Physical Activity and Sedentary Behaviour in Obstructive Airway Diseases.

Laura Cordova Rivera

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STATEMENT OF ORIGINALITY

I hereby certify that the work embodied in the thesis is my own work, conducted under normal supervision. The thesis contains no material which has been accepted, or is being examined, for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968 and any approved embargo.

25th September 2018

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I hereby certify that this thesis is in the form of a series of papers. I have included as part of the thesis a written declaration from each co-author, endorsed in writing by the Faculty Assistant Dean (Research Training), attesting to my contribution to any jointly authored papers

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PUBLICATIONS INCLUDED AS PART OF THIS THESIS

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STATEMENT OF CONTRIBUTION OF OTHERS

By signing below, I confirm that Research Higher Degree candidate, Laura Cordova Rivera, provided substantial intellectual input and contributions to defining the topic of literature review, gathering and evaluating source materials, critically analysing and synthesising information from published sources and manuscript preparation/writing to the publication entitled:

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Signature:

Full Name of Co-Author: **Prof Vanessa McDonald**

Signature:

Full name of Assistant Dean Research Training: **Prof Derek Laver**

Date: 17/09/2018

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Signature:

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Signature:

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Signature:

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Signature:

Full Name of Co-Author: **Ms Heather Powell**

Signature:

Full name of Assistant Dean Research Training: **Prof Derek Laver**

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Signature:

Full Name of Co-Author: **Dr. Sarah Ashley Hiles**

Signature:

Full name of Assistant Dean Research Training: **Prof Derek Laver**

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CONFERENCE PRESENTATIONS & PUBLICATIONS FROM THIS THESIS

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Poster presentation by Laura Cordova Rivera

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The International Society of Behavioral Nutrition and Physical Activity (ISBNPA) 17th annual meeting 2018, 3 - 6 June 2018, Hong Kong.

Oral presentation by Laura Cordova Rivera

Cordova-Rivera L, Gibson PG, Gardiner PA, McDonald VM. Determinants of physical activity in obstructive airway diseases.

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ABPA: Allergic bronchopulmonary aspergillosis

ACQ: Asthma control questionnaire

ACT: Asthma control test

AFL: Airflow limitation

AOR: Adjusted odds ratio

ATS: American Thoracic Society

AQLQ: Asthma quality of life questionnaire

AusDiab: Australian Diabetes, Obesity and Lifestyle

BMI: Body mass index

CAT: COPD Assessment Test

CI: Confidence interval

COPD: Chronic obstructive pulmonary disease

CPM: Count per minutes

ERS: European Respiratory Society

FeNO: Fractional exhaled nitric oxide levels

FER: Forced expiratory ratio (FEV_1/ FVC)

FEV_1: Forced expiratory volume in the first second

FVC: Forced vital capacity

GINA: Global Initiative for Asthma

GOLD: Global Initiative for Chronic Obstructive Lung Disease

GORD: Gastroesophageal reflux disease

HRCT: High resolution computed tomography

HRQoL: Health-related quality of life

Hs-CRP: High sensitivity C-reactive protein

ICS: Inhaled corticosteroids

ICU: Intensive Care Unit

IFN γ: Interferon gamma

IgE: Immunoglobulin E

IL: Interleukin

ILC2: Innate lymphoid cells type 2

IQR: Interquartile range

Kcal: Kilocalories

Kg: Kilogram

Mcg: Micrograms

METs: Metabolic equivalent of task

Ml: Millilitre

Mg: Milligram

mMRC: Medical Research Council

MVPA: Moderate and vigorous physical activity

NAEPP: National Asthma Education and Prevention Program

NHANES: National Health and Nutrition Examination Survey

LABA: Long-acting β2-agonist

LAMA: Long-acting anti muscarinic antagonists

OAD: Obstructive airway diseases

OR: Odds ratio

OSA: obstructive sleep apnoea

PA: Physical activity

SABA: Short acting β2 agonist

SD: Standard deviation

SGRQ: Saint George Respiratory Questionnaire

TGF-β: Transforming growth factor beta

T_H2: Type 2 helper

TNF-α: Tumour necrosis alpha

WHO: World Health Organisation

6MWD: six-minute walked distance

6MWT: six-minute walk test

ABSTRACT AND SYNOPSIS

Severe asthma, chronic obstructive pulmonary disease (COPD) and bronchiectasis are well-recognised public health priorities by the World Health Organisation. People affected by these obstructive airway diseases (OAD) can suffer from considerable impairment in their quality of life due to the high burden of symptoms, exacerbations/lung attacks, and associated morbidity. All of these shared characteristics may also be detrimental to the person's ability to carry out activities of daily life, and are likely to lead to a vicious circle of physical activity reduction and deconditioning that will impair health-related quality of life.

In the general population, engaging in healthy levels of physical activity and reducing sedentary time have been regarded as highly beneficial in the prevention and treatment of several chronic diseases. In COPD, the impairment in these behaviours has been widely characterised and the importance of addressing them as part of disease management is recognised and accepted. However, in severe asthma and bronchiectasis, the characterisation of physical activity and sedentary time and the role of optimising these behaviours in disease management is largely under-researched.

In this Thesis, I characterise the degree of physical activity levels and sedentary time in a severe asthma population and examined whether the activity levels were comparable to that found in moderate to severe COPD and bronchiectasis. I also investigated the associations between physical activity levels, pulmonary and extrapulmonary characteristics, and health-related quality of life in these diseases. In my studies I found that compared to people without respiratory diseases, people with severe asthma engage in lower levels of moderate and vigorous intensity physical activity but similar levels of sedentary time. Better parameters in both behaviours were associated with better disease features, including exercise capacity, asthma control, and systemic inflammation. When comparing these results

with bronchiectasis and moderate to severe COPD populations, I found that lower levels of physical activity is a shared behavioural characteristic of people with OAD, albeit to a lesser degree in severe asthma and bronchiectasis. Shared pulmonary characteristics differed between diseases but nevertheless, exercise capacity and airflow limitation explain an important proportion of physical activity levels in OAD. Finally, I demonstrate that physical activity and other extrapulmonary characteristics including skeletal muscle strength and comorbidities, are statistically and clinically associated with health-related quality of life in bronchiectasis and severe asthma. The associations were stronger for the activity and impact domain and suggest that health-related quality of life in these diseases could be improved by addressing these extrapulmonary characteristics.

The findings of this Thesis have extended our knowledge of the characterisation of physical activity and sedentary time in severe asthma and bronchiectasis. Lower levels of physical activity are a prevalent feature in OAD populations and should be considered as a treatable extrapulmonary risk factor for the management of several disease outcomes not only in COPD, but also in severe asthma and bronchiectasis populations.

1. Chapter 1: Obstructive Airway Diseases and Activity Behaviours: Background

In *Part 1* of this chapter, I present a description of the diseases of severe asthma, COPD and bronchiectasis in terms of definitions, prevalence, burden of the disease, pathogenesis, diagnosis and treatment; followed by an overview of why the assessment of physical activity may be important in these diseases. In part 2 of this chapter, I will provide a thorough description of the movement behaviours physical activity and sedentary time, and the current state of research of the characterisation of these behaviours in COPD and bronchiectasis. A published literature review of these behaviours in asthma is included in Chapter 2.

Part one

1.1. Obstructive Airway Diseases

Definition of the term obstructive airway diseases

The term obstructive airway disease (OAD) is related to chronic respiratory conditions that affects the lower respiratory airway. The present thesis will focus on the common obstructive airway diseases of severe asthma, COPD and bronchiectasis.

The cardinal feature of OAD is airflow limitation during exhalation, which may or may not be reversible, either spontaneously or with the use of bronchodilator medication. In healthy people, after a maximal inhalation, more than 70% of the inspired air can be exhaled in the first second of exhalation. In the case of OAD, the air is trapped within the lungs, exhalation time is prolonged, and less than 70% of exhaled air can be exhaled in the first second. This results in an increased work of breathing and clinical symptoms of OAD. In clinical practice, spirometry is the most widely used and reproducible lung function test to diagnose and monitor OAD. The spirometry findings for OAD are defined as a forced expiratory volume in

the first second (FEV_1) below 80% of the predicted for matched healthy population (FEV_1 < 80%), and a FEV_1/forced vital capacity (FEV_1/FVC) ratio below 0.7[1, 2]. In asthma, especially in mild and moderate asthma, the airway obstruction is reversible either spontaneously or after therapy. Reversibility of these parameters is defined as an increase equal to or greater than 200ml and 12% in FEV_1, post administration of 200-400 mcg of short acting β2 agonist (SABA), such as Salbutamol[1, 3].

In addition to the obstructive pulmonary findings, the aforementioned OAD share several clinical, functional and biological features. Symptoms such as cough, dyspnoea, sputum production, impaired exercise tolerance, and activity limitation are common characteristics among people with OAD[4]. Exacerbations are also common in these populations, impacting prognosis[1, 2, 5] and potentially leading to a more pronounced lung function decline[6-9]. Biological characteristics such as systemic and airway inflammation are also common and impact comorbidities and treatment responsiveness[10-13]. These pulmonary and extrapulmonary characteristics have a high negative toll on the health status of people with OAD, affecting their physical, mental, emotional and social spheres, and therefore impairing their quality of life[14-16].

Overlap among asthma, COPD and bronchiectasis has been widely described. Physician-diagnosed concurrence of asthma and COPD has been estimated to range between 15 and 20% of patients[17]. This coexistence is associated with more frequent exacerbations and higher health care use, poorer quality of life, and an accelerated decline in lung function[17-19]. Bronchiectasis also frequently overlaps with severe asthma and COPD[5, 20-24], but its consequences are less well studied. A recent review found that the overlap with moderate-severe COPD ranges from 4% to 72%, and around 20% and 30% in severe or uncontrolled asthma[15].

Severe asthma, COPD and bronchiectasis are well recognised as public health priorities by the World Health Organization (WHO)[25]. In Australia, asthma is one of the nine National Health Priority Areas since 1999[26]. According to the Australian Burden of Disease Study 2011, respiratory conditions were ranked as the sixth leading contributor to total burden of disease and injury. COPD and asthma were the highest contributors for this burden (46% and 29% of the total burden of all respiratory conditions, respectively)[27]. The definitions, pathogenesis, treatments, and burden of these diseases will be individually discussed through this chapter. Since these diseases share many common features, which may relate to the common defining characteristic of expiratory airflow limitation, in section 1.1.1.4 I will explore the proposed label-free approach to OAD management and focus on the question whether physical activity may be a treatable trait in OAD.

1.2. Asthma and Severe Asthma

1.2.1. Definition, prevalence, and disease burden.

Asthma definition

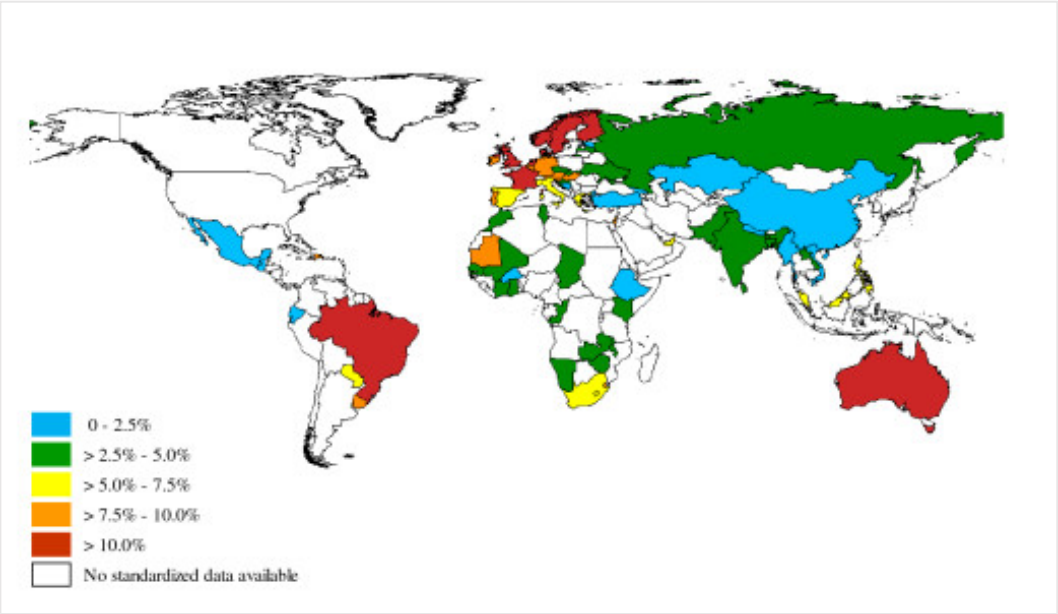
The Global Initiative for Asthma (GINA) has described asthma as "*a heterogeneous disease, usually characterised by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation*"[1].

Symptoms are often worse at night or on waking, and can be also triggered by exercise, exposure to irritants or allergens, weather changes or viral respiratory infections. These symptoms may vary in intensity, and they are usually reversible, either spontaneously or with the use of medication. Asthma is frequently associated with atopy, and can develop in both childhood and throughout the lifespan[1].

Asthma prevalence

It has been estimated that asthma affects as many as 334 million people worldwide[28]. The incidence and prevalence of the disease varies between geographical regions (Figure 1-A). According to the World Health Survey 2002-2003, the highest prevalence of asthma symptoms in adults was observed in Australia, Northern and Western Europe and Brazil[29].

Figure 1-A: Worldwide prevalence of clinical asthma.



Extracted from (29): To et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health. 2012. Figure 1, page 6. http://creativecommons.org/licenses/by/2.0. No changes made

In Australia, it has been estimated that in 2015, 2.4 million people (9.9% of the population) had a diagnosis of asthma, and that by 2020 this figure will increase to three million people[30].

Asthma burden

Mortality and health-related costs

A study analysing the WHO Mortality Database (1993-2012 period) from 46 countries, reported that the mortality rates in the age group 5-34 years old have plateaued since 2006[31]. According to the Australian Bureau of Statistics, the number of deaths in Australia due to asthma as an underlying cause was 421 and 455 people in 2015 and 2016, respectively. About 76.1% of those deaths occurred in people aged 65 years and older. Additionally, it was reported that in 2016, 69% of those deaths occurred in females (312 asthma-related deaths in females compared to 143 in males). Females aged 75 and over were three times more

likely to die from asthma than their males counterparts[32]. The total government costs for 2016-2019 are projected to be $4.0 billion[30].

Comorbidities

Asthma has been associated with the presence of several comorbidities, including mental health conditions (i.e. anxiety, depression), allergic rhinitis, rhinosinusitis, food allergies and anaphylaxis, gastro-oesophageal reflux disease (GORD), obstructive sleep apnoea (OSA) and obesity[1]. The concurrent management of this comorbidities is recommended in order to avoid further disease burden, with the consequent impairment in quality of life[1].

Severe asthma definition

Severe asthma is a subset of difficult-to-treat asthma, which is defined as asthma that remains uncontrolled despite treatment with high-dose inhaled glucocorticoids or other controllers, or that requires such treatment in order to be controlled. Patients with "difficult-to-treat-asthma" are regarded as having severe asthma when issues such as inhalation technique, adherence to treatment, and management of conditions and triggers that may be impacting on asthma control have been addressed, and therefore have been excluded as a contributing factor of symptoms[33].

The current definition of severe asthma, proposed by The “International European Respiratory Society/American Thoracic Society (ERS/ATS) Taskforce on definition, evaluation and treatment of severe asthma” defines severe asthma as “asthma which requires treatment with guideline suggested medications for GINA steps 4–5 asthma (high dose inhaled corticosteroids (ICS) and long-acting β2-agonist (LABA) or leukotriene modifier/theophylline) for the previous year or systemic corticosteroids for ≥50% of the previous year to prevent it from becoming ‘‘uncontrolled’’ or which remains ‘‘uncontrolled‘‘

despite this therapy''[33] Synonyms of this definition include severe refractory asthma or severe treatment-resistant (or refractory) asthma.

Asthma control relates to the extent to which certain characteristics are present in a patient. This includes an interrelationship between the presence, frequency and intensity of asthma symptoms, the presence (or risk of occurrence) of exacerbations that worsen prognosis, and/or the degree of lung function impairment[34].

The ERS/ATS taskforce guideline defines uncontrolled asthma with the presence of at least one of the following criteria[33]:

- Poor symptom control: scores in the Asthma Control Questionnaire[35] (ACQ) or Asthma Control Test (ACT)[36] >1.5 or <20, respectively. Alternatively, scoring as "not well controlled" in the National Asthma Education and Prevention Program (NAEPP)/GINA guideline. An example of a person with score higher that 1.5 in the ACQ would be someone that during the past week was: woken up at night a few times by asthma symptoms, woken up in the morning with mild symptoms, was limited slightly in daily activities due to symptoms, experienced a little shortness of breath and wheeze, had on average a least 1-2 puffs of SABA each day[35].
- Frequent severe exacerbation: defined as having two or more bursts of systemic corticosteroids (>3 days each) in the last 12 months.
- A serious exacerbation: defined as having at least one hospitalisation, Intensive Care Unit (ICU) stay or mechanical ventilation in the previous year.
- Airflow limitation: defined as FEV_1 < 80% after appropriate bronchodilator withhold and in the presence of a FEV_1/FVC below normal parameters.
- Controlled asthma that worsens with the reduction of the high doses of inhaled corticosteroids or systemic corticosteroids (or additional biologics).

Severe asthma shares some common features with milder forms of the diseases, including symptoms (breathlessness, wheezing, cough, chest tightness), and daily variability of these symptoms (worse at night and early in the morning). However, in people with severe asthma symptoms may be ongoing and more intense (e.g. unable to sleep due to asthma symptoms versus hardly ever waking up at night due to asthma). The variability of the symptoms during the day can also change towards a more persistent pattern due to the development of incomplete reversibility of airflow limitation. As such, in people with severe asthma breathlessness thorough exercise can be a more prominent feature than the exercise-induced bronchoconstriction observed in milder and moderate disease. The intensity and frequency of these symptoms contributes to the fact that exacerbations or lung attacks are common in people with severe asthma. These exacerbations or attacks can vary from having a mild increase in the normal frequency/intensity of symptoms, to that which requires medication with oral corticosteroids, hospitalisation or even treatment in intensive care units. As such, self-management education that promotes prompt recognition of worsening of symptoms and timely treatment is important. After an exacerbation or attack, it is also important that the patient's asthma management plan is reviewed by the treating physician. This would help to identify possible triggers and would guide the adjustment of treatment, and adoption of preventive measures.

Severe asthma prevalence

The prevalence of the disease has been estimated as 3.6 to 8.1% of the total asthma population according to studies carried out in The Netherlands[37] and Denmark[38], respectively (Figure 1-B). It is currently unknown what is the prevalence of severe asthma in Australia[39], but there are estimates of the prevalence of uncontrolled asthma. In a cohort of 2868 people

with current asthma aged 16 years old or older (57.1% female; median age group, 40-49 years), 22.7 and 23% of people respectively were categorised as having either "not well controlled" or "very poorly controlled" asthma, according to the ACT score [40].

Figure 1-B: Pictogram of severe asthma prevalence according to Hekking et al.[37]

High intensity treatment (orange + green + blue icons): 23.5% of all asthma patients; difficult to treat asthma (green + blue icons) (poor asthma control + high intensity treatment): 17.4% of all asthma patients; severe (refractory) asthma (blue icons = poor asthma control + high intensity treatment + good adherence + correct inhaler technique): 3.7% of all asthma patients. Purple icons: those asthma patients not on high intensity treatment (76.5%) Adapted from Severe Asthma Toolkit website: https://toolkit.severeasthma.org.au/ Used with permission.

Severe asthma burden

Mortality and health-related cost

Mortality rates in people with severe asthma have not been widely addressed. Data from a long-term severe asthma cohort on long-term oral corticosteroid treatment (20 years follow-up; n=52; 37.5% female; aged [mean ± standard deviation [SD] 49.9±18.9 years) showed that from the 26 deaths observed, 38% were attributable to a fatal asthma attack. The authors also reported that the median (interquartile range [IQR]) time in years until death was 9 (3-13) years, and that mortality predictors were baseline poor asthma control and the number

of exacerbations during the first year of follow-up[41]. Similarly, in a longitudinal study from the USA (2-years average follow-up) higher severity of asthma scores and poorer perceived asthma control scores were both significantly associated with an increased risk of mortality in adults with severe atshma[42]. In Australia, a case-series analyses from 2013 also identified as risk factors for asthma death living in rural and remote location, history of psychosocial issues (social disengagement, mental illness, living alone, being unemployed), history of smoking, drug and alcohol dependence, allergies, respiratory tract infections, inadequate treatment and delayed treatment[43]. Lastly, and as previously stated in this section, according to the 2016 Australian report on asthma-related mortality, females between 55 and 74 years old were almost twice as likely (1.8) to die from asthma than males of the same age, while women aged 75 and older were three times (3.05) more likely to die from asthma than their males counterparts*[32]. While the higher prevalence of asthma in women from adolescence[44] is a phenomenon that has been attributed to hormonal changes[45, 46], environmental and lifestyle (e.g. smoking, obesity) factors[46], it remains unclear why this mortality trend in females compared to males exists[47].

An important proportion of the cost and resources required to effectively manage asthma are expended upon these 3 to 8.1% of people with severe disease, whose poor control persists despite treatment with high doses of inhaled corticosteroids and additional controllers. It has been estimated that severe asthma accounts for 60% of the healthcare costs due to asthma, and that the cost per severe asthma patient is ten times higher than in those with mild disease[48].

* Data from the "Australian Bureau of Statistics (ABS) Customised Report 2016"

Health Status in Severe Asthma

Compared to the general asthma population, the prevalence of comorbidities in severe asthma is even higher[49, 50]. For instance, in a study carried out by Shaw and colleagues where patients from 11 European countries were included (n=421 severe asthma),the proportion of people suffering from GORD in the non-smoking severe asthma, smoking severe asthma and moderate-mild asthma groups were 47%, 64% and 21%, respectively[49]. Similarly, the scores in the anxiety and depression symptoms questionnaire in people with severe asthma were almost twice as high compared to participant with milder disease[49]. The increased burden that severe asthma has on patients, compared to milder forms of the disease, has been recently characterised by McDonald and colleagues using the treatable treat approach. This approach characterises patients with chronic airway diseases based on the presence of measurable and potentially treatable characteristics that have an impact on patients' prognosis (this approach will be further discussed in section 1.6)[51]. Using data from The Australasian Severe Asthma Web-based Database, McDonald and colleagues concluded that people with severe asthma presented a statistically significantly higher prevalence of treatable traits than people with non-severe disease, including being more prone to: exacerbations, obesity, OSA, depression, systemic inflammation, and GORD. The study also found that several of these traits were significantly associated with an increased risk of exacerbation, with depression, OSA, and previous exacerbation some of the better predictors of future exacerbations[52]. The risk of severe exacerbations is also higher in people with severe asthma. In the described study, 24% of participants with severe asthma had an emergency visit due to exacerbation in the last year compared to the non-severe group that had 3.9%, and 22.1% of patients with severe asthma had a hospitalisation compared to 2% in the milder group[52]. Similarly, Shaw and colleagues reported that people with severe

asthma and people with mild/moderate asthma had a mean of 2.5 and 0.4 exacerbations, respectively[49].

As a result of this high pulmonary and extrapulmonary morbidity burden, which includes associated comorbidities and symptoms, patients with severe asthma experience important impairments in their health-related quality of life (HRQoL) in comparison with less severe forms of the disease[14, 49]. Literature on patients' perspectives of the disease supports the findings of clinical research on health status, and extends this knowledge beyond the characterisation of clinical characteristics, highlighting the impact that the disease has on patients' lives, on their relatives and on their close community[53]. A systematic review evaluating patient's perspectives concluded that severe asthma was disempowering for patients and a threat to their identity and life roles[54]. The high personal toll also includes other spheres of their life including their employment performance[55], functional and activity limitations[56], and the burden of treatment (mostly associated with the frequent consumption of oral corticosteroids)[53, 54]. Regarding this last issue, it is important to note that in addition to the burden associated with the dependency on several medications for the control of their symptoms, people with severe asthma are at risk of developing several health complications related to the use of systemic corticosteroids. These can include metabolic disorders, depression, and bone density abnormalities[57].

1.2.2. Pathogenesis of severe asthma

Variable airflow limitation is one of the critical features of asthma, and results in the characteristic symptoms of wheezing, shortness of breath, coughing and chest tightness. The narrowing of the airway is the result of a complex interaction between key pathobiological features such as airway inflammation, airway hyper-responsiveness, airway remodelling and mucus hypersecretion. Asthma is a complex and heterogeneous condition, since the clinical

spectrum of patients and their responsiveness to medication varies according to the degree of the presence of the mentioned pathophysiological features[1].

Severe asthma presents the same pathophysiological mechanisms described in asthma: airway inflammation, airway hyperresponsiveness and airway remodelling. The severity of the symptoms and non-response to traditional pharmacological measures are due to a more persistent, heterogeneous and intricate combination of inflammatory mechanisms and to the pathophysiological features resulting from these, including airway remodelling with its consequent incomplete reversibility of airflow limitation[58].

Inflammation

The characterisation of the inflammatory phenotypes in severe asthma has been recognised as a clinically relevant issue, since these will determine the response to different treatments, including corticosteroids and biological agents, and the possible effects on physiological characteristics (e.g. mucus production and remodelling). Recognised inflammatory phenotypes are:

- Persistent type-2 inflammation: The type-2 inflammation is characterised by the presence of cytokines (interleukin (IL)-4, -5 and -13) produced by type 2 helper T (T_H2) cells or innate lymphoid cells type 2 (ILC2) as an immunologic response to allergens and non-allergic agents, including infectious agents and irritants. IL-13 plays a role in promoting hyper-responsiveness, remodelling and mucus production. IL-4 and -5 drive the production of Immunoglobulin E (IgE) and eosinophils, respectively. These cytokines are also involved in the activation of mast cells, which also induce airway smooth-muscle contraction, remodelling, mucus secretion and an amplification of the inflammatory process[34]. There is usually an allergic component associated with this inflammatory type. Nevertheless, unlike in milder types of asthma, in severe

asthma the mechanisms driving the type-2 inflammatory process may not be necessarily related to IgE production nor allergy[59]. Type-2 inflammation is also associated with airway eosinophilia (≥3% of eosinophils in sputum sample[60]), which is considered a marker of greater disease severity[61], including poorer lung function and near-fatal asthma attacks[59].

The type-2 inflammatory pattern is the most prevalent inflammatory mechanism in asthma and in severe asthma[59]. A clearer clinical difference between asthma severities in regards of this phenotype, is that in milder types of asthma people with the type-2 inflammatory phenotype are responsive to the use of glucocorticosteroids, and therefore the inflammatory process resolves after treatment[34]. In severe asthma, however, the persistence of this inflammatory pattern (i.e. sputum eosinophilia) indicates a suboptimal response to glucocorticosteroids, which may be due to the impairment of the mechanisms that regulate the inflammatory reaction[58]. The clinical importance of this inflammatory pattern in relation to treatment with monoclonal antibodies will be discussed in the treatment section (Section 1.2.4).

- Neutrophilic inflammation (*Non-type 2 inflammation*): this type of inflammation is less well characterised in asthma both in terms of its mechanism and its clinical implications. However, it is an inflammatory pattern that has been associated with more severe disease[62], less response to corticosteroids and lower lung function[34]. It has been proposed that relevant mechanisms driving this inflammation are Type-1 T_H1 cells which produce interferon gamma (IFN)γ, or IL-17-producing T_H17 cells. Sputum neutrophilia is defined as the presence of ≥60% neutrophils in induced sputum samples[63].

- Mixed inflammation: this is a less common type of inflammation, and it is defined by the persistence of a combination of eosinophilia and neutrophilia in sputum. This inflammatory pattern has been associated with higher disease burden and airflow limitation. The cytokines involved are IL-6 and IL-17, which concurrently promote the production of T_H2 and T_H17 cells resulting in the presence of both inflammatory patterns[34].
- Paucigranulocytic (An absence of inflammatory granulocytes): this pattern is defined by the absence of eosinophilia and neutrophilia in sputum, and it is also less common than the type 2 and non-type 2 inflammatory phenotypes[34].

Airway hyper-responsiveness

Airway hyper-responsiveness is a hallmark of asthma and defined as an increased reactivity of the smooth muscle in the airway wall to different exogenous and endogenous stimulus (e. g. allergens, virus or exercise) that results in airway narrowing. These exposures trigger an exaggerated release of inflammatory mediators in the airway (mostly type-2 inflammatory mediators such as IL-13 and mast cells) which in addition to causing inflammation and airway oedema, also act on local nerves and smooth muscle cells of the bronchi prompting bronchoconstriction and the consequent airway narrowing[64].

Airway remodelling and mucus hypersecretion

Airway remodelling and mucus hypersecretion can also be present in a patient's airways and are usually more intense in patients with severe asthma. These structural changes are driven by repeated airway insults and chronic inflammation associated with asthma, which may alter the normal airway repair process[59]. Remodelling of the airway wall includes subepithelial fibrosis[65], increased airway smooth muscle (because of these cells' hypertrophy and hyperplasia which leads to increased thickness of the airway wall), and increased blood

vessels in airway walls. These changes, which have been associated with the presence of persistent eosinophilic inflammation[66, 67], airway hyper-responsiveness[68] and bronchoconstriction[65], may result in incomplete reversibility of the characteristic airway obstruction and cause fixed airflow limitation, contributing to the long-term lung function decline[68]. Additionally, the alteration of the mucus secreting mechanisms leads to mucus hypersecretion[68] and the concomitant build-up of mucus in the airway. This also contributes to airflow limitation.

1.2.3. Diagnosis and classification

The diagnosis of asthma is achieved after performing a physical assessment and taking a thorough history in relation to the presence and patterns of respiratory symptoms. It is objectively assessed by the demonstration of variable expiratory airflow limitation, ultimately through assessment of pre- and post-bronchodilator spirometry, and by the assessment airway hyperresponsiveness through bronchial provocation tests, either using direct bronchoconstriction challenges, such as methacholine, or indirect challenge using mannitol or hypertonic saline[1]. Pre/post bronchodilator spirometry findings consistent with asthma in adults are an improvement of baseline values in FEV_1 and/or FVC higher than 12% and 200mL at least 15 minutes post administration of 200-400 mcg of short acting β2 agonist bronchodilator treatment[1, 3].

The ERS/ATS guidelines on severe asthma recommend a systematic approach for the diagnosis of the condition[33]. This approach includes:

Confirming asthma diagnosis and identify difficult-to-treat asthma: through a thorough history of asthma symptoms, triggers (environmental and occupational factors), pulmonary function test, and identification and management of contributing factors. Comorbidities (such as OSA, GORD, mental health problems), aggravating factors (such as smoking,

occupational exposure to irritants, obesity, allergens exposure), and disease management issues (such as availability and adherence to treatment, inhaler technique) are contributing factors that need to be identified and addressed before considering a severe asthma diagnosis.

Differentiate severe asthma from milder asthma: after contributing factors have been addressed, severe asthma is diagnosed in people who have been using high intensity treatment in the previous year (high dose inhaled corticosteroids plus either LABA or leukotriene modifier/theophylline, or systemic corticosteroids for over 50% of the last year) in order to avoid their asthma becoming uncontrolled.

Is severe asthma controlled or uncontrolled?: Uncontrolled asthma is defined by the presence of at least one of the following parameters: ACQ[35] or ACT[36] scores of >1.5 or <20 respectively, or by frequent (≥2) severe exacerbations in the last year with use of oral corticosteroid, or by serious exacerbation (hospitalisation, ICU stay or mechanical ventilation) in the last year, or by airflow limitation (FEV1 < 80%) after appropriate bronchodilator withhold. People with uncontrolled asthma while on high intensity treatment (as described above) and in whom aggravating factors have been addressed, or those people with controlled or partially-controlled asthma whose control worsen at the reduction of corticosteroid treatment, are considered as having severe asthma.

The heterogeneity of severe asthma is demonstrated by its variation in clinical presentations, pathobiological, physiological characteristics and outcomes. An example of this was reported by authors in the Severe Asthma Research Program, who proposed to classify adult patients with asthma into five different clusters of the disease predominantly based on clinical characteristics[69]:

- People with early onset atopic: They identified three groups of mild (Cluster 1), moderate (Cluster 2) and severe asthma (Cluster 4), according to reductions in lung function, medication needs, and frequency of exacerbations. This is the most easily recognised asthma phenotype which usually responds well to oral corticosteroids. These clusters are associated with type-2 inflammation (mediated by IgE and eosinophils).
- A late-onset, obese and non-atopic cluster (Cluster 3): which is most common in older females displaying moderate FEV_1 baseline reductions and frequent oral corticosteroid use to control exacerbations. This cluster has been associated with persistent type-2 eosinophilic inflammation[70].
- Adults with late-onset but long-duration and with very severe asthma symptoms (Cluster 5), who are likely non-allergic, and that have features of fixed airflow limitation or decreased reversibility.

Both, Cluster 4 and 5 fulfil the criteria of the severe asthma definition, and they mostly differ in their allergic status, and in their baseline lung function parameters and reversibility patterns.

In addition to the reported cluster classification[69], asthma can be also classified according to its inflammatory phenotype. Some identified phenotypes include[71]: allergic asthma (driven by type-2 inflammation/IgE), eosinophilic asthma (type-2 inflammation/IL5) and non-eosinophilic asthma. The relevance of this classification lies in the potential ability to predict response to asthma treatment, such as corticosteroids, monoclonal antibodies or macrolides.

The Centre of Excellence in Severe Asthma has recently developed a checklist to aid with the characterisation and diagnosis of severe asthma[72] (Table 1-1).

Table 1-1: Severe asthma checklist: for diagnosis and classification.

Clinical question	*Assessment*
Has the diagnosis been confirmed?	Clinical history and objective evidence of variability on symptoms and lung function.
Is it severe?	Positive history of: poor control, airflow obstruction, frequent exacerbations or life-threatening episodes
Is treatment optimal?	Treatment with: high dose of ICS and LABA or other controller, or moderate dose ICS and ≥2 controller
Are self-management skills optimal?	i.e.: inhaler technique, adherence, monitoring, written action plan.
Are trigger factors identified and managed?	i.e.: allergens, cigarette smoke, emotional stress, respiratory viral infection.
Is co-morbidity identified and managed?	i.e.: sino-nasal disease, dysfunctional breathing, OSA, Anxiety and/or Depression, GORD, obesity.
What is the pattern of airway inflammation?	i.e.: Eosinophilic (sputum assessment, FeNO, blood eosinophils), Neutrophilic (sputum assessment).
What is the optimal individualised management plan?	Developed with evidenced based interventions that target clinical issues identified during a systematic and multidimensional assessment, in partnership with patients and clinicians, considering patient preferences.

From (69) https://www.severeasthma.org.au/severe-asthma-checklist/. ICS: Inhaled corticosteroids; LABA: long-acting β2 agonist; OSA: obstructive sleep apnoea; GORD: gastro-oesophageal reflux; FeNO: fractional exhaled nitric oxide levels. Extracted from the Severe Asthma Toolkit. Used with permission.

1.2.4. Treatment

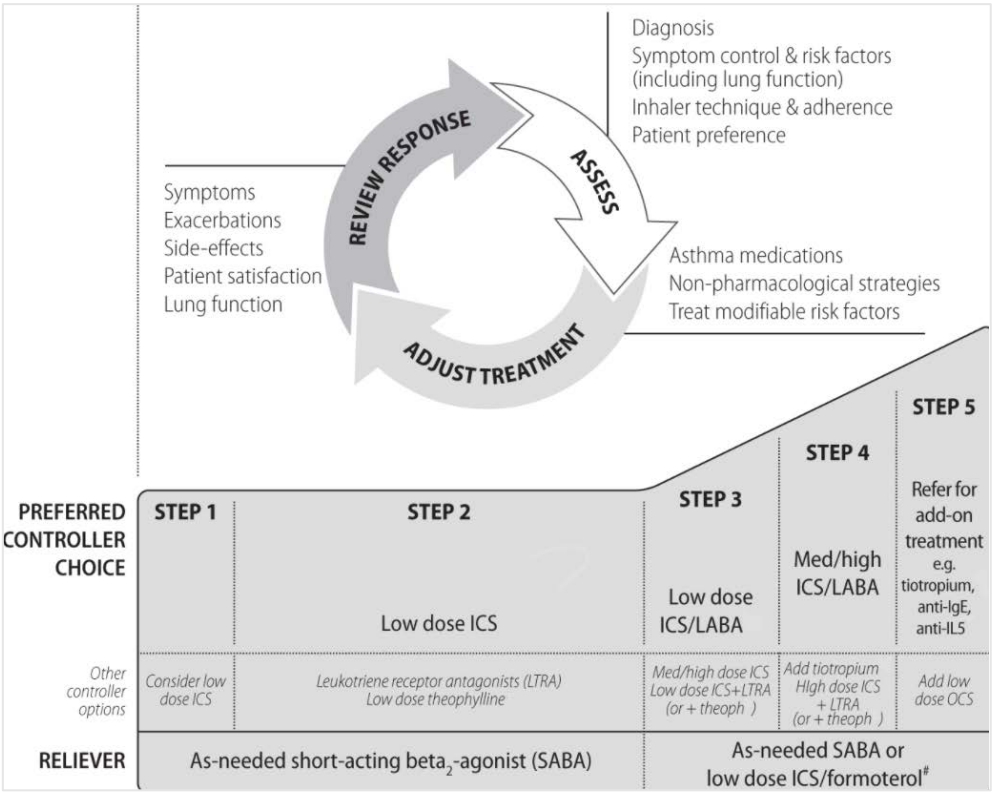
Asthma treatment

Long-term asthma management focuses on achieving good symptom control, minimising future risk of exacerbation, fixed airflow limitation and treatment side-effects. This is achieved through the continuous assessment of: treatment prescription and adherence to

therapy, and with appropriate self-management education (including correct use of inhalers and written-action plans, self-monitoring of symptoms, and avoidance of triggers) There is increasing recognition of the importance of developing a patient-health care provider partnership, to achieve better treatment outcomes[1].

Pharmacotherapy is escalated based on symptoms, risk of exacerbations and lung function, and back titrated as these outcomes improve (stepped approach). Asthma pharmacotherapy includes inhaled corticosteroids and bronchodilator therapy[1]. Figure 1-C presents the Global Initiative for Asthma stepwise approach for adjusting treatment in adults.

Figure 1-C: Step-wise approach to control symptoms and minimise future risk.



Reproduced from (1): Global Strategy for Asthma Management and Prevention, 2018. Box 3-5, Page 44. Used with permission. Information related to children has been omitted. # Low dose ICS/formoterol is the reliever medication for patients prescribes low dose budesonide/formoterol or low dose formoterol maintenance and reliever therapy.

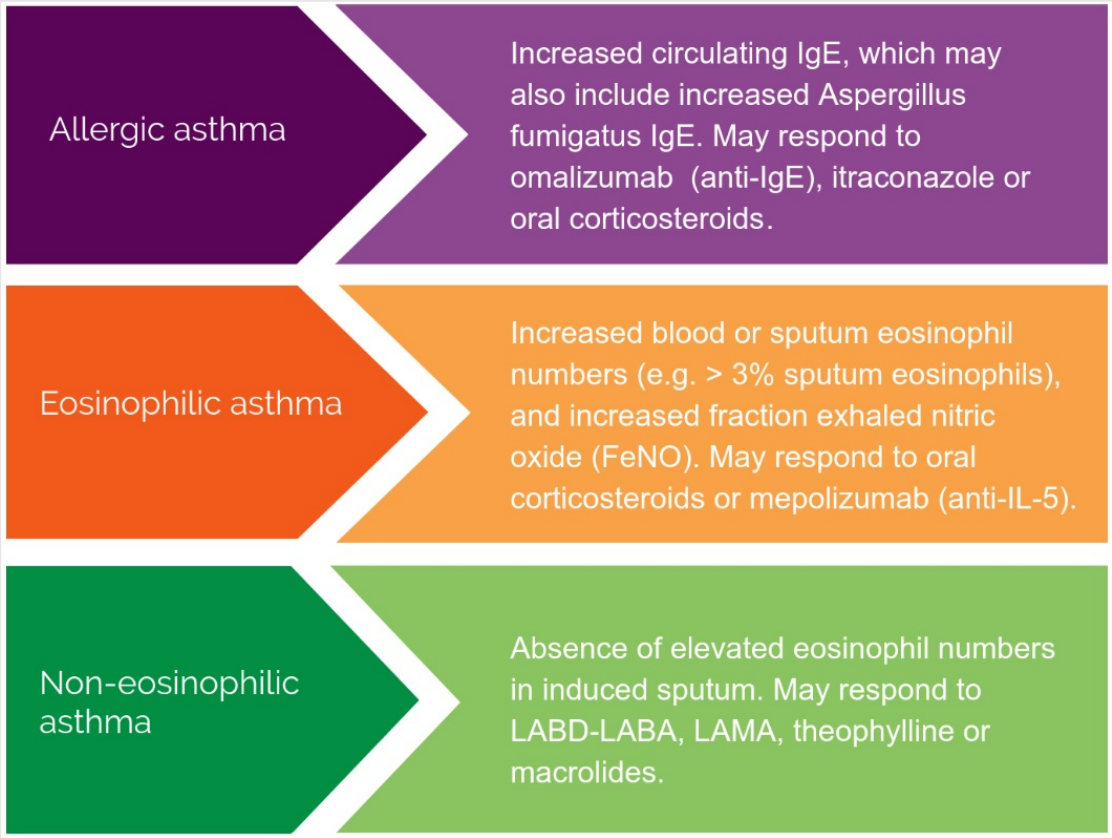
Severe asthma treatment

The management of severe asthma should involve a multidisciplinary team[73], and should include the systematic assessment and management of airway, comorbidities and risk factors[74]. Referral to tertiary care and severe asthma clinics are paramount for the assessment of symptoms, biological characteristics, exposure to triggers and associated comorbidities in severe asthma[74] (Refer to Table 1.1 in section 1.2.3).

In terms of medication targeting the airway, pharmacotherapy moves away from the stepped approach, and focuses on more individualised therapy targeted to specific traits identified in patients. By definition, patients with severe asthma have already reached maximum treatment levels as defined in the step approach. Patients with severe asthma are commonly treated with high dose inhaled corticosteroids (≥1000 mcg of beclomethasone or equivalent) and LABA (GINA step 4). Add-on therapies (GINA step 5) such as leukotriene receptor antagonists, theophylline, long-acting anti muscarinic antagonists (LAMA), and monoclonal antibody therapies could be prescribed and reassessed by a respiratory physician if required[33]. The characterisation of the asthma inflammatory phenotype guides the prescription of monoclonal antibody therapies[75], such as anti-IgE (Omalizumab) for severe allergic asthma, and anti-IL5 (Mepolizumab) for eosinophilic severe asthma. Treatments for non-eosinophilic asthma may include LABA, LAMA, theophylline or macrolides[76] (Figure 1-D).

Bronchial thermoplasty is a non-pharmacological measure aimed at reducing the bulk of airway smooth muscle and thereby reducing the potential for airway constriction. Its use in severe asthma should follow an Institutional Review Board-approved systematic registry or clinical study[33]

Figure 1-D: Choice of treatment according to inflammatory phenotypes in severe asthma.



Extracted from the Severe Asthma Toolkit website: https://toolkit.severeasthma.org.au/ Used with permission. IgE: Immunoglobulin E; LABD: long-acting bronchodilator; LABA: long-acting β-agonist, LAMA: long-acting muscarinic antagonist.

Comorbidities including sino-nasal disease, anxiety and depression disorders, GORD and obesity, are common in severe asthma[52]. Their assessment and treatment can result in improvements in asthma features and quality of life of patients[73].

The assessment and management of risk factors including smoking, allergens, and others triggers, and poor self-management should also be considered. The GINA guidelines recommend that people with asthma should engage in regular physical activity for its general health benefits, and as a coadjutant for the management of obesity[1]. Further analysis of this rationale will be provided in Chapter 2.

The participation of patients in pulmonary rehabilitation programmes has been less widely studied in asthma compared with COPD or bronchiectasis[77-80]. Nevertheless, it has been suggested that exercise training has several benefits on asthma control, exercise capacity[81-84], airway inflammation[85] and quality of life[81, 86]. Studies assessing people with moderate to severe asthma, have also found that exercise training may have a positive impact on systemic inflammation, airway hyper-responsiveness, and quality of life. A positive impact of exercise training on asthma control and airway inflammation has also been reported in patients with worse asthma control[82, 87]. Despite this evidence, studies evaluating the inclusion of patients with severe asthma in pulmonary rehabilitation programmes are scarce[88]. The fact that severe asthma patients are less likely to be referred to these programmes (compared with patients with mild to moderate asthma) may be secondary to this scarcity. It is worth nothing however, that the only recommendation in the GINA guidelines regarding the referral to pulmonary rehabilitation programmes, is made for patients with features of asthma and COPD overlap[1]. Despite this, the current Official ATS/ERS Statement on Pulmonary Rehabilitation states that there is now more evidence to support the inclusion of patient with asthma in pulmonary rehabilitation programmes[89].

1.3. Chronic Obstructive Pulmonary Disease (COPD)

1.3.1. Definition, prevalence and disease burden

Definition

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD is defined as a "…*common, preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases*"[2].

COPD is a serious and progressive lung disease, characterised by airflow limitation that is not fully reversible following bronchodilator medication. COPD is typically characterised by two respiratory pathophysiological features: small airway disease and parenchymal destruction[2]. The main respiratory symptoms of COPD include shortness of breath, initially with strenuous activities and later with minimal or no exertion, as well as cough and/or chronic bronchitis, and wheeze. Additionally, it is associated with significant extrapulmonary morbidity. Chronic respiratory symptoms may precede the development of airflow limitation, and they may also exist in absence of altered spirometric values[90]. Exacerbations, or the acute worsening of symptoms resulting in escalation of therapy, are also common in COPD, especially as airflow limitation increases[91]. According to severity, exacerbations could be mild, moderate and severe, with severe being those cases when patients require hospitalisation or visits the emergency room. Severe exacerbations are associated with poor prognosis and increased mortality[92].

Tobacco smoking is the predominant cause of COPD in the developed world. Other causes that have been associated with COPD include exposure to biomass fuel, outdoor and occupational air pollution, some respiratory infections during childhood, and chronic asthma. However, COPD also occurs in non-smokers or without the presence of these risk factors, indicating that genetic[93] and/or other environmental factors may be involved[94].

Prevalence

Worldwide, the global prevalence of COPD in 2010 was estimated as 11.7%, with 384 million COPD cases[95]. These estimates come from large scale studies, such as the Burden of Obstructive Lung Disease[94], which used standardised methodologies, including spirometry, for diagnosis. In Australia, between 2006 and 2010 the prevalence of GOLD stage II or higher COPD (FEV_1 <80% predicted and lower) was 7.5% in people over 40 and 29.2% in people older than 75[96].

In Australia, the expenditure associated to COPD management in 2008 was $8.8 billion. Costs related to productivity loss due to un-employability, absenteeism and premature death accounted for 77% of this figure. Direct health care expenditure accounted for 10% or $0.9 billion of this number[97].

Burden

Mortality and health-related cost

The Global Burden of Disease Study[98] reported that in 2012 three million deaths, or 6% of global mortality, were due to COPD, positioning the disease as the fourth leading cause of death worldwide[99]. When compared to international figures, the Australian rate of death for COPD is lower than in other developed countries[100]. For instance, according to the World Ranking of COPD mortality rates for the period 2007-2011, the mortality rates for Australia, the United Kingdom (UK) and USA were approximately 80, 120 and 140 deaths per 100,000 population, respectively[100]. Nevertheless, it still represents an important public health problem, especially in older people, and among people living in socioeconomically disadvantaged areas. In 2013, COPD accounted for 4.4% of all deaths among people of 55 years old and older, positioning it as Australia's fifth leading cause of death. In 2007-2011, the median age of death due to COPD was 81 years[101].

Comorbidities

COPD is associated with significant extrapulmonary comorbidities that can worsen disease severity. Common systemic effects include cardiovascular disease, diabetes mellitus and metabolic disorders, sleep disorders, skeletal muscle dysfunction, bone density alterations, weight loss and cachexia, anxiety and depression and progressive activity limitation due to breathlessness[2, 102-104]. People with COPD tend to rate their health status worse than people without the disease. According to the Australian Health Survey, 22% of people with COPD aged 45 years or over rated their health status as poor, compared to 6% of age-matched participants without COPD[105].

1.3.2. Pathogenesis of COPD

The defining feature of COPD is persistent expiratory airflow limitation. Additional pathophysiological features include gas trapping and gas exchange abnormalities secondary to parenchymal tissue destructions, mucus hypersecretion, pulmonary hypertension, exacerbations and systemic morbidity. Important processes underpinning these pathophysiological changes include chronic inflammation, oxidative stress and protease/antiprotease imbalance. Persistent airflow limitation and parenchymal tissue destruction (resulting in emphysema) are the result of inflammatory and structural changes occurring in the airways, lung parenchyma, and pulmonary vasculature[106]. The narrowing of the small airways is caused by an amplified chronic inflammatory response to exogenous irritants (i.e. cigarette smoke, smoke from biomass fuel), a response is in part genetically determined. The inflammatory cells that play a major role in COPD are macrophages, neutrophils and T and B lymphocytes. The amplification of the inflammatory process and the induction of structural changes leading to the narrowing of the small airways and destruction of the lung parenchyma are closely related to inflammatory mediators released by these

inflammatory cells. Some of these inflammatory mediators include pro-inflammatory cytokines (such as tumour necrosis alpha (TNF-α), IL -1β and IL-6) and growth factors (such as transforming growth factor beta [TGF-β])[107]. Some patients will also present an increased number of eosinophils, T_H2 and ILC2 cells, especially in those where clinical characteristics of asthma are overlapping with COPD[108]. An imbalance in the oxidative and antioxidant mechanisms[108, 109] is also closely related to persistent inflammation and also play an important role in the pathogenesis of COPD. Oxidants are generated by exogenous irritants (i.e. smoke) and then released as a product of the abnormal inflammatory process[108, 109].

In addition to chronic inflammation, the destruction of the lung parenchyma is also due to an imbalance in the production of proteases (that break-down the lung connective tissue)[109] and antiproteases (that counteract this break-down)[110]. The increased production in proteases, derived from inflammatory and epithelial cells, mediates the destruction of the elastin in the lung parenchyma, contributing to the development of emphysema[110].

Peribronchiolar and interstitial fibrosis is another pathological feature that is secondary to the inflammatory process and to the repeated injury of the airway, and that negatively impact on the development of small airways disease.

Generally, the inflammatory and structural changes observed in the airways worsen with disease severity and persists after smoking cessation[108]. An important physiological abnormality in COPD, is hyperinflation[111]. Static hyperinflation (increase of end-expiratory lung volume) is the result of the reduced lung elastic-recoil due to emphysema in addition to the peripheral expiratory airflow limitation. Dynamic hyperinflation occurs when air is trapped within the lungs with each successive breath due to increased respiratory demands (i.e. exercise, exacerbations), reducing the inspiratory capacity and altering the contractile

properties of respiratory muscles. As such, it has an important role in dyspnoea and reduced exercise capacity, and physical activity engagement[112-114].

Elevated levels of systemic inflammation are reported to be prevalent in some COPD patients[115, 116] and has been recognised as a contributor to the increased burden of comorbidities found in this condition[117].

1.3.3. Diagnosis and classification

In their 2017 update, the GOLD guidelines recommend considering a clinical diagnosis in patients presenting with dyspnoea, chronic cough or sputum production, and/or a history of exposure to disease risk factors[2]. The diagnosis is confirmed by spirometry. A post-bronchodilator FEV_1/FVC <0.7 ratifies the presence of persistent airflow limitation[2]. The severity of airflow limitation, or GOLD classification, is presented in Table 1-2.

Table 1-2: Classification of severity of airflow limitation in COPD.

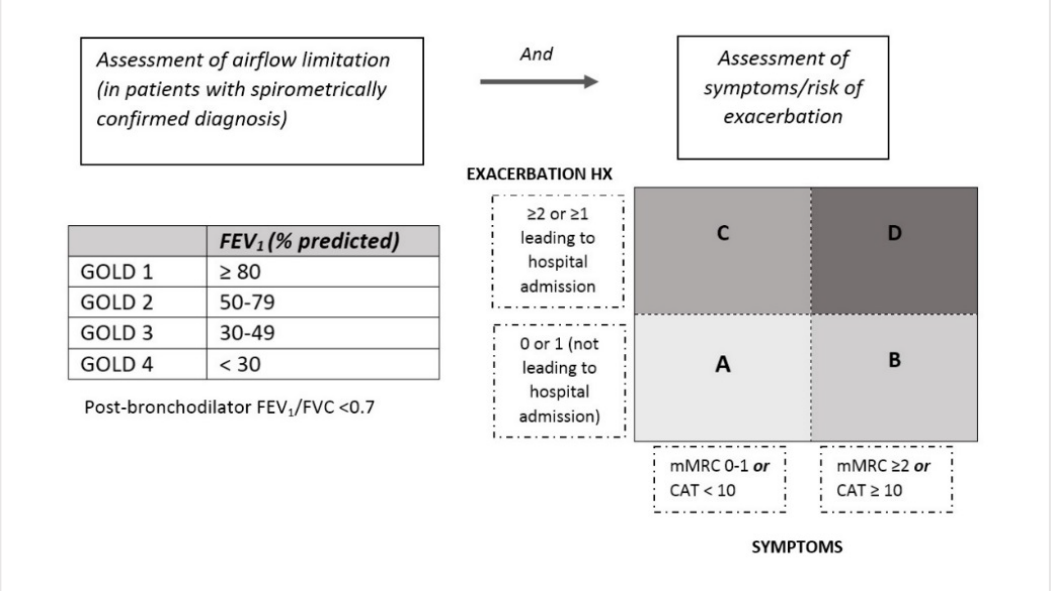
		In patients with post-bronchodilator FEV_1/FVC < 0.7
GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4	Very Severe	$FEV_1 < 30\%$ predicted

From (2)

In order to address the multiple dimensions of the diseases, in their 2011 document the GOLD strategy implemented the "ABCD assessment tool", which aimed to categorise patients based on their severity of airflow limitation (as per Table 1.2) but also taking into account the domains of symptoms (measured with the COPD Assessment Test [CAT™]), breathlessness (measured with the modified Medical Research Council [mMRC[118]]), and risk of exacerbation

(according to previous exacerbations or hospitalisations due to exacerbations). However, due to some limitations noted, the 2017 GOLD guideline now proposes a refined version of the ABCD assessment tool, in which the A-D categorisation is derived exclusively from patients' symptoms (measured either with CAT™ or mMRC) and their exacerbation history. Spirometric classification (Gold 1-4) remains the cornerstone for diagnosis and management, but it is not considered for the ABCD classification. For instance, with this refined approach, a patient with a FEV_1% predicted of 35, a CAT of 9 (i.e. mild clinical impact) and a severe exacerbation in the last year will be considered GOLD grade 3 - group C (number and letter). This new assessment approach highlights the importance of symptoms and exacerbation risk to effectively guide treatment in COPD, while acknowledges that the FEV_1 is of limited utility when making treatment decisions for individualised patient care[2]. Figure 1-E explains the redefined ADCD approach[2].

Figure 1-E: The redefined ABCD assessment tool.



Reproduced from (2): Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018. Figure 2.4, page 33. Used with permission.

Additional assessment tools proposed in the 2017 GOLD guidelines include blood eosinophils count and assessment of comorbidities. Despite acknowledging that further research is needed[2], the use of blood eosinophils count as a surrogate of eosinophilic airway inflammation[13] appears to have a predictive role as a marker of exacerbation risk and on the effect of inhaled corticosteroids for exacerbation prevention[119, 120]. This is mostly true in patients displaying an increased eosinophilic inflammatory pattern of the airway (T_H2 inflammation), a pattern associated with asthma-COPD overlap[108, 121] and therefore, with increased treatment response to corticosteroid therapy[122, 123].

In terms of comorbidities, multidimensional assessment screening for comorbidities and risk factors have been proposed as a way to identify pulmonary and extrapulmonary treatment targets that aim to guide the design of personalised disease management[124, 125]

1.3.4. Treatment

The main goals of stable COPD management are to reduce symptoms and to reduce frequency and severity of exacerbations. Additional goals are to improve health status and exercise tolerance, to prevent disease progression, and to reduce mortality[2]. Therapeutic interventions that play and important role in the management of the disease include pharmacologic therapy such as bronchodilators, inhaled corticosteroids, vaccinations, and non-pharmacological interventions. These include self-management interventions, pulmonary rehabilitation, increasing levels of physical activity, and identification and reduction of risk factors, particularly smoking, which is one of the risk factors that has the greatest impact on disease aetiology, outcomes and progression[2]. Pharmacological treatment is recommended according to assessment of symptoms and risk of exacerbations (ABCD tool), and it is based on escalation and de-escalation of medication according to these outcomes. Table 1-3 shows the pharmacological treatment according to A-D assessment.

Table 1-3: Pharmacological approach according to ABCD assessment.

Group	*Preferred treatment*	*Effects to be evaluated*	*Alternative treatment*	*Further actions*
A	SABA or LABA	Dyspnoea	-	-
B	LABA or LAMA	Dyspnoea	LAMA + LABA	-
C	LAMA	Persistent exacerbation	LAMA + LABA* or LABA + ICS	-
D	LABA + LAMA LABA + ICS^ LAMA#	Persistent exacerbation	LABA+LAMA+ICS or LABA+ICS Macrolide	Roflumilast (FEV_1 <50% predicted+ chronic bronchitis) Macrolide (in former smokers)

*From (2).SABA and LABA: short and long-acting bronchodilator; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroid. *preferred treatment. ^ For patients with findings suggestive of asthma-COPD overlap and/or high blood eosinophil count. # In case a single bronchodilator is chose as initial treatment. Further actions are considered for patients who still have exacerbations after treatment with LABA+LAMA+ICS.*

The participation in pulmonary rehabilitation programmes is considered a core component of COPD management, and it is associated with major improvements in outcomes commonly encountered in COPD patients, such as dyspnoea, exercise capacity, symptoms, skeletal muscle dysfunction, and health status. Pulmonary rehabilitation also leads to reduced health care utilisation in patients with COPD[2, 89, 126]. Exercise training is an important part of pulmonary rehabilitation. It commonly includes an endurance training component; most commonly in the form of cycling or walking[127]; and a resistance or strength training component[128], targeting the upper and lower limb muscles. In addition to exercise training, pulmonary rehabilitation programmes have an important educational component aimed at:

- the recognition of symptoms,
- promotion disease management knowledge and self-management skills,
- the provision of education and encouragement in health behaviour change aimed at the adoption of healthier behaviours (i.e. physical activity) and reduction of risk factors (i.e. smoking)[89].

Physical activity as a non-pharmacological intervention will be discussed in more detail later in this chapter.

Additional non-pharmacological strategies include influenza vaccination for all patients >65 years old, long term oxygen therapy for hypoxic patients when severity and exacerbation frequency increases, and education in end of life and palliative care[2] options.

1.4. Bronchiectasis

1.4.1. Definition, prevalence and disease burden

Definition

Bronchiectasis is a chronic pulmonary condition defined as an abnormal and permanent dilation and distortion of the bronchi and bronchioles, resulting from chronic inflammation of the airways, and leading to progressive destruction of the bronchial walls and lung parenchyma. This permanent bronchial damage can lead to a vicious cycle of bacterial infections and impaired mucus clearance[129]. Airflow limitation and cough with mucus hypersecretion are its main clinical features, but the condition is usually also associated with other impairments and comorbidities such as chronic rhinosinusitis, fatigue, dyspnoea, haemoptysis and thoracic pain[130].

The aetiology of bronchiectasis is multifactorial and may be difficult to ascertain. Common causes include post-infection (both in childhood and adulthood), different airway insults such as impairment of the immune system leading to repeated infections, and congenital causes (Table 1-4). Historically, a major differentiation has been made between cystic fibrosis and non-cystic fibrosis related bronchiectasis. Cystic fibrosis is a recessive genetic condition that affects a number of organs, especially the lungs and digestive system. In terms of this lung disease it has clinical characteristics that also include chronic cough, sputum production, repeated chest infections, and bronchiectasis results. Current bronchiectasis guidelines however, have emphasised the terminological differentiation between bronchiectasis and bronchiectasis due to cystic fibrosis since the latter is a different disease both in pathophysiology and in its treatment features[131].

Table 1-4: Prevalence of common aetiological causes of bronchiectasis.

	Aliberti et al.[132] (n=1145)	***Chalmers and Hill.[133] (review)***	***Shoemark et al.[134] (n=165)***
Idiopathic	34	30–53%	26
Post severe infection	26	33–42%	32
Connective tissue disease	8	3–6%	2
Immunodeficiency	5	1–8%	7
ABPA	4.9 (asthma 3.2)	1–7% (associated with asthma)	8
Ciliary dysfunction	1.8	1–2%	10
Congenital	0.5	<1%	-
Inflammatory bowel disease	2.2	1–2%	3

ABPA: allergic bronchopulmonary aspergillosis

Prevalence

The global prevalence of bronchiectasis is not accurately known, but studies from the USA[135] and UK[136] have found an increased incidence of the condition compared to previous data. For instance, Quint and colleagues reported that between the 2004-2013 periods, the prevalence of bronchiectasis in the UK increased from 301.2/100,000 to 485.5/100,000 in men, and from 350.5/100,000 to 566.1 in women[136]. Several publications have also reported older populations, especially females, are at a higher risk of developing bronchiectasis[23, 135, 136]. There are little data available for the overall prevalence or incidence of bronchiectasis in Australia[23]. However, studies have shown that the prevalence of bronchiectasis is disproportionately high in indigenous populations from Australia and New Zealand[137-139]. In Australia, a study of Central Australian Indigenous children found a prevalence of 1.5 % of

the population, while no case of bronchiectasis was found among non-indigenous children[137]. Disadvantaged socioeconomic conditions and poor access to health care services, including timely access to antibiotic treatment and vaccination programmes (such as influenza and pneumococcal vaccination programmes), are among causes of these disparities[138]

Burden

Mortality and health-care use

There are scarce data reporting on mortality in bronchiectasis. Quint and colleagues reported an age-adjusted mortality rate in the UK (2004-2013 period) of 1437.7 per 100,000[136]. In Australia, the age-standardised mortality rate for bronchiectasis between 2001 and 2013 has remained relatively steady at less than 2.2 deaths per 100,000 population[100]. This figure includes bronchiectasis both as the underlying or associated cause of death. In terms of health care use, bronchiectasis was the principal and secondary diagnosis of 5,010 and 9,018 hospitalisations respectively in the 2006-2007 period in Australia. In agreement with international data, hospitalisation for women were twice as high compared to men, a trend that becomes more evident in older age groups[23]. The economic burden of bronchiectasis has been suggested to be similar to COPD, and that this increases as measures of severity, such as exacerbations and hospitalisations, deteriorate[131].

Health status

Individuals with bronchiectasis suffer from significant respiratory morbidity and poor HRQoL[140-142]. People with bronchiectasis share similar clinical characteristics with people with moderate to severe COPD and severe asthma, such as increased dyspnoea, impaired exercise capacity, and frequent exacerbations. In addition, bronchiectasis can often overlap with these diseases, worsening its severity[5, 20-22]. For instance, Martinez-Garcia et al. reported that the prevalence of bronchiectasis in a cohort of 201 patients with COPD GOLD 2-4 was 57.2%, and

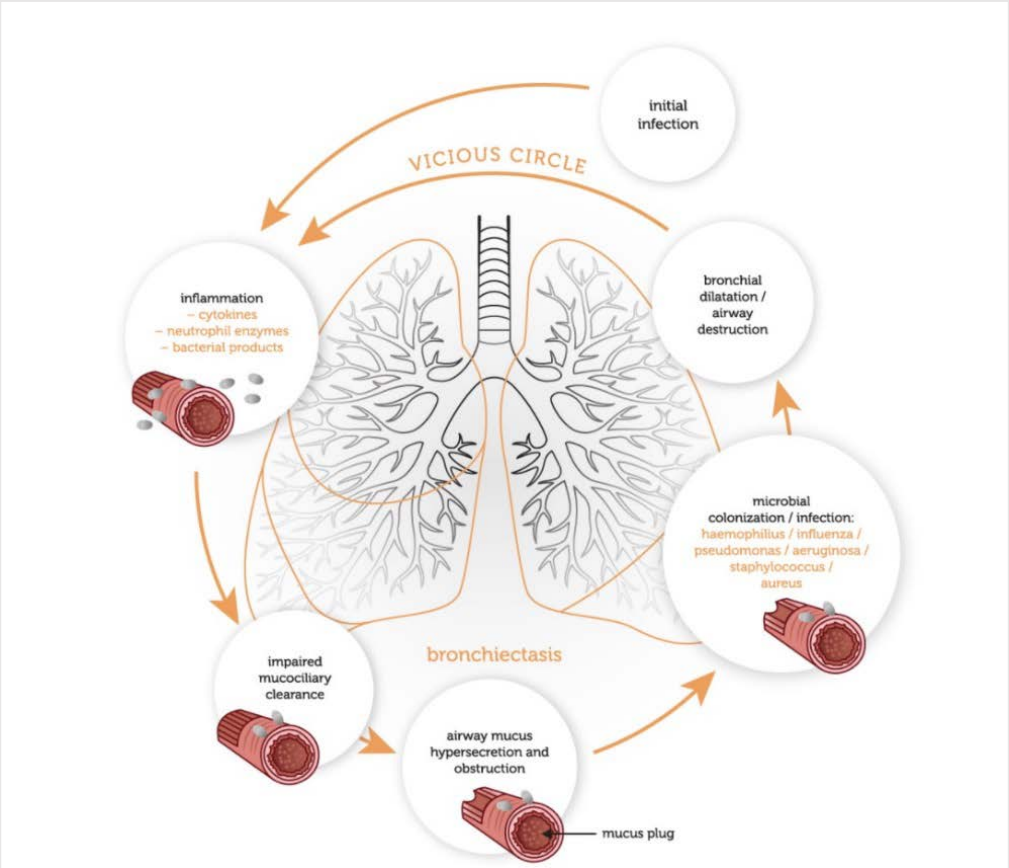
that the condition was associated with a 2.5 fold increased adjusted mortality ratio (hazard ratio (95% CI) 2.54 (1.16–5.56); $p < 0.02$)[21]. The overlap with COPD has also been associated with higher levels of airway inflammation and requiring longer recovery-time post exacerbation[22]. In regard to asthma, overlap between these conditions has been also associated with a higher risk of experiencing exacerbations than when bronchiectasis is the only respiratory diagnosis[5, 20].

