Physical activity and pulmonary rehabilitation in difficult-to-treat asthma associated with elevated body mass index

Dr Helen Clare Ricketts, MBChB, MRCP (UK)

Submitted in fulfilment of the requirements for the degree of MD, School of Medicine, Dentistry and Nursing, College of Medical, Veterinary and Life Sciences, University of Glasgow

Submitted November 2022.

Thesis Abstract

This thesis studies physical activity levels, pulmonary rehabilitation and their effects in participants with difficult-to-treat asthma associated with elevated body mass index (BMI). The three results chapters present the original research which I conducted during my period of study. All three chapters are presented as contracted papers, two of which have been peer-reviewed and published in scientific journals. This thesis has been approved for submission as an 'alternative format' thesis by the Higher Degrees Committee of the University of Glasgow.

The focus of the thesis is exercise in participants with difficult-to-treat asthma associated with elevated body mass index. There are two research questions addressed by the thesis, do asthma severity or body mass index affect physical activity levels in asthma? The first results chapter concludes that they both do. Secondly, does pulmonary rehabilitation improve asthma control in this group of participants? The results of the work suggest that it may lead to some improvements in asthma control, but not to a clinically significant degree.

"Physical activity levels in asthma: relationship with disease severity, body mass index and novel accelerometer-derived metrics" was published in the Journal of Asthma, online version published 2nd August 2022. This paper reports physical activity (PA) levels in participants with varying degrees of asthma severity and body mass index (BMI). It incorporates the use of two novel accelerometer-based metrics and how they correlate with asthma control. This paper provides an introduction into how difficult-to-treat asthma and elevated BMI affect physical activity and leads onto the main work in pulmonary rehabilitation.

"A pragmatic randomised controlled trial of tailored pulmonary rehabilitation in participants with difficult-to-control asthma and elevated body mass index" was published in BMC Pulmonary Medicine, online version published 24th September 2022. This paper presents the initial outcomes at completion of an eight-week asthma-tailored pulmonary rehabilitation programme, comparing participants who completed PR with a control group who had usual care.

The final results chapter, “Immediate and longer-term effects of an asthma tailored pulmonary rehabilitation programme in overweight and obese participants with difficult-to-treat asthma” has been submitted to Respiratory Medicine, to be considered for publication. This paper presents wider results of the above trial in a prospective observational format, as everyone who was randomised to usual care was invited to participate in PR after completion of the initial 8-week observation period. Here we consider the immediate and longer-term outcomes of a larger group of participants undergoing PR, and look at possible predictors of response.

Contents

List of tables

List of figures

Thesis preface/summary

This thesis considers exercise in terms of physical activity and pulmonary rehabilitation, and evaluates their relationship with difficult-to-treat asthma associated with obesity. The introduction includes a definition and basic introduction to both asthma and obesity, and considers the research questions, before looking at the currently available literature in the field. Materials and methods are covered in the methods section.

The following three chapters present the original research which makes up the thesis. All three chapters are presented in the format of scientific papers, two of which have been peer-reviewed and published in journals, with adaptations for the thesis to avoid excessive repetition.

"Physical activity levels in asthma: relationship with disease severity, body mass index and novel accelerometer-derived metrics" was published in the Journal of Asthma, online version published 2nd August 2022. Here physical activity (PA) levels in participants with different degrees of asthma severity and body mass index (BMI) are recorded and reported. This includes the use of two novel accelerometer-based metrics and assesses how they correlate with asthma control. Participants with mild-moderate asthma of both healthy and overweight BMI spent significantly more time performing activity compared with those with difficult-to-treat asthma with elevated BMI, and this was the case even when age and BMI were considered as confounding variables. In addition, average acceleration (AA), an accelerometer-based metric which represents volume of PA, correlated with markers of asthma control, and when participants were split into quartiles based on AA, the highest quartile had significantly lower BMI, lower doses of inhaled corticosteroids, better lung function, fewer exacerbations and better asthma control and asthma related quality of life scores. This paper provides an introduction into how asthma and body mass index affect physical activity and leads onto the main focus of the thesis- pulmonary rehabilitation.

"A pragmatic randomised controlled trial of tailored pulmonary rehabilitation in participants with difficult-to-control asthma and elevated body mass index" was

published online in BMC Pulmonary Medicine on 24th September 2022. This paper presents the initial outcomes at completion of an eight-week asthma-tailored pulmonary rehabilitation programme. It compares participants who completed PR with a control group who received usual care. The group who underwent PR had statistically significant improvements in 6-point asthma control questionnaire score (ACQ), Medical Research Council (MRC) dyspnoea score, six-minute walk distance (6MWD), and Borg score at completion of 6-minute walk test (6MWT), although none of these improvements met the minimum important clinical difference. In addition, there were high drop-out rates (in line with real-world pulmonary rehabilitation) and challenges with recruitment which suggest the format studied is not the optimal PR format for asthma. What the optimal format would be is currently not known, but alternative options will be considered throughout the thesis.

The final results chapter, "Immediate and longer-term effects of an asthma tailored pulmonary rehabilitation programme in participants with difficult-to-treat asthma associated with elevated body mass index" has been submitted to Respiratory Medicine to be considered for publication. This paper presents wider results of the above trial in a prospective observational format. All participants who were randomised to usual care in the randomised controlled trial was invited to participate in PR after completion of the initial 8-week observation period. This paper considers the immediate and longer-term outcomes of larger group of participants undergoing PR, as well as aiming to define predictors of response. Most of the significant results from the randomised controlled trial were replicated in this format, and several improvements were maintained at 1 year's follow up.

Acknowledgements

The undertaking of this work has taken a great deal of time and effort from a large number of people. Initially I would like to thank my main supervisor Douglas Cowan who has helped with ideas, advice and encouragement at every stage of the work and this work would not have been completed without him. My primary university supervisor Mike Lean has provided a great deal of advice and knowledge from his extensive research experience and has been incredibly helpful. My colleague Varun Sharma helped cover the final visits whilst I was on maternity leave, helped with some data analysis and critically analysed my papers and has provided insightful advice. Rekha Chaudhuri has provided advice from the beginning to end of the work, and her input has been invaluable.

The research nurses with whom I worked were wonderful and again, this work would not have been possible without them- Femke Steffensen, Helen Bannister, Lynne Turner and Anna Goodfellow in particular. I would also like to thank the staff of the Glasgow Royal Infirmary Clinical Research Facility for their assistance in booking appointments, looking after our participants and maintaining the equipment.

The Glasgow Royal Infirmary Pulmonary Rehabilitation Team led by Elaine Mackay and Jacquie Fabian were an integral part of the work in the pulmonary rehabilitation studies, and this none of this would have been possible without them. Gordon MacDonald provided some excellent talks for the education aspect of the PR and his sessions were some of the most thought-provoking for the participants.

My reviewers, Peter Langhorne and Terry Quinn provided a lot of encouragement and useful advice throughout the reviews they conducted. The university staff at MVLS graduate school and the School of Medicine provided support and guidance throughout my period of study.

Duncan Buchan from the University of the West of Scotland was instrumental in teaching me how to use accelerometers. He wrote the R script used to extract data from each accelerometer, and transformed and processed this in the GGIR package to provide meaningful output for me to analyse. Julien Baker was also involved with aspects of the accelerometer data collection in the physical activity study.

Most of this work was funded from an NHS endowment grant belonging to the supervisor Douglas Cowan. The third chapter was funded by a joint innovation grant from Asthma UK and the Chief Scientist's Office awarded in 2018. I am grateful for this funding which allowed the work to be completed.

Finally I would like to thank my family- my husband Dean and my parents Cheryl and Mark for their unwavering support, encouragement and childcare provision, and my sister Laura for her encouragement and support. I thank my daughters Olivia and Anna for being wonderful. I look forward to having more free time to spend with you all once this thesis is complete!

Author's declaration

I declare that the work contained in this thesis is my own work and has not been submitted for any other degree at the University of Glasgow or any other educational institution. Other colleagues have contributed to published and submitted papers as in the accompanying declaration document and stated in each chapter.

Signed: *H. C. Ricketts*
Name: Helen Clare Ricketts

List of Publications

Ricketts HC, Cowan DC; Asthma, obesity and targeted interventions; Current Opinion in Allergy and Clinical Immunology; 2019, 19: 68-74. DOI:10.1097/ACI.0000000000000494.

Ricketts HC, Buchan DS, Steffensen F, Chaudhuri R, Baker JS, Cowan DC; Physical activity levels in asthma: relationship with disease severity, body mass index and novel accelerometer-derived metrics; Journal of Asthma, 2022 Aug 2;1-11. DOI:10.1080/02770903.2022.2102037

Ricketts HC, Sharma V, Steffensen F, Goodfellow A, Mackay E, MacDonald G, Buchan DS, Chaudhuri R, Cowan DC. A pragmatic randomised controlled trial of tailored pulmonary rehabilitation in participants with difficult-to-control asthma and elevated body mass index; BMC Pulmonary Medicine, 2022 Sep 24;22(1):363. DOI: 10.1186/s12890-022-02152-2

List of abbreviations

6MWD- six-minute walk distance
6MWT- six-minute walk test
AA- average acceleration
A and E- accident and emergency department
ABPA- allergic bronchopulmonary aspergillosis
ACT- asthma control test
ACQ6- 6-point asthma control questionnaire
ACQ- full (7-point) asthma control questionnaire
AHR- airway hyperreactivity
ANOVA- analysis of variance
AQLQ- asthma-related quality of life questionnaire
ATS- American Thoracic Society
BD- bronchodilator
BDP- beclomethasone dipropionate dose equivalent
BMI- body mass index
BTS- British Thoracic Society
CI- confidence interval
COPD- chronic obstructive pulmonary disease
DAR- Difficult Asthma Registry
DFB- dysfunctional breathing
DOW- difficult-to-treat asthma, overweight group
ENMO- Euclidean Norm Minus One
ERS- European Respiratory Society
ERV- expiratory reserve volume
FEV_1- forced expiratory volume in 1 second
FeNO- fraction of exhaled nitric oxide
FRC- functional residual capacity
FVC- forced vital capacity
GLI- Global Lung Initiative
GORD- gastro-oesophageal reflux disease
GP- General Practitioner
H2A- H2 receptor antagonist

HADS- hospital anxiety and depression scale

ICS- inhaled corticosteroid

ICU- intensive care unit

IG- intensity gradient

IgE- immunoglobulin E

IL-4- interleukin-4

IL-5- interleukin-5

IL-13- interleukin-13

ILD- interstitial lung disease

ILO- intermittent laryngeal obstruction

IQR- interquartile range

LABA- long-acting beta-2 agonist

LAMA- long-acting muscarinic antagonist

LPA- light physical activity

LTRA- leukotriene receptor antagonist

MCID- minimum clinically important difference

MHW- mild-moderate asthma, healthy weight group

MOW- mild-moderate asthma, overweight group

MRC- Medical Research Council

MVPA- moderate-vigorous physical activity

OCS- oral corticosteroid

PA- physical activity

PEFR- peak expiratory respiratory flow rate

PPI- proton pump inhibitor

PR- pulmonary rehabilitation

REC- regional ethics committee

SABA- short-acting beta-2 agonist

SAFS- severe asthma with fungal sensitisation

SD- standard deviation

SIGN- Scottish Intercollegiate Guidelines Network

T2-high- features consistent with high degree of type 2 inflammation

T2-low- features consistent with no/low degree of type 2 inflammation

TH2- T helper cells type 2

TLC- total lung capacity

TNF-α- tumour necrosis factor alpha

UC- usual care

V1- visit 1

V2- visit 2

V3- visit 3

WHO- World Health Organisation

Chapter 1: Introduction and Literature Review

1.1. What is asthma?

Asthma is a common and heterogeneous airways disease characterised by symptoms of wheeze, shortness of breath, cough and chest tightness. It is associated with features of airway inflammation, typically chronic, along with either airway hyper-reactivity or variable expiratory airflow limitation(Global Initiative for Asthma 2022). It is a very common diagnosis, affecting approximately 8% of adults in the United Kingdom(Asthma UK 2019). By definition it is heterogeneous, and there is a dramatic variation in symptom burden, from patients with only a minor infrequent cough to those with constant disabling symptoms of breathlessness.

Diagnosis of asthma relies on a good clinical history accompanied by evidence of variable airflow obstruction. Ideally this is demonstrated on spirometry with reversibility or there may be evidence of airway hyper-reactivity on bronchial challenge testing(Scottish Intercollegiate Guidelines Network 2016; Global Initiative for Asthma 2022). In primary care, the diagnosis is often made on the basis of significant variability on peak expiratory flow monitoring. Measurements such as fraction of exhaled nitric oxide (FeNO), eosinophil count (blood and/or sputum) and immunoglobulin E (IgE), both in total and to specific aero-allergens, can be used to provide supportive evidence of asthma(British Thoracic Society and Scottish Intercollegiate Guidelines Network. 2019).

Treatment of asthma is traditionally with inhaled corticosteroids (ICS) and short-acting beta-2 agonists (SABA) initially. More recently, use of formoterol, a long-acting beta-2 agonist (LABA), in a combination inhaler with budesonide ICS for as required use has demonstrated improved outcomes compared to use of SABA alone(O'Byrne et al. 2018) or SABA and ICS(Bateman et al. 2018). In patients who continue to have symptoms despite ICS, options include the addition of long-acting beta-2 agonists (LABA), long acting muscarinic antagonists (LAMA), leukotriene receptor antagonists (LTRA), as well as up-titration of ICS in a stepwise fashion. Oral corticosteroids (OCS) are sometimes given long-term in

patients who remain symptomatic despite high dose ICS with LABA, LAMA and LTRA(Scottish Intercollegiate Guidelines Network 2016; Global Initiative for Asthma 2022). Oral corticosteroids increase appetite, and often lead to weight gain and are associated with numerous other side-effects including development of diabetes mellitus and osteoporosis.

More recently, biologic therapies targeting specific pathways involved in airway inflammation have become part of the treatment of severe or difficult-to-treat asthma in those with suitable phenotypes. They treat T2-high disease- i.e. where type 2 airway inflammation is the driver of symptoms and exacerbations. There are four biologic therapies currently approved for use in Scotland. Omalizumab, which targets IgE in allergic asthma, was the first available (Norman et al. 2013). Mepolizumab (Haldar et al. 2009) and benralizumab(Nair et al. 2017) target interleukin-5 (IL-5) and lower eosinophil count in eosinophilic asthma. Dupilumab acts on the IL-4 and IL-13 pathways and reduces eosinophil counts in eosinophilic asthma(Castro et al. 2018). Bronchial thermoplasty involves the direct application of heat to distal airways using a probe inserted via a bronchoscope. Improvements in asthma control have been demonstrated to be sustained at >10 years of follow-up(Chaudhuri et al. 2021). There is likely to be a significant placebo effect.

Co-morbidities frequently co-exist with asthma, including gastro-oesophageal reflux disease (GORD), rhinosinusitis, obesity, depression and dysfunctional breathing. Identification and treatment of co-morbidities is important in order to improve asthma control and overall well-being. In some cases it can be difficult to determine whether symptoms are entirely due to asthma or whether the co-morbidity is responsible for a degree of symptoms. This is particularly the case with obesity and asthma. Detailed clinical history is important in determining cause of symptoms.

Difficult-to-control(British Thoracic Society and Scottish Intercollegiate Guidelines Network. 2019) or difficult-to-treat(Global Initiative for Asthma 2022) asthma is a term used to describe patients with asthma that inadequately controlled despite prescription of high-dose asthma therapies. Control is considered to be inadequate when patients have ongoing asthma symptoms or

frequent exacerbations. In these patients, confirmation of the diagnosis of asthma is important, and thorough assessment is required to identify why their asthma symptoms persist. Common reasons include suboptimal treatment adherence, co-morbidities including psychosocial issues, obesity, dysfunctional breathing, and in some cases genuine severe asthma.

According to the Global Initiative for Asthma, uncontrolled asthma is defined as either persistent asthma symptoms, or frequent exacerbations requiring OCS (≥2 per year), or severe exacerbations requiring hospital admission (≥1 per year). The term difficult-to-treat asthma means asthma which remains uncontrolled despite moderate or high dose ICS-LABA inhalers, or needs high levels of treatment to induce asthma control. It may be difficult-to-treat for a number of reasons including poor treatment adherence or poor inhaler technique and smoking. Severe asthma is a subset of difficult-to-treat asthma where asthma remains uncontrolled despite adherence to high dose ICS/LABA and management of other factors(Global Initiative for Asthma 2022a).

Despite development of new treatments based upon better understanding of the pathology behind severe asthma, there remain some patients with asthma that is resistant to treatment. Investigation of new therapies that may help these patients is an important aim of asthma research in the future. Identification of treatable traits in asthma may allow more bespoke treatment targeted to that particular individual and can improve outcomes(McDonald et al. 2019). Traits can be pulmonary, extra-pulmonary or behaviour/risk related; and in order to be a treatable trait, the characteristic must be recognisable, modifiable and clinically relevant(Agusti et al. 2016). Common treatable traits in airways disease include eosinophilic airway inflammation, airflow limitation due to airway smooth muscle hyper-reactivity, airway remodelling and co-morbidity(Pavord et al. 2018). Recently, asthma is described as T2-high or T2-low, depending on whether there is expression of type-2 airway inflammation (T2-high) or not (T2-low). Biomarkers for T2-high inflammation include blood and sputum eosinophils and fraction of exhaled nitric oxide (FeNO). The monoclonal antibodies currently in use are targeted at the pathways involved in T2 inflammation, including IL-4, IL-5 and IL-13, and have revolutionised asthma

management in recent years. Treatment options for T2-low asthma are much more limited.

Obesity associated asthma is a specific asthma phenotype that is increasingly recognised, and is often difficult to treat. A recent cross-sectional study identified a number of clusters of obese asthma, including one associated with higher levels of physical activity where asthma was reasonably well controlled, and a number associated with low levels of physical activity, high anxiety and depression scores, high doses of ICS and LABA and poorly controlled asthma(Freitas et al. 2021). This demonstrates the spectrum of obesity associated with asthma, from people who are physically fit but happen to have both asthma and obesity, to those who are markedly obese and very symptomatic of symptoms which could be attributed to asthma.

Identification of suitable treatments for obesity associated asthma is the focus of this thesis and I will discuss the mechanisms thought to be responsible for obese asthma along with current evidence on treatment in this chapter.

1.2. What is obesity?

Obesity is most commonly defined by body mass index (BMI), which is calculated by dividing weight in kilograms by the square of height in metres, i.e.:

Body mass index = weight in kg ÷ (height in m)^2

BMI from 18.5 up to 24.9 kg/m^2 is considered to be healthy. A BMI of 25 up to 29.9 kg/m^2 is classified as overweight and a BMI ≥30 kg/m^2 or over is classed as obese(National Health Service United Kingdom 2018). BMI is the most widely used tool for recognising obesity as it is easy to use and applicable to all adults. There are limitations, notably that it does not take into account muscle mass so may be inaccurate in some people e.g. athletes and body builders. In addition, it was primarily developed in an adult white male population, so is less reliable in other ethnic groups or female sex. It is not widely use in children. A single BMI is not a perfect measure of health, but it can be useful to help recognise excess adiposity, and help to risk assess for complications of this.

The numbers of people classified as overweight and obese has been rising over recent years and worldwide the number of obese adults has almost tripled since 1975. In 2016, 39% (1.9 billion people) of the adult population worldwide were classified as overweight and 13% (650 million) as obese(World Health Organisation 2018). Individuals become overweight due to a mismatch in the balance between calories consumed in diet and calories used in activity. On a population level there are many factors behind the increase in obesity including increased availability of high fat and high energy foods coupled with more sedentary lifestyles and jobs. These phenomena are occurring throughout both poor and affluent countries(World Health Organization 2003) and are likely contributing to the rising global prevalence of obesity.

Obesity is implicated in the development of a number of health problems including type 2 diabetes mellitus, coronary artery disease, hypertension, osteoarthritis and some malignancies(World Health Organization 2003). As rates of obesity rise it is likely that the prevalence of these conditions will also rise, and as such we are facing a global crisis.

Obesity has also been implicated in the development of asthma, and will now be discussed further in a literature review on this topic. It is recognised that obesity both increases the frequency and severity of asthma and makes it more difficult to treat. Initially I will cover potential mechanisms linking obesity and asthma, before considering the effects of a number of targeted interventions, namely exercise and pulmonary rehabilitation; weight loss via dietary restriction with or without exercise; and surgery.

1.3. Asthma and Obesity: Literature Review

1.3.1. Introduction

Evidence that asthma and obesity are linked has been accumulating for over 20 years. In 1999, Camargo *et al*, using Nurses' Health Study II data, showed that BMI over 30 was associated with 2.8 times increased risk of developing

asthma(Camargo et al. 1999). Subsequent studies corroborated the increased risk of developing asthma with rising BMI(Mokdad et al. 2003; Beuther and Sutherland 2007) and demonstrated that airway hyperreactivity (AHR) increases as BMI rises(Chinn et al. 2002; Burgess et al. 2017). Further research has attempted to identify the underlying mechanism(s) behind this.

Two phenotypes of obese asthma have been described, initially by Holguin and colleagues in 2011(Holguin et al. 2011). The first phenotype comprises individuals with childhood and adolescent early-onset asthma. These individuals are more frequently atopic with high IgE levels and often have severe disease with significant airway obstruction and airway hyperreactivity. It is hypothesised that these individuals first develop asthma then subsequently gain weight becoming obese, which leads to a worsening in asthma severity(Holguin et al. 2011). The second obese asthma phenotype is late-onset, non-atopic disease with a lower degree of airway obstruction. It is postulated that in these individuals, obesity directly leads to asthma(Holguin et al. 2011). The association of obesity with late-onset asthma is significantly more common than that with early-onset asthma, and occurs most frequently in post-menopausal females(Chen Y, Dales R, Tang M 2002; Holguin et al. 2011). The second asthma phenotype has been further characterised with the description of a specific sub-phenotype of females with late-onset asthma and sputum neutrophilia(Scott et al. 2017).

People with obesity associated asthma tend to have a higher burden of symptoms(Vortmann and Eisner 2008), more severe disease with poorer lung function and more frequent exacerbations(Akerman et al. 2004; Taylor et al. 2008; Holguin et al. 2011; Barros et al. 2017). There is also evidence suggesting they are more resistant to standard treatments including inhaled corticosteroids(Boulet and Franssen 2007; Sutherland et al. 2008). Consequently, a significant proportion of the difficult asthma workload is represented by obese asthma, which can be particularly difficult to treat. In this age of precision medicine and identification of treatable traits it is important to acknowledge that traditional asthma management may be less successful in obese asthma, and we need to identify and evaluate specific

interventions that may be utilised to best manage this subset of severe asthmatics with obesity(McDonald et al. 2019).

1.3.2. Mechanisms of obesity related asthma

The mechanisms by which obesity leads to asthma are not fully understood, but appear to be multifactorial. In early-onset obese asthma where there is a significant allergic component, it appears that obesity causes a worsening in asthma, with more symptoms. In these children and adolescents, treatment should target airway inflammation as well as weight reduction(Holguin et al. 2011). Obesity leads to symptoms such as breathlessness, due to mechanical effects such as carrying extra load, splinting of the diaphragm and deconditioning. In patients with late-onset obese asthma where the obesity may predate the asthma, weight loss has been shown to improve asthma control(Dixon et al. 2011). In the clinical setting, it may be that some of these patients do not actually have asthma, and their symptoms may be due to abnormal breathing dynamics as a result of obesity.

Throughout the remainder of this thesis, unless specified, the term obese asthma will be used to describe people with asthma and obesity, including both of the two phenotypes described.

1.3.2.1 Mechanical Effects

Obesity has direct effects on lung physiology and mechanics. Extra adipose tissue on the chest wall and abdomen increases intra-abdominal pressure leading to a requirement for increased respiratory effort for normal respiration. The functional residual capacity (FRC) and expiratory reserve volume (ERV) of the lungs are reduced in obesity, causing respiration to occur at lower lung volumes(Jones and Nzekwu 2006). In addition, a Danish cross-sectional study showed risk of airflow obstruction was elevated in obese (odds ratio 1.7, 95% CI 1.08-2.68, p=0.023) and overweight (odds ratio 3.1, 95% CI 1.97-4.78, p<0.001) participants(Baarnes et al. 2019). Airway closure, along with airway narrowing, is a key element in reducing FEV_1, and is associated with gas trapping and hyperinflation. Kaminsky et al demonstrated that obesity was associated with

increased airway closure in response to methacholine challenge in participants with asthma(Kaminsky et al. 2019), independent of asthma control, which is corroborated by a further 2019 study by Peters(Peters et al. 2019).

Salome *et al* confirmed that obese patients (without asthma) have reduced lung volumes, but demonstrated no significant change in response to methacholine challenge. However, obese patients had increased elastic load on methacholine challenge compared with non-obese subjects along with an increased perception of work of breathing(Salome et al. 2008). Airway hyperreactivity is one of the hallmarks of asthma and a large study of 7000 individuals in China demonstrated that both extremes of BMI was associated with symptomatic AHR(Celedon et al. 2001). This is in direct contrast to the Salome paper, with reasons for the differences unclear.

The reduction in functional residual capacity and tidal volumes associated with obesity also causes reduced tension in airway smooth muscle which potentially leads to increased airway smooth muscle stiffness and airflow obstruction(Ali and Ulrik 2013). This may lead to airway remodelling and contribute to the increased rate of asthma in obesity.

1.3.2.2. Inflammation and Effects of Adipokines

Obesity itself induces a state of low-grade inflammation(Visser et al. 2001). Adipokines, cytokines produced by adipose tissue, are thought to have direct effects on the lungs and are implicated in obese asthma. Adiponectin acts to reduce inflammation in many tissues including airways, and levels are lower in obese patients(Kern et al. 2003). Shore *et al* demonstrated in a murine model that administration of adiponectin reduced airway inflammation in response to inhalation of an allergen, and also reduced AHR, likely through effects on TH2 cells(Shore et al. 2006). This supports the hypothesis that reduced adiponectin levels in the obese may be implicated in the development of asthma, and why people with pre-existing asthma may experience worsening asthma if they become obese.

Leptin, a pro-inflammatory cytokine involved in appetite regulation, is thought to play a role in several obesity related diseases including the metabolic syndrome(Loffreda et al. 1998). Leptin levels are elevated in obese patients and in a murine model, elevated leptin levels accentuate the inflammatory process in the airways(Shore et al. 2005).

Tumour necrosis factor alpha (TNF-α) receptor 2 deficiency was demonstrated in a murine model to be associated with a reduction in airway hyperreactivity(Williams et al. 2013). Resistin(Ballantyne et al. 2016) and interleukin-6(Peters et al. 2016) have also been implicated. There is evidence that hyperglycaemia and high insulin levels found in metabolic syndrome are associated with airway smooth muscle proliferation and epithelial damage(Peters et al. 2018), which may lead to airway hyper-responsiveness and airway remodelling.

1.3.2.3. Other Contributing Factors

There are several other factors that may play a role in obese asthma. Diet is thought to have some influence, including diets high in saturated fatty acids(Wood et al. 2011). This may be through their influence on the gut microbiome which can adversely contribute to inflammation. Conversely, breast feeding seems to be protective against both asthma(Dogaru et al. 2014) and obesity(Yan et al. 2014). High fat and low fibre diets can be associated with alterations in digestive tract flora, which can affect the lungs. Trompette and colleagues demonstrated in a murine model that low fibre diets caused lower levels of serum propionate (a short chain fatty acid) and increased risk of allergic airway inflammation. Administration of propionate led to a reduction in TH2 cell production and lowered risk of allergic airway inflammation(Trompette et al. 2014).

Factors active during foetal development and early life may also have a role in the relationship between asthma and obesity. Antibiotics given early in life alter the gut microbiome and may affect immune system development, increasing the risk of asthma(Pitter et al. 2016) and obesity(Bailey et al. 2014) in later life. Low birth weight has also been demonstrated to be associated with

asthma(Nepomnyaschy and Reichman 2006) and obesity(Law et al. 1992). In a twin study genetics have been implicated in the development of asthma and obesity, with 8% of the genetic component of obesity shared with asthma(Hallstrand et al. 2005). There also appears to be a gender link; the obese asthma phenotype being more common in females(Castro-Rodriguez et al. 2001; Chen Y, Dales R, Tang M 2002), perhaps due to the effects of oestrogen.

1.3.3. Management of Obese Asthma

Traditional asthma management with inhaled corticosteroids and beta-2 agonists(British Thoracic Society and Scottish Intercollegiate Guidelines Network 2014) is the mainstay of treatment in obese asthma but has been demonstrated to be less effective(Boulet and Franssen 2007). Reasons include that the symptoms are not driven by asthma, but by mechanical effects of obesity, and reduction of inflammation may not affect symptoms. New more efficacious strategies are needed for this population. The obese asthma phenotype has been identified and is commonly associated with physical inactivity and uncontrolled asthma(Freitas et al. 2021). As obesity causes or at least contributes to the development of asthma, as well as making pre-existent asthma worse, targeting obesity may have favourable impact on asthma outcomes. A review of the current evidence for interventions relevant to obese asthma including pulmonary rehabilitation and weight loss by surgical and non-surgical methods follows.

1.3.4. Asthma and Physical Activity

A 2018 systematic review of 42 articles looking at physical activity (PA) in asthma, revealed that levels of PA are lower in people with asthma compared to healthy controls, and that higher levels of PA may be associated with improved asthma control(Cordova-Rivera et al. 2018a). It also recommended further work looking at sedentary time and associations with asthma. A number of these studies used questionnaires to measure activity levels, which puts them at risk of reporting bias, but more recent studies did use activity monitors. There was also wide variability in the methods of asthma diagnosis, with a number of studies using patient reported asthma, and others only considering asthma

diagnosed according to robust criteria with airflow obstruction and airway hyperresponsiveness. When obesity was considered as a confounding variable when comparing PA in asthmatics with healthy controls, the differences were less or no longer significant in a number of studies(Westermann et al. 2008; Bacon et al. 2015; Russell et al. 2017). This therefore suggests that the link between obesity and asthma control may be closer than the link between PA and asthma control. The existing literature seems to suggest being thin and sedentary is more closely linked with good asthma control than being overweight and active.

More recent studies looking at asthma and PA include a cluster analysis of participants with clinically stable moderate-severe asthma identified phenotypes where increased sedentary time, female sex and anxiety symptoms were associated with poorly controlled asthma (i.e. frequent symptoms or exacerbations) and one cluster where increased levels of physical activity were associated with improved asthma control(Freitas et al. 2021). Other studies have confirmed that individuals with severe asthma have lower levels of moderate-vigorous physical activity (MVPA) when compared with healthy controls(Cordova-Rivera et al. 2018b; Neale et al. 2020), but to our knowledge no previous studies have compared activity levels in asthmatics grouped by asthma severity and body mass index (BMI).

