–9.3)	7.1 (5.8–8.4)	0.251
Blood eosinophils $\times 10^9$/litre	31; Friedman	0.3 (0.2–0.5)	0.2 (0.1–0.4)	0.2 (0.1–0.3)	0.059
FeNO, parts per billion	34; Friedman	33.5 (11.5–53.3)	24.5 (12.8–49.0)	25.5 (9–46.3)	0.365
Pre-BD FEV_1%, mean (95% CI)	54; MEM	73.4 (67.2–77.5)	72.1 (66.9–77.4)	70.9 (65.7–76.0)	0.478
Pre-BD FEV_1/FVC, mean (95% CI)	54; MEM	65.9 (63.3–68.4)	64.9 (61.9–67.8)	64.7 (60.9–68.4)	0.928
% FEV_1 reversibility	33; Friedman	3.6 (−1.4 to 8.1)	2.5 (−0.1 to 0.7)	3.8 (0–8.3)	0.754
6MWD, meters	32; Friedman	390 (334–450)	410 (323–460)	395 (285–456)	0.418
Borg score	32; Friedman	2 (0.5–3)	1 (0–2)	1 (0.5–2)	0.035
Inactive time, minutes/day	21; Friedman	1180 (1121–1222)	1176 (1124–1228)	1152 (1082–1220)	0.368
LPA, minutes/day	21; Friedman	206 (166–250)	203 (173–264)	219 (188–277)	0.854
MVPA, minutes/day	21; Friedman	41 (27–76)	51 (27–70)	48 (28–80)	0.505

Abbreviations: Asthma exacerbations, annualised number of asthma exacerbations requiring prednisolone; GP visits, annualised visits to a general practitioner; ED visits, annualised visits to emergency departments; Hospital stays, annualised number of hospital stays; BMI, body mass index; MRC, Medical Research Council; ACQ6, 6-point asthma control questionnaire; AQLQ, asthma-related quality of life questionnaire; HADS, hospital anxiety and depression scale; FeNO, fraction exhaled nitric oxide; pre-BD FEV1, pre-bronchodilator forced expiratory volume in 1 second; Pre-BD FEV_1/FVC, pre-bronchodilator forced expiratory volume in 1 second/forced vital capacity ratio; 6MWD, six-minute walk distance; LPA, light physical activity; MVPA, moderate-vigorous physical activity; CI, confidence interval; MEM, mixed effects model.

There were significant but small changes in BMI, with median (IQR) at: V1, 32.8 kg/m^2 (29.7–36.0); V2, 32.1 (29.4–35.5); and V3, 32.5 (28.9–34.8), p=0.009. The 6-minute walk distance did not change between visits. In addition, there was a significant reduction in the number of participants taking maintenance OCS, with 16 (36%) at V1, 13 (29%) at V2, and 12 (27%) at V3, p=0.039.

Significant differences were found for asthma exacerbations requiring prednisolone (median (IQR) 3 (2–5), 0 (0–4.7), and 1.5 (0–4.2), p=0.003) and urgent, unscheduled GP visits (median (IQR) 2 (0–3.5), 0 (0–5.1), and 0 (0–2.9), p=0.025) but not for emergency department attendances or hospital admissions for asthma. Nor were there any significant differences in physical activity measured by accelerometry.

Immediate and One-Year ACQ6 Responders to PR and Predictors of Response

A total of 27 of 56 (48%) participants were ACQ6-responders (ie achieved MCID of ≥-0.5) between V1 and V2 (early-responders). Of 48 participants, 16 (33%) were ACQ6-responders between V1 and V3 (late-responders). Of these 16, 9 maintained response at 1 year, and 7 had a new significant improvement. Of the original 27 responders, 9 (33%) maintained benefit at 1 year, 12 (44%) lost benefit, with 6 (22%) lost to follow-up.

Table 3 compares immediate ACQ6-responders and non-responders, ie those who achieved an improvement of ≥0.5, the minimum clinically important difference in ACQ6 score, between visits 1 and 2. Significant differences were found for baseline MRC dyspnoea score (mean (SD) 3.2 (1.1) vs 2.6 (1.1); p=0.040), baseline ACQ6 score (mean (SD) 2.9 (1.3) vs 2.0 (1.3); p=0.015), baseline AQLQ score (mean (SD) 3.7 (1.1) vs 4.6 (1.2); p=0.009), as well as similar differences in baseline symptom, activity, and emotional AQLQ domains.