1.4.2. Pathogenesis of bronchiectasis

The abnormal and permanent dilation and distortion of the bronchi and bronchioles, is the result of distinct and cyclic phases of infections, which may lead to altered pulmonary defence mechanisms and chronic inflammation[143, 144]. The infective insult, accompanied by an ineffective host-immune mechanism, leads to an exaggerated inflammatory response[145], mediated mostly by neutrophils, lymphocytes and macrophages. The release of these inflammatory mediators in the bronchi, especially neutrophils, promote tissue damage, impairing the function of the cilia epithelium and stimulating hypersecretion from the mucous glands[146]. The impaired mucociliary clearance and excess of sputum production create the optimal conditions to make the airways susceptible to microbial colonisation. Even though findings of bacterial colonisation and inflammatory markers are intermittent in patients with bronchiectasis, in some patients these findings are persistent, which worsen the prognosis of the condition. Pathogens commonly found in the sputum of bronchiectasis patients are Haemophilus influenza, Pseudomonas aeruginosa and Staphylococcus aureus. Again, neutrophils play an important role facilitating bacterial adherence into the lung epithelium[143, 145]. As a result of the bacterial colonisation, further chronic inflammatory processes are triggered, which accentuate the tissue damage, and lead to the characteristic permanent dilatation of the bronchi, which consequently, will make the airway prone to a

self-perpetuating cycle of infection, chronic inflammation and sputum production (Figure 1-F).

Figure 1-F: The vicious circle of bronchiectasis.



Extracted from Bronchiectasis Toolbox website: http://bronchiectasis.com.au/. Used with permission.

1.4.3. Diagnosis and classification

Bronchiectasis is suspected with the presence of episodes of productive cough (≥3 per year, each lasting ≥4 weeks) accompanied or not by other respiratory symptoms. The diagnosis is reliably confirmed by high resolution computed tomography (HRCT) scan of the lung, and as such it is a condition that can go under-diagnosed unless the patient has been investigated by a respiratory specialist[147].

According to the morphological findings from the HRCT, the bronchiectasis pattern can be classified as cylindrical, varicose, and saccular or cyst. More than one type of bronchiectasis focus may be present in the same patient.

Based on the presence of the bacterial organism in sputum culture (either Pseudomonas aeruginosa or other type of infection) and sputum production versus dry cough, four clinical phenotypes of bronchiectasis have been identified. According to this categorisation, the Pseudomonas cluster was associated with most severe disease, worst radiological findings and inflammatory patterns, and lowest functional status, while the cluster of patients with dry cough was associated with less severe disease[132].

1.4.4. Treatment

The goals of bronchiectasis management include monitoring severity, avoiding excessive decline in lung function, minimising infective exacerbations, and optimising general wellbeing, symptom control and health-related quality of life [131]. Thus, the management of the condition involves the combined effort of a multidisciplinary health care team. Treatment strategies can include the use of antibiotics to treat infections or as a prophylactic measure, a daily routine of breathing and sputum clearance techniques which should be supervised by a specialised physiotherapist, pulmonary rehabilitation in the case of impaired exercise capacity[126], Influenza vaccinations and, when appropriate, surgery[131, 147, 148]. As with severe asthma and COPD, education of symptoms, timely use of written action plans, and reduction of risk factors such as smoking, play an important role in the management of the disease[131, 147, 148].

The pharmacological management of the disease can include antibiotic therapy, bronchodilators, and muco-active agents. Therapy is dictated by the general status of the patient, since in stable patients only exercise and airway clearance regime may be sufficient.

Antibiotics, the cornerstone of pharmacological management in bronchiectasis, are recommended in three situations: to attempt eradication of new bacterial isolates, to treat exacerbations, and in some specific cases, as a long-term maintenance therapy when chronic colonisation has been observed. Guidelines recommend that the type of antibiotic should be selected according to results of lower airway culture test when possible, clinical severity and patient characteristics[148]. Bronchodilators can be prescribed in case of bronchoconstriction and reversibility. Inhaled corticosteroids are only recommended in patients with underlying asthma or COPD. In terms of muco-active agents to facilitate airway clearance, the current guidelines from the Thoracic Society of Australia and New Zealand states that agents such as isotonic and hypertonic saline and mannitol are not currently recommended for routine use. Nevertheless, a therapeutical trial of these agents in patients with frequent exacerbations is suggested[147].

1.5. Summary Part 1: OAD section

Severe asthma, COPD and Bronchiectasis are chronic conditions of the lower respiratory airway that are underpinned by complex inflammatory processes resulting in airflow limitation of different severity and reversibility.

Shared characteristics of these diseases include cough, wheezing, reduced exercise capacity, dyspnoea, higher susceptibility to respiratory infections, and high prevalence of comorbidities. Overlap between these diseases is also common, and usually leads to worse clinical presentation. Medication, including bronchodilator and anti-inflammatory agents, are used to control symptoms and to manage exacerbation. However, dependency on several medications is common, increasing the risk of developing further comorbidities. As a result, these diseases pose a high burden in patient's health status and in the health system.

Non-pharmacological treatments and reduction of risk factors are important coadjutants in the management of these diseases, especially in COPD. Among these strategies, the promotion of physical activity and reduction of sedentary time are promising strategies due to the positive health impact show in several studies on health outcomes (see sections 1.2.1.1 and.1.2.1.2).

In the next section, I will give some context regarding characterising physical activity and sedentary time as a non-pharmacological strategy for the management of OAD, and I will define the label-free approach to be used in part of this thesis.

1.6. Is physical activity a treatable trait in OAD?

In the last few years, there has been an increasing recognition of the need to revise and update traditional management approaches for chronic airway diseases, and most specifically for COPD and severe asthma[12, 51, 125, 149]. Proposed reasons for this change include: the lack of progression in reducing the excessive disease burden [31, 150]; the high level of overlap found in these conditions[1, 17-21] which in cases makes it difficult to distinguish a clear diagnosis and may eventually lead to patients' over or under treatment with the consequent suboptimal treatments outcomes and loss of resources; and the fact that "labelling" a patient with a given diagnosis does not fully recognise the biological and clinical heterogeneity of the diseases[149].

In order to address these issues, a label-free paradigm for chronic airway diseases has been proposed, where these diseases are managed using a precision medicine model, based on the identified treatable traits[51]. The concept of personalised medicine has been defined as "treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations"[151]. In 2016, Agusti and colleagues proposed the "treatable traits management approach for chronic airway diseases" which refers to phenotypic or endotypic characteristics found in OAD that can be assessed and potentially targeted with treatment[51]. Clinical phenotypic characteristics refers to a measurable single or multiple disease feature, that describe differences between people with the disease, and that relate to clinically meaningful outcomes, such as symptoms, response to therapy, biological and/or radiological features or death[152].

The identification of these traits requires a thorough assessment which encompasses several domains of the diseases. Gibson and McDonald in 2010, suggested that rather than trying to

differentiate between diseases that show a high degree of overlap (in this particular case, asthma and COPD in the elderly) with the concomitant difficulty to distinguish one disease from another; a better approach may be to describe "the patterns of airways disease on the basis of clinical and pathophysiological features" and to subsequently tailor interventions according to the features identified[125]. They proposed that a multidimensional assessment[125, 153] covering the domains of airway, comorbidities, risk factors, and behavioural factors, could identify issues that were clinically significant, but that were not commonly addressed with a "label-centred" approach[153]. This approach was later updated as the CARe model[154] (Figure 1-G), which highlights the Comorbidities, Airway, and Risk Factors domains.

Figure 1-G: The CARe approach for assessment and treatment of chronic airway diseases.

Extracted from (154): Gibson P; McDonald V. Phenotyping Asthma and COPD. BRN Rev. 2016; 2. Figure 1, page 242. Used with permission.

The treatable-traits model for the management of patients with chronic airway disease[51], also identifies pulmonary, extra-pulmonary and behavioural characteristics (i.e. traits) that

are responsive to treatment (i.e. treatable). More recently in 2017, the Lancet Commission into Asthma lead by Pavord and colleagues, supported this idea recommending that in addition to investigating and treating adjacent comorbidities, behavioural and environmental factors present in patients with chronic airway diseases, the two dominant traits that needed to be the assessed and managed were eosinophilic airway inflammation, due to its impact on risk of exacerbations/lung attacks, and airflow limitation, because of its impact on symptoms[12].

It is important to evaluate where physical activity lies in this new OAD management paradigm. It has been suggested that the link between physical exercise (the subset of the physical activity behaviour that is planned, structured and repetitive body movement done for the improvement and maintenance of physical fitness[155]) and the improvement of clinical outcomes in OAD can be explained through several physiological pathways in addition to the improvement in cardiovascular fitness. In COPD for instance, exercise training has shown beneficial effects on measures of cardiovascular function[156, 157] (e.g. heart rate variability, aortic pulse wave velocity) and in muscle function even in patients with severe disease[89]. The positive muscle adaptations observed after training have been linked to an improvement on exercise capacity, and to a reduction of the ventilatory requirements for a given submaximal work rate through the betterment of the oxidative capacity of the skeletal muscle[89]. In asthma, it has been suggested that the benefits of exercise may be due to the physical extension occurring in the airway smooth muscle as a result of an increased tidal volume and respiratory rate during exercise[158], to a reduction in bronchial hyperresponsiveness and systemic inflammation[87], and to an increase in energy expenditure that may contribute to weight loss[82]. Physical inactivity could be considered an impairment in the risk factor domain likely to be present in people with each of the chronic airway diseases regardless of the primary diagnosis. Characteristics and symptoms such as dyspnoea, cough, impaired exercise

capacity, sputum production, airflow limitation and comorbidities are common findings among OAD patients, which are likely to negatively impact the amount of physical activity and sedentary time in which these patients engage. Physical activity is defined as any bodily movement generated by skeletal muscle and resulting in energy expenditure[159]. Meanwhile, sedentary behaviour is defined as the engagement in activities whilst lying down or sitting and expending low levels of energy, during waking hours. Importantly, physical activity and sedentary time are measurable and potentially treatable risk factors, which are known to impact on morbidity and mortality in general populations[160-164]. Therefore, it is likely that physical activity and sedentary time are relevant in the new model of treatable traits for OAD. Despite this evidence, physical activity and sedentary time have not been widely characterised nor addressed in OAD as treatable risk factors, outside of COPD.

A reason for this disparity, may be related to the fact that research into these behaviours has mostly followed a label-centric approach towards COPD. Since the seminal study of Pitta and colleagues in 2005[165], there has been a growing body of evidence characterising these impairments in COPD and examining the associations of sedentary time and physical activity, the latter to a greater extent, with important disease outcomes[166]. This work is summarised further in section.1.7.5. This evidence has highlighted the importance for people with COPD to engage in physical activity and exercise programmes, such a pulmonary rehabilitation, with the concomitant benefits extending beyond the respiratory system[89]. Currently, research in COPD has slightly moved away from characterising these behaviours only, and it now focuses on developing and testing interventions aimed at promoting healthier movement behaviours in this population[167-169].

In severe asthma and bronchiectasis, however, whilst some studies have demonstrated the effectiveness of exercise training programmes on disease outcomes such as bronchial

hyperresponsiveness, quality of life, exacerbations and dyspnoea[87, 170], interventions aimed at improving physical activity and decreasing sedentary time levels are scarce[84]. Reasons for this paucity may relate to the limited available evidence characterising these behaviours in these population. The importance of generating this knowledge is to create a base of evidence that can: estimate if the impairment of these behaviours exists in these diseases and if so, to what extent; and to describe the associations of these behaviour with relevant disease outcomes. This new knowledge can guide the direction of treatment interventions for severe asthma and bronchiectasis, since extrapolating what is known in COPD to these conditions may lead to the design of ineffective interventions.

In order to have a better understanding of this gap in knowledge, in Part 2 of this chapter I will present the definitions of physical activity and sedentary time, describe the different measurement methods for these behaviours, and review the published evidence of the characterisation and impact of these behaviours on COPD, bronchiectasis and severe asthma.

1

Part Two

1.7. Activity behaviours

1.7.1. Physical activity: definition, health impact, and characterisation on general populations

The WHO has defined physical activity as any bodily movement generated by skeletal muscle and resulting in energy expenditure[159]. This definition includes different domains of physical activity, such as leisure-time activity, commuting or transportation physical activity, occupational physical activity, and household chores physical activity. In general, leisure-time physical activity encompasses all those activities performed outside of work, transportation and house chores and which are done at a personal preference. Planned exercise (i.e. exercise training at home, gym sessions, etc.) sports or jogging would be examples of this domain[171]. Physical activity can be categorised according to its absolute and/or relative intensity. Absolute intensity refers to the rate of energy expenditure required to perform any physical activity, and is commonly divided into in light, moderate and vigorous intensity physical activity (Table 1-5)[172]. The metabolic equivalent of task (METs) is a common reference to measure absolute intensity[161]. METs provide estimates of intensity based on energy expenditure, where 1-MET is equal to the energy spent by a person when sitting quietly in a chair. This is also known as the resting metabolic rate and accounts for approximately 3.5 ml O_2 x Kg body weight^{-1} x minutes or hours^{-1} [173]. Relative intensity refers to the ease or difficulty with which a person performs a certain activity, and it is more closely related to physiological parameters of the individual (i.e. percent of aerobic capacity, percent of maximal heart rate, or levels of breathlessness)[174].

Table 1-5: Examples of METs equivalents of light, moderate and vigorous physical activity.

Term	*METs*	*Examples*
Light physical activity	1.1 - 2.9	- Walking slowly around home, store, or office (2.0 METs) - Standing performing light work such as making bed, washing dishes, ironing, preparing food or store clerk (2.0–2.5 METs)
Moderate physical activity	3.0 - 5.9	- Walking the dog (3.0 METS), walking at 6.4 km/hr on the level, firm surface, very brisk pace (5.0 METS) - Heavy cleaning: washing windows, car, clean garage, sweeping floors or carpet, vacuuming, mopping (3.0–3.5 METs)
Vigorous physical activity	≥ 6	- Walking at very, very brisk pace on the level, firm surface (7.2 km/hr) (6.3 METs) or running at 8 km/hr (8.0 METs) - Carrying heavy loads such as bricks (7.5 METs)

Adapted from Ainsworth et al. (172). MET: Metabolic equivalent of task.

There is substantial evidence that participation in regular physical activity decreases the risk of several diseases and cancers, such as coronary heart disease, stroke, type 2 diabetes mellitus, hypertension, depression, colon cancer, and breast cancer[160, 161], and reduces the risk of all-cause and cardiovascular mortality[160, 175]. Likewise, inactivity, or failing to meet the recommended levels of physical activity, has been regarded as the fourth leading risk factor for global mortality, contributing to 6% of deaths globally[161], and 9% of premature mortality[176]. Additionally, it has been estimated that inactivity contributes to increase the burden of disease from coronary heart disease, type 2 diabetes mellitus, breast and colon cancer by 6%, 7%, 10% and 10%, respectively[176].

As a significant and modifiable risk factor, global and local organisations have endeavoured to promote engagement in physical activity, highlighting the health benefits associated with

maintaining an active lifestyle. The creation of physical activity guidelines responds to the need for giving an evidence-based framework that summarises the minimum amount of activity required by age group, to promote the health benefits associated with activity. Table 1-6 illustrates the current WHO's recommendation for adults and older adults[161].

Table 1-6: Current recommendations of physical activity for adults.

Adults 18 to 64 years	-Weekly, at least 150 minutes of moderate-intensity aerobic physical, or at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week, or an equivalent combination of both. -Aerobic activity should be performed in bouts of at least 10 minutes duration**. -For additional health benefits, adults should increase their moderate-intensity aerobic physical activity to 300 minutes per week or engage in 150 minutes of vigorous-intensity aerobic physical activity weekly, or an equivalent combination of moderate- and vigorous-intensity activity. -Muscle-strengthening activities should be done at least twice weekly
Older adults (⩾65 years)	-Weekly, at least 150 minutes of moderate-intensity aerobic physical, or at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week, or an equivalent combination of both. -Aerobic activity should be performed in bouts of at least 10 minutes duration. -For additional health benefits, adults should increase their moderate-intensity aerobic physical activity to 300 minutes per week or engage in 150 minutes of vigorous-intensity aerobic physical activity weekly, or an equivalent combination of moderate- and vigorous-intensity activity. -People with poor mobility should perform physical activity to enhance balance and prevent falls on ⩾3 days/week -Muscle-strengthening activities involving major muscle groups should be done at least twice weekly. - In case health conditions impairing the ability to engage in the recommended levels of activity, people of this age group should still be as physically active as their abilities and condition allow

*From (161). **The 10-minutes bout recommendation has been recently excluded from the "2018 Physical Activity Guidelines Advisory Committee Scientific Report" (174), after research concluded that periods of any length of time are beneficial to reach the recommended total volume of physical activity, and its associated health benefits.*

Engaging in higher doses of physical activity than the recommended >150 minutes of moderate or >75 minutes of vigorous physical activity per week (or 500 to 1000 MET-minutes/week) results in enhanced improvements in health[160]. For instance, Arem and colleagues found that compared to people not reporting leisure time physical activity, those meeting the physical activity guidelines or doing up to twice as much that amount had a reduction in the relative risk of all-cause mortality of 31% [HR, 0.69 (95% CI, 0.67-0.70)]. This figure decreased to a 37% reduction in mortality risk for people engaging into 2 to 3 times the recommended levels of physical activity [HR, 0.63 (95% CI, 0.62-0.65)][177]. The authors also reported a plateau in the relative risk reduction 0.61 (39% lower mortality risk) in people doing 3 to 10 times the minimum recommended amount of activity[177]. According to the 2018 Physical Activity Guidelines Advisory Committee Scientific Report, similar dose-response curves to that reported by Arem and colleagues have been observed for cardiovascular disease incidence and mortality, and for the incidence of type 2 diabetes mellitus[174]. Non-adherence with the physical activity guidelines (doing less than the recommended amount of moderate and vigorous physical activity [MVPA]) is defined as physical inactivity[176, 178]. Importantly, engaging in lower or lighter levels of activity than those recommended in the guidelines versus not doing any MVPA still results in health benefits. In fact, studies have shown that the majority of the reduction in mortality risk associated to cardiovascular disease[179] (n=3038, adults of ≥50 years old from Great Britain with type 2 diabetes) or in all-cause mortality[177] (pooled data from 6 studies in the National Cancer Institute Cohort Consortium; n=661137; 62 years old median age [21-98 years old range]), is achieved by shifting from no physical activity to performing some level of physical activity. This is particularly important message to highlight, particularly for people with chronic respiratory diseases who may struggle to meet the current recommendations of MVPA.

Studies characterising the level of physical activity have reported that the proportion of adults adhering to the guidelines of physical activity is low[180, 181]. For instance, in the 2003–2004 National Health And Nutrition Examination Survey (NHANES), Troiano[180] et al. reported that adults engaging in device-measured 30 minutes/day of physical activity were less than 5%[180]. Similarly, in the 2007-2009 Canadian Health Measure Survey (CHMS), Colley et al. reported that 15% of adults engaged in the recommended levels and patterns of physical activity (150 minutes/week of MVPA in 10 minutes-bouts), and the number dropped to 5% for people engaging in 150 minutes of MVPA on a regular basis (i.e. 5 days /week)[181]. However, it is important to highlight that these estimates come from physical activity results measured with physical activity monitors. The development of the physical activity guidelines has been mostly based on self-report measures of physical activity (questionnaires). Therefore, comparing adherence between results obtained from activity monitors with questionnaires may result in inaccurate estimates. This point can be exemplified in the following results from Australia and the USA. In Australia, the 2014-2015 National Health Survey reported that 47.8% of adults aged 18-64 years and 25% of adults aged ≥65 years engaged in the recommended levels of aerobic physical activity. Almost 38% of adults aged 18-64 years did less than the recommended amount of physical activity, and 15% did not engage in aerobic physical activity in the last week. Similarly, in adults ≥65 years, 75.1% did less than the recommended amount of aerobic physical activity[182]. In the USA, results from the 2016 National Health Survey reported that close to 53% of people aged ≥18 years were meeting the aerobic physical activity guidelines[183]. Data reporting on the adherence to recommendations for muscle strengthening activities (muscle-strengthening activities at least twice/week) are less widely available, but data from the Australian National Nutrition and Physical Activity Survey 2011–2012 found that from the 52% of respondents meeting the MVPA guideline, only 15% of them were also meeting the muscle strengthening activity

recommendations[184]. Similarly estimates have been reported in the 2011 Behavioral Risk Factor Surveillance System (BRFSS) in the USA, where from the 51.6% of adults meeting the MVPA guideline, only 20.6% met both recommendations[185]. Similarly, in the 2016 National Health Survey, from the 53% of adults meeting the aerobic physical activity guidelines, only 22% were meeting both recommnedations[183].

In general, these studies also showed that males tended to be more active than females, that the levels of physical activity declines with age, and that higher levels of education were associated with higher likelihood of meeting the physical activity recommnedations[180-182, 184-186].

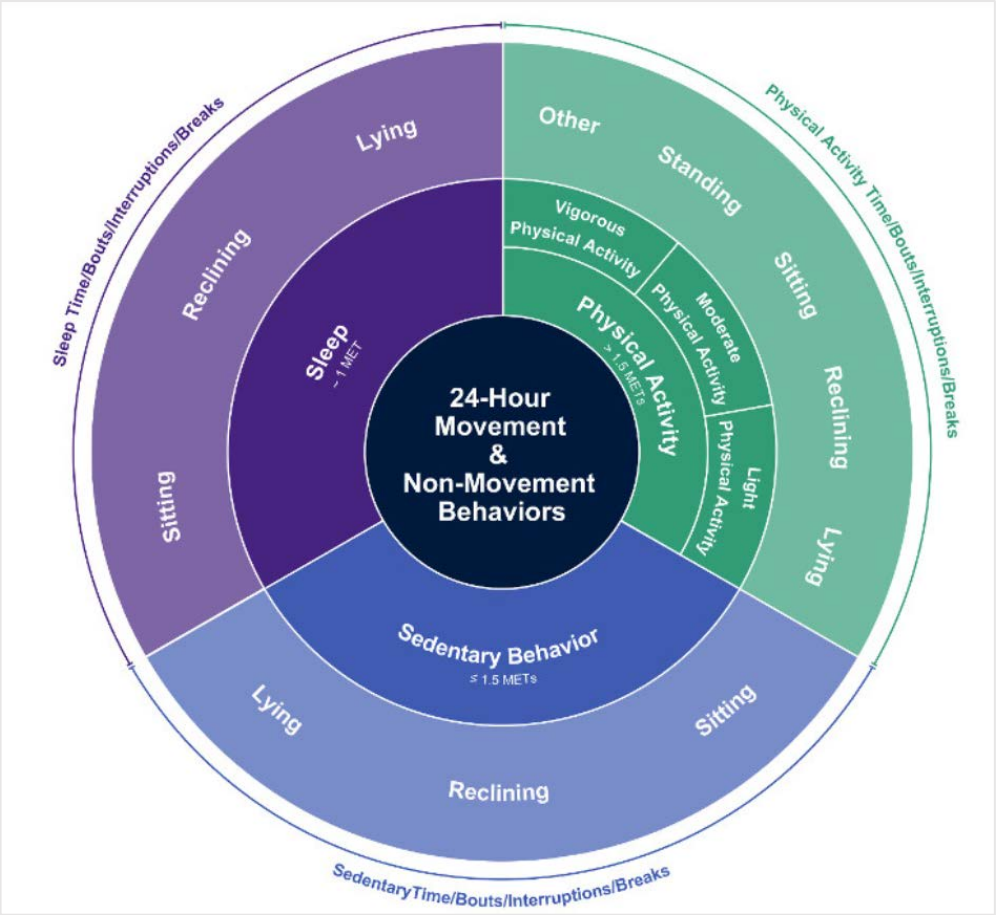
1.7.2. Sedentary behaviour: definition, health impact, and characterisation on general populations

Sedentary behaviour is a distinct entity from physical (in)activity, and refers to any waking behaviour in a lying or sitting position and expending low levels of energy (≤1.5 METs)[187] (Figure 1-H). Sedentary behaviours can occur in work, domestic, transport or leisure contexts with the most common sedentary behaviours being sitting while at work and watching television. Sedentary time is defined as the time spent in sedentary behaviours. This definition includes any duration and context (i.e. leisure time, work) of sedentary activities.

Previously, sedentary behaviour was commonly but erroneously used interchangeably with, or in place of inactivity (performing insufficient amount of MVPA). However, in the past decade or so, it has been recognised that sedentary behaviour is distinct from not meeting the physical activity guidelines as someone can meet the guidelines but still sit for the remainder of the day. As a result of the growing interest in the study of sedentary behaviour, the Sedentary Behaviour Research Network (SBRN) has recently undertaken a Terminology

Consensus Program where standardised terminologies and definitions were proposed[178]. Some of these definitions are reported in Table 1-7.

Figure 1-H: Conceptual model of movement and non-movement behaviours proposed by the SBRN.



Extracted from (178): Tremblay M et al. Sedentary Behavior Research Network (SBRN) - Terminology Consensus Project process and outcome. Int J Behav Nutr Phys Act, 2017. 4. Figure 3, page 11. http://creativecommons.org/publicdomain/zero/1.0/. No changes made.

Table 1-7: Terminologies and definitions proposed by the SBRN.

Term	*General definition*	*Examples*
Sedentary behaviour	Any waking behaviour characterised by an energy expenditure ≤1.5 metabolic equivalents (METs), while in a sitting, reclining, or lying posture.	Use of electronic devices (e.g., television, computer, phone) while sitting, reclining, or lying; reading/writing/talking while sitting; sitting in a bus, car or train.
Stationary behaviour	Stationary behaviour refers to any waking behaviour done while lying, reclining, sitting, or standing, with no ambulation, irrespective of energy expenditure.	Use of electronic devices (e.g., television, computer, phone) while sitting, reclining, lying, or standing *without ambulation*; reading/writing/drawing/painting/talking while sitting; sitting at school/work; sitting in a bus, car or train.
Sitting	A position in which one's weight is supported by one's buttocks rather than one's feet, and in which one's back is upright.	**Active sitting**: Working on a seated assembly line; playing guitar while seated; doing arm ergometry while in a wheelchair, etc. **Passive sitting**: Refer to sedentary behaviour examples while sitting.
Reclining	Body position between sitting and lying	**Passive reclining**: Lounging/slouching on a chair or couch while sedentary. **Active reclining:** Recumbent cycling.
Lying	To be in a horizontal position on a supporting surface	**Passive lying**: Lying on a couch, bed, or floor while sedentary. **Active lying**: Isometric plank hold.
Standing	A position in which one has or is maintaining an upright position while supported by one's feet.	**Active standing**: Standing while painting; standing while washing dishes, etc. **Passive standing**: Standing in a line; standing for a hallway discussion, etc. **Supported standing**: Standing while holding a couch, chair, or a parent's hand; standing with the aid of crutches
Screen time	Time spent on screen-based behaviours. These behaviours can be performed while being sedentary or physically active.	Watching TV while sitting, lying, or running. Playing active video games.
Sedentary behaviour pattern	The way sedentary behaviour is accumulated throughout the day or week while awake (e.g., the timing, duration and frequency of sedentary bouts and breaks).	**Prolonger**: Someone who accumulates sedentary time in extended continuous bouts. **Breaker**: Someone who accumulates sedentary time with frequent interruptions and in short bouts.

From (178): Tremblay M et al. Sedentary Behavior Research Network (SBRN) - Terminology Consensus Project process and outcome. Int J Behav Nutr Phys Act, 2017.http://creativecommons.org/publicdomain/zero/1.0/. Changes have been made.

High levels of sedentary time have been associated with several deleterious health outcomes in the general population, such as increased cardio-metabolic markers in adults[188, 189], and all-cause, cardiovascular-, colon and breast cancer-related mortality[164, 189, 190]. A positive dose-response relationship between the amount of sedentary behaviour and mortality has been reported for some studies, highlighting the deleterious effect of this behaviour on health outcomes. In their meta-regression analysis of one million participants, Ku and colleagues found that the mortality risk significantly increased as the total amount of sedentary time surpassed seven hours. In these studies, sedentary time was measured by questionnaires. In the studies using activity monitors, risk increased with nine hours of sedentary time[191]. Additionally, in their harmonised meta-analysis, Ekelund et al found that in the group of people engaging in 16 MET-h/week of physical activity, those sitting over 8 hours/day had a 12% increase risk of mortality compared to those sitting for less than 4 hours/day[192].

Recommendations for addressing the excess of sedentary time have been included in the physical activity guidelines of Australia[193] and the United Kingdom[194]. For instance, the Australian guideline "Make your move – Sit less. Be active for life!"[195] recommends:

- Minimising the amount of time spent in prolonged sitting.
- Breaking up long periods of sitting as often as possible.

The rationale behind promoting breaks in sedentary time (i.e. "the breaker" in Table 1.7) is based on observational evidence from cohort studies such as the National Health and Nutrition Examination Survey (NHANES) and the Australian Diabetes, Obesity and Lifestyle (AusDiab)[188, 196]. Interventional studies analysing the effect of frequent interruptions of sitting time (i.e. every 20-30 minutes) and its replacement with short bouts (i.e. <2 minutes) of light or moderate physical activity have shown a positive effect in metabolic biomarkers compared

to uninterrupted sitting[197-199]. Thus, the focus should not only be on reducing the total amount of sedentary time, but also on the promotion of more often and longer interruptions (breaks) of sedentary bouts. This is particularly relevant for people who spend long hours a day in sedentary behaviours (i.e. public transport drivers, computer-based workplaces, etc.). Some previous evidence suggested that the deleterious effects of sedentary time were independent of the amount of physical activity performed[164]. That means that even if a person was engaging in physical activity, if they also accumulated high levels of sedentary time, they would still be prone to the adverse health outcomes associated with high levels of sedentary time. However, in their meta-analysis Ekelund et al. found that the negative effect of sitting time on mortality was accentuated as physical activity decreased and reduced as it improved. For instance, in very inactive people (doing ≤5 minutes/day of moderate physical activity), those engaging in over 8 hours of sitting time/ day had a 27% increased risk of mortality compared with those accumulating less than 4 hours/day, while in those engaging in very high levels of physical activity (≥60 minutes/day) the difference on mortality risk between the different categories of sedentary time was negligible[192].

On the other hand, studies investigating the replacement of sedentary time with light or MVPA, have suggested possible improvements in cardio-metabolic biomarkers when shifting away from sedentary time[200].

Studies characterising the prevalence of sedentary time in the general population have pointed towards high levels of engagement of this behaviour. In regard to device-measured sedentary time, in the 2003–2004 NHANES, Matthews et al. reported that adults aged less than 60 years accumulated around 7.5 hours/day of sedentary time. This figure increased up to 8.41 hours/day in the 60 to 69 age group, and up to 9.28 hours/day in the 70 – 85 age group. The age group showing the lowest level of sedentary time were those in their

thirties[201]. Similarly, a study from the UK reported that 67% of adults aged ≥60 years accumulated over 8.5 hours/day of sedentary time, with 50% of those older adults accumulating more than 9.5 hours/day[202]. In terms of self-reported measures of sedentary behaviour, the same study also reported that the percentage of older adults reporting over 4.85 hours/day of leisure time sitting was 66.5%, and that 50% of those adults were reporting more than 6.6 hours[202]. Similarly, in the 2011-2012 Australian Health Survey concluded that adults spent an average of 39 hours per week (5.6 hours/day) in sedentary activities, with sitting at work a major sedentary activity (10 to 22 hours/ week). TV-time accounted for nearly 13 hours of sedentary time /week, a figure that increased up to 19 hours/ week in people aged ≥75 years[203].

Overall, physical inactivity and excessive sedentary time are prevalent in the general population, and are associated with several detrimental health outcomes. In addition to promoting physical activity, people should be encouraged to reduce their time in sedentary activities.

Next, I will focus on some of the existing tools for the measurement of these behaviours their advantages and disadvantages, and I will explain the measurements to be used in my research for characterising the level of physical activity and sedentary time.

1.7.3. Measurement of activity behaviours

The measurement of physical activity and sedentary time has gained relevance, due to the several benefits attributed to the recommended engagement in physical activity, and to the detrimental effects of being inactive and sedentary[204]. As a result of this, the need to find the best assessment tools to measure these behaviours has become evident. Methods to measure physical activity and sedentary time can be divided into subjective (e.g. questionnaires) and device (e.g. accelerometers) methods. Important characteristics to consider when choosing an assessment tool are reliability (i.e. does the test achieve consistent results on different settings, when there is no evidence of change?) and sensitivity (i.e. does the test detect changes over time?)[204]. Validity (i.e. does the test measure what is intended to measure?) is also an important characteristic to consider[204]. For physical activity, for instance, an important number of measurements have been validated against the doubly labelled water technique (DLW)[205-207]. DLW is an objective and highly accurate technique that measures total daily energy expenditure and it is considered the gold standard for physical activity measurement[208]. However, due to its high cost and impracticality in application to the general settings (laboratory-based execution) it is not frequently used in population-based research[208]. Direct observation has been used as a criterion for sedentary time[209]. Feasibility and practicality are also important factors to consider when deciding on a measurement tool[204].

In terms of physical activity, components that needs to be considered when measuring this behaviour can be summarised with the FITT principle[174, 210]:

- **F**requency (e.g. 5 days per week),
- **I**ntensity (light, moderate or vigorous),
- **T**ime (e.g. 30 minutes), and

- **T**ype (e.g. aerobic exercise).

It is also important to clarify that the measurement of physical activity differs from the measurement of exercise capacity or physical fitness, since physical activity relates to a behavioural concept whilst cardiorespiratory and physical fitness are related to physiological terms[155].

Similar to physical activity, the characterisation of sedentary time can be summarised with the SITT acronym[211]:

- **S**edentary behaviour frequency: number of bouts or periods of a certain duration (e.g. number of episodes of sedentary behaviour lasting >20 minutes)
- **I**nterruptions of sedentary behaviour (e.g. number of breaks of the sedentary period, such as standing up and walk or just standing up)
- **T**ime (duration) of the sedentary period (e.g. 30 minutes of uninterrupted sitting, total time of sitting during the day)
- **T**ype or activity behind the sedentary behaviour reported (e.g. was the person watching TV, travelling, or working while being sedentary.

In the following sections, I will provide some definitions and examples of subjective and device-measured assessments to measure physical activity and sedentary time.

1.7.3.1. *Subjective techniques*

Subjective techniques such as self-report logs, recall questionnaires, and typical week questionnaires, have been largely used in research since they are economic and easy tools to administer[212, 213]. They also have the advantage of capturing contextual information behind a given activity, for instance sitting while watching TV versus sitting while working or

travelling. This information may have value when developing interventions to target physical activity and sedentary time, since it may help to give directions towards the activities that need to be changed. On the other hand, they may be limited in their measurement properties, i.e. reliability[208]. Questionnaire-based reports tend to overestimate (or underestimate) the amount of physical activity (or sedentary time) performed[214, 215], and they are better at recalling activities at higher intensities[216]. An additional problem that may be encountered with questionnaire-based reports of movement behaviours, is the report of proxy end-points instead of the measurement of the behaviour itself[217]. An example of this are studies reporting only TV-time as a proxy of sedentary behaviour, without taking into account other type of sedentary activities in their assessment.

Questionnaires commonly utilised to quantify physical activity are the International Physical Activity Questionnaire (IPAQ, which also include a sitting time item both for the short and the long version of the questionnaire)[218], the Minnesota Leisure Time Physical Activity Questionnaire (Minnesota LTPA Q)[219], the Paffenbarger Physical Activity Index[220], and the 7-days physical activity recall[221]. Commonly used sedentary time questionnaires include the Past-day Adults Sedentary Time (PAST)[222], the Sedentary Behaviour Questionnaire (SBQ)[223], the Marshall Sitting Questionnaire[224] , the IPAQ (item for sitting time)[218], and the Measure of Older Adult Sedentary Time (MOST)[225].

1.7.3.2. *Device-assessed techniques*

A more accurate tool for measuring intensity, patterns of accumulation and total time of physical activity and sedentary time is with devices that measure body position, accelerations, or physiological responses such as inclinometers, pedometers, accelerometers, and multi-sensors devices[204]. They have become widely used in the last two decades or so, because they overcome some of the most common problems encountered

with questionnaires, such as the lower accuracy, and their reliance on self-reported data[180, 201]. This is because they provide day and time-stamped data, which basically means that they are able to capture the time spent in different movement behaviours and its domains (e.g. intensities and/or positions, patterns of accumulation at certain times of the day). This characteristic allows a more specific and complete examination of physical activity and sedentary behaviour through the profiling of these movement behaviours (simultaneous assessment and analysis)[226]. Accelerometer-based activity monitors are an example of the most commonly used objective measurement tools. They measure acceleration changes (or counts) in one or multi-axis planes depending on its technical characteristics. Counts are defined as the sum of raw acceleration outputs at a given frequency, into epochs or periods of time. Accelerometers commonly used in research are the ActiGraph (Pensacola, FL, USA), the Dynaport (McRoberts, The Hague, The Netherlands), the RT6 (StayHealthy, Monrovia, CA, USA), the activPAL (PAL Technologies, Glasgow, UK), the SenseWear (BodyMedia, Pittsburgh, PA, USA), the Axivity AX3 (Open Lab – Newcastle University, Newcastle upon Tyne, UK), and the IDEEA (MiniSun, Fresno, CA, USA). Some of these activity monitors, such as the activPal and the IDEEA are postural-based monitors, which allow them to capture sedentary time in a more accurate way compared to accelerometer "only" monitors.

Limitations recognised for some accelerometers include: missing upper limb movements for those worn at the hip[217], missing water-based activities for those that are not waterproofed, misinterpreting information of non-wearing as sedentary time[227], misinterpretation of vibration as a movement, not providing contextual information behind activity (sitting while watching TV versus sitting at work), and poor ability to distinguish between standing still and sitting/ lying[217]. However, they are quite easy to use and operate, relatively affordable, and they deliver objective measurements[217, 228].

Protocols for best practice have been developed for the use of activity monitors[228]. According to the recommendations, physical activity data in adults should be collected for a minimum of 4 to 7 days[180, 228] and for at least 10 hours/day[228]. General recommendations for the measurement of sedentary behaviour may depend on the type of device used. For instance, for activity monitors such as the ActiGraph, wear-time recommendations are as per those for physical activity[229]. Recommendations for monitors such as the activPAL, however, suggest to use a 24 hour wearing-time protocol, for a minimum of 7 days[230]. The use of these devices in conjunction with participant reported wear time diaries is highly recommended to help differentiate sedentary activities from sleeping or non-wearing period. In addition, non-wear time can be also calculated by either proprietary software or custom-written algorithms. In general, these algorithms determine whether the monitor was or was not worn from periods when little activity or no activity/movement was captured. For instance, in the ActiLife software (for the ActiGraph device) there are three wear time algorithms available. Two of them[180, 231] are considered "floating window algorithms" and classify non-wear time according to the number of consecutive zeros, or data below the activity threshold, in a certain epoch or pre-defined period of time. These algorithms can also be updated as per user preferences. The third algorithm is a "daily algorithm", which instead of looking at consecutive epochs for patterns, it breaks the file into calendar hours and flags them as valid or invalid based in the validation criteria[232]. Custom written algorithms have been also developed for the ActiGraph[227] and for other activity monitors[233, 234] , including the activPAL[235].

In the following section, I will focus on the activity monitor ActiGraph, since it is the monitor utilised during my research.

1.7.3.2.1. ActiGraph GT3X-BT

The ActiGraph GT3X-BT is a triaxial accelerometer that measures physical activity (including intensity of activity and steps), sedentary time, and sleep. I chose to use this activity monitor because it has been one of the most (or the most) common accelerometers used in research[236], especially in large epidemiological studies including NHANES[180, 237, 238], the Women's Health Study[239], the AusDiab study[240]and the Health Survey of England[241]. In addition, this monitor has been validated in COPD populations against DLW for the measurement of physical activity, being one of the most accurate in detecting different walking speeds[242] and in estimating activity energy expenditure[207, 243]. These points are important for my studies. By choosing to use this activity monitor, it will allow comparisons of the behavioural outputs of my data with those from other populations.

The device detects acceleration in the vertical (for the uniaxial mode), horizontal, and perpendicular axis, which are captured as raw data at rates ranging from 30 to 100 Hz (as per user preferences) and are stored in a raw, non-filtered/accumulated format in the units of gravity[244]. The device software (ActiLife 6.11.6 Data Analysis Software, ActiGraph Corp, Pensacola, FL USA) summarises the data into counts for a given epoch, with 1-minute a common epoch used in studies[245]. The ActiLife Software categorises these data into a level of intensity of physical activity according to a given cut-point. Cut-point is a term that refers to the movement-counts output in a certain period of time, for instance, count per minutes (CPM). Several studies have been carried out to determine the appropriate cut-point to categorise the different spectrums of movement intensity[180, 246-248]. The ActiGraph has 13 cut-points, 3 of them suitable for adults[180, 246, 247]. One of the most widely used cut-point to classify the levels of activity, and the cut-point to be used in this thesis, was developed by Freedson and colleagues[246] (Freedson's 1998 cut-point). Subsequent studies included the categorisation of sedentary time within this cut-point, as activity counts under the threshold

of 100 CPM[218, 249, 250]. This uniaxial cut-point has been validated both for physical activity[180] and sedentary time[188, 201] in studies characterising the level of these behaviours and associating the levels of activity and sedentary time with markers of cardiovascular disease. A cut-point devised for the tri-axial data, is the one proposed by Sasaki et al.[247] and known as the Vector Magnitude (VM3). This cut-point considers the sum of the three-axis squared, and then takes the square root of this value. Table 1-8 describes the different physical activity intensity spectrums according to the number of CPM in Freedson's 1998 cut-point.

Table 1-8: Activity spectrums and sedentary time based on Freedson's 1998 cut-point.

Sedentary: 0-99 CPM
Light: 100-1951 CPM
Moderate: 1952-5724 CPM
Vigorous and very vigorous: ≥ 5725CPM

From (246). CPM: count per minute. Data obtained from healthy adults.

However, to date there is no consensus on what is the correct cut-point, and several issues have been highlighted[217]. It has been pointed out that due to the dissimilar equations utilised to calculate physical activity energy expenditure from acceleration counts, the cut-points developed by different devices and studies have resulted in widely different cut-points for activity categories, which has hindered comparison between devices and studies[251]. As a result of this limitation, more recent research has suggested that a better estimation of physical activity energy expenditure and posture could be achieved with the utilisation of machine learning algorithms, which through the use of patterns extracted from raw acceleration data are able to derive information about sedentary and active time.[252, 253]

Some additional issues include[217]:

- Most of the cut-points were developed for middle-aged people, and thus the extrapolation of this information into elderly population is unclear.
- Most of the validation studies were performed in laboratory settings and may not represent activity under free-living conditions.
- Most of the "cut-point studies" were performed using uniaxial accelerometers, thus only giving outputs for the vertical axis. However, a study from 2012[254] showed a strong correlation among counts measured in the vertical axis with counts from the VM3.
- There are conflicting data regarding the most suitable cut-point to measure sedentary time in adult populations, with cut-points ranging from 25 to 500 CPM[209, 255-257]. However, the <100 CPM cut-point is easily comparable with estimates in the literature, since it has been shown to be detrimentally associated with cardiometabolic measures in adults[188], and previously reported in large population studies[201].

In addition to these issues, it is recognised that the ActiGraph is not as sensitive as postural-based accelerometers (such as the activPAL or IDEEA) to measure sedentary time[209]. One of the criteria of being sedentary is to be in a seated, reclined or lying position[178]. The inclinometer of the device does not perform as well as those from other devices[209]. As such, it relies on characterising time as sedentary based on accelerations, which is not as accurate as measuring postural changes.

The ActiGraph can be worn on the waist or wrist depending on the user/researcher preferences, and participants needs to remove the monitor during water-based activities[245].

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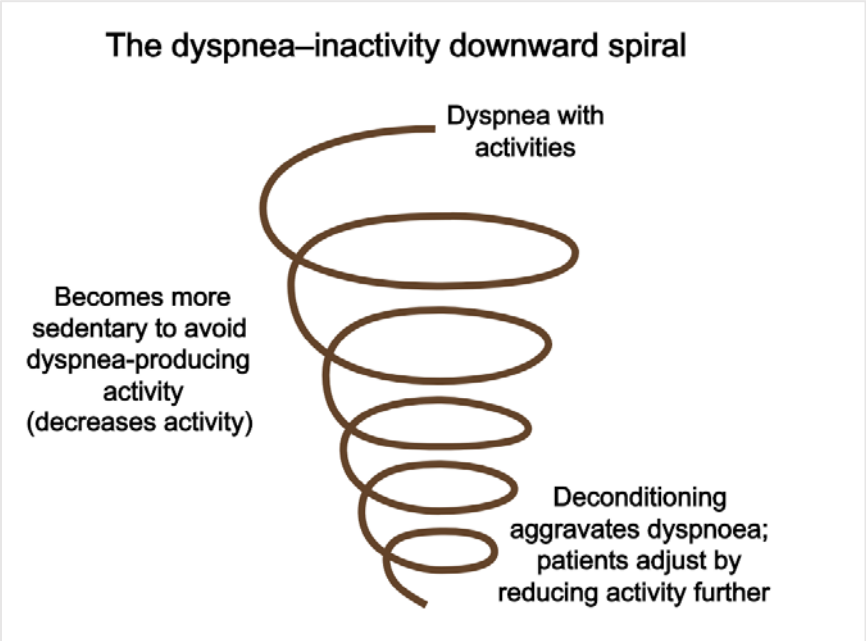
The study and measurement of the movement behaviours of physical activity and sedentary time are evolving and complex area of enquiry, that are closely related to public health messages aiming to reduce the potentially negative impact of these behaviours on chronic diseases. Several methods, including population-specific questionnaires and activity monitors, have been developed to address this. Among the latter, the accelerometer ActiGraph is one of the most widely used in research and in population-based studies. The ActiGraph wGT3X-BT is the activity monitor to be used in my studies.

In the next sections, I review the literature focusing on the role of these behaviours in the management of COPD and bronchiectasis populations.

1.7.4. Characterisation of activity behaviours in obstructive airway disease populations: what is the evidence?

As mentioned in section 1.6. (*Is physical activity a treatable trait in OAD?*), engagement in lower levels of physical activity is a risk factor likely to be encountered in people with OAD. Characteristics and symptoms such as dyspnoea, cough, impaired exercise capacity, sputum production and airflow limitation are common findings among these patients and are likely to have a negative impact on the amount of physical activity and sedentary time in which these patients engage. These impairments are likely to lead to what has been described in COPD as the "dyspnoea inactivity downward spiral"[258] (Figure 1-I), a clinical phenomenon where deconditioning is perpetuated and worsened due to a vicious circle of decreased activity and exercise capacity due to a dyspnoea-related avoidance of activity, that negatively impact on symptoms and further impairment of health status.

Figure 1-I: The dyspnoea inactivity downward spiral in COPD



Extracted from (258): Reardon J, Lareau S, ZuWallack R. Functional status and quality of life in chronic obstructive pulmonary disease. Am J Med. 2006 Oct;119. (Permission requested)

Currently, it is well known that physical impairment is a prominent feature of COPD[259]. Additionally, the few studies available suggest that the engagement in sedentary time in this population is also likely to be higher than in controls[165, 260]. However, to what extent this applies to other obstructive airway diseases, such as severe asthma and bronchiectasis, has not received the same degree of attention.

In the following sections, I will be summarising the current evidence of physical activity and sedentary time in severe asthma (Chapter 2), COPD and bronchiectasis. First, the prevalence of these behaviours in COPD will be summarised, followed by the evidence of how these behaviours are associated with several disease outcomes. A similar approach will be followed for the description of these behaviours in bronchiectasis. Evidence of prevalence and associations of these behaviours in adult asthma populations will be thoroughly addressed in Chapter 2.

1.7.5. Physical activity and sedentary behaviour in asthma and severe asthma

The GINA guidelines recommend that people with asthma should engage in regular physical activity for its general health benefits, and as a coadjutant for the management of obesity[1]. However, since the study of physical activity and sedentary behaviour in adults with asthma has not been extensively addressed in the literature, important research questions remain unaddressed, such as:

- To what extent adults with asthma may have decreased levels of engagement in physical activity and sedentary behaviour compared to adults without asthma?
- What is the relationship between engagement in these behaviours and asthma symptoms?
- Is the level of engagement in these behaviours is impacted by disease severity?

From the results presented in a systematic review of physical activity in adults and children with asthma conducted in 2012[261], it could be inferred that adults with asthma engage in lower levels of physical activity than controls. However, since the primary research question of this review was the evaluation of the potential causal relationship between physical inactivity and asthma development, neither the level of this behaviour nor its association with disease outcomes were topics addressed in depth.

In Chapter 2 of this thesis I present a published systematic review where the topics of the level of physical activity and sedentary behaviour in adults with asthma, and the association of these behaviours with disease characteristics are addressed.

1.7.6. Physical activity and sedentary behaviour in COPD

Physical activity in COPD

It has been suggested that intrinsic limitations of the use of self-report methods to measure physical activity are that they do not perform very well in recalling lighter intensities of activity[262]. Considering that people with COPD are likely to engage in both rather lighter intensity of activity and lower levels of activity, in this section I will focus exclusively on studies using physical activity monitors (i.e. accelerometers, pedometers) to measure this behaviour in people with COPD.

1.7.6.1. *Prevalence of physical activity in COPD*

In the last 20 years, the study of device-measured physical activity in COPD populations is a subject that has received considerably more research interest compared to other OAD[165, 259, 263-267]. In 1997, Schönhofer et al. described for the first time objectively measured levels of physical activity using a pedometer[267]. The authors found that the mean ± standard deviation (SD) daily movement count in the COPD group compared to controls was 3781 ±2320 versus 8590 ± 4060, respectively (significance not reported). However, movement counters or

pedometers are not able to provide information on time spent at different intensity levels, nor discriminate between different activities[267, 268]. In 2005, Pitta and colleagues added to this evidence base comparing the amount of active-time during the day, and measurement of the intensity of activity between people with COPD and controls[165]. Using a triaxial accelerometer (DynaPort Activity Monitor), they reported that people with COPD (mean ± SD FEV_1 43 ± 18% predicted) accumulated 45.6 % less minutes per day walking and that their intensity of walking (intensity levels) was 25% less intense than controls ($p < 0.0001$ both values).

Since this publication, there has been a growing number of studies measuring physical activity in COPD and examining associations with different diseases outcomes. In their systematic review, Vorrink et al. found that physical activity impairment was a common finding in people with COPD, and that compared to controls, patients have lowers levels of activity in terms of duration, intensity and activity counts[263]. The authors also found that COPD severity (measured by the GOLD airflow limitation parameters) was only moderately correlated with the decrease in physical activity[263]. However, it is unclear whether with the newly proposed ABCD assessment tool, this finding would hold true. Studies using a multisensor activity monitor (SenseWear) in COPD populations across different GOLD categories have reported that physical activity (measured as steps, physical activity levels or time in moderate-intensity activity) is progressively reduced in patients from GOLD II[266, 269], and that this reduction is more accentuated in activities of moderate intensity than in steps[269]. For instance, Troosters et al. found that, compared to controls, people categorised as GOLD II walked 30% less, but spent 59% less time engaged in moderate physical activity ($p < 0.02$ for the difference)[269]. In a meta-analysis of steps/day, Saunders et al. reported a pooled mean of 4579 (95% CI 4310 - 5208) steps/day for individuals with COPD (I^2 =95%, $P \leq 0.0001$). Fifty–five percent of the studies included in this review had a FEV_1% predicted lower

than 50%[270]. A study using ActiGraph GT3x in COPD participants (mean FEV_1% predicted of 55%), reported a mean (SD) of 4634±2697 steps/day, and a median [IQR] of 12 (4–26) minutes of MVPA/day[168].

1.7.6.2. *Associations with disease outcomes*

There are convincing data regarding the positive impact of physical activity on several important clinical end-points in COPD populations[271]. Its positive impact on mortality, exacerbations and health status, among other outcomes, has highlighted the importance of characterising this behaviour, and has guided treatment approaches to increase physical activity in COPD populations[271].

Longitudinal studies have showed that lower levels of physical activity are strongly related to increased risk of acute exacerbations resulting in hospitalisation[272, 273], length of time until first admission for exacerbation[274], and all-cause mortality in COPD patients[264, 272, 274].

Cross-sectional studies have also found that higher levels of physical activity were positively associated with clinical outcomes, such as exercise capacity[165, 259, 265], quadriceps muscle strength and mass [165, 265, 275]and health status[265, 276]; and negatively associated with dynamic hyperinflation[114], comorbidities[277] (such as metabolic syndrome[278], and type-2 diabetes[276]), systemic inflammation[265, 266, 279], and symptoms[271] .

Sedentary time in COPD

Despite the well-recognised benefit of physical activity in people with COPD, it is likely that some patients may struggle to engage in the recommended levels of physical activity due to the clinical impairments associated with the disease. This difficulty becomes even more pronounced in people with severe disease, especially in those people who need domiciliary-oxygen therapy to maintain their oxygen levels. Symptoms such as high levels of dyspnoea

even at rest, and general deconditioning also increase the difficulty to engage in physical activity. Along with encouraging the need to engage in at least some physical activity, the reduction of time spent in sedentary behaviours and the improvement of its patterns of accumulation (more often interruptions of sedentary time) could be seen as an achievable message for people with COPD. As sedentary time is closely and negatively correlated with light physical activity, a decrease in the former behaviour may be translated into a higher engagement in light physical activity[280]. In the following sections, I will be presenting the evidence of the study of sedentary behaviour in this population, and how it is associated with some health outcomes.

1.7.6.3. *Prevalence of sedentary time in COPD*

Sedentary time has not been examined in COPD as widely as physical activity, neither with devices nor with questionnaires. Nevertheless, some earlier studies also included measures of sedentary time. For instance, in 2005 Pitta et al. (using a triaxial accelerometer) reported that people with COPD engaged in more sedentary time than healthy controls (sitting time: 374 ± 139 versus 306 ± 108 minutes/ day and lying time 87±97 versus 29± 33 minutes a day, respectively $p < 0.004$ both). Similarly, a study comparing the levels of sedentary time between people with COPD and their partners found that COPD participants engaged in significantly higher levels of sedentary time (median [IQR]= 616 [566-663] versus 558 [498-606], $p < 0.0001$, respectively)[260]. Lastly, Furlanetto et al. reported that participants with COPD spent a median [IQR] of 7.52 [5.63–8.65] hours/day in a combination of sitting and lying position[281]. Furthermore, Hartman et al. reported that people with COPD (53% of the sample categorised as GOLD I and II) spent almost 9 hours per day sitting, and despite that the participants with COPD GOLD stage IV sat for about 40 minutes extra than people with COPD stage I or II, the amount of time spent sitting was not significantly different between

the different GOLD stages[282]. It is worth noting that none of the studies mentioned above used postural-based accelerometers, and in one of them measures of energy expenditure (hours/day engaging in <1.5 and < 2 METs) were also reported as sedentary time variables[281].

1.7.6.4. *Associations with disease outcomes*

Very few studies have assessed the impact or association of sedentary time on disease outcomes in COPD. However, some data point towards a detrimental effect in engaging in higher levels of sedentary time. For instance, Furlanetto et al. found[281] that spending >8.5 hours /day engaged in activities at < 1.5 MET was an independent predictor of mortality at follow-up [median (IQR) 62 (43–88) months of follow-up], even after adjusting for MVPA among other variables [hazard ratio (95%CI) 4.09 (1.90-8.79), p < 0.001]. The authors also concluded that none of the remaining sedentary variables assessed (hours/day spent: sitting, lying, sitting, and lying, in "activities" at < 2 MET) presented acceptable discrimination for the mortality analysis (low sensitivity and specificity). In their cross-sectional study, Hartman et al. reported that a more positive perception of treatment control, higher introjected regulation in exercise, not using sleep medication, and use of long-term oxygen therapy were independently associated with longer sitting time, measured with an accelerometer[282].

People with COPD engage in lower device-measured physical activity levels compared to people without respiratory diseases. This decrease can be observed from early stages of the disease (GOLD II), and it is associated with important disease outcomes and mortality. Sedentary behaviour has not been widely characterised, but there are data suggesting a deleterious effect on all-cause mortality in COPD participants. No studies have compared COPD physical activity levels and sedentary time with other respiratory diseases.

1.7.7. Physical activity and sedentary time in bronchiectasis

Exercise training (the subset of physical activity that is planned, structured, and repetitive[155]) in bronchiectasis has been associated with short and middle term positive respiratory outcomes, and less exacerbations over a one year period[283]. However, compared to COPD, the study of physical activity and sedentary time in bronchiectasis are areas that have not received the same level of research interest. As a result, it is unclear if the known benefits of structured exercise impact on the level of physical activity in people with bronchiectasis. In the following sections I will describe the evidence reporting on the levels of these behaviours in bronchiectasis populations.

Considering the scarcity of data on these topics, eligible studies will be reported regardless of the type of activity or sedentary measurement utilised (device-measured/ questionnaires).

Physical activity in bronchiectasis

1.7.7.1. *Prevalence of physical activity in bronchiectasis*

Studies measuring the level of physical activity in people with bronchiectasis have suggested a lower engagement in this behaviour, compared with people without the disease[284-287]. For instance, Gale et al.[285] found that compared to age-matched healthy controls, people with bronchiectasis reported less subjectively measured physical activity (34.6 ± 6 versus 40.8 ± 2.2 METs, (p = 0.019), respectively). De Camargo et al. also compared the levels of physical activity between a bronchiectasis and a control population with a pedometer, finding a similar trend towards lower levels of physical activity in people with bronchiectasis (mean difference (95%CI) 3,332 (1,758-4,890) steps/day, $p < 0.001$)[287]. Some studies characterised the level of physical activity in bronchiectasis without comparisons with control groups[284, 286]. For instance, Bradley et al.[284], using the ActiGraph GT3X+, reported that people with bronchiectasis accumulated 25 ± 20 minutes/day of MVPA, and 6001 ± 2780 steps/day.

Similarly, De Camargo et al. reported a median [IQR] of 8753 [5158 -12,632] steps/day[286]. Comparisons by disease severity showed that people with less severe disease have better physical activity levels. For instance, the mean ± SD of steps/day for people with mild disease was 6898 ± 2783 compared with 5137 ± 2532 for people with moderate to severe disease (p = 0.017)[284].

1.7.7.2. *Associations with disease outcomes*

In their cross-sectional study, Bradley et al.[284] reported that daily MVPA and steps/day were significantly associated with functional exercise capacity (measured by the modified shuttle test), explaining 25.8% and 32.2% of the variance in MVPA, respectively (p < 0.001). Significant associations were also reported for daily activity energy expenditure and the bronchiectasis quality of life questionnaire (QOL-B) for the respiratory symptoms domain (negative association), and for the MVPA in bouts greater than 10 minutes with the QOL-B social functioning domain (positive association)[284]. Similarly, a positive significant association between physical activity and exercise capacity was reported in other studies[286, 287], as a negative association was reported for dyspnoea score[287]. No significant association were found between physical activity and lung function (FEV_1% predicted)[284] nor quadriceps muscle strength[287].

Sedentary time in bronchiectasis

1.7.7.3. *Prevalence of sedentary time in bronchiectasis*

To date, only one study has reported on sedentary time in a bronchiectasis population. Bradley et al. reported that people with bronchiectasis accumulated a mean 634 ± 77 minutes/day or approximately 10.6 hours/day. The authors utilised the ActiGraph GT3X+ to measure this behaviour[284].

1.7.7.4. *Associations with disease outcomes*

Bradley et al. found that sedentary time was only significantly associated with the Marcus decisional balance questionnaire. No associations were found for sedentary time and clinical respiratory outcomes such as exercise capacity, lung function or health status[284].

The measurement of physical activity in bronchiectasis is considerably less researched than in COPD. Data available suggest lower engagement in this behaviour compared to people without respiratory disease, although the degree of reduction seems to be less severe compared to people with COPD. Very few studies have described associations with disease characteristics, with exercise capacity the clinical outcome displaying the strongest association. Measures of sedentary time are scarce.

1.8. Summary Part 2: movement behaviours section

Physical activity and sedentary behaviour are distinct behaviours independently associated with several health outcomes, including the incidence and prognosis of cardiovascular diseases, type-2 diabetes mellitus, osteoporosis, and breast and colon cancer. Considered important modifiable risk factors, several countries, including Australia, have released public health recommendations aimed at promoting the engagement of healthy-enhancing levels of physical activity, while discouraging high and continuous engagement in sedentary time. The measurement of these behaviours is an evolving area, and nowadays the use of devices to quantify the different levels of these behaviours has become more accessible and common than in the past. In COPD, physical activity is very well characterised. The engagement in low activity levels has been regarded as a predictor of exacerbation resulting in hospitalisation and increasing the likelihood of all-cause mortality in this disease. As a result, clinical guidelines and research initiatives are now testing approaches to increase physical activity levels in this population. Physical activity levels in bronchiectasis have been considerably less studied, but evidence suggests that these sit at a midpoint between values found in people without respiratory diseases and people with moderate to severe COPD. Sedentary behaviour in both diseases has been considerably less characterised, although in COPD studies have suggested a higher engagement compared to controls, and a detrimental association between sedentary time and mortality risk.

In section 1.9 of this chapter, I will present the motivation, aims and hypotheses of this thesis. In Chapter 2, I will provide a thorough review of the literature on physical activity and sedentary time in asthma.

1.9. Motivation for the present thesis

In section 1.7.4. (*Characterisation of activity behaviours in obstructive airway disease populations: what is the evidence?*), I reviewed the available literature and reported that physical activity impairment is a common finding in COPD and bronchiectasis. Similarly, these populations, especially COPD, seem to engage in high levels of sedentary time, although this finding requires further research. Higher levels of activity and lower levels of sedentary time are associated with important disease outcomes in COPD. In bronchiectasis, less data are available, but higher levels of physical activity have been associated with better exercise capacity, health status, and less dyspnoea. People with severe asthma are likely to be affected by similar activity impairment and high engagement of sedentary time as people with other obstructive airway diseases are. However, these behaviours have not been widely addressed in severe asthma. Similarly, associations of these behaviours with clinical and biological outcomes of the disease have not been explored. For this reason, it is unclear how the levels of physical activity and sedentary time in people with severe asthma compares to those found in other obstructive airway diseases, such as COPD and bronchiectasis. As a result, it is also unclear whether lower physical activity levels are a prevalent characteristic in people with obstructive airway diseases, and therefore a risk factor that should be addressed jointly, and not only in COPD.

Lastly, it is unclear if shared pulmonary and extrapulmonary characteristics of these diseases are associated with the level of physical activity performed, nor how physical activity is interrelated with other extrapulmonary outcomes in their relationship with health status in bronchiectasis and severe asthma.

If physical activity impairment (and sedentary time) in obstructive airway diseases is to be considered a treatable trait, these are questions that need to be addressed.

In this thesis, I examine the levels of physical activity and sedentary time in severe asthma and their association with disease clinical and biological characteristics, and the level of physical activity in severe asthma compared to diseases such as bronchiectasis and COPD. Furthermore, I explore the relationship of this behaviour with shared pulmonary and extrapulmonary characteristics of these diseases, and its relationship with health status.

In order to frame the study of physical activity and sedentary time in severe asthma, in the next chapter (Chapter 2) I will first provide a thorough revision of the literature on the prevalence of these behaviours in adults with asthma (including people with different disease severity), and how these behaviours relate with different asthma outcomes. In the first primary data chapter of my thesis (Chapter 3), I characterise the level of physical activity and sedentary time in a severe asthma population compared to healthy controls, and I assess the association of these behaviours with different clinical and biological outcomes of the disease. In Chapter 4, I compare the levels of physical activity found in severe asthma to diseases such as bronchiectasis and COPD, followed by an analysis of the association of this behaviour with shared characteristics of these diseases as an OAD group. Lastly, in Chapter 5 I examined the interrelationship between health-related quality of life, physical activity and other extrapulmonary outcomes that have been previously associated with health status in asthma, COPD and bronchiectasis. This last study was carried out in a severe asthma and bronchiectasis population with similar clinical characteristics and levels of physical activity.

1.10. Aims and Hypotheses:

The principal aim of this thesis is to assess whether physical activity impairment is a prominent characteristic in severe asthma and bronchiectasis, as it is in other obstructive airway diseases such as COPD.

I hypothesised that lower levels of physical activity are a characteristic shared by individuals with the obstructive airway diseases of asthma, COPD and bronchiectasis.

Specific aims and hypotheses

Aim 1: To update and synthesise the evidence in relation to the prevalence of physical activity and sedentary time in adults with asthma (Chapter 2).

Hypotheses 1: Adults with asthma will present lower levels of physical activity and higher engagement in sedentary time than adults without asthma.

Aim 2: To synthetise the evidence on the associations of physical activity and sedentary time with clinical and biological outcomes in people with asthma (Chapter 2).

***Hypotheses 2*:** Better physical activity and sedentary time parameters will be associated with better clinical and biological markers of asthma in adults.

Aim 3: To characterise the level of physical activity and sedentary time in a severe asthma population, compared to age and sex-matched controls (Chapter 3)

Hypothesis 3: People with severe asthma will present lower levels of physical activity and higher levels of sedentary time than people without respiratory diseases.

Aim 4: To assess the associations of physical activity and sedentary time with clinical and biological characteristics of the severe asthma population (Chapter 3)

Hypothesis 4: In people with severe asthma, higher physical activity and lower sedentary time will be associated with better clinical and biological asthma characteristics.

Aim 5: To characterise the prevalence and intensity of physical activity in people with severe asthma and bronchiectasis, compared to people without respiratory disease and to people with moderate-severe COPD (Chapter 4).

***Hypothesis 5*:** People with bronchiectasis and severe asthma will present lower levels of physical activity compared to people without respiratory disease, but their degree of physical activity impairment would not be as severe as that found in participants with moderate to severe COPD.

Aim 6: To test whether physical activity is associated with shared clinical and biological characteristics found in OAD (Chapter 4).

***Hypothesis 6*:** In people with obstructive airway diseases, physical activity will be associated with shared clinical disease characteristics.

Aim 7: To explore the interrelationships between several extrapulmonary outcomes, including physical activity, comorbidities, skeletal muscle function, among others with health-related quality of life in an obstructive airway disease population composed of participants with severe asthma and bronchiectasis (Chapter 5).

Hypothesis 7: In people with severe asthma and bronchiectasis, better extrapulmonary characteristics, such as higher physical activity, fewer comorbidities, and better skeletal muscle function, will be associated with improved health-related quality of life in participants with severe asthma and bronchiectasis.

1.11. Study design and methods of primary data studies

Table 1-9: Overview of the design and methods of papers included as part of this thesis.

Short title and chapter	***Design***	***Participants***	***Assessments***	***Data analysis***
Physical activity and sedentary time in severe asthma *(Chapter 3)*	Cross-sectional study, descriptive and comparative	61 adults with severe asthma and 61 sex- and age-matched participants without respiratory disease	Demographic features, anthropometric measures (weight, height, BMI), clinical characteristics including smoking history, medical history, medication use, severe exacerbations, atopy, anxiety and depression scores (HADS). Assessments included in analyses: lung function (spirometry), functional exercise capacity (6MWD), systemic (hs-CRP) and airway inflammation (eosinophils and neutrophils in sputum, Feno levels), asthma controls (ACQ), quality of life (AQLQ), physical activity and sedentary time (ActiGraph wGT3X-BT). Data collection: Participants from this study were recruited concurrently between March 2014 and April 2017.	Differences between groups: Student *t* test, Wilcoxon rank sum test. Associations between variables: simple and multivariable linear regression analyses (movement behaviours as independent variables), logistic regression analyses, Spearman rank correlation and collinearity analyses.