1.3.5. Pulmonary Rehabilitation

Pulmonary rehabilitation (PR) is an education and exercise programme designed specifically for patients with chronic respiratory disease, primarily chronic obstructive pulmonary disease (COPD). It is usually delivered by healthcare professionals experienced in respiratory disease and is typically delivered in a health care setting. It is used as a treatment for several respiratory conditions including COPD, interstitial lung disease (ILD), and bronchiectasis(Bolton et al. 2013). The majority of evidence supportive of PR comes from trials done in patients with COPD, and evidence of the benefits dates back as far as 1997. A Cochrane review in 2015 found that it improves quality of life including breathlessness and fatigue, and that there were improvements in both physical

exercise and maximal exercise capacity(McCarthy et al. 2015). These benefits were all statistically and clinically significant. There is also evidence to suggest that pulmonary rehabilitation improves psychological status(Griffiths et al. 2000). Traditionally pulmonary rehabilitation has been reserved for patients with COPD with a Medical Research Council (MRC) dyspnoea score of 3 or more, as the original studies included patients predominantly at this stage. There is some evidence to suggest that patients who are MRC dyspnoea score of 2 also benefit, and as such the guidelines suggest they are also referred(Evans et al. 2009; Man et al. 2011).

1.3.5.1. Pulmonary Rehabilitation in Asthma

There are several studies of the effects of pulmonary rehabilitation in children with asthma, but fewer in adults and only a very small number that evaluated impact in adults with obese asthma.

A 2013 meta-analysis of the effects of exercise training in asthma found that there was some evidence of improvement in AHR, quality of life, asthma symptoms and exercise capacity, but recommended further work to clarify(Eichenberger et al. 2013). In addition, a 2021 systematic review and meta-analysis looking at 9 PR studies with a pooled total of 418 participants demonstrated improvements in AQLQ and 6MWD, but not in ACQ or FEV_1(Feng et al. 2021). They also recommended further larger randomised controlled trials be performed to provide further information, which may help elucidate reasons for improvements in AQLQ but not ACQ, where there is reasonable correlation between responses on both.

A randomised controlled trial of 21 adults with asthma assessed a 1 year programme involving a 1 hour exercise session per week, i.e. significantly lower than the government recommended activity guidelines(Department of Health 2011). This showed significant improvements both in overall AQLQ score, and in the activity and emotional domains of AQLQ(Meyer et al. 2015). There were only 13 subjects in the intervention group, and only 3 had severe asthma. Furthermore, individuals with BMI >35 were excluded. Whether the findings of this study can be extrapolated to obese asthma is unclear.

A single blind randomised controlled trial by Franca-Pinto and colleagues(Franca-Pinto et al. 2015) randomised 58 individuals with moderate-severe asthma to a treatment group undergoing aerobic training sessions and a control group given a sham intervention of breathing exercises, both supervised by a physiotherapist. Both groups had 24 sessions lasting 40 minutes over 12 weeks. 43 individuals completed the programme and were included in analysis. Treatment was associated with a reduction in AHR to histamine of 1 doubling dose (p=0.039) and an improvement in AQLQ (-0.9 point between group difference, p=0.034). There was also a reduction in exacerbations (0.6 vs. 1.5 exacerbations per person, p=0.021). This larger study with more robust findings supports a role for exercise training in asthma. However, these results have not been replicated in other studies and it remains somewhat of an outlier in the literature. Post hoc analysis of the treatment group suggested those with higher AHR and TH2-high asthma at baseline were more likely to have significant improvements. Of the 464 people considered for eligibility, 303 were excluded for reasons which are not clearly detailed in the paper, so perhaps selection of participants led to these results.

A smaller randomised controlled trial(Turner et al. 2011) assessed the effects of a short six-week exercise programme comprising three hour long classes a week in older moderate-severe asthmatics and showed significant improvements in symptom and activity domains of AQLQ in the intervention group, which were sustained at 3 months. This small study involved 34 participants with a mean age of 68 years and severity of asthma was defined according to FEV_1, rather than the GINA definition, so it is not clear whether the results are applicable to the wider population with obese asthma as a whole.

More recently, a study of 49 individuals demonstrated that improvements in quality of life following pulmonary rehabilitation were greater in patients with uncontrolled asthma at the start of the intervention(Sahin and Naz 2019). This was an 8 week course of pulmonary rehabilitation with two 2 hour sessions per week including strength and aerobic exercise. The patients were split into 2 groups (partially controlled/uncontrolled asthma), based on baseline asthma control test (ACT) score. The primary end point of ACT score improved in both groups, but to a greater degree in the group who were uncontrolled at the start.

This could simply represent regression to the mean. Both groups had an improvement in six minute walk distance (6MWD), although this did not reach the minimum clinically important difference (MCID).

A further recent feasibility study(Majd et al. 2020) looked at asthma-tailored PR recruited 61 participants and randomised 51, 34 to PR and 17 usual care (UC). Retention rates at completion were 62% and 53% respectively, so worse than the typical completion rate of around 70%, and results were suggestive of improvements in asthma control and exercise performance, but further study recommended.

1.3.5.2. Pulmonary rehabilitation in obese asthma

There is little published data regarding the role of pulmonary rehabilitation in obese asthma, there is still fewer where phenotypes of obese asthma are considered separately. In one retrospective cohort study (n=138; 53 obese and 85 not), the efficacy of an exercise intervention was compared between obese and non-obese asthmatic patients(Türk et al. 2017a). The intervention lasted 12 weeks with 3 hours of exercise per week, supervised by a physiotherapist and accompanied by 4 hours of educational talks. 6MWD improved significantly in both groups; by a median of 50m (IQR 15-84m, $p<0.001$) in the non-obese and 45m (IQR 13-77m, $p<0.001$) in the obese group, and over MCID of 35m. There was significant improvement in asthma control questionnaire (ACQ) in both groups, although this was of uncertain clinical significance. This study suggests that pulmonary rehabilitation may provide benefit in obese asthma.

A further study by the same research group looked at the effects of a pulmonary rehabilitation programme consisting of two 1 hour sessions of exercise a week for 12 weeks for obese asthmatics during the waiting period for bariatric surgery(Türk et al. 2017b). This very small study of 4 intervention subjects demonstrated improvements in ACQ, AQLQ, 6MWD and BMI.

A more recent study by the Türk group looked at effects of a 12 week PR programme comprising three sessions of high-intensity interval training each week along with a 1500 kilocalorie diet and a psychological intervention, on two

groups one with and one without access to an online self-help management tool along with a control group who were given advice to lose weight and exercise(Türk et al. 2020). BMI improved in both of the intervention groups but not in the control group. ACQ improved by -0.67 (-1.42 to 0) in PR only group and -0.66 (-1.17 to -0.33), both $p<0.05$, in group with PR and self-management tool.

Other studies have involved exercise as part of a weight loss programme in obese asthma and will be considered next.

1.3.6. Weight Loss in Obese Asthma

Given that, particularly in late-onset obese asthma, obesity predates the onset of asthma and may be a causative factor, achieving significant weight loss may have significant impact on asthma outcomes. Bariatric surgery is most successful for weight loss, and its impact in obese asthma has been studied.

1.3.6.1. Bariatric Surgery

A longitudinal cohort study(van Huisstede et al. 2015) of 78 individuals in 3 groups (asthmatics undergoing bariatric surgery, and two control groups: non-asthmatics undergoing bariatric surgery; and obese asthmatics not undergoing bariatric surgery) unsurprisingly demonstrated significant improvements in BMI in the surgical groups with a median decrease of $14kg/m^2$ at 12 month follow up. Significant improvements in asthma symptoms (measured on ACQ) occurred in both asthma groups (asthmatic surgical group, median change -0.8 points, and asthmatic controls, median change -0.7 points). Significant improvements in asthma related quality of life occurred in both groups undergoing bariatric surgery (asthmatic surgical group, median increase 1.1 points, non-asthmatic surgical group, median increase 0.6 points) with no change in the non-surgical asthmatics. Improvements in ACQ and AQLQ in non-asthmatic participants here highlights that although validated for use in asthma, changes in symptoms not due to asthma, namely reduced breathlessness due to weight loss, can lead to significantly improved scores even when asthma is not present. Surgery was associated with improvements in FEV_1, FRC and total lung capacity (TLC) at 12

months in both groups, including those without asthma, likely reflecting amelioration of restrictive effects of obesity. In the asthmatic surgical group, half of those with positive methacholine challenge at baseline had a negative test at follow up. There were increases in step count in both surgical groups at 12 months. However, at baseline the asthmatic surgical group had median FEV_1 86% predicted (range 66-119), median ACQ score 1.1 (range 0.4-2.9) and median ICS dose of 600 µg/day BDP equivalent, implying less severe asthma, so the extent to which the results can be applied to severe obese asthma is uncertain.

An earlier prospective observational study(Dixon et al. 2011) also showed significant improvement in ACQ from 1.64 (+/-1.06 SD) to 0.63 (+/-0.97 SD), ($p<0.001$) and a reduction in exacerbations and $ß_2$-agonist use. In agreement with the previous study, AHR (on methacholine testing) decreased significantly 12 months after surgery in obese asthma group ($p=0.03$).

A third study(Boulet et al. 2012) also demonstrated significant improvements in BMI, asthma symptoms, reduction in use of asthma medications and AHR, again on methacholine challenge testing, along with improvements in FEV_1, forced vital capacity (FVC), FRC and ERV in obese asthmatic patients who underwent bariatric surgery.

The majority of bariatric surgery studies include data for one year. However, two studies have looked at outcomes in obese asthmatics 5 years after surgery and demonstrated lasting improvements in ACT and mini-asthma related quality of life questionnaire (mini-AQLQ) scores(Maniscalco et al. 2017) and in BMI, FEV_1 and FVC(Hewitt et al. 2014; Maniscalco et al. 2017).

Most patients with obese asthma are not considered for bariatric surgery. It has limited availability in the UK, which is the main barrier to treatment. In NHS Greater Glasgow and Clyde, bariatric surgery is only offered via specialist weight management services. Referral criteria include having a BMI between 35 and 60 kg/m^2, age between 18 and 55 years, type 2 diabetes diagnosed within the last 10 years and glycosylated haemoglobin of <9%. Patients must complete a 12 week lifestyle programme and have lost at least 5 kgs, and been through a rigorous multi-disciplinary team assessment before they may be offered bariatric

surgery(Greater Glasgow and Clyde 2021). Bariatric surgery tends to lead to a large reduction in BMI, in the region of 15 kg/m^2 in above studies. Non-surgical weight loss programmes lead to smaller reductions in weight but are more accessible.

1.3.6.2. Non-Surgical Weight Loss Studies

One randomised controlled trial(Ma et al. 2015) of 330 participants assessed the effects of a lifestyle intervention (12 months including exercise and low calorie diet) with a 7-10% weight loss target in poorly controlled obese asthma. The mean weight loss from baseline was 5kg (5%) at 6 months and 4kg (4%) at 12 months in intervention group, versus 1.1 kg (1.3%, $p<0.001$) and 2.1 kg (2.1%, $p<0.001$) respectively in controls. No significant change in ACQ or mini-AQLQ occurred suggesting the small degree of weight loss achieved was insufficient to induce change in asthma outcomes.

In contrast, in another small prospective controlled parallel group study(Pakhale et al. 2015) of 22 individuals, 16 of whom were allocated to a 3 month weight loss programme, mean weight loss in the intervention group was 16.5 ± 9.9 kg and weight loss was associated with significant improvements in AHR ($p=0.009$), lung function (FEV_1, $p=0.009$ and FVC, $p=0.010$), and improvements in ACQ ($p<0.001$) and AQLQ ($p=0.003$).

Another study(Scott et al. 2013) compared the effects of low calorie diet, exercise or combined diet and exercise interventions on outcomes in a 10 week randomised controlled trial in 48 obese asthmatics. Mean weight reduction was 8.3 ± 4.2% BMI in the dietary group ($p<0.001$), 8.3 ± 4.9% in the combined intervention group ($p<0.001$), and 1.8 ± 2.6% in the exercise only group ($p<0.063$), suggesting the dietary component was vital for weight loss. Significant improvements in AQLQ and ACQ were noted in the dietary and combined intervention groups only. This study suggests that weight loss of 5-10% via diet with or without exercise may be associated with significant improvements in asthma outcomes and for many this will be a more realistic goal.

A further randomised controlled trial(Freitas et al. 2015; Freitas et al. 2017) evaluated the effects of a weight loss and exercise programme compared to a weight loss only programme in obese asthmatics. Weight loss was greater in the combined intervention group with mean weight loss of 6.8% ± 3.5 standard deviations (SD) compared with 3.1% ± 2.6 SD in the weight loss programme only group ($p<0.001$). There were clinically significant improvements in ACQ in 69% of the weight loss plus exercise group and 36% of the weight loss only group ($p=0.030$). The activity limitation domain of AQLQ improved in both groups ($p<0.001$), but more so in the combined group. FEV_1, FVC and ERV significantly improved in weight loss plus exercise group, but not in weight loss only group. Likewise in the weight loss plus exercise group there were significant decreases in exhaled nitric oxide, serum leptin, IL-4 and 6, and TNF-α, and increases in adiponectin.

Another paper based on the same study(Freitas et al. 2018) demonstrated an improvement in step count ($p<0.001$) and time spent in moderate-vigorous physical activity (MVPA) of 18.2 ± 17.9 minutes per day ($p<0.001$) in the weight loss plus exercise group. There was also a reduction in the number of participants with symptoms of depression, measured by the hospital anxiety depression score (HAD) with a mean score reduction -4.6 ± 4.2 points in the combined group compared with -0.4 ± 3.3 in the weight loss only group ($p<0.01$). MCID for HAD score is 1.7 points(Lemay et al. 2019).

These studies suggest that targets for weight loss should be in the region of at least 5-10%, ideally more, and interventions that combine exercise with dietary strategies are of more benefit.

1.4.1. Summary of current evidence and research questions

In summary, two obese asthma phenotypes are recognised; early-onset, allergic obese asthma and late-onset, non-allergic obese asthma. Obesity may be causative in the development of the latter, and in the former it is likely to at least adversely affect outcomes. Most of the literature considered here does not differentiate between these two phenotypes in their results and conclusions.

This may in part explain some of the conflicting results. This is an area where further research could be targeted, as it may be that these two groups respond in different ways, or to different degrees, to the same intervention. In the late-onset asthma group, it can be postulated that many of the symptoms are due primarily to obesity, and in fact, the pro-inflammatory and mechanical effects of obesity may completely explain the diagnosis of asthma. This is worthy of further study, but is beyond the scope of this thesis. In the work in this thesis, all participants have a diagnosis of asthma according to the pre-specified criteria and are overweight or obese, but we studied the group as a whole and did not consider T2-high or T2-low groups individually.

Weight loss, exercise and pulmonary rehabilitation can play a role in management of obese asthma, and target weight loss should be ≥10% for clinically significant impact. Bariatric surgery is the most effective weight loss strategy, and were it widely available it may be the most useful tool in treatment of obesity with asthma. The mortality of bariatric surgery is perhaps surprisingly low, at around 0.08%(Robertson et al. 2021), lower than the all-cause mortality for obesity, which makes it an attractive option. Its role in severe asthma is unclear, but the evidence suggests it would be very useful. More studies are needed to evaluate the effects of weight loss and exercise in severe obese asthma and develop the best strategies to optimise outcomes in these patients who comprise a significant proportion of the difficult asthma population.

The focus of the thesis is on exercise in participants with difficult-to-treat asthma associated with elevated body mass index. There are two main research questions addressed by the thesis, do asthma severity and/or body mass index affect exercise in asthma? Secondly, does exercise in the format of pulmonary rehabilitation improve asthma control in this group of participants? In the work in this thesis, all participants have a diagnosis of asthma according to the pre-specified criteria (see methods) and are overweight or obese, but we studied the group as a whole and did not consider T2-high or T2-low groups individually. We acknowledge that T2-high and T2-low phenotypes may respond differently to PR, but due to the challenges of recruitment, have not considered them as separate entities. This may be a focus of future research, and it would be very

interesting to see how different phenotypes of obese asthma respond to different treatments, but it is outwith the scope of this thesis.

Chapter 2: Materials and Methods

2.1. Regulatory Approval

The studies described in this thesis were reviewed and approved by the West of Scotland Regional Ethics Committee. They were also reviewed and approved by the NHS Greater Glasgow and Clyde Research and Development Office. All participants received information sheets for the relevant study and had the opportunity to ask questions prior to granting written informed consent.

2.2. Recruitment Methods

The recruitment methods used for each individual study are explained in each of chapter, with an overview here. Participants in the pulmonary rehabilitation studies were recruited predominantly from tertiary care asthma clinics. The majority of participants were recruited from the North East Glasgow Difficult Asthma Clinic which takes place at Stobhill Hospital. The electronic record of each patient attending the clinic each week was reviewed, and those who met the inclusion criteria were marked on the clinic list. The clinician who assessed each patient at clinic mentioned the study to them, and if they were interested they were given a patient information sheet (PIS). Interested potential participants were then contacted by a member of the research team at a later date and if they were still interested an appointment for the first visit was made. None of the studies differentiated between T2-high and T2-low asthma, this was not an entry criterion, and anyone who met the entry criteria was invited to participate, with no further consideration given to their asthma phenotype.

The consultant clinicians running asthma services throughout NHS Greater Glasgow and Clyde were contacted and informed about the study and asked to nominate any patients they felt would be suitable and would benefit from the studies. Towards the end of the recruitment period the clinic lists were reviewed and anyone meeting the inclusion criteria identified so the clinician

could mention the study to them directly, offer a PIS if interested and pass on their details with consent for the study team to make contact.

The mild-moderate asthma participants for the activity study were recruited from general practices throughout NHS Greater Glasgow and Clyde. An email invitation was sent to local practices in the area inviting them to participate in the study, and two GPs with a specialist interest in respiratory medicine also agreed on behalf of their practices. When the practice agreed to take part, the practice manager performed a search of all registered patients and identified those who met the inclusion criteria. A pack including an invitation letter, a PIS and a stamped addressed envelope to return an expression of interest form was sent by the practice to these patients. The study team then screened all replies to confirm inclusion criteria were met and contacted them via phone or email to arrange a visit.

A small number of participants for the activity study in chapter 3 were recruited via a secondary care general respiratory clinic run by the research clinicians, where they had attended for investigation of asthma that was found to be mild-moderate and for which they were on low dose ICS. In addition, some other participants were recruited as they expressed an interest in taking part in asthma research studies to the research team.

2.3. Tests Performed

2.3.1. Weight and height

Weight was measured in kilograms without shoes using calibrated scales. Height was measured in centimetres using a stadiometer. Weight and height were used to calculate body mass index using an online calculator produced by the NHS(BMI calculator | Check your BMI - NHS | Please fill in your details. [no date]). Weight was measured at each visit, but measurement of height was not repeated and was assumed to be consistent throughout the study.

2.3.2. Spirometry

Spirometry was carried out according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines on Spirometry(Graham et al. 2019). An electronic desktop spirometer was used, manufactured by Vitalograph Ltd, Maids Moreton, Buckingham, United Kingdom. The spirometer machine was calibrated before the first test every day with a standardised 3L calibration syringe, and was serviced by the manufacturer on an annual basis. The predicted values used were those from the Global Lung Initiative (GLI 2012(Quanjer et al. 2012)), and height and date of birth was entered into the spirometer to calculate the participant's predicted values.

Participants were asked to withhold their bronchodilator inhalers before the test if possible. They were asked to avoid use of SABA for 6 hours prior to testing, LABA for 24 hours and LAMA for 36 hours, as per guidelines(Graham et al. 2019). Participants did not always manage to withhold inhalers for these time periods, and we went ahead with the tests even if inhalers had been used beforehand.

Participants were sat at rest in a chair and their height, sex and date of birth entered into the spirometer in order to calculate the predicted values. They were asked to inhale to full inspiration, then immediately place the mouthpiece into their mouth and perform a forced expiration. This was described as forcibly blowing out as much air as possible as quickly as possible, then on to complete expiration with verbal encouragement from the supervising staff member. The test was performed 3 times if there was under 150 millilitres (ml) variability between three FEV_1 and FVC values. The highest result of those with ≤150 ml variability was used. If the participant was unable to get 2 results within 150 ml in 3 blows, the test was repeated until they did so, or were too tired to continue, with a maximum of 8 attempts. The participant was then advised to take an inhaled bronchodilator (their usual reliever treatment, either 400 mcg salbutamol or 1 mg of terbutaline, through a spacer if they usually use one) and the test repeated 15 minutes after.

Peak expiratory flow was also reported from spirometry results using the Vitalograph spirometer as described above. The peak flow was taken as the highest value for peak flow recorded in both the pre- and post-bronchodilator tests.

2.3.3. Fraction of Exhaled Nitric Oxide (FeNO)

The fraction of exhaled nitric oxide was measured using a NIOX VERO machine, manufactured by Circassia Pharmaceuticals Inc, Morrisville, USA. Participants were instructed to exhale fully, then inhale through the mouthpiece(Dweik et al. 2011). Subsequently they blew out at a steady volume to keep the cloud seen on the screen between the two markers.

2.3.4. Six-minute walk test

The six minute walk test (6MWT) was carried out according to the American Thoracic Society (ATS) guidelines 2002(Crapo et al. 2012). A 30 metre course was marked out in a quiet corridor with cones at either end. Research subjects had pulse, blood pressure and oxygen saturation measured before the test was commenced, and were asked to give a baseline score on the Borg scale for breathlessness (see 2.3.5.).

Before beginning, the test was explained fully, including that the aim was to walk as far as possible in six minutes between the two cones at the participant's own pace. Participants were advised to use any walking aids they needed, and were permitted to take a short-acting bronchodilator before beginning the test if they wished to do so. A chair was available for participants to sit in if they wished to rest. A portable pulse oximeter was worn on a finger during the test and pulse and oxygen saturations recorded every minute. The distance walked was recorded every minute and the participant was told when every minute had elapsed. A repeat Borg score was documented at the end of the test along with the total distance walked and lowest oxygen saturation reached. Participants performed a practice test and a repeat test, and the longest distance (6MWD) from either test was used, along with the Borg score from the corresponding walk.

2.3.5. Borg breathlessness scale

The Borg scale(Mahler, D. A; Horowitz 1994) is a numerical scale ranging from 0 to 10, where a participant scores both their breathlessness and exertion. On the breathlessness scale, 0 represents no shortness of breath at all, 0.5 represents 'very, very slight, just noticeable breathlessness', 1 represents very slight shortness of breath up to 10 representing maximal breathlessness. On the exertion scale, 0 represents nothing at all, and 10 represents maximum exertion. A written description of what each number (0, 0.5, then whole numbers 1-10) represent was included with the chart.

2.3.6. Asthma Control Questionnaire (ACQ)

The Juniper Asthma Control Questionnaire was produced by Quality of Life Technologies(Juniper et al. 1999) to provide a simple and quick assessment of asthma control in any environment. The original version of the ACQ uses a 7 point scale, where 6 questions are graded by the participant and FEV_1 added in by the clinician.

In the studies in this thesis, an ACQ6 was used; this version does not include FEV_1, just six questions. The six questions ask about symptoms experienced by the participant over the last week, and cover nocturnal wakening, early morning symptoms, limitation in activities, dyspnoea, wheeze and frequency of SABA use. The participant selects responses graded from 0-6 with 0 being the best response (i.e. no symptoms), and 6 being the worst (i.e. significant symptoms). The scores for each question are totalled and then divided by 6 to get a mean overall score.

A score of 0 suggests complete asthma control, and a score of 6 suggests completely uncontrolled asthma. Scores <0.75 suggest adequate asthma control and scores >1.5 reflect poorly controlled asthma(Juniper et al. 2006). A change in 0.5 is considered the minimum clinically important difference(Juniper et al. 2013). The ACQ is validated for use in clinical practice and research(Juniper et al. 1999).

We acknowledge that although this questionnaire is validated for use in clinical practice and research in asthma, being obese without asthma may also lead to high scores. The symptoms in the questions are not specific to asthma and may be affected by other problems including obesity.

2.3.7. Asthma Quality of Life Questionnaire (AQLQ)

The Juniper AQLQ is produced by Quality of Life Technologies(Juniper et al. 1999). It is a 32-question document where questions can be grouped into 4 domains- symptoms, activity limitation, emotional function and environmental stimuli. The questions cover a range of aspects related to each domain and thus help assess the impact of asthma on quality of life in a broad assessment.

The instruction is to respond to each question with regards to the last 2 weeks, and each question is graded from 1 to 7, where 1 means asthma has had a significant impact on that aspect of quality of life and 7 means asthma has had no impact on that aspect of quality of life. The total score is the mean of all responses, and the score for each domain is the mean of all responses within that domain. The maximum score is 7 which suggests minimal impact of asthma on quality of life, and the minimum is 1, which suggests significant impact. The AQLQ has been validated for use in clinical practice and research(Juniper et al. 2013). A change of 0.5 points is considered the minimal clinically important difference (MCID)(Juniper et al. 1994).

Again, it is acknowledged that participants without asthma but with obesity may score highly on this questionnaire. However given all participants had asthma diagnosed according to strict criteria, and the score is validated for use, it was used.

2.3.8. Hospital Anxiety and Depression (HAD) Scale

The HAD scale consists of 14 questions, 7 relating to symptoms associated with depression and 7 to anxiety. Each questions has 4 responses, each scored from 0-3, with 3 representing significant anxiety or depressive symptoms(Zigmond and Snaith 1983). The scores for each domain are totalled and scores of over 8

suggest mild, over 11 moderate and over 15 severe anxiety or depression(Stern 2014). It has been validated for assessment of anxiety and depression in clinical practice(Bjelland et al. 2002). MCID in COPD patients is considered to be 1.5 in each category(Puhan et al. 2008a).

2.3.9. Medical Research Council Dyspnoea Scale

Medical Research Council (MRC) dyspnoea scale(MRC breathlessness scales: 1952 and 1959 – UKRI.) grades dyspnoea from 1 to 5, as below:

1. Breathless only on significant exertion
2. Breathless on hurrying on the flat or walking up an incline
3. Walking more slowly than most other people on the flat, or need to stop when walking at own pace for about 15 minutes or 1 mile
4. Need to stop when walking 100 yards or a few minutes on the flat
5. Too breathless to leave the house, or breathlessness on dressing

It has been validated for use in both research and clinical practice(Bestall et al. 1999). There is no defined value for MCID on the MRC dyspnoea scale.

2.3.10. Blood Sampling

Blood sampling was done via venepuncture. A full blood count was taken in an EDTA tube and analysed in NHS Greater Glasgow and Clyde's haematology laboratory at Glasgow Royal Infirmary. The eosinophil count is one component of a full blood count.

2.4. Accelerometry

The accelerometers used in the studies in this thesis are model wGT3X-BT and were manufactured by the ActiGraph Corporation (Pensacola, Florida, USA). Participants verbally confirmed their non-dominant wrist and were instructed to wear the device at all times (i.e. for 24 hours per day), removing only for water-based activities. Each accelerometer was synchronised with GMT and initialised to capture data at 30Hz. Devices were programmed to commence data collection shortly after distribution. The low frequency extension was not

enabled. Device placement was demonstrated, and all participants were fitted with their device prior to leaving the testing session.

Following return of the device, all data was downloaded using ActiLife (v.6.14.3; ActiGraph, Pensacola, USA) and saved in raw format as .gt3x files. These files were subsequently converted to time-stamp free .csv files and exported into R v3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) for processing using the GGIR package v2.1.0(Migueles et al. 2019). This processing method detected non-wear time, abnormally high values and auto-calibrated the raw triaxial accelerometer signals using local gravity as a reference(van Hees et al. 2013; Van Hees et al. 2014). The GGIR package then calculated Euclidean Norm Minus One (ENMO) (1 *g*) averaged over 5 second epochs and expressed in milli-gravitational (m*g*) units as described in the literature(Van Hees et al. 2014). *The data extraction and processing described in this paragraph was carried out by Dr Duncan S Buchan, University of West of Scotland.*

Files were excluded from subsequent analyses if post-calibration error was over 0.01 *g*, there were fewer than 4 days, including at least 1 weekend day, of valid wear (defined as ≥ 16 hours per day)(Rowlands et al. 2018) or wear data was not present for each 15 minute period of the 24 hour cycle. The default non-wear setting was used, whereby invalid data were imputed by the average at similar time-points on different days of the week (separating weekend and weekdays) (van Hees et al. 2013). This ensured outcome variables were calculated based on the entire 24 hour cycle.

Physical activity was expressed as: inactive time defined as the time accumulated below an acceleration of 30 m*g*; in light PA (LPA), i.e. time spent between 30–99 m*g*(Bakrania et al. 2016); and moderate-vigorous PA (MVPA) defined as the time accumulated above an acceleration of 100 m*g*(Hildebrand et al. 2014). Results were also expressed as average acceleration (AA, ENMO, m*g*) which represents the volume of PA, and using the intensity gradient (IG), which represents the intensity of accelerations throughout the period of wear(Rowlands 2018). AA and IG together provide information about the volume and intensity of PA, as well as using all the information collected during the period of device wear.

Average acceleration provides a measure of the volume of activity. It encompasses all data generated in the 24 hour period, and calculates the average in all of the tri-axial accelerations. This can more accurately quantify the total amount of PA, rather than relying purely on MVPA. For example, someone who is sedentary all day but performs one period of intense activity can more easily be compared to someone who is active at a lower intensity but over a longer time period.

The intensity gradient reflects the negative curvilinear relationship between intensity and time accumulated in that intensity and is always negative. A lower IG reflects less time in increasing intensity(Rowlands 2018; Buchan et al. 2019). The IG was calculated and generated in GGIR (argument IG levels=TRUE) following the same procedures as described elsewhere(Rowlands et al. 2018).

Together, the IG and AA provide a measure of the volume and intensity of activity undertaken throughout the monitoring period and importantly use all the acceleration data collected. Another benefit, is the values are independent of device location, cutpoints and equipment used, so they can be compared with results from other papers reporting them. Including IG and AA allow for subsequent analysis to explore whether they were associated with ACQ6 and AQLQ, and whether these associations were independent of one another. In doing so, we may be able to identify which metric is more important for improving ACQ6 and AQLQ which could inform future interventions.

It is important to point out that the values generated in these results sections for inactive time, LPA and MVPA are specific to the devices, wear location, cutpoints and methods used to calculate them. Comparing groups in the same study is valid, but they cannot be directly compared to results from other datasets. This is not the case for AA and IG which can be compared with other datasets. In addition, inactive time, LPA and MVPA cannot be used to define whether participants have met recommended activity targets(Department of Health 2011). What constitutes MVPA in this dataset does not necessarily

correlate with moderate or vigorous activity by other definitions. In this study, a gentle walk would be classified as moderate-vigorous activity, with light activity encompassing activities such as ironing and cooking. The values generated may look excessive, particularly considering the population studied, but their utility is merely to compare to the other groups with the same methods of analysis, rather than to the general population.