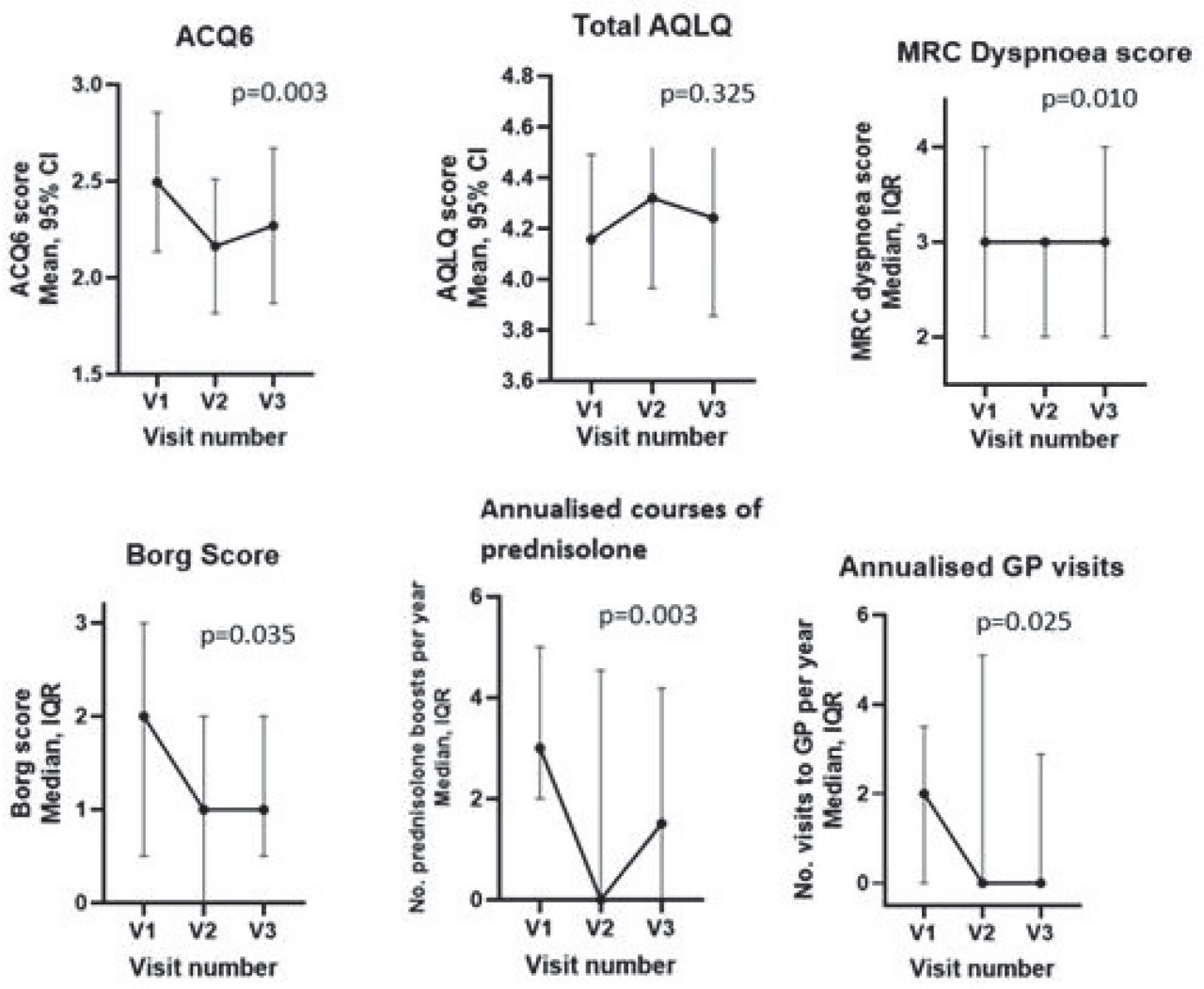

Figure 2 Graphs showing results of relevant outcomes at visits 1 (V1), 2 (V2), and 3 (V3). Abbreviations: ACQ6, 6-point asthma control questionnaire; AQLQ, asthma-related quality of life questionnaire; MRC, Medical Research Council; GP, general practitioner.