Short title and chapter	Design	Participants	Assessments	Data analysis
Physical activity in obstructive airway diseases *(Chapter 4)*	Cross-sectional study, descriptive and comparative	62 adults with severe asthma, 60 adults with bronchiectasis, 67 adults with moderate to severe COPD, and 63 people without respiratory diseases	Demographic features, anthropometric measures (weight, height, BMI), clinical characteristics including smoking history, severe exacerbation, medical history, medication use, anxiety and depression scores (HADS), health-related quality of life (SGRQ). Assessments included in analyses: lung function (spirometry), functional exercise capacity (6MWD), systemic (hs-CRP) and airway inflammation (eosinophils and neutrophils in sputum, dyspnoea (mMRC) physical activity and sedentary time (ActiGraph wGT3X-BT).	Differences between and within groups: One-way analysis of variance, Kruskal–Wallis, Chi-square test as appropriate. Associations between variables and interaction effects: simple and multivariable regression models (steps/day and MVPA dependent variable), Spearman rank correlation.

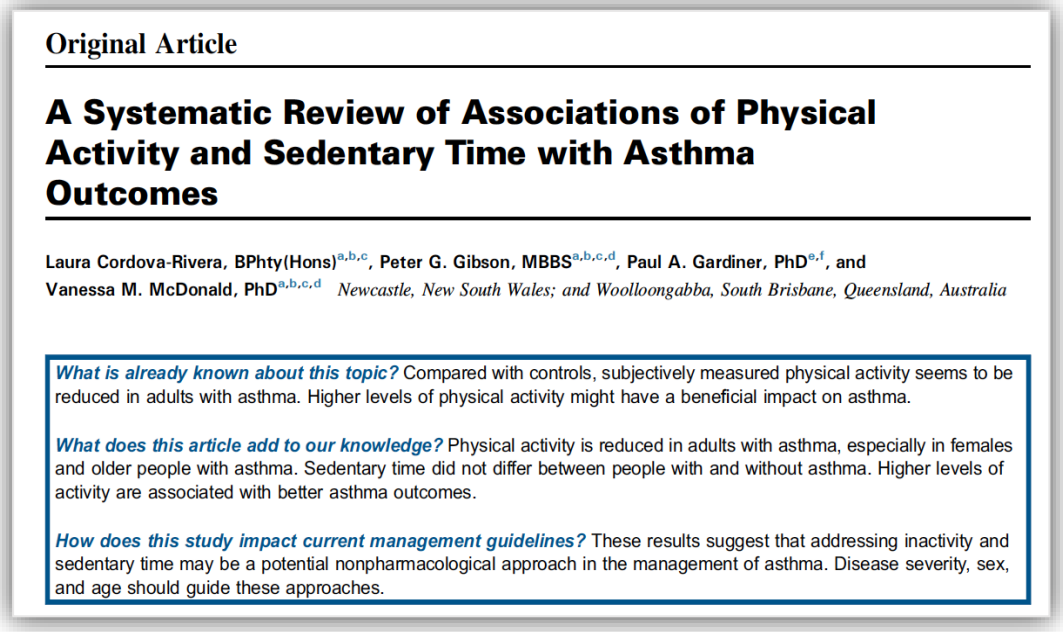
Short title and chapter	Design	Participants	Assessments	Data analysis
Physical activity and health status in obstructive airway diseases *(Chapter 5)*	Cross-sectional study, descriptive and comparative	70 adults with severe asthma and 61 adults with bronchiectasis	Demographic features, anthropometric measures (weight, height, BMI), clinical characteristics including smoking history, medication use, functional exercise capacity (6MWT), lung function (spirometry). Assessments included in analyses: health-related quality of life (SGRQ), physical activity (ActiGraph wGT3X-BT), comorbidities (CCI score, osteopenia, osteoporosis), anxiety and depression symptoms (HADS score), systemic inflammation (hs-CRP), skeletal muscle function (isometric leg strength and presence of sarcopenia).	Differences between groups: Student *t* test, Wilcoxon rank sum test. Associations between variables and interaction effects: simple and multivariable regression models (SGRQ total score and by domain score as dependent variable). Multiple imputation by chained equations analyses.

BMI: body mass index; HADS: Hospital Anxiety and Depression scale; 6MWD: 6-minute walked distance; hs-CRP: high sensitivity C-reactive protein; ACQ: Asthma Control Questionnaire, AQLQ: Asthma Quality of Life Questionnaire; SGRQ: Saint George Respiratory Questionnaire; mMRC: modified Medical Research Council scale; CCI: Charlson Comorbidity Index.

2. Chapter 2: Physical activity and Sedentary Time in Adults with Asthma

This chapter has been published in JACI: In Practice.

Citation: Cordova-Rivera L, Gibson PG, Gardiner PA, McDonald VM. *A systematic review of associations of physical activity and sedentary time with asthma outcomes.* J Allergy Clin Immunol Pract. 2018 Mar 3. pii: S2213-2198(18)30127-2. doi:10.1016/j.jaip.2018.02.027



Original Article

A Systematic Review of Associations of Physical Activity and Sedentary Time with Asthma Outcomes

Laura Cordova-Rivera, BPhty(Hons)[a,b,c], Peter G. Gibson, MBBS[a,b,c,d], Paul A. Gardiner, PhD[e,f], and Vanessa M. McDonald, PhD[a,b,c,d] *Newcastle, New South Wales; and Woolloongabba, South Brisbane, Queensland, Australia*

What is already known about this topic? Compared with controls, subjectively measured physical activity seems to be reduced in adults with asthma. Higher levels of physical activity might have a beneficial impact on asthma.

What does this article add to our knowledge? Physical activity is reduced in adults with asthma, especially in females and older people with asthma. Sedentary time did not differ between people with and without asthma. Higher levels of activity are associated with better asthma outcomes.

How does this study impact current management guidelines? These results suggest that addressing inactivity and sedentary time may be a potential nonpharmacological approach in the management of asthma. Disease severity, sex, and age should guide these approaches.

An invited short summary of this article has been highlighted in the "Latest Research" section of the American Academy of Allergy, Asthma & Immunology (AAAAI) website

See **Appendix I** for the published article and supplementary data.

See **Appendix II** for the summary published in the AAAAI website.

Overview of this Chapter

Lower levels of physical activity and/or high engagement in sedentary behaviour are common findings in COPD and bronchiectasis, and these behaviours seem to be associated with important adverse disease outcomes. Chapter 1 of this Thesis reviewed these associations for COPD and bronchiectasis, however, literature on these behaviours in people with asthma has not been extensively reviewed, and thus it is unclear whether they are prevalent in this group.

To address this gap, I aim to update and synthesise the evidence in relation to the prevalence of physical activity and sedentary time in adults with asthma and report the associations of these behaviours with clinical and biological outcomes in people with asthma.

I hypothesised that adults with asthma will present lower levels of physical activity and higher engagement in sedentary time than adults without asthma, and that better physical activity and sedentary time parameters will be associated with better clinical and biological markers of asthma in adults.

This chapter contains the published version of the literature review, which has not been updated since publication.

2.1. Abstract

Background: Physical inactivity and high sedentary time are associated with adverse health outcomes in several diseases. However, their impact in asthma is less clear.

Objective: We aimed to synthesise the literature characterising physical activity and sedentary time in adults with asthma, to estimate activity levels using meta-analysis, and to evaluate associations between physical activity and sedentary time and the clinical and physiological characteristics of asthma.

Methods: Articles written in English and addressing the measurement of physical activity or sedentary time in adults ≥18 years old with asthma were identified using four electronic databases. Meta-analysis was used to estimate steps/day in applicable studies.

Results: There were 42 studies that met the inclusion criteria. Physical activity in asthma was lower compared to controls. The pooled mean (95%CI) steps/day for people with asthma was 8390 (7361, 9419). Physical activity tended to be lower in females compared with males, and in older people with asthma compared with their younger counterparts. Higher levels of physical activity were associated with better measures of lung function, disease control, health status, and health care use. Measures of sedentary time were scarce and indicated a similar engagement in this behaviour between asthma participants and controls. High sedentary time was associated with higher health care use, and poorer lung function, asthma control and exercise capacity.

Conclusions: People with asthma engage in lower levels of physical activity compared to controls. Higher levels of physical activity may positively impact on asthma clinical outcomes. Sedentary time should be more widely assessed.

2.2. Introduction

Asthma is an obstructive airway disease that causes symptoms of dyspnoea, wheezing, and chest tightness. These symptoms, and the fear of provoking exercise induced bronchoconstriction (EIB), may have a negative impact on the engagement in physical activity in people with asthma[1, 288, 289].

Physical activity and sedentary time have been widely studied in the general population[160] and in chronic obstructive pulmonary disease (COPD). People with COPD are considerably less active and more sedentary than people without respiratory conditions[165, 259]. Furthermore, inactivity in COPD is associated with more exacerbations resulting in hospitalisation[273], a reduced time to readmission[272], and increased all-cause mortality[264, 272, 274]. As a result, there are well-established exercise programmes for people with COPD that seek to address physical inactivity[89, 126]. In asthma however, the role of physical activity and sedentary time is less clear[166], and thus guidelines and interventions to target these behaviours in this population are limited.

In a prior systematic review in adults and children, Eijkemans et al. suggested that people engaging in higher levels of physical activity might have a lower risk of asthma incidence[261]. In adults with asthma, they also found a trend towards lower levels of physical activity compared to controls[261]. However, none of the included studies used objective measures (accelerometry) to quantify physical activity in adults, and sedentary time was not addressed. Another review found that children and adolescents with and without asthma engage in a similar amount of objectively measured physical activity[290]. Despite this evidence, there are no reviews of the literature that have evaluated the prevalence of sedentary time in adults with asthma, nor reviewed the use of accelerometry to quantify physical activity and sedentary time in this population. Additionally, the degree to which the level of physical

activity and sedentary time impact on the airway symptoms or clinical outcomes in adults with asthma has not been reviewed.

Our aim therefore is to update and synthesise the evidence in relation to the prevalence of physical activity and sedentary time in adults with asthma. We conducted a meta-analysis of studies reporting steps/day in people with asthma and sought to evaluate the associations of these behaviours with the clinical and physiological characteristics of the disease.

2.3. Methods

2.3.1. Literature search

Articles written in English and addressing the measurement of physical activity or sedentary time in adults (≥18 years) with asthma were identified by a comprehensive search using the Medline, Embase, PEDro, and Cochrane databases. Search was conducted in April 2017, and updated in October 2017, and included all articles published until the search date.

Eligible studies were those that: examined the prevalence and patterns of these behaviours in asthma populations, or studies analysing the association of these behaviours with clinical or biological markers of the disease. We did not include a filter for study design. Details of the search strategy are provided in Table 2-1.

Table 2-1: Search Strategy.

	Search strategy: (#1) AND (#2 OR #3)
#1	Asthma* or wheez* or "bronchoconstriction"
#2	"physical activity" or ("physical exercise" or "exercise") or "walking" or "motor activity"
#3	("sedentary behaviour" OR "sedentary behavior" OR "sedentary time") OR ("sedentary lifestyle") OR ("internet time") OR ("computer time") OR ("television watching" OR "television viewing" OR "television time") OR ("TV watching" OR "TV viewing" OR "TV time") OR ("screen time") OR "sitting time" OR "reading time"

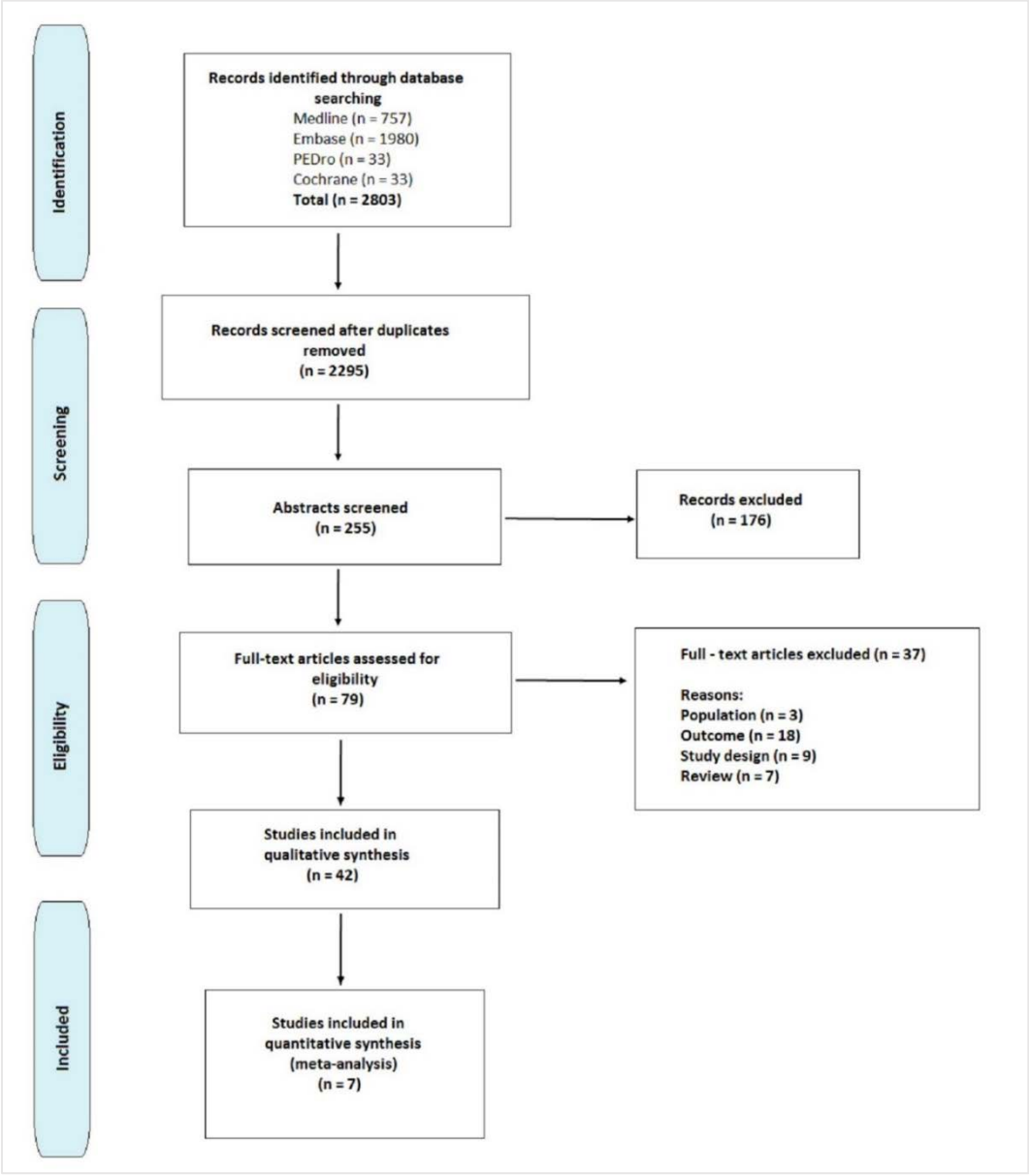
2.3.2. Analysis

Statistical analysis was performed using STATA 13 (Stata Corp., College Station, TX, USA). The continuous outcome (mean steps/day) from relevant studies[291-297] was pooled using the random-effect model. Authors of three studies were contacted and provided further details of their results[291, 295, 296].

2.4. Results

The initial search yielded 2803 references. A flow diagram[298] of the literature search is provided in Figure 2-A.

Figure 2-A: PRISMA Flow Diagram Literature search.



Updated 31 October 2017

We identified 42 eligible studies investigating physical activity and/or sedentary time in adults with asthma. Population characteristics are presented in Table 2-2. From these studies, 18 compared the level of these behaviours in asthma to a control group[291-294, 296, 299-311]. Table 2-3 summarises the physical activity measurements utilised in these 18 studies. Three studies[295, 297, 312] without a control group were also included in Table 2-3 in order to provide further details of the activity monitors used. Associations with disease characteristics were assessed in 24 studies[291-293, 296, 297, 300, 301, 305, 307, 311-325] (Table 2-4). Additionally, two studies reported physical activity as a confounder of body mass index (BMI)[326, 327], and two studies reported physical activity prior to a randomised controlled trial (RCT) exercise intervention[295, 328]. In five studies, the association between current asthma and different levels of physical activity was assessed[329-333]. In general, the studies were quite heterogeneous in terms of the population and assessments of activity/sedentary time. Studies included 193,821 asthma participants and 1,417,540 controls. Most participants were women, and in 31% of the studies the mean age was under 45 years old. Twenty-three studies used a self-reported asthma diagnosis[299-305, 308, 310, 311, 314, 315, 317-319, 321, 322, 326, 329-333]. Disease severity or level of control was reported in 15 studies, and populations included people with mild, moderate, and severe asthma[291-293, 295-297, 306, 307, 311, 319, 320, 323, 326-328].

Table 2-2: Demographic characteristics of studies included.

		Asthma participants					Controls		
Cross-sectional studies									
	Country	**N**	**Female (%)**	**Age**	**Current smoking (%)**	**Disease severity (%)**	**n**	**Female (%)**	**Age**
Bacon 2015[313]	Canada	643	60	53.4 ± 15.4	8.7	n/r	n/a	n/a	n/a
Bahmer 2017[291]	Germany	146	51 Severe 53 Mild to mod.	55.5 48.1	22 24	43.1 56.8	29	38	42.1
Beckett 2001[329]	USA	4547	52	18 to 30	41.1	n/r	4131	55.2	18-30
Barros 2017[326]	Portugal	2578	62	20 to >85	21.4	Current: 44 Persist: 38 Severe:18	30066	52.4	20 to >85
Bruno 2016[292]	Italy	24	66	38.5 ± 14.2	n/r	Mild to mod.	18	55	43.1±14.3
Chen 2001 [299]	Canada	1070	61.7	12 to >70	26.7	n/r	15743	55	12 to >70
Cordova-Rivera 2017[293]	Australia	61	52.5	59 [43 – 68]	6.6	Severe	61	52.5	54 [34 – 63]
Doggett 2015 [300]	Canada	1830	69.2	20 to >55	33.1	n/r	18978	54.4	20 to >55
Dogra 2006 [315]	Canada	11243	62	40 to 44	n/r	n/r	n/a	n/a	n/a
Dogra 2008 [302]	Canada	1772[$] 3123[^]	63[$] 68[^]	45 to 79	n/r	n/r	19864	57	65 to 79
Dogra 2009 [301]	Canada	6835	62	20 to 64	28.5	n/r	78051	51	20 to 64
Ford 2003[303]	USA	12489	64	18 to >70	n/r	n/r	147742	48.9	18 to >70
Ford 2004 [317]	USA	12111	63.7	44.2 (0.3)	26	n/r	n/a	n/a	n/a
Grammatopoulou 2010[327]	Greece	100	79	n/r	20	Mild: 58 Mod:32 Severe: 10	n/a	n/a	n/a

Iikura 2013[325]	Japan	437	53.3	64 [51–74]	7.1	n/r	n/a	n/a	n/a
	Country	**N**	**Female (%)**	**Age**	**Current smoking (%)**	**Disease severity (%)**	**n**	**Female (%)**	**Age**
Kilpelainen 2006[333]	Finland	10023	61	18-25	3.4 β	n/r	n/a	n/a	n/a
Liang 2015[304]	Australia	723	51β	18 to 29	2.7	n/r	1891	51 β	18 to 29
Ma 2016[328]	USA	330	10.6	47.6 ± 12.4	5.8	UA	n/a	n/a	n/a
Malkia 1998[305]	Finland	178	59	30 to 89	n/r	n/r	7015	30 to 89	n/r
Mancuso 2007[320]	USA	258	75	42 ± 12	11	Mild to mod	n/a	n/a	n/a
Moore 2015[294]	Canada	16	38	27.8 ± 6.1	n/r	n/r	16	50	26.6 ± 5.2
Ramos 2015[306]	Brazil	20	70	44 ± 6.0	n/r	Mod to severe	15	93	39 ± 6.0
Ritz 2010[307]	USA	20	70	28 ± 6.8	n/r	Mod	20	70	31.6 ± 5.9
Scott 2013[295]	Australia	14	78.6	43.3 [37-7.8]	30.8	Mild inter: 8 Mild persist:23 Mod: 54 Severe: 15	n/a	n/a	n/a
Strine 2007[322]	USA	11962	65.5	18 to >75	23.6	n/r	n/a	n/a	n/a
Teramoto 2011[308]	USA	880	57.2	18 to >70	n/r	n/r	2960	n/r	18 to >70
Tsai 2011[309]	Taiwan	27	44	60.8 ± 10.2	11	n/r	27	37	56.8 ± 1.1
Vancampfort 2017[310]	LMICs	11857	50.8 β	18 to >65	n/r	n/r	216167	50.8 β	n/a
Van 't Hul 2016[296]	The Netherlands	226	62	47.3 ± 15.3	n/r	CA:17 PC:18 UA: 65	201	75.6	42.3 ± 16.3

Verlaet 2013[311]	Portugal	CA:125 UA:78	53 85	43 ± 28 54 ± 21.5	33	61.6 38.4	606	50.5	53 ± 24
Vermeulen 2016[297]	Belgium	20	65	39.0 ± 11.9	n/r	CA: 10 PC: 10 UA: 80	n/a	n/a	n/a
Vogt 2008[332]	USA	311	72.3	18 to > 75	n/r	n/r	4420	n/a	n/a
Westermann 2008[323]	USA	258	75.9	42 ± 12	n/r	Mild to mod	n/a	n/a	n/a
Yamasaki 2017[312]	Japan	18	55.6	63 ± 11	0	n/r	n/a	n/a	n/a
Yawn 2015[324]	USA	533	76	40.6	15.4	n/r	n/a	n/a	n/a
Zahran 2013[330]	USA	74779	76	18 to >65	19.5	n/r	869519	51.3	18 - 65+

Longitudinal studies

	Country	**Follow-up**	**n**	**Female (%)**	**Age***	**Current smoking (%)**	**Disease severity (%)**	**n**	**Female (%)**	**Age***
Bedard 2017[331]	France	Up to 11 years	15353	100	59.2 ± 6.3	8.5	n/r	n/a	n/a	n/a
Brumpton 2017[314]	Norway	Mean 11.6 years	1329	51.6	44.1 ± 12.9	25.1	n/r	n/a	n/a	n/a
Fisher 2016[316]	Denmark	Mean 16 years	1347	61.8	57.1 ± 4.5	34.9	n/r	n/a	n/a	n/a
Garcia-Aymerich 2007[318]	Denmark	Mean 11 years	153	n/r	52.4 ± 11.6	n/r	n/r	n/a	n/a	n/a

Garcia- Aymerich 2009[319]	USA	Mean 2 years	2818	100	62.7 ± 6.9	5.8	Mild inter: 20.3 Mild persist:35.6 Mod: 34.6 Severe: 9.5	n/a	n/a	n/a

*Age reported as mean± SD or (SE), or median [IQR], or range. # Cross-sectional data from a longitudinal cohort. B: % reported for the whole sample; & only participants with asthma at baseline. $ Values for older adults; ^ values for middle aged adults, * results reported correspond to cross-sectional data. n/a: not assessed; n/r: not reported; Inter: intermittent; Persist: persistent; Mod: moderate asthma; CA: controlled asthma; PC: partially controlled; UA: uncontrolled asthma; LMICs: low and medium income countries.*

2.4.1. Prevalence of physical activity

Among studies using a control group, eleven[291-293, 296, 300, 302, 303, 305, 306, 308, 310] (asthma sample =32,606) reported less physical activity in asthma, and six reported no difference[294, 301, 304, 307, 309, 311] (asthma sample=7824). One study[299] (asthma sample size=1,070) reported increased physical activity in younger adults with asthma (<40 years old), but decreased in older participants (>50 years old).

Activity monitors were used in 8 studies[291-297, 312]. Five of them included a control group[291-293, 295, 296] (Table 2-3 and 2-4). A meta-analysis (Figure 2-B) found that the weighted mean (95%CI) number of steps/day for people with asthma was 8390 (7361, 9419). In the four studies that compared the volume and/or intensity of activity, people with asthma tended to accumulate less physical activity than controls (Table 2-5).

Some studies reported an effect of age and sex on activity in asthma. Three studies reported that the decrease in activity in people with asthma was mostly seen in older participants (≥50 years old)[299, 303, 310]. For instance, despite their overall results showing that people with asthma were more inactive than controls, Ford et al.[303] did not find statistically significant differences in the association between activity and asthma status in people under the age of 60. Some studies reported that males with asthma presented higher levels of activity than females with asthma or than their healthy counterparts[305, 311, 323, 324]. Furthermore, two studies demonstrated that the decrease in activity that develops in older people with asthma occurs earlier, or exclusively, in females than males[299, 302]. Dogra et al.[302] for instance, found that the levels of physical activity between middle-age and older males with asthma were similar, while older females with asthma were considerably less active than their younger counterparts.

Table 2-3: Physical activity measurements in studies with a control group.

	Studies using questionnaires				
Study	**Asthma definition**	**PA or ST measurement**	**PA or ST domain**	**Recall period**	**Outcome**
Chen 2001[299]	Self-reported asthma diagnosed by a health professional	PA questionnaire from National Population Health Survey Canada	LTPA	12-month	Mean daily energy expenditure (EE) (kcal $kg^{-1}day^{-1}$)
Doggett 2015[300]	Self-reported physician-diagnosed asthma and use of asthma medication.	Questionnaire	LTPA Television-viewing time (TVT)	PA: 1-week TVT: typical week in last 3 months	PA: frequency and intensity of (measured as increase of heart rate and breathing) TVT: >10 and ≤ 10 hours/week as high and low TVT respectively
Dogra 2008[302]	Self-reported physician-diagnosed asthma	Questionnaire from CCHS cycle 2.1	LTPA	n/r	Active (≥ 1.5 kcal/kg/day) Inactive (<1.5 kcal kg/day) (estimated from EE)
Dogra 2009[301]	Self-reported physician-diagnosed asthma	From CCHS cycle 3.1	LTPA	n/r	Active (>3.0 kcal/kg/day), "Moderately active" (1.5–3.0 kcal/kg/day), "inactive" (<1.5 kcal/kg/day)
Ford 2003[303]	Self-reported physician-diagnosed asthma	Questionnaire from 2000 BRFSS	LTPA	1-month	Frequency and duration. EE/week, and PA Index
Liang 2015[304]	Self-reported asthma	Questionnaire from Australian National Health Survey 2007-08	PA	1-week	Intensity and frequency ≥ 800 MET: meeting PA guidelines
Malkia 1998[305]	Self-reported physician-diagnosed asthma and spirometry.	Questionnaire	LTPA, PA at work and during commuting.	n/r	Intensity and frequency METs at work and spare time. PA during commuting
Ramos 2015[306]	Asthma diagnosed by a physician	IPAQ - short form	LTPA	Average day in the last week	PA from EE + duration [METs- min/week]
Ritz 2010[307]	Asthma diagnosed by a physician	Electronic diary	PA in the past 30 minutes	3 times/day for 21 days	Frequency and intensity

Teramoto 2011[308]	Self-reported current or lifetime asthma diagnosed by a health professional	Questionnaire from 2009 Nevada BRFSS	LTPA	1-month	Engagement on PA, meet PA guidelines. Minutes/ week of MVPA
Tsai 2011[309]	Asthma diagnosed by a physician	Stanford 7-Day Physical Activity Recall	LTPA	1-week	Frequency and Intensity METs
Vancampfort 2017[310]	Self-reported lifetime diagnosis of asthma	Extract from IPAQ	LTPA	1-week	Volume of MVPA (<150 minutes/week = low PA)
Verlaet 2013[311]	Self-reported asthma	IPAQ - short form	LTPA Daily sitting time	Average day in the last week	LTPA: MET-min/week Volume of daily sitting time in minutes.
	Studies using activity monitors				
	Asthma definition	**PA or ST measurement**	**PA or ST domain**	**Wear- time protocol**	**Outcome**
Bahmer 2017[291]	Physician-diagnosed asthma, and in specialist care for > 3 months.	SenseWear Pro Armband	Total PA	Worn for 1 week. Inclusion: ≥5 days of 22.5 h	Steps/day Average minutes of at least moderate activity/day (EE>3 METs)
Bruno 2016[292]	Recruited according the ATS criteria	SenseWear Armband	Total PA	Worn over triceps area for 4 days, 24 h/day (excluded water-based activities) Inclusion: n/r	PA level (mins/day); Active EE (kcal/day); steps/day; Total EE (kcal/day)
Cordova-Rivera 2017[293]	Asthma diagnosed by a respiratory physician according to GINA guidelines.	ActiGraph wGT3X-BT	Sedentary time Total PA	Worn on dominant hip for 14-consecutive days, 24 h/day (sleeping and non-wear time excluded)	Minutes/day of: sedentary time, light PA and moderate and vigorous and very vigorous PA. Steps/day
Moore 2015[294]	History of asthma and any of the following: positive spirometry, positive AHR, ≥10% decrease in FEV_1 after an exercise challenge	SenseWear Pro3 Armband	Total PA	Worn over triceps area of dominant arm for 3 days, 24 h/day. Inclusion: preferably 2 weekdays, 1 weekend day.	Steps/day Energy expenditure

*Scott 2013[295]	Physician-diagnosed asthma, and history of AHR	Pedometer	Steps	Worn for 7 days, recording steps a diary, (prior randomisation)	Steps/day
Van't Hul 2016[296]	Asthma diagnosed by a respiratory physician and use of asthma medication.	DynaPort MoveMonitor	Total PA Sitting and lying time	Worn on lower lumbar spine for 7 consecutive days, 24 h/day (excluded water-based activities). Inclusion: ≥2 (PA) and ≥5 (lying) days of ≥22.5 h.	Hours/day in walking, sitting, and lying. Steps/day D. PA level (total EE/day): >1.70 active, 1.40 - 1.69 predominantly sedentary, <1.40 very inactive.
*Vermeulen 2016[297]	Previous asthma diagnosis, asthma exacerbation.	SenseWear Armband	Total PA	Worn for 7 days Inclusion: n/r	Steps/day, % of time at an intensity: < 3 METs, 3 to 6 METs, 6 to 9 METs and ≥ 9 METs
*Yamasaki 2017[312]	Asthma diagnosed by a respiratory physician.	Actiwatch 2	Total PA	Worn for 7 days Inclusion: n/r	Activity counts

*PA: physical activity; ST: sedentary time; LTPA: leisure time physical activity; EE: energy expenditure; CCHS: Canada community health survey; kcl: kilocalorie; BRFSS: Behavioral risk factor surveillance system; MET: metabolic equivalent task; IPAQ: International physical activity questionnaire; AHR: airway hyperresponsiveness; MVPA: moderate to vigorous PA; n/r: not reported. *These studies did not have a control group but were included in this table to provide further details of the activity monitors used.*

2.4.1.1. Reduced physical activity in people with asthma.

From the 11 studies reporting lower levels of physical activity in people with asthma compared to controls[291-293, 296, 300, 302, 303, 305, 306, 308, 310], four studies used activity monitors[291-293, 296]. Van't Hul et al.[296] found that people with asthma spent significantly less time walking, engaging in vigorous physical activity, and accumulated less steps/day than controls. Cordova-Rivera et al.[293] reported that in participants with severe asthma, steps/day and moderate and vigorous physical activity (MVPA) were reduced by 31.4% and 47.5% respectively compared to controls ($p < 0.001$ both results).

From the studies using questionnaires, Teramoto et al.[308] reported that control participants spent an additional 60 minutes/week engaged in moderate physical activity and 67 minutes/week in vigorous activity compared to the asthma group ($p < 0.001$). Ford et al.[303] reported that people with current asthma were more inactive (asthma=30.9%, never asthma=27.8% $p < 0.001$) and engaged in less vigorous physical activity (asthma=12.7%, never asthma=14.8% $p < 0.001$) than people without a history of asthma. Vancampfort et al.[310] reported that asthma was significantly associated with low physical activity (engaging in <150 min/week of moderate and vigorous physical activity), especially in people >50 years old (odds ratio (OR)(95%CI) 1.67(1.33-2.10), $p < 0.0001$).

The level of activity decreased with loss of asthma control[296], and increasing asthma severity[291, 292]. Bahmer et al.[291] reported that both steps/day and the time spent in MVPA in participants with severe asthma were reduced by 21% and 17% respectively, compared with participants with less severe disease ($p < 0.05$).

2.4.1.2. Maintained physical activity in people with asthma.

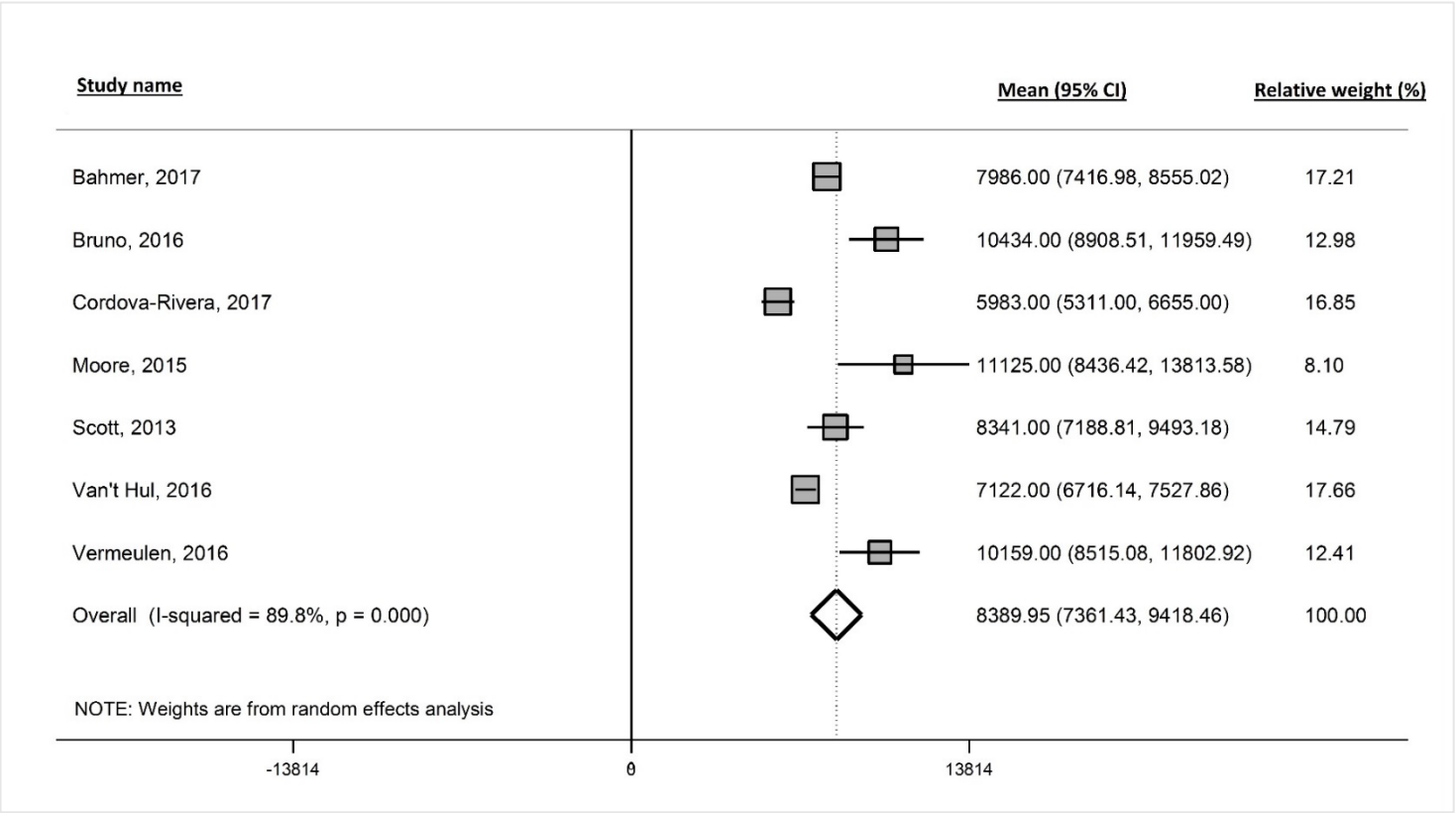
In six studies there were no consistent differences in the level of the activity between the asthma and control groups[294, 301, 304, 307, 309, 311]. One study used an activity monitor[294]. Verlaet

et al.[311] found that the proportion of participants performing MVPA was similar among people with controlled and uncontrolled asthma compared with controls; 32%, 38.5% and 33.7% ($p > 0.05$) for each group respectively. Liang et al.[304] reported that the prevalence ratio (95% CI) for young adults with asthma (<30 years old) engaging in physical activity at the recommended level was 1.09 (0.92, 1.28) compared to those without asthma.

2.4.1.3. Increased physical activity in people with asthma.

Chen et al.[299] found that younger adults with asthma achieved higher levels of activity compared to their age-matched healthy counterparts, whereas this pattern of activity reversed in the older age group, especially in females. The mean [Standard Error (SE)] energy expenditure (EE) for men in the 25-39 years age group with asthma versus their control group was 2.16 (0.22) compared to 1.72 (0.15) kcal kg/day^{-1}; and 1.60 (0.14) versus 1.28 (0.06) kcal kg/day^{-1} in the female asthma group compared to female controls ($p = 0.02$ for both). At the age of 40 this trend started to reverse, becoming statistically significant in women >55 years, and for both sexes in the ≥70 years group. In the age group ≥70 years, males with asthma reported a mean (SE) EE of 0.72 (0.34) versus age-matched controls 1.45 (0.15) kcal kgday^{-1}, while females reported a mean of 0.79 (0.17) versus 1.17 (0.07) kcal kg/day^{-1} ($p \leq 0.02$ both results).

Figure 2-B: Forest plot of standardised mean (95% confidence intervals) for steps/day.



Authors: Bahmer et al., Scott et al., and Van't Hul et al. were contacted and provided the mean and standard deviation of their results.

2.4.2. Prevalence of sedentary time

Sedentary time was reported by four studies[293, 296, 300, 311]. Two used an activity monitor[293, 296]. Van't Hul et al. reported that asthma participants spent more time lying down compared to controls (hours/day mean difference (95% CI) 0.59 (0.15, 1.03) P<0.01), but less time sitting than controls ($p > 0.05$)[296]. Similarly, another study did not find a significant difference in sedentary time between people with severe asthma and controls (minutes/day mean ± SD 674.4 ± 71 versus 676.2 ± 65, respectively $p > 0.05$)[293]. Doggett et al.[300] reported that the time spent watching TV for over 10 hours/week was 50.4% in the asthma population compared to 42.9% in the non-asthma group ($p < 0.05$).

2.4.3. Associations between physical activity or sedentary time and asthma health outcomes

Twenty-seven studies reported associations between the level of activity and asthma health outcomes. Five were longitudinal[314, 316, 318, 319, 321]. Associations with sedentary time were addressed in three studies[293, 300, 311]. Table 2-4 reports the main findings of these studies. Further descriptions of these association are summarised in the online supplement.

The relationship between physical activity and lung function was assessed in 10 studies[291-293, 296, 305, 307, 312, 314, 318, 320]. Weak but significant associations were reported in eight studies[291-293, 305, 307, 312, 314, 318], from which two were of longitudinal design[314, 318]. Measures of asthma control or asthma related health status were reported in 13 studies, 12 of them of cross-sectional design[293, 296, 297, 307, 311, 313, 315, 317, 320, 321, 323-325]. Most of the studies found a positive association between higher physical activity and better clinical outcomes, although in some studies these associations were attenuated to the null when BMI was included as a confounder[313, 321, 323, 324]. For instance, in their longitudinal analysis, Russell et al.[321] reported that the protective effect found for light physical activity on current asthma (defined as

reporting asthma symptoms, taking asthma medication, or having an asthma exacerbation in the last 12 months) was no longer significant after adjusting for BMI. Vigorous physical activity was associated with more asthma symptoms in three studies[307, 311, 321].

Measures of health care utilisation were evaluated in six studies[300, 301, 316, 319, 322, 324]. Less physical activity was associated with increased exacerbation and/or higher health care utilisation in four of them[300, 301, 319, 322]. However, contradicting results were reported in the two longitudinal cohorts[316, 319]. Positive associations between measures of exercise capacity and physical activity were reported in two cross-sectional studies[293, 320]. Higher physical activity (steps/day) was associated with lower systemic inflammation (high-sensitivity CRP) in one study[293]. No significant associations were found between physical activity and measures of eosinophilic airway inflammation[293].

Higher levels of sedentary time were associated with worse asthma clinical outcomes in two cross-sectional studies[293, 300]. In one of them, these associations were no longer significant after adjustment for physical activity[293]. Doggett et al.[300] reported an increased OR (95% CI) for GP consultations 2.59 (2.34, 2.87), and hospitalisations in the past year 1.95 (1.82, 2.08) and past 5 years 1.13 (1.07, 1.18) (p <0.001 for all results) for adults with asthma who reported >10 hours of television time/week compared to those who reported ≤10 hours.

Table 2-4: Association between physical activity or sedentary time with asthma outcomes.

Citation	*Outcome measures*	*Conclusions*
Bacon 2015[313]	PA, ACQ and AQLQ	Participants engaging in high levels of PA (20.1±8.9 METs-h/week) were nearly 2.5 times more likely to have good control (ACQ ≤ 0.8) compared with inactive patients [AOR (95% CI) 2.47 (1.06–5.73)]. Results for AQLQ were not significant.
*Bahmer 2017[291]	Steps, spirometry, body plethysmography, impulse oscillometry.	Decreased PA in asthma is associated with airway resistance and small airway dysfunction, but not with airway limitation.
Brumpton 2016[314]	PA, lung function decline.	Less decline in FEV_1/FVC in active asthma participants than inactive asthma participants [FEV_1/FVC (%): -0.14 (-0.27, -0.01) (p = 0.03)]
*Bruno 2016[292]	PA, FEV1/FVC, fat free mass and Intracellular water.	PA positively correlated with FEV_1/FVC. [Rho = 0.34 (p < 0.05)]
*Cordova-Rivera 2017[293]	ST, MVPA, Steps, 6MWD, spirometry, ACQ, AQLQ, hs-CRP, FeNO, sputum eosinophilia.	Higher levels of PA and lower levels of ST were positively associated with most of the clinical/biological outcomes, especially for Steps and exercise capacity (coeff (95% CI) 0.02 (0.00 to 0.04); p < .01) and systemic inflammation, and MVPA and ACQ (coeff (95% CI) -1.94 (-3.69 to -0.18); P= 0.032).
Doggett 2015[300]	ST (TV time), PA, health care use.	High levels of TV time associated with: more consultations (AOR (95% CI) 2.59 (2.34 2.87), hospital stays in the last year (AOR 1.95 (1.82, 2.08) and in the past 5 years (AOR = 1.13 (1.07, 1.18) Insufficient PA associated with higher health care use: hospital stays in the past year (AOR 1.16 (1.08, 1.23) or past 5 years (AOR 1.22 (1.16, 1.28)
Dogra 2006[315]	PA (EE), self-reported measures of health.	Higher PA associated to better self-reported health outcomes.
Dogra 2009[301]	PA (EE), health care use.	Lower PA levels associated with higher health care use in people with asthma: Overnight hospital stays (AOR (95%CI) 1.78 (1.31, 2.41); ≥3 GP consultations (AOR 1.26 (1.03, 1.55)
Fisher 2016[316]	PA, asthma readmission.	No association between PA and asthma hospital readmissions in people with asthma.

Ford 2004[317]	PA, QoL.	Physical inactivity (compared to VPA) significant independent predictor of impaired QoL: Poor or fair health OR (95% CI)2.36 (1.72, 3.22); >14 days with activity limitation: 2.76 (1.89 4.02); >14 days physically or mentally limited: 1.90 (1.59 2.32)
Garcia-Aymerich 2009[319]	PA (METs-h/week), asthma exacerbation.	Higher levels of PA associated with a lower risk of asthma exacerbation.
Garcia-Aymerich 2007[318]	Levels of PA, lung function decline.	MVPA in participants with asthma improved lung function decline by gaining 10 ml and 7 ml/ year of FEV_1 and FVC respectively, compared to the low PA group (significance not reported)
Ikura 2013 [325]	PA and asthma control test (ACT)	In MVRA, periodical PA (>3 METs-h/week) was significantly associated with better asthma outcome (coefficient = 0.152, p = 0.002)
Mancuso 2007[320]	PA (EE), 2MWT, CRT, asthma control (ACQ), severity, and lung function (spirometry).	PA positively correlated with physical performance in both test (2MWT Rho = 0.38; CRT Rho= - 0.39). In MVRA, better asthma control associated with more EE from walking, but not with total EE. FEV_1 associated with PA only in SLRA.
Malkia 1998[305]	PA Intensity (METs), lung function (spirometry).	Weak but significant positive correlations of PA intensity and lung function in men only (Rho FEV_1=0.26; PEF=0.35)
Ritz 2010[307]	PA intensity, lung function (spirometry), SOB, social activity, inhaler use.	Higher PA levels associated with higher PEF, higher FEV_1 in the morning and evening only, and more SOB.
Russell 2016[321]	PA with follow-up current asthma (CA) and asthma symptoms (AS)	LPA ≥3 times/week at baseline associated with less follow-up CA [OR (95%CI) 0.44(0.22 0.89)]. Result attenuated by BMI. Result for VPA $p > 0.05$
		Asthma participants with normal BMI show a significant reduction of AS associated with PA, while the overweight and obese category did not.
Strine 2007[322]	Inactivity and measures of asthma severity.	People with asthma who were inactive had significantly poorer control compared to those who were not: >3 ER/year (AOR (95%CI):2.4 (1.6, 3.6); GP visit/year (AOR:1.5 (1.1, 2.0); Absenteeism >2 weeks/year: (AOR: 1.7 (1.3, 2.0); daily symptoms (AOR: 2.5 (1.9, 3.4); Inhaler 30+ times/month (AOR: 1.9 (1.5, 2.5)

*Van't Hul 2016[296]	PA, ACQ, AQLQ and lung function (spirometry).	Low PA was correlated with poorer asthma control. No correlation between spirometry and PA (value not reported) Nil reference regarding AQOL.
*Vermeulen 2016[297]	Steps/day, activity limitation (ACQ question 3)	No correlation found between PA and activity limitation.
Verlaet 2013[311]	PA or daily sitting time (ST), and asthma control (CARAT Questionnaire)	MPA and ST predictor of controlled asthma in men: (AOR (95% CI) 1.84 (1.02, 3.30); (OR: 1.87 (1.06, 3.28) respectively. VPA doubled the risk of uncontrolled asthma in women: AOR: 1.94 (1.13-3.35).
Westermann 2008[323]	Exercise habits, asthma severity and asthma control (ACQ)	Higher BMI was more closely associated with exercise habits than were asthma control and severity, after adjusting for demographic variables.
Yamasaki 2017[312]	PA, oxidative stress and antioxidants in blood, spirometry, FeNO, levels of vitamins in serum, vitamin intake.	Significant correlations only for PA (Activity counts/minute) and FEV_1/FVC.
Yawn 2015[324]	Volume and intensity of PA, asthma control (APGAR), exacerbations.	Low PA associated with asthma control only in SLRA.

** Studies using activity monitors. PA: physical activity, ST: sedentary time; PAL: physical activity level; LTPA: leisure-time PA; LPA: light PA; VPA: vigorous PA; MVPA: moderate and vigorous PA; Steps: average steps/day; ACQ: asthma control questionnaire; AQLQ: asthma quality of life questionnaire; QoL: quality of life; 6MWD: -minute walk distance; hs-CRP: high sensitivity C-reactive protein, FeNO: fraction of exhaled nitric oxide; SOB: shortness of breath; 2MWT: 2-minute walk test; EE: energy expenditure; METs: metabolic equivalent task; RM: repetition maximum; FEV_1: forced expiratory volume in the first second; ER: emergency room; AOR: adjusted odd ratio; CI: confidence interval; SLRA: simple linear regression analysis; MVRA: multi-variable regression analysis; OR: odds ratio; AHR: adjusted hazards ratio*

Table 2-5: Activity outcomes from activity monitors.

		Steps per day			***Volume/Intensity of PA or Sedentary time (minutes⁺ or hours^/ day)***		
	N	**Asthma**	**Controls**	***p*-value**	**Asthma**	**Controls**	***p*-value**
Bahmer 2017[291]	SA: 63 MA: 83 C:29	SA: 6174 [4822-9277] MA: 7841 [6534 - 10252]	8,912 [6800 - 11127]	**< 0.001**	SA:125 [68 - 172] MVPA⁺ MA:151 [99 - 197]	163 [110 – 207]	**<0.05 #**
Bruno 2016[292]	A: 24 C: 18	10,434 ± 3,813	10860 ± 3042	> 0.05	PA⁺: 69.7 ± 84.2 AEE: 335 [380] & kcal/day	93.2 ± 101 486.7 [435]	**0.04** **0.04**
Cordova-Rivera 2017[293]	SA: 61 C: 61	5362 [3999 - 7817]	7817 [6072 - 10014]	**0.0002**	ST⁺ 674.4 ± 71 LPA⁺ 193 ± 57.5 MVPA⁺ 21.9 [12.8 -37.9]	676.2 ± 65 171 ± 50.6 41.7 [29.3, 65.8]	> 0.05 **0.029** **<0.0001**
Moore 2015[294]	A: 16 C: 16	11125 ± 5487	10711 ± 2675	> 0.05	n/a	n/a	
Scott 2013[295]	A: 33	8341 ± 3377	n/a		n/a	n/a	
Van't Hul 2016[296]	A: 226 C: 201	7593 [7155 - 8030]	8,795 [8326 - 9263]	**0.001**	Sitting^: 8.21 [7.95 - 8.48] PAL: 1.53 [1.51 - 1.55] LPA^: 1.7 [1.65 - 1.88] MPA^: 1.66 [1.58 - 1.74] VPA^: 0.34 [0.30 - 0.38]	8.6 [8.29 - 8.86] 1.57 (1.55-1.59) 1.91 [1.80-2.02] 1.64 [1.55-11.7] 0.45 [0.41-0.49]	> 0.05 **0.034** > 0.05 > 0.05 **<0.001**
Vermeulen 2016[297]	A:20	10159 ± 3751	n/a		MET 0-3 (% time): 87.2 MET 3-6 (% time): 12.07	n/a	
Yamasaki 2017[312]	A: 18	n/a	n/a		⁺Activity counts: 283.3 ± 81.1	n/a	

SA: severe asthma, MA: mild to moderate asthma. A: asthma, C: controls. Results expressed as mean ± standard deviation or median [IQR]. + reported as minutes/day. ^ Reported as hours/day. # P value for whole asthma sample compared to healthy control. &: reported as median [IQR] by the authors. PA: physical activity; AEE: active energy expenditure; kcal: kilocalories; PAL: physical activity level; MVPA: minutes of at least moderate PA/day. LPA: light physical activity, MPA: moderate PA, VPA: vigorous PA, ST: sedentary time, n/a: not assessed; MET 0-3: metabolic equivalent task of light PA; MET 3-6: moderate PA. Statistically significant results in bold.

2.5. Discussion

This review summarises the literature in relation to the prevalence of physical activity and sedentary time in people with asthma, and the associations between these behaviours and different disease outcomes. We found that people with asthma undertake less physical activity than people without asthma, and that the level of activity in asthma seems to be influenced by age, sex, and disease severity.

We also found that people with asthma average 8390 steps/day. This is almost double the value observed in COPD, where an average of 4579 steps/day was reported (FEV_1% < 50% in 55% of studies included)[270]. This suggests that while physical activity may be reduced in asthma, the degree of reduction is not as severe as in COPD. Nevertheless, there are subgroups in the asthma population where physical activity is lower[291-293, 296]. The two studies including people with severe asthma reported a median of around 5800 step/day[291, 293]. Therefore, the estimate of 8390 steps may not be a value applicable to more severe asthma populations. However, considering that this is the first meta-analysis of steps performed in adults with asthma, and that the objective measurement of physical activity in asthma is a fairly recent topic, this value provides a reference that can be updated and developed with future studies.

We found that physical activity seems to be influenced by sex. Several studies reported better activity outcomes in men with asthma compared to women. Similar findings have been reported in children with asthma compared to controls, suggesting that lower levels of activity are only present in women[334, 335]. In the general population it has also been found that both girls[336] and adult females[337, 338] do less activity than their male counterparts. However, the fact that the decline in activity in middle-aged and older people with asthma is seen earlier in women[299, 302], may suggest that the disease consequences are more severe, or

have a greater impact on health in females. Supporting this observation is evidence suggesting that among people with similar asthma severity, women tend to have poorer self-reported measures of asthma control and health status[339] and are twice as likely to be admitted to hospital due to acute asthma[340]. From a societal perspective, this sex difference could also be due to changes in physical activity after retirement, with women retiring at an earlier age[302].

We also identified a potential effect of age on the level of physical activity, showing that the decrease in activity is more pronounced, or even exclusive, in the older asthma population[299, 303, 304, 310]. This is in line with evidence that younger people with asthma engaged in similar[290] or higher[335, 341] levels of activity compared to their age-matched controls. Plausible biological reasons could relate to the age-related changes in the lung leading to an increased work of breathing that are more extreme in people suffering from respiratory morbidity. Furthermore, older people with asthma are likely to have a longer duration of disease, therefore may have more airway remodelling resulting in incomplete reversibility of airflow limitation[125]. It is also worth mentioning that in the last 30 years, there has been a growing body of evidence that supports the adherence to exercise in people with asthma. This contradicts previous beliefs that people with asthma should avoid exercise and physical activity[342]. It is likely that the age-effect identified in this review is linked to this paradigm shift. Finally, people over 50 years of age with obstructive airway disease show a high degree of overlap in features of both asthma and COPD[125], so it is possible that the activity levels of older people with asthma could be similar to that of COPD populations[165, 259, 270]; a finding that requires further investigation, and may focus physical activity interventions to an older age group.

In terms of the associations with physical activity, there was a trend showing that higher physical activity was modestly associated with better lung function in people with asthma. In two longitudinal studies, a trend towards slower lung function decline in active people with asthma compared to inactive people was reported[314, 318]. Studies carried out in the general population[343, 344] have suggested that this positive impact may be due to the counteracting effect that physical activity may have on the age-related chest wall stiffening[343], or to a potential positive impact on inspiratory muscle endurance[345]. Among the cross-sectional studies, the results were less consistent. Interestingly, in two of the studies reporting a positive association between spirometric values and physical activity[292, 307] participants were relatively young (mean age <39 years), with moderate disease severity, whereas studies in severe or uncontrolled asthma population, did not find an association[291, 296]. A systematic review of RCTs of physical training in asthma[86] concluded that exercise was not significantly associated with spirometric parameters. Similarly, in COPD, spirometric values have shown a weak to moderate association with physical activity[271]. Bahmer et al.[291] reported that airway resistance and small airway dysfunction were better markers of physical activity than spirometric values in moderate and severe asthma participants. Whether the association between airflow limitation and physical activity is modulated by time since diagnosis or disease severity, needs further investigation.

Some studies reported a positive association between physical activity and asthma control[293, 296, 311, 313, 325] or health status[293, 317], which is in line with studies reporting the beneficial impact of exercise protocols on these clinical outcomes[81, 83, 87, 346]. In some studies, however, the strength of these associations was attenuated to the null when confounders such as BMI were included[313, 321, 323, 324], which suggests that the association between obesity and asthma control is stronger than the association between activity and asthma control. Studies addressing the relationship between current or incident asthma, BMI and physical activity,

have shown similar results[329, 331]. Nevertheless, another study found that the association between asthma control and MVPA was still significant after adjusting for BMI, among other confounders[293]. This suggests that MVPA may still have a modest but independent positive effect on asthma control, in addition to its important role in weight management[347]. Some authors also found an increase in asthma symptoms due to engagement in vigorous physical activity[307, 311, 321]. Similar findings have been previously reported, especially in females[335, 341]. A link between strenuous exercises (a component of vigorous physical activity) and the development of EIB or exercise-induced asthma symptoms has been well-documented in the literature[348, 349]. In fact, a dose-response relationship has been proposed, where both very low levels of activity (inactivity) and vigorous activity are associated with higher risk of asthma symptoms, while exercise carried out at a moderate level shows a protective effect[349].

In terms of the association with asthma exacerbation and health care use, Garcia-Aymerich et al.[319] found a longitudinal dose-related protective effect of physical activity on risk of hospital admission for asthma exacerbation. Fisher et al.[316] did not observe a significant association between activity engagement and risk of readmission in people with asthma. However, they observed the same pattern in the COPD population, and attributed this lack of association to the small number of participants with asthma and COPD at baseline. Longitudinal studies in COPD have found that physical inactivity is strongly related to acute exacerbations resulting in hospitalisation, reduced length of time until admission for an exacerbation, and increased all-cause mortality[264, 272-274]. The body of evidence for asthma is considerably less, and unlike studies conducted in COPD[264, 274], very few have relied on objective physical activity measures to assess the associations of this behaviour with disease outcomes.

Data on exercise capacity was scarce[293, 320], but the available evidence suggests that physical activity, especially steps, is positively associated with functional exercise capacity. Interestingly, a weaker effect was observed for MVPA which may suggest that the biggest benefits are obtained by engaging in light to moderate, but more continuous physical activity, rather than shorter but intense periods[293]. Exercise training in patients with asthma can improve cardiopulmonary fitness, assessed by the direct oxygen consumption[86], and exercise capacity measured by the 6MWD improves immediately after a 6-week exercise programme (3 weekly supervised sessions of walking training and strength exercises) and at three months follow-up[83]. In an RCT, improvement in aerobic capacity and weight loss were independently associated with improvements in asthma control[82]. This highlights the potential benefit of promoting physical activity as a way to improve different impairments in asthma, which despite of being assessed as different clinical outcomes, still affect the person in multiple dimensions of the disease.

Fewer studies have examined sedentary time in asthma. Both studies using activity monitors did not find significant differences between people with asthma and controls[293, 296], but both groups were highly sedentary. A third study[300] reported that people with asthma had higher time watching television than controls. However, in this study a self-reported proxy of sedentary time was used. Higher sedentary time was associated with decreased exercise capacity, lung function, and asthma control[293], but these associations were attenuated to the null when physical activity was included as a confounder. This suggests that the deleterious effect of sedentary time may be overcome when engaging in some physical activity[192]. Nevertheless, promoting frequent and longer breaks of sedentary time may be a more achievable goal than increasing activity levels in people with obstructive airway disease. In COPD, there are data linking objectively measured sedentary behaviour as an independent predictor of mortality[281]. Studies measuring sedentary time with postural-based

accelerometers[209] are required to explore to what extent sedentary time is occurring in asthma and whether it is associated with poorer asthma outcomes.

2.5.1. Strength and limitations

This review followed a structured search protocol and used several electronic databases. Since the review of Eijkemans et al.[261], there have been a growing number of studies addressing the prevalence of physical activity in asthma. Additionally, the use of activity monitors in asthma is a relatively new topic and was not addressed in the previous review. Our review also adds to the literature summarising the evidence of the impact of physical activity on different asthma outcomes. Furthermore, to our knowledge, there is no review reporting measures of sedentary time in people with asthma. However, there are some limitations that need to be considered. Our analysis was restricted to studies published in English, and thus we may have missed literature published in other languages. Additionally, since we only included studies conducted in adults, these results should not be generalised to children. In terms of the studies included, there was a great deal of heterogeneity in the clinical asthma and activity outcomes measures, as well as population characteristics. Furthermore, most of the studies were of cross-sectional design. Therefore, reverse causation of the associations reported must be considered as a possibility. Finally, most of the studies were performed either in mild or moderate asthma populations, or severity was not reported. As such, the severe asthma population may be underrepresented in this review, but this highlights the need for further research in this more complex population. Nevertheless, this review provides a complete update of prevalence and associations of these two behaviours in people with asthma and provides insight of the gaps in the literature that need to be addressed in future studies.

2.6. Conclusions

People with asthma appear to engage in lower levels of physical activity compared to controls. Disease outcomes seem to improve as the volume or intensity of physical activity increase. However, studies that use objective measures of activity, participants with asthma diagnosed according to guidelines[1], and more standardised measures of clinical asthma outcomes are needed. Also, further studies addressing sedentary time in asthma might help to understand whether this behaviour is present, and to what extent is associated with poorer asthma outcomes. Specifics subgroups, such as those over 50 years old, and those with severe asthma are under researched, and an understanding of how age and severity interact in the relationship between activity and asthma clinical or biological outcomes is needed. Longitudinal studies and RCTs exploring the direction of the relationships between physical activity and asthma outcomes are also needed to improve the consistency of the evidence. The results of this review strongly support the need to undertake this research.

2.7. Supplementary information

Associations between physical activity and sedentary time in asthma health outcomes

Twenty-seven studies reported associations between the level of activity and asthma health outcomes. Five were longitudinal[314, 316, 318, 319, 321]. Associations with sedentary time were addressed in 3 studies[293, 300, 311]. Table 2.5 reports the main findings of these studies.

The relationship between physical activity and lung function was assessed in 10 studies[291-293, 296, 305, 307, 312, 314, 318, 320]. Weak but significant associations were reported in 8 studies[291-293, 305, 307, 312, 314, 318], from which 2 were of longitudinal design[314, 318]. Brumpton et al.[314] reported that active people with asthma had a slower decline in lung function at follow-up compared with

inactive individuals. The mean decline in the FEV_1/FVC ratio was 0.36% and 0.22% per year among inactive and active participants with asthma, respectively (p <.03). Bahmer et al.[291] reported that fewer steps/day were associated with increased airway resistance and small airway dysfunction. Van't Hul et al.[296] did not find any correlation between measures of physical activity and spirometric assessments.

Asthma control and health status

Measures of asthma control or asthma-related health status were reported in 13 studies[293, 296, 297, 307, 311, 313, 315, 317, 320, 321, 323-325], 12 of them of cross-sectional design[293, 296, 297, 307, 311, 313, 315, 317, 320, 323-325].The results suggest that higher levels of moderate and vigorous physical activity (MVPA) were associated with better asthma control. However, vigorous physical activity was also associated with more asthma symptoms[307, 311, 321]. Bacon et al.[313] concluded that participants who engaged in the recommended levels of activity were almost 2.5 times more likely to have good asthma control compared with less active participants (AOR 2.47; 95% CI 1.06, 5.73). Cordova-Rivera et al.[293] also found a positive association between higher volume of MVPA and better asthma control even after adjusting for the time spent sedentary and confounders such as BMI, age, and smoking status. The authors reported that a 15-minute increase in MVPA was associated with an improved asthma control questionnaire score of 0.29 units (p < 0.032, adjusted R^2 for the model: 0.18). Russell et al.[321] found that physical activity was positively associated with asthma symptoms only in participants with normal weight (BMI < 25), whereas this was not observed in participants with a BMI > 25. In addition, in their longitudinal analysis, the relationship between baseline light activity and follow-up current asthma (defined as reporting asthma symptoms, taking asthma medication, or having an asthma exacerbation in the last 12 months) was attenuated to the null after adjusting for BMI. Among studies reporting negative effects of activity, Verlaet et al.[311] found that vigorous

activity doubled the risk of uncontrolled asthma in females (AOR 1.94; 95% CI 1.13, 3.35); $p < 0.05$), and in their longitudinal analysis, Russell et al.[321] found a non-significant negative trend on current asthma from higher engagement in vigorous physical activity (AOR [95% CI]) of current asthma for 1 to 2 vigorous activity sessions/week: 0.75 (0.38, 1.46) versus >3 sessions/week: 1.03 (0.42, 2.49). In terms of health status, Ford et al[317] reported that inactive people with asthma were more than twice as likely to report poor or fair health compared with those doing regular vigorous activity (OR [95% CI] 2.36 [1.72, 3.22]).

Exacerbations and heath care use

Measures of health care utilization were evaluated in 6 studies[300, 301, 316, 319, 322, 324], 2 of which were longitudinal cohorts[316, 319]. In 4 studies, less physical activity was associated with increased exacerbation and/or higher health care utilization[300, 301, 319, 322]. A longitudinal study involving women with asthma[319] demonstrated that the higher the level of activity performed, the lower the risk of admission for exacerbation ($p = 0.05$ for trend). Strine et al.[322] reported that inactive people with asthma were more likely to have ≥ 3 visits to the emergency department for asthma in the last year (AOR [95% CI] 2.4 [1.6, 3.6]) compared with their active peers. Conversely, Fisher et al[316] did not find any association between readmission for asthma (mean follow-up 16 years) and participation (yes/no) in physical activity. However, they reported a non-significant trend in the association between readmission for asthma and the time spent in activity. Participants engaging in >4 hours/week of gardening and cycling had a 10% and 22% reduced risk of readmission for asthma, respectively, compared with participants spending <4 hours (hazard ratio [95% CI] for gardening 0.90 [0.58, 1.39] and cycling 0.78 [0.49, 1.25]).

Exercise capacity

Measures of exercise capacity were evaluated in 2 cross-sectional studies[293, 350]. Cordova-Rivera et al.[293] found that steps/day were strongly associated with the 6-minute walk distance, even after adjustment for sedentary time and other confounders. The authors reported that every 1000-step/day increase was associated with an increased 6-minute walk distance of 20 m ($p < 0.01$, adjusted R^2 for the model: 0.35).

Biological markers

There was a significant association between steps/day and systemic inflammation (high-sensitivity C-reactive protein [hs-CRP]) in one of the studies. The authors report that every 1000-step increase was associated with a decrease of hs-CRP of 17%, after adjusting for sedentary time and other confounders. The same study did not find a significant association between MVPA and hs-CRP. No significant association was found between physical activity and measures of eosinophilic airway inflammation[293].

Sedentary time and health outcomes

Detrimental associations between sedentary time and outcomes such as exercise capacity, lung function, and asthma control were reported in one cross-sectional study[293]. However, these associations were no longer significant after adjustment for physical activity. Doggett and Dogra[300] reported an increased OR (95% CI) for GP consultations, 2.59 (2.34, 2.87), and hospitalizations in the past year, 1.95 (1.82, 2.08), and past 5 years, 1.13 (1.07, 1.18) ($p <$ 0.001 for all results), for people who reported >10 hours of television time a week compared with those who reported ≤ 10 hours.

In the next chapter, I will further explore the movement behaviours of physical activity and sedentary time in a severe asthma population compared to age- and sex-matched people without respiratory disease.