2.5. Pulmonary Rehabilitation Programme Format

The PR course lasted eight weeks, with one in-hospital session per week comprising an hour of education on asthma topics, followed by an hour of exercise. International guidelines recommend at least two supervised weekly sessions(Bolton et al. 2013; Spruit et al. 2013), but we suspected that multiple attendances may be a prohibitive factor in recruitment, therefore we pragmatically offered only one supervised session each week and encouraged two further independent sessions each week. We did not monitor compliance with additional sessions.

2.5.1. Pulmonary rehabilitation education

The educational component was delivered on a rolling basis by multidisciplinary staff including asthma consultants, respiratory registrars, respiratory clinical nurse specialists, a GP with a specialist interest in asthma and physiotherapists who work in the PR team. Dieticians helped to write the healthy eating talk, but they did not deliver it themselves as they were unable to provide regular input. The topics covered are listed below:

- What is asthma? Diagnosis, co-morbidities
- Asthma treatments
- Asthma treatments, inhaler technique and 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

2.5.2. Pulmonary rehabilitation exercise

The exercise sessions were delivered in a hospital gymnasium by the PR Team. Participants confirmed they were not suffering from an asthma exacerbation before starting each session, and were encouraged to use their SABA inhaler 15 minutes prior to the exercise. The exercises were taken from the local chronic obstructive pulmonary disease (COPD) PR programme and comprised a seated or standing warm-up followed by multiple resistance and aerobic exercises. The intensity of exercise was tailored to the individual, based on the distance they walked during the baseline six-minute walk test (6MWT) along with their current activity profile as assessed on verbal interview by the physiotherapists. There was a progressive increase in number of repetitions and/or resistance each week.

Most participants began with one set of 12 repetitions of each strength exercise in the first week. This was then increased to two sets of 12 and then three sets of 12 repetitions as the weeks progressed, depending on how well the participant had managed the previous week. A description of strength exercises follows:

- Leg extensions: sitting in a chair, raise the leg from floor to horizontal. This was progressed with the addition of ankle weights (1-3 kg)
- Bicep curls: standing, holding a pole or weight and flexing arms to a fully bent elbow. This was progressed with the addition of dumbbells (0.5-5 kg)
- Sit-to-stand: sitting in a chair then standing up. There was no progression here
- Step ups: stepping from the floor onto a box approximately 30 cm off the ground, then off again. This was progressed by the addition of ankle weights
- Pole raises: standing up and raising a plastic pole from waist height to shoulders then above head to full arm extension. This was progressed by the addition of weights

- Knee lifts: standing on the spot then lifting knee up until thigh perpendicular with the floor. This was progressed by the addition of ankle weights

Aerobic exercises involved:

- Walking: walking on the flat around the room at a comfortable pace for 3 minutes. This was advanced by walking for a longer time period, and then up and down a ramp.
- Exercise bike: pedalling on a stationary exercise bike with low resistance for 3 minutes. This was advanced by increasing resistance and time

Some participants performed regular exercise prior to recruitment, and managed longer distances on the baseline 6MWT. They had the exercises adapted to make them more challenging. Some participants were advised to spend a longer time on aerobic exercises. Some participants had more difficult strength training exercises using weights machines and heavier weights. The exercise for each participant was tailored to their ability at baseline and intensity was progressed throughout the eight sessions.

2.6. Data Handling and Statistical Analysis

2.6.1. Data Handling

A case report form was designed for completion at the time of each study visit. The hard copies of these will be stored for 10 years from completion of the project. The data was transcribed onto an Excel database (Microsoft Corporation, Redmond, Washington, United States), stored on NHS and secure hard drive along with University of Glasgow OneDrive account (Microsoft). Electronic copies will be kept in an approved repository after completion of this period of study.

2.6.2. Statistical Analysis

Detailed descriptions of statistical analysis including individual tests used are found in each chapter for each individual study.

Statistics have been calculated using GraphPad Prism version 9 (GraphPad Software, San Diego, California), along with Minitab Statistical Software (Minitab LLC, Pennsylvania, USA).

Baseline characteristics and results are expressed as mean with standard deviation (SD) or 95% confidence interval (95% CI), median and interquartile range (IQR) and number and proportions. Normality testing was performed with the D'Agostino-Pearson test. A p value of <0.05 was considered to be significant.

Chapter 3: Physical activity levels in asthma: relationship with disease severity, body mass index and novel accelerometer-derived metrics

Published in Journal of Asthma, August 2022.

Full author list: Helen Clare Ricketts, Duncan S Buchan, Femke Steffensen, Rekha Chaudhuri, Julien S Baker and Douglas C Cowan.

3.1. Abstract

3.1.1. Objectives

Patients with asthma may feel limited in physical activity (PA). Reduced PA has been demonstrated in people with asthma versus healthy controls, and increasing PA associated with improved asthma outcomes. Obesity commonly co-exists in people with difficult-to-treat asthma, and worsens outcomes. We compared PA levels in participants with difficult-to-treat asthma and elevated body mass index (BMI) (DOW group) and two mild-moderate asthma groups: one with BMI <25 kg/m^2 (MHW) and one with BMI ≥25 (MOW).

3.1.2. Methods

This cross-sectional study used 7-day recordings from wrist-worn accelerometers to compare PA between groups. Inactive time, light PA (LPA), moderate-vigorous PA (MVPA) were measured, along with two novel metrics: intensity gradient (IG) reflecting PA intensity, and average acceleration (AA) reflecting PA volume. PA parameters were compared using ANOVA or Kruskall-Wallis testing. Correlation and linear regression analyses explored associations between PA parameters and asthma outcomes. As AA was the PA parameter correlated most closely with asthma-related outcomes, an exploratory analysis compared outcomes in highest and lowest AA quartiles.

3.1.3. Results

75 participants were recruited; 57 accelerometer readings were valid and included in analysis. Inactive time was significantly higher ($p<0.001$), and LPA ($p<0.007$), MVPA ($p<0.001$), IG ($p<0.001$) and AA ($p<0.001$) all significantly lower in DOW versus MHW and MOW groups, even after adjusting for age and BMI. Quartiles based on AA had significantly different asthma profiles.

3.1.4. Conclusions

Overweight/obese participants with difficult-to-treat asthma performed less PA, and activity of reduced intensity and volume. Increased AA is associated with improvement in several asthma-related outcomes. Increased PA should be recommended to relevant patients.

3.2. Introduction

Asthma is a common, heterogeneous condition which varies from mild with minimal impact on quality of life to difficult-to-treat asthma with persistent symptoms and/or frequent exacerbations despite significant treatment(Global Initiative for Asthma 2022a). Physical activity (PA) is associated with positive outcomes in adults including reduced risk of early mortality(Ekelund et al. 2019). The World Health Organisation's PA recommendations suggest adults should achieve ≥150 minutes of moderate intensity PA, or ≥75 minutes of vigorous PA each week(Bull et al. 2020). Many individuals with asthma find that symptoms limit their participation in PA, particularly exertional breathlessness(Dockrell et al. 2007; Shim et al. 2013). A 2018 systematic review of 42 articles on asthma and PA demonstrated that participants with asthma performed less PA than healthy controls, and higher levels of PA were associated with better asthma control(Cordova-Rivera et al. 2018a).

Some studies have demonstrated that individuals with severe asthma have reduced moderate-vigorous PA (MVPA) compared with healthy controls(Cordova-

Rivera et al. 2018b; Neale et al. 2020), but to our knowledge no previous studies have compared activity levels in asthmatics grouped by asthma severity and body mass index (BMI). In some studies, when BMI was considered as a confounding variable, links between PA and asthma were less or no longer significant(Westermann et al. 2008; Bacon et al. 2015; Russell et al. 2017). This may suggest that obesity plays a bigger role than PA in asthma control, and should be considered along with PA and asthma.

Most recent studies used accelerometers to record PA, but several(Cordova-Rivera et al. 2018b; Neale et al. 2020; Freitas et al. 2021) used cut-points created on a different accelerometer model to that studied, which may render some of this data invalid(Migueles et al. 2017). The majority of studies recommended wearing devices during waking hours, which may lead to loss of data.

In this study our objective was to compare PA levels between groups with different degrees of asthma severity and body mass index, to determine whether these differences impacted on physical activity. Building on deficiencies in previous literature, we used appropriate cut-points for the accelerometer model, and collected data for 24 hours per day, for a 7 days to accurately quantify all PA. We also include average acceleration (AA) which reflects volume of PA and intensity gradient (IG) which reflects PA intensity. These novel metrics enable direct comparison with other studies reporting them, as cut points are not involved and use of different accelerometers does not affect data analysis. A secondary aim was to explore whether PA correlated with selected markers of asthma control, and if so, which PA parameters were most closely linked. We also considered whether any PA outcomes could be used to independently predict asthma control.

We hypothesised that PA would be reduced in individuals with difficult-to-treat asthma who were overweight when compared to those with milder asthma with healthy or elevated BMI and that this might identify a treatable trait for which

specific targeted interventions could be developed. We also hypothesised that PA would correlate with markers of asthma control and severity, and that they may predict asthma outcomes.

3.3. Materials and Methods

3.3.1. Study Design

This was a cross-sectional study using accelerometers to compare activity levels across three groups: participants with mild-moderate asthma with BMI <25 kg/m^2 (mild-moderate, healthy weight- MHW group), participants with mild-moderate asthma with elevated BMI (≥25) (mild-moderate, overweight- MOW group), and participants with difficult-to-treat asthma with BMI ≥25 (difficult-to-treat, overweight- DOW group). These groups were selected, as we wished to explore the impact of both obesity and difficult-to-treat asthma on activity levels.

The study was a sub study in a larger project registered at ClinicalTrials.gov (ID NCT03630432) and approved by the West of Scotland Regional Ethics Committee (REC reference 16/WS/0200). It took place between May 2017 and January 2020 in Glasgow Royal Infirmary. It was funded by a Chief Scientists Office/Asthma UK Innovation Grant 2018 (AUK/CSO/18/01).

3.3.2. Study Populations

Participants were aged 18-80 years. The MHW and MOW groups were recruited from general practice. They had an asthma diagnosis recorded in medical notes and prescription of asthma medication within 12 months. They had an asthma control questionnaire-6 (ACQ6) ≤1.5, <2 systemic corticosteroid boosts and no asthma-related hospital admissions in the previous year. Maximum permitted treatment was medium dose inhaled corticosteroids (ICS) with long acting β2-

agonists (LABA). General Practitioners identified potential candidates to whom study information packs were posted. Those responding were screened to confirm eligibility before arranging a study visit.

The DOW group comprised individuals attending the baseline, pre-intervention visit for a study evaluating the impact of pulmonary rehabilitation in adults with difficult-to-treat asthma associated with obesity. Inclusion criteria included BMI ≥25 kg/m^2, asthma with characteristic symptoms(Global Initiative for Asthma 2018) and either 200 mls and 12% improvement from baseline in forced expired volume in one second (FEV_1) after either bronchodilator, anti-inflammatory medication or between visits; or positive bronchial challenge (PC_{20} methacholine or histamine <8 mg/ml or PD_{15} mannitol <635mg). Individuals were on at least high dose ICS and LABA and had difficult-to-treat asthma(British Thoracic Society and Scottish Intercollegiate Guidelines Network. 2019) defined as either ≥2 courses of prednisolone, or ≥1 hospital admissions in the last 12 months, or ACQ6 of >1.5. Exclusion criteria included intensive care unit admission with asthma in previous 6 months, exacerbation requiring oral steroids and/or antibiotics within four weeks, significant co-morbidity or mobility problems, pregnancy/breastfeeding, or commencement of biologic therapy within 6 months.

3.3.3. Study Measurements

Study participants had one single visit to the Clinical Research Facility. All participants gave written informed consent prior to commencement of the study. Data on demographics, medical history, medications and exacerbations was obtained through participant interview and review of electronic records. Several questionnaires were completed including asthma quality of life questionnaire (AQLQ)(Juniper et al. 2013) and asthma control questionnaire-6 (ACQ6)(Juniper et al. 1999).

Height and weight were measured, and BMI calculated. Participants performed fraction of exhaled nitric oxide (FeNO) using a NIOX VERO machine (Circassia Pharmaceuticals Inc, Morrisville, USA) and peak expiratory flow rate (PEFR). Spirometry(Graham et al. 2019) was performed before and 15 minutes after 400 mcg of inhaled salbutamol using an electronic spirometer (Vitalograph, Maids Moreton, UK). A blood sample was taken for blood eosinophil count. Two 6-minute walk tests (6MWT) were performed as per American Thoracic Society guidelines(American Thoracic Society 2002), with the furthest distance used for analysis. Borg scale(Mahler, D. A; Horowitz 1994) for breathlessness on completion of the furthest walk was recorded.

3.3.4. Accelerometry

Each participant was asked to wear an ActiGraph wGTX3-BT (ActiGraph, Pensacola, FL, USA) accelerometer on their non-dominant wrist continually for seven days (except when bathing or swimming). Participants were shown how to fit the accelerometer, which was programmed as described earlier (chapter 2, section 2.4). Accelerometers returned and information downloaded and processed as described in section 2.4. The PA outcomes calculated included inactive time, which was defined as time accumulated below an acceleration of 30 mg, and light physical activity (LPA) defined as time spent between 30–99 mg.(Bakrania et al. 2016) Moderate-vigorous physical activity (MVPA) was defined as time accumulated above an acceleration of 99 mg.(Hildebrand et al. 2014) We also expressed PA as average acceleration (AA, ENMO, mg) which provides a measure of the volume of activity undertaken throughout the day and intensity gradient which describes the intensity distribution of accelerations across the monitoring period(Rowlands 2018)- see chapter 2, section 2.4 for further details.

3.3.5. Statistical Analysis

Results are expressed as mean ± SD, mean (95% CI), median (IQR) or numbers and proportions. D'Agostino-Pearson testing was used to determine normality. Comparisons between the three groups (MHW, MOW and DOW) were made using one-way ANOVA for normally distributed data, with Tukey's multiple comparisons test, or Kruskal-Wallis with Dunn's multiple comparison test for skewed data. Chi-square test was used to compare proportions, with Kruskal-Wallis used where small values invalidated Chi-square.

Analysis of covariance was performed on all activity parameters, using age and BMI as covariates. Correlation analysis assessed associations between activity metrics and selected asthma measures, to try and determine whether PA reflected asthma control. Simple and multiple linear regression were performed using ACQ6 and AQLQ as dependent variables and each PA parameter in turn as independent variables. For multiple linear regression, age, gender and BMI were added to the models as potential confounders. Regression analyses aimed to assess whether PA parameters could predict asthma outcomes.

Participants were divided into quartiles based on AA recordings, and asthma measures were compared between highest and lowest quartiles using unpaired t and Mann-Whitney U tests depending on normality. A p value of <0.05 was considered to be statistically significant. Statistical tests were performed using GraphPad Prism v9 (GraphPad Software, San Diego California, USA) and Minitab Statistical Software (Minitab LLC, Pennsylvania, USA).

3.4. Results

3.4.1. Baseline characteristics

A total of 75 participants were recruited, 25 per group. Baseline characteristics are shown in table 3.1. Median age was higher in the overweight groups- median (IQR): 38 (27-62) in MHW, 62 (54-67) in MOW and 57 (48-63) years in DOW, p<0.001. Median (IQR) BMI was significantly different, in part due to study design: MHW group 23.2 kg/m^2 (21.7 – 24), MOW 29 (27 - 32) and DOW 36.2 (33 - 40.3), p=0.001.

Co-morbidities were more prevalent in the DOW group as seen in table 3.1, including: GORD (16% MHW, 52% MOW, 88% DOW, p<0.001), psychological illness (24% MHW, 24% MOW, 64% DOW, p=0.003) and osteoporosis. As anticipated, asthma treatment burden was significantly higher in DOW group, with beclomethasone dipropionate (BDP)-equivalent inhaled steroid dose mean (95% CI) MHW 420 µg (280-560), MOW 536 (418-653), DOW 1904 (1729-2079), p<0.001. In addition add-on asthma treatments were prescribed in the DOW group but not other groups: LAMA (92%), maintenance prednisolone (48%), omalizumab (24%), and mepolizumab (8%). Asthma exacerbations were more frequent in DOW group, whether measured by annualised prednisolone courses (median (IQR) 0 (0-1) MHW, 0 (0-0) MOW and 3 (2-5) DOW, p<0.001) or GP attendances (median (IQR) 0 (0-1) MHW, 0 (0-0) MOW and 1 (0-3) DOW, p=0.005).

Table 3.1- Baseline characteristics of groups

	MHW Mild-moderate, asthma healthy weight n=25	**MOW Mild-moderate, asthma overweight n=25**	**DOW Difficult asthma, overweight, n=25**	**P value**
Age, years	38 (27-62)	62 (54-67)	57 (48-63)	**<0.001**
Age at diagnosis	23 (±20)	34 (±22)	31 (±19)	0.135
Disease duration, years	18 (8-28)	29 (8-42)	24 (15-37)	0.160
Gender: Female	17 (68)	12 (48)	13 (52)	0.321
Smoking Status: Never smoker	20 (80)	16 (64)	12 (48)	
Current smoker	2 (8)	0 (0)	3 (12)	0.622
Ex-smoker	3 (12)	9 (36)	10 (40)	
Pack years	5 (3 - 24)	15 (2 - 23)	22 (9 - 28)	0.186
Atopy	4 (16)	3 (12)	16 (64)	**<0.001**
Allergic rhinitis	18 (72)	14 (56)	22 (88)	**0.042**
Perennial rhinitis	10 (40)	5 (20)	15 (60)	**0.016**
Nasal polyps*	1 (4)	4 (16)	5 (20)	0.228
Eczema	9 (36)	5 (20)	7 (28)	0.452
GORD	4 (16)	13 (52)	22 (88)	**<0.001**
DFB/ILO*	0 (0)	1 (4)	8 (32)	**0.001**
Anxiety or depression	6 (24)	6 (24)	16 (64)	**0.003**
SAFS/ABPA*	0 (0)	0 (0)	8 (32)	**<0.001**
Osteopenia/osteoporosis*	1 (4)	1 (4)	13 (52)	**<0.001**
SABA inhaled*	24 (96)	24 (96)	25 (100)	0.602
LAMA*	0 (0)	0 (0)	23 (92)	**<0.001**
ICS alone	10 (40)	12 (48)	0 (0)	**<0.001**
ICS/LABA	10 (40)	13 (52)	25 (100)	**<0.001**
BDP equivalent, mcg, mean (95% CI)	420 (280-560)	536 (418-653)	1904 (1729-2079)	**<0.001**
Prednisolone maintenance*	0 (0)	0 (0)	12 (48)	**<0.001**
Prednisolone maintenance dose, mg	0	0	6 (4 to 8)	**<0.001**
Montelukast	2 (8)	0 (0)	18 (72)	**<0.001**
Theophylline*	0 (0)	1 (4)	12 (48)	**<0.001**
Omalizumab*	0 (0)	0 (0)	6 (24)	**0.002**
Mepolizumab*	0 (0)	0 (0)	2 (8)	0.130
In 1 year: Prednisolone boosts	0 (0 - 1)	0 (0 - 0)	3 (2 - 5)	**<0.001**
GP attendances	0 (0 - 1)	0 (0 - 0)	1 (0 - 3)	**0.005**
A & E attendances	0 (0 - 0)	0 (0 - 0)	0 (0 - 1)	**0.007**
Hospital admissions	0 (0 - 0)	0 (0 - 0)	0 (0 - 1)	**<0.001**
BMI, kg/m^2	23.2 (21.7 - 24)	29 (27 - 32)	36.2 (33 - 40.3)	**<0.001**
MRC dyspnoea scale	1 (1 - 1)	1 (1 - 1)	2 (2 - 3.5)	**<0.001**
ACQ6	0.5 (0 - 0.8)	0.3 (0.2 - 0.7)	2.8 (1.85 - 3.3)	**<0.001**
AQLQ: Overall	6.2 (5.7 - 6.7)	6.5 (5.6 - 6.8)	4 (3.1 - 5.1)	**<0.001**
Symptom domain	6.2 (5.8 - 6.7)	6.4 (6.1 - 6.8)	4.1 (3.2 - 5)	**<0.001**
Activity domain	6.3 (5.8 - 6.9)	6.3 (5.2 - 6.8)	3.8 (3.2 - 4.6)	**<0.001**

Emotional domain	6.6 (5.9 - 7)	6.6 (5.9 - 7)	4.6 (3.2 - 5.6)	**<0.001**
Environmental domain	5.8 (5.3 - 6.7)	6.5 (5.5 - 7)	4.5 (2.3 - 5.4)	**<0.001**
Eosinophils (x10^9/L)	0.2 (0.1 - 0.3)	0.1 (0.1 - 0.2)	0.3 (0.1 - 0.4)	0.203
FeNO, ppb	22 (15 - 29)	20 (18 - 25)	39 (16 - 71)	0.185
PEF, L/min	487 (436 - 543)	478 (402 - 576)	398 (314 - 485)	**0.011**
pre-BD FEV_1, % pred.- mean (95% CI)	95.1 (90 - 100)	93.8 (88 - 100)	66.4 (59 - 74)	**<0.001**
pre-BD FEV_1/FVC % - mean (95% CI)	73.7 (69-78)	71.4 (68-75)	65.4 (62-69)	**0.007**
% change in FEV_1 post-BD	3.5 (0.5 to 5.5)	4.8 (-0.4 to 5.9)	3.3 (-1.0 to 13)	0.744
Best 6MWD, m	574 (528- 619)	517 (483- 550)	322 (268-376)	**<0.001**
Borg score post 6MWT	0 (0 to 1)	0 (0 to 1)	3 (1 to 3)	**<0.001**

Table 1 legend: Data expressed as mean ± SD, median (IQR) or number and proportion unless otherwise specified. * refers to p values calculated using Kruskall-Wallis, remaining proportions p values calculated using Chi-square test. Abbreviations used in table: GORD gastro-oesophageal reflux disease, DFB dysfunctional breathing, ILO intermittent laryngeal obstruction, SAFS- severe asthma with fungal sensitisation, ABPA allergic bronchopulmonary aspergillosis, SABA short acting beta-2 agonist, LAMA- long acting muscarinic antagonist, ICS inhaled corticosteroid, LABA long acting beta-2 agonist, BDP beclomethasone dipropionate dose equivalent, mcg micrograms, mg milligrams, PPI proton pump inhibitor, H2A H2 receptor antagonist, OOH out of hours, A&E accident and emergency department, GP General Practitioner, ICU intensive care unit, BMI body mass index, MRC Medical Research Council dyspnoea score, ACQ6 Asthma Control Questionnaire 6, AQLQ Asthma Quality of Life Questionnaire, HAD Hospital Anxiety and Depression scale, FeNO fraction of exhaled nitric oxide, PEFR peak expiratory flow rate, pre-BD pre-bronchodilator, FEV1 forced expiratory volume in 1 second, pred.- predicted, FVC forced vital capacity, post-BD post bronchodilator, 6MWT 6 minute walk test.

For MHW, MOW and DOW groups respectively, median (IQR) for ACQ6 was 0.5 (0-0.8), 0.3 (0.2-0.7) and 2.8 (1.85-3.3), p=0.001. Blood eosinophils and FeNO were not significantly different between groups but peak flow (p=0.011), pre-bronchodilator FEV_1 % predicted (p=0.001) and FEV_1/FVC (forced vital capacity) ratio (p=0.007) were all significantly lower in the DOW group.

3.4.2. Accelerometer Results

The processing criteria left 57 valid recordings for analysis: 15 in MHW group, 17 in MOW and 25 in DOW. Results are displayed in table 3.2 and figures 3.1 and 3.2.

Table 3.2- Accelerometer Results

	MHW (mild-moderate healthy weight)	MOW (mild-moderate overweight)	DOW (Difficult-to-treat overweight)	P value	Between group comparisons p values		
					MHW/ MOW	MOW/ DOW	MHW/ DOW
Inactive time	1079 (1037 - 1122)	1128 (1094 - 1161)	1202 (1170 - 1234)	**<0.001**	<0.212	**<0.008**	**<0.001**
LPA	259 (228 - 289)	237 (212 - 263)	196 (171 - 222)	**0.007**	<0.653	**<0.033**	**<0.003**
MVPA	103 (80 - 127)	79 (58 - 99)	42 (33 - 52)	**<0.001**	<0.128	**<0.027**	**<0.001**
Intensity gradient	-2.63 (-2.97 - -2.33)	-2.62 (-2.74 - -2.55)	-2.85 (-2.96 - -2.73)	**<0.001**	>0.999	**<0.005**	**<0.001**
Average acceleration	27.8 (21.7 - 31.0)	24.4 (20.4 - 27.5)	17.1 (13.7 - 20.5)	**<0.001**	<0.486	**<0.004**	**<0.001**

Table 2 legend: Abbreviations used in table: MVPA- moderate to vigorous physical activity, LPA- light physical activity. Units: inactive time, LPA and MVPA= $min.d^{-1}$ minutes per day, AA=$mg.d^{-1}$ milligravitational units per day, IG has no specified unit. Data expressed as mean and 95% confidence intervals for inactive time, LPA and MVPA; or median and IQR for intensity gradient and average acceleration

There were significant differences for time spent in each PA category. Inactive time was mean (95% CI) 1079 (1037-1122) minutes per day ($min.d^{-1}$) in MHW, 1128 (1094-1161) in MOW and 1202 (1170-1234) in DOW, $p<0.001$. LPA in MHW was mean (95% CI) 259 (228-289) $min.d^{-1}$, in MOW 237 (212-263) and 196 (171-222) in DOW, $p=0.007$. For MVPA mean (95% CI) was 103 (80-127) $min.d^{-1}$ in MHW, 79 (58-99) in MOW and 42 (33-52) in DOW, $p<0.001$. To locate where the difference was, multiple comparisons testing was performed (as per section 3.3.5). There was no significant difference between MHW and MOW groups (inactive time $p<0.212$, LPA $p<0.653$ and MVPA $p<0.128$) but there was between MHW and DOW (inactive time $p<0.001$), LPA $p<0.003$ and MVPA $p<0.001$) and MOW and DOW (inactive time $p<0.008$, LPA $p<0.033$ and MVPA $p<0.027$).

Figure 3.1- Time spent in activity thresholds

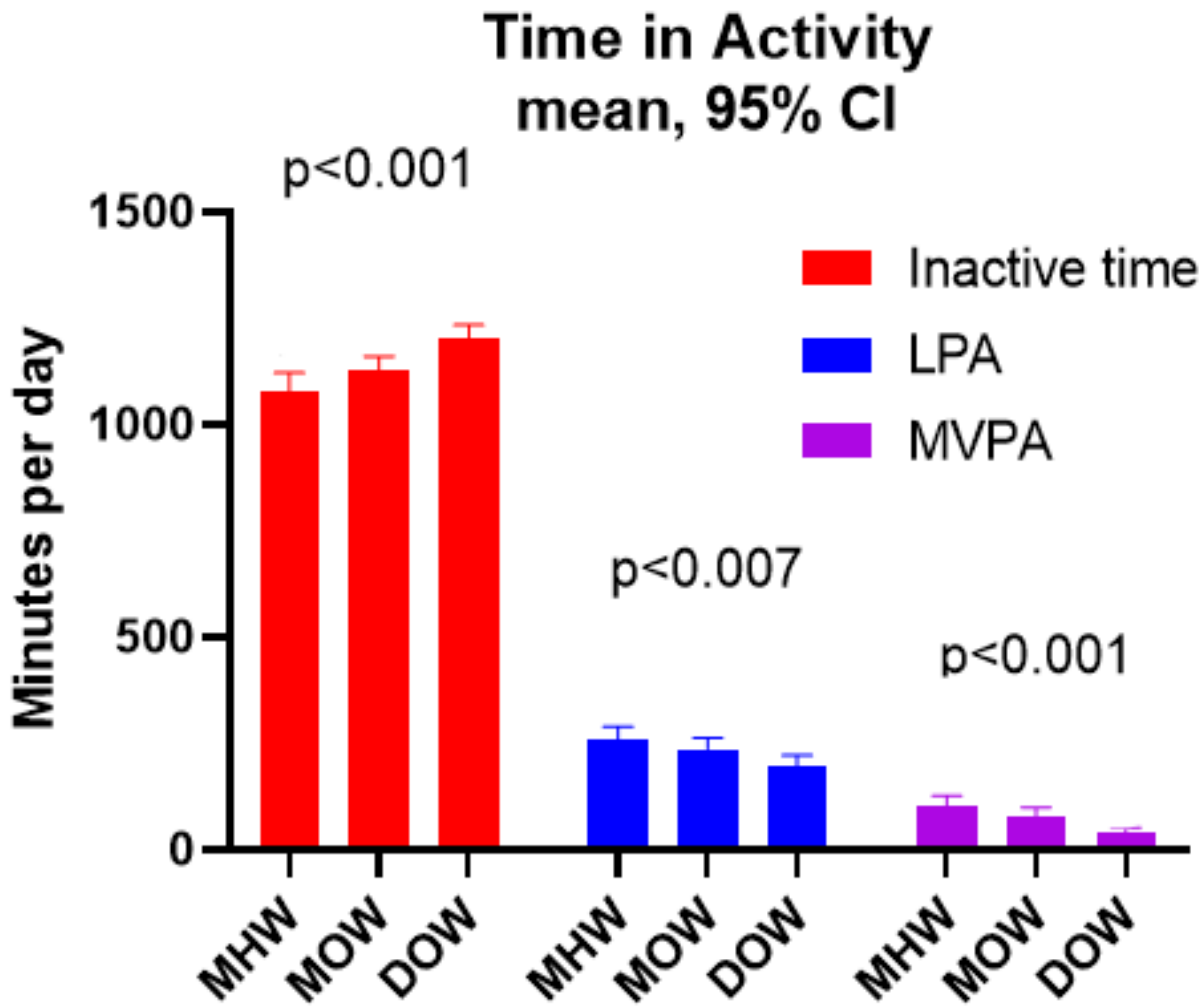

Figure 3.1 legend: Bar chart showing mean and 95% confidence intervals for inactive time, light and moderate-vigorous physical activity across the three groups.

Median (IQR) for MHW, MOW and DOW respectively were: intensity gradient -2.63 (-2.97 to -2.33), -2.62 (-2.74 to -2.55), and -2.85 (-2.96 to -2.73), p<0.001; and average acceleration 27.8 (21.7-31.0) mg.d, 24.4 (20.4-27.5) and 17.1 (13.7-20.5), p<0.001. Again, when multiple comparisons testing was performed, there was no significant difference between MHW and MOW groups (IG p>0.999, AA p<0.486), but there was between MHW and DOW (IG p<0.001, AA p<0.001), and MOW and DOW (IG p<0.005, AA p<0.004).