Table 4 compares long-term ACQ-responders and non-responders, ie those who achieved an improvement of ≥0.5, the minimum clinically important difference in ACQ6 score, between visits 1 and 3, versus those who did not. There

Table 3 Table Comparing the Baseline Characteristics of Those Who Responded in Terms of ACQ6 Between Visits 1 (V1) and 2 (V2) to Those Who Did Not Respond. ACQ6 Response Was Defined as an Improvement of ≥0.5, the Minimum Important Clinical Difference in ACQ6 Score, Between Visits 1 and 2. All Results Expressed as Mean (Standard Deviation), Median (Interquartile Range), or Number and Percentage

Category	ACQ6 Responders (n=27)	ACQ6 Non-responders (n=29)	P value
Age, years	55 (12)	58 (9)	0.217
Sex: Male	15 (56%)	9 (38%)	0.104
BMI, kilogram/metre^2	33.9 (31–35.9)	32.5 (28.5–38.4)	0.617

(*Continued*)

Table 3 (Continued).

Category	ACQ6 Responders (n=27)	ACQ6 Non-responders (n=29)	P value
Pack years	0 (0–20)	0 (0–11)	0.335
Allergic rhinitis	16 (59%)	22 (76%)	0.254
Perennial rhinitis	8 (30%)	19 (65%)	0.009
Psychological illness	18 (67%)	17 (59%)	0.589
Maintenance OCS	10 (37%)	9 (31%)	0.779
Asthma exacerbations	4 (2–4)	3 (2–5.5)	0.381
GP visits	1 (0–3)	2 (1–4)	0.172
ED visits	0 (0–0)	0 (0–1)	0.236
Hospital admissions for asthma	0 (0–1)	0 (0–1)	0.161
MRC dyspnoea score	3.2 (1.1)	2.6 (1.1)	0.040
ACQ6	2.9 (1.3)	2.0 (1.3)	0.015
AQLQ: Overall AQLQ Symptoms AQLQ Activity AQLQ Emotional AQLQ Environmental	3.7 (1.1) 3.7 (1.4) 3.6 (1.1) 3.9 (1.7) 4.1 (1.5)	4.6 (1.2) 4.7 (1.4) 4.4 (1.3) 4.8 (1.4) 4.7 (1.4)	0.009 0.010 0.015 0.030 0.109
HADS Anxiety HADS Depression	9.3 (2.5) 9.4 (4.8)	8.5 (5.3) 7.4 (4.6)	0.602 0.111
Blood eosinophils $\times 10^9$/litre	0.3 (0.1–0.4)	0.3 (0.2–0.65)	0.269
FeNO, parts per billion	20 (10–41)	36 (15.5–64.5)	0.061
Pre-BD FEV_1% predicted	72.8 (16.2)	72.6 (15.8)	0.964
Pre-BD FEV_1/FVC	65.1 (10.4)	65.9 (9.3)	0.751
% FEV_1 change with BD	1.0 (−3.2 to 5.8)	4.9 (−1.6 to 8.4)	0.233
6MWD, meters	375 (280–410)	405 (315–450)	0.210
Borg score	2.3 (1.2)	2.0 (1.5)	0.420
Time between V1-V2, days	87 (63–102)	95 (76–109)	0.262

Abbreviations: OCS, oral corticosteroid; asthma exacerbations, annualised number of asthma exacerbations requiring prednisolone; GP visits, annualised visits to a general practitioner; ED visits, annualised visits to emergency departments; hospital stays, annualised number of hospital stays; BMI, body mass index; MRC, Medical Research Council; ACQ6, 6-point asthma control questionnaire; AQLQ, asthma-related quality of life questionnaire; HADS, hospital anxiety and depression scale; FeNO, fraction exhaled nitric oxide; pre-BD FEV_1, pre-bronchodilator forced expiratory volume in 1 second; Pre-BD FEV_1/FVC, pre-bronchodilator forced expiratory volume in 1 second/forced vital capacity ratio; 6MWD, six-minute walk distance.

were similar results with significant differences for baseline MRC dyspnoea score (median (IQR) 3 (3–4) vs 2 (2–4); p=0.033), baseline ACQ6 score (mean (SD) 3.1 (1.3) vs 2.1 (1.3); p=0.013), AQLQ score (mean (SD) 3.7 (1.3) vs 4.5 (1.3); p=0.038) as well as similar differences in baseline AQLQ symptom score.