3. Chapter 3: Physical Activity and Sedentary Time in Adults with Severe Asthma

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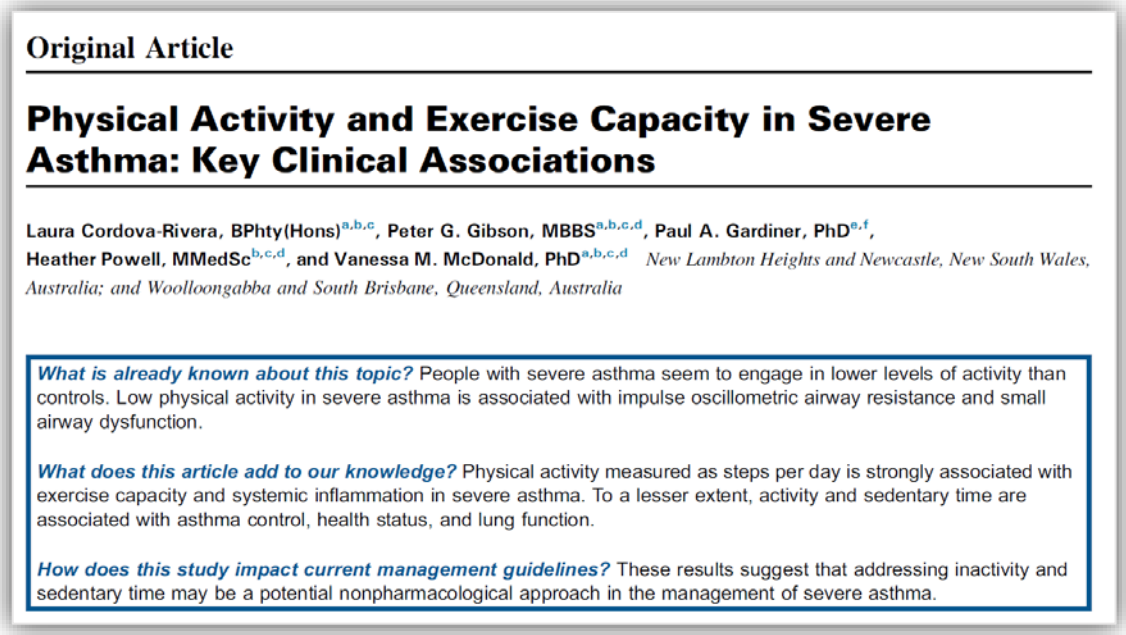

Original Article

Physical Activity and Exercise Capacity in Severe Asthma: Key Clinical Associations

Laura Cordova-Rivera, BPhty(Hons)[a,b,c], Peter G. Gibson, MBBS[a,b,c,d], Paul A. Gardiner, PhD[e,f], Heather Powell, MMedSc[b,c,d], and Vanessa M. McDonald, PhD[a,b,c,d] *New Lambton Heights and Newcastle, New South Wales, Australia; and Woolloongabba and South Brisbane, Queensland, Australia*

What is already known about this topic? People with severe asthma seem to engage in lower levels of activity than controls. Low physical activity in severe asthma is associated with impulse oscillometric airway resistance and small airway dysfunction.

What does this article add to our knowledge? Physical activity measured as steps per day is strongly associated with exercise capacity and systemic inflammation in severe asthma. To a lesser extent, activity and sedentary time are associated with asthma control, health status, and lung function.

How does this study impact current management guidelines? These results suggest that addressing inactivity and sedentary time may be a potential nonpharmacological approach in the management of severe asthma.

A short summary of this article has been highlighted in the "Latest Research" section of the American Academy of Allergy, Asthma & Immunology (AAAAI) website.

See **Appendix III** for the published article.

See **Appendix IV** for the summary published in the AAAAI website.

See **Appendix V** for a detailed explanation of physical activity analyses.

This article was featured with an Editorial which has been included as Appendix VI.

Overview of this Chapter

Physical activity impairment and/or high engagement in sedentary behaviour are common findings in COPD and bronchiectasis (Chapter 1), as well as in adults with asthma (Chapter 2). These behaviours seem to be associated with important disease outcomes in asthma, such as asthma control, health status and exercise capacity. The level of activity seems also to be influenced by sex, age and disease severity. Asthma is a heterogeneous disease, and while, in general, some aspects of physical activity were less impaired in asthma than COPD, there were very few studies that addressed physical activity and sedentary time in severe asthma. This is important, because severe asthma is likely to be the stage of the disease when these behaviours may be more impaired.

To address this knowledge gap, in this chapter I will present the results from a published cross-sectional study that aimed to characterise the level of physical activity and sedentary time in a severe asthma population. The results will be compared to controls without chronic respiratory diseases, and I will assess the associations of physical activity and sedentary time with clinical and biological characteristics of the severe asthma population.

I hypothesised that people with severe asthma will present lower levels of physical activity and higher levels of sedentary time than people without respiratory diseases, and that in people with severe asthma, higher physical activity and lower sedentary time will be associated with better clinical and biological asthma characteristics.

3.1. Abstract

Background: Physical inactivity and sedentary time are distinct behaviours that may be more prevalent in severe asthma, contributing to poor disease outcomes. Physical activity and sedentary time in severe asthma however have not been extensively examined.

Objective: We aimed to objectively measure physical activity and sedentary time in people with severe asthma compared with age-matched control participants, describing the associations of these behaviours with clinical and biological outcomes. We hypothesised that people with severe asthma would be less active and more sedentary. In addition, more activity and less sedentary time would be associated with better clinical outcomes and markers of systemic and airway inflammation in people with severe asthma.

Methods: Adults with severe asthma (n = 61) and sex- and age-matched controls (n = 61) underwent measurement of lung function, exercise capacity, asthma control, health status, and airway and systemic inflammation. Physical activity and sedentary time were measured using an accelerometer.

Results: The severe asthma and control groups were matched in terms of age and sex (32 [53%] females in each group). Individuals with severe asthma accumulated less minutes per day in moderate and higher intensity activity, median (IQR) 21.9 (12.9-36.0) versus 41.7 (29.5-65.2) ($p < 0.0001$) and accumulated 2,232 fewer steps per day ($p < 0.0002$). However, they engaged in more light-intensity physical activity. No differences were found for sedentary time. In a multivariate regression model, steps per day were strongly and independently associated with better exercise capacity in participants with severe asthma (coefficient, 0.0169; 95% CI, 0.008-0.025; $p < 0.001$).

Conclusions: People with severe asthma perform less moderate and vigorous activity than do controls. Higher levels of activity and lower levels of sedentary time are associated with better exercise capacity, asthma control, and lower levels of systemic inflammation.

3.2. Introduction

Severe asthma is a heterogeneous and complex disease, in which diverse clinical and physiological presentations are common[33]. Severe asthma represents a high patient and healthcare burden[351]. It is, thus, necessary to explore novel strategies to improve health status in severe asthma and to minimise this burden. The importance of multidisciplinary management approaches in severe asthma has been recognised[352]. Within these, the identification and subsequent management of modifiable risk factors or behaviours, such as inactivity, can be seen as an adjunct strategy for the management of the disease[154].

In general populations, physical activity and exercise are regarded as highly beneficial, leading to positive health outcomes[161, 176, 353]. Engagement in excess sedentary time is an important risk factor for the development of several chronic diseases and premature mortality[163, 164]. Physical activity is defined as any bodily movement generated by the skeletal muscles and resulting in energy expenditure. Depending on intensity and metabolic equivalent of task (MET) units, it is classified in light, moderate or vigorous physical activity, where light corresponds to the lower METs or energy expenditure[161]. Mild stretching, low impact dancing, and running correspond to examples of light, moderate and vigorous physical activity, respectively[172]. Sedentary time, refers to activities performed while awake, in a lying or sitting position and expending low levels of energy (≤ 1.5 METs)[354]. The physical activity and sedentary guidelines recommend engaging in at least 150 minutes/week of moderate activity, or 75 minutes/week of vigorous activity (or equivalent combination), and to sit less and for shorter periods of time[355]. In other obstructive airway diseases such as Chronic Obstructive Pulmonary Disease (COPD), physical inactivity and sedentary time are increased compared to healthy controls[165, 259]. These behaviours have been independently associated with worse clinical and inflammatory outcomes[271], and increased mortality in this disease[272, 281]. In asthma, a potential link between inactivity and mortality has not been

reported. However, higher adherence to physical activity in asthma has been associated with better asthma control[296], reduced exacerbations[319] and reduced health care use[322]. Data on inflammatory parameters are scarce[335].

In severe asthma, inactivity and sedentary time are likely to be particularly extreme due to the poor disease control and associated comorbidities, such as obesity, anxiety, and depression[33]. Despite this, very few studies have objectively measured physical activity in this population [291], and the prevalence of sedentary time has not been addressed in severe asthma. In addition, very few studies have assessed the impact of these behaviours on health outcomes in the disease[291].

The aims of this study therefore were to objectively measure physical activity and sedentary time in a severe asthma population compared with age-matched controls, and to describe the associations of these behaviours with clinical measures such as asthma control, health status, exercise capacity, lung function, and markers of airway and systemic inflammation. We hypothesised that people with severe asthma are less active and more sedentary than are their age- and sex-matched counterparts, and that higher levels of physical activity and lower levels of sedentary time in severe asthma are associated with better clinical outcomes and lower levels of systemic and airway inflammation. In addition, we sought to test the hypothesis that moderate-intensity physical activity can counteract the detrimental health outcomes associated with high levels of sedentary time, as it has been previously suggested[192, 356].

3.3. Methods

3.3.1. Participant selection

A cross-sectional characterisation study was conducted. Adults with severe asthma and sex- and age-matched controls were recruited and underwent a multidimensional assessment

with objective measures of physical activity and sedentary time. Participants with severe asthma were recruited consecutively from the respiratory ambulatory care clinics at John Hunter Hospital (Newcastle, Australia) and the clinical research databases of the Priority Research Centre for Healthy Lungs at the University of Newcastle (Newcastle, Australia). Participants with respiratory physician-diagnosed severe asthma were eligible if they met the current guideline definition for severe asthma[33]: prescribed Global Initiative for Asthma step 4 treatment or above, defined as 1,000 mg inhaled corticosteroid fluticasone equivalent and long-acting b2-agonists[1] had evidence of airflow limitation (FEV_1 <80% predicted), and ongoing poor asthma control (Asthma Control Questionnaire [ACQ][35] score ≥ 1.5 units or had experienced a severe exacerbation in the last 12 months requiring oral corticosteroids). Participants were clinically stable during visits (no increase in asthma symptoms in the last 4 weeks). Otherwise, their enrolment was postponed until they were stable. Exclusion criteria included malignancy with poor prognosis (< 3 months). Age- and sex-matched controls were recruited via the research database of the Hunter Medical Research Institute and community advertisement and were eligible if they were older than 18 years and non-smokers and had no objective evidence of chronic respiratory disease.

Ethics approval was granted by the human research ethics committees of the Hunter New England Local Health District (08/08/20/3.10) and the University of Newcastle, Australia. The study was conducted according to Good Clinical Practice Guidelines and each participant provided written informed consent.

3.3.2. Procedures

3.3.2.1. Clinical Measurements

Participants underwent a multidimensional assessment[125] involving measurement of height and weight, allergy skin prick tests, serum IgE, comorbidities[357], anxiety and depression[358], and smoking status. Further assessments are described below.

3.3.2.2. Exercise capacity

The 6-minute walk test was performed according to current guidelines[359] to measure exercise capacity. The 6-minute walk distance (6MWD) was calculated[360].

3.3.2.3. Asthma control and health status.

Asthma control was assessed using the ACQ[35]. Higher scores represent poorer asthma control. Health status was measured using the Asthma Quality of Life Questionnaire (AQLQ)[361]. Higher scores represent better asthma-related quality of life. A change of 0.5 or more units is considered clinically significant for both questionnaires[362, 363].

3.3.2.4. Airflow Limitation

Airflow limitation was assessed by measuring spirometry: FEV_1, forced vital capacity, and FEV1/forced vital capacity ratio (Medgraphics, CPFS/D USB Spirometer; BreezeSuite v7.1, MGC Diagnostics, Saint Paul, Minn)[364]. FEV_1 and forced vital capacity percent predicted were calculated using the Third National Health and Nutrition Examination Survey predicted equations[365].

3.3.2.5. Airway Inflammation

Eosinophilic airway inflammation was assessed in 2 ways: using fraction of exhaled nitric oxide (FENO) (ANALYZER CLD 88 Series with DENOX 88; Eco Physics AG, Duernten, Switzerland)[366] and from sputum eosinophil counts obtained from induced sputum. The

samples were induced[367] using nebulised 4.5% or 0.9% saline if the prebronchodilator FEV_1 was less than or equal to 1 L. Lower respiratory sputum portions were selected and dispersed using dithiothreitol. Total cell counts and cell viability (Trypan blue exclusion) were performed, followed by preparation of cytospins for differential cell counts using May-Grunwald Giemsa. Airway eosinophilia was defined as sputum differential eosinophil count of greater than or equal to 3%[60].

3.3.2.6. *Systemic Inflammation*

Systemic inflammation was measured by peripheral blood high sensitivity C-reactive protein (hs-CRP) and analysed through the Hunter Area Pathology Service.

3.3.2.7. *Physical Activity and Sedentary Time*

Physical activity and sedentary time were assessed using the ActiGraph wGT3X-BT (ActiGraph, Pensacola, Fla), a device widely used in research[180, 188, 201], and validated for populations with COPD[207]. This is a small device (4.6 cm x 3.3 cm x 1.5 cm) that participants were fitted with to wear on a belt around their waist, positioned over the dominant hip, for 14 consecutive days. They were instructed to remove the monitor during water-based activities and to record sleeping time and non-wear periods in a diary. The ActiGraph measures time-varying changes in force and activity levels recorded as counts, which are then summed over a user-specified time frame, or epoch[245]. The device was initialised using the ActiLife 6.11.6 Data Analysis Software (ActiGraph, Pensacola, Fla), to collect raw data (accelerations or counts) in the vertical axis at 30 Hz rate in an epoch length of time of 10 seconds. Sleep and any non-wear time were estimated from the diaries and visual examination of the ActiGraph data and removed before classification. ActiLife software was used to summarise the data. We classified time according to the widely used Freedson's 1998 cutoff points: Sedentary (0-99 counts per minute [CPM]), light physical activity (100-1951

CPM), and moderate and above physical activity (≥1952 CPM)[246]. The ActiGraph also captures steps per day. Our measures of physical activity and sedentary time were daily time in sedentary time (min/d), daily time in light physical activity (min/d), daily time in moderate- to vigorous-intensity physical activity (MVPA) (min/d), and daily number of steps (Steps [steps/d]). We reported both MVPA and Steps because although the MVPA describes the volume of moderate- to high-intensity activity and can be compared with the physical activity recommendations[355], Steps is an output easy to interpret and could be used as a motivational and informative tool both for patients and for clinicians. Sedentary time and light physical activity were standardised for wear time by the residuals method[368]. The data were considered valid if there were recordings of 4 or more days, with 10 or more hours of recording each day.

3.3.3. Statistical Analysis

Data were analysed using STATA 13 (Stata Corporation, College Station, Texas). Values are expressed as means with CIs for parametric data and medians with interquartile range for nonparametric data. Differences between the group with severe asthma and the age-and sex-matched control group were assessed using the Student t test or the Wilcoxon rank sum test based on normality.

The associations between the different clinical and biological outcomes and the behavioural variables (sedentary time, MVPA, and Steps) adjusting for potential confounders (body mass index and current smoking status) were estimated using simple linear regression analysis. Each behavioural variable was used as a predictor of a given clinical or biological outcome (dependent variable: FEV_1% predicted, 6MWD, ACQ score, AQLQ score, FENO, and hs-CRP). Age and sex were regarded as biological confounders and included in all the models. Behavioural variables and confounders with a *p* value of less than 0.2 were also included in a

stepwise multiple linear regression analysis to identify the associations between each behavioural variable (sedentary time, MVPA, and Steps) and each biological/clinical outcome (model 1). To test whether moderate physical activity (Steps or MVPA) can counteract the detrimental health outcomes associated with sedentary time, further models were used, adjusting for sedentary time as well as other confounders (model 2). Assumptions for linear regressions were met. Collinearity between the activity (MVPA or Steps) and sedentary variables was rejected. Hs-CRP and FENO were transformed to the natural logarithm for the linear regression. This means that the dependent variable changes by 100 x [exp (coefficient) - 1] percent for each 1-unit increase in the independent continuous variable. Logistic regressions were used to test the associations of sedentary and active time with airway eosinophilia, and the association between better performance in the 6-minute walk test (defined as ≥ median [≥499 m]) and higher engagement (≥ 30 minutes) in MVPA. Spearman rank correlation tested the relationship between activity variables and 6MWD. Results were reported as significant when *p* was less than 0.05.

3.4. Results

3.4.1. Characterisation of the study population

A total of 143 participants (those with severe asthma = 74, controls = 69) completed the study and 122 (those with severe asthma = 61, controls = 61) were included in the analysis; 21 participants were excluded because of not having valid accelerometer data (those with severe asthma = 8, controls = 5) or because they did not fulfil the disease inclusion criteria after assessment (those with severe asthma = 5, controls = 3). Participants with severe asthma had long-standing disease (median, 27 years) and poor asthma control. They also had a higher body mass index and increased prevalence of atopy, lower lung function, and higher

scores of anxiety and depression compared with age- and sex-matched controls. Demographic and clinical characteristics are presented in Table 3-1

Table 3-1: Demographics and clinical characteristics.

	Severe asthma	***Controls***	***p -value***
N	61	61	
Gender, F|M (% females)	32|29 (52.46)	32|29 (52.46)	1
Age (years), median [IQR]	59 [43 - 68]	54 [34 - 63]	0.0633
BMI (kg/m^2), mean (95%CI)	30.00 (28.06, 31.89)	25.40 (24.42, 26.38)	**0.0001**
Smoking status, (%) current | ex	6.6|47.5	0 |29.5	
Pack year, mean (95%CI)	5.0 (2.71, 7.28)	3.0 (-0.43, 6.35)	0.322
Years since diagnosis, median [IQR]	27.11 [15.03 - 50.76]	n/a	
OCS, % participants medicated	39.34	n/a	
ICS* dose (mcg), mean(95%CI)	1091.10 (961.25, 1220.96)	n/a	
Pre-bronchodilator FEV_1 (litres), mean (95%CI)	2.27 (2.05, 2.49)	3.20 (2.98, 3.42)	**<0.0001**
Pre-bronchodilator FEV_1%pred, mean (95%CI)	75.12 (69.41, 80.82)	96.94 (93.44, 100.45)	**<0.0001**
Pre-bronchodilator FVC (litres), mean (95%CI)	3.39 (3.13, 3.66)	4.01 (3.75, 4.27)	**0.0012**
Pre-bronchodilator FVC% pred, mean (95%CI)	87.01 (82.32, 91.71)	96.51 (93.16, 99.85)	**0.0013**
FEV_1/FVC ratio, mean (95%CI)	0.67 (0.63, 0.69)	0.80 (0.78, 0.81)	**<0.0001**
Hs-CRP (mg/L), median [IQR]	1.8 [1 - 6]	1.1 [0.6 - 2.5]	**0.0024**
FeNO (ppb), median [IQR]	11.5 [5.42 - 31.45]	9.84 [4.6 - 18.3]	0.1024
Sputum Eosinophilia (≥3%), n (%)	29 (59.2)	5 (11.36)	**<0.0001**
IgE (IU/mL), median [IQR]	225.500 [70 - 498]	n/a	
Atopy, n (%)	48 (82.76)	35 (58.33)	**0.0037**
HADS (anxiety score), mean (95%CI)	6.67 (5.70, 7.64)	3.80 (3.02, 4.58)	**<0.0001**
HADS (depression score), mean (95%CI)	4.57 (3.81, 5.34)	1.37 (0.92, 1.82)	**<0.0001**
CCI score ≥ 1, n (%)	16 (26.70)	2 (3.28)	**0.0003**
ACQ (units), mean (95%CI)	2.23 (1.95 - 2.50)	n/a	
AQLQ (unit), mean (95%CI)	5.15 (4.85 - 5.46)	n/a	

Severe exacerbation past year, median [IQR]	2 [1 - 5]	n/a	
6MWD (meters), median [IQR]	499 [417.7 - 542.2]	616.2 [568.4 - 659.30]	**<0.0001**
6MWD % predicted, mean (95%CI)	71.78 (68.13, 75.44)	85.71 (82.51, 88.92)	**<0.0001**

MI: body mass index; OCS: oral corticosteroids; ICS: inhaled corticosteroids, ICS: Fluticasone equivalent; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; hs-CRP: high sensitivity c-reactive protein; eNO: fractional exhaled nitric oxide; IgE: immunoglobulin E; HADs: hospital anxiety and depression scale; CCI: Charlson comorbidity index, ACQ: asthma control questionnaire; AQLQ: asthma quality of life questionnaire; 6MWD: 6-minute walk distance ; n/a: not applicable or not assessed. Bold indicates statistical significance (p < 0.05)*

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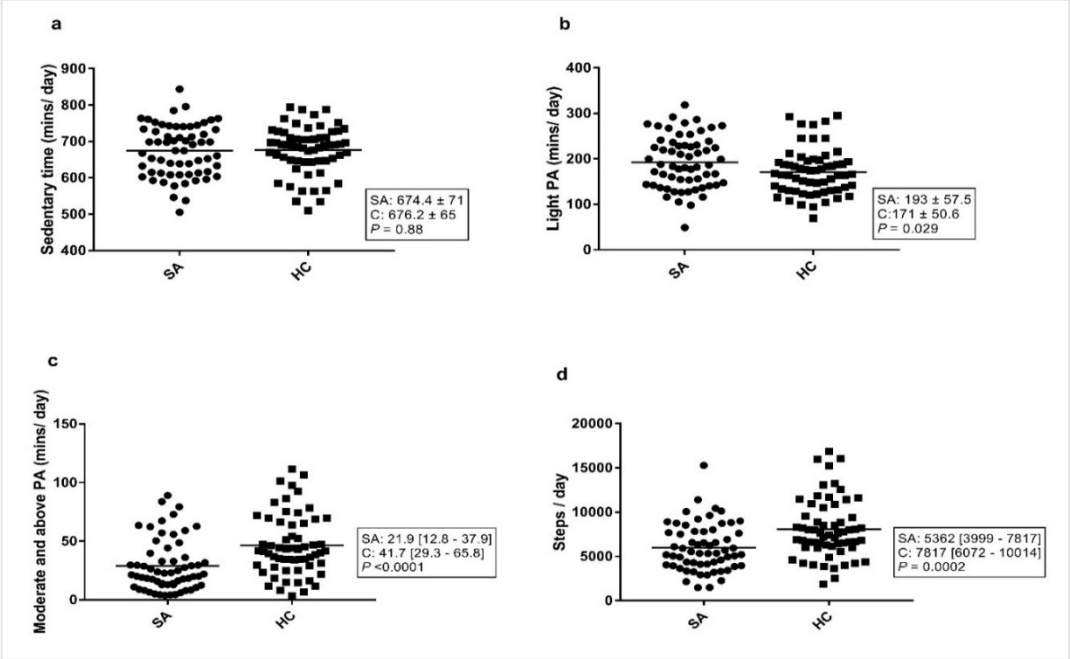
3.4.2. *Physical activity and sedentary time in the group with severe asthma and the age- and sex-matched control group*

Compared with controls, people with severe asthma performed less activity of at least moderate intensity. The group with severe asthma had a median difference of 19.8 fewer minutes of MVPA per day ($p < 0.0001$) and 2455 fewer steps per day ($p < 0.001$). Conversely, the population with severe asthma engaged in more light physical activity, with a mean (95% CI) difference of 21.7 (2.2-41.1) more minutes per day ($p = 0.029$). No statistically significant differences were found in sedentary time between the 2 populations (Figure 3-A).

Figure 3-A: Sedentary time (a), light PA (b), moderate and vigorous PA (c) and steps/day (d) in severe asthma and age- and sex-matched controls.



Values reported as mean ± SD or median [interquartile range]. Number of participants in each group (n= 61). HC: controls, SA: severe asthma; PA: physical activity

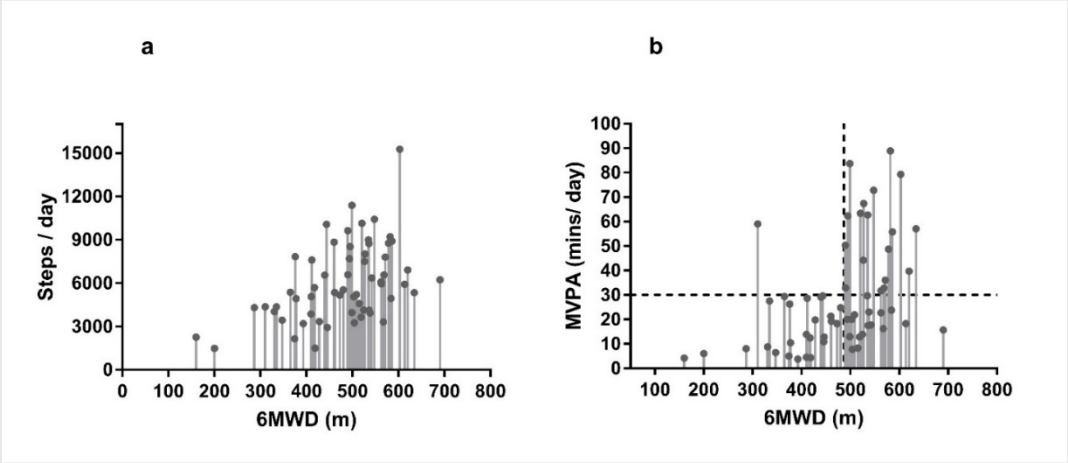
3.4.3. Associations of physical activity and sedentary time with clinical outcomes and biological markers in participants with severe asthma

3.4.3.1. *Exercise capacity.*

Physical activity (Steps and MVPA) and sedentary time were significantly associated with exercise capacity, explaining 35.25%, 29.69%, and 27.3% of the adjusted variance in the 6MWD, respectively (Table 3-2/model 1). For every additional 1,000 steps, there was a 16.9-m increase in the 6MWD. For every minute increase in sedentary time, there was a decrease of 0.47 m in the 6MWD. Accordingly, every additional hour spent sedentary is associated with a 28.2-m reduction in the 6MWD.

There was a linear relationship between Steps and the 6MWD (Figure 3-B, a). For MVPA (Figure 3-B, b) there was also an apparent threshold effect where those participants with a 6MWD performance of greater than or equal to the median (499 m) were also the participants engaging daily in 30 minutes or more of MVPA, a volume of activity that fits within the physical activity recommendations12 (OR, 6.09; p = 0.005). This suggests that a value of around 500 m in the 6MWD could identify individuals engaging in recommended levels of MVPA. Simultaneously including sedentary time with MVPA or Steps in the model attenuated the associations of MVPA and sedentary time to the null. However, the association of Steps with exercise capacity remained similar and still statistically significant (Table 3-2/model 2). A 1,000-step increase was associated with better performance in the 6MWD by 21 m. This suggests that regardless of the time spent sedentary, higher levels of walking were still strongly associated with a significant improvement in exercise capacity.

Figure 3-B: Relationship between physical activity and 6MWD.



A, Rho=0.453; B, Rho=0.502 (p < 0.001 both)

Table 3-2: Association of physical activity and sedentary time with exercise capacity as 6MWD.

Model 1.	***Models for 6MWD***		
	Coefficient (95%CI)	**Significance**	**Adj. R2**
ST	-0.47 (-0.79, -0.14)	**0.006**	0.27
MVPA	1.70 (0.64, 2.75)	**0.002**	0.30
Steps	0.01 (0.00, 0.02)	**0.000**	0.35
Model 2			
Steps	0.02 (0.00, 0.04)	**0.010**	0.35
ST	0.18 (-0.39, 0.75)	0.531	
MVPA	1.24 (-0.32, 2.80)	0.117	0.29
ST	-0.19 (-0.66, 0.28)	0.429	

BMI, Body mass index; PA, physical activity; ST, sedentary time. Model 1 = each behavioural variable (ST, MVPA, or Steps) as a predictor of exercise capacity. Model 2 = PA (Steps or MVPA) as a predictor of exercise capacity, after adjustment for ST and confounders. Models adjusted for age, sex, and BMI. Bold indicates statistical significance (p < 0.05).

3.4.3.2. *Lung function, asthma control, and health status.*

The activity and sedentary variables were also significantly associated with lung function, asthma control, and health status, except for Steps and FEV_1% predicted, and sedentary time and the AQLQ score. In contrast to the impact of activity on exercise capacity, the effect on these clinical outcomes was weaker but nonetheless statistically significant and biologically plausible. For every 10-minute increase in MVPA, the ACQ score decreased (improved) by 0.21 units, whereas the AQLQ score increased (improved) by 0.16 units (Table 3-3/model 1). These results suggest that a 25-minute increase in MVPA is associated with a clinically significant improvement in ACQ score (0.52 units). Regarding sedentary time, every 100-minute increase in this behaviour is associated with a clinically significant decline in the ACQ score (0.51 units). The only activity variable that remained statistically significant after adjustment for sedentary time was ACQ score and MVPA. Every 15-minute increase in MVPA was associated with a decrease (improved) of 0.29 units in ACQ score (Table 3-3/model 2). The coefficient of sedentary time was also attenuated to the null in this model. In the remaining models, the activity (MVPA or Steps) and sedentary variables together were mutually excluded. Nevertheless, in most of the models, the direction of the coefficients indicated that the decrease in sedentary time and the increase in activity led to modest improvements in clinical marker

Table 3-3: Association of physical activity and ST with clinical outcomes.

Model 1	*Models for FEV_1 (%)*			*Models for AQLQ (units)*			*Models for ACQ (units)*		
	Coefficient (95%CI) *	**Sig**	**Adj. R^2**	**Coefficient (95%CI) ***	**Sig**	**Adj. R^2**	**Coefficient (95%CI) ***	**Sig**	**Adj. R^2**
ST	-7.90 (-15.63, -0.17)	**0.045**	0.10	-0.35 (-0.76, 0.04)	0.081	0.15	0.51 (0.14, 0.89)	**0.007**	0.12
MVPA	28.69 (3.31, 54.07)	**0.027**	0.11	1.59 (0.29, 2.89)	**0.018**	0.19	-2.15(-3.33, -0.97)	**0.001**	0.19
Steps	0.17 (-0.03, 0.38)	0.096	0.08	0.01 (0.00,0.02)	**0.015**	0.20	-0.01(-0.02, -0.00)	**0.005**	0.13
Model 2									
Steps	-0.00(-0.38, 0.37)	0.994	0.08	0.01(-0.00, 0.03)	0.078	0.19	-0.00(-0.02, 00.0)	0.304	0.12
ST	-7.95(-22.25, 6.35)	0.27		0.19 (-0.53, 0.23)	0.597		0.21 (-0.47, 0.90)	0.537	
MVPA	20.65 (-17.43, 58.73)	0.282	0.10	1.59 (-0.37, 3.55)	0.111	0.18	-1.94(-3.69, -0.18)	**0.032**	0.18
ST	-3.27 (-14.78, 8.23)	0.571		-0.00 (-0.59, 0.59)	0.998		0.08(-0.44, 0.62)	0.740	

*Adj., Adjusted; BMI, body mass index; Sig., significance; ST, sedentary time. For rationale of models 1 and 2, refer to captions in Table 3.2. All models adjusted for age and sex. AQLQ score adjusted for smoking status. ACQ score adjusted for smoking status and BMI. Bold indicates statistical significance ($p < 0.05$). *Coefficients and CI expressed as x 10^{-2}.*

3.4.3.3. *Biological markers.*

No relationship was found between the behavioural variables and eosinophilic airway inflammation measured by sputum cell counts (Table 3-4). In simple linear regression analyses, the significance level for FENO was more than 0.2 and thus not included in the stepwise model.

Steps were significantly associated with hs-CRP. For every increase of 1000 steps, the hs-CRP was reduced by 13%. No relationship was found between hs-CRP and MVPA or sedentary time (Table 3-5/model 1). Only Steps remained significantly associated with hs-CRP after adjustment for sedentary time. For every increase of 1000 steps, the hs-CRP was reduced by 17% (Table 3-5/model 2). The coefficients for the associations of sedentary time were attenuated to the null. The model explained 48.6% of the variance in systemic inflammation.

Table 3-4: Association of physical activity and ST with airway inflammation.

Simple logistic regression airway eosinophilia			
	Odds ratio (95%CI)	**Sig**	**Adj. R^2**
ST	1.00 (0.99, 1.01)	0.315	0.02
MVPA	1.01(0.98, 1.035)	0.470	0.01
Steps	1.00(0.99, 1.00)	0.246	0.02

ST, Sedentary time. Airway eosinophilia defined as eosinophil count of ≥ 3% in sputum cell

Table 3-5: Association of physical activity and sedentary time with inflammatory biomarkers.

Model 1	*SLR models for Ln-FeNO*			*Models for Ln_hs-CRP*		
	Coefficient (95%CI) *	**Sig**	**Adj. R^2**	**Coefficient (95%CI) ***	**Sig**	**Adj. R^2**
ST	1.92 (-2.23, 6.07)	0.358	-0.00	3.36(-0.08, 6.80)	0.56	0.45
MVPA	-1.02(-14.74, 12.70)	0.882	-0.02	-10.47 (-21.79, 0.84)	0.069	0.45
Steps	-0.02(-0.13, 0.08)	0.617	-0.01	-0.13(-0.22, -0.03)	**0.006**	0.49
Model 2						
Steps	N/D			-0.17(-0.34, -0.00)	**0.038**	0.49
ST				-2.09(-8.24, 4.04)	0.497	
MVPA	N/D			-5.15(-21.95, 11.63)	0.54	0.45
ST				2.20 (-2.92, 7.32)	0.393	

*Adj., Adjusted; BMI, body mass index; Ln_FENO, natural logarithm FENO; Ln_hs-CRP, natural logarithm hs-CRP; ND, not done; Sig., significance; SLR, simple linear regression analysis; ST, sedentary time. For rationale of models 1 and 2, refer to captions in Table 3.2. Ln_hs-CRP was adjusted for age, sex, and BMI. Bold indicates statistical significance ($p < 0.05$). *Coefficients and CI expressed as x 10^{-3}.*

3.5. Discussion

This study has described the extent to which individuals with severe asthma engage in physical activity and sedentary time compared with a sex- and age-matched control population. We have demonstrated that people with severe asthma are considerably less active. In addition, we found that levels of activity and sedentary time are strongly and independently associated with exercise capacity, and to a lesser extent with other important clinical and biological outcomes. Our results also demonstrate that the detrimental effects of sedentary time are attenuated when participants engage in some physical activity, especially of moderate or higher intensity.

In terms of the levels of activity and sedentary time, our results are consistent with those of several studies conducted in patients with mild and moderate asthma using both objective and subjective activity measurement[291, 296, 299, 300, 303]. However, very few studies have

objectively examined physical activity in patients with severe asthma[291], and to our knowledge this is the first study to report levels of sedentary time in this population. Our finding that people with severe asthma move 31.4% fewer steps per day compared with a control group is consistent with the finding of a recent study that reported 31% lower steps[291]. However, in comparison to Bahmer et al[291], our study reported a larger difference in MVPA between people with severe asthma and controls (47.5% vs 23%), and the participants in our study were less active than the participants in the Bahmer et al[291] study (22 min/d vs 125 min/d of MVPA). It should be noted though that the authors[291] used a different device to measure MVPA (SenseWear Pro Armband; BodyMedia, Pittsburgh, Pa). Studies using the ActiGraph in a bronchiectasis population[284] have reported similar activity results as our study.

We observed that the difference in physical activity between patients with severe asthma and controls is larger for higher intensities of activity than for Steps. This finding has also been reported in patients with mild to moderate COPD[269], and suggests that activity limitation is first manifested at higher intensities of activity rather than lighter. In fact, our population with severe asthma accumulated more minutes in light physical activity than did healthy controls.

In the general adult population, a widely promoted target for a desirable level of activity is 10,000 steps[369]. Our population with severe asthma achieved only 5362 daily steps, thus a little more than half of the recommended level, and similar to the level reported in patients with moderate to severe COPD[266, 269] and patients with bronchiectasis[284]. This suggests that people with obstructive airway disease regardless of diagnosis are engaging in levels of activity that are far below those recommended for adult populations. Direct comparisons between these populations have not yet been reported.

The beneficial role of physical activity and exercise on outcomes such as exacerbations, asthma control, cardiopulmonary fitness, and health status has been previously described in populations with general asthma[86, 87, 313, 319, 322]. However, to our knowledge, this is the first time that the association between exercise capacity and objectively measured physical activity and sedentary time has been reported in patients with severe asthma. Sedentary time attenuated the associations of MVPA with exercise capacity but not the associations of Steps with exercise capacity. This suggests that the greatest benefit on exercise capacity is achieved by performing activity of light to moderate intensity distributed throughout the day, rather than more vigorous but sporadic activity.

The 6MWD has been identified as a predictor of survival in COPD[370] and associated with hospitalisation and increased mortality[371-373]. In COPD, a 6MWD of 350 m or less is regarded as poor performance[372]. We found that individuals with a 6MWD of 499 m or more were 6 times more likely to engage in recommended levels of MVPA (≥30 minutes daily)[355], suggesting that this distance may be a suitable cutoff for people with severe asthma. However, this requires further investigation. A difference of 30 m or more has been proposed as the minimal clinically important difference, and furthermore a decrease of this magnitude is associated with increased risk of death in COPD[374]. To date the 6MWD minimal clinically important difference for severe asthma is not known. However, the fact that an increase of 1,000 steps was associated with an increase of 22 m (after adjusting for sedentary time) indicates the potential benefits of targeting physical activity as a modifiable behaviour in severe asthma.

Our study also found that physical activity and sedentary time are associated with asthma control, health status, and lung function. The strength of the associations was rather modest and a very large change in activity (>4,000 Steps or >25 minutes of MVPA) was necessary to

reach the 0.5 unit minimal clinically important difference defined for the ACQ[363] and the AQLQ[362]. However, because the promotion of activity in severe asthma should be considered as an adjunct treatment, it may contribute to improved disease control when combined with pharmacological and other risk factor management.

We did not find any association between the activity or sedentary variables and measures of eosinophilic airway inflammation. However, it should also be noted that our population was on maximum-intensity inhaled corticosteroid therapy, and this may have modified any potential relationship between the behavioural variables and airway eosinophilia or FENO. This is further supported by the finding that FENO levels, a marker of corticosteroid responsiveness[366], were not different between the severe asthma and control populations, suggesting that FENO was suppressed by inhaled corticosteroid treatment. These findings suggest that the pathway of inactivity in severe asthma may be more related to breathlessness and/or exercise capacity than to airway inflammation.

Others have reported the positive impact of exercise on markers of airway inflammation (FENO and sputum eosinophilia). This may relate to the baseline characteristics of the participants rather than exercise itself as studies have reported decrease in FENO after a bout of exercise in physically inactive people with asthma and not in those who were active[375], and participants with increased inflammatory parameters (FENO ≥26 ppb and ≥3% sputum eosinophils) had the greatest improvement after exercise training[87]. Whether the positive effects of exercise on airway inflammation can be reproduced by shifting to higher and extended levels of daily physical activity needs further investigation.

In terms of systemic inflammation, we found that more steps per day were associated with lower hs-CRP levels, after adjustment for body mass index, sedentary time, and other confounders. This suggests a potential benefit of physical activity as a complementary

therapy to target systemic inflammation in severe asthma. The role of hs-CRP in the clinical management of severe asthma is still unclear. However, there are data linking systemic inflammation to increased risk of exacerbation[10], and to increased asthma severity[376]. Exercise also appears to have anti-inflammatory effects[377]. In COPD, it has been demonstrated that higher levels of physical activity are independently associated with lower levels of hs-CRP[278, 378]. However, very little data exist on systemic inflammation and exercise in asthma. One study reported a reduction in serum proinflammatory cytokines (IL-6 and monocyte chemotactic protein 1) after aerobic training[87]. Interestingly, Scott et al[379] reported decreases in serum IL-6 levels with exercise and diet, but not with exercise alone, and no change in hs-CRP with either intervention. Our findings may support the idea that activity carried out at a moderate level has a more beneficial effect on systemic inflammation than more strenuous, but acute, activity.

Our study has some limitations. Because of its cross-sectional design, it is not possible to infer causality of our findings. We chose to use the ActiGraph because despite of being developed as a research tool, it is becoming increasingly used in population studies[180, 356] as well as in clinical setting studies[284]. This device has been validated in populations with COPD, being one of the most accurate in detecting different walking speeds[242] and estimating activity energy expenditure[207, 243]. However, sedentary time has been shown to be more accurately measured with postural-based accelerometers, such as activPAL[209]. Also, there are conflicting data regarding the most suitable cutoff point for ActiGraph to measure sedentary time in adult populations, with cutoff points ranging from 25 to 500 CPM[209, 255-257]. It has been suggested that both activity and sedentary parameters can vary greatly depending on the cutoff point used[257]. The less than 100 CPM cutoff point that we used has been shown to be detrimentally associated with cardiometabolic measures in adults[188], and previously reported in large population studies[201]. Thus, our prevalence results could be compared with

previous estimates in the literature[188, 229, 284]. In addition, considering the scarce information available on sedentary time in patients with severe asthma, these data provide useful insight into how this behaviour is associated with both different spectrums of activity and different disease outcomes. Last, we acknowledge that we have not addressed several comorbidities, such as cardiovascular diseases and musculoskeletal conditions that may negatively impact on the level of activity and sedentary time or interact with some of the dependent outcomes. This is an area for future research. These conditions, however, are not more prevalent in patients with severe asthma than in a control group[33], and so our study design would account for these issues.

3.6. Conclusions

This study reports novel data on physical activity and sedentary time in patients with severe asthma. We found that severe asthma is associated with lower levels of MVPA. Higher levels of activity and lower levels of sedentary time were linked to better exercise capacity, asthma control, and decreased systemic inflammation. Our results highlight a need to develop and test interventions in patients with severe asthma that aim to improve exercise capacity and systemic inflammation by increasing walking and decreasing sedentary time and improve asthma control by increasing the volume of MVPA.

I have now reviewed the levels of physical activity and sedentary time in asthma populations and addressed these behaviours in participants with severe asthma, confirming that the negative impact of the disease on these behaviours is similar to other obstructive airway diseases in terms of prevalence and/or association with disease characteristics. However, direct comparisons between people with severe asthma, COPD and bronchiectasis have not yet been reported.

In order to address this gap in the literature, in Chapter 4 I will characterise physical activity in an obstructive airway disease population composed of people with severe asthma, COPD and bronchiectasis.

4. Chapter 4: Physical Activity in Obstructive Airway Diseases

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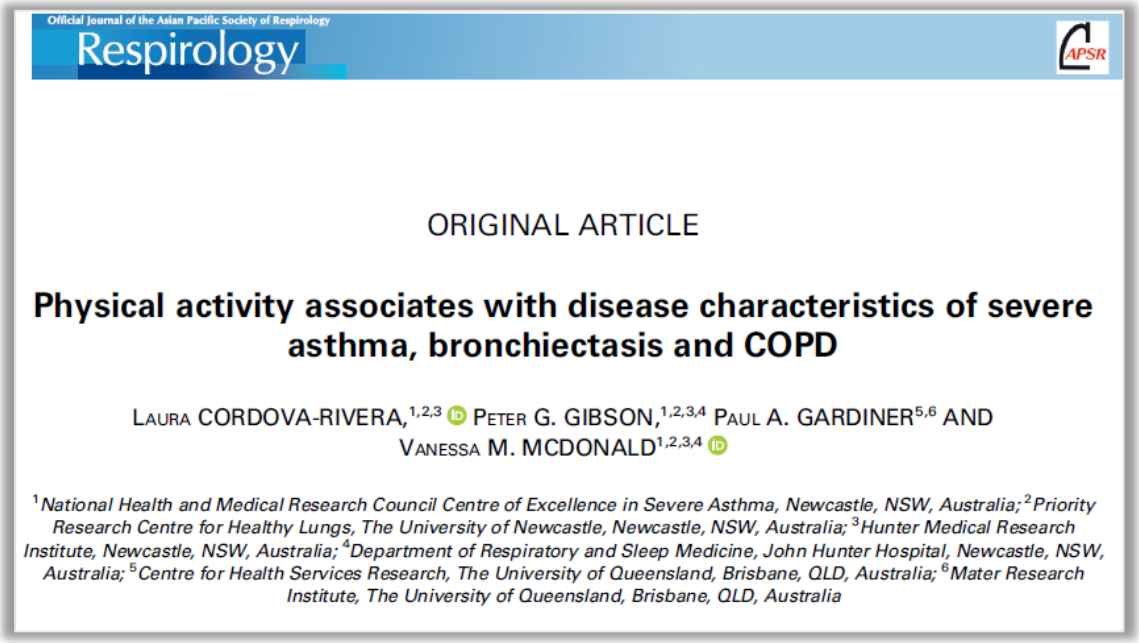

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ORIGINAL ARTICLE

Physical activity associates with disease characteristics of severe asthma, bronchiectasis and COPD

LAURA CORDOVA-RIVERA,[1,2,3] PETER G. GIBSON,[1,2,3,4] PAUL A. GARDINER[5,6] AND VANESSA M. MCDONALD[1,2,3,4]

[1]*National Health and Medical Research Council Centre of Excellence in Severe Asthma, Newcastle, NSW, Australia;* [2]*Priority Research Centre for Healthy Lungs, The University of Newcastle, Newcastle, NSW, Australia;* [3]*Hunter Medical Research Institute, Newcastle, NSW, Australia;* [4]*Department of Respiratory and Sleep Medicine, John Hunter Hospital, Newcastle, NSW, Australia;* [5]*Centre for Health Services Research, The University of Queensland, Brisbane, QLD, Australia;* [6]*Mater Research Institute, The University of Queensland, Brisbane, QLD, Australia*

See **Appendix VII** for the published article.

This article was featured with an Editorial which has been included as Appendix VIII.

Overview of this Chapter

Severe asthma, COPD and bronchiectasis share features such as airflow limitation, reduced exercise capacity, dyspnoea and systemic inflammation. These shared characteristics are likely to impact on the patients' physical activity level.

As reviewed in Chapter 1, the interrelationship that exists between disease characteristics and the level of physical activity in people with COPD has been widely characterised. These findings have highlighted the importance of promoting physical activity as a component of disease management in this population.

In severe asthma and bronchiectasis, however, physical activity impairment has not been extensively studied, and thus the interrelationship with disease characteristics is less clear.

Considering that data characterising physical activity in different OAD are necessary for the development of interventions addressing this impairment in the whole OAD population, in this chapter I aim to characterise the prevalence and intensity of physical activity in people with severe asthma and bronchiectasis, compared to people without respiratory disease and to people with moderate to severe COPD. Additionally, I aim to test whether physical activity is associated with shared clinical and biological characteristics found in OAD.

I hypothesise that people with bronchiectasis and severe asthma will present lower levels of physical activity compared to people without respiratory disease, but their degree of physical activity impairment would not be as severe as that found in participants with moderate-severe COPD. Additionally, in people with obstructive airway diseases, physical activity will be associated with shared clinical disease characteristics.

With these data, I aim to provide a more complete picture of the interrelationship between clinical associations of physical activity in OAD.

4.1. Abstract:

Background: Physical activity in obstructive airway diseases (OAD) is likely to be impaired. However, this has not been extensively studied outside of chronic obstructive pulmonary disease (COPD). We describe physical activity levels in severe asthma and bronchiectasis compared to moderate-severe COPD and to controls and tested the cross-sectional associations of physical activity (steps/day) with shared disease characteristics in the OAD group.

Method: Adults with OAD (SA=62, COPD=67, bronchiectasis=60) and controls (n=63) underwent a multidimensional assessment, including device-measured physical activity levels.

Results: The OAD group included 189 participants (58.7% female), median [IQR] age 67 [58 - 72] years and mean forced expiratory volume in the first second percentage predicted (FEV_1%) of 69.4%. Demographic characteristics differed between groups. Compared to controls (52.4% female, aged 55 [34–64] years, median 7640 steps/day), those with severe asthma, bronchiectasis and COPD accumulated less steps/day: median difference -2255, -2289, and -4782, respectively ($p \leq 0.001$). Compared to COPD, severe asthma and bronchiectasis participants accumulated more steps/day: median difference 2375 and 2341, respectively ($p \leq 0.001$). No significant differences were found between the severe asthma and bronchiectasis group. Exercise capacity, FEV_1% predicted, dyspnoea and systemic inflammation differed between groups, but were each significantly associated with steps/day in OAD. In the multivariable model adjusted for all disease characteristics, exercise capacity and FEV_1% predicted remained significantly associated.

Conclusion: Physical activity impairment is common in OAD. The activity level was associated with shared characteristics of these diseases. Interventions to improve physical activity

should be multifactorial and consider the level of impairment and the associated characteristics.

4.2. Introduction

Asthma, chronic obstructive pulmonary disease (COPD) and bronchiectasis are obstructive airway diseases (OAD) that cause significant burden to individuals and health systems[23].

Whilst these conditions have different pathophysiological processes[4], there are commonalities. They are all chronic conditions affecting the lower respiratory airways[23, 125], and share similar clinical characteristics. Additionally, exacerbations are common, increasing the disease burden[23]. These shared characteristics may challenge the person's ability to perform daily activities, and often lead to deconditioning and poor health status.

It is well established that individuals with COPD are considerably less active than people without respiratory disease[165, 259, 270], and that the degree of physical activity is associated with important disease outcomes[271]. The focus in COPD now is to develop and test interventions that improve physical activity and decrease sedentary time[168, 380]. In severe asthma and bronchiectasis however, there has been little research that objectively characterises these behaviours, or that have focused on interventions to improve them[84]. In order to develop such interventions, data characterising physical activity are needed. Furthermore, the extent to which physical activity impairment is associated with shared clinical and biological characteristics in OAD populations is also unknown. Understanding these similarities and differences is important, in order to develop targeted interventions.

We have previously reported[293, 381] that people with severe asthma have lower physical activity levels compared to controls, and that this behaviour is associated with important disease outcomes. In the present study, we aimed to characterise the degree and intensity of physical activity in people with severe asthma and bronchiectasis, compared to people

with moderate-severe COPD and to people without respiratory disease. In addition, we sought to understand whether the physical activity impairment likely to be found in OAD is associated with shared disease characteristics. We hypothesised that participants with severe asthma and bronchiectasis would engage in more physical activity than participants with COPD; but in lower activity levels than controls. Additionally, we hypothesised that in the OAD group, physical activity would be associated with characteristics shared by the three diseases.

4.3. Methods

Adults (≥18 years) with and without respiratory disease were recruited between March 2014 and June 2017 to a cross-sectional study that included measurement of physical activity.

Participants with physician-diagnosed[2, 33] severe asthma, bronchiectasis or moderate-severe COPD were recruited via the respiratory clinics at John Hunter Hospital (Newcastle, Australia), and the research databases of the Centre for Healthy Lungs and the Hunter Medical Research Institute (HMRI). Controls were recruited via the research database of the HMRI. Participants were required to be without exacerbation within the 4-weeks prior the study visits. Detailed inclusion and exclusion criteria are described in *S-1, as a Supplementary information.*

Ethics approval was granted from the Human Research Ethics Committees of the Hunter New England Local Health District (severe asthma, bronchiectasis, and controls ([08/08/20/3.10]; COPD [12/12/12/3.06]) and the University of Newcastle. The study was conducted according to Good Clinical Practice Guidelines and each participant provided written informed consent.

4.3.1. Measurements

Participants underwent a multidimensional assessment[125] involving measures of body mass index (BMI), comorbidities[357], exacerbations, respiratory health status[382], and smoking status. Further assessments included:

4.3.1.1. *Exercise capacity*

The 6-minute walk test (6MWT) was performed according to current guidelines[359]. The predicted 6-minute walk distance (6MWD) was calculated[360].

4.3.1.2. *Airflow limitation*

Spirometry was used to measure post-bronchodilator forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC ratio (Medgraphics, CPFS/D™ USB Spirometer, BreezeSuite v7.1, MGC Diagnostics, Saint Paul, MN, USA). Predicted values were calculated using NHANES III reference equations[365].

4.3.1.3. *Dyspnoea*

Scores ≥2 from the modified Medical Research Council Dyspnoea Scale (mMRC)[118] defined positive presence of dyspnoea. This cutoff is associated with higher risk of mortality in COPD[383].

4.3.1.4. *Airway inflammation*

Eosinophil and neutrophil counts were obtained from induced sputum samples using nebulised 4.5% saline, or 0.9% according to FEV_1[384]. Total cell counts and cell viability (Trypan blue exclusion) from lower respiratory sputum portions were performed, followed by cytospins' preparation for differential cell counts using May-Grunwald–Giemsa.

4.3.1.5. *Systemic inflammation*

High-sensitivity C-reactive protein (hs-CRP) was measured in peripheral blood and analysed using enzyme-linked immunosorbent assay.

4.3.2. Physical activity

Physical activity data were obtained from accelerations detected in the vertical axis using the ActiGraph wGT3X-BT (ActiGraph, Pensacola, Fl) accelerometer. The device was initialised[245] to collect accelerations at 30 Hz rate in epochs of 10-seconds. Participants wore the monitor for 14 consecutive days on a belt around their waist over the dominant hip; and removed the monitor during water-based activities. Data were summarised using the ActiLife 6.11.6 Data Analysis Software[245] and were considered valid if there were ≥4 days of recordings, with ≥10 hours of recording/day. Non-wear time was removed[231] from the analysis. Moderate and vigorous physical activity (MVPA) was categorised according to the Freedson 1998 cut-point[246] (MVPA ≥1952 counts/minute).

For physical activity levels, we reported the average steps/day and the mean minutes/day in MVPA. For the disease outcomes analysis, we reported steps/day, since it is an output easy to compare and that could be used as a motivational and informative tool for patients and clinicians[369].

4.3.3. Statistical Analysis

Data were analysed using STATA 13 (Stata Corp., College Station, TX, USA). Differences between the severe asthma, bronchiectasis, COPD, and the control groups were assessed using one-way analysis of variance, Kruskal–Wallis or Chi-square test as appropriate.

Analyses of the associations between physical activity and shared disease characteristics were performed by disease, and in the combined diseases group (OAD group). The associations between physical activity (dependant variable), disease characteristics (independent variables: 6MWD, FEV_1%predicted, dyspnoea score ≥2, hs-CRP, sputum eosinophils and sputum neutrophils), and potential confounders (current smoking and BMI) were separately estimated in the OAD group using simple linear regression analysis against steps/day. Confounders (BMI) and each independent variable with a *p*-value < 0.2 (6MWD, FEV_1%predicted, dyspnoea, sputum eosinophils, hs-CRP) were included into separate linear regression analyses to identify variables associated with physical activity. Age and sex were included in all models as biological confounders. We tested the interaction effects between diagnosis and each independent variable on steps/day (*S-2; Supplementary information*). A final model including all the independent variables was used to identify independent associations with physical activity in the OAD group. The association between exacerbation and physical activity was also tested in simple linear regression analyses *(S-3 & S-4; Supplementary information).* Assumptions for linear regressions were met. Based on the observed effect size in the final regression model (f^2=0.916, adjusted R^2= 0.4782, α = 0.05), the study has 100% power to detect the effect. Spearman's rank correlation tested relationships between steps/day and disease outcomes. A *p*-value <0.05 was considered statistically significant.

4.4. Results

A total of 296 participants (severe asthma=75, bronchiectasis=67, COPD=83, controls=71) completed the study and 252 (severe asthma=62, bronchiectasis=60, COPD=67, controls=63) were included in the analysis. Reasons for exclusion were invalid accelerometer data (severe asthma=8, bronchiectasis=5, COPD=4, controls=5), not fulfilling the inclusion criteria after

assessment (severe asthma=5, bronchiectasis=2, controls=3) or inability to complete all assessments (COPD=12).

The clinical characteristics of each group differed (Tables 4-1 and 4-2). As expected, the disease groups had worse clinical/biological characteristics than controls. The severe asthma and COPD groups had higher BMI, and both the bronchiectasis and COPD group were older than controls. Participants were treated according to current guidelines.[2, 33]

Table 4-1: Demographics and clinical characteristics of participants.

	Severe asthma[#] (n=62)	***Bronchiectasis[#] (n=60)***	***COPD[X] (n=67)***	***Control[&] (n=63)***	***p- value****	***OAD (n=189)***
Age, years	58.0 [43.0 – 68.0][X#]	68.0 [62.0 – 73.0][&#]	70.0 [64.0 - 75.0][&]	55.0 [34.0 – 64.0]	**<0.0001**	67.0 [58.0 - 72.0]
Females, %	51.6[#]	86.7[&#x]	38.8	52.4	**<0.001**	58.7
BMI, kg/m^2	28.6 [24.6 - 33.7][&#]	25.6 [21.7 - 27.6][X#]	30.1 [26.9 - 33.5][&]	25.3 [22.3 - 27.6]	**<0.0001**	27.7 [23.8 - 31.6]
Years since diagnosis	27.6 [15.1 – 51.0]	16.0 [5.0 - 57.0]	6.0 [3.0 – 14.0]	N/A		14.6 [5.0-41.0]
Current smoker, %	8.1	1.7	0.0	0.0	**0.031**	3.2
Smoking Pack/years	0.0 [0.0 - 5.4][X]	0.0 [0.0 - 2.1][X]	42.6 [31.3 - 70.5][&]	0.0 [0.0 – 3.0]	**<0.0001**	5.0 [0 – 36.0]
CCI score ≥1, %	27.9	35.0	100.0	3.17	**<0.001**	55.9
Medication, % participant prescribed						
OCS, %	40.3	3.0	3.0	0.0		15.0
Combination ICS/LABA, %	97.0	63.3	70.2	0.0		77.0
ICS, %	13.0	5.0	16.4	0.0		12.0
LAMA, %	52.0	38.3	91.0	0.0		61.4
LABA, %	0.0	2.0	16.4	0.0		6.4
Omalizumab, %	11.3	N/A	N/A	N/A		3.7
Mepolizumab, %	6.5	N/A	N/A	N/A		2.1

*Results reported as median [interquartile range] or percentage. OAD group not included in the hypothesis tests. *P-value correspond to the differences within group (COPD, SA, BE, Controls). Between groups differences: X = result statistically significant different with COPD group; & = result statistically significant different with Control group; #= result statistically significant different between severe asthma and bronchiectasis group. COPD: chronic obstructive pulmonary disease; OAD: obstructive airway disease group; BMI: body mass index; CCI: Charlson Comorbidity Index; OCS: oral corticosteroid; ICS/LABA: inhaled corticosteroid/ long acting beta agonist; LAMA: long-acting muscarinic antagonist.*

Table 4-2: Clinical and biological characteristics.

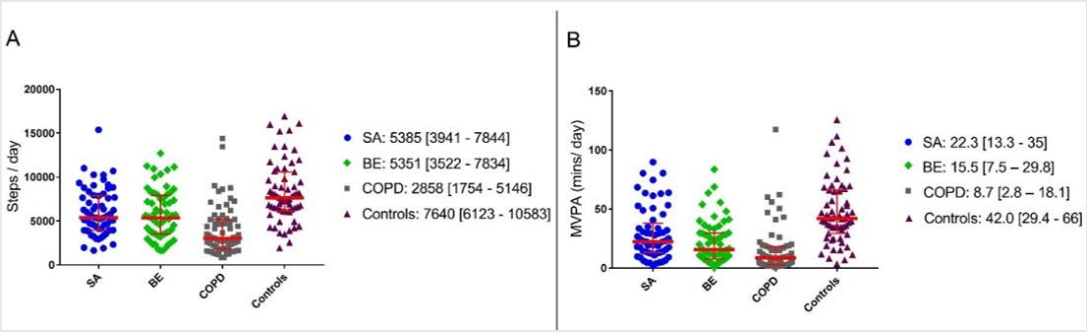
	Severe asthma[#] (n=62)	***Bronchiectasis[#] (n=60)***	***COPD[X] (n=67)***	***Control[&] (n=63)***	***p- value****	***OAD (n=189)***
Post FEV_1% predicted, %	75.8 (70.4, 81.3)[&X]	76.9 (70.9, 82.8)[&X]	56.4 (52.5, 60.3)[&]	100.6 (96.7, 104.5)	**<0.0000**	69.4 (66.2, 72.5)
Post FVC % predicted, %	87.5 (83.1, 91.8)[&X]	81.1 (76.3, 86.0)[&]	78.7 (74.6, 82.7)[&]	96.6 (93.2, 100.1)	**<0.0000**	82.3 (79.7, 84.9)
Post FEV_1/FVC ratio	0.66 [0.56 - 0.77][&X]	0.73 [0.65 - 0.79][&X]	0.56 [0.44 - 0.67][&]	0.82 [0.77 - 0.86]	**<0.0001**	0.66 [0.55 - 0.76]
6MWD, m	477.8(452.0, 503.5)[&X]	453.4 (424.2, 482.6)[&X]	383.5 (353.5, 413.6)[&]	609.5 (589.0, 629.9)	**<0.0000**	435.9(418.6, 453.1)
6MWD % predicted, %	72.1 [64.7 - 82.6][&]	76.6 [62.9 - 82.0][&X]	66.0 [46.9 - 77.2][&]	86.8 [77.9 - 92.7]	**<0.0001**	70.9 [59.1 - 80.1]
Dyspnoea score ≥ 2, %	50.0[&]	32.0[&X#]	53.0[&]	0.0	**<0.001**	45.2
GOLD quadrant, %	N/A	N/A	B= 17.9; C=4.5; D=76.1	N/A		N/A
GOLD stage, %	N/A	N/A	2= 64.2; 3=30.0; 4=6.0	N/A		
Oxygen dependent, %	0	3.3	3.8	0	**<0.001**	2.6
Severe exacerbation, n	190[X]	18[#X]	44	0	**<0.001**	
SGRQ, score	41.2 [27.5 - 55.1][X]	36.0 [23.8 - 52.5][X]	50.3 [39.5 - 66.6]	N/A	**<0.0001**	45.2 [32 - 58]
Hs-CRP, mg/L	1.8 [1.0 – 6.0][&]	2.8 [1.4 – 7.0][&]	3.8 [1.9 – 10.0][&]	1.1 [0.6 - 2.5]	**<0.0001**	2.9 [1.4 - 7.8]
Eosinophils, %	3.6 [0.8 - 13.5][&#]	1.3 [0.6 -2.1][&#]	1.8 [0.75 - 3.8][&]	0.45 [0.0 – 1.0]	**<0.0001**	1.5 [0.75 - 4]
Neutrophils, %	35.0 [17.8 - 59.3][#]	78.1 [61.3 - 85.3][&X#]	48.8 [29.5 - 71.8][&]	27.3 [15.5 - 42.8]	**<0.0001**	53.3 [28.5 - 79.3]

*Results reported as mean (95% confidence interval) (post FEV1% predicted, FVC % predicted and 6MWD), median [interquartile range] or percentage. OAD group not included in the hypothesis tests. *P-value correspond to the differences within group (COPD, SA, BE, Controls). Between groups differences: X = result statistically significant different with COPD group; & = result statistically significant different with Control group; #= result statistically significant different between severe asthma and bronchiectasis group. COPD: chronic obstructive pulmonary disease; OAD: obstructive airway disease group; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; 6MWD: 6-minute walk distance; GOLD: Global Initiative for Chronic Obstructive Lung Disease, Severe exacerbation: total number in last year as per severe asthma and GOLD guidelines definitions (bronchiectasis as per GOLD guidelines), SGRQ: Saint George Respiratory Questionnaire; hs-CRP: high sensitivity C-reactive protein.*

4.4.1. Characterisation of physical activity

Compared to controls, the severe asthma and bronchiectasis groups had lower physical activity, with a median difference of around 2270 less steps/day ($p < 0.001$ both), and a median of 19.7 ($p = 0.006$) and 26.5 ($p < 0.0001$) less minutes/day of MVPA, respectively. Compared to COPD, the severe asthma and bronchiectasis groups had higher physical activity levels, with a median of 2374 and 2341 more steps/day ($p < 0.0001$ both), and a median of 13.6 ($p < 0.0001$) and 6.8 ($p = 0.0024$) more minutes/day of MVPA (Figure 4-A). No significant differences were observed between the severe asthma and bronchiectasis population.

Figure 4-A: Physical activity comparison for steps/day (A) and MVPA (B).



MVPA: moderate and vigorous physical activity; SA: severe asthma; BE: bronchiectasis; COPD: chronic obstructive pulmonary disease; Controls: adults with no respiratory disease; SA n=62; BE n=60; COPD n=67; Controls n=63.

4.4.2. Characteristics associated with physical activity in OAD

After adjustment for significant confounders, 6MWD, FEV_1% predicted, dyspnoea, sputum eosinophils% and hs-CRP were all associated with steps/day in the combined OAD group (Table 4-3). Regression models by disease (Table 4-4) show a similar pattern, as indicated by overlapping confidence intervals in forest plots (*S-5; Supplementary information*). The correlations between some measured outcomes and steps/day are shown in Figure 4-B. The 6MWD had the strongest correlation with physical activity, and the regression model explained 43% of the adjusted variance in steps/day. Every 100-metre increase in exercise capacity was associated with an increase of 1500 steps/day. Dyspnoea, airflow limitation, systemic inflammation, and sputum eosinophils were weaker associations of physical activity, but statistically significant, nonetheless. Associations between disease outcomes and MVPA are reported in *S-6; Supplementary information*.

The full regression model shows that better exercise capacity and lung function remained independently and positively associated with physical activity in OAD (Table 4-3). Dyspnoea, hs-CRP and sputum eosinophils were no longer significant. The full model explained 48% of the variance in steps/day in OAD.

Table 4-3: Associations of physical activity in obstructive airways diseases.