Figure 3.2- Average acceleration and intensity gradient results

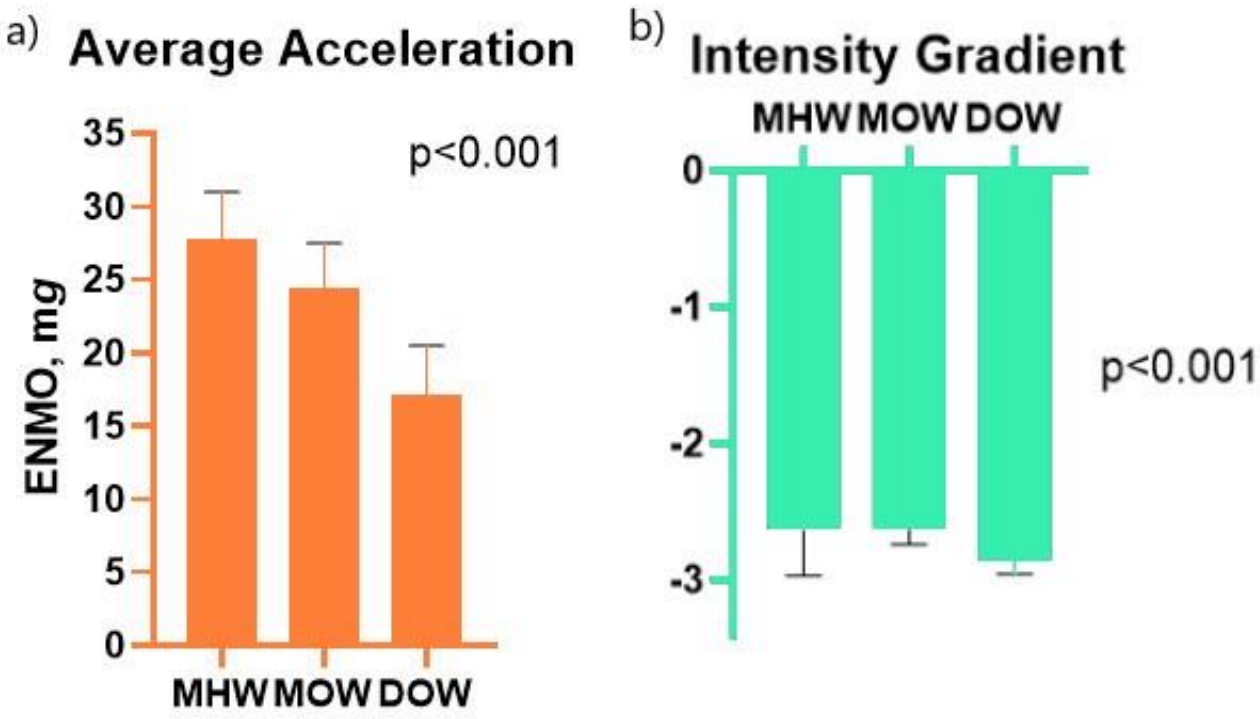

Figure 3.2 legend: Bar charts showing a) average acceleration and b) intensity gradient across the three groups.

At baseline, there were significant differences in age and BMI between groups, but all results remained significant after correcting for age and BMI in analysis of covariance.

3.4.3. Correlation Analysis

Correlation analyses investigated possible associations between PA parameters and selected asthma measures (table 3.3). The asthma outcome measures selected covered asthma control/quality of life scores, use of healthcare, biomarkers, treatment burden and asthma severity. AQLQ and ACQ6 both correlated with all activity parameters. 6MWD was most closely correlated with markers of activity: inactive time $r=-0.569$, $p<0.001$, LPA $r=0.394$, $p<0.002$, MVPA $r=0.680$, $p<0.001$, IG $r=0.690$ $p<0.001$ and AA $r=0.719$, $p<0.001$. For the

majority of the correlation analyses with significant p values, the correlation co-efficients did not suggest strong correlation.

Table 3.3- Correlations of PA parameters and relevant asthma measures

Variable	Inactive time		LPA		MVPA		Intensity Gradient		Average Acceleration	
	r	p	r	p	r	p	r	p	r	p
BDP dose (µg)	**0.476**	**<0.001**	**-0.343**	**0.009**	**-0.548**	**<0.001**	**-0.507**	**<0.001**	**-0.591**	**<0.001**
Prednisolone maintenance dose	0.171	0.205	-0.103	0.445	-0.202	0.131	**-0.221**	**0.009**	**-0.273**	**0.040**
Prednisolone boosts per year	**0.346**	**0.009**	**-0.262**	**0.049**	**-0.435**	**<0.001**	**-0.47**	**<0.001**	**-0.475**	**<0.001**
Annual A&E visits	0.157	0.244	-0.192	0.153	-0.161	0.232	**-0.267**	**0.045**	-0.212	0.098
BMI (kg/m^2)	**0.507**	**<0.001**	**-0.410**	**0.002**	**-0.484**	**0.001**	**-0.402**	**0.002**	**-0.573**	**<0.001**
ACQ6	**0.427**	**0.001**	**-0.368**	**0.005**	**-0.423**	**0.001**	**-0.367**	**0.005**	**-0.463**	**<0.001**
Overall AQLQ	**-0.462**	**<0.001**	**0.438**	**<0.001**	**0.448**	**<0.001**	**0.442**	**<0.001**	**0.531**	**<0.001**
AQLQ symptoms	**-0.375**	**0.004**	**0.336**	**0.011**	**0.386**	**0.003**	**0.409**	**0.002**	**0.451**	**<0.001**
AQLQ activity	**-0.529**	**<0.001**	**0.498**	**<0.001**	**0.493**	**<0.001**	**0.452**	**<0.001**	**0.580**	**<0.001**
AQLQ emotional	**-0.422**	**0.001**	**0.385**	**0.003**	**0.441**	**<0.001**	**0.427**	**<0.001**	**0.501**	**<0.001**
AQLQ environmental	-0.188	0.161	0.215	0.108	0.190	0.157	**0.283**	**0.033**	**0.262**	**0.049**
HADS anxiety	-0.032	0.811	-0.097	0.473	0.136	0.315	0.182	0.175	0.138	0.307
HADS depression	-0.248	0.064	0.174	0.195	**0.276**	**0.038**	**0.307**	**0.020**	**0.321**	**0.015**
Eosinophil count (x 10^9/L)	0.179	0.187	-0.152	0.264	-0.174	0.199	-0.153	0.260	-0.235	0.082
FeNO (ppb)	**0.334**	**0.014**	-0.266	0.052	**-0.375**	**0.005**	-0.151	0.276	**-0.301**	**0.027**
Pre-BD FEV1 % predicted	**-0.495**	**<0.001**	**0.476**	**<0.001**	**0.441**	**0.001**	**0.544**	**<0.001**	**0.560**	**<0.001**
6MWD (m)	**-0.569**	**<0.001**	**0.394**	**0.002**	**0.680**	**<0.001**	**0.690**	**<0.001**	**0.719**	**<0.001**
Borg score post 6MWT	**0.423**	**0.001**	**-0.399**	**0.002**	**-0.396**	**0.0023**	**-0.280**	**<0.001**	**-0.434**	**<0.001**

Table 3.3 legend: Significant p values and corresponding correlation co-efficients highlighted in bold. Abbreviations used in table: LPA- light physical activity, MVPA- moderate-vigorous physical activity, BDP- budesonide-equivalent dose of inhaled corticosteroid, GP- general practitioner, A&E- accident and emergency, BMI- body mass index, ACQ6- 6 point asthma control questionnaire, AQLQ- asthma quality of life questionnaire, HAD- hospital anxiety and depression score, FeNO- fraction of exhaled nitric oxide, pre-BD- pre-bronchodilator, FEV1- forced expiratory volume in 1 second, 6MWD- six-minute walk distance, 6MWT- six-minute walk test.

Of the five activity parameters, AA was most closely correlated with asthma measures. We therefore compared the highest and lowest AA quartiles (table

3.4). The highest quartile comprised nine participants from MHW group and five from MOW. The lowest quartile comprised two from MOW and twelve from DOW group. In highest and lowest AA quartiles respectively: BMI mean (SD) was 24.3 (2.3) kg/m^2 vs. 37.5 (7.3), p<0.001; BDP dose was 479 (345) µg vs. 1179 (569), p<0.001; annual prednisolone boosts were 0 (0-0.3) vs. 2 (0.8-5.5), p<0.001. ACQ6 was 0.5 (0.4) vs. 2.4 (1.3), p<0.001 and AQLQ was 6.3 (0.6) vs. 4.2 (1.6), p=0.001.

Table 3.4- Comparison of highest and lowest quartiles based on average acceleration

Parameter	Highest AA Quartile	Lowest AA Quartile	P value
Age (years)	47.4 (15.7)	58.4 (10.7)	**0.041**
BDP equivalent dose (mcg)	479 (345)	1179 (569)	**<0.001**
Annual prednisolone boosts	0 (0-0.3)	2 (0.8-5.5)	**<0.001**
Annual GP visits	0 (0-0.25)	0 (0-3)	0.133
Annual A&E Visits	0 (0)	0 (0-1)	0.115
BMI (kg/m^2)	24.3 (2.3)	37.5 (7.3)	**<0.001**
MRC Dyspnoea score	1 (1-1)	3 (2-3.25)	**<0.001**
ACQ6	0.5 (0.4)	2.4 (1.3)	**<0.001**
AQLQ overall	6.3 (0.6)	4.2 (1.6)	**<0.001**
AQLQ symptoms	6.5 (6.1-6.8)	4.0 (2.9-5.9)	**0.001**
AQLQ activity	6.6 (5.9-6.9)	3.5 (2.7-5.1)	**<0.001**
AQLQ emotional	6.8 (6.6-7)	4.1 (2.9-5.7)	**<0.001**
AQLQ environmental	6.4 (5.7-7.0)	5 (2.2-6.5)	0.084
HADS anxiety	5.9 (3.0)	8.3 (4.7)	0.116
HADS depression	2 (0-6)	8.5 (3.8-10.5)	**<0.001**
Eosinophils (x10^9/L)	0.2 (0.1-0.2)	0.3 (0.1-0.4)	0.328
FeNO (parts per billion)	23 (16-44)	42 (19-64)	0.346
Pre-BD FEV1 % predicted	94.9 (12.4)	64 (19.0)	**<0.001**
Pre-BD FEV1/FVC ratio	70.6 (9.4)	65.0 (9.7)	0.138
6MWD (metres)	556 (66)	289 (127)	**<0.001**
Borg Score	0 (0-1)	3 (1-3)	**0.003**

Table 3.4 legend. Results are expressed as mean (SD) and median (IQR). Abbreviations used in table: BDP- budesonide-equivalent dose of inhaled corticosteroid, GP- general practitioner, A&E- accident and emergency, BMI- body mass index, MRC Medical Research Council, ACQ6 6-point asthma control questionnaire, AQLQ- asthma quality of life questionnaire, HAD- hospital anxiety and depression score, FeNO- fraction of exhaled nitric oxide, pre-BD- pre-bronchodilator, FEV1- forced expiratory volume in 1 second, FEV1/FVC ratio forced expiratory volume in 1 second/forced vital capacity, 6MWD- six-minute walk distance.

3.4.4. Regression Analysis

Regression analysis was used to assess whether PA parameters could be used to predict ACQ6 or AQLQ, i.e. whether PA predicted asthma control or quality of life. In univariate linear regression (table 3.5), all PA parameters had a p value which was significant, but the R^2 values were tiny, meaning this was not relevant.

Table 3.5- Simple linear regression results

Dependent Variable	Independent Variable	p value	β coefficient	R^2
ACQ6	Inactive time	**<0.001**	0.007	0.227
	LPA	**<0.001**	-0.010	0.194
	MVPA	**0.003**	-0.01	0.150
	IG	**0.008**	-1.63	0.121
	AA	**0.001**	-0.061	0.175
AQLQ	Inactive time	**<0.001**	-0.008	0.239
	LPA	**<0.001**	0.010	0.197
	MVPA	**0.002**	0.013	0.162
	IG	**0.002**	1.998	0.168
	AA	**<0.001**	0.068	0.199

Table 5 legend: Abbreviations used in table: ACQ6- 6-point asthma control questionnaire, LPA- light physical activity, MVPA- moderate-vigorous physical activity, IG- intensity gradient, AA- average acceleration, AQLQ- asthma quality of life questionnaire

In multiple linear regression models incorporating age, gender and BMI as additional independent variables; inactive time, MVPA, IG and AA remained significantly predictive of ACQ and AQLQ to a small degree, i.e. the p values were below 0.05, but R^2 values small. There was no significant association with LPA (table 3.6). There was no evidence of multicollinearity.

Table 3.6- Multiple linear regression results.

Dependent variable	Model p value	Independent PA parameter	β co-efficient	β co-efficient p value	R^2
ACQ	<0.001	Inactive time	0.004	**0.038**	0.445
	<0.001	LPA	-0.004	0.159	0.419
	<0.001	MVPA	-0.010	**0.011**	0.469
	<0.001	IG	-1.383	**0.019**	0.458
	<0.001	AA	-0.043	**0.026**	0.452
AQLQ	<0.001	Inactive time	-0.005	**0.016**	0.464
	<0.001	LPA	0.005	0.095	0.431
	<0.001	MVPA	0.012	**0.005**	0.486
	<0.001	IG	1.885	**0.002**	0.505
	<0.001	AA	0.054	**0.007**	0.480

Table 6 legend: ACQ and AQLQ as dependent variables with PA parameter plus BMI, age and gender as independent variables. Abbreviations used in table: ACQ6- 6 point asthma control questionnaire, LPA- light physical activity, MVPA- moderate-vigorous physical activity, IG- intensity gradient, AA- average acceleration, AQLQ- asthma quality of life questionnaire.

3.5. Discussion

This cross-sectional study was designed to compare PA levels of individuals with difficult-to-treat asthma associated with elevated BMI (DOW group) to two control groups of individuals with mild-moderate asthma and either healthy (MHW) or elevated (MOW) BMI. We demonstrated the DOW group had significantly more inactive time and less time engaged in PA than the control groups, even when corrected for both age and BMI. Correspondingly, both intensity and volume of PA were lower in DOW group. To our knowledge this is the first time IG and AA have been recorded in these populations.

Other studies have measured PA in asthmatics using accelerometry, but not in phenotypes distinguished by both BMI and asthma severity. Neither have AA nor IG been measured previously. As such, previous studies are not directly comparable to ours. One cross-sectional study used hip-worn accelerometers and measured PA in participants with severe asthma along with age and gender-matched healthy controls(Cordova-Rivera et al. 2018b). After adjusting for

smoking status and BMI, the severe asthma group completed almost 20 fewer minutes MVPA per day than controls (p<0.001) but mean (95% CI) 22(2-41) minutes more LPA per day than the control group, p=0.029. They did not find differences in sedentary time between groups, thus results are quite different from ours. Perhaps part of this could be explained by the addition of obesity in our equivalent 'severe asthma' dataset.

Another cross-sectional study looked at groups with mild-moderate (n=83) and severe (n=63) asthma and healthy controls (n=29) and measured PA with arm-worn accelerometers(Bahmer et al. 2017). Moderate activity was lowest in the severe asthma group with median of 125 (68-172) minutes per day, compared to 151 (99-197) in mild-moderate asthma and 163 in healthy controls, p<0.05, all a lot higher than our MVPA results.

A third study compared activity levels of severe asthmatics (n=48) with healthy controls (n=48) using arm-worn accelerometers(Neale et al. 2020). BMI was significantly higher in the asthma group (33 ± 6.7 $kg.m^{-2}$) compared to control (26.4 ± 4.4), p<0.001. Mean FEV_1 was 71.2 ± 20.1% predicted in the severe asthma group compared to median 66.4 (59–74)% in our corresponding group. Wear time was significantly lower in the severe asthma group for unspecified reasons, and once this and differences in BMI between groups were accounted for, the severe asthma group did fewer steps per day (p=0.009) but there was no significant difference in total MVPA or stationary time. Total time spent in MVPA in the asthma group was similar to our study at 44 (±46) minutes per day, with 91 (±80) minutes in the control group, although as previously mentioned, the number of minutes are not directly comparable due to different monitors and methods of data analysis.

We found time spent in MVPA was markedly reduced in the DOW group with a median (IQR) of 42 (33-52) minutes compared to almost double in the MOW group of 79 (58-99) minutes and almost 2.5 times in the MHW group, 103 (80-127) minutes, p<0.001. Differences in other parameters were less dramatic, but

across all PA parameters the DOW group were significantly less active. These findings fit with previous studies, but we have extended observations by comparing groups based on BMI and asthma severity. When individual groups were compared, differences between the MHW and MOW groups were not significant (inactive time p=0.064, LPA p=0.251 and MVPA p=0.097), but differences between MHW/DOW and MOW/DOW groups were statistically significant. The difference between the values suggests this is likely of clinical significance too, although there is no minimum clinically important difference (MCID) specified for these groups. This may suggest that degree of asthma severity is more important in determination of PA. We cannot infer from our data whether difficult-to-treat asthma is a cause or an effect of this. However, since age and BMI corrected results were significantly different between the difficult-to-treat asthma group and the two mild asthma groups, asthma severity may be more closely linked to activity. It is not possible to state whether the DOW group move less because their asthma is more severe, or they are deconditioned due to obesity which leads to worsening asthma. It is likely that these both play a role.

In correlation analysis, asthma control (ACQ6) and quality of life (AQLQ) were both significantly associated with all PA parameters with both improving with increasing activity. Other markers of asthma control including number of exacerbations requiring prednisolone were similarly correlated, as was exercise tolerance (measured by 6MWT) and perception of exertional breathlessness (measured by Borg score post-6MWT). This suggest that participants with lower BMI, better asthma control, less frequent exacerbations, and less severe asthma (higher pre-BD FEV_1) are more physically active. Further work is required to prove the benefits of increased PA before we could recommend increased PA as part of routine asthma management in difficult-to-treat obese asthmatics.

Group selection criteria led to many significant differences between groups at baseline, including treatments, co-morbidity and age. We corrected results using age and BMI as covariates, but differences between groups remained. A number of baseline differences are directly due to recruitment criteria (BMI) and

several others are features of difficult-to-treat asthma e.g. co-morbidities and increasing treatment burden. As such the differences between groups were mostly anticipated and may help explain reasons behind differing activity levels.

Once accelerometer readings were processed, a number were excluded based on pre-determined criteria to allow accurate comparison. This unfortunately meant we lost more readings from the MHW/MOW groups, because there was a much larger dataset available for the DOW group so any invalid readings were replaced for this group. It is possible that this may have led to less robust findings. However, our strict inclusion criteria mean our data is reflective of complete 24-hour cycles, whereas in other studies using shorter wear times large amounts of data could be missing. Compliance in our study was good, with only 8 recordings excluded due to insufficient wear time, comparable to similar studies of healthy adults. Overall therefore, we can be confident in the robustness of our data.

Another possible limitation was wrist placement of devices, which reduced the comparability of our data with other studies. It is important to be aware that the values reported are wear location specific and should not be compared to values provided from different wear locations. However, inclusion of IG and AA mean this data can be compared to future studies reporting them, as IG and AA are independent of location, device and processing. In addition, wrist placement meant we were unable to obtain reliable step counts or separate moderate from vigorous PA with these devices and processing methods, but we felt wrist placement would improve compliance which was high.

3.6. Conclusions

This cross-sectional study demonstrated that time, intensity and volume of PA were all significantly lower in overweight participants with difficult-to-treat asthma compared with healthy weight and overweight participants with mild-moderate asthma, and these differences persisted when age and BMI were considered as confounding variables. Average acceleration is a novel

accelerometry-based biomarker reflecting volume of PA and correlates with asthma control and quality of life. Measurement of AA and increasing volume of PA may have a role in targeting exercise/activity programmes to individuals with obesity and difficult-to-treat asthma who are most likely to benefit from this intervention.

Chapter 4: A pragmatic randomised controlled trial of tailored pulmonary rehabilitation in participants with difficult-to-treat asthma and elevated body mass index

Published in BMC Pulmonary Medicine, September 2022.

Full author list: Helen Clare Ricketts, Varun Sharma, Femke Steffensen, Anna Goodfellow, Elaine Mackay, Gordon MacDonald, Duncan S Buchan, Rekha Chaudhuri and Douglas C Cowan.

4.1. Abstract

4.1.1. Background

Difficult-to-treat asthma associated with elevated body mass index (BMI) is challenging to treat, with limited therapeutic options. The effects of pulmonary rehabilitation (PR) in this population are uncertain, and warrant further investigation.

4.1.2. Methods

This is a randomised controlled trial of an eight-week asthma-tailored PR programme versus usual care (UC) in participants with difficult-to-treat asthma and BMI ≥25 kg/m^2. PR comprised two hours of education and supervised exercise per week, with encouragement for two individual exercise sessions. The primary outcome was the difference in change in Asthma Quality of Life Questionnaire (AQLQ) in PR versus UC groups between visits. Secondary outcomes included difference in change in Asthma Control Questionnaire-6 (ACQ6), and a responder analysis comparing the proportion of participants reaching the minimum clinically important differences for AQLQ and ACQ6.

4.1.3. Results

95 participants were randomised 1:1 to PR or UC. Median age was 54 years, 60% were female and median BMI was 33.8 kg/m^2. Mean (95% CI) AQLQ was 3.9 (1.2) and median (IQR) ACQ6 2.8 (1.8-3.6). 77 participants attended a second visit and had results analysed. Median (IQR) change in AQLQ was not significantly different: 0.3 (-0.2 to 0.6) in PR and -0.1 (-0.5 to 0.4) in UC, p= 0.139. Mean change in ACQ6 was significantly different: -0.4 (95% CI -0.6 to -0.2) in PR and 0 (-0.3 to +0.3) in UC, p=0.015, but below the minimum clinically important difference (±0.5). In the ACQ6 responder analysis, the minimum clinically important difference of -0.5 was reached by 18 PR participants (54.5%) versus 10 UC (22.7%), p=0.009. The dropout rate was 31% between visits in the PR group, and time to completion was significantly prolonged in the PR group at 94 (70-107) days vs. 63 (56-73) in UC, p<0.001.

4.1.4. Conclusions

PR improved asthma control and reduced perceived breathlessness in participants with difficult-to-treat asthma and elevated BMI. However, this format appears to be suboptimal for this population with high drop-out rates and prolonged time to completion.

4.2. Background

Difficult-to-treat asthma(Global Initiative for Asthma 2022a) is defined as asthma with ongoing symptoms or frequent exacerbations, despite treatment with a minimum of medium or high dose inhaled corticosteroids (ICS) plus long-acting β2 agonist (LABA). Evidence indicates obesity can both lead to and worsen asthma(Camargo et al. 1999). Obese asthma is associated with increased symptoms(Vortmann and Eisner 2008), frequent exacerbations(Akerman et al. 2004; Barros et al. 2017) and resistance to traditional therapies including ICS(Boulet and Franssen 2007; Sutherland et al. 2008). In an analysis of 2225 patients registered with British Thoracic Society (BTS) Difficult Asthma Registry, mean BMI was 30.8 kg/m^2 (SD 7.1)(Jackson et al. 2021). Obesity rates are increasing worldwide, with an almost threefold increase since 1975(World Health Organisation 2018). Experts recommend personalisation of asthma treatment

with identification of treatable traits(Pavord et al. 2018; McDonald et al. 2019). Obese asthma is a phenotype that could be specifically targeted.

Pulmonary rehabilitation (PR) describes an exercise and education programme that has proven beneficial in respiratory conditions including chronic obstructive pulmonary disease (COPD)(Bolton et al. 2013). Benefits in this population include improvements in quality of life(McCarthy et al. 2015) and mental health(Griffiths et al. 2000). The role of PR in asthma is unclear, as few studies have evaluated the effects. A recent small study (n=34) demonstrated weight reduction and improved asthma control after intensive PR(Türk et al. 2020). Another feasibility study suggested some improvements but acknowledged high dropout rates(Majd et al. 2020).

4.3. Methods

4.3.1. Study Aim and Design

Our objective was to evaluate the impact of a tailored PR programme in overweight/obese individuals with difficult-to-treat asthma. We aimed to assess effects on asthma-related quality of life and control, as well as other measures of disease burden, exercise tolerance, activity levels and mental health.

This was an unblinded, randomised controlled parallel group trial of asthma tailored PR in individuals with difficult-to-treat asthma who were overweight/obese. Participants were randomised 1:1 to PR or usual care (UC). Randomisation was by a third-party drawing from an envelope. Study visits took place at baseline (V1) and eight weeks, or completion of eight PR sessions (V2). The study took place between May 2017 and December 2020 in Glasgow Royal Infirmary. It was registered with clinicaltrials.gov (ID NCT03630432) and approved by West of Scotland Regional Ethics Committee (reference 16/WS/0200).

4.3.2. Study Participants

Participants were recruited from tertiary asthma clinics across the greater Glasgow region. Participants were aged 18-80 years, with BMI ≥25kg/m^2. Asthma was diagnosed according to Global Initiative for Asthma guidelines (Global Initiative for Asthma 2018), with characteristic symptoms and at least one of: 12% and 200mls increase in forced expiratory volume in 1 second (FEV_1) after inhaled/nebulised short-acting β-2 agonist (SABA), or ≥4 weeks of anti-inflammatory treatment, or between visits; or positive bronchial challenge test (PC_{20} methacholine or histamine<8 mg/ml or PD_{15} mannitol<635mg). Asthma was uncontrolled despite at least high dose ICS and LABA(Scottish Intercollegiate Guidelines Network 2016), with either ≥2 courses OCS, ≥1 asthma-related hospitalisation, or asthma control questionnaire-6 (ACQ6) score >1.5 within the previous year. Exclusion criteria included an exacerbation requiring OCS and/or antibiotics within four weeks; significant co-morbidity; mobility problems likely to influence study conduct; pregnancy/breastfeeding; and intensive care unit (ICU) admission or commencement of biologic therapy within the preceding six months.

A substantial amendment was approved in August 2018. This removed FEV_1/FVC ratio ≤70% and Medical Research Council (MRC) Dyspnoea Score ≤3 from inclusion criteria. Within exclusion criteria, minimum time from ICU admission to recruitment was reduced to 6 months from 12, and a 6 month period following discontinuation of antifungal, biologic therapy or Airsonett device was removed. These changes were made to widen recruitment and were not expected to impact on study outcomes.

Individuals expressing an interest in participation received a Patient Information Sheet and were invited to provide written informed consent prior to commencing study.

4.3.3. Pulmonary Rehabilitation Programme

The PR course lasted eight weeks, with one in-hospital session per week comprising an hour each of education and exercise. International guidelines recommend at least two supervised weekly sessions(Bolton et al. 2013; Spruit et al. 2013), but acknowledging attendance may be an issue, we pragmatically reduced to one supervised session and encouraged two further independent sessions each week. Compliance with this was not monitored.

4.3.3.1. Pulmonary rehabilitation education

The educational component was delivered on a rolling basis by multidisciplinary staff. Topics covered are listed in table 4.1. Further details are available in methods, chapter 2 section 2.5.1.

Table 4.1- Pulmonary Rehabilitation Educational Topics

Educational Topics
What is asthma: diagnosis, co-morbidities.
Asthma treatments.
Treatment, inhaler technique and personalised asthma management.
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.

4.3.3.2. Pulmonary rehabilitation exercise

The exercise was delivered in a hospital gym by the PR Team. Asthma stability was verbally confirmed before starting each session, and pre-exercise administration of SABA inhaler was encouraged. Exercises were taken from the local PR programme and comprised a warm-up followed by resistance and aerobic exercises. Training intensity was individually tailored based on distance walked during baseline six-minute walk test (6MWT) and current activity profile as assessed on verbal interview by the physiotherapists. There was progressive increase in repetitions/resistance each week. Full details are in methods, section 2.5.2.

Some participants already exercised regularly and managed longer distances on the baseline 6MWT. They had the exercises adapted to make them more challenging. Some participants were advised to spend a longer time on aerobic exercises. Some participants had more difficult strength training exercises using weights machines and heavier weights. The exercise for each participant was tailored to their ability at baseline and progressed throughout the eight sessions.

If sessions were missed participants were contacted by telephone or email, and reattendance was encouraged. All participants were asked to attend eight sessions. At completion, participants were encouraged to continue regular exercise and offered referral to community-based facilities.

4.3.4. Study Measurements

At V1, information including demographics, medical history and medications was obtained by participant interview and using electronic medical records. Participants completed several questionnaires including asthma quality of life questionnaire (AQLQ)(Juniper et al. 1992; Juniper et al. 2013); ACQ6(Juniper et al. 1994; Juniper et al. 1999); MRC dyspnoea score(Bestall et al. 1999); and hospital anxiety and depression scale (HADS)(Stern 2014).

Height and weight were recorded, and BMI calculated. Participants performed fraction of exhaled nitric oxide (FeNO) using NIOX VERO machine (Circassia Pharmaceuticals, Morrisville, USA). Peak expiratory respiratory flow (PEFR) and spirometry were performed before and 15 minutes after inhaled salbutamol, on a Vitalograph (Maids Moreton, U.K.) spirometer. Blood samples were taken for eosinophil count. Two 6MWTs were carried out with the furthest distance and corresponding Borg score at completion used for analysis.

Each participant wore an ActiGraph wGTX3-BT (ActiGraph, Pensacola, Florida, USA) accelerometer on their non-dominant wrist continually for seven days (except when bathing/swimming) to estimate physical activity (PA).

At completion of V1, participants were randomised, with the PR course starting one week later. Both groups were advised to continue their pre-study asthma management, with changes allowed throughout the study as clinically indicated. Inhaler technique was reviewed and corrected if necessary. All participants were provided with a personalised asthma management plan.

V2 was scheduled for eight weeks after V1. V2 was postponed until eight PR sessions were completed, if necessary. V2 followed the same format. Anyone who attended V2 was regarded as completing PR, no matter how many sessions they attended, hence analysis was intention-to-treat.

Those randomised to the UC group had V2 scheduled for eight weeks later, and no other contact between visits. They were offered the opportunity to complete PR following V2.

Following accelerometer return, data was downloaded using ActiLife v.6.14.3 (ActiGraph, USA), and processed as detailed in methods, section 2.4.

4.3.5. Statistical Analysis

Baseline characteristics and results are expressed as mean with standard deviation(SD), median and interquartile range (IQR) or numbers and proportions. The primary outcome was difference in change in AQLQ between visits for PR versus UC groups. Analysis was on the basis of intention to treat, with everyone who attended V2 included in analysis, regardless of number of sessions completed. The primary outcomes looked at change between visits, and it was not possible to calculate change for those who failed to attend a second visit.

Per protocol analysis would merely have included everyone who attended 8 sessions of PR.