Regression analyses (Tables 5 and 6) confirmed the above results, suggesting that participants with a worse baseline ACQ6 or AQLQ score were more likely to respond to PR.

Table 4 Comparing the Baseline Characteristics of Those Who Responded in Terms of ACQ6 Between Visits 1 and 3 to Those Who Did Not Respond. ACQ6 Response Was Defined as an Improvement of ≥0.5, the Minimum Important Clinical Difference, in ACQ6 Score Between Visits 1 and 3. All Results Expressed as Mean (Standard Deviation), Median (Interquartile Range), or Number and Percentage

Category	ACQ Responders (n=16)	ACQ Non-responders (n=32)	P value
Age, years	56 (12)	57 (11)	0.906
Sex: Male	7 (44%)	14 (41%)	>0.999
BMI, kilogram/metre^2	31.6 (30.2–35.2)	34.1 (29.3–38.0)	0.326
Pack years	0 (0–19)	0 (0–16)	0.843
Allergic rhinitis	11 (69%)	20 (63%)	0.757
Perennial rhinitis	8 (50%)	14 (44%)	0.764
Psychological illness	8 (50%)	20 (64%)	0.537
Maintenance OCS	6 (38%)	10 (31%)	0.750
Asthma exacerbations	4 (2.25–5)	2.5 (2–4)	0.056
GP visits	2 (0–3)	2 (0.3–4)	0.578
ED visits	0 (0–0.75)	0 (0–1)	0.950
Hospital admissions	0 (0–1)	0 (0–1)	0.789
MRC dyspnoea score	3 (3–4)	2 (2–4)	0.033
ACQ6	3.1 (1.3)	2.1 (1.3)	0.013
AQLQ: overall AQLQ Symptoms AQLQ Activity AQLQ Emotional AQLQ Environmental	3.7 (1.3) 3.6 (1.4) 3.6 (1.2) 4.0 (1.8) 3.6 (1.7)	4.5 (1.3) 4.6 (1.4) 4.2 (1.3) 4.6 (1.5) 4.6 (1.5)	0.038 0.018 0.123 0.223 0.061
HADS Anxiety HADS Depression	8.6 (4.7) 8.4 (4.8)	8.2 (4.7) 7.4 (4.3)	0.814 0.442
Blood eosinophils ×10^9/litre	0.3 (0.2–0.5)	0.2 (0.1–0.4)	0.211
FeNO, parts per billion	41 (12.5–65.8)	19 (11.8–47)	0.284
Pre-BD FEV_1% predicted	75.4 (17.8)	72.3 (15.8)	0.542
Pre-BD FEV_1/FVC	68.0 (11.0)	64.2 (9.5)	0.216
% FEV_1 change with BD	1.7 (6.8)	3.6 (7.8)	0.405
6MWD, meters	340 (234–450)	390 (315–450)	0.331
Borg score	2 (1.3)	2.2 (1.5)	0.620
Time between V1–V2, days	95 (77–106)	89 (69–105)	0.500

Abbreviations: OCS, oral corticosteroid, asthma exacerbations – annualised number of asthma exacerbations requiring prednisolone; GP visits, annualised visits to a general practitioner; ED visits, annualised visits to emergency departments; hospital stays, annualised number of hospital stays; BMI, body mass index; MRC, Medical Research Council; ACQ6, 6-point asthma control questionnaire; AQLQ, asthma-related quality of life questionnaire; HADS, hospital anxiety and depression scale; FeNO, fraction exhaled nitric oxide; pre-BD FEV1, pre-bronchodilator forced expiratory volume in 1 second; Pre-BD FEV_1/FVC, pre-bronchodilator forced expiratory volume in 1 second/forced vital capacity ratio; 6MWD, six-minute walk distance; time between V1-V2, time between visit 1 and visit 2.