Separate models for clinical and biological outcomes	***Associations of steps/day with disease characteristics in OAD***		
	Coefficient (95%CI)	**Significance**	**Adj. R^2**
a. 6MWD (m)	15.10 (12.10, 18.10)	**<0.001**	0.433
b. FEV_1% predicted (%)	52.62 (34.99, 70.25)	**<0.001**	0.153
Reference: ≤1 scores c. Dyspnoea (≥2 score)	-1689.4 (-2476, -902.1)	**0.001**	0.204
d. hs-CRP (mg/L)	-36.96 (-61.35, -12.56)	**0.003**	0.190
e. Eosinophils (%)	50.25 (0.40, 100.11)	**0.048**	0.161
Full model	***Independent associations of steps/day in OAD***		***Adj. R^2= 0.478***
6MWD (m)	12.40 (8.51, 16.28)	**<0.001**	
FEV_1% predicted (%)	18.96 (0.53, 37.40)	**0.044**	
Dyspnoea (≥2 score)	-42.40 (-813.95, 729.16)	0.914	
hs-CRP (mg/L)	0.69 (-20.33, 21.71)	0.948	
Eosinophils (%)	25.88 (-14.49, 66.24)	0.207	
BMI (kg/m^2)	-54.15 (-104.05, -4.26)	**0.034**	
Age	-27.74 (-55.3 -0.19)	**0.048**	

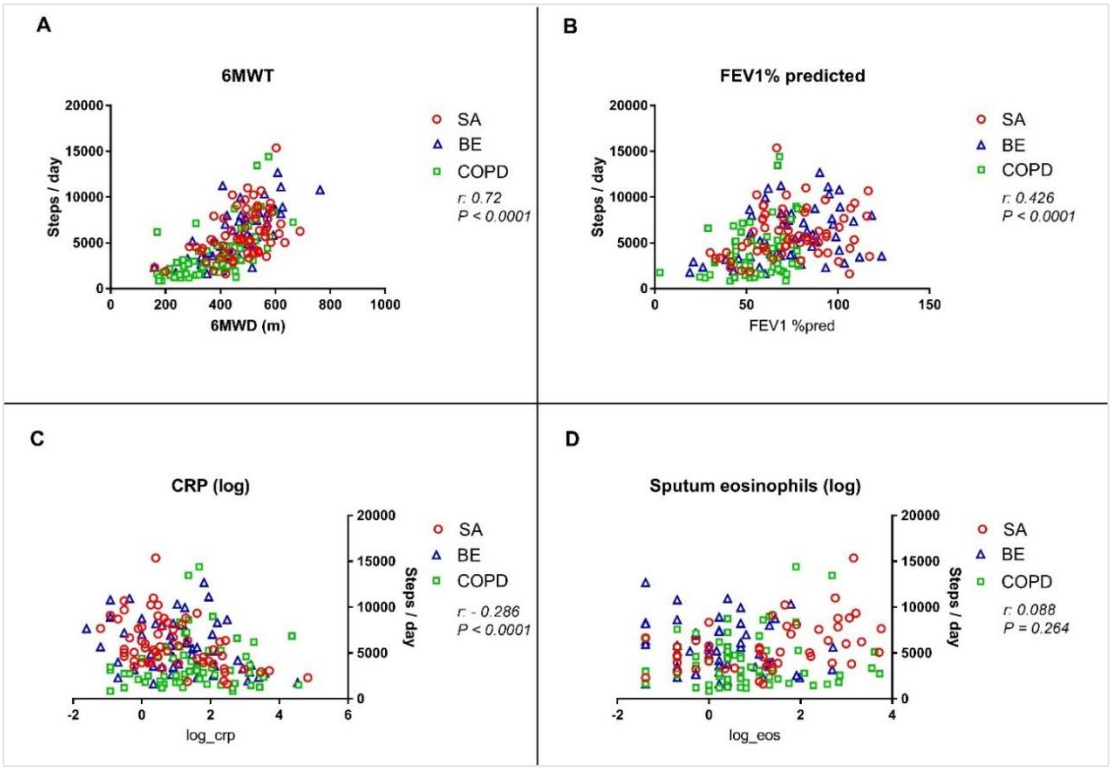
Each model adjusted for confounders: age, gender, and BMI (except FEV_1%predicted). Dyspnoea was transformed into a binary variable and considered positive when scores were ≥2. Confounders (BMI, age and sex) explained a 13% of the variance in steps/day in the full model. Sex not significant in the full model. OAD: obstructive airway diseases; 6MWD: 6-minute walk distance; FEV1% predicted: forced expiratory volume in the first second; hs-CRP: high sensitivity C-reactive protein; BMI: body mass index. Statistically significant results in bold.

Table 4-4: Regression models of associations of disease characteristics with steps/day by diagnosis.

	Associations of steps/day with disease outcomes by disease		
	6MWD (m)		
	Coefficient (95%CI)	**Significance**	**Adj. R^2**
Severe asthma	12.76 (6.27, 19.26)	**<0.001**	0.259
COPD	12.01 (7.63, 16.39)	**<0.001**	0.485
Bronchiectasis	17.37 (12.26, 22.47)	**<0.001**	0.503
	FEV_1% predicted (%)		
Severe asthma	33.71 (2.04, 65.38)	**0.037**	0.060
COPD	46.20 (4.52, 87.88)	**0.030**	0.055
Bronchiectasis	45.52 (15.77, 75.27)	**<0.01**	0.124
	Dyspnoea (≥2 score) ***(versus scores ≤1)***		
Severe asthma	-1534.53 (-2966.27, -102.80)	**0.036**	0.129
COPD	-1310.93 (-2536.58, -85.28)	**0.036**	0.286
Bronchiectasis	-2270.94 (-3710.32, -831.56)	**0.003**	0.213
	hs-CRP (mg/L)		
Severe asthma	-45.82 (-84.92, -6.72)	**0.022**	0.153
COPD	-15.52 (-52.71, 21.67)	0.407	0.243
Bronchiectasis	-84.34 (-132.33, -36.35)	**<0.001**	0.279
	Eosinophils (%)		
Severe asthma	87.87 (16.34, 159.40)	**0.017**	0.124
COPD	22.99 (-50.20, 96.18)	0.532	0.239
Bronchiectasis	-113.40 (-351.35, 124.55)	0.343	0.103

Models adjusted for confounders: age, sex, and BMI (except FEV_1% predicted). Dyspnoea was transformed into a binary variable and considered positive when scores were ≥2. OAD: obstructive airway diseases; 6MWD: 6-minute walk distance; FEV1% predicted: forced expiratory volume in the first second; hs-CRP: high sensitivity C-reactive protein; BMI: body mass index. Statistically significant results in bold.

Figure 4-B: Pearson's correlation of physical activity (steps/day) with 6MWT (A); FEV_1% predicted (B); hs-CRP (C); and Sputum eosinophils% (D).



SA: severe asthma; COPD: chronic obstructive pulmonary disease, BE: bronchiectasis; 6MWD: 6-minute walk distance; FEV_1: forced expiratory volume in the first second; CRP: high sensitivity C-reactive protein. Hs-CRP and eosinophils % transformed to natural logarithm.

4.5. Discussion

In this study we characterised the level of physical activity in a group of people with severe asthma and bronchiectasis, compared to moderate-severe COPD and controls. For the first time, we have shown that people with both severe asthma and bronchiectasis engage in lower levels of physical activity than people without respiratory disease, but higher levels compared to people with COPD. The intensity and volume of activity were similar in the severe asthma and bronchiectasis groups, and the degree of physical activity impairment in OAD could be explained in an important proportion by exercise capacity and airflow limitation.

We aimed to characterise and compare the level of physical activity impairment in different OAD. A robust body of research exists in COPD, highlighting that physical activity is markedly decreased[271], and that this decrease is strongly associated with exacerbations and mortality[264, 271, 272]. As such, the promotion of physical activity in COPD is an important component of disease management[380], and a desirable indirect outcome of pulmonary rehabilitation[89, 380].

Whilst the degree of physical inactivity and its impact is well established in COPD, in severe asthma and bronchiectasis there is a paucity of research that: characterises this important and modifiable risk-factor, that makes comparisons to disease groups with similar characteristics, or that has described the clinical associations of physical activity in these conditions. This is important in order to generate an evidence-base that can guide the direction of treatment interventions for severe asthma and bronchiectasis. Extrapolating what is known in COPD to these conditions may lead to the design of ineffective interventions. In an era of personalised medicine this new knowledge will help design individualised treatment programmes.

Our severe asthma and bronchiectasis populations moved a median of 5360 steps/day each, resulting in a median difference of 2350 more steps compared to our COPD population. Previous studies conducted in severe asthma[291] and bronchiectasis[284] have reported a median of approximately 6000 steps/day, which is consistent with our results. When compared with severe asthma, our bronchiectasis population also accumulated fewer minutes of MVPA, although not statistically significant. These differences were explained by the fact that our bronchiectasis participants were mostly females, a trend previously reported[337]. Overall our data confirm that physical activity impairment exists in severe asthma and bronchiectasis, but to a lesser degree than in COPD.

Whilst we highlight the importance of characterising these behaviours in specific disease groups, we also combined the disease populations to identify if shared clinical characteristics of OAD are associated with physical activity. In the recently proposed 'treatable traits' management approach[51], deconditioning was proposed as an extrapulmonary trait to be addressed. We suggest that physical activity itself is a trait to be targeted, and we report that this occurs albeit to different degrees across diagnosis groups. These groups also shared clinical and biological features that were all associated with physical activity impairment. Therefore, we have identified potential treatment targets that might address the physical inactivity trait, not only in COPD but also in severe asthma and bronchiectasis.

The 6MWD explained the highest proportion of variance in steps/day in the OAD group. This test has been endorsed as a valid outcome measure in people with chronic respiratory disease to measure functional exercise capacity[359], and is an important predictor of COPD mortality[370, 385]. Despite being widely used in COPD and increasingly validated in bronchiectasis[286], it is not routinely recommended in severe asthma[33], and thus, assessment of functional exercise capacity in severe asthma is scarce[83]. The reasons for its underuse may

relate to fear of provoking exercise-induced bronchoconstriction, or that "uncontrolled asthma" is listed as one of the guideline contraindications[359]. We did not encounter any adverse-events performing the test in our severe asthma population.

FEV_1% predicted was also independently associated with the level of physical activity in the OAD group. Considering that the degree of airflow limitation categorises disease severity, and that increased severity has been associated with lower activity levels[269, 284, 381], these results are somewhat expected. Interesting though, in the full model airflow limitation was a stronger predictor of steps/day than dyspnoea, despite the latter being one of the most disabling symptoms in diseases such as COPD and severe asthma.

Activity-related dyspnoea was common in our OAD population. We found that higher dyspnoea scores (≥2) modestly explained the adjusted variance in physical activity in the individual model, but it did not remain significant in the full model. It could be that breathlessness alone is not enough to explain the physical activity impairment found in these diseases, and that the evaluation of symptoms in different domains could give a more accurate picture. This is in line with recommendations made in COPD guidelines[2].

In our full multivariate model, the inflammatory markers of hs-CRP and sputum eosinophils were not independently associated with physical activity, despite displaying a moderate to weak associations individually. This is probably related to the strong association found with the 6MWD, which by itself accounted for most of the variance in physical activity. Despite this, systemic inflammation was still significantly associated with steps/day in the OAD group, which is in line with evidence in COPD[271] and in severe asthma[293].

Exercise capacity was a better predictor of physical activity than airflow limitation. This may be due to the fact that functional exercise capacity gives an estimate of the person's ability to endure exercise[380], which is a subset of physical activity[155]. In COPD, the mechanisms

behind exercise limitation are multifactorial, and include the impairment of the ventilatory, cardiovascular, metabolic and locomotor muscle systems[386]. It is likely that these mechanisms also play a role in severe asthma and bronchiectasis, especially in patients showing a degree of overlap between these conditions.

Lastly, in the general population, physical activity has been positively associated with the prevention of different chronic diseases[160, 176]. Considering the comorbidity burden found in OAD populations, the promotion of physical activity may generate benefits beyond respiratory symptoms alone.

Our study has some limitations. Its cross-sectional design does not infer causality of our findings. Additionally, we have not considered important comorbidities, disease characteristics, sociodemographic and environmental characteristics nor behaviours (i.e. sedentary time) that may impact in the engagement of physical activity or interact with diseases' outcomes. Lastly, our populations are not demographically nor clinically matched, which limit comparison of our findings. Nevertheless, diagnosis was not a significant interaction in the relationship between the independent variables and steps/day.

4.6. Conclusion

Physical activity impairment is a shared behavioural characteristic of people with COPD, severe asthma and bronchiectasis. Shared clinical characteristics, such as exercise capacity and airflow limitation explain an important proportion of this impairment in OAD. Both of these traits can be targeted by specific treatments, making physical activity impairment a "treatable trait" that requires consideration in the management of these diseases. Treatment studies aimed at improving physical activity in these populations are needed and our data may inform such interventions.

4.7. Supplementary information

S-1: Inclusion and exclusion criteria

All participants were adults (≥18 years), and able to provide written consent.

Participants with severe asthma, COPD and bronchiectasis were recruited from the respiratory ambulatory care clinics at John Hunter Hospital (Newcastle, Australia), the clinical research databases of the Priority Research Centre for Healthy Lungs at the University of Newcastle and the Hunter Medical Research Institute (Newcastle, Australia). Participants without respiratory disease were recruited from the clinical research databases of the Priority Research Centre for Healthy Lungs and the Hunter Medical Research Institute and community advertisement. Data from severe asthma, healthy controls and bronchiectasis participants were extracted from two cross-sectional studies aimed at characterising these populations (ethics approval: 08/08/20/3.10). Healthy control participants were matched by age and sex with severe asthma participants, and data from part of these cohorts have been previously published by the authors[1]. Data from COPD participants were extracted from the baseline assessment of a randomised control trial (ACTRN 12613000046707, ethics approval 12/12/12/3.06).

Participants with a respiratory physician diagnosis of severe asthma according to American Thoracic Society/European Respiratory Society Severe Asthma Task Force[2] were included if they had: evidence of airway hyper-responsiveness *or* variable airflow limitation, *and* were on high dose inhaled corticosteroid (≥1000 mcg of Fluticasone or equivalent) *and* long acting beta-agonist *or* maintenance prednisone, *and* had a post-bronchodilator forced expiratory volume in the first second (FEV_1) < 80% *or* FEV_1/forced vital capacity (FVC) <70% *or* an asthma control questionnaire score ≥1.5 *or* had a severe exacerbation in the last 12-months with oral corticosteroid use. Exclusion criteria included: current lung cancer or other blood, lymphatic

or solid organ malignancy, and poor survival (<3 months), and prolongation of the QTc interval >480.

Participants with bronchiectasis were included if they had a primary diagnosis of bronchiectasis confirmed by HRCT of chest. Exclusion criteria included diagnosis with respiratory diseases other than asthma or COPD.

Participants with a confirmed diagnosed of COPD according to current guidelines[3] were included if they had: a post-bronchodilator FEV_1% predicted < 80%, *and* FEV_1/FVC < 70% *or* objective confirmation from computed tomography of chest, *and* an acute exacerbation within the previous 12-months *and* were in Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage ≥2, *and* receiving baseline therapy in accordance to GOLD strategy recommendations. Exclusion criteria included: current smoker, treatment with Macrolides, Tetracycline and oral corticosteroids, *and* hypersensitive to Macrolides, pregnancy or breastfeeding, impaired liver function, prolongation of the QTc interval (<480 mS), uncontrolled medical illness that would preclude participation in the study, and primary diagnosis of other significant respiratory disease. Controls participants were non-smokers with no objective evidence of respiratory disease.

Exclusions criteria for all groups also included: inability to attend study visits, and recent (past 4-weeks) exacerbation or respiratory tract infection.

S-2: Adjusted simple linear regression models testing interaction effects between diagnosis and each independent variable on steps/day.

Interaction of diagnosis in the relationship between steps/day and independent variables		
	Coefficient (95% CI)	***p*-value**
6MWD* COPD (vs. severe asthma)	2.61 (-4.74, 9.98)	0.483
6MWD* bronchiectasis (vs. severe asthma)	6.47 (-0.98, 13.92)	0.088
FEV_1% predicted* COPD (vs. severe asthma)	12.48 (-39.17, 64.15)	0.633
FEV_1% predicted* bronchiectasis (vs. severe asthma)	11.80 (-31.20, 54.82)	0.588
Dyspnoea ≥2(vs. scores ≤1)* COPD (vs. severe asthma)	-91.60 (-1937, 1754)	0.922
Dyspnoea ≥2(vs. scores ≤1)* bronchiectasis (vs. severe asthma)	-1002.22 (-2946.91, 942.46)	0.309
hs-CRP* COPD (vs. severe asthma)	21.22 (-35.41, 77.86)	0.460
hs-CRP* bronchiectasis (vs. severe asthma)	-35.20 (-96.52, 26.10)	0.258
%eosinophils in sputum* COPD (vs. severe asthma)	-69.78 (-175.59, 36.02)	0.194
%eosinophils in sputum* bronchiectasis (vs. severe asthma)	-222.87 (-466.19, 20.44)	0.072

Coefficients for the interaction between diagnosis label and independent variables on steps/day (dependent variables), tested in adjusted simple linear regression models adjusted for age, sex, BMI and diagnosis (severe asthma, COPD and bronchiectasis.). FEV_1% predicted adjusted only for diagnosis. 6-minute walk distance; FEV_1% predicted: forced expiratory volume in the first second; hs-CRP: high sensitivity C-reactive protein; BMI: body mass index.

S-3: Associations between the levels of physical activity and exacerbations

We assessed the relationship between exacerbations (number of severe exacerbations and frequent exacerbator) as a predictor of the level of physical activity (dependent variable: steps/day and MVPA) in linear regression models.

Severe exacerbations in severe asthma and COPD were defined according to guidelines:

- Severe asthma (including severe and serious exacerbations): at least one hospitalisation, Intensive Care Unit stay or mechanical ventilation, or two or more bursts of systemic corticosteroids (>3 days each) in the previous year.
- COPD: patients requiring hospitalisation or visit to emergency rooms.

Since a definition for severe exacerbation in bronchiectasis has not yet been agreed[387], for the purpose of this analysis we defined severe exacerbations in bronchiectasis as per COPD criteria.

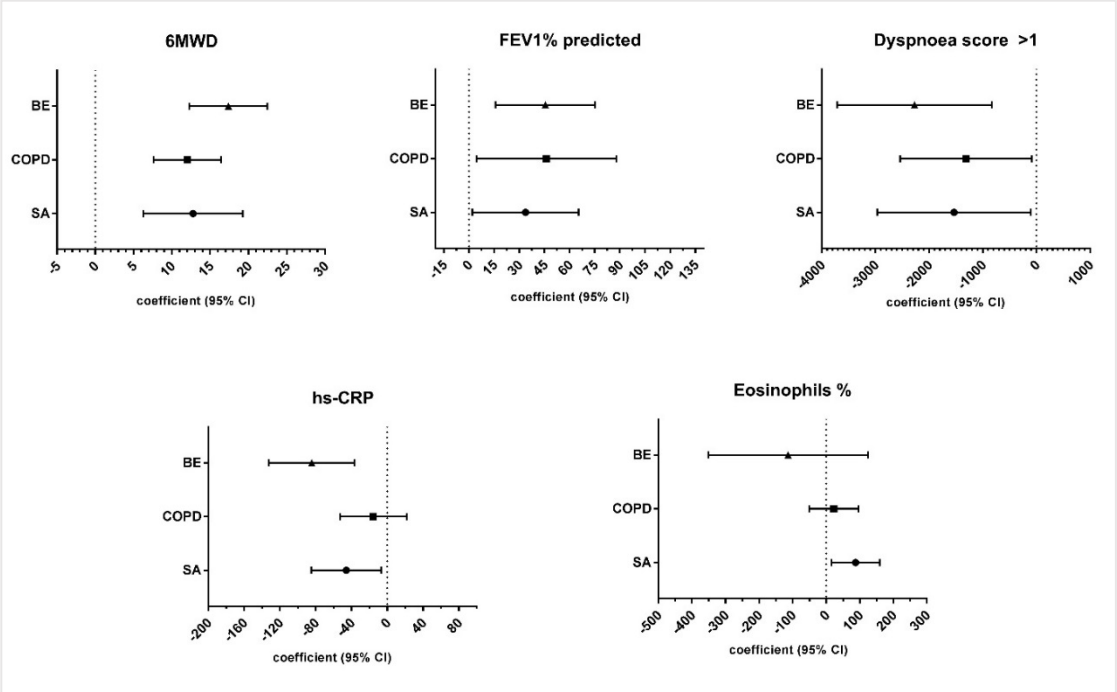
"Frequent exacerbator" was defined as having a severe exacerbation or ≥2 moderate exacerbations in the last year.

The total number of severe exacerbations in the severe asthma, COPD and bronchiectasis group were 190, 44 and 18 exacerbations, respectively. The proportion of frequent exacerbator in the severe asthma, COPD and bronchiectasis group were 93.4%, 80.6% and 58.3%, respectively. Table S-4 reports in the association of the simple linear regression models using steps/day for both exacerbations' outcomes.

S-4: Associations between physical activity and exacerbations.

	Associations of Steps/day with number of severe exacerbations	
	Coefficient (95%CI)	**p-value**
Severe asthma	-235.1 (-458.9, -11.3)	**0.040**
COPD	-15.8 (-756.8, 725.2)	0.966
Bronchiectasis	-1269.5 (-2277.1, -261.9)	**0.014**
	Associations of MVPA with number of severe exacerbations	
Severe asthma	-1.7 (-3.6, 0.2))	0.075
COPD	-1.0 (-6.2, 4.2)	0.697
Bronchiectasis	-6.5 (-13.1, 0.2)	0.056
	Associations of Steps/day and frequent exacerbator	
Severe asthma	-116 (-2915, 2683)	0.934
COPD	584 (-1139, 2308)	0.501
Bronchiectasis	-142.6 (-1628, 1343)	0.848
	Associations of MVPA and frequent exacerbator	
Severe asthma	6.5 (-16.5, 29.6)	0.573
COPD	5.2 (-6.9, 17.3)	0.394
Bronchiectasis	-3.2 (-12.8, 6.4)	0.508

S-5: Forest plots of associations of clinical and biological outcomes with steps/day by disease.



Coefficients (95% CI) of clinical outcomes as predictors of steps/day in linear regression models by disease, adjusted by age, sex, and BMI (except FEV1% predicted). 6MWD: 6-minute walked distance, FEV1% predicted: forced expiratory volume in the first second, hs-CRP: high sensitivity C-reactive protein; eosinophils: percentage of eosinophils in sputum.

S-6: Clinical and biological characteristics associated with moderate and vigorous physical activity in the OAD group.

Separate models for clinical and biological outcomes	**Associations of MVPA with disease characteristics in OAD of MVPA in OAD**		
	Coefficient (95%CI)	**Significance**	**Adj. R2**
6MWD (m)	0.10 (0.07, 0.12)	**<0.0001**	0.3442
FEV_1% predicted (%)	0.34 (0.21, 0.47)	**<0.001**	0.1220
Dyspnoea (≥2 score)	-13.51 (-19.19, -7.82)	**<0.001**	0.1878
hs-CRP (mg/L)	-0.20 (-0.38, -0.02)	**<0.032**	0.1231
Eosinophils (%)	0.25 (-0.13, 0.62)	0.193	0.1201
Full model	**Independent associations of MVPA in OAD**		**Adj. R2 = 0.3923**
6MWD (m)	0.08 (0.04, 0.11)	**<0.001**	
FEV_1% predicted (%)	0.18 (0.03, 0.32)	**0.019**	
Dyspnoea (≥2 score)	-2.91 (-8.98, 3.16)	0.346	
hs-CRP (mg/L)	0.05 (-0.11, 0.22)	0.525	
Eosinophils (%)	0.09 (-0.23, 0.41)	0.580	
BMI (kg/m^2)	-0.05 (-0.44, 0.34)	0.808	
Female	-8.26 (-13.88, -2.64)	**0.004**	

Each model (except FEV_1% predicted) adjusted for confounders: age, gender, and BMI. Dyspnoea was transformed into a binary variable and considered positive when scores were ≥2. Confounders (BMI, age and sex) explained a 9.7% of the variance in MVPA. Age not significant in the full model. MVPA is activity at ≥1942 count per minutes as measured by Actigraph wGT3X-BT accelerometer. OAD: obstructive airway diseases; 6MWD: 6-minute walk distance; FEV1% predicted: forced expiratory volume in the first second; hs-CRP: high sensitivity C-reactive protein; BMI: body mass index. MVPA: moderate and vigorous physical activity. Statistically significant results in bold.

In this chapter, I have addressed important common pulmonary characteristics shared by people with OAD and highlighted that physical activity could be considered as an extrapulmonary treatable trait not only in COPD, but also in severe asthma and bronchiectasis. However, data characterising the interrelationship between physical activity, other extrapulmonary features including comorbidities, and health-related quality of life is limited. Health related quality of life is an important multidimensional and patient-related end-point that help to inform clinicians about the perceived impact that the disease has in a patient.

In order to address this gap in the literature, in Chapter 5 I characterise the different relationships between physical activity and others extrapulmonary features and comorbidities with health-related quality of life in participants with severe asthma and bronchiectasis.

5. Chapter 5: Extrapulmonary Associations of Health Status in Severe Asthma and Bronchiectasis: comorbidities and functional outcomes.

This chapter is currently under peer-review in the journal Respiratory Medicine. Resubmission has been invited

Citation: Cordova-Rivera L, Gibson PG, Gardiner PA, Hiles SA, McDonald VM. **Extrapulmonary disease characteristics and health-status in severe asthma and bronchiectasis.** ***Under peer review.***

Overview of this Chapter

In the previous chapter, I characterised the degree of physical inactivity in severe asthma, bronchiectasis, and moderate to severe COPD. In addition to concluding that the levels of physical activity were lower in OAD compared to controls, and that the degree of reduction in severe asthma and bronchiectasis was similar; I demonstrated that despite these differences this behaviour was still significantly associated with important pulmonary outcomes. People with severe asthma and bronchiectasis also present several well-characterised extrapulmonary characteristics, including higher presence of comorbidities and anxiety and depression symptoms. Other extrapulmonary characteristics, such as skeletal muscle strength, have not been very well characterised in severe asthma or bronchiectasis. As a result, the impact of these characteristics is unclear. This contrasts again with knowledge in COPD, where several of these extrapulmonary disease characteristics are recognised treatment targets for improving health-related quality of life (HRQoL).

In this chapter, I aimed to explore the interrelationship between several extrapulmonary outcomes, including physical activity, comorbidities, skeletal muscle function, among others with health-related quality of life in an obstructive airway disease population composed of participants with severe asthma and bronchiectasis.

I hypothesised that better extrapulmonary characteristics, such as higher physical activity, fewer comorbidities, and better skeletal muscle function, will be associated with improved health-related quality of life in participants with severe asthma and bronchiectasis.

With these data, I aim to generate knowledge that could guide future interventions that aim to improve quality of life in severe asthma and bronchiectasis.

5.1. Abstract

Background: Severe asthma and bronchiectasis are heterogeneous diseases that contribute to disability beyond the pulmonary system. The magnitude of the impact that these extrapulmonary features has on health-related quality of life (HRQoL) is unknown.

Methods: We analysed the cross-sectional relationships between HRQoL (St. George's Respiratory Questionnaire; SGRQ) and extrapulmonary characteristics, including physical activity (steps/day), anxiety and depression, isometric leg strength, systemic inflammation, and several comorbidities in adults with severe asthma (n=70) and bronchiectasis (n=61).

Results: Participants with severe asthma and bronchiectasis had similar SGRQ total scores (mean scores 43.7 and 37.8 for severe asthma and bronchiectasis; $p>0.05$), and similar pulmonary and extrapulmonary characteristics. The associations between extrapulmonary variables and HRQoL did not differ according to diagnosis (all interactions $p>0.05$). Greater anxiety and depressive symptoms, fewer steps/day and greater systemic inflammation were statistically associated with poorer HRQoL in both diseases ($p<0.05$). Lower isometric leg strength in severe asthma, and greater Charlson Comorbidity Index in bronchiectasis were also associated with poorer HRQoL ($p<0.05$). In the multivariable regression model performed in the combined disease groups, anxiety and depression, steps/day, systemic inflammation and isometric leg strength remained independently associated with HRQoL. Associations between extrapulmonary characteristics and SGRQ domains were stronger for the activity and impact domains, than symptoms.

Conclusion: In severe asthma and bronchiectasis, extrapulmonary features including physical activity and leg strength have a significant impact on HRQoL, especially within the activity and impact domains. These features should be considered as part of the assessment of these conditions, and they may represent additional treatment targets to improve HRQoL.

5.2. Introduction

Severe asthma and bronchiectasis contribute a high burden of illness. Severe asthma affects 3-10% of the asthma population[33], but discordantly is responsible for over 50% of the asthma-related healthcare costs[351]. Additionally, mortality from asthma has not improved over recent years, and it is rising in Australia, the UK and USA[12]. Bronchiectasis is less prevalent, nevertheless its incidence is also rising in Europe and the USA[388]. Moreover, individuals with bronchiectasis suffer high morbidity secondary to recurrent chest infections[389].

The ongoing disease burden from obstructive airway diseases such as asthma, bronchiectasis and chronic obstructive pulmonary disease (COPD), has led to calls for a different approach to disease management that more effectively addresses the complexity and heterogeneity of these diseases[12, 51, 125]. The proposed treatable traits strategy, for instance, recognises that patients have specific disease components (called 'traits') that can be identified and treated (hence 'treatable traits') and this will lead to improved patient outcomes[51]. While most pharmacological therapies target the airway domain in severe asthma, bronchiectasis and COPD, it is recognised that traits outside the airway may also be important. The impact of a trait on quality of life is a useful determinant of clinically important traits, and therefore, it is necessary to test whether these extrapulmonary characteristics represent important traits that could be addressed.

Although severe asthma and bronchiectasis have different aetiologies and pathogenesis, they share similar pulmonary and extrapulmonary characteristics that together impair health-related quality of life (HRQoL)[14, 15], making this outcome an ongoing burden for these patients[14, 390, 391]. HRQoL is an important multidimensional and patient-related outcome that focuses on the physical, mental, emotional, and social impact that the disease has on

patient's wellbeing[392]. In COPD, extrapulmonary features including physical inactivity, skeletal muscle dysfunction, and comorbidities are known to negatively impact HRQoL,[102, 128, 271] and represent important targets for treatment.[392]

We have recently shown that the deficits in exercise capacity and airflow limitation between severe asthma and bronchiectasis patients are similar, and that these pulmonary characteristics are associated with impairment in physical activity[393] *(see Chapter 4)*. However, it remains unclear how extrapulmonary characteristics, such as physical activity, muscle strength, and comorbidities are associated with HRQoL in patients with severe asthma and bronchiectasis, and whether there is an interrelationship between other extrapulmonary characteristics and health-status. This is important because if extrapulmonary features do impact HRQoL, then they may present useful treatment targets in these diseases, which require specific and individualised interventions in order to optimise HRQoL[14].

In this study, we aimed to describe relationships between HRQoL and extrapulmonary characteristics, including physical activity, muscle strength, comorbidities, systemic inflammation and anxiety and depression with HRQoL in participants with severe asthma and bronchiectasis. Secondarily, we tested whether the relationship between extrapulmonary characteristics and HRQoL differed for severe asthma and bronchiectasis, by testing the interaction between diagnosis and extrapulmonary characteristics in our analyses.

We hypothesised that extrapulmonary traits will have similar impacts in severe asthma and bronchiectasis, and that better function in these variables will be significantly and independently associated with a lesser degree of impairment in HRQoL.

5.3. Methods

Adults (≥18 years) with respiratory physician-diagnosed severe asthma or bronchiectasis were recruited from the respiratory clinics at John Hunter Hospital and the clinical research databases of the Priority Research Centre for Healthy Lungs (Newcastle, Australia) between March 2014 and June 2017. Data from severe asthma and bronchiectasis participants were extracted from two cross-sectional studies aimed at characterising these populations. Participants were required to be without exacerbation within the 4-weeks prior the study-visits.

Ethics approval was granted from the Human Research Ethics Committees of the Hunter New England Local Health District (08/08/20/3.10) and the University of Newcastle. The study was conducted according to Good Clinical Practice Guidelines and all participants provided written informed consent.

Participants with a respiratory physician diagnosis of severe asthma according to American Thoracic Society/European Respiratory Society Severe Asthma Task Force[33] were included if they had:

1. Evidence of airway hyper-responsiveness *or* variable airflow limitation, *and*

2. Were on high dose inhaled corticosteroid (≥1000 mcg of Fluticasone or equivalent) *and* long acting beta-agonist *or* maintenance prednisone, *and*

3. Had a post-bronchodilator forced expiratory volume in the first second (FEV_1) < 80% *or* FEV_1/forced vital capacity (FVC) <70% *or* an asthma control questionnaire score ≥1.5 *or* had a severe exacerbation in the last 12-months with oral corticosteroid (OCS) use.

Participants with bronchiectasis[131] were included if they had a primary diagnosis of bronchiectasis confirmed by high resolution chest computed tomography. Exclusion criteria included diagnosis with respiratory diseases other than asthma or COPD.

Exclusions criteria for both groups also included: inability to attend study visits, and recent (past 4-weeks) exacerbation or respiratory tract infection.

Ethics approval was granted from the Human Research Ethics Committees of the Hunter New England Local Health District (08/08/20/3.10) and the University of Newcastle. The study was conducted according to Good Clinical Practice Guidelines and all participants provided written informed consent.

5.3.1. Procedures

Participants attended two visits and underwent a multidimensional assessment[125] involving measures of airflow limitation, exercise capacity, height, weight, and smoking status. Further assessments included:

5.3.1.1. *Health-related quality of life*

Total and domain score of the Saint George Respiratory Questionnaire (SGRQ)[394] were calculated. Higher scores represent higher impairment. The minimal clinically important difference (MCID) is ≥4 units[395].

5.3.1.2. *Physical activity*

Steps/day were measured using the ActiGraph wGT3X-BT (ActiGraph, Pensacola, Florida). Participants wore the monitor 24-hours a day for 14-consecutive days on their dominant hip. The device was initialised using the ActiLife 6.11.6 Data Analysis Software. Data from valid days (≥4 days with ≥10 hours of recording each) were averaged as daily mean steps/day.

5.3.1.3. *Isometric leg strength*

The better of two attempts was recorded to the nearest 0.1 kg resistance using a platform-leg and back dynamometer (Baseline®, USA). Participants attempted to smoothly extend their knees as forcefully as possible.

5.3.1.4. *Body composition and bone mineral density*

Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Dual-energy X-ray absorptiometry (DXA) GE Lunar Prodigy Pro DEXA scanner (GE Healthcare, Giles HP8-4SP, UK) was used to measure skeletal muscle-mass and bone mineral density. Appendicular skeletal muscle-mass index was calculated from the lean soft tissue in upper and lower limbs divided by height squared. Scores ≤7.26 (males) and ≤5.45 (females) Kg/m^2 were indicative of sarcopenia[396]. Osteopenia and osteoporosis in the non-dominant hip were defined by a T-score between –1.0 and –2.5, and ≤-2.5, respectively[397].

5.3.1.5. *Comorbidities and systemic inflammation*

Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS). A score in either domain ≥8 indicates possible anxiety or depression[358]. Comorbidity-related prognosis was calculated using the age-adjusted Charlson Comorbidity Index (CCI), from the medical history. Systemic inflammation was measured using peripheral blood high-sensitivity C-reactive protein (hs-CRP), and analysed using enzyme-linked immunosorbent assay (Siemens Healthcare Diagnostics, Marburg, Germany).

5.3.2. Statistical analysis

Data were analysed using STATA 13 (Stata Corp., College Station, TX, USA). Since the distribution of hs-CRP was skewed, we performed natural log-transformation (ln) for this variable to ensure assumptions of regression analyses were met. Descriptive statistics were

calculated. Missing values of the variables leg strength (n=21), bone density (n=8), steps/day (n=9) and sarcopenia (n=4) were estimated using multiple imputation by chained equations. Categorical values were imputed via augmented logistic or multinomial logistic regression and continuous variables were imputed via predictive mean matching. Variables used in the imputation model (sarcopenia, bone density, leg and arm strength, ln(hs-CRP), CCI score, total fat mass, HADS score, dyspnoea score, BMI, age, gender, SGRQ total, FEV_1, steps/day, moderate and above physical activity, and 6-minute walk distance) were selected based on significant associations with the missing variables or because they were either independent or dependent variables in our full regression model assessing determinants of HRQoL. Burn-in and iteration were 100, and 30 datasets were created. Convergence plots indicated good model fit. No statistically significant differences were observed in the Student's t-test for the SGRQ scores between participants with missing and non-missing values for imputed variables (p>0.05).

Associations with HRQoL [Dependent variable: SGRQ total score; independent variables: steps/day, isometric leg strength, sarcopenia, osteopenia or osteoporosis, ln(hs-CRP), HADS total score, and CCI score] were examined using linear regression by disease groups (Models A). Age, sex and BMI were included in each analysis as biological confounders. Further adjusted regression models tested interaction effects between each independent variable and diagnosis on the outcome HRQoL (*Table S-1 - Supplementary Information*). As diagnosis was not a statistically significant effect modifier of these relationships, the disease groups were combined to increase statistical power for multivariable regression analyses.

Independent variables with a $p < 0.2$ and confounders were included into a multivariable linear regression analysis to identify independent determinants of HRQoL total score (Model-B). This analysis was repeated by SGRQ domain scores.

To produce a better visual representation of dose-response relationship, steps/day, ln(hs-CRP), HADS, and isometric leg strength were transformed into tertiles (CCI into median split), and tested in age-, sex- and BMI-adjusted simple (Models C-1) and fully-adjusted multivariable (Model C-2) regression models against SGRQ. Using models C-1, predicted values of SGRQ were calculated for each tertile (or dichotomous value). A $p < 0.05$ was considered statistically significant.

5.4. Results

A total of 131 (SA=70, bronchiectasis=61) participants were included in the analysis. Compared to bronchiectasis participants, the severe asthma group were younger, included more males, had higher BMI, and longer disease duration (Table 5-1). Respiratory characteristics were not significantly different between groups. In bronchiectasis, more participants had reduced bone density and sarcopenia, and isometric leg strength was, on average, lower. Nevertheless, in adjusted linear regression analyses diagnosis was not a significant effect modifier for any of the independent variables (*Table S-1 - Supplementary Information*), hence we also present an analysis of severe asthma and bronchiectasis combined.

Table 5-1: Baseline Participants Characteristics.

	Severe asthma n = 70	***Bronchiectasis n = 61***	***p***	***Groups Combined n = 131***
Age (years), median [IQR]	55 [42 - 68]	68 [62 - 73]	**<0.001**	63.5 [51 -70]
Female, %	54.3	86.9	**<0.001**	68.9
BMI (kg/m^2), mean ± SD	30.4 ± 7.7	25.6 ± 5.0	**<0.001**	28.7± 7.0
Years since diagnosis, median [IQR]	33.3 [15.4 – 51.0]	16.0 [5.0 - 56.5]	0.057	23.0 [10.1 – 52.0]
Current smoker, %	7.1	1.7	0.133	4.1
Packs/year, median [IQR]	0 [0 - 5.4]	0 [0 - 3.5]	0.483	0 [0 – 5.0]
Clinical characteristics				
Post FEV_1 (% predicted), mean ± SD	75.8 ± 21.2	76.6 ± 23.0	0.847	76.2 ± 22.0
Post FVC (% predicted), mean ± SD	86.4 ± 16.7	80.9 ± 18.6	0.078	83.8 ± 17.7
Post FER, mean ± SD	0.68 ± 0.1	0.71 ± 0.1	0.149	0.70 ± 0.1
6MWD (m), mean ± SD	469.5 ± 103.8	452.5 ± 110.3	0.370	461.7 ± 106.7
6MWD (% predicted), median [IQR]	71.7 [64.1 - 80.8]	76.5 [62.9 - 82.0]	0.432	73.2 [63.9 - 81.6]
SGRQ (total score), mean ± SD	43.7 ± 20.0	37.8 ± 17.0	0.070	40.9 ± 19.9
Extrapulmonary characteristics				
Steps/day, median [IQR]	5385 [3941-7844]	5350 [3522-7834]	0.825	5385 [3807-7844]
CCI (score), median [IQR]	0 [0-1]	0 [0-3]	0.226	0 [0-2]
Osteopenia|Osteoporosis, %	20.6 | 3.2	51.7 | 6.7	**0.001**	35.8 | 4.9
HADS (total score), median [IQR]	11 [7-14]	8 [5-13]	**0.028**	9.0 [6 - 14.0]
Sarcopenia, %	11.8	27.1	**0.028**	18.9
Leg strength(kg), median [IQR]	83 [55 - 123]	57 [43 – 70]	**0.001**	61.5 [49.0 - 111.0]
Hs-CRP (mg/L), median [IQR]	2.0 [1.1- 6.6]	2.8 [1.4 - 7]	0.305	2.5 [1.3 - 7.0]

Description of tertiles	***1st tertile***	***2nd tertile***	***3rd tertile***
Steps/day	1631-4125	4204-7015	7048-15379
hs-CRP, mg/L	0.2-1.5	1.6-4.9	5-125.7
HADS, score	0-7	8-12	13-29
Leg strength, kg	10-54	55-95	100-190
	Below median	***Above median***	
CCI, score	0-0	1-7	

BMI: body mass index; $FEV_{1:}$ forced expiratory volume in the first second; FVC: forced vita capacity; FER: forced expiratory ratio; 6MWD: 6-minute walked distance; SGRQ: Saint George Respiratory Questionnaire; CCI: Charlson Comorbidity Index; HADS: Hospital Anxiety and Depression Scale; hs-CRP: high-sensitivity C-reactive protein. Descriptive statistics are from non-imputed data. Statistically significant results in bold captions. Description of tertiles: Results expressed as range. CCI transformed into median split.

5.4.1. Associations of HRQoL in Severe Asthma and Bronchiectasis

In simple linear regression models adjusted for age, sex and BMI (Table 5-2), the variables steps/day, (ln)hs-CRP and HADS were each statistically significantly associated with HRQoL in both disease populations. In severe asthma, a significant association was also found between leg strength and SGRQ, and in bronchiectasis between CCI and SGRQ. Despite the lack of statistically significant results for CCI in severe asthma, leg strength in bronchiectasis, and sarcopenia in both diseases, the direction of the coefficients suggested that better values in these parameters were associated with better HRQoL.

In the multivariable linear regression model including both disease populations combined, steps/day, HADS, ln(hs-CRP), and leg strength were independently associated with HRQoL. The model explained 43.9% of the variance in the SGRQ scores (Table 5-3).

Table 5-2: Adjusted simple linear regression models (models A) of each extrapulmonary characteristic, adjusted for age, sex and BMI, as a determinant of SGRQ in severe asthma and bronchiectasis.

Extrapulmonary determinants of SGRQ: severe asthma models			
Extrapulmonary variable	**Coefficient (95% CI)**	***p*-value**	**Adj. R^2**
Physical activity (steps/day)	-0.003 (-0.005, -0.001)	**0.003**	0.152
Comorbidities (CCI, score)	2.177 (-1.008, 5.362)	0.177	0.045
Systemic inflammation [Ln(hs-CRP)]	7.912 (3.093, 12.730)	**0.002**	0.158
Depression and anxiety (HADS, score)	1.284 (0.566, 2.002)	**0.001**	0.180
Reference: no sarcopenia Sarcopenia	11.219 (-4.567, 27.004)	0.160	0.048
Isometric leg strength (kg)	-0.210 (-0.343, -0.077)	**0.002**	0.162
Reference: normal bone density Osteopenia	4.148 (-8.371, 16.667)	0.510	0.026
Osteoporosis	12.781 (-15.51, 41.079)	0.368	
Extrapulmonary determinants of SGRQ: bronchiectasis models			
Extrapulmonary variable	**Coefficient (95% CI)**	***p*-value**	**Adj. R^2**
Physical activity (steps/day)	-0.003 (-0.004, -0.001)	**0.001**	0.242
Comorbidities (CCI, score)	3.086 (0.944, 5.228)	**0.006**	0.179
Systemic inflammation [Ln(hs-CRP)]	5.975 (2.982, 8.968)	**<0.001**	0.273
Depression and anxiety (HADS, score)	1.521 (0.953, 2.088)	**<0.001**	0.383
Reference: no sarcopenia Sarcopenia	9.915 (-0.038, 19.870)	0.051	0.129
Isometric leg strength (kg)	-0.015 (-0.221, 0.191)	0.882	0.071
Reference: normal bone density Osteopenia	6.123 (-3.077, 15.322)	0.187	0.136
Osteoporosis	-11.882 (-31.340, 7.637)	0.227	

Models A: Each extrapulmonary variable model is adjusted for age, sex and BMI. CCI adjusted for sex and BMI. Confounders explained 3.36% and 8.1% of variance in the SGRQ for severe asthma and bronchiectasis, respectively. SGRQ: St George's Respiratory Questionnaire, Ln(hs-CRP): natural logarithm of high sensitivity C-reactive protein, HADS: Hospital Anxiety and Depression Scale, CCI: Charlson Comorbidity Index. Statistically significant results in bold font.

Table 5-3: Multivariable regression model of extrapulmonary determinants of SGRQ in the combined disease populations (model B, all characteristics and confounders in single regression model).

Extrapulmonary associations of SGRQ in severe asthma and bronchiectasis. Model adj. R^2= 0.439		
	Coefficient (95% CI)	***p*-value**
Physical activity (steps/day)	-0.002 (-0.003, -0.001)	**0.008**
Comorbidities (CCI, score)	1.596 (-0.102, 3.294)	0.065
Systemic inflammation [Ln(hs-CRP)]	3.118 (0.728, 5.508)	**0.011**
Depression and anxiety (HADS, score)	1.171 (0.764, 1.579)	**<0.001**
Reference: no sarcopenia Sarcopenia	-0.470 (-8.102, 7.162)	0.903
Isometric leg strength (kg)	-0.097(-0.185, -0.009)	**0.031**
Reference: normal bone density		
Osteopenia	0.488 (-5.715, 6.691)	0.876
Osteoporosis	-5.646 (-18.079, 6.786)	0.370
Age, years	-0.206 (-0.412, 0.001)	0.051
Reference: male		
Female	-4.181 (-11.749, 3.387)	0.276
BMI, kg/m^2	0.272 (-0.197, 0.742)	0.253

Models B: SGRQ: St George Respiratory Questionnaire, Ln(hs-CRP): natural logarithm of high sensitivity C-reactive protein, HADS: Hospital Anxiety and Depression Scale, CCI: Charlson comorbidity Index, Sarcopenia= presence of sarcopenia; Osteopenia and Osteoporosis: presence of the condition. Age, sex and BMI explained the 6.7% variance in the SGRQ.

In the analysis peformed by SGRQ domain, the extrapulmonary variables were most substantially associated with the activity domain, followed by impacts. HADS was the only variable displaying a significant association with symptoms (Table 5-4)

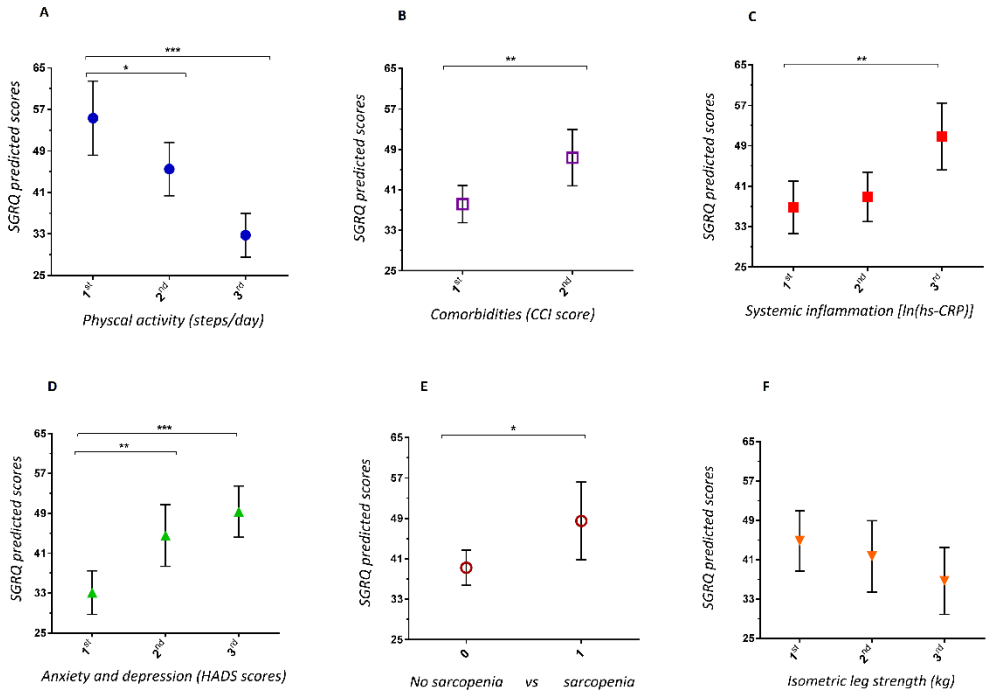
Table 5-4: Multivariable regression model (model B) of extrapulmonary determinants of domains of SGRQ.

Extrapulmonary determinants of SGRQ in the combined population of disease groups						
	Symptoms (Adj. R^2= 0.146)		***Activity (Adj. R^2= 0.453)***		***Impact (Adj. R^2= 0.355)***	
	Coefficient (95% CI)	***p*-value**	**Coefficient (95% CI)**	***p*-value**	**Coefficient (95% CI)**	***p*-value**
Physical activity (steps/day)	-0.001 (-0.003, 0.001)	0.181	-0.002 (-0.004, -0.001)	**0.005**	-0.001 (-0.002, -0.000)	**0.030**
Comorbidities (CCI, score)	0.172 (-2.396, 2.739)	0.895	2.886 (0.491, 5.281)	**0.019**	1.457 (-0.249, 3.163)	0.094
Systemic inflammation [Ln(hs-CRP)]	2.14104 (-1.454, 5.736)	0.241	3.324 (-0.046, 6.694)	0.053	3.3676 (0.969, 5.766)	**0.006**
Depression and anxiety (HADS, score)	0.9646 (0.351, 1.578)	**0.002**	1.422 (0.848, 1.997)	**<0.001**	1.082 (0.673, 1.491)	**<0.001**
Reference: no sarcopenia Sarcopenia	7.690 (-3.768, 19.148)	0.186	-1.016 (-11.788, 9.756)	0.852	-2.800 (-10.438, 4.838)	0.469
Isometric leg strength (kg)	-0.080 (-0.217, 0.056)	0.247	-0.167 (-0.293, -0.041)	**0.010**	-0.059 (-0.147, 0.029)	0.188
Reference: normal bone density Osteopenia Osteoporosis	 -2.533 (-12.027, 6.961) -13.280 (-32.867, 6.307)	 0.598 0.182	 -0.898 (-9.471, 7.675) -3.241 (-20.607, 14.125)	 0.836 0.712	 2.002 (-4.301, 8.305) -4.550 (-17.121, 8.020)	 0.530 0.475
Age, years	-0.189 (-0.502, 0.123)	0.233	-0.331 (-0.622, -0.040)	**0.026**	-0.137 (-0.345, 0.0707)	0.194
Reference: males Female	-6.746 (-18.224, 4.732)	0.247	-2.320 (-13.092, 8.453)	0.670	-4.516 (-12.097, 3.066)	0.240
BMI, kg/m^2	0.119 (-0.591, 0.829)	0.741	0.754 (0.093, 1.415)	**0.026**	0.040 (-0.429, 0.509)	0.865

Models B by domains of impairment: SGRQ: St George Respiratory Questionnaire, Ln-CRP: natural logarithm of high sensitivity C-reactive protein, HADS: Hospital Anxiety and Depression Scale, CCI: Charlson comorbidity Index, Sarcopenia= presence of sarcopenia. Age, sex and BMI explained the 0.7%, 11.8%, 2.7% of variance in the symptoms, activity and impact domains scores, respectively

The analyses of the tertile models (models C-1 & C-2) performed in the combined disease groups showed that fewer steps/day and increased HADS scores were associated with greater HRQoL impairment (Figure 5-A, Model C-1). The differences in the SGRQ predicted scores for each tertile were greater than the 4-unit SGRQ MCID. Systemic inflammation also showed statistically and clinically significant differences between the first and third tertile. While the differences between tertiles for isometric leg strength were not statistically significant, the mean difference between tertiles 1 and 3 was 8.1 units, twice the SGRQ MCID. Similarly, being sarcopenic was statistically associated with a predicted SGRQ score which was 2-fold greater than the MCID ($p < 0.05$) (Figure 5-A).

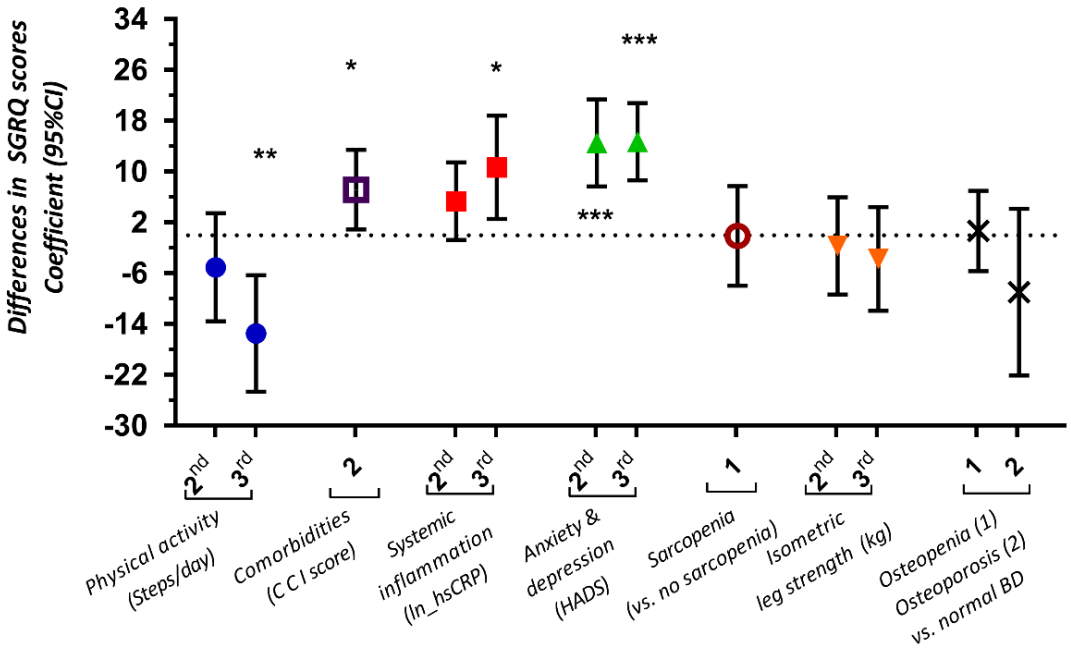
Figure 5-A: Differences in the predictive value of SGRQ (mean, 95% confidence interval) based on Models C-1 in the combined disease groups.



Adjusted simple linear regression models using categorical steps/day [A], CCI B], ln(hs-CRP) [C]; HADS scores [D], sarcopenia [E] and leg strength [F]). Models adjusted by sex, BMI and age (CCI=sex and BMI only). Each mark on the Y axis represents a MCID (4 points). p< 0.05; ** p< 0.01; ***p< 0.001. Steps/day, ln(hs-CRP); HADS scores and leg strength transformed into tertiles. CCI transformed into median split as lower (1st) and higher (2nd) half of median, respectively. SGRQ: St George Respiratory Questionnaire, ln(hs-CRP):natural logarithm of high sensitivity C-reactive protein, HADS: Hospital Anxiety and Depression Scale, CCI: Charlson comorbidity Index*

In model C-2 (multivariable tertile model), higher SGRQ scores were significantly associated with greater reduction in physical activity, higher systemic inflammation, HADS and CCI scores (Figure 5-B; *Table S-2* - *Supplementary Information*).

Figure 5-B: Coefficients (95%CI) from the multivariable full model of predictors of SGRQ using categorical independent variables (model C-2).



*Model adjusted by sex, BMI and age. * p< 0.05; ** p< 0.01; ***p< 0.001. Steps/day, ln-hsCRP, HADS and Strength transformed into tertiles.2nd and 3rd: second and third tertile, respectively. 1st tertile or absence of the condition used as a reference category. CCI transformed into median split: CCI 1(reference category) & 2: below and above median, respectively. SGRQ: St George Respiratory Questionnaire, Ln-CRP: natural logarithm of C-reactive protein, HADS: Hospital Anxiety and Depression Scale, CCI: Charlson Comorbidity Index; BD: bone density; Sarcopenia 1= presence of sarcopenia.*

5.5. Discussion

In this study, we analysed the relationships between extrapulmonary disease characteristics and HRQoL in adults with severe asthma and bronchiectasis. Extrapulmonary disease characteristics represent one of the three proposed treatable trait domains[51], and have proven to be important determinants of HRQoL in COPD[102, 128, 271]. We found that extrapulmonary characteristics had similar impacts in both severe asthma and bronchiectasis. Moreover, the traits of steps/day, isometric leg strength, and systemic inflammation, were significantly associated with HRQoL. Increasing severity of these variables was associated with statistically and clinically significant impairments in HRQoL.

Data characterising the interrelationship between HRQoL and extrapulmonary characteristics outside the comorbidity domain in severe asthma and bronchiectasis populations are scarce. Qualitative studies in severe asthma give some perspective of the extent of HRQoL impairment, and the importance to patients of improving this outcome.[53] Considering the multifactorial nature of HRQoL, and the deleterious consequences that HRQoL impairment has on wellbeing, addressing this knowledge gap is of utmost importance. Specifically, it may identify potential clinically important treatment targets, or treatable traits, that aim to improve the physical and psychosocial impact of the disease[14].

Physical activity was significantly and independently associated with HRQoL, both in the analyses by each disease as well as in the combined disease groups. We have previously reported on the degree of physical activity reduction and its impact on respiratory markers in severe asthma and bronchiectasis[393] *(see Chapter 4)*. This means that impaired physical activity impacts both extrapulmonary and airway domains in the treatable traits model of care, and raises the possibility that treating this component of the disease may lead to widespread benefits. The benefits of engaging in physical activity for the airway domain are recognised[271, 381]. These include reduced risk of exacerbations and healthcare use, better asthma control, and better exercise-capacity. Our results suggest that physical activity interventions may have broader effects and improve HRQoL for people with severe asthma and bronchiectasis. Therefore, targeted interventions for these populations need to be designed and tested. We observed a clear dose-response relationship in the tertile regression models. For each tertile increase in steps/day, the predicted mean score of the SGRQ (Figure 5-A) significantly decreased (improved HRQoL) by close to 3-times the MCID. Additionally, in the multivariable tertile model participants accumulating >7048 steps/day (tertile 3) displayed a statistically significant difference in the SGRQ, compared to tertile 1 (≤4125 steps/day) of more than 3-times the MCID (Figure 5-B; *Table S-2* - *Supplementary*

Information). This dose-response relationship is recognised in physical activity guidelines, since a protective effect on morbidity is observed at a defined volume (>150 mins/week) and intensity (moderate-vigorous)[174]. Additionally, while some evidence suggest that supervised exercise training can improve health status in people with moderate-severe asthma[81, 87], exercise protocols of lower intensities have not replicated these results[84, 398]. Our findings indicate that >7000 steps/day may be the level of physical activity associated with clinically significant improvements in HRQoL, and thus it could be considered an activity target. To achieve this, based on our data, patients would need to engage in at least a 24% increase in steps/day.

Physical activity has also been linked to several of the other extrapulmonary characteristics, including muscle-strength and sarcopenia. The non-significant association between strength and SGRQ in bronchiectasis could be because the strength measurements obtained in this group were rather low, which could have led to a floor effect in the analysis. Similarly, the small number of people with sarcopenia in the severe asthma group may have not been enough to detect a significant association with HRQoL. It is likely that the age difference between disease populations may have played a role in these differences, since both muscle strength and muscle mass are known to decrease with age[396]. Nevertheless, both in severe asthma and bronchiectasis the regression coefficients denoted a beneficial relationship between the absence of the condition and better scores in the SGRQ. When analysing these variables in a larger population (combined disease group) we found that improved function in these measures was significantly and clinically associated with better HRQoL. In COPD, skeletal muscle dysfunction is considered an important systemic consequence that is not exclusive to severe disease[275], and that has been associated with increased health-care use and mortality in COPD[128]. Deconditioning, the complex physiological process that occurs secondary to inactivity and results in functional loss, is considered as one of the main

mechanisms underpinning skeletal muscle dysfunction[128], and is closely related to poor disease outcomes[258]. In severe asthma and bronchiectasis, muscle-strength is considerably less studied. There is a trend towards decreased quadriceps muscle-strength in bronchiectasis[140, 287], but very little data exists reporting an association between strength and HRQoL[140]. In moderate to severe asthma, impairment of quadriceps endurance, but not strength, was observed both in adults[306] and children[399]. Considering that in severe asthma and bronchiectasis, factors affecting muscle-strength may not be as common as those seen in severe COPD, it is likely that decreased muscle-strength and its impact on HRQoL will be more tenuous in these conditions. Supporting this hypothesis, we have previously reported that the decrease in physical in moderate-severe COPD is worse than that found in severe asthma and bronchiectasis[393] (*see Chapter 4*). In addition, systemic inflammation, which is a prevalent feature in chronic respiratory diseases[153, 400], and is regarded as a precursor of muscle-atrophy and weakness[128], was lower in our severe asthma and bronchiectasis population compared to previously reported values for COPD[393]. Lastly, low BMI, another factor associated with muscle-depletion, sarcopenia, and skeletal muscle dysfunction in COPD[128], was not common in our populations. Despite the lower prevalence of factors that adversely impact skeletal muscle function in severe asthma and bronchiectasis, our results nonetheless demonstrate that improved muscle function was significantly and clinically associated with better HRQoL, alluding to the potential benefit of addressing these outcomes. Additionally, corticosteroids commonly used in severe asthma, may affect muscle metabolism and strength[401]. Integrated disease management programmes, including pulmonary rehabilitation[89], could be an approach to address this feature.

Higher levels of systemic inflammation remained associated with poorer HRQoL in all the analyses, a trend mostly observed in participants with hs-CRP levels >5.0 mg/L (tertile 3). Hs-CRP is a recognised independent predictor of cardiovascular events in healthy populations[402],

and associated with increased risk of exacerbation in severe asthma[52] and in COPD[403]. In bronchiectasis, high hs-CRP levels have been reported both during exacerbation and in stable disease, and positively correlate with poorer HRQoL and disease severity[400]. In severe asthma and bronchiectasis no treatment studies have targeted systemic inflammation. Its detrimental relationship with HRQoL needs further investigation.

Comorbidity was also associated with HRQoL. Of all extrapulmonary characteristics we examined, HADS explained the highest proportion of variance in the SGRQ. Additionally, in the multivariable tertile model, the differences in the SGRQ were statistically and clinically meaningful for each tertile compared with the reference. Anxiety and depression are common in severe asthma[52] and bronchiectasis[404] and their impact on HRQoL in these diseases has been recognised[14, 404]. However, studies reporting interventions that target these traits are scarce. In severe asthma, only one feasibility study has been reported[405]. In bronchiectasis, no study has targeted anxiety and depression, and in an RCT of exercise training, mood did not improve[164]. Therefore, the assessment, recognition and treatment of psychological health in these conditions is a priority and may improve HRQoL[73].

We performed analysis by SGRQ domains to test the relationships between its different domains and the extrapulmonary characteristics. The only variable significantly associated with the symptom domain was HADS. Reasons may be that symptoms are more closely related to pulmonary characteristics and therefore, be more efficiently addressed with pharmacological measures[391]. The extrapulmonary characteristics however, explained 45.3% and 35.5% of the variance of the activity and impact domain scores, respectively. This suggests that extrapulmonary characteristics are important drivers in HRQoL. The activity domain refers to impairment of activities that are limited by breathlessness, a symptom that is known to be associated with lower physical activity[393] *(see Chapter 4)*. This domain has

been suggested as a better measure of asthma control when assessing the impact of the disease in asthma populations[406], and therefore characterising this domain and its associations with other disease characteristics is needed[407]. We provide important information in that regard and suggest that the activity and impact domains could be addressed by these extrapulmonary outcomes.

Our study has some limitations. Its cross-sectional design does not infer causality of our findings. Also, our populations are not demographically matched, which limits comparison between groups. Nevertheless, after adjusting for age and sex, diagnosis was not a significant interaction in the relationship between SGRQ and the extrapulmonary variables. Another limitation was that comorbidities not scored in the CCI were not assessed and therefore, the weight of this variable may be underestimated. In COPD, however, cardiovascular or multiple comorbidities were not associated with significantly higher SGRQ scores[102]. Lastly, isokinetic equipment is considered a more sensitive option to measure muscle-strength, but access is limited. We measured muscle-strength using a static measure, which may not accurately inform dynamic function. However, our measure tested strength at multiple joints, assessing extension strength through the whole lower limb rather than isolated muscles. Despite these limitations, our study provides novel and important data for interventions aiming to improve HRQoL in severe asthma and bronchiectasis populations.

5.6. Conclusion

Decreased physical activity, anxiety and depression, leg strength and systemic inflammation are shared extrapulmonary characteristics that are independently associated with HRQoL in severe asthma and bronchiectasis, especially with the activity and impact domains. Our results suggest that these extrapulmonary features should be considered as part of the multidimensional assessment of these conditions, and they may represent treatable traits in

severe asthma and bronchiectasis. Future research should focus on exploring targeted extrapulmonary interventions that address all of the dimensions that negatively impact the HRQoL of patients with severe asthma and bronchiectasis.

5.7. Supplementary information

S-1: Adjusted simple linear regression models testing interaction effect between diagnosis and each independent variable

Interaction of diagnosis in the relationship between SGRQ and independent variables

	Coefficient (95% CI)	***p*-value**
Steps/day * bronchiectasis (vs. severe asthma)	-0.000 (-0.002, 0.002)	0.868
CCI score * bronchiectasis (vs. severe asthma)	1.037 (-2.628, 4.701)	0.577
Ln(hs-CRP) * bronchiectasis (vs. severe asthma)	0.489 (-4.887, 5.866)	0.857
HADS score * bronchiectasis (vs. severe asthma)	0.174 (-0.747, 1.096)	0.708
Sarcopenia (vs. no sarcopenia) * bronchiectasis (vs. severe asthma)	-2.338 (-19.499, 14.822)	0.788
Isometric leg strength* bronchiectasis (vs. severe asthma)	0.076 (-0.100, 0.252)	0.393
Osteopenia (vs. normal bone density) * bronchiectasis (vs. severe asthma)	4.061 (-10.658, 18.780)	0.586
Osteoporosis (vs. normal bone density) * bronchiectasis (vs. severe asthma)	-23.549 (-55.032, 7.935)	0.141

Each model adjusted by age, sex and BMI. CCI adjusted by sex and BMI. Severe asthma used as reference diagnosis for bronchiectasis (dummy variable). CCI: Charlson comorbidity index; Ln(hs-CRP): natural logarithm of high sensitivity C-reactive protein; HADS: hospital anxiety and depression scale questionnaire.

S-2: Multivariable regression model of independent non-respiratory determinants of SGRQ - categorical outputs (Models B.1)

Predictors of SGRQ in severe asthma and bronchiectasis ***Adj. R^2=0.4117***		
	Coefficient (95% CI)	***p*- value**
1st tertile (reference category)		
Steps/day, 2nd tertile	-5.066 (-13.573, 3.441)	0.240
Steps/day, 3rd tertile	- 15.473 (-24.664, -6.281)	**0.001**
Below median (reference category)		
CCI score, above median	7.167 (0.907, 13.427)	**0.025**
1st tertile (reference category)		
Ln(hs-CRP), 2nd tertile	5.341 (-0.772, 11.453)	0.086
Ln(hs-CRP), 3rd tertile	10.673 (2.534, 18.813)	**0.011**
1st tertile (reference category)		
HADS score, 2nd tertile	14.540 (7.689, 21.392)	**<0.001**
HADS score, 3rd tertile	14.736 (8.661, 20.811)	**<0.001**
No sarcopenia (reference category)		
Sarcopenia	-0.101 (-7.934, 7.732)	0.980
1st tertile (reference category)		
Isometric leg strength, 2nd tertile	-1.673 (-9.319, 5.973)	0.665
Isometric leg strength, 3rd tertile	-3.755 (-11.915, 4.405)	0.363
Normal bone density (reference category)		
Osteopenia	0.668 (-5.668, 7.005)	0.835
Osteoporosis	-8.963 (-22.068, 4.142)	0.178
Age, years	-0.136 (-0.346, 0.074)	0.202
Male (reference category)		
Female	-0.575 (-8.078, 6.927)	0.879
BMI, kg/m^2	0.209 (-0.298, 0.717)	0.415

Model adjusted for age, sex and BMI. Steps/day, ln(hs-CRP), HADS and Isometric leg strength transformed into tertiles. CCI transformed into median split. SGRQ: St George Respiratory Questionnaire, Ln(hs-CRP): natural logarithm of high sensitivity C-reactive protein, HADS: Hospital Anxiety and Depression Scale, CCI: Charlson comorbidity Index, BMI: body mass index.