The minimum clinically important difference (MCID) for AQLQ is 0.5(Juniper et al. 1994). Mean (SD) AQLQ for a similar population is 3.5(1.2) (unpublished local data contributed to BTS DAR). To demonstrate a difference of 0.5 mean change between visits, a sample size of 180 was calculated, assuming α 0.05, ß 0.2 and power 0.8. It was considered benefits may be larger than anticipated, and was agreed with regional ethics committee at the outset, that an interim analysis would be performed after recruitment of 100. This coincided with the start of the Covid-19 pandemic and no further recruitment was possible due to legal guidelines on face-to-face contact.

Normality testing was performed with D'Agostino-Pearson test. At baseline, comparisons were made using Chi-squared or Fisher's exact test for proportions, unpaired t test for normally distributed data, and Mann-Whitney U test for skewed data*.

Data obtained from individuals attending both V1 and V2 were used to compare effects of PR with UC. Change for each individual was calculated; then mean/median change for each group compared using unpaired T or Mann-Whitney U test*. A responder analysis compared proportion of individuals achieving the MCID of 0.5 points improvement in ACQ6(Juniper et al. 1994) and AQLQ(Juniper et al. 1992) using Chi-squared test. In a post-hoc analysis, FeNO and eosinophil levels were compared between ACQ6 and AQLQ responders/non-responders. A p-value of <0.05 was considered statistically significant. Statistical tests were performed using GraphPad Prism v9(GraphPad Software, San Diego).

**A number of these statistical tests were initially performed by Dr Varun Sharma, with repeat testing to confirm results performed by Dr Helen Clare Ricketts.*

4.4. Results

4.4.1. Baseline Characteristics

101 individuals gave informed consent to participate. Six were excluded as inclusion/exclusion criteria were not met, and 95 were randomised; 48 to PR and 47 to UC.

Figure 4.1- Flowchart of recruitment

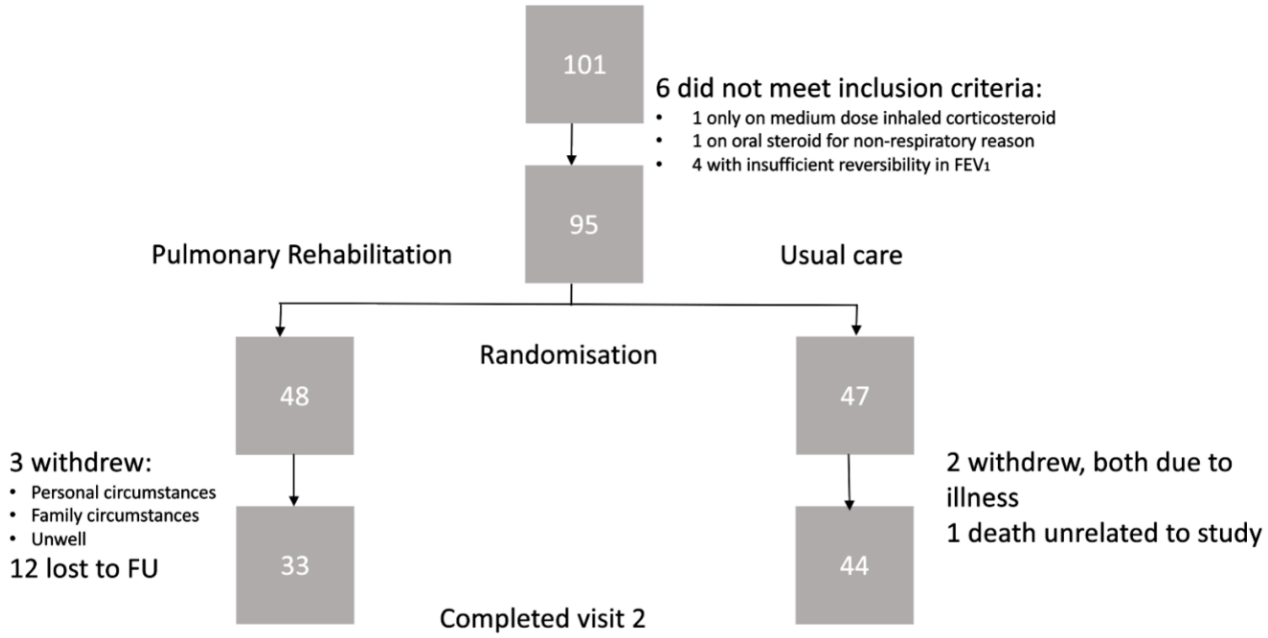

Figure 4.1 legend: A flowchart demonstrating recruitment, randomisation and follow-up

Baseline characteristics are displayed in table 4.2. Median (IQR) age was 54 (47-64) years and 57 (60%) were female. The commonest co-morbidities were gastro-oesophageal reflux disease (80%), allergic rhinitis (72%) and psychological illness (64%). Median number of co-morbidities was 6 (5-7). Participants had a high treatment burden, with 30 (32%) taking regular OCS. 20% were taking biologics- either omalizumab or mepolizumab, as these were the only drugs available during the recruitment period. Median BMI was 33.8 (29.6-38.9) kg/m^2 with 70 (74%) obese. Baseline ACQ6 was 2.8 (1.8-3.6) and AQLQ 3.9 (1.2). With the exception of montelukast use, there were no significant differences between groups at baseline.

77 participants attended V2 and were included in analysis, 33 (69%) in PR group and 44 (94%) in UC. Within the PR group, 28 (85%) completed eight PR sessions, 5 completed fewer than five sessions: the mean (SD) number of sessions attended was 7.1 (2.3). Intended time between visits was 56 days, but median was 94 (70-107) days in the PR group and 63 (56-73) in the UC group, p<0.001. This was due to non-attendance at PR sessions prolonging time to completion.

Table 4.2- Characteristics at baseline of all participants recruited

	Overall n = 95	**Pulmonary Rehabilitation Group (PR) n=48**	**Usual Care Group (UC) n= 47**	**p value : PR vs UC**
Age, years	54 (47 to 64)	53 (47 to 61)	56 (47 to 65)	0.287
Sex: Female Male	57 (60) 38 (40)	28 (58.3) 20 (41.7)	27 (61.7) 18 (38.3)	0.900
Smoking: Ex-smoker Lifelong non-smoker Current smoker	41 (43.2) 47 (49.5) 7 (7.4)	19 (39.6) 25 (52.1) 4 (8.3)	22 (46.8) 22 (46.8) 3 (6.4)	0.7621
Pack years	20 (10 to 35)	20 (10 to 35)	20 (8 to 34)	0.931
Age at asthma diagnosis	31 (7 to 47)	33 (9 to 48)	30 (5 to 46)	0.455
Duration of asthma, years	21 (10 to 39)	19 (6 to 39)	25 (14 to 39)	0.176
Atopy	61 (64.2)	31 (64.6)	30(63.8)	0.891
Allergic rhinitis	68 (71.6)	35 (72.9)	33 (70.2)	0.949
Perennial rhinitis	46 (48.4)	23 (47.9)	23 (48.9)	0.916
Nasal polyps	14 (14.7)	5 (10.4)	9 (19.1)	0.362
Nasal surgery	19 (20.0)	6 (12.5)	13 (27.7)	0.112
Eczema	20 (21.1)	8 (16.7)	12 (25.5)	0.419
GORD	76 (80.0)	38 (79.2)	38 (80.9)	0.959
DFB/ILO	17 (17.9)	12 (25.0)	5 (10.6)	0.119
Psychological illness	61 (64.2)	32 (66.7)	29 (61.7)	0.771
Emphysema	8 (8.4)	2 (4.2)	6 (12.8)	0.159
Bronchiectasis	14 (14.7)	7 (14.6)	7 (14.9)	0.805
SAFS/ABPA	18 (18.9)	10 (20.8)	8 (17.0)	0.832
Diabetes mellitus	14 (14.7)	5 (10.4)	9 (19.1)	0.362
Hypertension	24 (25.3)	11 (22.9)	13 (27.7)	0.767
Cardiac disease	17 (17.9)	7 (14.6)	10 (21.3)	0.560
Osteopenia/osteoporosis	35 (36.8)	18 (37.5)	17 (36.2)	0.938
SABA nebs	35 (36.8)	19 (39.6)	16 (34.0)	0.729
LAMA	78 (82.1)	41 (85.4)	37 (78.7)	0.560
ICS/LABA	95 (100)	48 (100)	47 (100.0)	>0.999
BDP equivalent dose, mcg	2000 (1600-2000)	2000 (1600-2400)	1600 (1600-2000)	0.106
Prednisolone maintenance	30 (31.6)	16 (33.3)	14 (29.8)	0.880
Prednisolone dose, mg	6.3 (5.6 to 6.9)	10.0 (5.0 to 10.0)	5.0 (5.0 to 7.5)	0.232
Montelukast	66 (69.5)	39 (81.3)	27 (57.4)	0.022

Theophylline	38 (40.0)	21 (43.8)	17 (36.2)	0.586
Azithromycin	13 (13.7)	6 (12.5)	7 (14.9)	0.967
Omalizumab	11 (11.6)	3 (6.3)	8 (17.0)	0.187
Mepolizumab	8 (8.4)	3 (6.3)	5 (10.6)	0.486
Antihistamine	61 (64.2)	30 (62.5)	31 (66.0)	0.891
Nasal steroid	42 (44.2)	24 (50.0)	18 (38.3)	0.346
PPI/H2A	72 (75.8)	37 (77.1)	35 (74.5)	0.954
In last year: Exacerbations	4.0 (2.0-5.0)	3.5 (2.0-5.3)	4.0 (2.0-5.0)	0.990
GP attendances	2 (0 to 5)	3 (0 to 5)	2 (1 to 4)	0.771
A & E attendances	0 (0 to 1)	0 (0 to 1)	0 (0 to 1)	0.829
Hospital admissions	0 (0 to 1)	0 (0 to 0)	0 (0 to 0)	0.328
ICU admissions	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0.745
BMI, kg/m2	33.8 (29.6 to 38.9)	33.8 (29.6 to 37.8)	33.1 (29.6 to 40.6)	0.916
MRC dyspnoea scale	3 (2-4)	3 (2-4)	3 (2-4)	0.423
ACQ6	2.8 (1.8 to 3.6)	2.8 (1.5 to 3.8)	2.8 (2.2 to 3.5)	0.448
AQLQ: Overall	3.9 ± 1.2	4.1 ± 1.3	3.7 ± 1.0	0.132
Symptom domain	3.9 ± 1.3	4.2 ± 1.5	3.7 ± 1.1	0.114
Activity domain	3.8 ± 1.2	3.9 ± 1.3	3.7 ± 1.6	0.452
Emotional domain	4.0 ± 1.6	4.3 ± 1.6	3.8 ± 1.5	0.134
Environmental domain	4.1 ± 1.5	4.3 ± 1.5	3.8 ± 1.5	0.075
HADS: Anxiety score	9.0 ± 4.8	8.5 ± 4.7	9.4 ± 4.9	0.377
Depression score	8.1 ± 4.3	8.1 ± 4.3	8.2 ± 4.3	0.904
Eosinophils (x10^9/L)	0.3 (0.1 to 0.4)	0.3 (0.2 to 0.5)	0.2 (0.1 to 0.4)	0.160
FeNO (ppb)	24 (14 to 49)	21 (13 to 48)	24 (16 to 50)	0.531
PEFR (L/min)	398.2 ± 102.6	409.0 ± 104.8	387.2 ± 99.1	0.305
pre-BD FEV1 (% predicted)	71.9 ± 16.8	73.0 ± 16.4	70.7 ± 17.1	0.518
pre-BD FEV1/FVC %	65 (59 to 71)	66 (62 to 72)	65 (58 to 70)	0.296
% change FEV1 post-BD	4.8 (-0.9 to 12.2)	4.7 (-2.2 to 13.4)	4.8 (2.6 to 11.1)	0.787
6MWT, metres	390 (315 to 450)	410 (349 to 450)	390 (263 to 428)	0.162
Borg score post- 6MWT	2.0 (1.0 to 3.0)	2.5 (1.0 to 3.0)	2.0(1.0 to 3.0)	0.783
Accelerometry: Inactive time	1170 (1107 - 1237)	1177 (1114 - 1238)	1150 (1104 - 1239)	0.515
Minutes per day. Time in LPA	218 (169 to 267)	211 (164 to 250)	236 (170 to 288)	0.229
Time in MVPA	48 (28 to 72)	51 (32 to 74)	40 (27 to 68)	0.260
Intensity gradient	-2.8 ± 0.2	-2.78 ± 0.16	-2.84 ± 0.16	0.101
Average acceleration	19.2 ± 6.4	18.4 (15-22)	19.5 (15-23)	0.816

Table 2 Legend: Values expressed as number (proportion), mean ± SD or median (IQR) unless otherwise specified. Abbreviations used in table: PR pulmonary rehabilitation, UC usual care control group, GORD gastro-oesophageal reflux disease, DFB dysfunctional breathing, ILO intermittent laryngeal obstruction, SAFS severe asthma with fungal sensitisation, ABPA allergic bronchopulmonary aspergillosis, SABA short acting beta-2 agonist, LABA long acting beta-2 agonist, LAMA- long acting muscarinic antagonist, ICS inhaled corticosteroid, BDP beclomethasone dipropionate dose equivalent, PPI proton pump inhibitor, H2A H2 receptor antagonist, A and E accident and emergency

department, GP General Practitioner, ICU intensive care unit, BMI body mass index, MRC Medical Research Council dyspnoea score, ACQ6 Asthma Control Questionnaire 6, AQLQ Asthma Quality of Life Questionnaire, HADS Hospital Anxiety and Depression Scale, FeNO fraction of exhaled nitric oxide, PEFR peak expiratory flow rate, pre-BD pre-bronchodilator, FEV1 forced expiratory volume in 1 second, FVC forced vital capacity, post-BD post bronchodilator, 6MWT 6 minute walk test, LPA light physical activity, MVPA moderate-vigorous physical activity.

4.4.2. Primary Outcome

Results are displayed in table 4.3/figure 4.2. The mean (SD) AQLQ at V1 was 4.4 (1.2) in the PR group and 3.8 (1.0) in the UC group, p=0.037. At V2, AQLQ was 4.5 (1.2) in the PR group and 3.9 (1.1) in the UC group, p=0.018. The median (IQR) change in AQLQ was not significantly different: 0.3 (-0.2 to 0.6) in the PR group and -0.1 (-0.5 to 0.4) in the UC group, p=0.139. As significant differences were observed between groups at V1 and V2 at baseline, post-hoc multiple regression analysis adjusting for baseline was performed. This confirmed no significant difference in change between groups.

There were no statistically or clinically significant differences in change in any of the AQLQ domains, but there was a numerical trend towards benefit of PR in the activity domain; +0.5 (-0.4 to 1) in PR and -0.1 (-0.6 to 0.5) in UC, p=0.057.

Table 4.3- Key results of participants who completed the study

		PR group (n=33)	UC group (n=44)	p-value *PR vs. UC*
Overall AQLQ	V1	4.4 ± 1.2	3.8 ± 1.0	**0.037**
	V2	4.5 ± 1.2	3.9 ± 1.1	**0.018**
	Change	0.3 (-0.2 to 0.6)	-0.1 (-0.5 to 0.4)	0.139
AQLQ Symptom	V1	4.4 ± 1.5	3.8 ± 1.1	0.062
	V2	4.6 ± 1.4	3.9 ± 1.2	**0.022**
	Change	0.4 (-0.3 to 0.7)	0.0 (-0.6 to 0.5)	0.179
AQLQ Activity	V1	4.1 ± 1.3	3.8 ± 1.1	0.221
	V2	4.4 ± 1.2	3.8 ± 1.1	0.045
	Change	0.5 (-0.4 to 1.0)	-0.1 (-0.6 to 0.5)	0.057
AQLQ Emotional	V1	4.6 ± 1.5	3.9 ± 1.5	**0.036**
	V2	5.0 (3.6 to 6.2)	4.0 (2.9 to 5.0)	**0.013**
	Change	0.2 (-0.2 to 0.6)	0.0 (-0.75 to 0.75)	0.248
AQLQ Environmental	V1	4.8 ± 1.3	3.9 ± 1.5	**0.007**
	V2	4.5 ± 1.5	4.0 ± 1.6	0.186
	Change	-0.2 (-0.8 to 0.5)	0.0 (-0.5 to 0.7)	0.320
ACQ6	V1	2.3 ± 1.4	2.8 ± 1.0	0.103
	V2	1.9 ± 1.4	2.8 ± 1.2	**0.018**
	Change*	-0.4 (-0.6 to -0.2)	0.0 (-0.3 to 0.3)	**0.015**
MRC	V1	2 (2 to 4)	3 (2 to 4)	0.414
	V2	2 (2 to 3)	3 (2 to 4)	**0.080**
	Change	0 (-1 to 0)	0 (0 to 1)	**0.022**
HADS Anxiety	V1	8 ± 5	9 ± 5	0.269
	V2	8 ± 5	9 ± 5	0.104
	Change	-1 ± 3	0 ± 3	0.332
HADS Depression	V1	9 (4 to 10)	8 (5 to 12)	0.723
	V2	8 (4 to 11)	8 (4 to 11)	0.296
	Change	-1 (-3 to 1)	0 (-2 to 1)	0.361
BMI kg/m^2	V1	33.8 (29.8 to 38.0)	33.0 (29.3 to 40.1)	0.804
	V2	34.1 (29.8 to 38.3)	33.1 (29.5 to 40.6)	0.933
	Change	-0.1 (-0.7 to 0.7)	0.1 (-0.2 to 0.6)	0.209
Eosinophils (x10^9/L)	V1	0.30 (0.20 to 0.50)	0.20 (0.10 to 0.40)	0.096
	V2	0.20 (0.10 to 0.43)	0.25 (0.10 to 0.40)	0.994
	Change	0.00 (-0.10 to 0.00)	0.00 (-0.10 to 0.10)	0.057
FeNO (ppb)	V1	32 (13 to 53)	24 (15 to 49)	0.919
	V2	22 (13 to 68)	24 (12 to 41)	0.628
	Change	-4 (-11 to 4)	-4 (-13 to 3)	0.563
Pre-BD FEV_1/FVC ratio	V1	65 ± 9	64 ± 9	0.523
	V2	66 ± 11	66 ± 11	0.900
	Change	1 ± 5	2 ± 6	0.194
Pre-BD FEV_1 % predicted	V1	77 (65 to 85)	71 (61 to 83)	0.406
	V2	74 (64 to 89)	74 (61 to 89)	0.754
	Change	3 (-6 to 8)	2 (-3 to 6)	0.982
% change FEV_1 post BD	V1	-0.65 (-3.09 to 9.18)	4.7 (2.5 to 11.65)	0.097
	V2	2.48 (-0.51 to 7.69)	4.07 (-0.99 to 7.79)	0.960
	Change	2.75 (-4.72 to 7.67)	-1.71 (-7.60 to 4.15)	0.170

6MWD (metres)	V1	390 (345 to 458)	392 (278 to 439)	0.618
	V2	420 (368 to 468)	380 (301 to 430)	0.055
	Change	20 (-5 to 40)	-10 (-40 to 25)	**0.035**
Borg score	V1	2 (1 to 3)	2 (0.63 to 3)	0.597
	V2	1 (0 to 2)	2 (1 to 3)	**0.009**
	Change	-1 (-2 to 0)	0 (-1 to 1)	**0.015**
Accelerometry:	V1	1177 (1114 to 1238)	1150 (1104 to 1239)	0.515
Inactive time (min.d^{-1})	V2	1175 (1093 to 1234)	1175 (1096 to 1241)	0.841
	Change	11 (-53 to 32)	-4 (-35 to 84)	0.274
Accelerometry: LPA	V1	211 (164 to 250)	236 (170 to 288)	0.253
(min.d^{-1})	V2	236 (170 to 288)	228 (170 to 290)	0.425
	Change	-8 (-18 to 34)	-4 (-61 to 27)	0.296
Accelerometry:	V1	51 (32 to 74)	40 (27 to 68)	0.260
MVPA (min.d^{-1})	V2	44.7 (30.1 to 80.3)	38.9 (24.9-63.3)	0.319
	Change	-1 (-9 to 15)	0 (-11 to 9)	0.361
Accelerometry: IG	V1	-2.78 ± 0.16	-2.84 ± 0.16	0.101
	V2	-2.77 ± 0.14	-2.81 ± 0.17	0.326
	Change	0.025 ± 0.11	0.002 ± 0.13	0.883
Accelerometry: AA	V1	18.4 (15-22)	19.5 (15-23)	0.816
(ENMO, m*g*)	V2	17.8 (15-24)	18.3 (15-22)	0.742
	Change	0.71 (-0.69 to 3.08)	-0.39 (-4.28 to 6.7)	0.199

Table 4.3 Legend: Values are expressed as mean ± SD, median (IQR) or *mean (95% CI). Abbreviations used in table: PR pulmonary rehabilitation, UC usual care, AQLQ asthma quality of life questionnaire, ACQ6 6-point asthma control questionnaire, MRC Medical Research Council dyspnoea score, HAD hospital anxiety and depression scale, BMI body mass index, FeNO fraction of exhaled nitric oxide, ppb parts per billion, pre-BD pre-bronchodilator, FEV_1 forced expiratory volume in 1 second, FVC forced vital capacity, 6MWD six minute walk distance, LPA light physical activity, MVPA moderate-vigorous physical activity, IG intensity gradient, AA average acceleration.

Figure 4.2- Key results

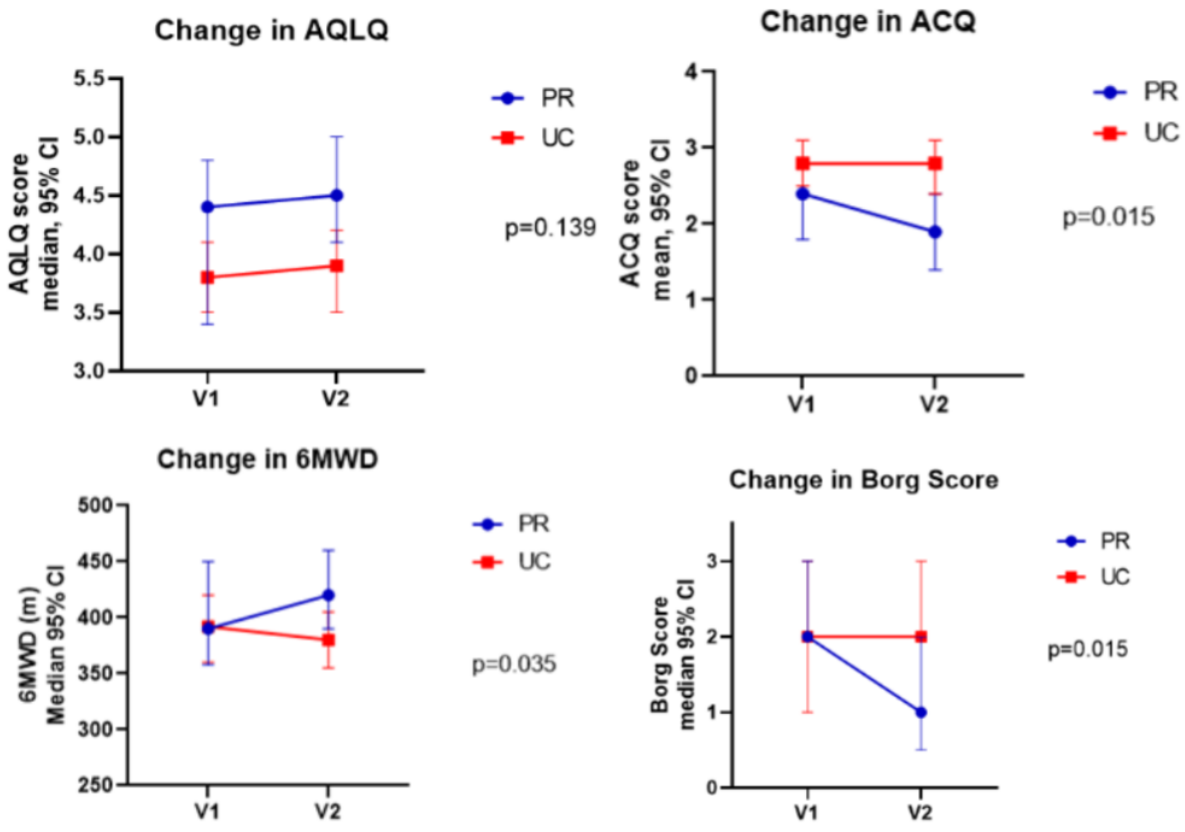

Figure 4.2 legend: Graphical representation of key results. Abbreviations used: AQLQ- asthma quality of life questionnaire, PR- pulmonary rehabilitation group, UC- usual care group, V1- visit 1, V2- visit 2, CI- confidence intervals, ACQ6- 6-point version asthma control questionnaire, 6MWD- six minute walk distance.

4.4.3. Secondary outcomes

There was no significant difference in the proportion of participants that reached the MCID for improvement in overall AQLQ: 13 (39%) in PR and 10 (23%) in UC, p=0.184 (table 4.4/figure 4.3). There were trends towards differences in symptom (p=0.058) and activity domains (p=0.053).

Table 4.4- Participants that met the minimum clinically important difference

	PR group (n=33)	UC group (n=44)	p-value
Change in overall AQLQ ≥ +0.5	13 (39)	10 (23)	0.184
Change in symptoms ≥ +0.5	16 (49)	11 (25)	0.058
Change in activity ≥ +0.5	17 (52)	12 (27)	0.053
Change in emotional ≥ +0.5	11 (33)	13 (30)	0.806
Change in environmental ≥ +0.5	10(30)	15(34)	0.916
Change in ACQ6 ≥ -0.5	18(55)	10(23)	**0.009**

Table 4.4 Legend: Demonstrates number and proportion of participants meeting the MCID for change in AQLQ overall and each AQLQ domain, plus in ACQ6. Abbreviations used in table: AQLQ asthma quality of life questionnaire, ACQ6 6-point asthma control questionnaire.

The mean (SD) ACQ6 at V1 was 2.3 (1.4) in the PR group and 2.8 (1.0) in the UC group, p=0.103. At V2 it was 1.9 (1.4) in the PR group and 2.8 (1.2) in the UC group, p=0.018. Mean change in ACQ6 was -0.4 (95% CI -0.6 to -0.2) in the PR group versus 0 (-0.3 to +0.3) in the UC group, p=0.015 (table 4.3/figure 4.2). There was a significant difference in the proportion of participants reaching the MCID for ACQ6: 18 (55%) in PR versus 10 (23%) in UC, p=0.009 (table 4.4/figure 4.3). In addition, the proportion with clinically significant worsening (≥+0.5) was higher in the UC group: 15 (34%) compared with 2(6%) in the PR group, p=0.008.

The MRC dyspnoea score at V1 was median (IQR) 2 (2-4) in the PR group and 3 (2-4) in the UC group, p=0.414. At V2 it was 2 (2-3) in the PR group and 3 (2-4) in the UC group, p=0.008. Median change was significantly different: 0 (-1 to 0) in the PR group versus 0 (0 to 1) in the UC group, p=0.022.

The 6MWD at V1 was (median) 390 (345 to 458) metres in the PR group and 392 (278-439) metres in the UC group, p=0.618. At V2 was 420 (368-468) m in the PR group and 380 (301-430) m in the UC group, p=0.055. There was a significant difference in change: +20 metres (-5 to +40) in the PR group and -10 (-40 to +25) metres in the UC group, p=0.035. In addition, the median change in Borg

breathlessness scale after 6MWT was significantly different: -1 (-2 to 0) in the PR group and no change (-1 to +1) in the UC group, p=0.015.

There were no significant changes in either HADS domain, nor in BMI, blood eosinophil count, FeNO nor any spirometric value. Accelerometry results at both time points were available for 25 participants in PR and 32 in UC. There were no significant differences in any PA parameter (inactive time, light physical activity and moderate-vigorous physical activity) between visits.

4.4.4. Post-hoc analysis

Within the PR group, baseline FeNO was significantly lower in those who achieved an improvement of at least 0.5 points, the minimum clinically important difference for ACQ6 (ACQ6 responders) compared to those who did not achieve an improvement of at least 0.5 points (ACQ6 non-responders). The median (IQR) was 18 (8.5-41) parts per billion in ACQ6 responders compared to 47 (17-71) ppb in ACQ6 non-responders, p=0.020 (table 4.5). The same phenomenon was noted when AQLQ was considered. There were no differences in blood eosinophils.

Table 4.5- Responder analysis- comparing those who met or did not meet the MCID for ACQ6 and AQLQ

	ACQ6 responder, n=17	**ACQ6 non-responder, n=15**	**P value**
Blood eosinophils, mean (95% CI)	0.27 (0.18 – 0.37)	0.42 (0.26 – 0.58)	0.095
FeNO, median (IQR)	18 (8.5-41)	47 (17-71)	**0.020**
	AQLQ responder, n=12	**AQLQ non-responder, n=20**	**P value**
Blood eosinophils, mean (95% CI)	0.29 (0.19 – 0.39)	0.38 (0.24 – 0.51)	0.294
FeNO, median (IQR)	14 (8.5 – 44.5)	40 (19 – 71)	**0.038**

Table 4.5 Legend: Abbreviations used in table: ACQ6 asthma control questionnaire (6-point version), AQLQ asthma quality of life questionnaire, FeNO fraction of exhaled nitric oxide. Units in table- blood eosinophils number $x10^9$/L, FENO parts per billion.