Table 5 Simple Logistic Regression. Significant Variables: MRC Dyspnoea Score, ACQ6, AQLQ, AQLQ Symptoms, AQLQ Activity, AQLQ Emotional, Perennial Rhinitis. Dependent Variable: ACQ Response (1) or Non-Response (0) Between Visit 1 and Visit 2. Classification Cut off, 0.5

Independent Variable	ROC Curve Analysis, Area under Curve (Standard Error)	95% Confidence Interval	P Value	Negative Predictive Value (%)	Positive Predictive Value (%)
MRC dyspnoea score	0.648 (0.073)	0.50–0.79	0.058	56.8	57.9
ACQ6	0.671 (0.072)	0.53–0.81	0.028	61.3	60.0
AQLQ: overall	0.681 (0.071)	0.55–0.83	0.016	67.9	64.3
AQLQ Symptoms	0.701 (0.071)	0.56–0.84	<0.001	65.5	63.0
AQLQ Activity	0.680 (0.071)	0.54–0.82	0.021	63.0	58.6
AQLQ Emotional	0.649 (0.07)	0.51–0.79	0.056	62.5	62.5
Perennial rhinitis	0.679 (0.07)	0.54–0.82	0.021	70.4	65.5

Abbreviations: MRC, Medical Research Council; ACQ6, 6-point asthma control questionnaire; AQLQ, asthma-related quality of life questionnaire.

Table 6 Simple Logistic Regression, Dependent Variable: ACQ Response (1) or Non-Response (0) Between Visit 1 and Visit 3. Significant Variables: MRC Dyspnoea Score, ACQ6, AQLQ Overall, AQLQ Symptoms

Independent Variable	ROC Curve Analysis, Area under Curve (Standard Error)	95% CI	P value	Positive Predictive Value (%)	Negative Predictive Value (%)
MRC dyspnoea score	0.684 (0.077)	0.53–0.84	0.040	71.9	43.8
ACQ6	0.725 (0.078)	0.57–0.88	0.011	71.8	55.6
AQLQ: overall	0.690 (0.083)	0.53–0.85	0.034	69.1	50.0
AQLQ Symptoms	0.720 (0.080)	0.56–0.88	0.014	74.4	66.7

Abbreviations: MRC, Medical Research Council; ACQ6, 6-point asthma control questionnaire; AQLQ, asthma-related quality of life questionnaire.

Discussion

Difficult-to-treat asthma associated with obesity presents significant therapeutic challenges, but our earlier work suggested that asthma-tailored pulmonary rehabilitation has favourable short-term impacts on asthma control, breathlessness, and exercise tolerance in this population.[23] In this prospective, observational, cohort study, we evaluated the immediate and one-year outcomes of this intervention in a larger group than the initial randomised controlled trial with difficult-to-treat asthma and BMI ≥25 kg/m^2. As in the original randomised controlled trial, we have again demonstrated immediate improvements in ACQ6, MRC dyspnoea score, and Borg score. We also show significant reductions in asthma exacerbations, urgent unscheduled GP visits, and proportion of participants on maintenance OCS. Furthermore, these benefits were sustained at one year. Response to the intervention as defined by clinically significant improvement in asthma control was associated with poorer asthma control and quality of life at baseline, as well as increased baseline breathlessness.

The participants in this study were older, with mean age 60 years, tended to be female (60%), were often diagnosed with asthma in adulthood, and had a long duration of disease (median ~20 years). Although eligibility criteria included BMI ≥25 kg/m^2, median (IQR) in our study was 33.8 (29.5–38.7) indicating that the majority of participants were obese

and not just overweight. We did not measure other indices of body fat distribution such as waist circumference, a marker of abdominal fat mass, that may have higher value in prediction of risk for cardio-metabolic disease,[30] but nevertheless our study participants would be expected to have increased risk of diabetes, hypertension, dyslipidaemia, and coronary heart disease. There was a significant burden of co-morbidity, and in particular psychological illness in over 60%. The burden of disease related to asthma was high in our study population. All were using high-dose ICS/LABA, with large proportions using additional therapies, including long-acting muscarinic antagonists in over 80%, maintenance prednisolone in over a quarter, and biologic treatments in over 20%. Despite significant treatment burden, median exacerbation rate at baseline was 4 events/year, with mean ACQ 2.7 and mean AQLQ 4.0, indicating poorly controlled asthma and reduced asthma-related quality of life, respectively. Therefore, our study population represents high asthma-related burden for which there is an unmet need, and for which pulmonary rehabilitation may be beneficial. Benefits of a programme including an exercise component may also extend to management of co-morbidities and, in particular, improving cardio-metabolic risk.