6. Chapter 6: Discussion

6.1. Major findings and discussion

Overview

Severe asthma, COPD and bronchiectasis are common obstructive airway diseases that contribute greatly to the illness burden in our community[27, 98]. As reviewed in Chapter 1 of this Thesis, the distinctive airflow limitation observed in each of these diseases has its genesis in different etiological and pathophysiological mechanisms, which nevertheless, are all underpinned by abnormal and persistent inflammatory processes[15, 34, 106]. The burden of these diseases on patients can also be explained by the presence of shared, recurrent and debilitating symptoms such as breathlessness, chest tightness, cough, recurrent infections and by frequent and disabling exacerbations[15, 408]. In COPD, these symptoms are tightly related to a vicious-circle in which the reduction of exercise capacity and lower levels of physical activity lead to physical deconditioning, promoting a feeling of dependency, depression, social isolation and further impaired health status[102, 128, 271]. In terms of the non-pharmacological management of these disease characteristics, important advances have been achieved for COPD, where the characterisation and promotion of physical activity has been an important area of research and is now recognised as an important objective in clinical practice[271]. Also reviewed in Chapter 1, was the promotion of physical activity and reduction of sedentary behaviour for the prevention and management of several chronic diseases and all-cause mortality, and that these are currently important public health messages[174, 195].

The focus of this Thesis is the characterisation and comparison of physical activity in obstructive airway diseases, and the associations of this behaviour with different disease characteristics common in severe asthma, bronchiectasis and COPD. The characterisation of

sedentary behaviour in a severe asthma population and its relationship with physical activity is a secondary focus of this Thesis. Consequently, after reviewing the current literature that characterises these behaviours in obstructive airway diseases, I have presented three primary data chapters in which I address the characterisation and cross-sectional associations of physical activity primarily, and sedentary behaviour to a lesser degree, with disease characteristics and health-related quality of life in adults with severe asthma, bronchiectasis and COPD.

Gaps in the literature and main findings

In the review of the literature presented in Chapter 1 and 2, I identified gaps in knowledge, including the paucity of literature on the characterisation and association of physical activity and sedentary time with pulmonary and extrapulmonary disease characteristics in severe asthma and bronchiectasis, and the lack of literature making direct comparisons of the level of physical activity among these obstructive airway diseases and COPD. The likely association that exist between health-related quality of life and physical activity in severe asthma and bronchiectasis was also largely under-researched.

As a way to address these gaps in knowledge, in Chapters 3, 4 and 5 I addressed the characterisation of physical activity in obstructive airway diseases, and its association with disease characteristics in different contexts. These include:

(i) the characterisation of physical activity and sedentary time in severe asthma, and the association of these behaviours with each other, and with prevalent diseases characteristics including asthma control, exercise capacity and systemic inflammation (Chapter 3),

(ii) the characterisation and comparison of physical activity in severe asthma, bronchiectasis, moderate to severe COPD, and people without respiratory

diseases with important shared pulmonary characteristics of these diseases (Chapter 4), and lastly,

(iii) the characterisation of shared extrapulmonary characteristics in severe asthma and bronchiectasis, including physical activity, comorbidities, isometric muscle strength, and anxiety and depression, and their association with health-related quality of life (Chapter 5).

The main findings of these studies are:

- People with asthma of different severities engage in lower levels of physical activity compared to people without asthma. This lower physical activity trend tended to be more pronounced in females compared with males, and in older people with asthma compared to their younger counterparts. Higher levels of physical activity were associated with better measures in several disease characteristics. Sedentary behaviour has not been widely addressed in asthma, but there was also a trend showing a detrimental association between higher engagement in sedentary time and worse disease characteristics (Chapter 2).
- Compared to people without respiratory diseases, people with severe asthma engage in lower levels of moderate and vigorous physical activity. The levels of sedentary time were not significantly different between groups. Higher levels of activity and lower levels of sedentary time were linked to better exercise capacity, asthma control, and decreased systemic inflammation (Chapter 3).
- Physical activity impairment is a shared behavioural characteristic of people with COPD, severe asthma and bronchiectasis. The degree of impairment in severe asthma and bronchiectasis though, is not as severe as in moderate to severe COPD.

Shared clinical characteristics, such as exercise capacity and airflow limitation explain an important proportion of this impairment in OAD (Chapter 4).

- Physical inactivity and other extrapulmonary characteristics, including anxiety and depression, isometric leg strength and systemic inflammation are shared extrapulmonary characteristics that are independently associated with health-related quality of life in severe asthma and bronchiectasis populations, especially with the activity and impact domains.

Chapter 2: Physical activity and sedentary time in adults with asthma

In Chapter 2, I presented a literature review of physical activity and sedentary time in people with asthma. After conducting a systematic literature search in four electronic databases, I identified 42 studies measuring physical activity (mostly) or sedentary time in people with asthma. The main findings from this review were that people with asthma of different severities engage in lower levels of physical activity, a trend that seems to increase as people with asthma age, and that is more evident in females with asthma compared with males, and that higher levels of physical activity may have a beneficial impact on asthma outcomes. An important highlight of this review is that it is the first to include measures of physical activity using activity monitors. I therefore conducted a meta-analysis from eligible studies, finding that the pooled mean (95%CI) steps/day for people with asthma was 8390 (7361, 9419). Even though this figure may not truly represent older people with asthma or more severe asthma populations, this estimate provides a first reference that can be updated and developed with future studies. Another highlight of this review is that I investigated associations between levels of physical activity and disease characteristics. Higher levels of physical activity were associated with better measures of lung function, disease control, health status, and health

care use. Some of these beneficial associations, such as exacerbations and lung function, were also tested in longitudinal studies showing a weak but significant positive association. Measures of sedentary time had not been summarised previously in adults with asthma. There were considerably fewer studies measuring sedentary time in people with asthma compared with physical activity. There was not a clear trend in terms of level of engagement compared to people without asthma. However, the eligible studies reported a detrimental association between higher engagement in sedentary time and worse disease outcomes such as health care use, lung function, asthma control and exercise capacity.

In this review, I also identified a paucity of literature that reported on the measurement of physical activity and sedentary time in people with severe asthma, a knowledge gap that I aimed to address in Chapter 3.

Chapter 3: physical activity and sedentary time in severe asthma

In the first primary data study I present in this Thesis (Chapter 3), I used an accelerometer to measure the levels of physical activity and sedentary time in a severe asthma population and in people without respiratory diseases, and I examined the associations between these two behaviours with several disease outcomes. Data characterising the level of physical activity in severe asthma using an activity monitor were scarce. In a study from 2017, Bahmer and colleagues found that people with severe asthma were significantly less active than people without respiratory disease and to those with mild-moderate asthma[291]. The authors also found that this reduction was associated with measures of lung function[291]. Studies examining associations of the levels of physical activity with diseases outcomes other than airflow limitation in severe asthma or measuring sedentary time in this disease did not exist, as I identified in the literature review in Chapter 2.

In my study of 61 participants with severe asthma and 61 age- and sex-matched healthy controls, the levels of moderate to vigorous physical activity and steps/day of the severe asthma group were significantly decreased compared to controls. A different trend was observed for light physical activity, people with severe asthma accumulated slightly higher levels of physical activity compared to controls, and for sedentary time, where no statistically significant differences were observed between groups. Higher levels of physical activity (steps/day) were significantly associated with better exercise capacity and lower systemic inflammation, even after adjusting for the level of sedentary time. Similarly, higher levels of MVPA, adjusted for sedentary time, were significantly associated with better asthma control. These results suggest that different disease characteristics have different associations with the intensity of physical activity, and therefore interventions aiming at improving asthma control should aim for higher intensities of activities than those interventions aimed at improving exercise capacity. A second important finding was that, despite the detrimental significant associations found between sedentary time and most of the disease outcomes, these associations were attenuated to the null when adjusted for physical activity levels suggesting that the negative effects of sedentary time on respiratory outcomes could be mitigated by engaging in moderate physical activity. This important observation has implications for the design of future intervention studies in these patient groups.

This study was novel for several reasons. First, it was the second study reporting device-measured levels of physical activity in severe asthma. Second, I tested how physical activity was associated with several diseases' outcomes, including several outcomes that have not been very well characterised in severe asthma, such as exercise capacity and systemic inflammation. My study addresses the need identified by recent studies which have suggested these outcomes as potential treatment targets or markers for the disease[82, 376]. Lastly, sedentary time had not been characterised nor associated with disease characteristics

before my study. Together, and as highlighted in an editorial which accompanied my publication[409], my research suggests that physical inactivity should be addressed in people with severe asthma, and that the activity message should consider coaching patients regarding different spectrums of movement and intensities to achieve the expected goals.

Chapter 4: Physical Activity in Obstructive Airway Diseases

The fact that the disease characteristics measured in Chapter 3 are also prevalent in bronchiectasis and COPD led to my second study (Chapter 4), where I aimed to extend the characterisation and comparison of physical activity in severe asthma to other obstructive airway diseases including the widely researched COPD[271], and bronchiectasis, a disease in which the measurement of this behaviour has received slightly more attention than in severe asthma[284, 286, 287], but it is still considerably less well-researched than COPD.

In this study, which included 189 participants with obstructive airway disease and 63 healthy controls, I found that people with severe asthma engaged in similar levels of physical activity compared to people with bronchiectasis, which also means that both diseases presented lower activity levels compared to the group without respiratory diseases. Conversely, both disease populations presented significantly higher levels of physical activity compared to moderate to severe COPD. These similarities and differences in severity were also observed in disease characteristics, such as airflow limitation, exercise capacity, dyspnoea, and systemic and airway inflammation. These characteristics were significant predictors of physical activity in obstructive airway disease, especially exercise capacity and airflow limitation.

The importance of these data lie in the fact that to date, there was no study making direct comparisons between these populations in terms of physical activity reductions and

associations with disease outcomes. In fact, despite that recommendations have been made to include diseases other than COPD in pulmonary rehabilitation programmes to improve outcomes such as exercise capacity and to address inactivity[89, 410], very little data exists in severe asthma particularly, to support this recommendation. This is even more important after the recently recognised need to revise and update traditional treatment approaches for diseases like COPD and severe asthma[12, 51, 125, 149]. The proposed label-free treatable traits management approach[51] for instance, suggests that the management of chronic airway diseases should be based around measurable, clinically important, and treatable characteristics of these diseases rather than the diagnosis itself. Some of the disease characteristics that were significantly associated with physical activity in my study, such as exercise capacity, airflow limitation and systemic inflammation, have also been suggested as treatment targets by this model. In terms of physical activity, however, my study takes a step forward in suggesting that it is reduced physical activity, instead of its consequent deconditioning, that is the trait that should be targeted.

The reason for this is because lower levels of physical activity:

(i) are prevalent across all these conditions,

(ii) occurs earlier in the disease than deconditioning, and therefore it could have a preventive role on the latter, and lastly

(iii) it is associated with other characteristics present in obstructive airways disease including exercise capacity, airflow limitation, systemic inflammation and dyspnoea, which despite of being present at different degrees of severity in each disease, they still predict physical activity levels and therefore could be treatment goals for improving this behaviour.

We expect that these data would guide future interventions aiming at addressing physical inactivity in obstructive airway disease, especially in severe asthma and bronchiectasis, where few data or tailored activity treatment programmes exist.

Chapter 5: Physical activity and health status in severe asthma and bronchiectasis

After testing that physical activity was significantly associated with pulmonary characteristics in obstructive airway disease, in Chapter 5 I sought to test the extent to which physical activity and other extrapulmonary characteristics of severe asthma and bronchiectasis are associated with HRQoL impairment. As a multidimensional and patient-related outcome, improving HRQoL should be one of the foremost goals for patient-centred management in chronic diseases[14, 411]. Data concerning the impact of pulmonary characteristics on HRQoL in obstructive airway disease have been published elsewhere[49, 141, 404]. However, there is a scarcity of evidence concerning the association between HRQoL and physical activity and other extrapulmonary characteristics of OAD, specifically for severe asthma and bronchiectasis.

To address this knowledge gap, I evaluated the impact of extra pulmonary characteristics on HRQoL in 70 people with severe asthma and 61 with bronchiectasis. I found that, after adjusting for potential confounders, higher levels of physical activity, isometric muscle strength of the lower limbs and muscle mass, as well as lower levels of depressive and anxiety symptoms, and systemic inflammation were associated with better quality of life in people with severe asthma and bronchiectasis. In addition, as the first study characterising extrapulmonary features in severe asthma and bronchiectasis as an obstructive airway disease entity, and investigating the associations of these features with HRQoL, this study provides relevant clinical messages including:

(i) the severity of extrapulmonary characteristics is similar between these populations, and so is their interaction with health status,

(ii) some of these extrapulmonary characteristics, such as skeletal muscle dysfunction, are widely addressed in COPD but their impact on other diseases is under-recognised,

(iii) increasing severity of these variables was associated with statistically and clinically significant impairments in HRQoL. The latter point was highlighted as an important observation in Chapter 5 for physical activity. The differences between people in the highest tertile of physical activity compared to those in the lowest tertile (7000 steps/day versus <4200 steps/day, respectively) was 15 units. This was almost 4 times the minimal clinically important difference of four units, for the St. George Respiratory Questionnaire, and a greater difference than that displayed by well-recognised predictors of health status, such as anxiety and depression.

Overall, from this study I contribute evidence that suggests these extrapulmonary characteristics are potential important treatment targets for interventions aimed at improving health status in these populations, especially for the domains of Activity and Impact of the disease. This study also adds to my previous studies to strengthen the evidence to consider physical activity interventions as a non-pharmacological strategy to improve both pulmonary and extrapulmonary clinical problems in obstructive airway diseases.

6.2. Limitations of this Thesis

The most evident limitation of my Thesis is that the cross-sectional design used in all my studies does not allow me to ascertain directionality of the findings. However, it is likely that the relationship between movement behaviours and disease outcomes follows a bidirectional relationship. This is also backed by the existent and robust body of research for physical activity in COPD. My studies have provided evidence on how the different diseases and their characteristics are associated with physical activity, and this characterisation can guide common, and therefore more efficient strategies to improve this behaviour in obstructive airway diseases.

An additional limitation of my Thesis relates to the differences in populations. In Chapter 4 and 5, the disease populations had demographic characteristics which were considerably different between each other. It needs to be acknowledged that comparing more matched populations in terms of age and sex would have given a more accurate picture of the true impact of the disease on physical activity. Nevertheless, it also needs to be recognised in light of the aetiology and epidemiology of these diseases[37, 96, 136], it would be very difficult to match moderate to severe COPD populations to severe asthma and bronchiectasis populations, given the different characteristics of people with these conditions. In terms of age for instance, Toelle et al[96] illustrated the difference in prevalence at different ages for people with COPD. In their study, the weighted prevalence of people with COPD GOLD stage II or higher increased from 2% at the age of 40-54, up to 7.3%, and 29.2% at the age range of 55-74 and ≥75 years old, respectively. This is in agreement with the age of our COPD population. In regards to severe asthma, in the prevalence study carried out by Hekking and colleagues, the reported age (mean ± SD) was 62.5 years old, very similar to our median age of our severe asthma population[37]. In bronchiectasis, Quint et al. reported that in 2013 the overall prevalence of bronchiectasis per 10,000 people increased from 254.9 cases up to 1239.7 for

people in their fifties and seventies, respectively[136]. So, overall, the age differences observed in our studies reflect the mean age of real-world disease populations. These age differences will irremediably impact on other clinical characteristics, such as airflow limitation and exercise capacity. Nevertheless, the statistical analysis concluded that, despite the differences between populations, there were no statistically significant interactions between the different diagnoses and the relationship between physical activity and the disease outcomes.

Finally, the measurement of sedentary behaviour in this Thesis was limited to the population with severe asthma only, despite that the paucity of data addressing this behaviour extends to COPD and bronchiectasis. In each of the studies I have presented I also collected sedentary time data using the activPAL. This work with be published during my post-doctoral period. In the next section of this chapter (future directions), I will expand on this topic and how I plan to address this.

6.3. Future directions

What is the prevalence of sedentary behaviour in obstructive airway disease other than severe asthma, and how is this behaviour associated with disease outcomes in those bronchiectasis and COPD?

The data presented in Chapter 3 show that sedentary time was not significantly different in severe asthma compared to people without respiratory disease. In addition, the study shows that when considering physical activity and sedentary time together in the analysis (adjusting for each other), the once statistically significant associations between disease characteristics and sedentary time were attenuated to the null. Since sedentary behaviour has not been

extensively addressed in others obstructive airway diseases, it is unclear whether in bronchiectasis and COPD a similar trend would be observed.

To address this question, I am currently investigating associations between the level and pattern of this behaviour in bronchiectasis and COPD compared to people without respiratory diseases. I am planning to follow a similar approach as that reported in Chapters 3 and 4, with the advantage that in this future work, the measurement of this behaviour will be extracted from a more accurate device (the inclinometer and accelerometer activPAL).

After completion of this work, studies aimed at targeting physical activity in obstructive airway disease will be able to incorporate the knowledge of the relationship between these behaviours in these diseases, which may optimise the results of these interventions. Additionally, it could prompt clinical guidelines to incorporate messages regarding sedentary time as a non-pharmacological strategy in OAD.

Additionally, data in Chapter 5 could be enriched by the consideration of sedentary behaviour as a confounding predictor of poor health status in bronchiectasis and severe asthma.

In term of directions to further extend the knowledge from this Thesis, future longitudinal studies measuring physical activity or sedentary time as an exposure variable could provide more detailed information on the direction of the relationship between these behaviours and disease outcomes.

Furthermore, qualitative studies in severe asthma and bronchiectasis researching patients' perspective on physical activity are needed. The development of these studies, together with the new knowledge generated by my Thesis, will be useful for the design and implementation of future targeted person-centred physical activity interventions aimed at improving this behaviour in people with severe asthma and bronchiectasis.

6.4. Conclusions

Lower levels of physical activity are prevalent in obstructive airway diseases. The decrease in activity seems to be more pronounced in moderate to severe COPD than in severe asthma and bronchiectasis, diseases where the levels of physical activity is similar. Physical activity was significantly associated with clinical and biological characteristics prevalent in the three diseases, and with better health-related quality of life. Levels of sedentary behaviour seems to be similar between severe asthma and healthy population, and its associations with disease characteristics were weaker than those for physical activity. Data characterising and comparing this behaviour in bronchiectasis and COPD is required to define its levels of engagement and associations across obstructive airway diseases. Overall, the research undertaken in this Thesis provides evidence to consider physical activity as a common strategy to improve clinical and biological markers in obstructive airway diseases.

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APPENDIX I: CHAPTER 2 - PUBLISHED ARTICLE

Original Article

A Systematic Review of Associations of Physical Activity and Sedentary Time with Asthma Outcomes

Laura Cordova-Rivera, BPhty(Hons)[a,b,c], Peter G. Gibson, MBBS[a,b,c,d], Paul A. Gardiner, PhD[e,f], and Vanessa M. McDonald, PhD[a,b,c,d] *Newcastle, New South Wales; and Woolloongabba, South Brisbane, Queensland, Australia*

What is already known about this topic? Compared with controls, subjectively measured physical activity seems to be reduced in adults with asthma. Higher levels of physical activity might have a beneficial impact on asthma.

What does this article add to our knowledge? Physical activity is reduced in adults with asthma, especially in females and older people with asthma. Sedentary time did not differ between people with and without asthma. Higher levels of activity are associated with better asthma outcomes.

How does this study impact current management guidelines? These results suggest that addressing inactivity and sedentary time may be a potential nonpharmacological approach in the management of asthma. Disease severity, sex, and age should guide these approaches.

BACKGROUND: Physical inactivity and high sedentary time are associated with adverse health outcomes in several diseases. However, their impact in asthma is less clear.
OBJECTIVE: We aimed to synthesize the literature characterizing physical activity and sedentary time in adults with asthma, to estimate activity levels using meta-analysis, and to evaluate associations between physical activity and sedentary time and the clinical and physiological characteristics of asthma.
METHODS: Articles written in English and addressing the measurement of physical activity or sedentary time in adults ≥18 years old with asthma were identified using 4 electronic databases. Meta-analysis was used to estimate steps/day in applicable studies.
RESULTS: There were 42 studies that met the inclusion criteria. Physical activity in asthma was lower compared with controls. The pooled mean (95% confidence interval) steps/day for people with asthma was 8390 (7361, 9419). Physical activity tended to be lower in females compared with males, and in older people with asthma compared with their younger counterparts. Higher levels of physical activity were associated with better measures of lung function, disease control, health status, and health care use. Measures of sedentary time were scarce, and indicated a similar engagement in this behavior between participants with asthma and controls. High sedentary time was associated with higher health care use, and poorer lung function, asthma control, and exercise capacity.
CONCLUSIONS: People with asthma engage in lower levels of physical activity compared with controls. Higher levels of physical activity may positively impact on asthma clinical outcomes. Sedentary time should be more widely assessed. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;■:■-■)

Key words: *Asthma; Physical activity; Sedentary time; Accelerometry; Questionnaire; Associations; Clinical outcomes; Meta-analysis*

Asthma is an obstructive airway disease that causes symptoms of dyspnea, wheezing, and chest tightness. These symptoms, and the fear of provoking exercise-induced bronchoconstriction (EIB), may have a negative impact on the engagement in physical activity in people with asthma.[1-3]

[a]National Health and Medical Research Council Centre of Excellence in Severe Asthma, Newcastle, New South Wales, Australia
[b]Priority Research Centre for Healthy Lungs, The University of Newcastle, Newcastle, New South Wales, Australia
[c]Hunter Medical Research Institute, New Lambton Heights, New South Wales, Australia
[d]Department of Respiratory and Sleep Medicine, John Hunter Hospital, Newcastle, New South Wales, Australia
[e]Centre for Health Services Research, Faculty of Medicine, The University of Queensland, Woolloongabba, Queensland, Australia
[f]Mater Research Institute, The University of Queensland, South Brisbane, Queensland, Australia
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Corresponding author: Vanessa M. McDonald, PhD, Hunter Medical Research Institute, Level 2 West Wing, 1 Kookaburra Circuit, New Lambton Heights, NSW 2305, Australia. E-mail: vanessa.mcdonald@newcastle.edu.au.
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Abbreviations used
BMI- Body mass index
CI- Confidence interval
COPD- Chronic obstructive pulmonary disease
EE- Energy expenditure
EIB- Exercise-induced bronchoconstriction
MVPA- Moderate and vigorous physical activity
OR- Odds ratio
RCT- Randomized control trial
SE- Standard error

Physical activity and sedentary time have been widely studied in the general population[4] and in chronic obstructive pulmonary disease (COPD). People with COPD are considerably less active and more sedentary than people without respiratory conditions.[5,6] Furthermore, inactivity in COPD is associated with more exacerbations resulting in hospitalization,[7] a reduced time to readmission,[8] and increased all-cause mortality.[8-10] As a result, there are well-established exercise programs for people with COPD that seek to address physical inactivity.[11,12] In asthma, however, the role of physical activity and sedentary time is less clear,[13] and thus guidelines and interventions to target these behaviors in this population are limited.

In a prior systematic review in adults and children, Eijkemans et al[14] suggested that people engaging in higher levels of physical activity might have a lower risk of asthma incidence. In adults with asthma, they also found a trend toward lower levels of physical activity compared with controls.[14] However, none of the included studies used objective measures (accelerometry) to quantify physical activity in adults, and sedentary time was not addressed. Another review found that children and adolescents with and without asthma engage in a similar amount of objectively measured physical activity.[15] Despite this evidence, there are no reviews of the literature that have evaluated the prevalence of sedentary time in adults with asthma, nor reviewed the use of accelerometry to quantify physical activity and sedentary time in this population. In addition, the degree to which the level of physical activity and sedentary time impact on the airway symptoms or clinical outcomes in adults with asthma has not been reviewed.

Our aim therefore is to update and synthesize the evidence in relation to the prevalence of physical activity and sedentary time in adults with asthma. We conducted a meta-analysis of studies reporting steps/day in people with asthma, and sought to evaluate the associations of these behaviors with the clinical and physiological characteristics of the disease.

METHODS

Literature search

Articles written in English and addressing the measurement of physical activity or sedentary time in adults (≥18 years) with asthma were identified by a comprehensive search using the Medline, Embase, PEDro, and Cochrane databases. The search was conducted in April 2017, and updated in October 2017, and included all articles published until the search date.

Eligible studies were those that examined the prevalence and patterns of these behaviors in asthma populations, or studies analyzing the association of these behaviors with clinical or biological markers of the disease. We did not include a filter for study design. Details of the search strategy are provided in Table I.

TABLE I. Terms search

Search strategy: (#1) AND (#2 OR #3)	
#1	Asthma* or wheez* or "bronchoconstriction"
#2	"physical activity" or ("physical exercise" or "exercise") or "walking" or "motor activity"
#3	("sedentary behaviour" OR "sedentary behavior" OR "sedentary time") OR ("sedentary lifestyle") OR ("internet time") OR ("computer time") OR ("television watching" OR "television viewing" OR "television time") OR ("TV watching" OR "TV viewing" OR "TV time") OR ("screen time") OR "sitting time" OR "reading time"

Analysis

Statistical analysis was performed using STATA 13 (Stata Corp., College Station, Tex). The continuous outcome (mean steps/day) from relevant studies[16-22] was pooled using the random-effect model. Authors of 3 studies were contacted, and provided further details of their results.[16,20,21]

RESULTS

The initial search yielded 2803 references. A flow diagram[23] of the literature search is provided in Figure 1.

We identified 42 eligible studies investigating physical activity and/or sedentary time in adults with asthma. Population characteristics are presented in Table II. From these studies, 18 compared the level of these behaviors in asthma with a control group.[16-19,21,27,28,30-32,37,39,41,42,44-47] Table III summarizes the physical activity measurements utilized in these 18 studies. Three studies[20,22,50] without a control group were also included in Table III to provide further details of the activity monitors used. Associations with disease characteristics were assessed in 24 studies[16-18,21,22,24,28,29,31,33,35,39,40,42,43,47,49-51,53-57] (Table IV). In addition, 2 studies reported physical activity as a confounder of body mass index (BMI),[26,34] and 2 studies reported physical activity before a randomized controlled trial (RCT) exercise intervention.[20,38] In 5 studies, the association between current asthma and different levels of physical activity was assessed.[25,26,48,52,58] In general, the studies were quite heterogeneous in terms of the population and assessments of activity/sedentary time. Studies included 193,821 participants with asthma and 1,417,540 controls. Most participants were women, and in 31% of the studies, the mean age was below 45 years. Twenty-three studies used a self-reported asthma diagnosis.[25-33,36,37,39,43,44,46-48,52,53,55-58] Disease severity or level of control was reported in 15 studies, and populations included people with mild, moderate, and severe asthma.[16-18,20-22,26,34,38,40-42,47,49,56]

Prevalence of physical activity

Among studies using a control group, eleven[16-18,21,28,30,32,39,41,44,46] (asthma sample = 32,606) reported less physical activity in asthma, and six reported no difference[19,31,37,42,46,47] (asthma sample = 7,824). One study[27] (asthma sample size = 1,070) reported increased physical activity in younger adults with asthma (<40 years old), but decreased physical activity in older participants (>50 years old).

Activity monitors were used in 8 studies.[16-22,50] Five of them included a control group[16-19,21] (Tables III and V). A meta-analysis (Figure 2) found that the weighted mean (95%

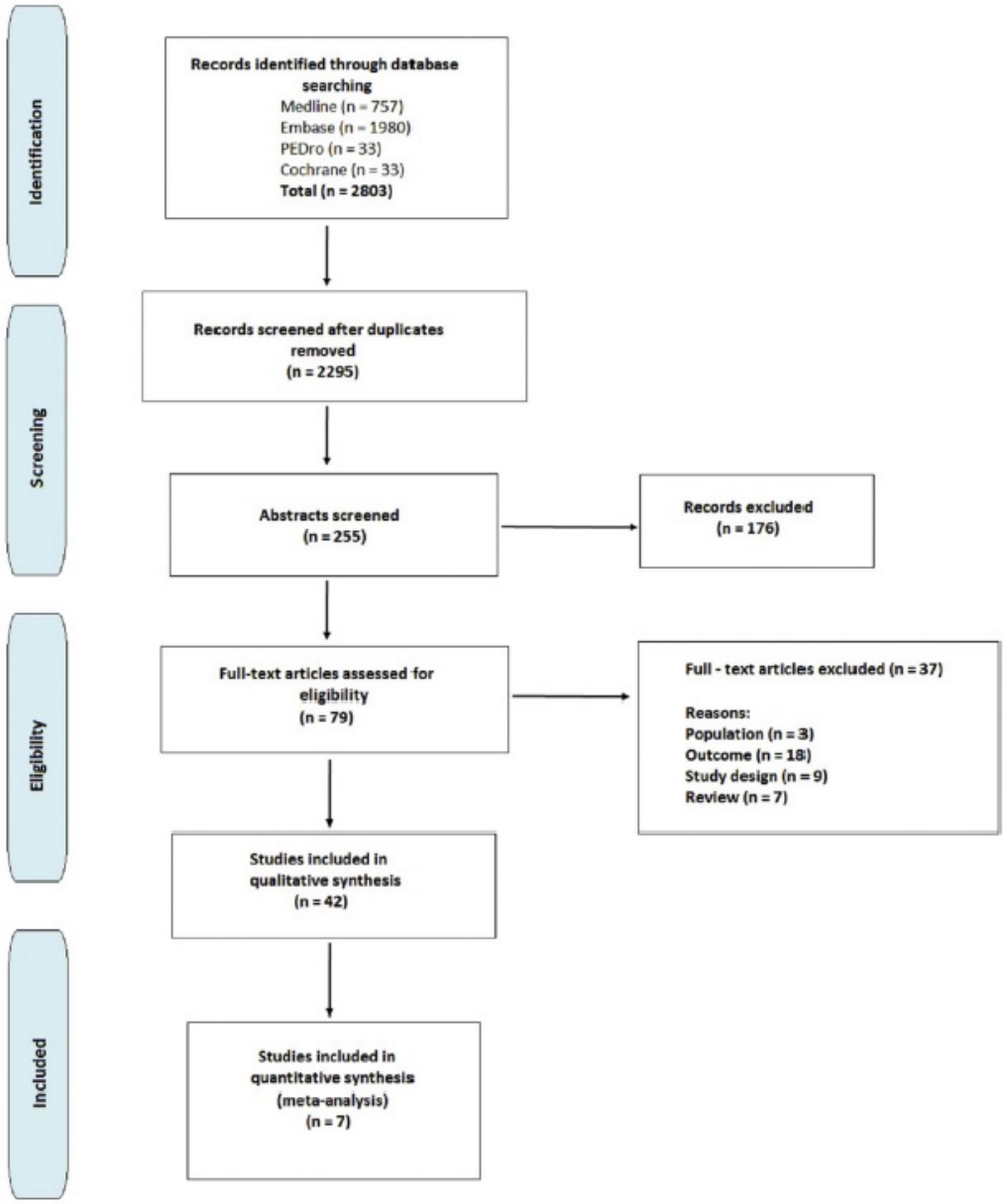

FIGURE 1. PRISMA Flow Diagram Literature search. Updated October 31, 2017.

confidence interval [CI]) number of steps/day for people with asthma was 8390 (7361, 9419). In the 4 studies that compared the volume and/or intensity of activity, people with asthma tended to accumulate less physical activity than controls (Table V).

Some studies reported an effect of age and sex on activity in asthma. Three studies reported that the decrease in activity in people with asthma was mostly seen in older participants (≥50 years old).[27,32,46] For instance, despite their overall results showing that people with asthma were more inactive than controls, Ford et al[32] did not find statistically significant differences in the association between activity and asthma status in people under the age of 60. Some studies reported that males with asthma presented higher levels of activity than females with

TABLE II. Demographic characteristics of studies included

		Asthma participants					Controls		
Cross-sectional studies	Country	n	Female (%)	Age	Current smoking (%)	Disease severity (%)	n	Female (%)	Age
Bacon et al 2015[24]	Canada	643	60	53.4 ± 15.4	8.7	n/r	n/a	n/a	n/a
Bahmer et al 2017[16]	Germany	146	51 severe 53 mild to mod.	55.5 48.1	22 24	43.1 56.8	29	38	42.1
*Beckett et al 2001[25]	USA	4,547	52	18 to 30	41.1	n/r	4131	55.2	18 to 30
Barros et al 2017[26]	Portugal	2,578	62	20 to >85	21.4	Current: 44 Persist: 38 Severe:18	30,066	52.4	20 to >85
Bruno et al 2016[17]	Italy	24	66	38.5 ± 14.2	n/r	Mild to mod.	18	55	43.1 ± 14.3
Chen et al 2001[27]	Canada	1,070	61.7	12 to >70	26.7	n/r	15,743	55	12 to >70
Cordova-Rivera et al 2017[18]	Australia	61	52.5	59 (43 to 68)	6.6	Severe	61	52.5	54 (34 to 63)
Doggett and Dogra 2015[28]	Canada	1,830	69.2	20 to >55	33.1	n/r	18,978	54.4	20 to >55
Dogra and Baker 2006[29]	Canada	11,243	62	40 to 44	n/r	n/r	n/a	n/a	n/a
Dogra et al 2008[30]	Canada	1,772† 3,123‡	63† 68‡	45 to 79	n/r	n/r	19,864	57	65 to 79
Dogra et al 2009[31]	Canada	6,835	62	20 to 64	28.5	n/r	78,051	51	20 to 64
Ford et al 2003[32]	USA	12,489	64	18 to >70	n/r	n/r	147,742	48.9	18 to >70
Ford et al 2004[33]	USA	12,111	63.7	44.2 (0.3)	26	n/r	n/a	n/a	n/a
Grammatopoulou et al 2010[34]	Greece	100	79	n/r	20	Mild: 58 Mod:32 Severe: 10	n/a	n/a	n/a
Iikura et al 2013[35]	Japan	437	53.3	64 (51 to 74)	7.1	n/r	n/a	n/a	n/a
Kilpelainen et al 2006[36]	Finland	10,023	61	18 to 25	3.4§	n/r	n/a	n/a	n/a
Liang et al 2015[37]	Australia	723	51§	18 to 29	2.7	n/r	1,891	51§	18 to 29
Ma et al 2016[38]	USA	330	10.6	47.6 ± 12.4	5.8	UA	n/a	n/a	n/a
Malkia and Impivaara 1998[39]	Finland	178	59	30 to 89	n/r	n/r	7,015	30 to 89	n/r
Mancuso et al 2007[40]	USA	258	75	42 ± 12	11	Mild to mod	n/a	n/a	n/a
Moore et al 2015[19]	Canada	16	38	27.8 ± 6.1	n/r	n/r	16	50	26.6 ± 5.2
Ramos et al 2015[41]	Brazil	20	70	44 ± 6.0	n/r	Mod to severe	15	93	39 ± 6.0
Ritz et al 2010[42]	USA	20	70	28 ± 6.8	n/r	Mod	20	70	31.6 ± 5.9
Scott et al 2013[20]	Australia	14	78.6	43.3 (37 to 7.8)	30.8	Mild inter: 8 Mild persist:23 Mod: 54 Severe: 15	n/a	n/a	n/a
Strine et al 2007[43]	USA	11,962	65.5	18 to >75	23.6	n/r	n/a	n/a	n/a
Teramoto and Moonie 2011[44]	USA	880	57.2	18 to >70	n/r	n/r	2,960	n/r	18 to >70
Tsai et al 2011[45]	Taiwan	27	44	60.8 ± 10.2	11	n/r	27	37	56.8 ± 1.1
Vancampfort et al 2017[46]	LMICs	11,857	50.8§	18 to >65	n/r	n/r	216,167	50.8§	n/a
Van't Hul et al 2016[21]	The Netherlands	226	62	47.3 ± 15.3	n/r	CA:17 PC:18 UA: 65	201	75.6	42.3 ± 16.3
Verlaet et al 2013[47]	Portugal	CA:125 UA:78	53 85	43 ± 28 54 ± 21.5	33	61.6 38.4	606	50.5	53 ± 24
Vermeulen et al 2016[22]	Belgium	20	65	39.0 ± 11.9	n/r	CA: 10 PC: 10 UA: 80	n/a	n/a	n/a
Vogt et al 2008[48]	USA	311	72.3	18 to > 75	n/r	n/r	4,420	n/a	n/a
Westermann et al 2008[49]	USA	258	75.9	42 ± 12	n/r	Mild to mod	n/a	n/a	n/a
Yamasaki et al 2017[50]	Japan	18	55.6	63 ± 11	0	n/r	n/a	n/a	n/a
Yawn et al 2015[51]	USA	533	76	40.6	15.4	n/r	n/a	n/a	n/a
Zahran and Bailey 2013[52]	USA	74,779	76	18 to >65	19.5	n/r	869,519	51.3	18 to 65+

Longitudinal studies	Country	Follow-up	n	Female (%)	Age	Current smoking (%)	Disease severity (%)	n	Female (%)	Age
Bedard et al 2017[58]	France	Up to 11 y	15,353	100	59.2 ± 6.3	8.5	n/r	n/a	n/a	n/a
Brumpton et al 2017[53]	Norway	Mean 11.6 y	1,329	51.6	44.1 ± 12.9	25.1	n/r	n/a	n/a	n/a

(continued)

TABLE II. *(Continued)*

Longitudinal studies	Country	Follow-up	n	Female (%)	Age	Current smoking (%)	Disease severity (%)	n	Female (%)	Age
Fisher et al 2016[54]	Denmark	Mean 16 y	1,347	61.8	57.1 ± 4.5	34.9	n/r	n/a	n/a	n/a
Garcia-Aymerich et al 2007[55]	Denmark	Mean 11 y	153	n/r	52.4 ± 11.6	n/r	n/r	n/a	n/a	n/a
Garcia-Aymerich et al 2009[56]	USA	Mean 2 y	2,818	100	62.7 ± 6.9	5.8	Mild inter: 20.3 Mild persist:35.6 Mod: 34.6 Severe: 9.5	n/a	n/a	n/a
Russell et al 2017[57]	Norway	Mean 10 y	209‖ 947¶	n/r n/r¶	n/r n/r¶	n/r n/r¶	n/r n/r¶	n/a	n/a	n/a

CA, Controlled asthma; *Inter*, intermittent; *IQR*, interquartile range; *LMIC*, low- and medium-income country; *Mod*, moderate asthma; *n/a*, not assessed; *n/r*, not reported; *PC*, partially controlled; *Persist*, persistent; *UA*, uncontrolled asthma.
Age reported as mean ± SD or (SE), or median (IQR), or range.
*Cross-sectional data from a longitudinal cohort.
†Values for older adults.
‡Values for middle-aged adults.
§% reported for the whole sample.
‖Only participants with asthma at baseline.
¶Results reported correspond to cross-sectional data.

asthma or their healthy counterparts.[39,47,49,51] Furthermore, 2 studies demonstrated that the decrease in activity that develops in older people with asthma occurs earlier, or exclusively, in females than males.[27,30] Dogra et al,[30] for instance, found that the levels of physical activity between middle-aged and older males with asthma were similar, whereas older females with asthma were considerably less active than their younger counterparts.

Reduced physical activity in people with asthma

From the 11 studies reporting lower levels of physical activity in people with asthma compared with controls,[16-18,21,28,30,32,39,41,44,46] 4 studies used activity monitors.[16-18,21] Van't Hul et al[21] found that people with asthma spent significantly less time walking, engaging in vigorous physical activity, and accumulated less steps/day than controls. Cordova-Rivera et al[18] reported that in participants with severe asthma, steps/day and moderate and vigorous physical activity (MVPA) were reduced by 31.4% and 47.5%, respectively, compared with controls ($P < .001$ both results).

From the studies using questionnaires, Teramoto and Moonie[44] reported that control participants spent an additional 60 minutes/week engaged in moderate physical activity and 67 minutes/week in vigorous activity compared with the asthma group ($P < .001$). Ford et al[32] reported that people with current asthma were more inactive (asthma = 30.9%, never asthma = 27.8%; $P < .001$) and engaged in less vigorous physical activity (asthma = 12.7%, never asthma = 14.8%; $P < .001$) than people without a history of asthma. Vancampfort et al[46] reported that asthma was significantly associated with low physical activity (engaging in <150 minutes/week of MVPA), especially in people >50 years old (odds ratio [OR] [95% CI] 1.67 [1.33-2.10]; $P < .0001$).

The level of activity decreased with loss of asthma control,[21] and increasing asthma severity.[16,17] Bahmer et al[16] reported that both steps/day and the time spent in MVPA in participants with severe asthma were reduced by 21% and 17%, respectively, compared with participants with less severe disease ($P < .05$).

Maintained physical activity in people with asthma

In 6 studies, there were no consistent differences in the level of the activity between the asthma and control groups.[19,31,37,42,45,47] One study used an activity monitor.[19] Verlaet et al[47] found that the proportion of participants performing MVPA was similar among people with controlled and uncontrolled asthma compared with controls; 32%, 38.5%, and 33.7% ($P > .05$) for each group, respectively. Liang et al[37] reported that the prevalence ratio (95% CI) for young adults with asthma (<30 years old) engaging in physical activity at the recommended level was 1.09 (0.92, 1.28) compared with those without asthma.

Increased physical activity in people with asthma

Chen et al[27] found that younger adults with asthma achieved higher levels of activity compared with their age-matched healthy counterparts, whereas this pattern of activity reversed in the older age group, especially in females. The mean (standard error [SE]) energy expenditure (EE) for men in the 25-39 years age group with asthma versus their control group was 2.16 (0.22) compared with 1.72 (0.15) kcal/kg/day; and 1.60 (0.14) versus 1.28 (0.06) kcal/kg/day in the female asthma group compared with female controls ($P = .02$ for both). At the age of 40, this trend started to reverse, becoming statistically significant in women >55 years, and for both sexes in the ≥70 years group. In the ≥70 years age group, males with asthma reported a mean (SE) EE of 0.72 (0.34) versus age-matched controls 1.45 (0.15) kcal/kg/day, whereas females reported a mean of 0.79 (0.17) versus 1.17 (0.07) kcal/kg/day ($P \leq .02$ both results).

Prevalence of sedentary time

Sedentary time was reported by 4 studies.[18,21,28,47] Two used an activity monitor.[18,21] Van't Hul et al[21] reported that participants with asthma spent more time lying down compared with controls (hours/day mean difference [95% CI] 0.59 [0.15, 1.03]; $P < .01$), but less time sitting than controls ($P > .05$). Similarly, another study did not find a significant difference in sedentary time between people with severe asthma and controls (minutes/day mean ± SD 674.4 ± 71 vs 676.2 ± 65, respectively; $P > .05$).[18] Doggett and Dogra[28] reported that the time spent watching TV for more than 10 hours/week was 50.4% in the asthma population compared with 42.9% in the nonasthma group ($P < .05$).

TABLE III. Physical activity measurements in studies with a control group

Studies using questionnaires

Study	Asthma definition	PA or ST measurement	PA or ST domain	Recall period	Outcome
Chen et al 2001[27]	Self-reported asthma diagnosed by a health professional	PA questionnaire from National Population Health Survey Canada	LTPA	12 mo	Mean daily energy expenditure (EE) (kcal/kg/day)
Doggett and Dogra 2015[28]	Self-reported physician-diagnosed asthma and use of asthma medication	Questionnaire	LTPA Television-viewing time (TVT)	PA: 1 wk TVT: typical week in last 3 mo	PA: frequency and intensity of (measured as an increase of heart rate and breathing) TVT: >10 h/wk as high TVT; ≤10 h/wk as low TVT
Dogra et al 2008[30]	Self-reported physician-diagnosed asthma	Questionnaire from CCHS cycle 2.1	LTPA	n/r	Active (≥1.5 kcal/kg/day), inactive (<1.5 kcal/kg/day) (estimated from EE)
Dogra et al 2009[31]	Self-reported physician-diagnosed asthma	From CCHS cycle 3.1	LTPA	n/r	Active (>3.0 kcal/kg/day), "moderately active" (1.5-3.0 kcal/kg/day), "inactive" (<1.5 kcal/kg/day)
Ford et al 2003[32]	Self-reported physician-diagnosed asthma	Questionnaire from 2000 BRFSS	LTPA	1 mo	Frequency and duration EE/week, and PA Index
Liang et al 2015[37]	Self-reported asthma	Questionnaire from Australian National Health Survey 2007-08	PA	1 wk	Intensity and frequency ≥800 MET: meeting PA guidelines
Malkia and Impivaara 1998[39]	Self-reported physician-diagnosed asthma and spirometry	Questionnaire	LTPA, PA at work and during commuting	n/r	Intensity and frequency METs at work and spare time. PA during commuting
Ramos et al 2015[41]	Asthma diagnosed by a physician	IPAQ—short form	LTPA	Average day in the last week	PA from EE + duration (METs min/wk)
Ritz et al 2010[42]	Asthma diagnosed by a physician	Electronic diary	PA in the past 30 min	3 times/d for 21 d	Frequency and intensity
Teramoto and Moonie 2011[44]	Self-reported current or lifetime asthma diagnosed by a health professional	Questionnaire from 2009 Nevada BRFSS	LTPA	1 mo	Engagement on PA, meet PA guidelines min/wk of MVPA
Tsai et al 2011[45]	Asthma diagnosed by a physician	Stanford 7-Day Physical Activity Recall	LTPA	1 wk	Frequency and intensity METs
Vancampfort et al 2017[46]	Self-reported lifetime diagnosis of asthma	Extract from IPAQ	LTPA	1 wk	Volume of MVPA (<150 min/wk = low PA)
Verlaet et al 2013[47]	Self-reported asthma	IPAQ—short form	LTPA Daily sitting time	Average day in the last week	LTPA: MET min/wk Volume of daily sitting time in min

Studies using activity monitors

Study	Asthma definition	PA or ST measurement	PA or ST domain	Wear-time protocol	Outcome
Bahmer et al 2017[16]	Physician-diagnosed asthma, and in specialist care for >3 mo	SenseWear Pro Armband	Total PA	Worn for 1 wk Inclusion: ≥5 d of 22.5 h	Steps/d Average minutes of at least moderate activity/day (EE>3 METs)
Bruno et al 2016[17]	Recruited according the ATS criteria	SenseWear Armband	Total PA	Worn over triceps area for 4 d, 24 h/d (excluded water-based activities) Inclusion: n/r	PA level (min/d); active EE (kcal/d); steps/d; total EE (kcal/d)

(continued)

TABLE III. *(Continued)*

Studies using activity monitors

Study	Asthma definition	PA or ST measurement	PA or ST domain	Wear-time protocol	Outcome
Cordova-Rivera et al 2017[18]	Asthma diagnosed by a respiratory physician according to GINA guidelines	ActiGraph wGT3X-BT	Sedentary time Total PA	Worn on dominant hip for 14 consecutive days, 24 h/d (sleeping and nonwear time excluded)	Min/d of: sedentary time, light PA and moderate and vigorous and very vigorous PA Steps/d
Moore et al 2015[19]	History of asthma and any of the following: positive spirometry, positive methacholine challenge, ≥10% decrease in FEV_1 after an exercise challenge	SenseWear Pro3 Armband	Total PA	Worn over triceps area of dominant arm for 3 d, 24 h/d Inclusion: preferably 2 wk/d, 1 weekend day	Steps/d Energy expenditure
*Scott et al 2013[20]	Physician-diagnosed asthma, and history of airway hyperresponsiveness	Pedometer	Steps	Worn for 7 d, recording steps a diary, (prior randomization)	Steps/d
Van't Hul et al 2016[21]	Asthma diagnosed by a respiratory physician and use of asthma medication	DynaPort MoveMonitor	Total PA Sitting and lying time	Worn on lower lumbar spine for 7 consecutive days, 24 h/d (excluded water-based activities) Inclusion: ≥2 (PA) and ≥5 (lying) days of ≥22.5 h	H/d in walking, sitting, and lying. Steps/d D PA level (total EE/d): >1.70 active, 1.40-1.69 predominantly sedentary, <1.40 very inactive
*Vermeulen et al 2016[22]	Previous asthma diagnosis, asthma exacerbation	SenseWear Armband	Total PA	Worn for 7 d Inclusion: n/r	Steps/d, % of time at an intensity: < 3 METs, 3-6 METs, 6-9 METs and ≥ 9 METs
*Yamasaki et al 2017[50]	Asthma diagnosed by a respiratory physician	Actiwatch 2	Total PA	Worn for 7 d Inclusion: n/r	Activity counts

BRFSS, Behavioral risk factor surveillance system; *CCHS*, Canada community health survey; *EE*, energy expenditure; *GINA*, Global Initiative for Asthma; *IPAQ*, International physical activity questionnaire; *kcl*, kilocalorie; *LTPA*, leisure time physical activity; *MET*, metabolic equivalent task; *MVPA*, moderate to vigorous PA; *n/r*, not reported; *PA*, physical activity; ST, sedentary time.
*These studies did not have a control group, but were included in this table to provide further details of the activity monitors used.

Associations between physical activity or sedentary time and asthma health outcomes

Twenty-seven studies reported associations between the level of activity and asthma health outcomes. Five were longitudinal.[53-57] Associations with sedentary time were addressed in 3 studies.[18,28,47] Table IV reports the main findings of these studies. Further descriptions of these associations are summarized in this article's Online Repository at www.jaci-inpractice.org.

The relationship between physical activity and lung function was assessed in 10 studies.[16-18,21,39,40,42,50,53,55] Weak but significant associations were reported in 8 studies,[16-18,39,42,50,53,55] from which 2 were of longitudinal design.[53,55] Measures of asthma control or asthma-related health status were reported in 13 studies, 12 of them of cross-sectional design.[18,21,22,24,29,33,35,40,42,47,49,51,57] Most of the studies found a positive association between higher physical activity and better clinical outcomes, although in some studies, these associations were attenuated to the null when BMI was included as a confounder.[24,49,51,57] For instance, in their longitudinal analysis, Russell et al[57] reported that the protective effect found for light physical activity on current asthma (defined as reporting asthma symptoms, taking asthma medication, or having an asthma exacerbation in the last 12 months) was no longer significant after adjusting for BMI. Vigorous physical activity was associated with more asthma symptoms in 3 studies.[42,47,57]

Measures of health care utilization were evaluated in 6 studies.[28,31,43,51,54,56] Less physical activity was associated with increased exacerbation and/or higher health care utilization in 4 of them.[28,31,43,56] However, contradicting results were reported in the 2 longitudinal cohorts.[54,56] Positive associations between measures of exercise capacity and physical activity were reported in 2 cross-sectional studies.[18,40] Higher physical activity (steps/day) was associated with lower systemic inflammation (high-sensitivity C-reactive protein) in one study.[18] No significant associations were found between physical activity and measures of eosinophilic airway inflammation.[18]

Higher levels of sedentary time were associated with worse asthma clinical outcomes in 2 cross-sectional studies.[18,28] In one of them, these associations were no longer significant after adjustment for physical activity.[18] Doggett and Dogra[28] reported an increased OR (95% CI) for general practitioner (GP) consultations, 2.59 (2.34, 2.87), and hospitalizations in the past year, 1.95 (1.82, 2.08), and past 5 years, 1.13 (1.07, 1.18) ($P < .001$ for all results) for adults with asthma who reported >10 hours of television time/week compared with those who reported ≤10 hours.

TABLE IV. Association between physical activity and sedentary time with asthma outcomes

Citation	Outcome measures	Conclusions
Bacon et al 2015[24]	PA, ACQ, and AQLQ	Participants engaging in high levels of PA (20.1 ± 8.9 METs h/wk) were nearly 2.5 times more likely to have good control (ACQ ≤ 0.8) compared with inactive patients (AOR [95% CI] 2.47 [1.06-5.73]). Results for AQLQ were not significant
*Bahmer et al 2017[16]	Steps, spirometry, body plethysmography, impulse oscillometry	Decreased PA in asthma is associated with airway resistance and small airway dysfunction, but not with airway limitation
Brumpton et al 2016[53]	PA, lung function decline	Less decline in FEV_1/FVC in active participants with asthma than inactive participants with asthma (FEV_1/FVC [%]: −0.14 [−0.27, −0.01] [$P = .03$])
*Bruno et al 2016[17]	PA, FEV_1/FVC, fat free mass (FFT) and intracellular water (ICW)	PA positively correlated with FEV_1/FVC (Rho = 0.34 [$P < .05$])
*Cordova-Rivera et al 2017[18]	ST, MVPA, Steps, 6MWD, spirometry, ACQ, AQLQ, hs-CRP, FeNO, sputum eosinophilia	Higher levels of PA and lower levels of ST were positively associated with most of the clinical/biological outcomes, especially for steps and exercise capacity (coeff [95% CI] 0.02 [0.00 to 0.04]; $P < .01$) and systemic inflammation, and MVPA and ACQ (coeff [95% CI] −1.94 [−3.69 to −0.18]; $P = .032$)
Doggett and Dogra 2015[28]	ST (TV time), PA, health care use	High levels of TV time associated with: more consultations (AOR [95% CI] 2.59 [2.34-2.87]), hospital stays in the last year (AOR 1.95 [1.82, 2.08]), and in the past 5 years (AOR = 1.13 [1.07, 1.18]) Insufficient PA associated with higher health care use: hospital stays in the past year (AOR 1.16 [1.08, 1.23]) or past 5 years (AOR 1.22 [1.16, 1.28])
Dogra and Baker 2006[29]	PA (EE), self-reported measures of health	Higher PA associated with better self-reported health outcomes
Dogra et al 2009[31]	PA (EE), health care use	Lower PA levels associated with higher health care use in people with asthma: overnight hospital stays (AOR [95% CI] 1.78 [1.31, 2.41]); ≥3 GP consultations (AOR 1.26 [1.03, 1.55])
Fisher et al 2016[54]	PA, asthma readmission	No association between PA and asthma hospital readmissions in people with asthma
Ford et al 2004[33]	PA, QoL	Physical inactivity (compared with VPA) significant independent predictor of impaired QoL: poor or fair health OR (95% CI) 2.36 (1.72, 3.22); >14 d with activity limitation: 2.76 (1.89, 4.02); >14 d physically or mentally limited: 1.90 (1.59, 2.32)
Garcia-Aymerich et al 2009[56]	PA (METs h/wk), asthma exacerbation	Higher levels of PA associated with a lower risk of asthma exacerbation
Garcia-Aymerich et al 2007[55]	Levels of PA, lung function decline	MVPA in participants with asthma improved lung function decline by gaining 10 and 7 mL/y of FEV_1 and FVC, respectively, compared with the low PA group (significance not reported)
Iikura et al 2013[35]	PA and asthma control test (ACT)	In MVRA, periodical PA (>3 METs h/wk) was significantly associated with better asthma outcome (coefficient = 0.152, $P = .002$)
Mancuso et al 2007[40]	PA (EE), 2MWT, CRT, asthma control (ACQ), severity, and lung function (spirometry)	PA positively correlated with physical performance in both test (2MWT Rho = 0.38; CRT Rho= −0.39) In MVRA, better asthma control associated with more EE from walking, but not with total EE. FEV_1 associated with PA only in SLRA
Malkia and Impivaara 1998[39]	PA intensity (METs), lung function (spirometry)	Weak but significant positive correlations of PA intensity and lung function in men only (Rho FEV_1 = 0.26; PEF = 0.35)
Ritz et al 2010[42]	PA intensity, lung function (spirometry), SOB, social activity, inhaler use	Higher PA levels associated with higher PEF, higher FEV_1 in the morning and evening only, and more SOB

(continued)

TABLE IV. *(Continued)*

Citation	Outcome measures	Conclusions
Russell et al 2016[57]	PA with follow-up current asthma (CA) and asthma symptoms (AS)	LPA ≥3 times/wk at baseline associated with less follow-up CA (OR [95% CI] 0.44 [0.22, 0.89]). Result attenuated by BMI. Result for VPA > 0.05 Asthma participants with normal BMI show a significant reduction of AS associated with PA, whereas the overweight and obese category did not
Strine et al 2007[43]	Inactivity and measures of asthma severity	People with asthma who were inactive had significantly poorer control compared with those who were not: >3 ER/y (AOR [95% CI]:2.4 [1.6, 3.6]); GP visit/year (AOR: 1.5 [1.1, 2.0]); absenteeism >2 wk/y: (AOR: 1.7 [1.3, 2.0]); daily symptoms (AOR: 2.5 [1.9, 3.4]); inhaler 30+ times/mo (AOR: 1.9 [1.5, 2.5])
*Van't Hul et al 2016[21]	PA, ACQ, AQLQ, and lung function (spirometry)	Low PA was correlated with poorer asthma control. No correlation between spirometry and PA (value not reported). Nil reference regarding AQOL
*Vermeulen et al 2016[22]	Steps/d, activity limitation (ACQ question 3)	No correlation found between PA and activity limitation
Verlaet et al 2013[47]	PA or daily sitting time (ST), and asthma control (CARAT Questionnaire)	MPA and ST predictor of controlled asthma in men: AOR (95% CI) 1.84 (1.02, 3.30); OR: 1.87 (1.06, 3.28), respectively. VPA doubled the risk of uncontrolled asthma in women: AOR: 1.94 (1.13-3.35)
Westermann et al 2008[49]	Exercise habits, asthma severity, and asthma control (ACQ)	Higher BMI was more closely associated with exercise habits than were asthma control and severity, after adjusting for demographic variables
Yamasaki et al 2017[50]	PA, measures of oxidative stress, and antioxidants in blood, spirometry, FeNO, serum levels of vitamins, dietary vitamin intake	Significant correlations only for PA (activity counts/minute) and FEV_1/FVC
Yawn et al 2015[51]	Volume and intensity of PA, asthma control (APGAR), exacerbations	Low PA associated with asthma control only in SLRA

2MWT, 2-min walk test; *6MWD*, 6-min walk distance; *ACQ*, asthma control questionnaire; *AHR*, adjusted hazards ratios; *AOR*, adjusted odd ratio; *AQLQ*, asthma quality of life questionnaire; *BMI*, body mass index; *CI*, confidence interval; *CRT*, chair raise test; *EE*, energy expenditure; *ER*, emergency room; FEV_1, forced expiratory volume in the first second; *FeNO*, fraction of exhaled nitric oxide; *FVC*, forced vital capacity; *GP*, general practitioner; *hs-CRP*, high-sensitivity C-reactive protein; *LPA*, light PA; *LTPA*, leisure-time PA; *MET*, metabolic equivalent task; *MVPA*, moderate and vigorous PA; *MVRA*, multi-variable regression analysis; *OR*, odds ratio; *PA*, physical activity; *PAL*, physical activity level; *QoL*, quality of life; *RM*, repetition maximum; *SLRA*, simple linear regression analysis; *SOB*, shortness of breath; *ST*, sedentary time; *Steps*, average steps/day; *VPA*, vigorous PA.
*Studies using activity monitors.

DISCUSSION

This review summarizes the literature in relation to the prevalence of physical activity and sedentary time in people with asthma, and the associations between these behaviors and different disease outcomes. We found that people with asthma undertake less physical activity than people without asthma, and that the level of activity in asthma seems to be influenced by age, sex, and disease severity.

We also found that people with asthma average 8390 steps/day. This is almost double the value observed in COPD, where an average of 4579 steps/day were reported (FEV_1% < 50% in 55% of studies included).[59] This suggests that although physical activity may be reduced in asthma, the degree of reduction is not as severe as in COPD. Nevertheless, there are subgroups in the asthma population where physical activity is lower.[16-18,21] The 2 studies including people with severe asthma reported a median of around 5800 steps/day.[16,18] Therefore, the estimate of 8390 steps may not be a value applicable to more severe populations. However, considering that this is the first meta-analysis of steps performed in adults with asthma, and that the objective measurement of physical activity in asthma is a fairly recent topic, this value provides a reference that can be updated and developed with future studies.

We found that physical activity seems to be influenced by sex. Several studies reported better activity outcomes in men with asthma compared with women. Similar findings have been reported in children with asthma compared with controls, suggesting that lower levels of activity are only present in women.[60,61] In the general population, it has also been found that both girls[62] and adult females[63,64] do less activity than their male counterparts. However, the fact that the decline in activity in middle-aged and older people with asthma is seen earlier in women[27,30] may suggest that the disease consequences are more severe or have a greater impact on health in females. Supporting this observation is evidence suggesting that among people with similar asthma severity, women tend to have poorer self-reported measures of asthma control and health status[65] and are twice as likely to be admitted to hospital because of acute asthma.[66] From a societal perspective, this sex difference could also be due to changes in physical activity after retirement, with women retiring at an earlier age.[30]

We also identified a potential effect of age on the level of physical activity, showing that the decrease in activity is more pronounced, or even exclusive, in the older asthma population.[27,32,37,46] This is in line with evidence that younger people with asthma engaged in similar[15] or higher[61,67] levels of activity

TABLE V. Activity outcomes from activity monitors

		Steps per day			Volume/intensity of PA or sedentary time (min* or h†/d)			
	N	Asthma	Controls	*P* value		Asthma	Controls	*P* value
Bahmer et al 2017[16]	SA: 63 MA: 83 C: 29	SA: 6,174 (4,822-9,277) MA: 7,841 (6,534-10,252)	8,912 (6,800-11,127)	**<.001**	MVPA*	SA: 125 (68-172) MA: 151 (99-197)	163 (110-207)	**<.05**‡
Bruno et al 2016[17]	A: 24 C: 18	10,434 ± 3,813	10,860 ± 3,042	>.05	PA*: 69.7 ± 84.2 AEE: 335 (380)§ kcal/d		93.2 ± 101 486.7 (435)	**.04** **.04**
Cordova-Rivera et al 2017[18]	SA: 61 C: 61	5,362 (3,999-7,817)	7,817 (6,072-10,014)	**.0002**	ST* LPA* MVPA*	674.4 ± 71 193 ± 57.5 21.9 (12.8-37.9)	676.2 ± 65 171 ± 50.6 41.7 (29.3, 65.8)	>.05 **.029** **<.0001**
Moore et al 2015[19]	A: 16 C: 16	11,125 ± 5,487	10,711 ± 2,675	>.05	n/a		n/a	
Scott et al 2013[20]	A: 33	8,341 ± 3,377	n/a		n/a		n/a	
Van't Hul et al 2016[21]	A: 226 C: 201	7,593 (7,155-8,030)	8,795 (8,326-9,263)	**.001**	Sitting†: 8.21 (7.95-8.48) PAL: 1.53 (1.51-1.55) LPA†: 1.7 (1.65-1.88) MPA†: 1.66 (1.58-1.74) VPA†: 0.34 (0.30-0.38)		8.6 (8.29-8.86) 1.57 (1.55-1.59) 1.91 (1.80-2.02) 1.64 (1.55-11.7) 0.45 (0.41-0.49)	>.05 **.034** >.05 >.05 **<.001**
Vermeulen et al 2016[22]	A: 20	10,159 ± 3,751	n/a		MET 0-3 (% time): 87.2 MET 3-6 (% time): 12.07		n/a	
Yamasaki et al 2017[50]	A: 18	n/a	n/a		*Activity counts: 283.3 ± 81.1		n/a	

Results expressed as mean ± standard deviation or median (IQR). Statistically significant results are in bold ($P < .05$).
A, Asthma; *AEE*, active energy expenditure; *C*, controls; *IQR*, interquartile range; *kcal*, kilocalories; *LPA*, light physical activity; *MA*, mild to moderate asthma; *MET 0-3*, metabolic equivalent task of light PA; *MET 3-6*, metabolic equivalent task of moderate PA; *MPA*, moderate PA; *MVPA*, moderate and vigorous physical activity PA/day; *n/a*, not assessed; *PA*, physical activity; *PAL*, physical activity level; *SA*, severe asthma; *ST*, sedentary time; *VPA*, vigorous PA.
*Reported as min/d.
†Reported as h/d.
‡*P* value for the whole asthma sample compared with healthy control.
§Reported as median (IQR) by the authors.

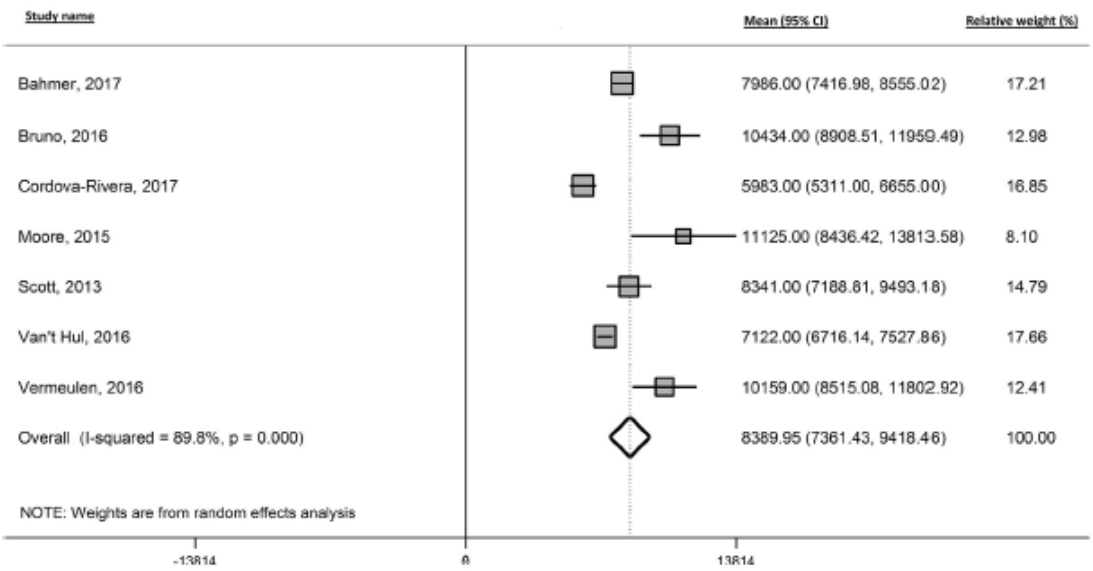

FIGURE 2. Forest plot of standardized mean (95% CI) for steps/day. Authors Bahmer et al, Scott et al, and Van't Hul et al were contacted, and they provided the mean and standard deviation of their results.

compared with their age-matched controls. Plausible biological reasons could relate to the age-related changes in the lung leading to an increased work of breathing that are more extreme in people suffering from respiratory morbidity. Furthermore, older people with asthma are likely to have a longer duration of disease, and therefore, may have more airway remodeling resulting in

incomplete reversibility of airflow limitation.[68] It is also worth mentioning that in the last 30 years, there has been a growing body of evidence that supports the adherence to exercise in people with asthma. This contradicts previous beliefs that people with asthma should avoid exercise and physical activity.[69] It is likely that the age effect identified in this review is linked to this paradigm shift. Finally, people more than 50 years of age with obstructive airway disease show a high degree of overlap in features of both asthma and COPD,[68] so it is possible that the activity levels of older people with asthma could be similar to that of COPD populations,[5,6,59] a finding that requires further investigation and may focus on physical activity interventions to an older age group.