Figure 4.3- Responder Analysis

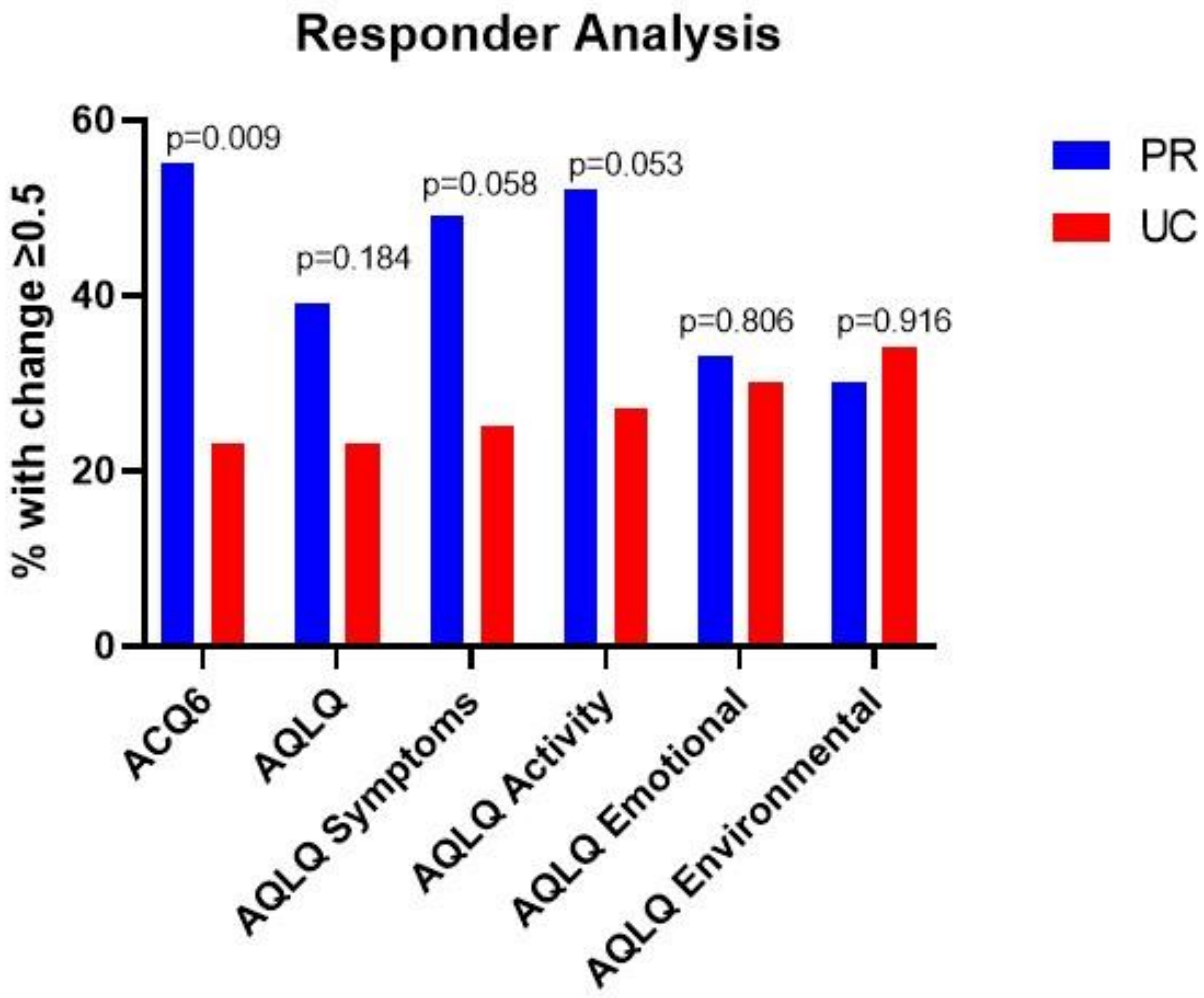

Figure 4.3 legend: Bar chart showing those who met the minimum clinically important difference for each questionnaire. Abbreviations used: ACQ6- 6-point asthma control questionnaire, AQLQ-asthma quality of life questionnaire, PR- pulmonary rehabilitation group, UC- usual care group.

4.4.5 Withdrawn patients

The participants who withdrew or were lost to follow up had slightly poorer asthma control at baseline, with mean ACQ6 2.2 (SD 1.4) for completers compared with 3.3 (1.1) for those who dropped out, $p<0.011$. In addition, AQLQ scores were better at baseline for completers: mean 4.4 (1.2) versus 3.4 (1.2), $p=0.008$. This may have impacted on whether to attend or to withdraw from the study.

There was only one episode of bronchospasm requiring nebulised SABA during exercise sessions. One participant in the UC group died following a cardiac event during the observation period. This was considered unrelated to study.

4.5. Discussion

Difficult-to-treat asthma associated with obesity is challenging to manage with limited therapeutic options. PR is a standard treatment for many chronic lung diseases but its role in the management of asthma remains unclear. In this pragmatic, randomised controlled trial we aimed to evaluate the effects of an asthma-specific PR programme for participants with difficult-to-treat asthma and elevated BMI. Although the primary outcome was not reached, we found statistically significant improvements in asthma control, symptoms and exercise tolerance which suggest PR may be beneficial in this group. Furthermore, the programme was safe and well-tolerated. However, there were significant numbers of non-completers and delays to completion, suggesting this current format of PR is suboptimal for this group.

The PR programme was delivered by a multidisciplinary team including doctors, nurses and physiotherapists, with input from dietetics. Educational topics aimed to improve understanding of asthma and benefits of PA. Informal feedback suggested education and peer support were invaluable. The exercises were adapted from local PR programme and individually tailored based on ability. There was encouragement to complete two further exercise sessions independently, but compliance with this was not monitored, as such we only know that one session per week was attended as a maximum.

In a retrospective cohort study, Türk et al looked at groups of obese (n=53) and non-obese (n=85) asthmatics undergoing 12 weeks of PR comprising 3 hours per week of supervised exercise and 4 hours of education(Türk et al. 2017a). 6MWD rose by median (IQR) 50m (15-84) in non-obese and 45m in obese group (13-77), $p<0.001$. The improvement in ACQ was statistically but not clinically significant: -0.3 points in non-obese, $p=0.021$ and -0.4 in obese, $p=0.019$. These results are

similar to ours. A further small study by the same group(Türk et al. 2017b) suggested improvements in ACQ, AQLQ, 6MWD and BMI following 12 weeks PR in obese asthmatics awaiting bariatric surgery.

A recent randomised controlled trial of 34 participants(Türk et al. 2020) evaluated the effects of 12 weeks PR including thrice-weekly high-intensity interval training, a 1500 kilocalorie diet and a psychological intervention, with or without an online self-management tool, compared to a control group who were advised to lose weight and exercise. Both intervention groups had reductions in BMI, but there was no change in the controls. ACQ improved by -0.67 (-1.42 to 0) in PR and -0.66 (-1.17 to -0.33) in PR plus online tool, both $p<0.05$. Our study involved shorter, less intensive PR, but similar outcomes.

Although the primary outcome was not met, there were trends towards differences for overall AQLQ, along with AQLQ activity and symptom domains in favour of PR. The trial was stopped early after the interim analysis due to the Covid-19 pandemic, and therefore it was underpowered. No post hoc power analysis was conducted. It is difficult to predict what the outcomes might have been had recruitment continued.

The most notable result was ACQ6, which improved significantly in the PR group with a mean reduction of 0.4 points, just short of the MCID of 0.5(Juniper et al. 1999). Furthermore, responder analysis for ACQ6 demonstrated 54.5% of participants in the PR group reached the MCID compared with 22.7% in the UC group, $p=0.009$. In addition, the proportion with clinically significant worsening of ACQ6 ($\geq+0.5$) was higher in the UC group, 15 (34.1%), versus 2 (6.1%) in the PR group, $p=0.008$.

We demonstrated significant effects of PR on 6MWD, albeit the 20m improvement in PR group was under the 35m MCID(Puhan et al. 2008b). This is smaller than the improvements seen in COPD PR trials. Reasons for this could include the population being younger and more active at baseline. There were

no significant changes in physical activity measured by accelerometry, suggesting this format of programme did not stimulate significant alterations to exercise behaviours. Perhaps this is because the one hour of supervised weekly exercise was insufficient to lead to change.

Our study population had difficult-to-treat asthma with many co-morbidities, significant treatment burden, frequent exacerbations and poor AQLQ/ACQ6 scores. This profile associated with T2-high characteristics would allow consideration of biologic treatment, but therapeutic options in T2-low asthma are limited. Although we did not separate T2-high and T2-low phenotypes as part of the study, of 95 participants randomised, 17 expressed T2-low features (both eosinophil count<150 x10^9/L and FeNO<25 ppb(Ortega et al. 2016; Castro et al. 2018)), eight in the PR group and nine in the UC group. A post-hoc analysis showed FeNO was significantly lower in responders than non-responders, but with no difference in eosinophil count. This suggests responders may be more likely to display T2-low features(Hinks et al. 2021). It makes sense that PR is more likely to lead to a significant improvement in participants where asthma symptoms are not related to high levels of inflammation. PR could therefore be specifically targeted at obese asthmatics of T2-low endotype, although this would require further study for confirmation.

4.5.2 Limitations and Future Directions

This study was underpowered, as the Covid-19 pandemic began immediately after the interim analysis rendering further recruitment impossible. The pandemic impacted other aspects of this study with discontinuation of PR sessions. Face-to-face visits were replaced with telephone calls resulting in some missing data.

Dropout rate was high, at 18 participants between visits. 48 were randomised to PR: 33 attended V2, 3 withdrew and 12 were lost to follow up, which equates to 31% dropping out before completion of PR. This is similar to real-world

experience, where approximately 30% commencing PR fail to complete(Garrod et al. 2006; Fischer et al. 2009). Time to completion was also prolonged, with median 94 (70-107) days between visits for the PR group compared to 63 (56-73) for those in the UC group, which may have influenced outcomes. Both drop-out rate and prolonged time to completion were impacted by many of our participants being of working age. Several struggled to attend sessions due to work. Additionally, childcare was an issue for several participants. Indeed, many who met the entry criteria and were approached with information about the study declined to participate for both work and childcare reasons. Asthma exacerbations were another reason for prolonged time to completion in the PR group, with 31 participants (40%) having one of more courses of OCS between visits; 15 (48%) of those were in the PR group and 16 (34%) in the UC group. It was also noted that participants who withdrew had higher baseline ACQ6 score and lower AQLQ scores, which is likely to reflect poorer asthma control and higher impact of asthma symptoms on ability to exercise and may contribute to the reasons for study withdrawal.

The drop-out rate and prolonged time to completion indicate that the traditional PR format is not ideal for this population of working age adults. It could be argued that given the drop-out rate for all comers to pulmonary rehabilitation is 30%(Garrod et al. 2006; Fischer et al. 2009), this format is not ideal for anyone. Possibilities for improving accessibility, and hopefully attendance and completion, include virtual sessions, community rather than hospital-based classes, and evening sessions.

Other referenced studies(Türk et al. 2017a; Türk et al. 2017b; Türk et al. 2020) involved intensive PR with multiple supervised weekly sessions. We aimed to be pragmatic, therefore included only one supervised session with encouragement for two further independent sessions. We did not record adherence to the additional sessions, and anticipate that many participants did not complete these. It is possible our results were consequently less impressive. It is worth noting that reducing the number of sessions did not improve completion rates.

In addition, exercises were adapted from COPD PR, tailored towards a typically older, frailer population. Some participants found they were not particularly challenged, which may have resulted in less perceived improvement. We did increase the intensity as described in chapter 2.5 as the weeks progressed in order to try and provide a challenge. Education was delivered on a rolling basis, so if exercise classes were missed some educational talks were too.

Further research is needed to explore the effects of PR in TH2-low obese asthma, and clarify the optimal programme format. Interactive, live online sessions at a variety of times including evenings, and on demand recorded sessions are likely to be more appealing and may improve attendance and completion rates. In addition, this may allow monitoring of number of weekly sessions, and would provide an accessible means of having three sessions per week. Further work could also assess whether the delivery of PR in conjunction with dietary intervention adds benefit in obese asthmatics.

4.6 Conclusions

This randomised controlled trial of pulmonary rehabilitation in participants with difficult-to-treat asthma and elevated BMI demonstrated statistically significant improvements in asthma control questionnaire score, exercise tolerance (as measured by six minute walk distance), and perception of breathlessness (as demonstrated by Borg score at completion of 6MWT and MRC dyspnoea scale) but the effects were small and of uncertain clinical significance. The intervention was safe and well-tolerated. However, this format of face-to-face daytime sessions was not optimal for our participants as demonstrated by the high drop-out rate and prolonged time to completion. Further studies are required to identify the optimal mode of delivery, the intensity and type of pulmonary rehabilitation in this population and whether it is associated with clinically relevant benefits.

Chapter 5- Immediate and longer-term outcomes of an asthma tailored pulmonary rehabilitation programme in overweight and obese participants with difficult-to-treat asthma

Submitted to Respiratory Medicine journal, November 2022.

Full author list: H Clare Ricketts, Varun Sharma, Femke Steffensen, Elaine Mackay, Gordon MacDonald, Duncan S Buchan, Rekha Chaudhuri, Douglas C Cowan.

5.1. Abstract

5.1.1. Introduction and aims

The management of difficult-to-treat asthma associated with elevated body mass index (BMI) is challenging, with limited therapeutic options. The benefits of pulmonary rehabilitation (PR) in this population are unclear, but our previous randomised controlled trial(Ricketts et al. 2022) demonstrated improvements including in 6-point asthma control questionnaire (ACQ6), six-minute walk distance (6MWD) and Borg score after 6MWD at 8 weeks. Here we aimed to assess immediate and longer-term effects of asthma-tailored PR in participants with difficult-to-treat asthma and BMI ≥25 kg/m^2, and identify predictors of response.

5.1.2. Methods

A prospective observational study comparing outcomes at baseline (V1), immediately after 8-weeks PR (V2), and at 52 weeks (V3). Baseline characteristics were compared in responders versus non-responders defined by achievement of minimum clinically important difference (MCID) for asthma control questionnaire (ACQ6) (0.5) at 8 and 52 weeks.

5.1.3. Results

Of 92 recruited participants, 56 attended V2 and 45 attended V3. Mean age was 60 (SD 13) years, 60% female and median (IQR) BMI 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 at completion of 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. 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 the MCID improvement in ACQ6.

5.1.4. Conclusions

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

5.2. 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 hyperreactivity(Global Initiative for Asthma 2018). Difficult-to-treat asthma describes asthma that remains uncontrolled (either ongoing symptoms or frequent exacerbations) despite medium or high dose inhaled corticosteroids (ICS) plus long-acting ß2 agonist (LABA), or in which control is only achieved when on high-dose ICS-LABA combination treatment(Global Initiative for Asthma 2022b). Obesity is associated with poorer outcomes in asthma (Chinn et al. 2002; Sideleva et al. 2012; Umetsu 2017), and resistance to steroids which have traditionally been the mainstay of treatment(Boulet and Franssen 2007).

Pulmonary rehabilitation (PR) is a standard treatment for chronic lung diseases including COPD, bronchiectasis and interstitial lung disease(Bolton et al. 2013; Mccarthy et al. 2015). There have been a small number of trials assessing the

role of PR in asthma with some promising findings(Türk et al. 2017a; Freitas et al. 2018; Sahin and Naz 2019; Türk et al. 2020), but the benefits are uncertain.

The previous chapter, chapter 4, presents the immediate outcomes from a randomised controlled trial of an 8-week course of asthma-tailored pulmonary rehabilitation in participants with difficult-to-treat asthma associated with elevated BMI(Ricketts et al. 2022). 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(Lingner et al. 2015; Türk et al. 2020). In the current chapter, the study design was of a prospective, observational, cohort study. We aimed to evaluate both immediate and longer-term outcomes of PR in overweight and obese patients with difficult-to-treat asthma, and additionally identify any factors which may predict response to PR.

5.3 Methods

5.3.1. Study Design

The original study was a randomised controlled trial of PR. It was registered at Clinicaltrials.gov (ID NCT03630432) and approved by the West of Scotland Regional Ethics Committee (reference 16/WS/0200). 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 chapter we present results for all individuals who underwent pulmonary rehabilitation, with study visits taking place immediately before PR (V1), immediately after completion of PR (V2) and 1 year after the first visit (V3). The group studied here includes everyone who was in the pulmonary rehabilitation group in chapter 4, plus those who were in the usual care group in

chapter 4 who subsequently went on to participate in pulmonary rehabilitation after the initial observation period was concluded.

5.3.2. Study Participants

Participants were recruited from tertiary asthma clinics and ward admissions throughout NHS Greater Glasgow and Clyde. The inclusion and exclusion criteria are listed in section 4.3.2. Written informed consent was obtained from all participants prior to any study activity taking place.

5.3.3. Pulmonary rehabilitation programme

The pulmonary rehabilitation programme was tailored specifically for asthma and lasted eight weeks, comprising of one in-hospital session per week. This involved one hour of education, and one hour of exercise. The education programme was delivered on a rolling basis by a range of professionals including respiratory and asthma medical and nursing staff, a General Practitioner and PR staff with some input from dietetics. The programme is described in detail in the methods chapter, section 2.5.

If participants missed a session during the course they were contacted via telephone and re-attendance encouraged. When the PR programme was completed, onward referral was made to community based exercise facilities at an appropriate level for each individual in order to encourage ongoing exercise.

5.3.4. Study Measurements

During V1, the baseline visit, medical history and electronic medical record assessment was undertaken. Participants completed ACQ6, asthma-related quality of life questionnaire (AQLQ), hospital anxiety and depression score (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(Graham et al. 2019), using an electronic desktop spirometer (Vitalograph, Maids Moreton, U.K.). Fraction of exhaled nitric oxide

(FeNO)(Dweik et al. 2011) was performed using NIOX VERO machine (Circassia Pharmaceuticals, Morrisville, USA). Two 6MWTs were completed as per American Thoracic Society Guidelines(American Thoracic Society 2002) and Borg score for breathlessness 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.

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 bathing or swimming. After accelerometer return the data was downloaded and processed as detailed in section 2.4.

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 for 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.

5.3.5. 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. Analysis used mixed effects models and repeated measures analysis of variance, or Friedman model as appropriate based on distribution. The mixed effects model could compute with missing values so n=54 for analysis of these outcomes. Friedman model could not compute with

missing data so n=45, including those who attended all 3 visits, or only those with complete data for 3 visits where visits took place virtually.

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. The differences between visits 1 and 2, and 1 and 3 were calculated and any participant demonstrating improvement of at least the MCID (≥0.5 points(Juniper et al. 1994)) was defined a responder. It is acknowledged that an improvement of 0.5 points means different things at different parts of the scale. For example, improving from an ACQ6 score of 1.9 to 1.4 represents achieving asthma control on this scale, whereas improving from 4.9 to 4.4 still represents poorly controlled asthma and may not be clinically relevant. This was not considered in the analysis. 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.

5.4 Results

101 participants provided written informed consent and were recruited into the original trial (see figure 5.1 for flowchart of recruitment). Of 95 randomised participants, 92 commenced pulmonary rehabilitation and 56 completed V2 after PR and were included in outcome analysis.

Figure 5.1- Flowchart of recruitment and progression through study

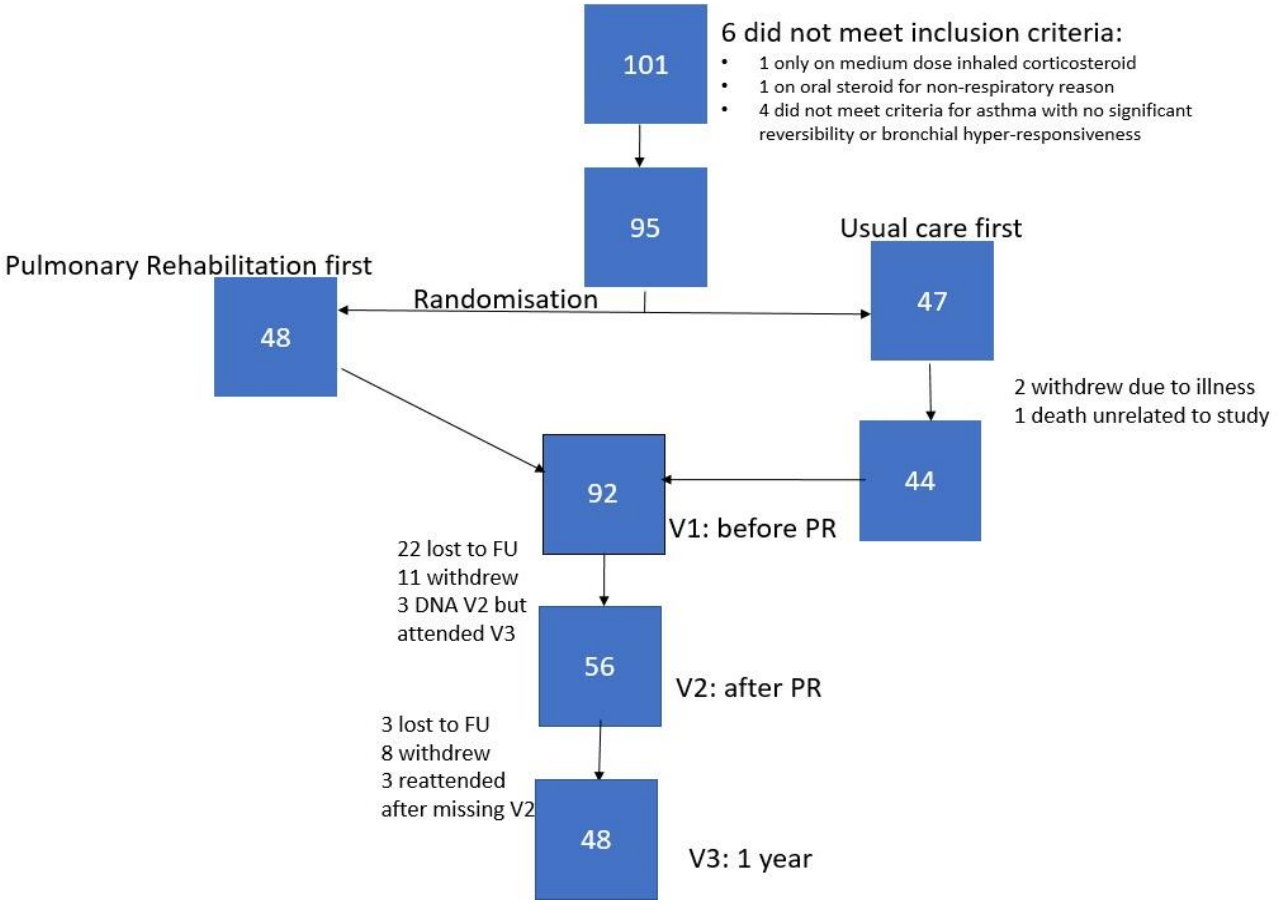

Figure 5.1- Flowchart of recruitment

5.4.1. Baseline characteristics

Results are displayed in table 5.1. For the 92 patients commencing PR, mean age was 60 years (±13), 60% were female, 92% were ex- or never-smokers, and median BMI was 33.8 kg/m^2 (29.5-38.7). The median (IQR) age at diagnosis was 30 years, and median asthma duration was 22 years. The commonest co-morbidities were gastro-oesophageal reflux disease (80%), allergic rhinitis (73%) and psychological illness (63%). Median daily beclomethasone dipropionate (BDP) dose was 1700 mcg (IQR 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 General Practitioner 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 (IQR) distance for 6MWT was 390 (335-450) metres. Median daily minutes spent inactive was 1176 (1107-1239) and in moderate-vigorous physical activity (MVPA) was 47.7 (25.2 - 66.8).

Table 5.1- Baseline characteristics of the recruited population

	All recruited, n = 92
Age, years – mean (±SD)	60 (13)
Male sex	37 (40%)
BMI, kg/m^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)
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/ILO	17 (19%)
Psychological illness	58 (63%)
Emphysema	7 (8%)
Bronchiectasis	14 (15%)
SAFS/ABPA	18 (20%)
LAMA	76 (83%)
BDP equivalent dose mcg	1700 (1600-2000)
Maintenance prednisolone	25 (27%)
Biologic therapy	19 (21%)
Prednisolone boosts, no. in last year	4 (2-5)
GP attendances, no. in last year	2 (0-4)
ED attendances, no. in last year	0 (0-1)
Hospital admissions, no. 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 (x10^9/L)	0.3 (0.01-0.4)
FeNO (ppb)	23 (12-46)
pre-BD FEV1 (% predicted) mean (±SD)	73.1 (±16.8)
pre-BD FEV1/FVC % mean (±SD)	65.9 (±10.0)
% change in FEV1 with BD	4.4 (-1.3 to 9.5)
6MWD, metres	390 (335-450)
Borg score post- 6MWT	2 (0.5-3)
Inactive time, minutes/day Light PA, minutes/day Moderate-vigorous PA, minutes/day	1176 (1107-1239) 215.4 (168.4 - 268.8) 47.7 (25.2 - 66.8)

Table 5.1 Legend: Displays the characteristics of the population recruited for this study, prior to any intervention. Results expressed as median (interquartile range) or number and % unless otherwise specified. Abbreviations used in table: GORD- gastro-oesophageal reflux disease, DFB- dysfunctional breathing, ILO intermittent laryngeal obstruction, 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 dipropionate 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.

5.4.2. Immediate and longer-term outcomes following PR

Results are displayed in table 5.2 and figure 5.2. 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. In multiple comparisons testing with Holm-Sidak's test, V1-V2 p=0.002, and V1-V3 p=0.031. 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. When multiple comparisons testing was performed with Dunn's test, there were no significant differences between any visits for either MRC dyspnoea score nor 6MWD. 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 5.2- Results at each visit for key asthma measures

Asthma Measure	n=	V1	V2	V3	P value (ANOVA)
BMI, kg/m^2	37	32.8 (29.7-36.0)	32.1 (29.4-35.5)	32.5 (28.9-34.8)	**0.009**
Asthma exacerbations	45	3 (2-5)	0 (0-4.7)	1.5 (0-4.2)	**0.003**
GP visits	45	2 (0-3.5)	0 (0-5.1)	0 (0-2.9)	**0.025**
ED visits	45	0 (0-0.5)	0 (0)	0 (0)	0.262
Hospital admissions for asthma	45	0 (0-1)	0 (0)	0 (0)	0.104
MRC dyspnoea score	45	3 (2-4)	3 (2-3)	3 (2-4)	**0.010**
ACQ6 mean (95% CI)	54	2.5 (2.1-2.9)	2.2 (1.8-2.5)	2.3 (1.9-2.7)	**0.003**
AQLQ total, mean (95% CI)	54	4.2 (3.8-4.5)	4.3 (4.0-4.7)	4.2 (3.9-4.6)	0.325
AQLQ Symptoms	54	4.2 (3.8-4.6)	4.3 (4.0-4.7)	4.3 (3.9-4.7)	0.467
AQLQ Activity	54	4.0 (3.6-4.3)	4.2 (3.9-4.6)	4.1 (3.7-4.6)	0.139
AQLQ Emotional	54	4.4 (3.9-4.8)	4.5 (4.1-5.0)	4.4 (3.9-4.9)	0.208
AQLQ Environmental	54	4.3 (3.9-4.7)	4.3 (3.9-4.7)	4.4 (3.9-4.9)	0.824
HADS: Anxiety	45	7 (5.5-11)	8 (4-13)	7 (3-11.5)	0.228
HADS Depression mean (95% CI)	54	8.2 (6.9-9.5)	8.0 (6.6-9.3)	7.1 (5.8-8.4)	0.251
Blood eosinophils x10^9/L	31	0.3 (0.2-0.5)	0.2 (0.1-0.4)	0.2 (0.1-0.3)	0.059
FeNO, ppb	34	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	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	65.9 (63.3-68.4)	64.9 (61.9-67.8)	64.7 (60.9-68.4)	0.928
% FEV_1 reversibility	54	3.6 (-1.4 to 8.1)	2.5 (-0.1 to 0.7)	3.8 (0-8.3)	0.754
6MWD, m	32	390 (334-450)	410 (323-460)	395 (285-456)	0.418
Borg score	32	2 (0.5-3)	1 (0-2)	1 (0.5-2)	**0.035**
Inactive time, min/d	21	1180 (1121-1222)	1176 (1124-1228)	1152 (1082-1220)	0.368
LPA, min/d	21	206 (166-250)	203 (173-264)	219 (188-277)	0.854
MVPA, min/d	21	41 (27-76)	51 (27-70)	48 (28-80)	0.505

Table 5.2 Legend: Table comparing results for relevant asthma outcomes between V1, V2 and V3. Results shown as median (interquartile range) unless otherwise specified. n= column displays number of participants included in that analysis (see section 5.2.5 for details of variation). Abbreviations used in table: 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.

There were also statistically, but not clinically significant 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. 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.

When looking at exacerbation rates, 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.

There were no significant differences in physical activity measured by accelerometry.

Figure 5.2- Graphs showing results of relevant outcomes

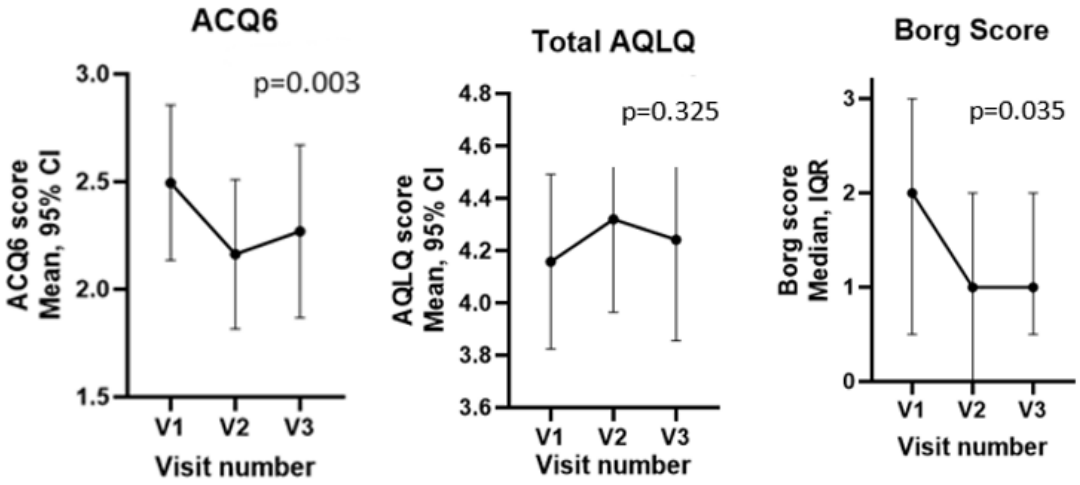

Figure 5.2 legend- Graphs displaying differences between visits using ANOVA testing

5.4.3. Immediate- and longer-term ACQ6 responders to PR and predictors of response

Results are shown in tables 5.3 and 5.4. An ACQ6-responder was defined as any participant who had an improvement of more than the MCID for ACQ6- i.e. their ACQ6 score reduced by ≥ 0.5. Early ACQ6 responder describes those who achieved the MCID between visits 1 and 2, and late ACQ6 responder describes those who achieved the MCID between visits 1 and 3.

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

Comparing immediate ACQ6-responders and non-responders, 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.

Table 5.3- Comparing immediate ACQ6 responders to non-responders

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, kg/m^2	33.9 (31-35.9)	32.5 (28.5-38.4)	0.617
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	3.7 (1.1)	4.6 (1.2)	**0.009**
AQLQ Symptoms	3.7 (1.4)	4.7 (1.4)	**0.010**
AQLQ Activity	3.6 (1.1)	4.4 (1.3)	**0.015**
AQLQ Emotional	3.9 (1.7)	4.8 (1.4)	**0.030**
AQLQ Environmental	4.1 (1.5)	4.7 (1.4)	0.109
HADS Anxiety	9.3 (2.5)	8.5 (5.3)	0.602
HADS Depression	9.4 (4.8)	7.4 (4.6)	0.111
Blood eosinophils $x10^9$/L	0.3 (0.1-0.4)	0.3 (0.2-0.65)	0.269
FeNO, ppb	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, metres	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

Table 5.3 legend: Table comparing the baseline characteristics of those who responded in terms of ACQ6 between visits 1 and 2 (immediate ACQ6 responders) 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 (SD), median (IQR) or number and percentage. Abbreviations used in table: 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.