A 2015 prospective observational study of an inpatient pulmonary rehabilitation programme in Germany reported improvements in asthma control test score in participants with asthma at the end of a 3-week intensive programme.[24] The mean ACT score improved by 4.58 points ($p<0.001$) at the end of the 3-week programme, and at one year the mean improvement was 2.48 points ($p<0.001$), MCID for ACT score is 3. In addition, they demonstrated small but statistically significant improvements in FEV_1 (mean 180 mL, 95% CI 120–210 mL, $p<0.001$), in 6MWD (mean improvement 59.89 m, 95% CI 49.09–70.69, $p<0.001$), and in FeNO at the end of the 3 weeks. We did not demonstrate these additional benefits, perhaps as our intervention was less intensive. However, our intervention is much more pragmatic and likely to fit into usual practice. Nonetheless we demonstrated similar improvements in asthma control which were maintained at one year, so this finding is consistent.

A retrospective observational study looked at a small group of participants with severe asthma ($n=28$) alongside participants with COPD ($n=164$) when evaluating a home-based 8-week PR programme and followed them up for 12 months.[31] In the asthma group, there were improvements in 6-minute stepper test at completion of PR (504±150 steps, $p<0.043$) and 12-month follow-up (538±163, $p<0.016$) compared to baseline (450±148), where MCID is 40 steps. They also assessed quality of life using a visual simplified respiratory questionnaire score and found no difference in this immediately post-PR, but an improvement at 12 months compared to baseline (baseline score 32.2±12.4, 12 months 39 ±18.6, $p<0.049$). The quality of life improvements at 12 months are similar to those in our study, although we did not demonstrate significant improvements in 6MWD which would equate to the stepper test.

Turk et al conducted a randomised controlled trial in people with asthma and obesity evaluating the impact of a 12-week pulmonary rehabilitation course involving three times weekly high-intensity interval training. They combined this with prescription of a 1500 kilocalorie diet, with (PR+SMS) or without (PR only) the use of an internet-based self-management support programme, and compared to a control group of participants instructed to lose weight and to exercise.[20] Only 34 participants were randomised, 14 to PR only, 7 to PR+SMS, and 10 to control. Nevertheless, significant weight loss occurred in both intervention groups but not in the control group (PR only: −4.9 ± 4.9 kg; PR +SMS: −10.9 ± 8.4 kg; control: −0.1 ± 1.7 kg). Likewise, ACQ improved significantly in PR only and PR+SMS groups, the median improvements exceeding the minimal clinically important difference of 0.5, but not in the control group (PR only: −0.67 (−1.42–0.00); PR+SMS: −0.66 (−1.17—0.33); control: −0.25 (−0.66–0.63)). When the PR only group was compared to the UC group, there were no differences in ACQ or AQLQ at 3 months, but after 12 months of follow-up the ACQ was significantly lower in the PR vs UC group ($p<0.011$). Again, this improvement in ACQ is consistent with our one-year outcomes.

A Cochrane review of randomised controlled trials of PR versus UC in adults with asthma was published in 2022 after the commencement of our study.[22] The review included 10 studies, ranging in size from $n=24$ to $n=412$ (with only 2 studies of >100 patients), and included 894 individuals in total. The review concluded that PR likely improves exercise capacity as measured by the 6MWT with mean difference (MD) between groups after programme completion of 79.8 meters (95% CI 66.5 to 93.1), the magnitude of mean change exceeding the MCID threshold; but longer-term improvements at one year were less convincing (MD 52.29 meters, 95% CI 0.7 to 103.9). We were unable to demonstrate a change in 6MWT distance immediately after PR or at one year, but this may be, at least partly, explained by loss of

follow-up data during the Covid-19 pandemic. The Cochrane review showed small improvements in asthma control measured by ACQ with MD between groups of −0.46 (95% CI −0.76 to −0.17) but with little or no difference in ACQ at 9 to 12 months (MD 0.09, 95% CI −0.35 to 0.53). Likewise, in our study, some of the improvement in ACQ on programme completion was lost by one year. We chose the AQLQ to evaluate effect on quality of life and did not demonstrate any change in this immediately following PR or at one year. Similar results were obtained in the Cochrane review immediately on programme completion (MD 0.87, 95% CI −0.13 to 1.86) and at longer-term follow-up (MD 0.58, 95% CI −0.23 to 1.38). However, quality of life as measured by St George's Respiratory Questionnaire was significantly improved immediately on programme completion (MD −18.51, 95% CI −20.77 to −16.25) and at longer-term follow-up (MD −13.4, 95% CI −15.93 to −10.88) in the Cochrane review. We, unfortunately, did not measure this outcome. The Cochrane review concluded that PR is probably associated with clinically meaningful improvements in exercise capacity and quality of life at programme completion, but with minimal effect on asthma control, but its conclusions were hampered by unclear methodology and small sample sizes, as well as variations in study design and intervention. Although we concede that our study was observational and not randomised controlled, this allowed us to evaluate the intervention in a much larger sample; a large randomised, controlled study of sufficient duration is required to confirm our short- and longer-term results.