In terms of the associations with physical activity, there was a trend showing that higher physical activity was modestly associated with better lung function in people with asthma. In 2 longitudinal studies, a trend toward a slower lung function decline in active people with asthma compared with inactive people was reported.[53,55] Studies carried out in the general population[70,71] have suggested that this positive impact may be due to the counteracting effect that physical activity may have on the age-related chest wall stiffening,[70] or to a potential positive impact on inspiratory muscle endurance.[72] Among the cross-sectional studies, the results were less consistent. Interestingly, in 2 of the studies reporting a positive association between spirometric values and physical activity,[17,42] participants were relatively young (mean age <39 years), with moderate disease severity, whereas studies in severe or uncontrolled asthma population did not find an association.[16,21] A systematic review of RCTs of physical training in asthma[73] concluded that exercise was not significantly associated with spirometric parameters. Similarly, in COPD, spirometric values have shown a weak-to-moderate association with physical activity.[74] Bahmer et al[16] reported that airway resistance and small airway dysfunction were better markers of physical activity than spirometric values in moderate and severe asthma participants. Whether the association between airflow limitation and physical activity is modulated by time since diagnosis or disease severity needs further investigation.

Some studies reported a positive association between physical activity and asthma control[18,21,24,35,47] or health status,[18,33] which is in line with studies reporting the beneficial impact of exercise protocols on these clinical outcomes.[75-78] In some studies, however, the strength of these associations was attenuated to the null when confounders such as BMI were included,[24,49,51,57] which suggests that the association between obesity and asthma control is stronger than the association between activity and asthma control. Studies addressing the relationship between current or incident asthma, BMI, and physical activity have shown similar results.[25,58] Nevertheless, another study found that the association between asthma control and MVPA was still significant after adjusting for BMI, among other confounders.[18] This suggests that MVPA may still have a modest but independent positive effect on asthma control, in addition to its important role in weight management.[79] Some authors also found an increase in asthma symptoms due to engagement in vigorous physical activity.[42,47,57] Similar findings have been previously reported, especially in females.[61,67] A link between strenuous exercises (a component of vigorous physical activity) and the development of EIB or exercise-induced asthma symptoms has been well documented in the literature.[80,81] In very low levels of activity (inactivity) and vigorous activity are associated with higher risk of asthma symptoms, whereas exercise carried out at a moderate level shows a protective effect.[81]

In terms of the association with asthma exacerbation and health care use, Garcia-Aymerich et al[56] found a longitudinal dose-related protective effect of physical activity on risk of hospital admission for asthma exacerbation. Fisher et al[54] did not observe a significant association between activity engagement and risk of readmission in people with asthma. However, they observed the same pattern in the COPD population, and attributed this lack of association to the small number of participants with asthma and COPD at baseline. Longitudinal studies in COPD have found that physical inactivity is strongly related to acute exacerbations resulting in hospitalization, reduced length of time until admission for an exacerbation, and increased all-cause mortality.[7-10] The body of evidence for asthma is considerably less, and unlike studies conducted in COPD,[9,10] very few have relied on objective physical activity measures to assess the associations of this behavior with disease outcomes.

Data on exercise capacity were scarce,[18,40] but the available evidence suggests that physical activity, especially steps, is positively associated with functional exercise capacity. Interestingly, a weaker effect was observed for MVPA that may suggest that the biggest benefits are obtained by engaging in light to moderate, but more continuous physical activity, rather than shorter but intense periods.[18] Exercise training in patients with asthma can improve cardiopulmonary fitness, assessed by the direct oxygen consumption,[73] and exercise capacity measured by the 6-minute walk distance improves immediately after a 6-week exercise program (3 weekly supervised sessions of walking training and strength exercises) and at 3 months' follow-up.[77] In an RCT, improvement in aerobic capacity and weight loss were independently associated with improvements in asthma control.[82] This highlights the potential benefit of promoting physical activity as a way to improve different impairments in asthma, which despite of being assessed as different clinical outcomes, still affect the person in multiple dimensions of the disease.

Fewer studies have examined sedentary time in asthma. Both studies using activity monitors did not find significant differences between people with asthma and controls,[18,21] but both groups were highly sedentary. A third study[28] reported that people with asthma had higher time watching television than controls. However, in this study, a self-reported proxy of sedentary time was used. Higher sedentary time was associated with decreased exercise capacity, lung function, and asthma control,[18] but these associations were attenuated to the null when physical activity was included as a confounder. This suggests that the deleterious effect of sedentary time may be overcome when engaging in some physical activity.[83] Nevertheless, promoting frequent and longer breaks of sedentary time may be a more achievable goal than increasing activity levels in people with obstructive airway disease. In COPD, there are data linking objectively measured sedentary behavior as an independent predictor of mortality.[84] Studies measuring sedentary time with postural-based accelerometers[85] are required to explore to what extent sedentary time is occurring in asthma and whether it is associated with poorer asthma outcomes.

Strength and limitations

This review followed a structured search protocol and used several electronic databases. Since the review of Eijkemans et al,[14]

there have been a growing number of studies addressing the prevalence of physical activity in asthma. In addition, the use of activity monitors in asthma is a relatively new topic, and was not addressed in the previous review. Our review also adds to the literature summarizing the evidence of the impact of physical activity on different asthma outcomes. Furthermore, to our knowledge, there is no review reporting measures of sedentary time in people with asthma. However, there are some limitations that need to be considered. Our analysis was restricted to studies published in English, and thus we may have missed literature published in other languages. In addition, because we only included studies conducted in adults, these results should not be generalized to children. In terms of the studies included, there was a great deal of heterogeneity in the clinical asthma and activity outcomes measures, as well as population characteristics. Furthermore, most of the studies were of cross-sectional design. Therefore, reverse causation of the associations reported must be considered as a possibility. Finally, most of the studies were performed either in mild or moderate asthma populations, or severity was not reported. As such, the severe asthma population may be underrepresented in this review, but this highlights the need for further research in this more complex population. Nevertheless, this review provides a complete update of prevalence and associations of these 2 behaviors in people with asthma and provides insight of the gaps in the literature that need to be addressed in future studies.

CONCLUSIONS

People with asthma appear to engage in lower levels of physical activity compared with controls. Disease outcomes seem to improve as the volume or intensity of physical activity increase. However, studies that use objective measures of activity, participants with asthma diagnosed according to guidelines,[1] and more standardized measures of clinical asthma outcomes are needed. Also, further studies addressing sedentary time in asthma might help to understand whether this behavior is present, and to what extent it is associated with poorer asthma outcomes. Specifics subgroups, such as those more than 50 years old, and those with severe asthma are underresearched, and an understanding of how age and severity interact in the relationship between activity and asthma clinical or biological outcomes is needed. Longitudinal studies and RCTs exploring the direction of the relationships between physical activity and asthma outcomes are also needed to improve the consistency of the evidence. The results of this review strongly support the need to undertake this research.

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ONLINE REPOSITORY
ASSOCIATIONS BETWEEN PHYSICAL ACTIVITY AND SEDENTARY TIME AND ASTHMA HEALTH OUTCOMES

Twenty-seven studies reported associations between the level of activity and asthma health outcomes. Five were longitudinal.[E1-E5] Associations with sedentary time were addressed in 3 studies.[E6-E8] Table IV reports the main findings of these studies.

LUNG FUNCTION

The relationship between physical activity and lung function was assessed in 10 studies.[E1,E3,E8-E15] Weak but significant associations were reported in 8 studies,[E1,E3,E8,E9-E13] from which 2 were of longitudinal design.[E1,E3] Brumpton et al[E1] reported that active people with asthma had a slower decline in lung function at follow-up compared with inactive individuals. The mean decline in the forced expiratory volume in 1 second/forced vital capacity ratio was 0.36% and 0.22% per year among inactive and active participants with asthma, respectively ($P = .03$). Bahmer et al[E9] reported that fewer steps/day were associated with increased airway resistance and small airway dysfunction. Van't Hul et al[E14] did not find any correlation between measures of physical activity and spirometric assessments.

ASTHMA CONTROL AND HEALTH STATUS

Measures of asthma control or asthma-related health status were reported in 13 studies,[E5,E7,E8,E12,E14-E22] 12 of them of cross-sectional design.[E7,E8,E12,E14-E22] The results suggest that higher levels of moderate and vigorous physical activity (MVPA) were associated with better asthma control. However, vigorous physical activity was also associated with more asthma symptoms.[E5,E7,E12] Bacon et al[E16] concluded that participants who engaged in the recommended levels of activity were almost 2.5 times more likely to have good asthma control compared with less active participants (adjusted odds ratio [OR] 2.47; 95% confidence interval [CI] 1.06, 5.73). Cordova-Rivera et al[E8] also found a positive association between higher volume of MVPA and better asthma control even after adjusting for the time spent sedentary and confounders such as body mass index (BMI), age, and smoking status. The authors report that a 15-minute increase in MVPA was associated with an improved asthma control questionnaire score of −0.29 units ($P = .032$, adjusted R^2 for the model: 0.18). Russell et al[E5] found that physical activity was positively associated with asthma symptoms only in participants with normal weight (BMI < 25), whereas this was not observed in participants with a BMI ≥25. In addition, in their longitudinal analysis, the relationship between baseline light activity and follow-up current asthma (defined as reporting asthma symptoms, taking asthma medication, or having an asthma exacerbation in the last 12 months) was attenuated to the null after adjusting for BMI.

Among studies reporting negative effects of activity, Verlaet et al[E7] found that vigorous activity doubled the risk of uncontrolled asthma in females (adjusted OR [95% CI] 1.94 [1.13, 3.35]; $P < .05$), and in their longitudinal analysis, Russell et al[E5] found a nonsignificant negative trend on current asthma from higher engagement in vigorous physical activity (adjusted OR [95% CI]) of current asthma for 1 to 2 vigorous activity sessions/week: 0.75 (0.38, 1.46) versus >3 sessions/week: 1.03 (0.42, 2.49).

In terms of health status, Ford et al[E18] reported that inactive people with asthma were more than twice as likely to report poor or fair health compared with those doing regular vigorous activity (OR [95% CI] 2.36 [1.72, 3.22]).

EXACERBATION AND HEALTH CARE USE

Measures of health care utilization were evaluated in 6 studies,[E2,E4,E6,E21,E23,E24] 2 of which were longitudinal cohorts.[E2,E4] In 4 studies, less physical activity was associated with increased exacerbation and/or higher health care utilization.[E4,E6,E23,E24] A longitudinal study involving women with asthma[E4] demonstrated that the higher the level of activity performed, the lower the risk of admission for exacerbation ($P = .05$ for trend). Strine et al[E23] reported that inactive people with asthma were more likely to have ≥3 visits to the emergency department for asthma in the last year (adjusted OR [95% CI] 2.4 [1.6, 3.6]) compared with their active peers.

Conversely, Fisher et al[E2] did not find any association between readmission for asthma (mean follow-up 16 years) and participation (yes/no) in physical activity. However, they reported a nonsignificant trend in the association between readmission for asthma and the time spent in activity. Participants engaging in >4 hours/week of gardening and cycling had a 10% and 22% reduced risk of readmission for asthma, respectively, compared with participants spending <4 hours (hazard ratio [95% CI] for gardening 0.90 [0.58, 1.39] and cycling 0.78 [0.49, 1.25]).

EXERCISE CAPACITY

Measures of exercise capacity were evaluated in 2 cross-sectional studies.[E8,E15] Cordova-Rivera et al[E8] found that steps/day were strongly associated with the 6-minute walk distance, even after adjustment for sedentary time and other confounders. The authors reported that every 1000-step/day increase was associated with an increased 6-minute walk distance of 20 m ($P = .01$, adjusted R^2 for the model: 0.35).

BIOLOGICAL MARKERS

There was a significant association between steps/day and systemic inflammation (high-sensitivity C-reactive protein [hs-CRP]) in one of the studies. The authors report that every 1000-step increase was associated with a decrease of hs-CRP of 17%, after adjusting for sedentary time and other confounders. The same study did not find a significant association between MVPA and hs-CRP. No significant association was found between physical activity and measures of eosinophilic airway inflammation.[E8]

SEDENTARY TIME AND HEALTH OUTCOMES

Detrimental associations between sedentary time and outcomes such as exercise capacity, lung function, and asthma control were reported in one cross-sectional study.[E8] However, these associations were no longer significant after adjustment for physical activity. Doggett and Dogra[E6] reported an increased OR (95% CI) for GP consultations, 2.59 (2.34, 2.87), and hospitalizations in the past year, 1.95 (1.82, 2.08), and past 5 years, 1.13 (1.07, 1.18) ($P < .001$ for all results), for people who reported >10 hours of television time a week compared with those who reported ≤10 hours.

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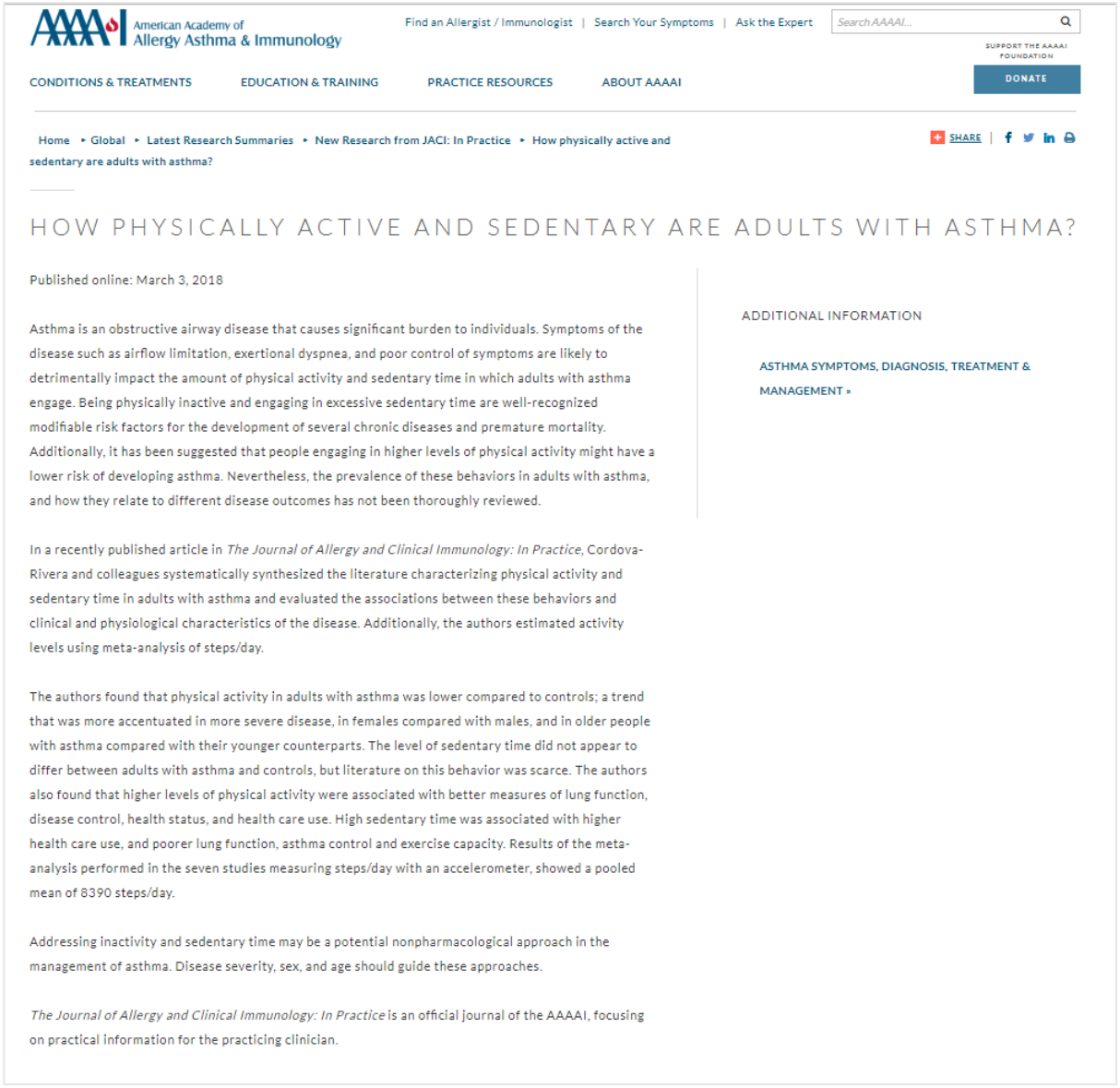
APPENDIX II: CHAPTER 2 – SUMMARY FROM AAAAI WEBSITE



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SHARE

HOW PHYSICALLY ACTIVE AND SEDENTARY ARE ADULTS WITH ASTHMA?

Published online: March 3, 2018

Asthma is an obstructive airway disease that causes significant burden to individuals. Symptoms of the disease such as airflow limitation, exertional dyspnea, and poor control of symptoms are likely to detrimentally impact the amount of physical activity and sedentary time in which adults with asthma engage. Being physically inactive and engaging in excessive sedentary time are well-recognized modifiable risk factors for the development of several chronic diseases and premature mortality. Additionally, it has been suggested that people engaging in higher levels of physical activity might have a lower risk of developing asthma. Nevertheless, the prevalence of these behaviors in adults with asthma, and how they relate to different disease outcomes has not been thoroughly reviewed.

In a recently published article in *The Journal of Allergy and Clinical Immunology: In Practice*, Cordova-Rivera and colleagues systematically synthesized the literature characterizing physical activity and sedentary time in adults with asthma and evaluated the associations between these behaviors and clinical and physiological characteristics of the disease. Additionally, the authors estimated activity levels using meta-analysis of steps/day.

The authors found that physical activity in adults with asthma was lower compared to controls; a trend that was more accentuated in more severe disease, in females compared with males, and in older people with asthma compared with their younger counterparts. The level of sedentary time did not appear to differ between adults with asthma and controls, but literature on this behavior was scarce. The authors also found that higher levels of physical activity were associated with better measures of lung function, disease control, health status, and health care use. High sedentary time was associated with higher health care use, and poorer lung function, asthma control and exercise capacity. Results of the meta-analysis performed in the seven studies measuring steps/day with an accelerometer, showed a pooled mean of 8390 steps/day.

Addressing inactivity and sedentary time may be a potential nonpharmacological approach in the management of asthma. Disease severity, sex, and age should guide these approaches.

The Journal of Allergy and Clinical Immunology: In Practice is an official journal of the AAAAI, focusing on practical information for the practicing clinician.

ADDITIONAL INFORMATION

ASTHMA SYMPTOMS, DIAGNOSIS, TREATMENT & MANAGEMENT »

APPENDIX III: CHAPTER 3 – PUBLISHED ARTICLE

Original Article

Physical Activity and Exercise Capacity in Severe Asthma: Key Clinical Associations

Laura Cordova-Rivera, BPhty(Hons)[a,b,c], Peter G. Gibson, MBBS[a,b,c,d], Paul A. Gardiner, PhD[e,f], Heather Powell, MMedSc[b,c,d], and Vanessa M. McDonald, PhD[a,b,c,d] *New Lambton Heights and Newcastle, New South Wales, Australia; and Woolloongabba and South Brisbane, Queensland, Australia*

What is already known about this topic? People with severe asthma seem to engage in lower levels of activity than controls. Low physical activity in severe asthma is associated with impulse oscillometric airway resistance and small airway dysfunction.

What does this article add to our knowledge? Physical activity measured as steps per day is strongly associated with exercise capacity and systemic inflammation in severe asthma. To a lesser extent, activity and sedentary time are associated with asthma control, health status, and lung function.

How does this study impact current management guidelines? These results suggest that addressing inactivity and sedentary time may be a potential nonpharmacological approach in the management of severe asthma.

[a]National Health and Medical Research Council Centre of Excellence in Severe Asthma, New Lambton Heights, New South Wales, Australia
[b]Priority Research Centre for Healthy Lungs, The University of Newcastle, Newcastle, New South Wales, Australia
[c]Hunter Medical Research Institute, New Lambton Heights, New South Wales, Australia
[d]Department of Respiratory and Sleep Medicine, John Hunter Hospital, Newcastle, New South Wales, Australia
[e]Centre for Health Services Research, The University of Queensland, Woolloongabba, Queensland, Australia
[f]Mater Research Institute, The University of Queensland, South Brisbane, Queensland, Australia
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Corresponding author: Vanessa M. McDonald, PhD, Level 2 West Wing, 1 Kookaburra Circuit, New Lambton Heights, NSW 2305, Australia. E-mail: vanessa.mcdonald@newcastle.edu.au.
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BACKGROUND: Physical inactivity and sedentary time are distinct behaviors that may be more prevalent in severe asthma, contributing to poor disease outcomes. Physical activity and sedentary time in severe asthma however have not been extensively examined.
OBJECTIVE: We aimed to objectively measure physical activity and sedentary time in people with severe asthma compared with age-matched control participants, describing the associations of these behaviors with clinical and biological outcomes. We hypothesized that people with severe asthma would be less active and more sedentary. In addition, more activity and less sedentary time would be associated with better clinical outcomes and markers of systemic and airway inflammation in people with severe asthma.
METHODS: Adults with severe asthma (n = 61) and sex- and age-matched controls (n = 61) underwent measurement of lung function, exercise capacity, asthma control, health status, and airway and systemic inflammation. Physical activity and sedentary time were measured using an accelerometer.
RESULTS: The severe asthma and control groups were matched in terms of age and sex (32 [53%] females in each group). Individuals with severe asthma accumulated less minutes per day in moderate and higher intensity activity, median (IQR) 21.9 (12.9-36.0) versus 41.7 (29.5-65.2) ($P < .0001$) and accumulated 2,232 fewer steps per day ($P = .0002$). However, they engaged in more light-intensity physical activity. No differences were found for sedentary time. In a multivariate regression model, steps per day were strongly and independently associated with better exercise capacity in participants with severe asthma (coefficient, 0.0169; 95% CI, 0.008-0.025; $P < .001$).
CONCLUSIONS: People with severe asthma perform less moderate and vigorous activity than do controls. Higher levels of activity and lower levels of sedentary time are associated with

Abbreviations used
6MWD- 6-minute walk distance
ACQ- Asthma Control Questionnaire
AQLQ- Asthma Quality of Life Questionnaire
COPD- Chronic obstructive pulmonary disease
FENO- Fractional exhaled nitric oxide
hs-CRP- High-sensitivity C-reactive protein
MVPA- Moderate- to vigorous-intensity physical activity

better exercise capacity, asthma control, and lower levels of systemic inflammation. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Severe asthma; Physical activity; Sedentary time; Accelerometry; Exercise capacity; Associations; Clinical outcomes*

Severe asthma is a heterogeneous and complex disease in which diverse clinical and physiological presentations are common.[1] Severe asthma represents a high patient and health care burden.[2] It is, thus, necessary to explore novel strategies to improve health status in severe asthma and to minimize this burden. The importance of multidisciplinary management approaches in severe asthma has been recognized.[3] Within these, the identification and subsequent management of modifiable risk factors or behaviors, such as inactivity, can be seen as an adjunct strategy for the management of the disease.[4]

In general populations, physical activity and exercise are regarded as highly beneficial, leading to positive health outcomes.[5-7] Engagement in excess sedentary time is an important risk factor for the development of several chronic diseases and premature mortality.[8,9] *Physical activity* is defined as any bodily movement generated by the skeletal muscles and resulting in energy expenditure. Depending on intensity and metabolic equivalent of task units, it is classified as light, moderate, or vigorous physical activity, where light corresponds to the lower metabolic equivalent of tasks or energy expenditure.[5] Mild stretching, low impact dancing, and running correspond to examples of light, moderate, and vigorous physical activity, respectively.[10] *Sedentary time* refers to activities performed while awake in a lying or sitting position and expending low levels of energy (≤1.5 metabolic equivalent of tasks).[11] The physical activity and sedentary guidelines recommend engaging in at least 150 min/wk of moderate activity, or 75 min/wk of vigorous activity (or equivalent combination), and to sit less and for shorter periods of time.[12] In other obstructive airway diseases such as chronic obstructive pulmonary disease (COPD), physical inactivity and sedentary time are increased compared with healthy controls.[13,14] These behaviors have been independently associated with worse clinical and inflammatory outcomes,[15] and increased mortality in this disease.[16,17] In asthma, a potential link between inactivity and mortality has not been reported. However, higher adherence to physical activity in asthma has been associated with better asthma control,[18] reduced exacerbations,[19] and reduced health care use.[20] Data on inflammatory parameters are scarce.[21]

In severe asthma, inactivity and sedentary time are likely to be particularly extreme due to the poor disease control and associated comorbidities, such as obesity, anxiety, and depression.[1] Despite this, very few studies have objectively measured physical activity in this population,[--] and the prevalence of sedentary time has not been addressed in severe asthma. In addition, very few studies have assessed the impact of these behaviors on health outcomes in the disease.[22]

The aims of this study therefore were to objectively measure physical activity and sedentary time in a severe asthma population compared with age-matched controls, and to describe the associations of these behaviors with clinical measures such as asthma control, health status, exercise capacity, lung function, and markers of airway and systemic inflammation.

We hypothesized that people with severe asthma are less active and more sedentary than are their age- and sex-matched counterparts, and that higher levels of physical activity and lower levels of sedentary time in severe asthma are associated with better clinical outcomes and lower levels of systemic and airway inflammation. In addition, we sought to test the hypothesis that moderate-intensity physical activity can counteract the detrimental health outcomes associated with high levels of sedentary time, as it has been previously suggested.[23,24]

METHODS

Participant selection

A cross-sectional characterization study was conducted. Adults with severe asthma and sex- and age-matched controls were recruited and underwent a multidimensional assessment with objective measures of physical activity and sedentary time. Participants with severe asthma were recruited consecutively from the respiratory ambulatory care clinics at John Hunter Hospital (Newcastle, Australia) and the clinical research databases of the Priority Research Centre for Healthy Lungs at the University of Newcastle (Newcastle, Australia). Participants with respiratory physician-diagnosed severe asthma were eligible if they met the current guideline definition for severe asthma[1]: prescribed Global Initiative for Asthma step 4 treatment or above, defined as 1,000 μg inhaled corticosteroid fluticasone equivalent and long-acting β2-agonists,[25] had evidence of airflow limitation (FEV_1 <80% predicted), and ongoing poor asthma control (Asthma Control Questionnaire [ACQ][26] score ≥1.5 units or had experienced a severe exacerbation in the last 12 months requiring oral corticosteroids). Participants were clinically stable during visits (no increase in asthma symptoms in the last 4 weeks). Otherwise, their enrolment was postponed until they were stable. Exclusion criteria included malignancy with poor prognosis (<3 months).

Age- and sex-matched controls were recruited via the research database of the Hunter Medical Research Institute and community advertisement, and were eligible if they were older than 18 years and nonsmokers and had no objective evidence of chronic respiratory disease.

Ethics approval was granted by the human research ethics committees of the Hunter New England Local Health District (08/08/20/3.10) and the University of Newcastle, Australia. The study was conducted according to Good Clinical Practice Guidelines and each participant provided written informed consent.

Procedures

Clinical measurements. Participants underwent a multidimensional assessment[27] involving measurement of height and weight, allergy skin prick tests, serum IgE, comorbidities,[28] anxiety and depression,[29] and smoking status. Further assessments are described below.

Exercise capacity. The 6-minute walk test was performed according to current guidelines[30] to measure exercise capacity. The 6-minute walk distance (6MWD) was calculated.

Asthma control and health status. Asthma control was assessed using the ACQ.[26] Higher scores represent poorer asthma control. Health status was measured using the Asthma Quality of Life Questionnaire (AQLQ).[31] Higher scores represent better asthma-related quality of life. A change of 0.5 or more units is considered clinically significant for both questionnaires.[32,33]

Airflow limitation. Airflow limitation was assessed by measuring spirometry: FEV_1, forced vital capacity, and FEV_1/forced vital capacity ratio (Medgraphics, CPFS/D USB Spirometer; BreezeSuite v7.1, MGC Diagnostics, Saint Paul, Minn).[34] FEV_1 and forced vital capacity percent predicted were calculated using the Third National Health and Nutrition Examination Survey predicted equations.[35]

Airway inflammation. Eosinophilic airway inflammation was assessed in 2 ways: using fraction of exhaled nitric oxide (F_{ENO}) (ANALYZER CLD 88 Series with DENOX 88; Eco Physics AG, Duernten, Switzerland)[36] and from sputum eosinophil counts obtained from induced sputum. The samples were induced[37] using nebulized 4.5% or 0.9% saline if the prebronchodilator FEV_1 was less than or equal to 1 L. Lower respiratory sputum portions were selected and dispersed using dithiothreitol. Total cell counts and cell viability (Trypan blue exclusion) were performed, followed by preparation of cytospins for differential cell counts using May-Grunwald Giemsa. Airway eosinophilia was defined as sputum differential eosinophil count of greater than or equal to 3%.[38]

Systemic inflammation. Systemic inflammation was measured by peripheral blood high-sensitivity C-reactive protein (hs-CRP) and analyzed through the Hunter Area Pathology Service.

Physical activity and sedentary time. Physical activity and sedentary time were assessed using the ActiGraph wGT3X-BT (ActiGraph, Pensacola, Fla), a device widely used in research,[39-41] and validated for populations with COPD.[42] This is a small device (4.6 cm × 3.3 cm × 1.5 cm) that participants were fitted with to wear on a belt around their waist, positioned over the dominant hip, for 14 consecutive days. They were instructed to remove the monitor during water-based activities and to record sleeping time and nonwear periods in a diary. The ActiGraph measures time-varying changes in force and activity levels recorded as counts, which are then summed over a user-specified time frame, or epoch.[43] The device was initialized using the ActiLife 6.11.6 Data Analysis Software (ActiGraph, Pensacola, Fla), to collect raw data (accelerations or counts) in the vertical axis at 30 Hz rate in an epoch length of time of 10 seconds. Sleep and any nonwear time were estimated from the diaries and visual examination of the ActiGraph data and removed before classification. ActiLife software was used to summarize the data. We classified time according to the widely used Freedson 1998 cutoff points: Sedentary (0-99 counts per minute [CPM]), light physical activity (100-1951 CPM), and moderate and above physical activity (≥1,952 CPM).[44] The ActiGraph also captures steps per day. Our measures of physical activity and sedentary time were daily time in sedentary time (min/d), daily time in light physical activity (min/d), daily time in moderate- to vigorous-intensity physical activity (MVPA) (min/d), and daily number of steps (Steps [steps/d]). We reported both MVPA and Steps because although the MVPA describes the volume of moderate- to high-intensity activity and can be compared with the physical activity recommendations,[12] Steps is an output easy to interpret and could be used as a motivational and informative tool both for patients and for clinicians. Sedentary time and light physical activity were standardized for wear time by the residuals method.[45] The data were considered valid if there were recordings of 4 or more days, with 10 or more hours of recording each day.

Statistical analysis

Data were analyzed using STATA 13 (Stata Corporation, College Station, Texas). Values are expressed as means with CIs for parametric data and medians with interquartile range for nonparametric data. Differences between the group with severe asthma and the age- and sex-matched control group were assessed using the Student *t* test or the Wilcoxon rank sum test based on normality.

The associations between the different clinical and biological outcomes and the behavioral variables (sedentary time, MVPA, and Steps) adjusting for potential confounders (body mass index and current smoking status) were estimated using simple linear regression analysis. Each behavioral variable was used as a predictor of a given clinical or biological outcome (dependent variable: FEV_1% predicted, 6MWD, ACQ score, AQLQ score, F_{ENO}, and hs-CRP). Age and sex were regarded as biological confounders and included in all the models. Behavioral variables and confounders with a *P* value of less than .2 were also included in a stepwise multiple linear regression analysis to identify the associations between each behavioral variable (sedentary time, MVPA, and Steps) and each biological/clinical outcome (model 1). To test whether moderate physical activity (Steps or MVPA) can counteract the detrimental health outcomes associated with sedentary time, further models were used, adjusting for sedentary time as well as other confounders (model 2). Assumptions for linear regressions were met. Colinearity between the activity (MVPA or Steps) and sedentary variables was rejected. Hs-CRP and F_{ENO} were transformed to the natural logarithm for the linear regression. This means that the dependent variable changes by 100 × [exp(coefficient) − 1] percent for each 1-unit increase in the independent continuous variable. Logistic regressions were used to test the associations of sedentary and active time with airway eosinophilia, and the association between better performance in the 6-minute walk test (defined as ≥median [≥499 m]) and higher engagement (≥30 minutes) in MVPA. Spearman rank correlation tested the relationship between activity variables and 6MWD. Results were reported as significant when *P* was less than .05.

RESULTS

Characteristics of the study population

A total of 143 participants (those with severe asthma = 74, controls = 69) completed the study and 122 (those with severe asthma = 61, controls = 61) were included in the analysis; 21 participants were excluded because of not having valid accelerometer data (those with severe asthma = 8, controls = 5) or because they did not fulfill the disease inclusion criteria after assessment (those with severe asthma = 5, controls = 3). Participants with severe asthma had long-standing disease (median, 27 years) and poor asthma control. They also had a higher body mass index and increased prevalence of atopy, lower lung function, and higher scores of anxiety and depression compared with age- and sex-matched controls. Demographic and clinical characteristics are presented in Table 1.

TABLE I. Demographic and clinical characteristics

Characteristic	Patients with severe asthma	Controls	*P* value
N	61	61	
Sex, F|M (% females)	32|29 (52.46)	32|29 (52.46)	1
Age (y), median (IQR)	59 (43 to 68)	54 (34 to 63)	0.0633
BMI (kg/m^2), mean (95% CI)	30.00 (28.06 to 31.89)	25.40 (24.42 to 26.38)	**0.0001**
Smoking status, current|ex (%)	6.6|47.5	0|29.5	
Pack-year, mean (95% CI)	5.0 (2.71 to 7.28)	3.0 (−0.43 to 6.35)	0.322
Years since diagnosis, median (IQR)	27.11 (15.03 to 50.76)	NA	
OCS, % participants medicated	39.34	NA	
ICS* dose (μg), mean (95% CI)	1091.10 (961.25 to 1220.96)	NA	
Prebronchodilator FEV_1 (L), mean (95% CI)	2.27 (2.05 to 2.49)	3.20 (2.98 to 3.42)	**<0.0001**
Prebronchodilator FEV_1% predicted, mean (95% CI)	75.12 (69.41 to 80.82)	96.94 (93.44 to 100.45)	**<0.0001**
Prebronchodilator FVC (L), mean (95% CI)	3.39 (3.13 to 3.66)	4.01 (3.75 to 4.27)	**0.0012**
Prebronchodilator FVC% predicted, mean (95% CI)	87.01 (82.32 to 91.71)	96.51 (93.16 to 99.85)	**0.0013**
FEV_1/FVC ratio, mean (95% CI)	0.67 (0.63 to 0.69)	0.80 (0.78 to 0.81)	**<0.0001**
hs-CRP (mg/L), median (IQR)	1.8 (1 to 6)	1.1 (0.6 to 2.5)	**0.0024**
F_{ENO} (ppb), median (IQR)	11.5 (5.42 to 31.45)	9.84 (4.6 to 18.3)	0.1024
Sputum eosinophilia (≥3%), n (%)	29 (59.2)	5 (11.36)	**<0.0001**
IgE (IU/mL), median (IQR)	225.500 (70 to 498)	NA	
Atopy, n (%)	48 (82.76)	35 (58.33)	**0.0037**
HADS (anxiety score), mean (95% CI)	6.67 (5.70 to 7.64)	3.80 (3.02 to 4.58)	**<0.0001**
HADS (depression score), mean (95% CI)	4.57 (3.81 to 5.34)	1.37 (0.92 to 1.82)	**<0.0001**
CCI score ≥1, n (%)	16 (26.70)	2 (3.28)	**0.0003**
ACQ score (units), mean (95% CI)	2.23 (1.95 to 2.50)	NA	
AQLQ score (units), mean (95% CI)	5.15 (4.85 to 5.46)	NA	
Severe exacerbation past 12 mo, median (IQR)	2 (1 to 5)	NA	
6MWD (m), median (IQR)	499 (417.7 to 542.2)	616.2 (568.4 to 659.30)	**<0.0001**
6MWD % predicted, mean (95% CI)	71.78 (68.13 to 75.44)	85.71 (82.51 to 88.92)	**<0.0001**

BMI, Body mass index; *CCI*, Charlson comorbidity index; *FVC*, forced vital capacity; *HADS*, Hospital Anxiety and Depression Scale; *ICS*, inhaled corticosteroid; *ICS**, fluticasone equivalent; *IQR*, interquartile range; *NA*, not applicable or not assessed; *OCS*, oral corticosteroid.
Bold indicates statistical significance ($P < .05$).

Physical activity and sedentary time in the group with severe asthma and the age- and sex-matched control group

Compared with controls, people with severe asthma performed less activity of at least moderate intensity. The group with severe asthma had a median difference of 19.8 fewer minutes of MVPA per day ($P < .0001$) and 2455 fewer steps per day ($P = .0002$). Conversely, the population with severe asthma engaged in more light physical activity, with a mean (95% CI) difference of 21.7 (2.2-41.1) more minutes per day ($P = .029$). No statistically significant differences were found in sedentary time between the 2 populations (Figure 1).

Associations of physical activity and sedentary time with clinical outcomes and biological markers in participants with severe asthma

Exercise capacity. Physical activity (Steps and MVPA) and sedentary time were significantly associated with exercise capacity, explaining 35.25%, 29.69%, and 27.3% of the adjusted variance in the 6MWD, respectively (Table II/model 1). For every additional 1,000 steps, there was a 16.9-m increase in the 6MWD. For every minute increase in sedentary time, there was a decrease of 0.47 m in the 6MWD. Accordingly, every additional hour spent sedentary is associated with a 28.2-m reduction in the 6MWD.

There was a linear relationship between Steps and the 6MWD (Figure 2, *A*). For MVPA (Figure 2, *B*) there was also an apparent threshold effect where those participants with a 6MWD performance of greater than or equal to the median (499 m) were also the participants engaging daily in 30 minutes or more of MVPA, a volume of activity that fits within the physical activity recommendations[12] (odds ratio, 6.09; $P = .005$). This suggests that a value of around 500 m in the 6MWD could identify individuals engaging in recommended levels of MVPA.

Simultaneously including sedentary time with MVPA or Steps in the model attenuated the associations of MVPA and sedentary time to the null. However, the association of Steps with exercise capacity remained similar and still statistically significant (Table II/model 2). A 1,000-step increase was associated with better performance in the 6MWD by 21 m. This suggests that regardless of the time spent sedentary, higher levels of walking were still strongly associated with a significant improvement in exercise capacity.

Lung function, asthma control, and health status. The activity and sedentary variables were also significantly associated with lung function, asthma control, and health status, except for Steps and FEV_1% predicted, and sedentary time and the AQLQ score. In contrast to the impact of activity on exercise capacity, the effect on these clinical outcomes was weaker but

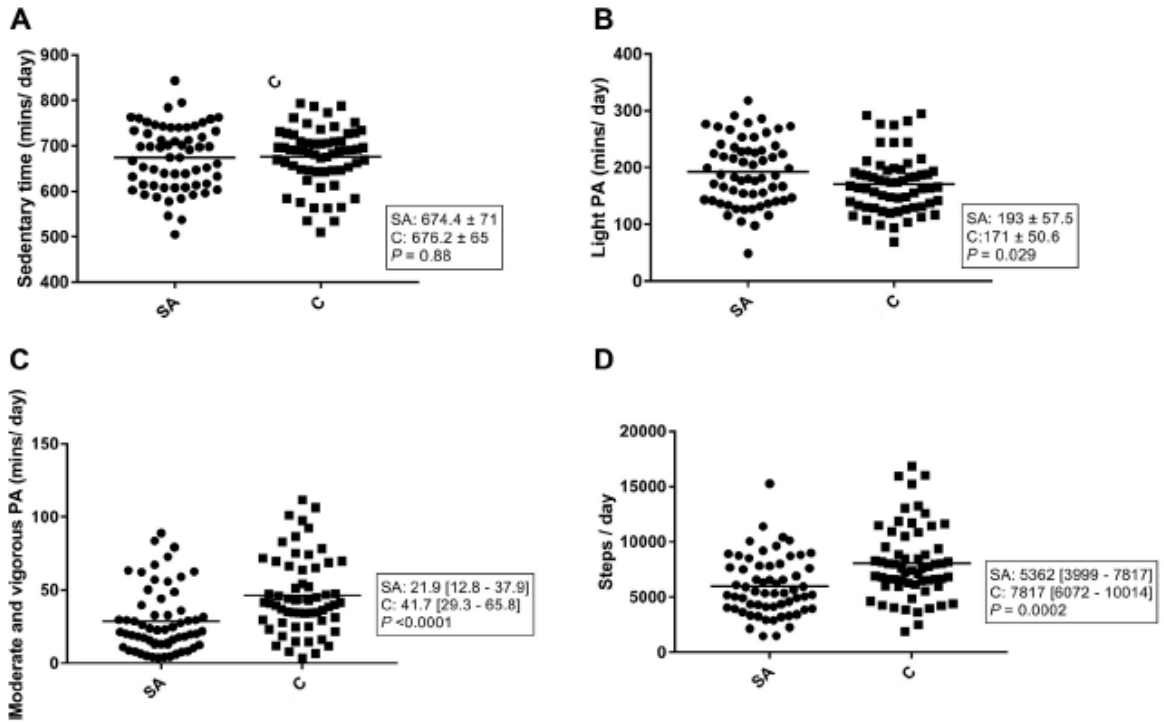

FIGURE 1. Sedentary time **(A)**, Light PA **(B)**, Moderate and vigorous PA **(C)**, and Steps **(D)** in severe asthma and aged-matched control. Values reported as mean ± SD or median [interquartile range]. Number of participants in each group (n = 61). *C*, controls; *PA*, physical activity; *SA*, severe asthma.

TABLE II. Association of physical activity and sedentary time with exercise capacity as 6MWD

	Models for 6MWD		
Model	**Coefficient (95% CI)**	**Significance**	**Adjusted R^2**
Model 1			
ST	−0.47 (−0.79 to −0.14)	**.006**	0.27
MVPA	1.70 (0.64 to 2.75)	**.002**	0.30
Steps	0.01 (0.00 to 0.02)	**.000**	0.35
Model 2			
Steps	0.02 (0.00 to 0.04)	**.010**	
ST	0.18 (−0.39 to 0.75)	.531	0.35
MVPA	1.24 (−0.32 to 2.80)	.117	
ST	−0.19 (−0.66 to 0.28)	.429	0.29

BMI, Body mass index; *PA*, physical activity; *ST*, sedentary time.
Model 1 = each behavioral variable (ST, MVPA, or Steps) as a predictor of exercise capacity. Model 2 = PA (Steps or MVPA) as a predictor of exercise capacity, after adjustment for ST and confounders. Models adjusted for age, sex, and BMI.
Bold indicates statistical significance ($P < .05$).

nonetheless statistically significant and biologically plausible. For every 10-minute increase in MVPA, the ACQ score decreased (improved) by 0.21 units, whereas the AQLQ score increased (improved) by 0.16 units (Table III/model 1). These results suggest that a 25-minute increase in MVPA is associated with a clinically significant improvement in ACQ score (0.52 units). Regarding sedentary time, every 100-minute increase in this behavior is associated with a clinically significant decline in the ACQ score (0.51 units).

The only activity variable that remained statistically significant after adjustment for sedentary time was ACQ score and MVPA. Every 15-minute increase in MVPA was associated with a decrease (improved) of 0.29 units in ACQ score (Table III/ model 2). The coefficient of sedentary time was also attenuated to the null in this model.

In the remaining models, the activity (MVPA or Steps) and sedentary variables together were mutually excluded. Nevertheless, in most of the models, the direction of the coefficients indicated that the decrease in sedentary time and the increase in activity led to modest improvements in clinical markers.

Biological markers. No relationship was found between the behavioral variables and eosinophilic airway inflammation measured by sputum cell counts (Table IV). In simple linear regression analyses, the significance level for FENO was more than .2 and thus not included in the stepwise model.

Steps were significantly associated with hs-CRP. For every increase of 1,000 steps, the hs-CRP was reduced by 13%. No relationship was found between hs-CRP and MVPA or sedentary time (Table V/model 1).

Only Steps remained significantly associated with hs-CRP after adjustment for sedentary time. For every increase of 1,000 steps, the hs-CRP was reduced by 17% (Table V/model 2). The coefficients for the associations of sedentary time were

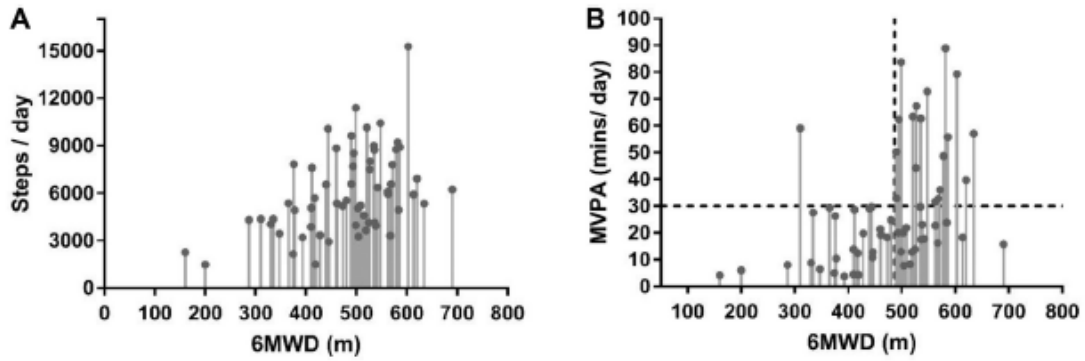

FIGURE 2. Relationship between physical activity and 6MWD in meters. **A**, $\rho = 0.453$. **B**, $\rho = 0.502$ ($P < .001$ both).

TABLE III. Association of physical activity and ST with clinical outcomes

	Models for FEV_1 (%)			Models for AQLQ (units)			Models for ACQ (units)		
Model	**Coefficient (95% CI)***	**Sig.**	**Adj. R^2**	**Coefficient (95% CI)***	**Sig.**	**Adj. R^2**	**Coefficient (95% CI)***	**Sig.**	**Adj. R^2**
Model 1									
ST	−7.90 (−15.63 to −0.17)	**.045**	0.10	−0.35 (−0.76 to 0.04)	.081	0.15	0.51 (0.14 to 0.89)	**.007**	0.12
MVPA	28.69 (3.31 to 54.07)	**.027**	0.11	1.59 (0.29 to 2.89)	**.018**	0.19	−2.15 (−3.33 to −0.97)	**.001**	0.19
Steps	0.17 (−0.03 to 0.38)	.096	0.08	0.01 (0.00 to 0.02)	**.015**	0.20	−0.01 (−0.02 to −0.00)	**.005**	0.13
Model 2									
Steps	−0.00 (−0.38 to 0.37)	.994		0.01 (−0.00 to 0.03)	.078		−0.00 (−0.02 to 00.0)	.304	
ST	−7.95 (−22.25 to 6.35)	.27	0.08	0.19 (−0.53 to 0.23)	.597	0.19	0.21 (−0.47 to 0.90)	.537	0.12
MVPA	20.65 (−17.43 to 58.73)	.282		1.59 (−0.37 to 3.55)	.111		−1.94 (−3.69 to −0.18)	**.032**	
ST	−3.27 (−14.78 to 8.23)	.571	0.10	−0.00 (−0.59 to 0.59)	.998	0.18	0.08 (−0.44 to 0.62)	.740	0.18

Adj., Adjusted; *BMI*, body mass index; *Sig.*, significance; *ST*, sedentary time.
For rationale of models 1 and 2, refer to captions in Table II. All models adjusted for age and sex. AQLQ score adjusted for smoking status. ACQ score adjusted for smoking status and BMI.
Bold indicates statistical significance ($P < .05$).
*Coefficients and CI expressed as $\times 10^{-2}$.

TABLE IV. Association of physical activity and ST with airway inflammation

	Simple logistic regression airway eosinophilia		
Predictors	**Odds ratio (95% CI)**	**Significance**	**Adjusted R^2**
ST	1.00 (0.99-1.01)	.315	0.02
MVPA	1.01 (0.98-1.035)	.470	0.01
Steps	1.00 (0.99-1.00)	.246	0.02

ST, Sedentary time.
Airway eosinophilia defined as eosinophil count of ≥3% in sputum cell.

attenuated to the null. The model explained 48.6% of the variance in systemic inflammation.

DISCUSSION

This study has described the extent to which individuals with severe asthma engage in physical activity and sedentary time compared with a sex- and age-matched control population. We have demonstrated that people with severe asthma are considerably less active. In addition, we found that levels of activity and sedentary time are strongly and independently associated with exercise capacity, and to a lesser extent with other important clinical and biological outcomes. Our results also demonstrate that the detrimental effects of sedentary time are attenuated when participants engage in some physical activity, especially of moderate or higher intensity.

In terms of the levels of activity and sedentary time, our results are consistent with those of several studies conducted in patients with mild and moderate asthma using both objective and subjective activity measurement.[18,22,46-48] However, very few studies have objectively examined physical activity in patients with severe asthma,[22] and to our knowledge this is the first study to report levels of sedentary time in this population. Our finding that people with severe asthma move 31.4% fewer steps per day compared with a control group is consistent with the finding of a recent study that reported 31% lower steps.[22] However, in comparison to Bahmer et al,[22] our study reported a larger difference in MVPA between people with severe asthma and controls (47.5% vs 23%), and the participants in our study were less active than the participants in the Bahmer et al[22] study (22 min/d vs 125 min/d of MVPA). It should be noted though that the authors[22] used a different device to measure MVPA (SenseWear Pro Armband; BodyMedia, Pittsburgh, Pa). Studies using the ActiGraph in a bronchiectasis population[49] have reported similar activity results as our study.

TABLE V. Association of physical activity and sedentary time with inflammatory biomarkers

	SLR models for Ln_FENO			Models for Ln_hs-CRP		
Model	Coefficient (95% CI)*	Sig.	Adj. R^2	Coefficient (95% CI)*	Sig.	Adj. R^2
Model 1						
ST	1.92 (−2.23 to 6.07)	.358	−0.00	3.36 (−0.08 to 6.80)	.56	0.45
MVPA	−1.02 (−14.74 to 12.70)	.882	−0.02	−10.47 (−21.79 to 0.84)	.069	0.45
Steps	−0.02 (−0.13 to 0.08)	.617	−0.01	−0.13 (−0.22 to −0.03)	**.006**	0.49
Model 2						
Steps				−0.17 (−0.34 to −0.00)	**.038**	
ST	ND			−2.09 (−8.24 to 4.04)	.497	0.49
MVPA				−5.15 (−21.95 to 11.63)	.54	
ST	ND			2.20 (−2.92 to 7.32)	.393	0.45

Adj., Adjusted; *BMI*, body mass index; *Ln_FENO*, natural logarithm FENO; *Ln_hs-CRP*, natural logarithm hs-CRP; *ND*, not done; *Sig.*, significance; *SLR*, simple linear regression analysis; *ST*, sedentary time.
For rationale of models 1 and 2, refer to captions in Table II. Ln_hs-CRP was adjusted for age, sex, and BMI.
Bold indicates statistical significance ($P < .05$).
*Coefficients and CI expressed as $\times 10^{-3}$.

We observed that the difference in physical activity between patients with severe asthma and controls is larger for higher intensities of activity than for Steps. This finding has also been reported in patients with mild to moderate COPD,[50] and suggests that activity limitation is first manifested at higher intensities of activity rather than lighter. In fact, our population with severe asthma accumulated more minutes in light physical activity than did healthy controls.

In the general adult population, a widely promoted target for a desirable level of activity is 10,000 steps.[51] Our population with severe asthma achieved only 5362 daily steps, thus a little more than half of the recommended level, and similar to the level reported in patients with moderate to severe COPD[50,52] and patients with bronchiectasis.[49] This suggests that people with obstructive airway disease regardless of diagnosis are engaging in levels of activity that are far below those recommended for adult populations. Direct comparisons between these populations have not yet been reported.

The beneficial role of physical activity and exercise on outcomes such as exacerbations, asthma control, cardiopulmonary fitness, and health status has been previously described in populations with general asthma.[19,20,53-55] However, to our knowledge, this is the first time that the association between exercise capacity and objectively measured physical activity and sedentary time has been reported in patients with severe asthma. Sedentary time attenuated the associations of MVPA with exercise capacity but not the associations of Steps with exercise capacity. This suggests that the greatest benefit on exercise capacity is achieved by performing activity of light to moderate intensity distributed throughout the day, rather than more vigorous but sporadic activity.

The 6MWD has been identified as a predictor of survival in COPD[56] and associated with hospitalization and increased mortality.[57-59] In COPD, a 6MWD of 350 m or less is regarded as poor performance.[58] We found that individuals with a 6MWD of 499 m or more were 6 times more likely to engage in recommended levels of MVPA (≥30 minutes daily),[12] suggesting that this distance may be a suitable cutoff for people with severe asthma. However, this requires further investigation. A difference of 30 m or more has been proposed as the minimal clinically important difference, and furthermore a decrease of this magnitude is associated with increased risk of death in COPD.[60] To date the 6MWD minimal clinically important difference for severe asthma is not known. However, the fact that an increase of 1,000 steps was associated with an increase of 22 m (after adjusting for sedentary time) indicates the potential benefits of targeting physical activity as a modifiable behavior in severe asthma.

Our study also found that physical activity and sedentary time are associated with asthma control, health status, and lung function. The strength of the associations was rather modest and a very large change in activity (>4,000 Steps or >25 minutes of MVPA) was necessary to reach the 0.5 unit minimal clinically important difference defined for the ACQ[33] and the AQLQ.[32] However, because the promotion of activity in severe asthma should be considered as an adjunct treatment, it may contribute to improved disease control when combined with pharmacological and other risk factor management.

We did not find any association between the activity or sedentary variables and measures of eosinophilic airway inflammation. However, it should also be noted that our population was on maximum-intensity inhaled corticosteroid therapy, and this may have modified any potential relationship between the behavioral variables and airway eosinophilia or FENO. This is further supported by the finding that FENO levels, a marker of corticosteroid responsiveness,[36] were not different between the severe asthma and control populations, suggesting that FENO was suppressed by inhaled corticosteroid treatment. These findings suggest that the pathway of inactivity in severe asthma may be more related to breathlessness and/or exercise capacity than to airway inflammation.

Others have reported the positive impact of exercise on markers of airway inflammation (FENO and sputum eosinophilia). This may relate to the baseline characteristics of the participants rather than exercise itself as studies have reported decrease in FENO after a bout of exercise in physically inactive people with asthma and not in those who were active,[61] and participants with increased inflammatory parameters (FENO ≥26 ppb and ≥3% sputum eosinophils) had the greatest improvement after exercise training.[54] Whether the positive effects of exercise on airway inflammation can be reproduced by shifting to higher and extended levels of daily physical activity needs further investigation.

In terms of systemic inflammation, we found that more steps per day were associated with lower hs-CRP levels, after adjustment for body mass index, sedentary time, and other confounders. This suggests a potential benefit of physical activity as a complementary therapy to target systemic inflammation in severe asthma. The role of hs-CRP in the clinical management of severe asthma is still unclear. However, there are data linking systemic inflammation to increased risk of exacerbation,[62] and to increased asthma severity.[63] Exercise also appears to have anti-inflammatory effects.[64] In COPD, it has been demonstrated that higher levels of physical activity are independently associated with lower levels of hs-CRP.[65,66] However, very little data exist on systemic inflammation and exercise in asthma. One study reported a reduction in serum proinflammatory cytokines (IL-6 and monocyte chemotactic protein 1) after aerobic training.[54] Interestingly, Scott et al[67] reported decreases in serum IL-6 levels with exercise and diet, but not with exercise alone, and no change in hs-CRP with either intervention. Our findings may support the idea that activity carried out at a moderate level has a more beneficial effect on systemic inflammation than more strenuous, but acute, activity.

Our study has some limitations. Because of its cross-sectional design, it is not possible to infer causality of our findings. We chose to use the ActiGraph because despite being developed as a research tool, it is becoming increasingly used in population studies[24,40] as well as in clinical setting studies.[49] This device has been validated in populations with COPD, being one of the most accurate in detecting different walking speeds[68] and estimating activity energy expenditure.[42,69] However, sedentary time has been shown to be more accurately measured with postural-based accelerometers, such as activPAL.[70] Also, there are conflicting data regarding the most suitable cutoff point for ActiGraph to measure sedentary time in adult populations, with cutoff points ranging from 25 to 500 CPM.[70-73] It has been suggested that both activity and sedentary parameters can vary greatly depending on the cutoff point used.[73] The less than 100 CPM cutoff point that we used has been shown to be detrimentally associated with cardiometabolic measures in adults,[41] and previously reported in large population studies.[39] Thus, our prevalence results could be compared with previous estimates in the literature.[41,49,74] In addition, considering the scarce information available on sedentary time in patients with severe asthma, these data provide useful insight into how this behavior is associated with both different spectrums of activity and different disease outcomes. Last, we acknowledge that we have not addressed several comorbidities, such as cardiovascular diseases and musculoskeletal conditions, that may negatively impact on the level of activity and sedentary time or interact with some of the dependent outcomes. This is an area for future research. These conditions, however, are not more prevalent in patients with severe asthma than in a control group,[1] and so our study design would account for these issues.

CONCLUSIONS

This study reports novel data on physical activity and sedentary time in patients with severe asthma. We found that severe asthma is associated with lower levels of MVPA. Higher levels of activity and lower levels of sedentary time were linked to better exercise capacity, asthma control, and decreased systemic inflammation. Our results highlight a need to develop and test interventions in patients with severe asthma that aim to improve exercise capacity and systemic inflammation by increasing walking and decreasing sedentary time, and improve asthma control by increasing the volume of MVPA.

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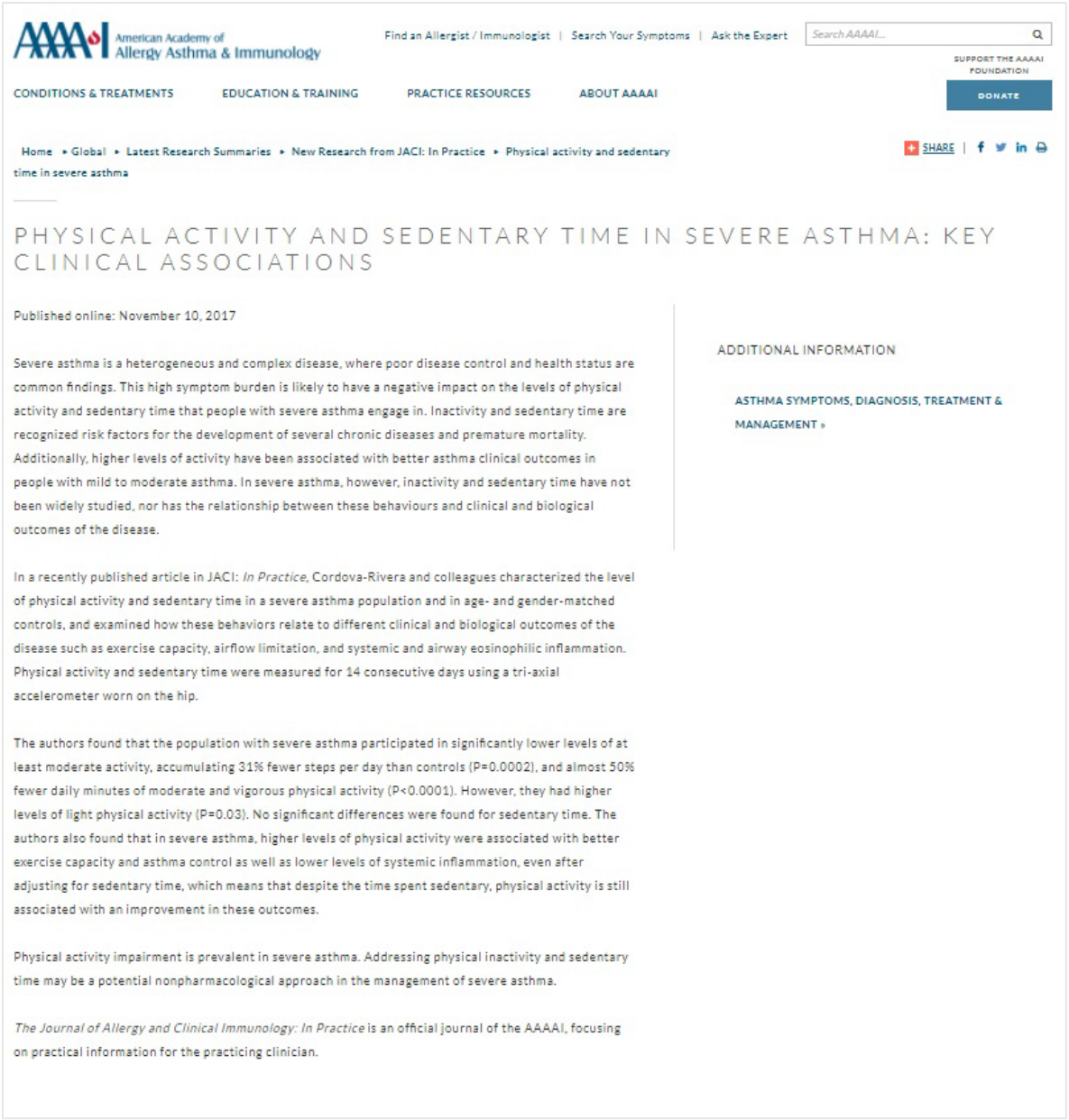
APPENDIX IV: CHAPTER 3 – SUMMARY FROM AAAAI WEBSITE



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SHARE

PHYSICAL ACTIVITY AND SEDENTARY TIME IN SEVERE ASTHMA: KEY CLINICAL ASSOCIATIONS

Published online: November 10, 2017

Severe asthma is a heterogeneous and complex disease, where poor disease control and health status are common findings. This high symptom burden is likely to have a negative impact on the levels of physical activity and sedentary time that people with severe asthma engage in. Inactivity and sedentary time are recognized risk factors for the development of several chronic diseases and premature mortality. Additionally, higher levels of activity have been associated with better asthma clinical outcomes in people with mild to moderate asthma. In severe asthma, however, inactivity and sedentary time have not been widely studied, nor has the relationship between these behaviours and clinical and biological outcomes of the disease.

In a recently published article in JACI: *In Practice*, Cordova-Rivera and colleagues characterized the level of physical activity and sedentary time in a severe asthma population and in age- and gender-matched controls, and examined how these behaviors relate to different clinical and biological outcomes of the disease such as exercise capacity, airflow limitation, and systemic and airway eosinophilic inflammation. Physical activity and sedentary time were measured for 14 consecutive days using a tri-axial accelerometer worn on the hip.

The authors found that the population with severe asthma participated in significantly lower levels of at least moderate activity, accumulating 31% fewer steps per day than controls (P=0.0002), and almost 50% fewer daily minutes of moderate and vigorous physical activity (P<0.0001). However, they had higher levels of light physical activity (P=0.03). No significant differences were found for sedentary time. The authors also found that in severe asthma, higher levels of physical activity were associated with better exercise capacity and asthma control as well as lower levels of systemic inflammation, even after adjusting for sedentary time, which means that despite the time spent sedentary, physical activity is still associated with an improvement in these outcomes.

Physical activity impairment is prevalent in severe asthma. Addressing physical inactivity and sedentary time may be a potential nonpharmacological approach in the management of severe asthma.

The Journal of Allergy and Clinical Immunology: In Practice is an official journal of the AAAAI, focusing on practical information for the practicing clinician.

ADDITIONAL INFORMATION

ASTHMA SYMPTOMS, DIAGNOSIS, TREATMENT & MANAGEMENT »

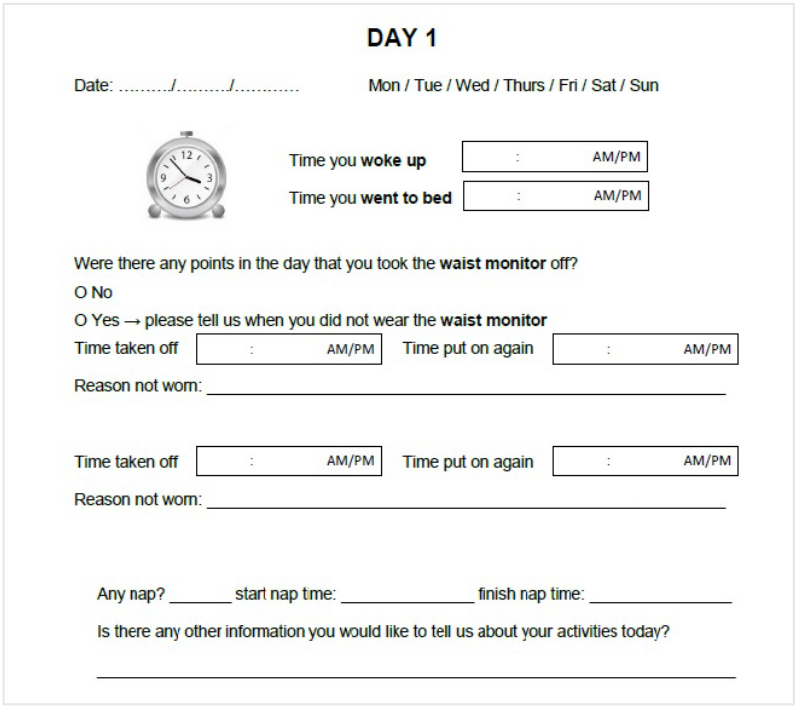
APPENDIX V: CHAPTER 3 – ANALYSIS OF MOVEMENT BEHAVIOURS

Measurement and analysis of physical activity and sedentary time in the article "Physical activity exercise capacity.in severe asthma: Key clinical association"

Physical activity and sedentary time were assessed using the ActiGraph wGT3X-BT (ActiGraph, Pensacola, Florida), a device widely used in research[180, 188, 201], and validated for COPD population[207]. This is a small device (4.6cm x 3.3cm x 1.5cm) that participants were fitted with to wear on a belt around their waist, positioned over the dominant hip, for 14 consecutive days at the end of the first visit. They were instructed to remove the monitor during water-based activities and to record sleeping time and non-wear periods in a diary (see Appendix X for a copy of the full diary). The ActiGraph measure time-varying changes in force and activity levels typically are recorded as counts, which are then summed over a user-specified time frame, or epoch[245]. The device was initialised using the ActiLife 6.11.6 Data Analysis Software, to collect raw data (accelerations or counts) in the vertical axis at 30 Hz rate in an epoch length of time of 10-seconds. The monitors were set up to start recording the day of the first visit, at 5:00 PM. After wearing the monitor for 14-days, participants returned to the research facility to undergo the second part of the visit and return the activity monitor. The monitor was then downloaded, and applied the wear time validation proposed by Choi and colleagues[231]. Since participants wore the monitor for 24 hours, compliance and sleep (nighttime and naps) were estimated from the diaries and visual examination of the ActiGraph data and excluded from the physical activity classification analysis. This was done by creating a digitalised and cross-checked version of the diary log. By undertaking this process I aimed to avoid misclassification of sleeping time as sedentary time. In addition, it allowed me to estimate and extract sleeping time even in if the diary was not fully completed by the participant. This process included the following:

- Data from the diaries given to participants (Appendix IX and picture S-V.I) were digitalised using the ActiLife log diary template (picture S-V.II). This template is in an Excel format, which can be downloaded from the scoring screen of the software and uploaded again into each data file once relevant information has been included. Sleeping time was regarded as "off time" in the log diary template. For instance, picture S-V.II shows data from a fictional participant for the period 26/12/2017 to 27/12/2017. The participant *woke up at 6:00 am* and took the monitor off at *10:00 am for a shower*, and put it on again at *10:15 am*. At *15:00*, the participant had a *30-minute nap*. The participant *went to sleep at 22:00 hrs.* and woke up at *06:00 am of the* following morning.