Comparing late ACQ-responders and non-responders produced 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.

Table 5.4- Comparing late ACQ6 responders with non-responders

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, kg/m^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	3.7 (1.3)	4.5 (1.3)	**0.038**
AQLQ Symptoms	3.6 (1.4)	4.6 (1.4)	**0.018**
AQLQ Activity	3.6 (1.2)	4.2 (1.3)	0.123
AQLQ Emotional	4.0 (1.8)	4.6 (1.5)	0.223
AQLQ Environmental	3.6 (1.7)	4.6 (1.5)	0.061
HADS Anxiety	8.6 (4.7)	8.2 (4.7)	0.814
HADS Depression	8.4 (4.8)	7.4 (4.3)	0.442
Blood eosinophils x10^9/L	0.3 (0.2-0.5)	0.2 (0.1-0.4)	0.211
FeNO, ppb	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, metres	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

Table 5.4 legend: Table comparing the baseline characteristics of those who responded in terms of ACQ6 between visits 1 and 3 (late ACQ6 responders) 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 (SD), median (IQR) or number and percentage. Abbreviations used in table: 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.

5.5. Discussion

5.5.1. General discussion

Difficult-to-treat asthma associated with obesity presents significant therapeutic challenges, and the results in chapter 4 suggested that asthma-tailored pulmonary rehabilitation may be associated with favourable impacts on asthma control, breathlessness and exercise tolerance in this population(Ricketts et al. 2022), but whether these effects are sustained is unclear. In this prospective, observational, cohort study, we evaluated the immediate and longer-term outcomes of this intervention in a larger group of patients than the initial randomised controlled trial with difficult-to-treat asthma and overweight/obese BMI. As in the original randomised controlled trial, we demonstrated statistically but not clinically significant improvements in ACQ6, MRC dyspnoea score and Borg score. Furthermore these benefits were sustained at one year. There were also significant reductions in asthma exacerbations, urgent unscheduled GP visits and proportion of participants on maintenance OCS, but these results are less reliable. 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.

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(Lingner et al. 2015). 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 mls, 95% CI 120-210 mls, $p<0.001$), in 6MWD (mean improvement 59.89m, 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.

Türk *et al* conducted a randomised controlled trial evaluating the impact of a 12 week pulmonary rehabilitation course involving three times weekly high-intensity interval training. They combined this with a 1500 kilocalorie diet, with or without online support tool and compared to a control group of participants instructed to try and lose weight and increase their exercise(Türk et al. 2020). Only 34 participants were randomised, but those in the PR and PR+online support at 3 months had significant improvements in ACQ of 0.67 and 0.66 compared to no significant improvement in the UC group 0.25, $p<0.029$. 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 longer-term outcomes.

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(Grosbois et al. 2019). 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.

As far as we are aware, no previous studies have demonstrated reductions in exacerbations following PR for asthma. 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 and as such may be subject to recall

bias. In addition, comparing exacerbations in an 8 week period with a 1 year period presents some challenges and renders the results less robust or reliable. It is noted that comparing number of exacerbations, GP and ED visits and hospital admissions in an 8 week period to a 1 year period is not always meaningful, as exacerbations do not occur at regular intervals, and it is unsurprising there were fewer exacerbations in the shorter time gaps. Therefore although statistically significant, these results are based on suboptimal data and are not likely to be clinically significant. The difference between visits 1 and 3 is more relevant. In future it would be prudent to contact GP surgeries to confirm number of exacerbations and prescriptions for prednisolone, and to purely compare exacerbations in the year prior to visit 1 and the year between visits 1 and 3. Further randomised controlled trials with robust measurement of exacerbation rates are needed to confirm or refute this finding.

With regards to reduction of exacerbations, it is worth noting that 3 of the participants who did have a significant reduction in number of exacerbations commenced treatment with mepolizumab during the follow-up period, and it is more likely that this led to the reduction than PR.

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 targeting this intervention to more symptomatic individuals is likely to increase the likelihood of successful outcomes. As such, it may be beneficial to study PR or exercise and education to participants with poor asthma control.

5.5.2. Limitations

There are a number of limitations in this study. This study is a prospective observational format. The initial study was a randomised controlled trial, but after completion of initial 8 week observation period, those who were randomised to the control group were offered PR. This led to a treatment group larger than the original randomised controlled trial (n=33 in intervention group),

but meant there was no longer a control group. Thus, outcomes may have been affected by other confounding factors. A randomised, controlled trial of longer duration 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. To minimise the impact of lost data in the analysis, data which was normally distributed was 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 strength of our findings.

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 completion, 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(Mccarthy et al. 2015) 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* (Casey et al. 2013)(drop-out rate 22%) and Hernandez(Hernández et al. 2000) *et al* (drop-out rate 38%), and drop-out rate was as high as 48% in one 2000 study(Troosters et al. 2000).

5.5.3. Future Directions

Future studies should further clarify the effects, both short and longer term, of pulmonary rehabilitation in difficult-to-treat asthma, and whether patients in

different BMI categories benefit equally or not. The optimal format for PR remains to be confirmed. 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 repeated courses are helpful. 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. Finally, a PR programme combined with a weight management programme may well lead to more favourable results.

5.6. 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 prednisolone courses. Participants with poorer asthma control, poorer asthma related 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.

Chapter 6: Thesis discussion and conclusions

6.1. Summary of findings

This thesis reports the outcomes of three pieces of work relating to difficult-to-treat asthma associated with elevated body mass index (BMI). In the first, chapter 3, we compared physical activity levels of a group with mild-moderate asthma and normal BMI, a group with mid-moderate asthma and elevated BMI, and a group with difficult-to-treat asthma and elevated BMI. Perhaps unsurprisingly, those with difficult-to-treat asthma spent significantly less time engaged in physical activity of light and moderate-vigorous intensity, as well as performing physical activity of reduced intensity and volume. These differences remained significant, even when differences in age and BMI were corrected for. In addition, when participants were ranked using the accelerometer-derived marker of volume of activity average acceleration, those with the highest average acceleration had significantly better controlled asthma including improved asthma control and asthma-related quality of life questionnaire scores, lower inhaled corticosteroid doses, fewer exacerbations requiring prednisolone, a better pre-bronchodilator FEV_1 and longer six-minute walk distance. The fact that difficult-to-treat overweight group had significantly worse activity profiles no matter which accelerometry measure was considered suggests that this is the group most in need of intervention to increase physical activity. This finding led on to the development of the studies assessing the impact of pulmonary rehabilitation in this population.

The second paper, chapter 4, reports the immediate outcomes of a randomised controlled trial of an asthma-tailored pulmonary rehabilitation programme in participants with difficult-to-treat asthma and elevated BMI, compared to participants receiving usual care. Here, the pulmonary rehabilitation group had statistically significant improvements in ACQ6, MRC (Medical Research Council) dyspnoea score, six-minute walk distance and Borg score at completion of six-minute walk distance. Unfortunately, these results did not meet clinical significance. However, when we performed secondary analyses and compared the proportion who achieved the minimum clinically important difference (MCID)

in ACQ6, there was a significant difference in favour of the pulmonary rehabilitation group. In addition, those who met the MCID were more likely to be of the T2-low phenotype, with low eosinophil count and FeNO, thus offering a potential treatment for this trait where there are no currently available treatment options. The programme was safe and well-tolerated, but the recruitment and retention of participants was challenging, and we suggest that the studied format was not ideal for this population. Disappointingly, the accelerometry data showed that pulmonary rehabilitation did not increase physical activity at any time point. It is possible that there was not sufficient exercise involved in the programme to induce change, or that participants did less activity on the days where they were not exercising so overall physical activity remained unchanged. It is possible that more intense exercise may be of benefit, but there remains a concern that this would be felt to be too difficult for some of this population, and it may have made recruitment and retention more challenging.

The third paper, chapter 5, reports outcomes of more participants undergoing pulmonary rehabilitation. Our study design was such that after the initial period of usual care was concluded, anyone who wished to do so could then take part in the pulmonary rehabilitation course. Chapter 5 therefore reports immediate and longer-term outcomes of a larger group of participants who underwent pulmonary rehabilitation. The results here showed statistically but not clinically significant improvements in ACQ6 and Borg breathlessness score after 6MWD, and these improvements were maintained at 12 months. There were reductions in number of exacerbations requiring prednisolone and unscheduled General Practitioner visits, but the methodology around these results is less robust. In addition, we tried to determine factors predicting positive response to pulmonary rehabilitation, and found that those with poorer baseline ACQ6, AQLQ and MRC dyspnoea scores were more likely to achieve the MCID for ACQ6 score in the immediate and longer term.

6.2 How our results relate to current literature

6.2.1 Physical activity and asthma

There are a number of previous studies of physical activity using accelerometry in participants with asthma, but each focuses on different aspects to our work. Cordova-Rivera *et al* published a systematic review(Cordova-Rivera et al. 2018a) on the subject of physical activity and asthma. The systematic review looked at 42 studies which reported on physical activity and asthma, of which only 8 used activity monitors to assess physical activity (7 used accelerometers and 1 used pedometer), with the remaining studies using self-reporting questionnaires. This systematic review did find that physical activity was lower in participants with asthma compared to healthy controls.

Many of the available studies merely consider those with asthma alongside healthy controls, such as the 2016 study from van t'Hul *et al*(Van't Hul et al. 2016). They demonstrated significant differences in step count ($p=0.001$) and vigorous physical activity ($p<0.001$) in favour of the control group, but no significant differences in light ($p=0.093$) or moderate ($p=0.679$) activity. Thus, our findings are not entirely in accordance with theirs.

The Cordova-Rivera group(Cordova-Rivera et al. 2018b) compared participants with severe asthma (n=61) with those with sex and age-matched healthy controls, and found that the participants with severe asthma spent less time engaged in moderate and vigorous physical activity- median (IQR) 21.9 (13.9-36) minutes per day compared to 41.7 (29.5-65.2), $p<0.001$. They also demonstrated a mean of 2232 fewer steps per day ($p=0.0002$) in the severe asthma group, but did note more time was spent engaged in light physical activity (mean (95% CI) 22(2-41) minutes, $p=0.029$) compared to the controls.

Bahmer et al(Bahmer et al. 2017) recruited 63 participants with severe asthma, 83 with mild-moderate asthma and 29 healthy controls, and measured physical activity for a week using an arm-worn accelerometer. They demonstrated a progressive increase in time spent in physical activity of at least moderate intensity, moving from healthy controls, to mild-moderate and to severe asthma,

as we did. Once differences in age, sex, obesity and smoking were accounted for, the differences in moderate or more intense physical activity were no longer significant, unlike our findings. The severe asthma group did significantly more steps per day than both heathy controls (p=0.013) and mild-moderate asthma (p=0.001).

Another paper comparing physical activity in participants with severe asthma with healthy controls(Neale et al. 2020) (n=48 both groups) also used arm-worn accelerometers and reported physical activity as light or moderate-vigorous. Their severe asthma group had a significantly higher BMI (33.0 ± 6.7 kg/m^2 compared to healthy controls 26.4 ± 4.4 (p<0.001)), much like our difficult-to-treat overweight asthma group. They reported values somewhat similar to ours, with 44 ± 46 minutes of moderate-vigorous physical activity per day in the severe asthma group, compared to 91 ± 80 in the healthy controls (p<0.001), but once the differences in BMI and wear-time were corrected for, there was no significant difference in moderate-vigorous physical activity between the groups. The severe asthma group did significantly fewer steps (p=0.009) than healthy controls after the corrections.

When considering physical activity with asthma studies overall, the literature suggests participants with asthma partake in fewer daily steps than healthy controls, and those with severe asthma take fewer steps than both healthy controls and participants with mild-moderate asthma. There were differences in moderate and vigorous physical activity, but these were no longer significant once differences in BMI/age/sex and wear time were considered. Our data however demonstrated significant differences in all accelerometer criteria-inactive time, light physical activity and moderate-vigorous physical activity, and these differences persisted when we corrected for differences in age and BMI. The differences in sex, smoking and wear time corrected for in other papers were not relevant in our population so were not considered as independent variables. In addition, we have added new information to the available literature by reporting physical activity using both the intensity gradient and average acceleration, and are the first to report these values in any asthma population. The finding that physical activity is consistently lower in participants with difficult-to-treat asthma with obesity suggests that increasing

physical activity may be a target in treating them, and led onto the development of the pulmonary rehabilitation studies.

6.2.2. Pulmonary rehabilitation in asthma

The previously published research on pulmonary rehabilitation in obese asthma has demonstrated some potential benefits, and our results add to that data. Türk *et al* recently published a randomised controlled trial (n=34) looking at pulmonary rehabilitation in the obese asthma population(Türk et al. 2020). They included a calorie restricted diet along with a psychological intervention for the pulmonary rehabilitation group, and a control group who received usual care. They demonstrated clinically and statistically significant improvements in ACQ in both pulmonary rehabilitation groups (-0.67 (-1.42 to 0) in pulmonary rehabilitation and -0.66 (-1.17 to -0.33) in pulmonary rehabilitation with online self-help tool) compared to the control group (both $p<0.05$). Our results for ACQ were statistically but not clinically significant, but we did a shorter (8 weeks rather than 12 weeks), less intense pulmonary rehabilitation programme, which may be more feasible to incorporate into clinical practice.

Another study by Türk et al took the format of a retrospective cohort study, and again looked at a 12 week intensive pulmonary rehabilitation intervention(Türk et al. 2017a). Here they demonstrated significant improvements in 6MWD, of median (IQR) 50m (15-84) in non-obese and 45m in obese group (13-77), $p<0.001$. These results are over the MCID of 35m. They also demonstrated statistically but not clinically significant improvements in ACQ: -0.3 points in non-obese, $p=0.021$ and -0.4 in obese, $p=0.019$. These findings are very similar to those of our randomised controlled trial, and the ACQ6 improvement in our observational study.

Both of the studies by the Turk group included high-intensity interval training for the exercise component of PR. This sounds more physically challenging than our exercise component. Their results varied between the two studies and there were inconsistencies, with one study providing clinically and statistically significant improvement in 6MWD but not ACQ, and the other in ACQ. Whether more intense exercise is the key to improvement is yet to be proven. There was

no measure of overall physical activity in these studies, so we do not know whether the intense exercise led to increases in total physical activity. Our results demonstrated no changes in PA after PR.

Other asthma pulmonary rehabilitation studies have been performed in populations with varying disease severity and without obesity as a criteria for entry. The ProKAR study evaluated the effects of a 3 week intensive inpatient pulmonary rehabilitation programme in Germany(Lingner et al. 2015). They reported improvements in mean ACT score by 4.58 points ($p<0.001$) at 3 weeks, and by 2.48 points at 1 year ($p<0.001$). Additionally, they demonstrated small but statistically significant improvements in FEV_1 ($p<0.001$), 6MWD (mean improvement 59.89m, 95% CI 49.09-70.69, $p<0.001$) and FeNO at the end of the 3 weeks. We did not demonstrate these additional benefits, although there were similar improvements in asthma control which were maintained at one year so this finding is consistent.

A 2019 Italian study also considered the effects of a 3 week, intensive inpatient pulmonary rehabilitation programme(Zampogna et al. 2019), by performing a retrospective analysis of participants undergoing the programme for severe asthma. They reported an improvement in six-minute walk distance along with a reduction in Borg breathlessness score, which corresponds with the findings of our randomised controlled trial.

Another smaller retrospective observational study looked at participants with severe asthma, as well as a group with COPD(Grosbois et al. 2019). They evaluated the effects of an 8 week pulmonary rehabilitation study, based at home. The asthma group had clinically significant improvements in a 6-minute stepper test at completion of PR ($p<0.043$) and at 12 months ($p<0.016$). Quality of life was assessed by a visual simplified respiratory questionnaire, and there were improvements at 12 months but not immediately after completion ($p<0.049$). These findings are similar to both of our studies with improvements in quality of life, and improvements in physical ability as demonstrated by the improvement in six-minute walk distance in our randomised controlled trial.

Our randomised controlled trial is one of the largest published trials looking at pulmonary rehabilitation in asthma. Unfortunately the study was underpowered, making it difficult to draw robust conclusions, but there were some promising findings with statistically albeit not clinically significant improvements in ACQ6 and 6MWD, which are in line with other pulmonary rehabilitation asthma studies. The observational format did show some improvements were maintained at 1 year, which is again in line with current evidence.

Overall, the literature, including this work, regarding the utility of pulmonary rehabilitation in asthma suggests that there are some benefits to be gained. However the outcomes are varied and sometimes conflicting. There are many possible reasons that may explain this, including varying phenotypes of obese asthma, e.g. T2-high may not respond to exercise as their disease is predominantly inflammatory driven. Therefore, despite our work adding to the available literature, no firm recommendations can be made to suggest inclusion of pulmonary rehabilitation in the therapeutic options for this group.

6.3. Study Limitations

There were several limitations in these studies, as covered in each chapter and expanded here.

6.3.1. The impact of the Covid-19 pandemic

The Covid-19 pandemic had a significant impact on the work, as it led to the early termination of the pulmonary rehabilitation programme. This meant the study was underpowered and ultimately it weakened our outcomes. In addition, a number of study visits had to be cancelled due to the pandemic, leading to longer than anticipated times between study visits. A number of follow-up visits had to be carried out virtually, meaning that there was a loss of study data including weight, lung function, FeNO and six-minute walk distance. All questionnaires were conducted over the telephone and as such this information is relatively complete.

In addition, redeployment of research staff into clinical areas, and to focus on Covid-19 research also meant there was less research nurse time available to work on the studies and led to further delays between anticipated visit times. These challenges affected all 3 studies in the thesis.

There were some unexpected benefits from the pandemic, particularly in allowing the development of technology and the acceptability of home-based interventions. This had transformed many areas of clinical practice, and may lead to significant changes in pulmonary rehabilitation format and delivery in future. Having virtual sessions increases accessibility to those in remote areas, those with lack of transport, physical mobility problems and psychological barriers to attending hospitals, and those in employment or with childcare responsibilities.

6.3.2. Recruitment and retention challenges

There were difficulties with recruitment and retention for the pulmonary rehabilitation study, with a high drop-out rate. Of the 101 participants recruited, of whom 96 were randomised, only 45 attended a third visit. This means the overall drop-out rate was 47%. The drop-out rates in real world pulmonary rehabilitation are relatively high, and a figure of around 30% is to be expected(Garrod et al. 2006; Fischer et al. 2009), but we exceeded that, particularly in the observational study in chapter 5 where the drop-out rate was 52%. Our study population was relatively young, with a median (IQR) age of 54 (47 to 64) years. This meant that a number of participants had employment, childcare and family responsibilities and found it difficult to attend our day time sessions and study visits. In addition, those who failed to complete had higher baseline ACQ6 score and lower AQLQ scores, suggesting poorer asthma control and higher impact of asthma symptoms on ability to exercise. This may also have contributed to study withdrawal, although this group is likely to represent those with the most to gain from exercise and increased physical activity.

In addition to the high drop-out rates, the group who underwent pulmonary rehabilitation also took longer than planned to complete the programme. In the randomised controlled trial, anticipated time between visits was 56 days: the

pulmonary rehabilitation group had a median (IQR) of 94 (70-107) days between visits compared to 63 (56-73) in the usual care group. This may have influenced outcomes, and likely reflects the competing pressures on participants time. Exacerbations during the PR period also likely influenced this difference- 31 participants (40%) of those enrolled in the randomised controlled trial had at least one course of oral corticosteroids between visits; 15 (48%) of those in pulmonary rehabilitation group and 16 (34%) in the usual care group. Exacerbations in the usual care group typically had no impact on time between visits, but those in the pulmonary rehabilitation group were advised not to attend classes when they felt unwell.

Recruitment also proved challenging, and a huge number of participants who met the entry criteria for the pulmonary rehabilitation study were unable to commit to attending. Many of these stated work and childcare as the major reasons, several felt like they would be unable to do any exercise, and a number were not interested in a group exercise dynamic. These are all issues to consider when planning for further study to look at optimal format of pulmonary rehabilitation in asthma.

We included only one weekly face-to-face session in our programme in order to be pragmatic and try to increase recruitment. We encouraged participants to undertake two further exercise sessions independently during each week, but we did not monitor this, and suspect that many did not do independent sessions. Our programme therefore did not meet the recommended number of supervised sessions in the guidelines, and this may contribute in part to the small number of significant outcomes.

6.3.3. Accelerometry

Accelerometry was included in all of the studies, and it formed the major basis of the activity study (chapter 3). There are a number of limitations related to accelerometry, one of which is that the devices were not waterproof, and had to be removed for swimming, meaning that any water based physical activities were excluded from the reported data. In addition, some data was excluded

from analysis from once the data was processed according to the pre-specified criteria. This was to ensure our results were robust, but did mean that there was a wide gap between the number of participants studied and the available accelerometer results. This is an issue in all accelerometer based research, and is not unique to this work. Unfortunately in order to ensure high quality results, unreliable data must be removed from analysis, but it does reduce the numbers in the observed groups.

6.4. Future directions for study

The format of the pulmonary rehabilitation programme here seemed to be suboptimal given the high drop-out rate and prolonged completion times, although the drop-out rate was close to the expected drop-out rate for all PR programmes. Changes to the format of PR are not asthma-specific, but could be applicable to all chronic respiratory diseases. The increased availability and accessibility of virtual meetings during the Covid-19 pandemic has made this an attractive option to explore for pulmonary rehabilitation, and would likely be helpful in improving recruitment and retention. There could be an option for initial face-to-face assessment and first session, then options for live streamed online sessions with interactivity, sessions to be taken 'on-demand' independently and some face-to-face sessions. In addition, a more community-centred approach where classes were in local gyms rather than in a central hospital with difficult parking may improve accessibility and attendance. Our sessions took place in the middle of the working day, which made attendance difficult for many participants who worked standard hours. If there was the option for evening or weekend sessions, this would improve accessibility. Patients with COPD attending pulmonary rehabilitation are more likely to be older and/or more limited functionally, and less likely to be in employment, so this format may be more acceptable to them than our asthma population.

The different obese asthma phenotypes, i.e. early-onset asthma with later development of obesity and late-onset asthma predated by obesity may respond in different ways, and it would be interesting to split participants into these two groups and consider their responses to PR separately. Splitting the groups into

T2-high and T2-low asthma was also not considered here, and this is something which would be interesting to consider in future research.

In addition to further work on pulmonary rehabilitation, more randomised controlled studies assessing the impact of significant weight loss via dietary restriction alone or in conjunction with pulmonary rehabilitation would be of value. Traditionally the recommended approach to weight loss has been to increase physical activity along with calorie restriction, and some previous studies(Scott et al. 2013; Freitas et al. 2015; Freitas et al. 2017; Freitas et al. 2018; Türk et al. 2020) have had some success with this. Further study of these two strategies in combination in difficult-to-treat asthma associated with obesity may well allow the development of new strategies and is likely to improve outcomes.

As well as looking at exercise and weight loss, studying use of drugs such as liraglutide and semaglutide for weight loss in participants with obese asthma would be fascinating. In theory these drugs should be of great benefit in this patient group, and would likely improve symptoms of asthma by alterations in chest wall mechanics independent of any other effects. Research looking at their effects would be valuable and likely to further advance the field. The current research suggest bariatric surgery is the most effective option for weight loss in this group, and leads to significant improvements in asthma control(Dixon et al. 2011; Boulet et al. 2012; van Huisstede et al. 2015; Maniscalco et al. 2017). Were bariatric surgery more widely available on the NHS it would may be the leading treatment for the obese asthma phenotype.

For those with T2-high asthma who are eligible for biologics, the evidence suggests biologic use is far more likely to induce improvements than exercise or PR. However, considering use of biologics alongside or followed by weight loss or exercise would be an interesting area for future research.

6.5 Incorporating study findings into clinical practice

The findings of our studies add weight to the suggestion in guidelines that exercise and healthy weight should be advised as part of general lifestyle advice

in routine asthma management(British Thoracic Society and Scottish Intercollegiate Guidelines Network. 2019). They are however not significant enough to recommend major changes to clinical practice. In reality, weight management and exercise is often poorly addressed in primary care, and can be challenging to incorporate into secondary asthma clinics. It is important that all aspects of personalised management of asthma are considered, and in participants with difficult-to-treat asthma associated with obesity, weight loss and increased physical activity are likely to be of significant benefit. The development of some more robust protocols and pathways could be considered in future as evidence expands and strengthens, but in the meantime it is important that clinicians address these challenges in consultations with patients.

The management of obese asthma remains challenging. The findings here suggest that pulmonary rehabilitation and increased physical activity alone are not sufficient to improve it. They may fit into a wider strategy, but on its own pulmonary rehabilitation is not the answer to management of obese asthma. Other asthma phenotypes in these patients should be addressed in the clinic. Other weight loss strategies including calorie restriction, drug treatments (liraglutide, semaglutide) and bariatric surgery should be studied in this group of patients, as they are likely to be more valuable than pulmonary rehabilitation.

6.6 Have the research questions been answered?

Two research questions were posed in chapter 1. Firstly, do asthma severity and and/or body mass index affect exercise in asthma? In chapter 3 we demonstrated that the difficult-to-treat asthma, overweight participants were significantly less active than the mild-moderate asthma counterparts, both with healthy and overweight BMI. They were less active in all of the physical activity domains- with lower levels of light and moderate-vigorous activity, lower average acceleration and reduced intensity gradient, and more inactive time. So the answer to this research questions is that asthma severity in particular seems to impact on physical activity.

The second research question was, does exercise in the format of pulmonary rehabilitation improve asthma control in this group of participants? This

question has not been comprehensively answered. The results, particularly in chapter 4, demonstrate statistically significant improvements in the 6-point asthma control questionnaire, but these results do not reach clinical significance. In addition, there were improvements in six-minute walk distance and breathlessness during the six-minute walk test, but again, these results do not reach clinical significance. Overall, the work in this thesis shows that this format of pulmonary rehabilitation does not significantly improve asthma control in this group of participants.

6.7 Conclusions

Chapter 3 demonstrates that participants with difficult-to-treat asthma associated with elevated body mass index have a significantly lower physical activity profiles than participants with mild-moderate asthma with both normal and elevated BMI, and this remains the case even when BMI and age are corrected for. We know that increased PA is associated with improved outcomes in asthma, and this study suggests this population are particularly inactive. This suggests that increasing PA and exercise should be a priority in this group of difficult-to-treat asthmatics.

The subsequent papers suggest that PR may have a role in the treatment of difficult-to-treat asthma associated with elevated BMI with some significant improvements including asthma control and exercise capacity. Unfortunately these improvements did not meet the minimum clinically important difference, and there were significant problems with recruitment and retention of participants, suggesting that the studied format of PR is suboptimal for this population, many of whom were of working age. Those most likely to achieve clinically significant improvements in asthma control by completing PR are those with poorer baseline asthma control, and as such these may be the best participants to target.

In summary, further work is required to determine the optimal format of PR, and the incorporation of dietary change/calorie restriction may allow further significant improvements in asthma control.

Bibliography

Agusti, A. et al. 2016. Treatable traits: Toward precision medicine of chronic airway diseases. *European Respiratory Journal* 47(2), pp. 410–419. doi: 10.1183/13993003.01359-2015.

Akerman, M.J.H., Calacanis, C.M. and Madsen, M.K. 2004. Relationship between asthma severity and obesity. *The Journal of asthma : official journal of the Association for the Care of Asthma* 41(5), pp. 521–526.

Ali, Z. and Ulrik, C.S. 2013. Obesity and asthma: a coincidence or a causal relationship? A systematic review. *Respiratory medicine* 107(9), pp. 1287–1300.

American Thoracic Society 2002. American Thoracic Society ATS Statement: Guidelines for the Six-Minute Walk Test. 166, pp. 111–117. doi: 10.1164/rccm.166/1/111.

Asthma UK 2019. Asthma: facts and statistics. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9312568.

Baarnes, C.B., Thuesen, B.H., Linneberg, A. and Ulrik, C.S. 2019. Determinants of airflow limitation in Danish adults – findings from the Health2006 cohort. *International Journal of Chronic Obstructive Pulmonary Disease* 14, p. 713. doi: 10.2147/COPD.S173815.

Bacon, S.L., Lemiere, C., Moullec, G., Ninot, G., Pepin, V. and Lavoie, K.L. 2015. Association between patterns of leisure time physical activity and asthma control in adult patients. *BMJ Open Respiratory Research* 2(1), pp. 1–7. doi: 10.1136/bmjresp-2015-000083.

Bahmer, T. et al. 2017. Physical activity, airway resistance and small airway dysfunction in severe asthma. *European Respiratory Journal* 49(1). doi: 10.1183/13993003.01827-2016.

Bailey, L.C., Forrest, C.B., Zhang, P., Richards, T.M., Livshits, A. and DeRusso, P.A. 2014. Association of antibiotics in infancy with early childhood obesity. *JAMA pediatrics* 168(11), pp. 1063–1069. doi: https://dx.doi.org/10.1001/jamapediatrics.2014.1539.

Bakrania, K. et al. 2016. Intensity Thresholds on Raw Acceleration Data: Euclidean Norm Minus One (ENMO) and Mean Amplitude Deviation (MAD) Approaches. Buchowski, M. ed. *PLOS ONE* 11(10), p. e0164045. doi: 10.1371/journal.pone.0164045.

Ballantyne, D., Scott, H., MacDonald-Wicks, L., Gibson, P.G. and Wood, L.G.

2016. Resistin is a predictor of asthma risk and resistin:adiponectin ratio is a negative predictor of lung function in asthma. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology* 46(8), pp. 1056–1065. doi: https://dx.doi.org/10.1111/cea.12742.

Barros, R., Moreira, P., Padrao, P., Teixeira, V.H., Carvalho, P., Delgado, L. and Moreira, A. 2017. Obesity increases the prevalence and the incidence of asthma and worsens asthma severity. *Clinical Nutrition* 36(4), pp. 1068–1074.

Bateman, E.D. et al. 2018. As-Needed Budesonide-Formoterol versus Maintenance Budesonide in Mild Asthma. *The New England journal of medicine* 378(20), pp. 1877–1887. doi: 10.1056/NEJMOA1715275.

Bestall, J.C., Paul, E.A., Garrod, R., Garnham, R., Jones, P.W. and Wedzicha, J.A. 1999. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 54(7), pp. 581–586. doi: 10.1136/thx.54.7.581.

Beuther, D.A. and Sutherland, E.R. 2007. Overweight, Obesity, and Incident Asthma. *American Journal of Respiratory and Critical Care Medicine* 175(7), pp. 661–666. doi: 10.1164/rccm.200611-1717OC.

Bjelland, I., Dahl, A.A., Haug, T.T. and Neckelmann, D. 2002. The validity of the Hospital Anxiety and Depression Scale: An updated literature review. *Journal of Psychosomatic Research* . doi: 10.1016/S0022-3999(01)00296-3.