As far as we are aware, only one other study has reported effect of PR on exacerbation rate in asthma.[22] In the study by Turk et al[20] described above there was no difference in proportion of patients with asthma exacerbation during the 3 month intervention between PR and usual care (16.7% versus 55.6%, respectively, p=0.16). During 12 months of follow-up, however, a higher exacerbation rate was seen in the usual care group versus PR (β (poisson rate) = 0.839 (CI 0.116–1.563), p=0.023; RR 2.314 (CI 1.123–4.773)). In our study, pulmonary rehabilitation was associated with reduction in exacerbations requiring prednisolone and urgent, unscheduled GP visit both at visits 2 and 3. However, these outcomes were based only on patient recollection so may be subject to recall bias. In future it would be prudent to confirm formally the numbers of exacerbations and prescriptions for prednisolone. Randomised controlled trials with robust measurement of exacerbation rates are needed to confirm this finding.

Identification of predictors of response to treatment would allow for targeting of this intervention to those who are most likely to benefit from it. In this study we demonstrated that participants with poorer ACQ6, AQLQ, and MRC dyspnoea scores at baseline were more likely to have clinically significant improvement in asthma control following PR. This suggests that targeting this intervention to more symptomatic individuals is likely to increase the likelihood of successful outcomes. We did not find other significant predictive associations, and specifically not with BMI, possibly because the range of BMI was relatively narrow.

Activity levels at baseline, 8 weeks, and 1 year were assessed using accelerometry. We are aware of only one study regarding the effects of PR on activity levels in adults with asthma.[22] In the study by Turk et al described above[20] there was no difference in daily step count or physical activity levels during the 3-month intervention between PR and usual care, but PR was associated with significantly higher daily step count versus usual care at 12 months (β=3200 (CI 1256–5144), p=0.005). Based on this and studies in COPD,[32] we hypothesised that activity levels might be increased following PR, at least in a proportion of patients, and that this might relate to outcome of PR. We found no difference in inactive time and time in light and moderate–vigorous physical activity between baseline, 8 weeks, and 1 year. Unfortunately it was not possible to draw firm conclusions as data were only available for 21 participants at these time points.

Limitations

There are a number of limitations in this work. The design of our original study had an initial 8-week randomised controlled trial, to provide scientific evidence as proof of concept for a novel intervention, followed by offering PR to those initially randomised to the control group. This allowed us to evaluate, in a prospective observational manner, the longer-term effects of PR in a larger treatment group than the original RCT (n=33 in intervention group). The promise of the intervention, albeit delayed 8 weeks, is also likely to have enhanced retention of control group participants. But we cannot exclude the possibility that outcomes may have been affected by other confounding factors. A randomised, controlled trial with longer duration of follow-up would be required to confirm our findings.

When the Covid-19 pandemic began in March 2020 all classes and visits were cancelled. Some participants were therefore unable to complete 8 PR sessions, and some participants were lost to follow-up. After a time some visits were able to take place remotely, but this meant loss of data including measurements of BMI, lung function, and 6MWTs. Questionnaires were conducted over the telephone, and information about exacerbations was relatively complete. The loss of data led to problems with statistical analysis. In order to minimise the impact of lost data in the analysis, data which were normally distributed were analysed with the full, incomplete dataset, but those which did not have a normal distribution analysis included only the participants who had data available for all 3 visits. This likely reduces the study power.

The format of the PR in this study was pragmatic, with only one weekly session and encouragement for participants to perform two sessions at home independently. However, despite this there was a significant drop-out rate: of 101 participants recruited into the initial trial, only 92 began PR, 54 had a second study visit after PR, and 48 attended the one-year follow-up visit. There were many potential reasons for the high drop-out rate (52%), including Covid-19, but the main barriers seemed to be perceived difficulty to exercise, personal, family, and work circumstances. The 2015 Cochrane review of PR[17] suggested that there was a high risk of bias if the drop-out rate of those randomly assigned to PR was >20%. Of the 65 studies included in this review, 22 had drop-out rates exceeding 20%, including those by Casey et al[33] (drop-out rate 22%) and Hernandez[34] et al (drop-out rate 38%), and drop-out rate was as high as 48% in one 2000 study.[35] We did not attempt to monitor or record completion of home exercise sessions in this pragmatic study and acknowledge that some of the participants may not have adhered to the 3 exercise sessions per week recommended by PR guidelines.[16] We performed post-hoc analyses to compare, firstly, patients who completed (n=56) versus did not complete (n=36) a second study visit, and, secondly, patients who completed 8 (n=48) versus completing <8 (n=44) PR sessions. Those attending the second study visit were older, were diagnosed with asthma at older age, had fewer GP and ED attendances, and had higher AQLQ, than those not attending. Age impacted on study engagement perhaps due to factors such as employment or childcare. Patients continuing in the study tended to be "less severe" in terms of healthcare attendances and asthma-related quality of life, and this may have impacted on the magnitude of the benefit seen with PR. Those completing 8 PR sessions were older, were diagnosed with asthma at older age, and had fewer ED attendances, than those completing <8 sessions. Again, age may have impacted on adherence to PR because of factors such as employment or childcare. Patients adhering to PR were "less severe" at least in terms of healthcare attendances, and this might also have impacted on potential to show benefit with PR.

Future Directions

Future studies should further clarify the effects, both immediate and longer term, of pulmonary rehabilitation in difficult-to-treat asthma, whether patients in different BMI categories benefit equally or not, and whether there is a gender difference in response to PR. The optimal format for PR remains to be confirmed. It needs to be accessible to patients regardless of age and other life commitments. For example, offering virtual and online classes both with and without an interactive element and with live and on-demand options may allow wider recruitment and improved retention of participants. Further studies could explore programme intensity, duration, and whether "revision courses" are helpful. Effects of PR in asthma of different severities should be evaluated and strategies to optimise adherence with PR in more severe phenotypes explored. Studying PR in participants with poorer baseline ACQ, AQLQ, and MRC dyspnoea scores may help confirm our findings that the intervention is more likely to be successful in this group. Given the potential benefits of breathing exercises,[36,37] respiratory muscle training,[38,39] and breathing retraining,[40] PR programmes that include a focus on these should be evaluated. Finally, weight management has not been adequately researched among people with severe asthma who are overweight and obese. A PR programme combined with an effective weight management programme, generating and sustaining substantial weight losses, may well lead to more favourable results and deserves a specific randomised trial.

Conclusions

This prospective observational cohort study demonstrated small but significant improvements in asthma control, along with reduced perception of breathlessness at rest and on activity immediately after completion of pulmonary

rehabilitation, and that these benefits were maintained at one year. In addition, there was a significant reduction in asthma exacerbations, measured by annualised number of visits to GP and courses of oral steroids. Participants with poorer asthma control, poorer quality of life, and more significant breathlessness at baseline were more likely to respond to pulmonary rehabilitation. A longer randomised, controlled trial is required to confirm these results, and future studies should identify the optimal format(s) to ensure PR accessibility and adherence in patient groups most likely to benefit.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the West of Scotland Regional Ethics Committee (reference 16/WS/0200). This is the local Ethics Committee for Glasgow including Glasgow Royal Infirmary and University of Glasgow; see West of Scotland Research Ethics Service - NHSGGC. Written informed consent was obtained from all participants prior to any study activity.

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Author Contributions

DCC conceived the idea for the work. DCC, FS, EM, RC, GM, and HCR made substantial contributions to the design. HCR, FS, and DCC were responsible for acquisition of data. HCR, VS, DCC, and DSB were responsible for data analysis. HCR and DCC were responsible for interpretation of data. HCR drafted the work, and DCC, RC, and ML substantively revised it. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Dr Helen Ricketts reports grants from GSK, outside the submitted work. Dr Varun Sharma reports personal fees from AstraZeneca, outside the submitted work. Professor Michael Lean reports personal fees from Counterweight, Novo nordisk, Eli Lilly, and Nestke, outside the submitted work. The authors declare that they have no other competing interests in this work.

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