BMI calculator | Check your BMI - NHS | Please fill in your details. [no date]. Available at: https://www.nhs.uk/live-well/healthy-weight/bmi-calculator/ [Accessed: 11 September 2022].

Bolton, C.E. et al. 2013. British Thoracic Society guideline on pulmonary rehabilitation in adults. *Thorax* 68(SUPPL. 2), pp. ii1–ii30. doi: 10.1136/thoraxjnl-2013-203808.

Boulet, L.-P. and Franssen, E. 2007. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. *Respiratory medicine* 101(11), pp. 2240–2247.

Boulet, L.-P., Turcotte, H., Martin, J. and Poirier, P. 2012. Effect of bariatric surgery on airway response and lung function in obese subjects with asthma. *Respiratory medicine* 106(5), pp. 651–660.

British Thoracic Society and Scottish Intercollegiate Guidelines Network. 2019. Sign 158: British guideline on the management of asthma. *Thorax* (July), pp. 1–214.

British Thoracic Society and Scottish Intercollegiate Guidelines Network 2014. British guideline on the management of asthma. *Thorax*

Buchan, D.S., McLellan, G., Donnelly, S. and Arthur, R. 2019. The use of the intensity gradient and average acceleration metrics to explore associations with BMI z-score in children. *Journal of Sports Sciences* 37(23), pp. 2751–2758. doi: 10.1080/02640414.2019.1664536.

Bull, F.C. et al. 2020. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *British Journal of Sports Medicine* 54(24), pp. 1451–1462. doi: 10.1136/bjsports-2020-102955.

Burgess, J.A. et al. 2017. Bronchial hyperresponsiveness and obesity in middle age: insights from an Australian cohort. *European Respiratory Journal* 50(3)

Camargo, C.A.J., Weiss, S.T., Zhang, S., Willett, W.C. and Speizer, F.E. 1999. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. *Archives of Internal Medicine* 159(21), pp. 2582–2588.

Casey, D. et al. 2013. The effectiveness of a structured education pulmonary rehabilitation programme for improving the health status of people with moderate and severe chronic obstructive pulmonary disease in primary care: the PRINCE cluster randomised trial. *Thorax* 68(10), pp. 922–928. doi: 10.1136/THORAXJNL-2012-203103.

Castro-Rodriguez, J.A., Holberg, C.J., Morgan, W.J., Wright, A.L. and Martinez, F.D. 2001. Increased incidence of asthmalike symptoms in girls who become overweight or obese during the school years. *American journal of respiratory and critical care medicine* 163(6), pp. 1344–1349.

Castro, M. et al. 2018. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. *New England Journal of Medicine* 378(26), pp. 2486–2496. doi: 10.1056/NEJMoa1804092.

Celedon, J.C., Palmer, L.J., Litonjua, A.A., Weiss, S.T., Wang, B., Fang, Z. and Xu, X. 2001. Body mass index and asthma in adults in families of subjects with asthma in Anqing, China. *American Journal of Respiratory & Critical Care Medicine* 164(10 Pt 1), pp. 1835–1840.

Chaudhuri, R. et al. 2021. Safety and effectiveness of bronchial thermoplasty after 10 years in patients with persistent asthma (BT10+): a follow-up of three randomised controlled trials. *The Lancet. Respiratory medicine* 9(5), pp. 457–466. doi: 10.1016/S2213-2600(20)30408-2.

Chen Y, Dales R, Tang M, K.D. 2002. Obesity may increase the incidence of

asthma in women but not in men: longitudinal observations from the Canadian National Population Health Surveys. *American Journal of Epidemiology* 155 (3)(February), pp. 191–7.

Chinn, S., Jarvis, D. and Burney, P. 2002. Relation of bronchial responsiveness to body mass index in the ECRHS. European Community Respiratory Health Survey 1. *Thorax* 57(0040-6376 (Print)), pp. 1028–1033.

Cordova-Rivera, L., Gibson, P.G., Gardiner, P.A. and McDonald, V.M. 2018a. A Systematic Review of Associations of Physical Activity and Sedentary Time with Asthma Outcomes. *Journal of Allergy and Clinical Immunology: In Practice* 6(6), pp. 1968-1981.e2. doi: 10.1016/j.jaip.2018.02.027.

Cordova-Rivera, L., Gibson, P.G., Gardiner, P.A., Powell, H. and McDonald, V.M. 2018b. Physical Activity and Exercise Capacity in Severe Asthma: Key Clinical Associations. *Journal of Allergy and Clinical Immunology: In Practice* 6(3), pp. 814–822. doi: 10.1016/j.jaip.2017.09.022.

Crapo, R.O. et al. 2012. ATS Statement: Guidelines for the Six-Minute Walk Test. *https://doi.org/10.1164/ajrccm.166.1.at1102* 166(1), pp. 111–117. doi: 10.1164/AJRCCM.166.1.AT1102.

Department of Health 2011. Physical activity guidelines for Adults (19-64 years). *Department of Health* 11, pp. 406–414. doi: 10.1542/peds.2012-2330.

Dixon, A.E. et al. 2011. Effects of obesity and bariatric surgery on airway hyperresponsiveness, asthma control, and inflammation. *Journal of Allergy & Clinical Immunology* 128(3), pp. 502–508.

Dockrell, M., Partridge, M.R. and Valovirta, E. 2007. The limitations of severe asthma: The results of a European survey. *Allergy: European Journal of Allergy and Clinical Immunology* 62(2), pp. 134–141. doi: 10.1111/j.1398-9995.2006.01304.x.

Dogaru, C.M., Nyffenegger, D., Pescatore, A.M., Spycher, B.D. and Kuehni, C.E. 2014. Breastfeeding and childhood asthma: systematic review and meta-analysis. *American journal of epidemiology* 179(10), pp. 1153–1167. doi: https://dx.doi.org/10.1093/aje/kwu072.

Dweik, R.A. et al. 2011. American Thoracic Society Documents An Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FE NO) for Clinical Applications. *Am J Respir Crit Care Med* 184, pp. 602–615. doi: 10.1164/rccm.912011ST.

Eichenberger, P.A., Diener, S.N., Kofmehl, R. and Spengler, C.M. 2013. Effects

of exercise training on airway hyperreactivity in asthma: a systematic review and meta-analysis. *Sports Medicine* 43(11), pp. 1157–1170.
Ekelund, U. et al. 2019. Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: Systematic review and harmonised meta-analysis. *The BMJ* 366. doi: 10.1136/bmj.l4570.
Evans, R.A., Singh, S.J., Collier, R., Williams, J.E. and Morgan, M.D.L. 2009. Pulmonary rehabilitation is successful for COPD irrespective of MRC dyspnoea grade. *Respiratory Medicine* . doi: 10.1016/j.rmed.2009.01.009.
Feng, Z., Wang, J., Xie, Y. and Li, J. 2021. Effects of exercise-based pulmonary rehabilitation on adults with asthma: a systematic review and meta-analysis. *Respiratory Research* 22(1), pp. 1–12. doi: 10.1186/S12931-021-01627-W/TABLES/3.
Fischer, M.J. et al. 2009. Drop-out and attendance in pulmonary rehabilitation: the role of clinical and psychosocial variables. *Respiratory medicine* 103(10), pp. 1564–1571. doi: 10.1016/j.rmed.2008.11.020.
Franca-Pinto, A. et al. 2015. Aerobic training decreases bronchial hyperresponsiveness and systemic inflammation in patients with moderate or severe asthma: a randomised controlled trial. *Thorax* 70(8), pp. 732–739.
Freitas, P.D. et al. 2015. The effects of exercise training in a weight loss lifestyle intervention on asthma control, quality of life and psychosocial symptoms in adult obese asthmatics: protocol of a randomized controlled trial. *BMC pulmonary medicine* 15, p. 124. doi: https://dx.doi.org/10.1186/s12890-015-0111-2.
Freitas, P.D. et al. 2017. The Role of Exercise in a Weight-Loss Program on Clinical Control in Obese Adults with Asthma. A Randomized Controlled Trial. *American Journal of Respiratory & Critical Care Medicine* 195(1), pp. 32–42.
Freitas, P.D. et al. 2018. Exercise Improves Physical Activity and Comorbidities in Obese Adults with Asthma. *Medicine and science in sports and exercise* 50(7), pp. 1367–1376. doi: https://dx.doi.org/10.1249/MSS.0000000000001574.
Freitas, P.D. et al. 2021. Identification of asthma phenotypes based on extrapulmonary treatable traits. *European Respiratory Journal* 57(1), p. 2000240. doi: 10.1183/13993003.00240-2020.
Garrod, R., Marshall, J., Barley, E. and Jones, P. 2006. Predictors of success 2006; and failure in pulmonary rehabilitation. *Eur Respir J.* 27(4), pp. 788–794.

Global Initiative for Asthma 2018. *Global Strategy for Asthma Management and Prevention (2018 Update)*.
Global Initiative for Asthma 2022a. Global Strategy for Asthma Management and Prevention: 2022 Update. Available at: https://ginasthma.org/gina-reports/ [Accessed: 22 August 2022].
Global Initiative for Asthma 2022b. *Global strategy for asthma management and prevention 2022*.
Graham, B.L. et al. 2019. Standardization of spirometry 2019 update an official American Thoracic Society and European Respiratory Society technical statement. *American Journal of Respiratory and Critical Care Medicine* 200(8), pp. E70–E88. doi: 10.1164/rccm.201908-1590ST.
Greater Glasgow and Clyde 2021. Weight Loss Surgery. Available at: https://www.nhsggc.scot/hospitals-services/services-a-to-z/specialist-weight-management-service-swms/weight-loss-surgery/ [Accessed: 2 May 2023].
Griffiths, T.L. et al. 2000. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: A randomised controlled trial. *Lancet* Jan 29(355(9201)), pp. 362–8. doi: 10.1016/S0140-6736(99)07042-7.
Grosbois, J.M., Coquart, J., Fry, S., Le Rouzic, O., Grosbois, T., Wallaert, B. and Chenivesse, C. 2019. Long-term effect of home-based pulmonary rehabilitation in severe asthma. *Respiratory Medicine* 157(August), pp. 36–41. doi: 10.1016/j.rmed.2019.08.015.
Haldar, P. et al. 2009. Mepolizumab and exacerbations of refractory eosinophilic asthma. *The New England journal of medicine* 360(10), pp. 973–984. doi: 10.1056/NEJMOA0808991.
Hallstrand, T.S., Fischer, M.E., Wurfel, M.M., Afari, N., Buchwald, D. and Goldberg, J. 2005. Genetic pleiotropy between asthma and obesity in a community-based sample of twins. *The Journal of allergy and clinical immunology* 116(6), pp. 1235–1241.
van Hees, V.T. et al. 2013. Separating Movement and Gravity Components in an Acceleration Signal and Implications for the Assessment of Human Daily Physical Activity. Müller, M. ed. *PLoS ONE* 8(4), p. e61691. doi: 10.1371/journal.pone.0061691.
Van Hees, V.T. et al. 2014. Autocalibration of accelerometer data for free-living physical activity assessment using local gravity and temperature: An evaluation on four continents. *Journal of Applied Physiology* 117(7), pp. 738–744. doi:

10.1152/japplphysiol.00421.2014.
Hernández, M.T.E., Rubio, T.M., Ruiz, F.O., Riera, H.S., Gil, R.S. and Gómez, J.C. 2000. Results of a home-based training program for patients with COPD. *Chest* 118(1), pp. 106–114. doi: 10.1378/chest.118.1.106.
Hewitt, S., Humerfelt, S., Sovik, T.T., Aasheim, E.T., Risstad, H., Kristinsson, J. and Mala, T. 2014. Long-term improvements in pulmonary function 5 years after bariatric surgery. *Obesity Surgery* 24(5), pp. 705–711.
Hildebrand, M., van Hees, V.T., Hermann Hannsen, B. and Ekelund, U. 2014. Age Group Comparability of Raw Accelerometer Output from Wrist- and Hip-Worn Monitors. *Medicine and science in sports and exercise* 46(9), pp. 1816–1824. doi: 10.1249/MSS.0000000000000289.
Hinks, T.S.C., Levine, S.J. and Brusselle, G.G. 2021. Treatment options in type-2 low asthma. *European Respiratory Journal* 57(1), p. 2000528. doi: 10.1183/13993003.00528-2020.
Holguin, F. et al. 2011. Obesity and asthma: an association modified by age of asthma onset. *Journal of Allergy & Clinical Immunology* 127(6), pp. 1486–93.e2.
van Huisstede, A. et al. 2015. Effect of bariatric surgery on asthma control, lung function and bronchial and systemic inflammation in morbidly obese subjects with asthma. *Thorax* 70(7), pp. 659–667.
Jackson, D.J. et al. 2021. Characterisation of patients with severe asthma in the UK Severe Asthma Registry in the biologic era. *Thorax* 76(3), pp. 220–227. doi: 10.1136/thoraxjnl-2020-215168.
Jones, R.L. and Nzekwu, M.-M.U. 2006. The effects of body mass index on lung volumes. *Chest* 130(3), pp. 827–833.
Juniper, E.F., Bousquet, J., Abetz, L. and Bateman, E.D. 2006. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respiratory Medicine* 100(4), pp. 616–621. doi: 10.1016/j.rmed.2005.08.012.
Juniper, E.F., Guyatt, G.H., Epstein, R.S., Ferrie, P.J., Jaeschke, R. and Hiller, T.K. 1992. Evaluation of impairment of health related quality of life in asthma: Development of a questionnaire for use in clinical trials. *Thorax* . doi: 10.1136/thx.47.2.76.
Juniper, E.F., Guyatt, G.H., Ferrie, P.J. and Griffith, L.E. 2013. Measuring Quality of Life in Asthma. *American Review of Respiratory Disease* . doi: 10.1164/ajrccm/147.4.832.

Juniper, E.F., Guyatt, G.H., Willan, A. and Griffith, L.E. 1994. Determining a minimal important change in a disease-specific quality of life questionnaire. *Journal of Clinical Epidemiology* . doi: 10.1016/0895-4356(94)90036-1.

Juniper, E.F., O'Byrne, P.M., Guyatt, G.H., Ferrie, P.J. and King, D.R. 1999. Development and validation of a questionnaire to measure asthma control. *European Respiratory Journal* 14(4)(4), pp. 902–907. doi: 10.1034/j.1399-3003.1999.14d29.x.

Kaminsky, D.A. et al. 2019. Older age and obesity are associated with increased airway closure in response to methacholine in patients with asthma. *Respirology (Carlton, Vic.)* 24(7), p. 638. doi: 10.1111/RESP.13496.

Kern, P.A., Di Gregorio, G.B., Lu, T., Rassouli, N. and Ranganathan, G. 2003. Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor-alpha expression. *Diabetes* 52(7), pp. 1779–1785.

Law, C.M., Barker, D.J., Osmond, C., Fall, C.H. and Simmonds, S.J. 1992. Early growth and abdominal fatness in adult life. *Journal of epidemiology and community health* 46(3), pp. 184–186.

Lemay, K.R., Tulloch, H.E., Pipe, A.L. and Reed, J.L. 2019. Establishing the Minimal Clinically Important Difference for the Hospital Anxiety and Depression Scale in Patients With Cardiovascular Disease. *Journal of cardiopulmonary rehabilitation and prevention* 39(6), pp. E6–E11. doi: 10.1097/HCR.0000000000000379.

Lingner, H., Ernst, S., Großhennig, A., Djahangiri, N., Scheub, D., Wittmann, M. and Schultz, K. 2015. Asthma control and health-related quality of life one year after inpatient pulmonary rehabilitation: The ProKAR Study. *Journal of Asthma* 52(6), pp. 614–621. doi: 10.3109/02770903.2014.996650.

Loffreda, S. et al. 1998. Leptin regulates proinflammatory immune responses. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* 12(1), pp. 57–65.

Ma, J. et al. 2015. Behavioral weight loss and physical activity intervention in obese adults with asthma. A randomized trial. *Annals of the American Thoracic Society* 12(1), pp. 1–11. doi: https://dx.doi.org/10.1513/AnnalsATS.201406-271OC.

Mahler, D. A; Horowitz, M.B. 1994. Perception of Breathlessness during exercise in patients with respiratory disease. *Medicine and science in sports and exercise*

September,(9), pp. 1078–81.
Majd, S. et al. 2020. A Feasibility Study of a Randomized Controlled Trial of Asthma-Tailored Pulmonary Rehabilitation Compared with Usual Care in Adults with Severe Asthma. *Journal of Allergy & Clinical Immunology in Practice* Nov-Dec(8(10)), pp. 3418–3427.
Man, W.D.C., Grant, A., Hogg, L., Moore, J., Barker, R.D. and Moxham, J. 2011. Pulmonary rehabilitation in patients with MRC dyspnoea scale 2. *Thorax* . doi: 10.1136/thx.2010.136085.
Maniscalco, M., Zamparelli, A.S., Vitale, D.F., Faraone, S., Molino, A., Zedda, A. and Motta, A. 2017. Long-term effect of weight loss induced by bariatric surgery on asthma control and health related quality of life in asthmatic patients with severe obesity: A pilot study. *Respiratory medicine* 130, pp. 69–74.
Mccarthy, B., Casey, D., Devane, D., Murphy, K., Murphy, E. and Lacasse, Y. 2015. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2015(2). doi: 10.1002/14651858.CD003793.pub3.
McDonald, V.M. et al. 2019. Treatable traits : a new paradigm for 21st century management of chronic airway diseases : Treatable Traits Down Under International Workshop report. *Eur Respir Journal* 53(1802058)
Meyer, A., Gunther, S., Volmer, T., Taube, K. and Baumann, H.J. 2015. A 12-month, moderate-intensity exercise training program improves fitness and quality of life in adults with asthma: a controlled trial. *BMC Pulmonary Medicine* 15, p. 56.
Migueles, J.H.. et al. 2017. Accelerometer Data Collection and Processing Criteria to Assess Physical Activity and Other Outcomes : A Systematic Review and Practical Considerations. *Sports Medicine* 47(9), pp. 1821–1845. doi: 10.1007/s40279-017-0716-0.
Migueles, J.H., Rowlands, A. V., Huber, F., Sabia, S. and van Hees, V.T. 2019. GGIR: A Research Community–Driven Open Source R Package for Generating Physical Activity and Sleep Outcomes From Multi-Day Raw Accelerometer Data. *Journal for the Measurement of Physical Behaviour* 2(3), pp. 188–196. doi: 10.1123/jmpb.2018-0063.
Mokdad, A.H., Ford, E.S., Bowman, B.A., Dietz, W.H., Vinicor, F., Bales, V.S. and Marks, J.S. 2003. Prevalence of Obesity, Diabetes, and Obesity-Related Health Risk Factors, 2001. *Jama* 289(1), pp. 2001–2004. doi:

10.1001/jama.289.1.76.
MRC breathlessness scales: 1952 and 1959 – UKRI. [no date]. Available at: https://www.ukri.org/publications/mrc-breathlessness-scales-1952-and-1959/ [Accessed: 31 August 2022].
Nair, P. et al. 2017. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. *The New England journal of medicine* 376(25), pp. 2448–2458. doi: 10.1056/NEJMOA1703501.
National Health Service United Kingdom 2018. NHS BMI Calculator. Available at: https://www.nhs.uk/live-well/healthy-weight/bmi-calculator/?tabname=you-and-your-weight.
Neale, J. et al. 2020. A comparison of daily physical activity profiles between adults with severe asthma and healthy controls. *European Respiratory Journal* 56(1), pp. 8–11. doi: 10.1183/13993003.02219-2019.
Nepomnyaschy, L. and Reichman, N.E. 2006. Low birthweight and asthma among young urban children. *American journal of public health* 96(9), pp. 1604–1610.
Norman, G. et al. 2013. Omalizumab for the treatment of severe persistent allergic asthma: a systematic review and economic evaluation. *Health technology assessment (Winchester, England)* 17(52). doi: 10.3310/HTA17520.
O'Byrne, P.M. et al. 2018. Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma. *The New England journal of medicine* 378(20), pp. 1865–1876. doi: 10.1056/NEJMOA1715274.
Ortega, H.G. et al. 2016. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *The Lancet Respiratory Medicine* 4(7), pp. 549–556. doi: 10.1016/S2213-2600(16)30031-5.
Pakhale, S., Baron, J., Dent, R., Vandemheen, K. and Aaron, S.D. 2015. Effects of weight loss on airway responsiveness in obese adults with asthma: does weight loss lead to reversibility of asthma?. *Chest* 147(6), pp. 1582–1590.
Pavord, I.D. et al. 2018. After asthma: redefining airways diseases. *The Lancet* 391(10118), pp. 350–400. doi: 10.1016/S0140-6736(17)30879-6.
Peters, M.C. et al. 2016. Plasma interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts. *The Lancet Respiratory Medicine* 4(7), pp. 574–584.
Peters, U. et al. 2019. BMI but not central obesity predisposes to airway closure during bronchoconstriction. *Respirology (Carlton, Vic.)* 24(6), p. 543. doi:

10.1111/RESP.13478.
Peters, U., Dixon, A.E. and Forno, E. 2018. Obesity and asthma. *The Journal of allergy and clinical immunology* 141(4), pp. 1169–1179. doi: https://dx.doi.org/10.1016/j.jaci.2018.02.004.
Pitter, G., Ludvigsson, J.F., Romor, P., Zanier, L., Zanotti, R., Simonato, L. and Canova, C. 2016. Antibiotic exposure in the first year of life and later treated asthma, a population based birth cohort study of 143,000 children. *European journal of epidemiology* 31(1), pp. 85–94. doi: https://dx.doi.org/10.1007/s10654-015-0038-1.
Puhan, M.A., Frey, M., Büchi, S. and Schünemann, H.J. 2008a. The minimal important difference of the hospital anxiety and depression scale in patients with chronic obstructive pulmonary disease. *Health and Quality of Life Outcomes* 6. doi: 10.1186/1477-7525-6-46.
Puhan, M.A., Mador, M.J., Held, U., Goldstein, R., Guyatt, G.H. and Schünemann, H.J. 2008b. Interpretation of treatment changes in 6-minute walk distance in patients with COPD. *European Respiratory Journal* 32(3), pp. 637–643. doi: 10.1183/09031936.00140507.
Quanjer, P.H. et al. 2012. Multi-ethnic reference values for spirometry for the 3-95-yr age range: The global lung function 2012 equations. *European Respiratory Journal* 40(6), pp. 1324–1343. doi: 10.1183/09031936.00080312.
Ricketts, H.C. et al. 2022. A pragmatic randomised controlled trial of tailored pulmonary rehabilitation in participants with difficult-to-control asthma and elevated body mass index. *BMC Pulmonary Medicine* 22, p. 363. doi: 10.1186/s12890-022-02152-2.
Robertson, A.G.N. et al. 2021. Perioperative mortality in bariatric surgery: meta-analysis. *British Journal of Surgery* 108(8), pp. 892–897. doi: 10.1093/BJS/ZNAB245.
Rowlands, A. V. 2018. Moving forward with accelerometer-assessed physical activity: Two strategies to ensure meaningful, interpretable, and comparable measures. *Pediatric Exercise Science* 30(4), pp. 450–456. doi: 10.1123/pes.2018-0201.
Rowlands, A. V., Edwardson, C.L., Davies, M.J., Khunti, K., Harrington, D.M. and Yates, T. 2018. Beyond Cut Points: Accelerometer Metrics that Capture the Physical Activity Profile. *Medicine and Science in Sports and Exercise* 50(6), pp. 1323–1332. doi: 10.1249/MSS.0000000000001561.

Russell, M.A. et al. 2017. Physical activity and asthma: A longitudinal and multi-country study. *Journal of Asthma* 54(9), pp. 938–945. doi: 10.1080/02770903.2017.1281293.

Sahin, H. and Naz, I. 2019. Comparing the effect of pulmonary rehabilitation in patients with uncontrolled and partially controlled asthma. *The Journal of asthma : official journal of the Association for the Care of Asthma* 56(1), pp. 87–94. doi: https://dx.doi.org/10.1080/02770903.2018.1443468.

Salome, C.M., Munoz, P.A., Berend, N., Thorpe, C.W., Schachter, L.M. and King, G.G. 2008. Effect of obesity on breathlessness and airway responsiveness to methacholine in non-asthmatic subjects. *International journal of obesity* 32(3), pp. 502–509.

Scott, H.A., Gibson, P.G., Garg, M.L., Pretto, J.J., Morgan, P.J., Callister, R. and Wood, L.G. 2013. Dietary restriction and exercise improve airway inflammation and clinical outcomes in overweight and obese asthma: a randomized trial. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology* 43(1), pp. 36–49. doi: https://dx.doi.org/10.1111/cea.12004.

Scott, H.A., Wood, L.G. and Gibson, P.G. 2017. Role of Obesity in Asthma: Mechanisms and Management Strategies. *Current allergy and asthma reports* 17(8), p. 53. doi: https://dx.doi.org/10.1007/s11882-017-0719-9.

Scottish Intercollegiate Guidelines Network 2016. SIGN 153 • British guideline on the management of asthma. (September 2016)

Shim, Y.M. et al. 2013. Physical deconditioning as a cause of breathlessness among obese adolescents with a diagnosis of asthma. *PloS one* 8(4), pp. e61022–e61022. doi: 10.1371/journal.pone.0061022.

Shore, S.A., Schwartzman, I.N., Mellema, M.S., Flynt, L., Imrich, A. and Johnston, R.A. 2005. Effect of leptin on allergic airway responses in mice. *Journal of Allergy & Clinical Immunology* 115(1), pp. 103–109.

Shore, S.A., Terry, R.D., Flynt, L., Xu, A. and Hug, C. 2006. Adiponectin attenuates allergen-induced airway inflammation and hyperresponsiveness in mice. *Journal of Allergy & Clinical Immunology* 118(2), pp. 389–395.

Sideleva, O. et al. 2012. Obesity and asthma: an inflammatory disease of adipose tissue not the airway. *American Journal of Respiratory & Critical Care Medicine* 186(7), pp. 598–605.

Spruit, M.A. et al. 2013. An Official American Thoracic Society/European

Respiratory Society Statement: Key Concepts and Advances in Pulmonary Rehabilitation. *https://doi.org/10.1164/rccm.201309-1634ST* 188(8). doi: 10.1164/RCCM.201309-1634ST.

Stern, A.F. 2014. The Hospital Anxiety and Depression Scale. *Occupational Medicine* . doi: 10.1093/occmed/kqu024.

Sutherland, E.R., Goleva, E., Strand, M., Beuther, D.A. and Leung, D.Y.M. 2008. Body mass and glucocorticoid response in asthma. *American journal of respiratory and critical care medicine* 178(7), pp. 682–687. doi: https://dx.doi.org/10.1164/rccm.200801-076OC.

Taylor, B., Mannino, D., Brown, C., Crocker, D., Twum-Baah, N. and Holguin, F. 2008. Body mass index and asthma severity in the National Asthma Survey. *Thorax* 63(1), pp. 14–20.

Trompette, A. et al. 2014. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. *Nature medicine* 20(2), pp. 159–166. doi: https://dx.doi.org/10.1038/nm.3444.

Troosters, T., Gosselink, R. and Decramer, M. 2000. Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: A randomized trial. *American Journal of Medicine* 109(3), pp. 207–212. doi: 10.1016/S0002-9343(00)00472-1.

Türk, Y. et al. 2020. Short-term and long-term effect of a high-intensity pulmonary rehabilitation programme in obese patients with asthma: a randomised controlled trial. *European Respiratory Journal* July 2(56(1)), p. 1901820.

Turk, Y., van Huisstede, A., Franssen, F.M.E., Hiemstra, P.S., Rudolphus, A., Taube, C. and Braunstahl, G.-J. 2017a. Effect of an Outpatient Pulmonary Rehabilitation Program on Exercise Tolerance and Asthma Control in Obese Asthma Patients. *Journal of Cardiopulmonary Rehabilitation & Prevention* 37(3), pp. 214–222.

Turk, Y., van Huisstede, A., Hiemstra, P.S., Taube, C. and Braunstahl, G.-J. 2017b. Pre-surgical Pulmonary Rehabilitation in Asthma Patients Undergoing Bariatric Surgery. *Obesity Surgery* 27(11), pp. 3055–3060.

Turner, S., Eastwood, P., Cook, A. and Jenkins, S. 2011. Improvements in symptoms and quality of life following exercise training in older adults with moderate/severe persistent asthma. *Respiration* 81(4), pp. 302–310.

Umetsu, D.T. 2017. Mechanisms by which obesity impacts upon asthma. *Thorax*

72(2), pp. 174–177.
Van't Hul, A.J. et al. 2016. Decreased physical activity in adults with bronchial asthma. *Respiratory Medicine* 114, pp. 72–77. doi: 10.1016/j.rmed.2016.03.016.
Visser, M., Bouter, L.M., McQuillan, G.M., Wener, M.H. and Harris, T.B. 2001. Low-grade systemic inflammation in overweight children. *Pediatrics* 107(1), p. E13.
Vortmann, M. and Eisner, M.D. 2008. BMI and health status among adults with asthma. *Obesity* 16(1), pp. 146–152.
Westermann, H., Choi, T.N., Briggs, W.M., Charlson, M.E. and Mancuso, C.A. 2008. Obesity and exercise habits of asthmatic patients. *Annals of Allergy, Asthma, & Immunology* 101(5), pp. 488–494.
Williams, A.S., Chen, L., Kasahara, D.I., Si, H., Wurmbrand, A.P. and Shore, S.A. 2013. Obesity and airway responsiveness: Role of TNFR2. *Pulmonary Pharmacology and Therapeutics* . doi: 10.1016/j.pupt.2012.05.001.
Wood, L.G., Garg, M.L. and Gibson, P.G. 2011. A high-fat challenge increases airway inflammation and impairs bronchodilator recovery in asthma. *Journal of Allergy & Clinical Immunology* 127(5), pp. 1133–1140.
World Health Organisation 2018. *Obesity and Overweight Fact Sheet*.
World Health Organization 2003. Diet, nutrition and the prevention of chronic diseases: report of a joint WHO/FAO expert consultation, Geneva, 28 January - 1 February 2002. *WHO Technical Report Series* , p. 149.
Yan, J., Liu, L., Zhu, Y., Huang, G. and Wang, P.P. 2014. The association between breastfeeding and childhood obesity: a meta-analysis. *BMC public health* 14, p. 1267. doi: https://dx.doi.org/10.1186/1471-2458-14-1267.
Zampogna, E. et al. 2019. Effectiveness of pulmonary rehabilitation in severe asthma: a retrospective data analysis. *Journal of Asthma* 57, pp. 1365–1371. doi: 10.1080/02770903.2019.1646271.
Zigmond, A.S. and Snaith, R.P. 1983. The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica* . doi: 10.1111/j.1600-0447.1983.tb09716.x.