Picture S-V.I: Screenshot of physical activity diary completed by participants (hardcopy).



DAY 1

Date: ...../...../..... Mon / Tue / Wed / Thurs / Fri / Sat / Sun

Time you **woke up** : AM/PM

Time you **went to bed** : AM/PM

Were there any points in the day that you took the **waist monitor** off?

O No

O Yes → please tell us when you did not wear the **waist monitor**

Time taken off : AM/PM Time put on again : AM/PM

Reason not worn: _____

Time taken off : AM/PM Time put on again : AM/PM

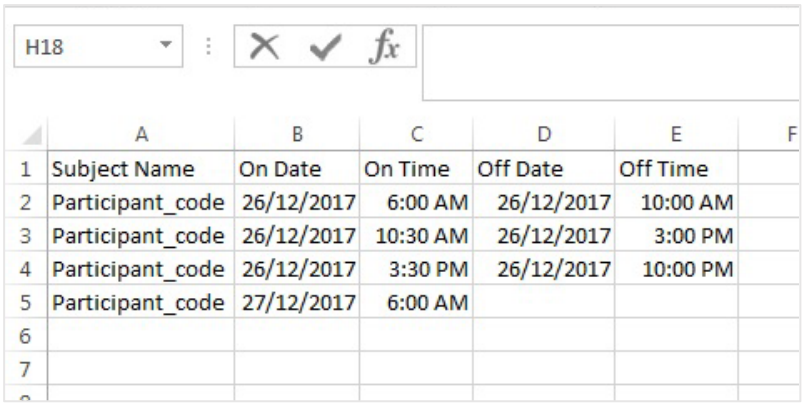
Reason not worn: _____

Any nap? _____ start nap time: _____ finish nap time: _____

Is there any other information you would like to tell us about your activities today?

_____

Picture S-V.II: ActiLife log diary template.

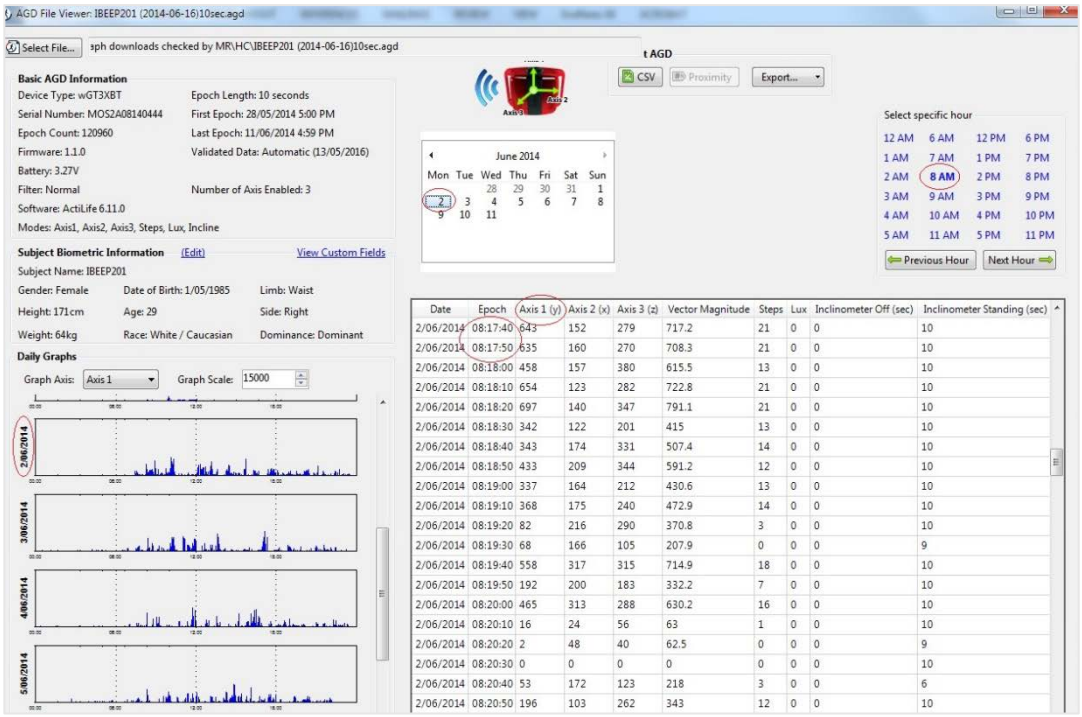


H18

	A	B	C	D	E	F
1	Subject Name	On Date	On Time	Off Date	Off Time	
2	Participant_code	26/12/2017	6:00 AM	26/12/2017	10:00 AM	
3	Participant_code	26/12/2017	10:30 AM	26/12/2017	3:00 PM	
4	Participant_code	26/12/2017	3:30 PM	26/12/2017	10:00 PM	
5	Participant_code	27/12/2017	6:00 AM			
6						
7						

- The ActiLife AGD File (Accumulated Device Data) of every participant was visually inspected and contrasted with the data reported in participant's diaries to update the log diary template. The AGD file (picture S-V.III) provides detailed information of the accelerations recorded every 10-seconds epochs. Recorded data from each day and time can be accessed by clicking in the desired day/hour. Times reported in participant's diaries were regarded as the main guide for creating the digitalised Excel templates. However, if there was a mismatch of a few minutes (<30 minutes) between the data reported and that observed in the AGD file, I recorded as the valid time the time observed in the latter one. This process was repeated for every day of recording per participant. In case of missing data on participant's diary (i.e. data not reported for any day/hour in the diary in the presence of available monitor's data), nighttime sleeping time was estimated from the AGD file. Additionally, data from the first day of recording were not logged into the Excel diary template, and thus excluded from the analysis. Data from the last day of recording were also excluded if the monitor recorded for less than 10 hours that day.

Picture S-V.III: Screenshot of AGD file



- Log diary templates including at least 4 days of recording with at least 10 hours per day (after excluding non-wear time) were uploaded into the device software after the data cleaning process.

ActiLife software was used to score and summarise the data, using the widely used Freedson 1998 algorithm[246] and the filter option "use subject log-diary". The output of this analysis was automatically exported into an Excel document, and then into the statistic program.

The Freedson 1998 cut-point[246] classifies activity as: Sedentary (0-99 counts per minute [CPM]); Light physical activity (100-1951 CPM); and Moderate and above physical activity (≥1952 CPM).

Additional analyses performed included the application of different cut-points for categorising sedentary time. The issue of the sedentary time cut-point was brought up by one of the reviewers of JACI: In Practice, who was questioning the accuracy of the 0-99 CPM

cut-point for defining sedentary time. Nevertheless, analysing the sedentary time data with different cut-points (<150 and <50 CPM) did not alter the non-significant results between severe asthma healthy controls participants. There is conflicting evidence in the literature regarding alternative sedentary time cut-points. Kozey-Keadle and colleagues[209] suggested that a <150 CPM cut-point may be more appropriate to define sedentary behaviour. Indeed, in a later study, the authors recommended a cut-point of 200 CPM using vector magnitude (triaxial accelerometer data). However, these ideas are contradicted by studies suggesting that lower cut-points (<50 CPM) are a better estimate of sitting time[255, 256]. Due to this lack of consensus, I opted to use the <100 cut-point, so that readers could compare the results of our study with previous estimates in the literature. Additionally, this cut-point has been shown to be detrimentally associated with cardiometabolic measures[188].

APPENDIX VI: CHAPTER 3 - EDITORIAL

Editorial

Challenges for the Clinician: Physical Activity Among Severe Asthmatic Patients with Comorbid Obesity

Sheniz Moonie, PhD, and Mary Beth Hogan, MD *Las Vegas, Nev*

Asthma and obesity are difficult comorbidities for the clinician to manage. Oral glucocorticosteroid bursts for uncontrolled asthma contribute to obesity, and both diseases limit exercise. To date, findings are limited in the literature regarding the relationship between physical activity status and sedentary behavior among patients with severe asthma. A novel case- control study of 122 participants performed by Cordova-Rivera et al[1] investigated physical activity and sedentary time recorded via usage of a triaxial accelerometer (Actigraph, Pensacola, Fla) and pedometer among adults with severe asthma. The results demonstrated that those with severe asthma had higher body mass index (BMI) (30 vs 25; $P < .0001$), and exercised with less high-intensity activity (19.8 minutes less higher intensity exercise per day; $P < .0001$) and less steps per day (2,455; $P < .0002$) compared with control patients.[1] Surprisingly, adult patients with asthma increased their time spent in light intensity exercise such as walking (21 minutes more per day; $P = .029$) with no difference noted in sedentary time compared with controls.[1] This finding is unexpected because those with severe asthma are perceived as being more sedentary. Participants with higher activity and reduced sedentary time had associated improved exercise capacity (6-minute walk test), asthma control, and lower inflammation (C-reactive protein). This study suggests that improving the ability to exercise of those with severe asthma either by time or intensity could result in improved asthma parameters while possibly addressing obesity.[1]

A novel aspect of this article was the use of a wearable accelerometer to measure exercise intensity among participants with severe asthma. By determining exercise intensity, Cordova-Rivera et al[1] addressed a limitation inherent in other studies, such as that performed by Bian et al,[2] which tracked both sleep and physical activity via a pedometer (FitBit, Boston, Mass) in adolescents with asthma. The combination of these measurements demonstrates that those with severe asthma are not performing high-intensity activity but are willing to walk. They attempt to increase their time in light exercise to achieve exercise goals. This suggests that clinicians could help each comorbid condition by more aggressively treating exercise symptoms to achieve higher intensity exercise activities, setting specific goals for walking (eg, longer periods of walking time), or to achieve specific higher step counts (10,000 steps/d are recommended for a healthy lifestyle).[3] Assessing exercise strategies among these comorbid patients would be an important area of future investigation for improving both BMI/metabolic status and exercise capacity simultaneously.

This issue does have implications for our commitment to asthma management. In 2014, Seggev et al[4] documented that patients with asthma aged 0 to 17 years in Southern Nevada required significantly more emergency department use than did adults; and pediatric patients also required more hospitalizations and primary care visits than did adults with asthma.[4] Regardless of age, asthma costs in the United States were approximately $56 billion, with costs per patient with asthma at $3,259 in 2007.[5,6] The comorbidity of asthma and obesity is a critical focus because children and adults with asthma tend to reduce activity because of concerns of experiencing exercise-induced bronchospasm, and, as such, may drive higher costs for medical care and experience decreased symptom control.[7] Ultimately, tolerating exercise is a sign of asthma control, and exercise itself in this study was linked to improved asthma control.

Lack of exercise coupled with rescue oral corticosteroid use may make weight management a challenge.[8] Multiple studies indicate that the risk of developing obesity during childhood and adolescence is increased for children with asthma, who are 51% more likely to become obese over the next decade compared with children without asthma.[9] This suggests a need to start these studies earlier in life with children, as well as with adult populations such as in the study by Cordova-Rivera et al. A previous study showed that as asthma severity worsens, physician adherence to prescribing based on National Heart, Lung, and Blood Institute guidelines also worsened.[10] This clinical disconnect may also result in unaddressed exercise-induced bronchospasm symptom control with long-term consequences of obesity development and uncontrolled asthma. Cordova-Rivera et al's novel article suggests that it may be desirable to research the factors influencing the individual patient's decision of how they want to exercise, with a goal of both improving lung function and reducing obesity. Specific strategies to overcome these patients' lack of desire to exercise, as well as examining issues such as perception of activity during employment time affecting home exercise goals, require further investigation. Tackling the comorbidities simultaneously through exercise may result in improvement in both asthma and obesity.

Optimistically, the study noted that extra time spent in active pursuits could pay health dividends for their patients. In keeping track of step counts, those with asthma with the highest number

University of Nevada, Las Vegas, Nev

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

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Corresponding author: Sheniz Moonie, PhD, School of Community Health Sciences, University of Nevada, Las Vegas, 4505 S Maryland Pkwy, Las Vegas, NV 89154. E-mail: sheniz.moonie@unlv.edu.

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of steps per day had better exercise capacity as measured by a 6-minute walk distance (6MWD; 499 m vs 616 m; $P < .001$).[1] Each additional 1,000 steps per day in Cordova-Rivera et al's study resulted in a 16.9-m increase in the 6MWD.[1] Conversely, the authors were able to note that a value of 500 m gained on the 6MWD could identify individuals engaging in desired amounts of physical activity and were 6 times more likely to engage in the recommended levels of moderate activity of at least 30 min/d. This could suggest a way forward for these patients, as for every 10-minute increase in moderate activity there was an associated improvement in asthma control, with increasing gains for longer periods of moderate physical activity. This has also been noted recently by other investigators of obesity and severe asthma.[11] Of note, there are no current 6MWD recommendations specifically for those with asthma, but a distance of less than 350 m is considered poor for patients with chronic obstructive pulmonary disease.

More studies are needed for specific recommendations for the population with severe asthma for achievable targets to be made. This is a point where future investigation may translate to improved therapeutic goals for clinicians treating those with severe asthma. For instance, there may be a benefit to obtaining a 6MWD for those with severe asthma as a goal-driven way to determine a patient's current exercise capability and target areas of improvement in exercise. Disappointingly, those with severe asthma using a pedometer achieved 5362 daily steps, only half the recommended level.[1] The authors surmised that this population needed coaching to increase steps by more than 4000 steps per day or 25 minutes of moderate exercise per day.

Further studies for exercise and the comorbidities of obesity and asthma need to address the following: (1) does exercise have the capability to improve asthma inflammation/control while improving chances of a lower BMI? (2) is obesity a limiting factor for exercise intensity itself? and (3) what is the best way to improve exercise among those with severe asthma (exercise type/length/pharmacologically) to achieve improved lung function and asthma control. In addition, the authors found that the study population had more depression and anxiety than controls. This may have been a confounding factor for why those with severe asthma exercised less than controls, possibly experiencing anxiety regarding disease exacerbation or depression that may have impaired completion of exercise. As such, the potential interplay between asthma, exercise, anxiety, and depression requires further study.[12]

Overall, a novel use of exercise technology provided multiple possible avenues for future study and improvement of comorbid asthma and obesity. Take home points for the clinician: our patients with severe asthma with obesity as a comorbidity are not exercising intensively enough to improve both conditions; they are however willing to do light exercise for longer periods of time, but this does not sufficiently replace the potential gains from moderately to highly intensive activity. This suggests a 2-pronged approach for our patients: to clinically address exercise symptoms better, and coach our patients more (step goals, distance goals, length and intensity of exercise) to improve asthma control. The goals may need to be adjusted such that as asthma improves, exercise goals are reset accordingly. It is important to continue investigation of how to encourage exercise to improve asthma and obesity outcomes among patients with severe asthma.

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APPENDIX VII: CHAPTER 4 – PUBLISHED ARTICLE

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Respirology

ORIGINAL ARTICLE

Physical activity associates with disease characteristics of severe asthma, bronchiectasis and COPD

LAURA CORDOVA-RIVERA,[1,2,3] PETER G. GIBSON,[1,2,3,4] PAUL A. GARDINER[5,6] AND VANESSA M. MCDONALD[1,2,3,4]

[1]National Health and Medical Research Council Centre of Excellence in Severe Asthma, Newcastle, NSW, Australia; [2]Priority Research Centre for Healthy Lungs, The University of Newcastle, Newcastle, NSW, Australia; [3]Hunter Medical Research Institute, Newcastle, NSW, Australia; [4]Department of Respiratory and Sleep Medicine, John Hunter Hospital, Newcastle, NSW, Australia; [5]Centre for Health Services Research, The University of Queensland, Brisbane, QLD, Australia; [6]Mater Research Institute, The University of Queensland, Brisbane, QLD, Australia

ABSTRACT

Background and objective: **Physical activity (PA) in obstructive airway diseases (OAD) is likely to be impaired but this has not been extensively studied outside of chronic obstructive pulmonary disease (COPD). We describe PA levels in severe asthma and bronchiectasis compared to moderate–severe COPD and to controls, and tested the cross-sectional associations of PA (steps/day) with shared disease characteristics in the OAD group.**

Methods: **Adults with OAD (severe asthma = 62, COPD = 67, bronchiectasis = 60) and controls (n = 63) underwent a multidimensional assessment, including device-measured PA levels.**

Results: **The OAD group included 189 participants (58.7% females), with median (interquartile range) age of 67 (58–72) years and mean forced expiratory volume in the first second (FEV_1) % predicted of 69.4%. Demographic characteristics differed between groups. Compared to controls (52.4% females, aged 55 (34–64) years, median 7640 steps/day), those with severe asthma, bronchiectasis and COPD accumulated less steps/day: median difference of −2255, −2289, and −4782, respectively ($P \leq 0.001$). Compared to COPD, severe asthma and bronchiectasis participants accumulated more steps/day: median difference of 2375 and 2341, respectively ($P \leq 0.001$). No significant differences were found between the severe asthma and bronchiectasis group. Exercise capacity, FEV_1% predicted, dyspnoea and systemic inflammation differed between groups, but were each significantly associated with steps/day in OAD. In the multivariable model adjusted for all disease characteristics, exercise capacity and FEV_1% predicted remained significantly associated.**

Conclusion: **PA impairment is common in OAD. The activity level was associated with shared characteristics of these diseases. Interventions to improve PA should be multifactorial and consider the level of impairment and the associated characteristics.**

SUMMARY AT A GLANCE

This is the first study characterizing and comparing the prevalence of physical activity (PA) between a severe asthma, bronchiectasis, chronic obstructive pulmonary disease (COPD) and a control population; and in testing the associations of key treatable and shared disease characteristics with the level of PA in obstructive airway diseases.

Key words: accelerometry, asthma, bronchiectasis, chronic obstructive pulmonary disease, motor activity.

INTRODUCTION

Asthma, chronic obstructive pulmonary disease (COPD) and bronchiectasis are obstructive airway diseases (OAD) that cause significant burden to individuals and health systems.[1]

Whilst these conditions have different pathophysiological processes,[2] there are commonalities. They are all chronic conditions affecting the lower respiratory airways[1,3] and share similar clinical characteristics. Additionally, exacerbations are common, increasing the disease burden.[1] These shared characteristics may challenge the person's ability to perform daily activities and often lead to deconditioning and poor health status.

It is well established that individuals with COPD are considerably less active than without respiratory disease,[4–6] and that the degree of physical activity (PA) is associated with important disease outcomes.[7] The focus in COPD now is to develop and test interventions that improve PA and decrease sedentary time.[8,9] In severe asthma and bronchiectasis, however, there has been little research that objectively characterizes these behaviours, or that have focused on interventions to improve them.[10] To develop such interventions, data

Correspondence: Vanessa M. McDonald, Priority Research Centre for Healthy Lungs, The University of Newcastle, Level 2 West Wing, 1 Kookaburra Circuit, New Lambton Heights, Newcastle, NSW 2305, Australia. Email: vanessa.mcdonald@newcastle.edu.au

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characterizing PA are needed. Furthermore, the extent to which PA impairment is associated with shared clinical and biological characteristics in OAD populations is also unknown. Understanding these similarities and differences is important, in order to develop targeted interventions.

We have previously reported[11,12] that patients with severe asthma have lower PA levels compared to controls, and that this behaviour is associated with important disease outcomes. In the present study, we aimed to characterize the degree and intensity of PA in patients with severe asthma and bronchiectasis, compared to patients with moderate–severe COPD and to individuals without respiratory disease. In addition, we sought to understand whether the PA impairment likely to be found in OAD is associated with shared disease characteristics. We hypothesized that participants with severe asthma and bronchiectasis would engage in more PA than participants with COPD, but in lower activity levels than controls. Additionally, we hypothesized that in the OAD group, PA would be associated with characteristics shared by the three diseases.

METHODS

Adults (≥18 years) with and without respiratory disease were recruited between March 2014 and June 2017 to a cross-sectional study that included measurement of PA.

Participants with physician-diagnosed severe asthma,[13] bronchiectasis[14] or moderate–severe COPD[15] were recruited via the respiratory clinics at John Hunter Hospital (Newcastle, Australia), and the research databases of the Department of Respiratory and Sleep Medicine, John Hunter Hospital, and the Hunter Medical Research Institute (HMRI). Controls were recruited via the research database of the HMRI. Participants were required to be without exacerbation within the 4 weeks prior the study visits. Detailed inclusion and exclusion criteria are described in Appendix S1 (Supplementary Information).

Ethics approval was granted from the Human Research Ethics Committees of the Hunter New England Local Health District (severe asthma, bronchiectasis, and controls ((08/08/20/3.10); COPD (12/12/12/3.06)) and the University of Newcastle. The study was conducted according to Good Clinical Practice Guidelines and each participant provided written informed consent.

Measurements

Participants underwent a multidimensional assessment[3] involving measures of body mass index (BMI), comorbidities,[16] exacerbations, respiratory health status[17] and smoking status. Further assessments included:

Exercise capacity

The 6-minute walk test (6MWT) was performed according to current guidelines.[18] The predicted 6-minute walk distance (6MWD) was calculated.[19]

Airflow limitation

Spirometry was used to measure post-bronchodilator forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC) and FEV_1/FVC ratio (Medgraphics, CPFS/D USB Spirometer, BreezeSuite v7.1, MGC Diagnostics, Saint Paul, MN, USA). Predicted values were calculated using NHANES III reference equations.[20]

Dyspnoea

Scores ≥2 from the modified Medical Research Council (mMRC) Dyspnoea Scale[21] defined positive presence of dyspnoea. This cut-off value is associated with higher risk of mortality in COPD.[22]

Airway inflammation

Eosinophil and neutrophil counts were obtained from induced sputum samples using nebulized 4.5% saline or 0.9% saline according to FEV_1.[23] Lower respiratory sputum portions were selected, dispersed, and total cell counts and cell viability performed, followed by preparation of cytospins and differential cell counts using May-Grunwald–Giemsa.

Systemic inflammation

High-sensitivity C-reactive protein (hs-CRP) was measured in peripheral blood, and analysed using enzyme-linked immunosorbent assay.

Physical activity

PA data were obtained from accelerations detected in the vertical axis using the ActiGraph wGT3X-BT (ActiGraph, Pensacola, FL, USA) accelerometer. The device was initialized[24] to collect accelerations at 30 Hz rate in epochs of 10 s. Participants wore the monitor for 14 consecutive days on a belt around their waist over the dominant hip, and removed the monitor during water-based activities. Data were summarized using the ActiLife 6.11.6 Data Analysis Software (ActiGraph)[24] and were considered valid if there were ≥4 days of recordings, with ≥10 h of recording/day.[25] Non-wear time was removed[26] from the analysis. Moderate and vigorous PA (MVPA) was categorized according to the Freedson 1998 cut-off point[27] (MVPA ≥ 1952 counts/min).

For PA levels, we reported the average steps/day and the mean min/day in MVPA. For the diseases outcomes analysis, we reported steps/day, as it is an output easy to compare and that could be used as a motivational and informative tool for patients and clinicians.[28]

Statistical analysis

Data were analysed using STATA 13 (Stata Corp., College Station, TX, USA). Differences between the severe asthma, bronchiectasis, COPD and the control groups were assessed using one-way analysis of variance, Kruskal–Wallis or chi-square test as appropriate.

Analyses of the associations between PA and shared disease characteristics were performed by disease and in the combined diseases group (OAD group). The

associations between PA (dependant variable), disease characteristics (independent variables: 6MWD, FEV_1% predicted, dyspnoea score ≥ 2, hs-CRP, sputum eosinophils and sputum neutrophils) and potential confounders (current smoking and BMI) were separately estimated in the OAD group using simple linear regression analysis against steps/day. Confounders (BMI) and each independent variable with a *P*-value of <0.2 (6MWD, FEV_1% predicted, dyspnoea, sputum eosinophils and hs-CRP) were included into separate linear regression analyses to identify variables associated with PA. Age and sex were included in all models as biological confounders.

We tested the interaction effects between diagnosis and each independent variables on steps/day (Table S1, Supplementary Information). A final model including all the independent variables was used to identify independent associations with PA in the OAD group. The association between exacerbation and PA was also tested in simple linear regression analyses (Appendix S2, Table S2, Supplementary Information). Assumptions for linear regressions were met. Based on the observed effect size in the final regression model ($f^2 = 0.916$, adjusted $R^2 = 0.4782$, $\alpha = 0.05$), the study has 100% power to detect the effect. Spearman's rank correlation tested relationships between steps/day and disease outcomes. A *P*-value of <0.05 was considered statistically significant.

RESULTS

A total of 296 participants (severe asthma = 75, bronchiectasis = 67, COPD = 83 and controls = 71) completed the study and 252 (severe asthma = 62, bronchiectasis = 60, COPD = 67 and controls = 63) were included in the analysis. Reasons for exclusion were: invalid accelerometer data (severe asthma = 8, bronchiectasis = 5, COPD = 4, controls = 5), not fulfilling the inclusion criteria after assessment (severe asthma = 5, bronchiectasis = 2, controls = 3) or inability to complete all assessments (COPD = 12).

The clinical characteristics of each group differed (Tables 1–2). As expected, the disease groups had worse clinical/biological characteristics than controls. The severe asthma and COPD groups had higher BMI, and both the bronchiectasis and COPD groups were older than controls. Participants were treated according to current guidelines.[13,15]

Characterization of PA

Compared to controls, the severe asthma and bronchiectasis groups had lower PA, with a median difference of around 2270 less steps/day ($P < 0.001$ both), and a median of 19.7 ($P = 0.006$) and 26.5 ($P < 0.0001$) less min/day of MVPA, respectively. Compared to COPD, the severe asthma and bronchiectasis groups had higher PA levels, with a median of 2374 and 2341 more steps/day ($P < 0.0001$ both), and a median of 13.6 ($P < 0.0001$) and 6.8 ($P = 0.0024$) more min/day of MVPA (Fig. 1). No significant differences were observed between the severe asthma and bronchiectasis population.

Characteristics associated with PA in OAD

After adjustment for significant confounders, 6MWD, FEV_1% predicted, dyspnoea, sputum eosinophils% and

Table 1 Demographics and clinical characteristics of participants

	SA† (*n* = 62)	BE† (*n* = 60)	COPD‡ (*n* = 67)	Control§ (*n* = 63)	*P*-value¶	OAD (*n* = 189)
Age (years)	58.0 (43.0–68.0)†‡	68.0 (62.0–73.0)†§	70.0 (64.0–75.0)§	55.0 (34.0–64.0)	**<0.0001**	67.0 (58.0–72.0)
Females (%)	51.6	86.7†‡§	38.8	52.4	**<0.001**	58.7
BMI (kg/m^2)	28.6 (24.6–33.7)†§	25.6 (21.7–27.6)†‡	30.1 (26.9–33.5)§	25.3 (22.3–27.6)	**<0.0001**	27.7 (23.8–31.6)
Years since diagnosis	27.6 (15.1–51.0)	16.0 (5.0–57.0)	6.0 (3.0–14.0)	N/A		14.6 (5.0–41.0)
Current smoker (%)	8.1	1.7	0.0	0.0	**0.031**	3.2
Smoking pack/years	0.0 (0.0–5.4)‡	0.0 (0.0–2.1)‡	42.6 (31.3–70.5)§	0.0 (0.0–3.0)	**<0.0001**	5.0 (0–36.0)
CCI score ≥ 1 (%)	27.9	35.0	100.0	3.17	**<0.001**	55.9
Medication (% participant prescribed)						
OCS	40.3	3.0	3.0	0.0		15.0
Combination ICS/LABA	97.0	63.3	70.2	0.0		77.0
ICS	13.0	5.0	16.4	0.0		12.0
LAMA	52.0	38.3	91.0	0.0		61.4
LABA	0.0	2.0	16.4	0.0		6.4
Omalizumab	11.3	N/A	N/A	N/A		3.7
Mepolizumab	6.5	N/A	N/A	N/A		2.1

Results reported as median (interquartile range) or percentage. OAD group not included in the hypothesis tests.

Results with statistically significant between-group differences: (†) between SA and BE groups, (‡) with COPD group, (§) with Control group.

¶*P*-value correspond to the differences within group (COPD, SA, BE and controls). Statistically significant results are in bold.

BE, bronchiectasis; CCI, Charlson Co-morbidity Index; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; OAD, obstructive airway disease; OCS, oral corticosteroid; SA, severe asthma.

Table 2 Clinical and biological characteristics

	SA† (*n* = 62)	BE† (*n* = 60)	COPD‡ (*n* = 67)	Control§ (*n* = 63)	*P*-value¶	OAD (*n* = 189)
Post FEV_1 (% predicted)	75.8 (70.4, 81.3)†§	76.9 (70.9, 82.8)†§	56.4 (52.5, 60.3)§	100.6 (96.7, 104.5)	**<0.0001**	69.4 (66.2, 72.5)
Post FVC (% predicted)	87.5 (83.1, 91.8)†§	81.1 (76.3, 86.0)§	78.7 (74.6, 82.7)§	96.6 (93.2, 100.1)	**<0.0001**	82.3 (79.7, 84.9)
Post FEV_1/FVC ratio	0.66 (0.56–0.77)†§	0.73 (0.65–0.79)†§	0.56 (0.44–0.67)§	0.82 (0.77–0.86)	**<0.0001**	0.66 (0.55–0.76)
6MWD (m)	477.8 (452.0, 503.5)†§	453.4 (424.2, 482.6)†‡§	383.5 (353.5, 413.6)§	609.5 (589.0, 629.9)	**<0.0001**	435.9(418.6, 453.1)
6MWD (% predicted)	72.1 (64.7–82.6)§	76.6 (62.9–82.0)†§	66.0 (46.9–77.2)§	86.8 (77.9–92.7)	**<0.0001**	70.9 (59.1–80.1)
Dyspnoea score ≥ 2 (%)	50.0§	32.0†‡§	53.0§	0.0	**<0.001**	45.2
GOLD quadrant (%)	N/A	N/A	B = 17.9; C = 4.5; D = 76.1	N/A		N/A
GOLD stage (%)	N/A	N/A	2 = 64.2; 3 = 30.0; 4 = 6.0	N/A		N/A
Oxygen dependent (%)	0	3.3	3.8	0	**<0.001**	2.6
Severe exacerbation (*n*)	190‡	18†‡	44	0	**<0.001**	
SGRQ score	41.2 (27.5–55.1)†	36.0 (23.8–52.5)†‡	50.3 (39.5–66.6)	N/A	**<0.0001**	45.2 (32–58)
hs-CRP (mg/L)	1.8 (1.0–6.0)§	2.8 (1.4–7.0)§	3.8 (1.9–10.0)§	1.1 (0.6–2.5)	**<0.0001**	2.9 (1.4–7.8)
Eosinophils (%)	3.6 (0.8–13.5)†§	1.3 (0.6–2.1)†§	1.8 (0.75–3.8)§	0.45 (0.0–1.0)	**<0.0001**	1.5 (0.75–4)
Neutrophils (%)	35.0 (17.8–59.3)†	78.1 (61.3–85.3)†‡§	48.8 (29.5–71.8)§	27.3 (15.5–42.8)	**<0.0001**	53.3 (28.5–79.3)

Results reported as mean (95% CI) (post FEV_1% predicted, FVC % predicted and 6MWD), median (interquartile range) or percentage. OAD group not included in the hypothesis tests. Statistically significant between-group differences results: (†) between SA and BE groups, (‡) with COPD group, (§) with Control group.

¶*P*-value correspond to the differences within group (COPD, SA, BE and controls). Statistically significant results are in bold.

6MWD, 6-min walk distance; BE, bronchiectasis; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; hs-CRP, high-sensitivity C-reactive protein; OAD, obstructive airway disease; SA, severe asthma; severe exacerbation, total number in last year as per SA and GOLD guidelines definitions (BE as per GOLD guidelines); SGRQ, St George Respiratory Questionnaire.

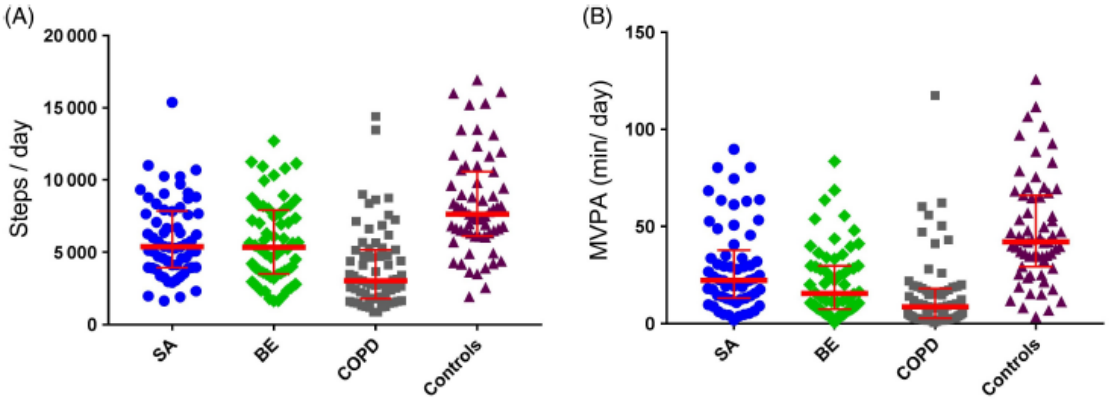

Figure 1 PA comparison for steps/day [median (IQR)] (SA: 5385 (3941–7844), BE: 5351 (3522–7834), COPD: 2858 (1754–5146), controls: 7640 (6123–10 583)) (A) and MVPA (SA: 22.3 (13.3–35), BE: 15.5 (7.5–29.8), COPD: 8.7 (2.8–18.1), controls: 42.0 (29.4–66)) (B). BE, bronchiectasis; controls, adults with no respiratory disease; MVPA, moderate and vigorous PA; PA, physical activity; SA, severe asthma. SA (●) $n = 62$, BE (◆) $n = 60$, COPD (■) $n = 67$, controls (▲) $n = 63$.

Table 3 Associations of physical activity in OAD

Separate models for clinical and biological outcomes	Associations of steps/day with disease characteristics in OAD		
	Coefficient (95% CI)	Significance	Adjusted R^2
6MWD (m)	15.10 (12.10, 18.10)	**<0.001**	0.433
FEV_1 (% predicted)	52.62 (34.99, 70.25)	**<0.001**	0.153
Dyspnoea (≥2 score)	−1689.4 (−2476, −902.1)	**<0.001**	0.204
Reference: ≤1 scores			
hs-CRP (mg/L)	−36.96 (−61.35, −12.56)	**0.003**	0.190
Eosinophils (%)	50.25 (0.40, 100.11)	**0.048**	0.161
Full model	Independent associations of steps/day in OAD		Adjusted $R^2 = 0.478$
6MWD (m)	12.40 (8.51, 16.28)	**<0.001**	
FEV_1 (% predicted)	18.96 (0.53, 37.40)	**0.044**	
Dyspnoea (≥2 score)	−42.40 (−813.95, 729.16)	0.914	
hs-CRP (mg/L)	0.69 (−20.33, 21.71)	0.948	
Eosinophils (%)	25.88 (−14.49, 66.24)	0.207	
BMI (kg/m^2)	−54.15 (−104.05, −4.26)	**0.034**	
Age	−27.74 (−55.3, −0.19)	**0.048**	

Each model adjusted for confounders: age, gender and BMI (except FEV_1% predicted). Dyspnoea was transformed into a binary variable and considered positive when scores were ≥ 2. Confounders (BMI, age and sex) explained 13% of the variance in steps/day in the full model. Sex not significant in the full model. Statistically significant results are in bold.

6MWD, 6-min walk distance; FEV_1, forced expiratory volume in the first second; hs-CRP, high-sensitivity C-reactive protein; OAD, obstructive airway disease.

hs-CRP were all associated with steps/day in the combined OAD group (Table 3). Regression models by disease (Table 4) show a similar pattern, as indicated by overlapping CI in forest plots (Fig. S1, Supplementary Information). No statistically significant interactions for diagnosis were found between the independent variables and steps/day (Table S1, Supplementary Information). The correlations between some measured outcomes and steps/day are shown in Figure 2. The 6MWD had the strongest correlation with PA, and the regression model explained 43% of the adjusted variance in steps/day. Every 100-m increase in exercise capacity was associated with an increase of 1500 steps/day. Dyspnoea, airflow limitation (AFL), systemic inflammation and sputum eosinophils were weaker associations of PA, but statistically significant nonetheless. Associations between disease outcomes and MVPA are reported in Table S3 (Supplementary Information).

The full regression model shows that better exercise capacity and lung function remained independently and positively associated with PA in OAD (Table 3). Dyspnoea, hs-CRP and sputum eosinophils were no longer significant. The full model explained 48% of the variance in steps/day in OAD.

DISCUSSION

In this study, we characterized the level of PA in a group of patients with severe asthma and

Table 4 Regression models of associations of disease characteristics with steps/day by diagnosis

	Associations of steps/day with disease outcomes by disease		
	Coefficient (95% CI)	Significance	Adjusted R^2
6MWD (m)			
Severe asthma	12.76 (6.27, 19.26)	**<0.001**	0.259
COPD	12.01 (7.63, 16.39)	**<0.001**	0.485
Bronchiectasis	17.37 (12.26, 22.47)	**<0.001**	0.503
FEV_1 (% predicted)			
Severe asthma	33.71 (2.04, 65.38)	**0.037**	0.060
COPD	46.20 (4.52, 87.88)	**0.030**	0.055
Bronchiectasis	45.52 (15.77, 75.27)	**<0.01**	0.124
Dyspnoea (≥2 score) (vs scores ≤ 1)			
Severe asthma	−1534.53 (−2966.27, −102.80)	**0.036**	0.129
COPD	−1310.93 (−2536.58, −85.28)	**0.036**	0.286
Bronchiectasis	−2270.94 (−3710.32, −831.56)	**0.003**	0.213
hs-CRP (mg/L)			
Severe asthma	−45.82 (−84.92, −6.72)	**0.022**	0.153
COPD	−15.52 (−52.71, 21.67)	0.407	0.243
Bronchiectasis	−84.34 (−132.33, −36.35)	**<0.001**	0.279
Eosinophils (%)			
Severe asthma	87.87 (16.34, 159.40)	**0.017**	0.124
COPD	22.99 (−50.20, 96.18)	0.532	0.239
Bronchiectasis	−113.40 (−351.35, 124.55)	0.343	0.103

Models adjusted for confounders: age, sex and BMI (except FEV_1% predicted). Dyspnoea was transformed into a binary variable and considered positive when scores were ≥ 2. Statistically significant results are in bold.

6MWD, 6-min walk distance; FEV_1, forced expiratory volume in the first second; hs-CRP, high-sensitivity C-reactive protein; OAD, obstructive airway disease.

bronchiectasis, compared to moderate–severe COPD and controls. For the first time, we have shown that patients with both severe asthma and bronchiectasis engage in lower levels of PA than individuals without respiratory disease, but higher levels compared to patients with moderate–severe COPD. The intensity and volume of activity were similar in the severe asthma and bronchiectasis groups, and the degree of PA impairment in OAD could be explained in an important proportion by exercise capacity and AFL.

We aimed to characterize and compare the level of PA impairment in different OAD. A robust body of research exists in COPD, highlighting that PA is markedly decreased,[7] and that this decrease is strongly associated with exacerbations and mortality.[7,29,30] As such, the promotion of PA in COPD is an important component of disease management,[9] and a desirable indirect outcome of pulmonary rehabilitation.[9,31]

Whilst the degree of physical inactivity and its impact is well established in COPD, in severe asthma and bronchiectasis, there is a paucity of research that characterizes this important and modifiable risk-factor, that makes comparisons to disease groups with similar characteristics or that has described the clinical associations of PA in these conditions. This is important in order to generate an evidence base that can guide the direction of treatment interventions for severe asthma and bronchiectasis. Extrapolating what is known in COPD to these conditions may lead to the design of ineffective interventions. In an era of personalized medicine, this new knowledge will help design individualized treatment programmes.

Our severe asthma and bronchiectasis populations moved a median of 5360 steps/day each, resulting in a median difference of 2350 more steps compared to our COPD population. Previous studies conducted in severe asthma[32] and bronchiectasis[33] have reported a median of approximately 6000 steps/day, which is consistent with our results. When compared with severe asthma, our bronchiectasis population also accumulated fewer minutes of MVPA, although not statistically significant. These differences were explained by the fact that our bronchiectasis participants were mostly females, a trend previously reported.[34] Overall, our data confirm that PA impairment exists in severe asthma and bronchiectasis, but to a lesser degree than in COPD.

Whilst we highlight the importance of characterizing these behaviours in specific disease groups, we also combined the disease populations to identify if shared clinical characteristics of OAD are associated with PA. In the recently proposed 'treatable traits' management approach,[35] deconditioning was proposed as an extrapulmonary trait to be addressed. We suggest that PA itself is a trait to be targeted, and we report that this occurs albeit to different degrees across diagnosis groups. These groups also shared clinical and biological features that were all associated with PA impairment. Therefore, we have identified potential treatment targets that might address the physical inactivity trait, not only in COPD but also in severe asthma and bronchiectasis.

The 6MWD explained the highest proportion of variance in steps/day in the OAD group. This test has been endorsed as a valid outcome measure in patients with chronic respiratory disease to measure functional exercise capacity,[18] and is an important predictor of COPD

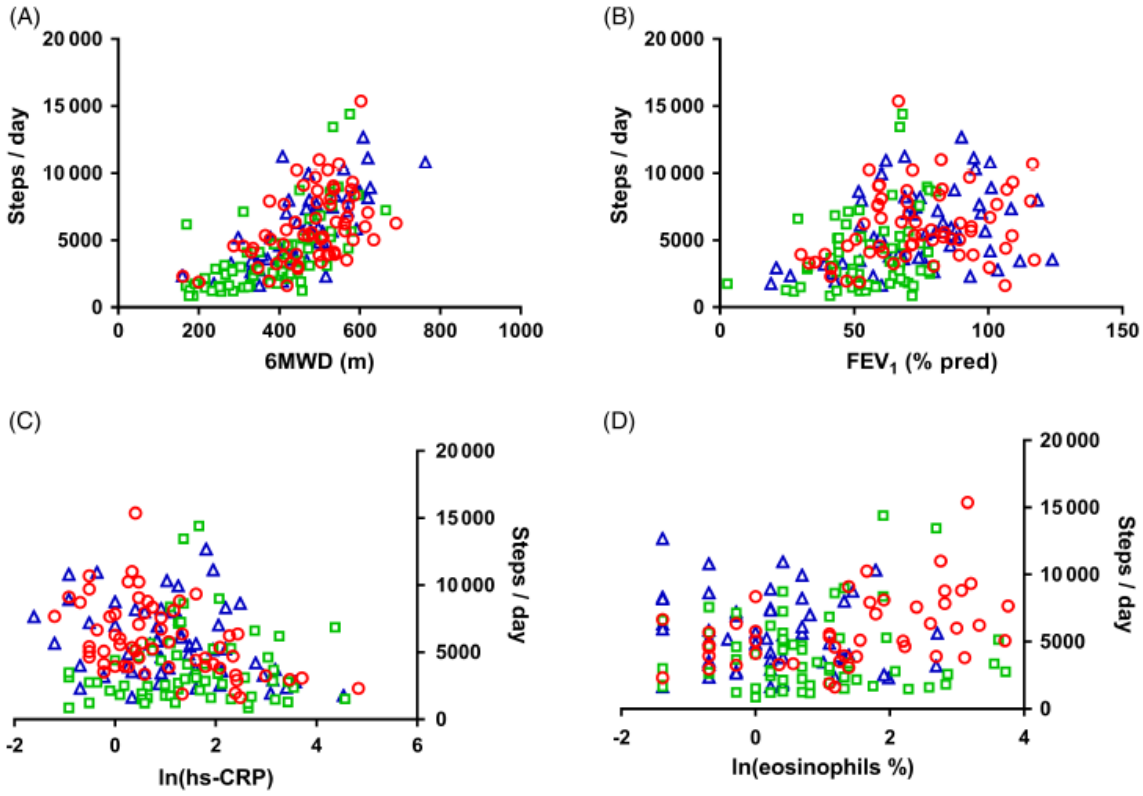

Figure 2 Pearson's correlation of physical activity (steps/day) with 6MWT (r: 0.72, $P < 0.0001$) (A), FEV_1% predicted (r: 0.426, $P < 0.0001$) (B), hs-CRP (r: −0.286, $P < 0.0001$) (C) and sputum eosinophils % (r: 0.088, $P = 0.264$) (D). ○, SA; △, BE; □, COPD. 6MWD, 6-min walk distance; 6MWT, 6-min walk test; BE, bronchiectasis; FEV_1 (% predicted), percentage predicted of forced expiratory volume in the first second; hs-CRP, high-sensitivity C-reactive protein; SA, severe asthma. hs-CRP and eosinophils % transformed to natural logarithm.

mortality.[36,37] Despite being widely used in COPD and increasingly validated in bronchiectasis,[38] it is not routinely recommended in severe asthma[13] and, thus, assessment of functional exercise capacity in severe asthma is scarce.[39] The reasons for its underuse may relate to fear of provoking exercise-induced bronchoconstriction, or that 'uncontrolled asthma' is listed as one of the guideline contraindications.[18] We did not encounter any adverse events performing the test in our severe asthma population.

FEV_1% predicted was also independently associated with the level of PA in the OAD group. Considering that the degree of AFL categorizes disease severity, and that increased severity has been associated with lower activity levels,[12,33,40] these results are somewhat expected. Interestingly, though, in the full model, AFL was a stronger predictor of steps/day than dyspnoea, despite the latter being one of the most disabling symptoms in diseases such as COPD and severe asthma.

Activity-related dyspnoea was common in our OAD population. We found that higher dyspnoea scores (≥2) modestly explained the adjusted variance in PA in the individual model, but it did not remain significant in the full model. It could be that breathlessness alone is not enough to explain the PA impairment found in these diseases, and that the evaluation of symptoms in different domains could give a more accurate picture. This is in line with recommendations made in COPD guidelines.[15]

In our full multivariate model, the inflammatory markers of hs-CRP and sputum eosinophils were not independently associated with PA, despite displaying moderate to weak associations individually. This is probably related to the strong association found with the 6MWD, which by itself accounted for most of the variance in PA. Despite this, systemic inflammation was still significantly associated with steps/day in the OAD group, which is in line with evidence in COPD[7] and in severe asthma.[11]

Exercise capacity was a better predictor of PA than AFL. This may be due to the fact that functional exercise capacity gives an estimate of the person's ability to endure exercise,[9] which is a subset of PA.[41] In COPD, the mechanisms behind exercise limitation are multifactorial, and include the impairment of the ventilatory, cardiovascular, metabolic and locomotor muscle systems.[42] It is likely that these mechanisms also play a role in severe asthma and bronchiectasis, especially in

patients showing a degree of overlap between these conditions.

Lastly, in the general population, PA has been positively associated with the prevention of different chronic diseases.[43,44] Considering the co-morbidity burden found in OAD populations, the promotion of PA may generate benefits beyond respiratory symptoms alone.

Our study has some limitations. Its cross-sectional design does not infer causality of our findings. Additionally, we have not considered important co-morbidities, disease characteristics, sociodemographic and environmental characteristics nor behaviours (i.e. sedentary time) that may impact the engagement of PA or interact with disease outcomes. Lastly, our populations are not demographically nor clinically matched, which limit comparison of our findings. Nevertheless, diagnosis was not a significant interaction in the relationship between the independent variables and steps/day.

Conclusion

PA impairment is a shared behavioural characteristic of patients with COPD, severe asthma and bronchiectasis. Shared clinical characteristics, such as exercise capacity and AFL, explain an important proportion of this impairment in OAD. Both of these traits can be targeted by specific treatments, making PA impairment a 'treatable trait' that requires consideration in the management of these diseases. Treatment studies aimed at improving PA in these populations are needed and our data may inform such interventions.

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Disclosure statement

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Abbreviations: 6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; AFL, airflow limitation; BE, bronchiectasis; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; HMRI, Hunter Medical Research Institute; hs-CRP, high-sensitivity C-reactive protein; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; MVPA, moderate and vigorous PA; OAD, obstructive airway disease; PA, physical activity; SA, severe asthma.

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Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Appendix S1. Inclusion and exclusion criteria.
Appendix S2. Associations between the levels of physical activity and exacerbations.
Figure S1. Forest plots of associations of clinical and biological outcomes with steps/day by disease.
Table S1. Adjusted simple linear regression models testing interaction effects between diagnosis and each independent variables on steps/day.
Table S2. Associations between physical activity and exacerbations.
Table S3. Clinical and biological characteristics associated with moderate and vigorous physical activity in the OAD group.
Visual Abstract Impaired physical activity and associated shared disease characteristics in severe asthma, bronchiectasis and COPD.

APPENDIX VIII: Chapter 4 - Editorial

Official Journal of the Asian Pacific Society of Respirology
Respirology

EDITORIAL

Is there a common pattern in physical activity levels comparing diverse chronic airway diseases?

Key words: accelerometry, motor activity, obstructive lung disease.

In recent years, physical activity (PA) has been recognized as a key component of prognosis and progression in patients with chronic obstructive pulmonary disease (COPD). Studies on determinants and outcomes of PA in this context have increased. Indeed, there is compelling evidence of the positive effects of PA on mortality and exacerbations in these patients,[1] and there is also evidence on clinical, functional and social determinants to keep patients physically active.[1–3] Information on the impact of PA is still scarce in other chronic airway diseases such as asthma or bronchiectasis. Are the levels, patterns and characteristics of PA similar in these respiratory chronic conditions compared to those in COPD? Increasing PA is considered a desirable outcome in the context of a comprehensive pulmonary rehabilitation programme.[4]

In a recent publication in *Respirology*, Cordova-Rivera *et al.*[5] compared the levels of PA among 189 participants with severe asthma, bronchiectasis or moderate to severe COPD with those of a control group made up of 63 healthy individuals using a valid accelerometer, the Actigraph WGT3X-BT (Penascola, FL, USA), as an assessment tool. The main findings were that patients with bronchiectasis or severe asthma showed lower levels of PA compared to controls (as it would be expected) but higher levels compared to patients with COPD. There were no differences between asthma and bronchiectasis, which was somewhat unexpected. Why are patients with asthma or bronchiectasis more active than patients with COPD?

Lung function (forced expiratory volume in the first second, FEV_1) and functional capacity measured by the 6-min walking test (6MWT) were independently associated with both steps/day and moderate to vigorous PA regardless of the diagnosis of COPD, severe asthma or bronchiectasis. Although prospective data have shown less lung function decline in active patients with severe asthma or COPD compared with inactive patients,[6,7] some other longitudinal data indicate a reduction in PA, while exercise capacity remains unchanged.[8] In view of these findings, are the clinical and research communities ready to foster a therapeutic role for PA in chronic airway diseases?

This is the first study[5] to highlight the similarities and differences among these three chronic airways diseases with the potential aim of developing interventions to improve PA. However, as PA is defined as a behaviour, efforts for improving and modifying PA should not focus on clinical, functional and biological determinants alone. Evidence and information about barriers and facilitators of PA in COPD are increasing. Primary care patients with COPD report that PA is limited by emotions, such as frustration and disappointment, more than by the severity of their underlying airflow obstruction. Hence, PA could be enabled by the belief that PA is beneficial at an individual level.[9]

There are some socio-familiar determinants, such as dog walking, grandparenting and the presence of a physically active loved one, that can facilitate patients with COPD to be physically active.[2,3] Hence, it could be said that interventions on PA should be integrated under the recent concept of 'interpersonal medicine', which includes a healthcare service focus on patients' circumstances, capabilities and preferences.[10] PA is a behaviour; hence, it is the patients' decision to be active or not and to spend time being sedentary or not (independent of the FEV_1 and 6MWT values). Interpersonal medicine involves the social environment of the patient (community, family, work, home, clinics, etc.) and all the members that constitute those 'ecosystems' (patients, families, clinicians, etc.).

Going further, the design of new studies assessing PA should be based on ecological models that include all the contributors to activity decisions, such as health and disease beliefs; symptoms; emotional characteristics; and social, cultural and environmental factors.[4,11] We should encourage interaction with pets, grandchildren, active loved ones or any element that influence and promote PA in our patients. This will enable clinicians, researchers, health providers, policymakers and patients to develop meaningful relationships and interventions for achieving patients' empowerment and adherence to long-term health-promoting behaviours.[4,10]

The main characteristics that limit PA in patients with chronic airways diseases are (again) clinical and functional variables such as the severity of airflow limitation, lower functional capacity and higher dyspnoea. However, it is important to point out that the results of this study allow further analysis of all PA determinants in other obstructive lung diseases aside from COPD. This knowledge on correlates and determinants in PA in chronic respiratory patients could guide a more personalized strategy to change health-related behaviour.

Elena Gimeno-Santos, PT, Psych, PhD
Respiratory Clinic Institute, Hospital Clinic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

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APPENDIX IX: Case Record File for severe asthma participants

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE_____/_____/_____	VISIT_____

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA
VISIT 1 PART A

VISIT 1 CHECKLIST	Sign Initials
Date of Visit 1 Part A _____/_____/_____	
Demographics	
Inclusion/Exclusion	
Patient Experience	
Patient related problems	
Clinical Data	
Other Medications	
Systemic Inflammation (blood collected)	
Adherence	
Exacerbation History	
Mucus Hyper-secretion	
Dyspnoea	
Inhaler technique	
Nutrition	
Sleep	
Smoking (ExCO collected)	
Exercise tolerance (6MWT)	
Sputum Induction	
Monitored	

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

SUBJECT DEMOGRAPHICS

SUBJECT ID: _____ MRN:_____

Surname: _____ First Name:_____

Middle Name: _____

Contact Details:

Street Address:_____

Suburb:_____ Post Code:_____

Phone Home:_____ Work:_____

Mobile:_____ Email:_____

Sex: Male ☐ Female ☐

Date of Birth: __ __/__ __/__ __ __ __

GP Name and
Address:_____

_____

_____

☞**REMOVE THIS SHEET FROM CRF**

_____

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE_____/_____/_____	VISIT_____

SUBJECT DEMOGRAPHICS --- VISIT 1

SUBJECT ID:_____ SUBJECT INITIALS: _____

** See Subject demographics file for contact details.

Sex: Male ☐ Female ☐

Date of Birth: __ __ /__ __/__ __ __ __

Age of asthma onset :

Measure height twice. Ask the subject to take a deep breath in while performing the measurement so they get to their full height. Both measures must be within 0.5cm of each other, if not repeat a third time. Then record the average of the 2 measures; this is the measure you will report

Height (without shoes): ☐☐☐.☐ cm

Height (without shoes): ☐☐☐.☐ cm

Average: ☐☐☐.☐ cm

Weight (without shoes): kg

BMI ☐☐.☐☐ kg/m2

	Litres	% predicted
Post BD FEV1		
Post BD FVC		
Post FER		

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

INCLUSION CRITERIA *Subjects must fulfil **ALL** of the following to be included in the study.*	**YES**	**NO**	**EXCLUSION CRITERIA** *Subjects with **any** of the following will **not** be included in the study.*	**YES**	**NO**
Able to provide informed written consent (file signed consent)	☐	☐	Inability to attend study visits	☐	☐
Previous Severe Asthma Diagnosis AND previous evidence of (below)	☐	☐	Current lung cancer or other blood, lymphatic or solid organ malignancy	☐	☐
BD response ≥12% OR Airway Hyper-responsiveness OR Peak Flow diary (diurnal variation≥15% or >50ml) **AND**	☐	☐	Expected prognosis poor <3 months survival	☐	☐
High Dose ICS ≥ 1000mcg AND LABA OR Maintenance Prednisone **AND**	☐	☐	Current Treatment with Omalizumab (xolair), Macrolides or statins. QTc >440s (discuss with investigator)	☐ ☐	☐ ☐
FEV_1 Post B_2: <80% Pred OR **FEV_1/FVC**<70% **OR** Asthma Control Questionnaire ≥1.5 OR Severe Exacerbation within prev 12 months with OCS use	☐	☐	Postpone if: Exacerbation in the last 4 weeks including any of the following: • Hospital admission • Emergency attendance • Commenced OCS or increased maintenance dose for acute symptoms (postpone visit for 4 weeks). • Antibiotics for chest infection	☐	☐

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE_____/_____/_____	VISIT_____

SHORT ASSESSMENT OF PATIENT SATISFACTION (SAPS) WITH INSTRUCTIONS

Instructions: After reading each question, circle the answer that best describes your situation. We know that sometimes answers may not describe you exactly, so please pick the answer that *most closely describes you.*

When you have finished, please check that you have answered all questions.

Q1. How happy are you with the effect of your treatment?
- Very happy....0
- Happy....1
- Neither happy nor unhappy....2
- Unhappy....3
- Very unhappy....4

Q2. How satisfied are you with the explanations the {doctor/other health professional} has given you about the results of your treatment?
- Very dissatisfied....0
- Dissatisfied....1
- Neither satisfied nor dissatisfied....2
- Satisfied....3
- Very satisfied....4

Q3. The {doctor/other health professional} was very careful to check everything when examining you.
- Strongly agree....0
- Agree....1
- Not sure....2
- Disagree....3
- Strongly disagree....4

Q4. How satisfied were you with the choices you had in decisions affecting your health care?
- Very dissatisfied....0
- Dissatisfied....1
- Neither satisfied nor dissatisfied....2
- Satisfied....3
- Very satisfied....4

Q5. How much of the time did you feel respected by the {doctor/other health professional}?
- All of the time....0
- Most of the time....1
- About half the time....2
- Some of the time....3
- None of the time....4

Q6. The time you had with the {doctor/other health professional} was not long enough.
- Strongly agree....0
- Agree....1
- Not sure....2
- Disagree....3
- Strongly disagree....4

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE_____/_____/_____	VISIT_____

Q7. Are you happy with the care you received in the {hospital/clinic}?

Very happy.....0
Happy.....1
Neither happy nor unhappy.....2
Unhappy.....3
Very unhappy.....4

Total

Scoring the SAPS:
1. Reverse the scores for #1, #3, #5, #7
2. Sum all scores. The score range is from 0 (extremely dissatisfied) to 28 (extremely satisfied)

PATIENT RELATED PROBLEMS

What is/are the biggest problem/s you experience as a result of your breathing problem?

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE _____/_____/_____	VISIT_____

MEDICAL HISTORY/COMORBIDITIES

Area (Provide diagnosis) Eg. IHD, hypertension, COPD	Y/N	Is the condition current?	Is the patient being treated for this condition?
Ear, nose and throat			
Eye			
Respiratory			
Cardiovascular			
Gastrointestinal			
Hepatobiliary / Pancreas			
Genitourinary (urinary both sexes and male reproductive)			
Reproduction (female)			
Cerebrovascular			
Blood and Lymphatic			
Endocrine and Metabolic			
Musculoskeletal			
Skin			
Psychiatric			
Cognitive			
Malignancy			
Other information			

CHARLESON

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

Clinical Data: Respiratory Medications

Please circle: Drug Name	Dose	Number of puffs	Frequency
Short acting β_2-agonist: Ventolin, Asmol, Airomir, Terbutaline			
Long acting β_2-agonists: Serevent, Foradile, Oxis, Onbrez			
Leukotriene modifier: Singulair			
Short acting anti-cholinergic: Atrovent			
Long acting anti-cholinergic: Spiriva, Seebri, Bretaris			
Nasal Steroids: Name			
Theophylline: Austyn, Neulin, Theo-Dur			
Oral Steroids Prednisone, Panafcort, Solone			
Inhaled Corticosteroids: Qvar, Pulmicort, Flixotide, Alvesco			
COMBINATIONS Seretide/Symbicort			
Oxygen			
Mucolytics			
How many days in the last week did you use your reliever medication? How many times on those days did you use your reliever?		/7 _____	
Other respiratory medications *(Drug, strength, dose, frequency, CPAP)*		Yes/No	
ALLERGIES – LIST		Yes/No	

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

Previous Treatment Trials

DRUG NAME (eg singulair/montelukast), omalizumab (xolaire), methotrexate/Rheumatrex/ Trexall, oral gold/auranofin/ Ridaura, theophylline/verapamil/ Calan, Verelan/ Verelan PM/ Isoptin/ Isoptin SR/ Covera HS OR macrolides/Biaxin, Clarithromycin, Ery-Tab, and Erythromycin.)	DATE COMMENCED AND CEASED	RESPONSE

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE_____/_____/_____	VISIT_____

OTHER MEDICATIONS

Drug	Route	Total Daily Dose (units)	Indication	Started Post Visit 1?	
				Yes	No

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

Infection

Sputum collected for bacteriology (initial) _____Time of collection: _____

Blood & Sputum Biomarkers

Blood collected for: FBC, CRP, RNA, serum, plasma.

(initial)_____Time of collection: _____

Tube required:

2 x 4mL EDTA blood (purple top)

1 x 9ml EDTA (purple top)

1 x 4ml Lithium heparin (green)

1 x 6ml serum (red)

Adherence

Medication use over the last three months

Please circle the answer:

In the last three month;

Have you at times been careless about using your inhaler? **Y/N**
Comment – ie .Describe how many missed doses in the last week

Have you ever forgotten to use your inhaler? **Y/N**
Comment

Have you ever stopped using your inhaler because you felt better? **Y/N**
Comment

Have you ever stopped using your inhaler because you felt worse? **Y/N**
Comment

Have you ever used your inhaler less than the doctor prescribed because you felt better? **Y/N**
Comment

Have you ever used your inhaler more than the doctor prescribed because you felt you were having an attack? **Y/N**
Comment

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

EXACERBATION QUESTIONNAIRE ***Questions relate to the last 12 months (visit 1A) or since last visit for follow up visits and relate to asthma only*** ***Retrospective exacerbation - complete as many details as possible***							
Severe Exacerbation					**Type**	**Y/N**	If Yes, details Date/ Name/ Dose/ Duration
Oral Steroids Prescribed tablets suspension injection	No 0		Yes 1		Hospitalization		
					ED visit		
					GP prescription		
Increase from a stable maintenance dose, for at least 3 day	No 0		Yes 1		**Details**		
Total number of severe exacerbations					# courses self administered via WAP		
Antibiotics (type, dose, courses)	**Details**						
Moderate Exacerbation							
Worsening of asthma symptoms ≥ *2 days* ?	No 0		Yes 1		If Yes, details		
Initiated your WAP?	No 0		Yes 1		If Yes, details		
Increase rescue bronchodilator (Ventolin, Asmol, Bricanyl) ≥ *2 days*	No 0		Yes 1		If Yes, details		
OR any inhale medication ≥ *2 days* ?							
Comments	e.g. trigger/exacerbation duration						

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE _____/_____/_____	VISIT_____

DYSPNOEA

Modified Medical Research Council Dyspnoea Scale

"We would like to assess your level of breathlessness"

Grade/Circle

0 "I only get breathless with strenuous exercise"

1 "I get short of breath when hurrying on the level or walking up a slight hill"

2 "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level"

3 "I stop for breath after walking about 100 yards or after a few minutes on the level"

4 "I am too breathless to leave the house" or "I am breathless when dressing"

Note to researcher: This is the modified MRC scale that uses the same descriptors as the original MRC scale in which the descriptors are numbered 1-5. The modified MRC scale (0-4) is used for calculation of BODE index.

EXACERBATION MANAGEMENT

Have you been prescribed a written action plan? Yes / No

Do you use your WAP? Yes / No

If not why not?_____

How many times have you used you WAP in the last 6 months_____

Note to researcher: Please ask for a copy of the WAP. If the participant has undergone an education programme within the last 12 months please also ask for a copy of their action plan prior to enrolment in the education programme.

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE _____/_____/_____	VISIT_____

Mucous Hypersecretion

1. When you don't have a cold, do you usually bring up phlegm from your chest OR have phlegm on your chest that is difficult to bring up? **Yes / No**

If ***Yes:***,1A. How many days in the past week have you coughed up sputum/phlegm? */7*

2A. Are there months in which you have this phlegm on most days? **Yes / No**

NB: "this phlegm" refers to phlegm that is brought up AND/OR phlegm that is stuck in the chest.

If Yes, ask both Questions 2B & 2C; If No, skip to Dyspnea]

2B. Do you bring up this phlegm on most days for as much as three months each year? **Yes / No**

2C. For how many years have you had this phlegm? (Circle)

Less than 2 years **2-5 years** **More than 5 years**

3. Have you produced sputum/phlegm for more than 3 consecutive months over the past 2 years? **Yes / No**

(**Note to researcher**: To Clarify - 'Have you produced sputum for 3 consecutive months for 2 consecutive years?')

4. How much sputum/phlegm do you cough up in the course of a day?

< Teaspoon Teaspoon 1 tblspoon 2 tblspoons ½ cup 1 cup

5. What part in the day do you cough up the most sputum/phlegm?

6. What colour is your sputum/phlegm at the most productive time?

clear / white / yellow / green / blood stained

7. What colour is your sputum/phlegm for the rest of the time?
clear / white / yellow / green / blood stained

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

Inhaler Technique

Please assess inhaler technique today.

Please use placebo devices. Each box must be entered using the following choices;

I = inadequate A = adequate O = optimal NU – Not Used

pMDI	☐	Accuhaler	☐	Handihaler	☐
Spacer	☐	Autohaler	☐	Nebuliser	☐
Turbuhaler	☐	Aerolizer	☐	Other device (specify)	☐

Number of devices used (peak flow *not* included) ☐

Note to researcher: refer to AMS inhaler device assessment sheet

Menstruation Effect on Asthma (Females only)

Does your asthma worsen prior to commencement of your period?

_____

Are you still having menstrual cycles?

_____

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE_____/_____/_____	VISIT_____

Laryngeal Dysfunction Questionnaire

1. Where do you feel the tightness?

   Neck ☐ jugular notch ☐ upper chest ☐ lower chest ☐ N/A ☐

2. Is it harder to breathe in than out? Y/N
(if answers to Q1 and Q2 are N/A and No then move onto Q7).

3. How quickly do your symptoms come on?
   (ie, tightness, breathing difficulty)
   Seconds
   < 3 minutes
   > 3 minutes

4. When the attack stops, (including after treatment), how quickly do your symptoms go away?
   Seconds
   < 5 minutes
   > 5 minutes

5. What triggers your symptoms? (eg: exercise, heart burn, pnd, pollution, cold air, talking)

---

6. Do asthma medications give you relief?
   No
   Yes (if Y within how many minutes?) _____ minutes
   N/A

7. Does your voice get hoarse or do you lose your voice? Y/N

8. Do you feel a lump in your throat? Y/N

9. Do you feel like you are choking or suffocating? Y/N

10. Do you have pins and needles around the lips or the fingertips? Y/N

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

Newcastle Laryngeal Hypersensitivity Questionnaire

1. There is an abnormal sensation in my throat. (O)

(circle one)

All of the time.....1
Most of the time.....2
A good bit of the time..... 3
Some of the time.....4
A little of the time.....5
Hardly any of the time.....6
None of the time..... 7

2. I feel phlegm and mucous in my throat (TT)

(circle one)

All of the time.....1
Most of the time.....2
A good bit of the time..... 3
Some of the time.....4
A little of the time.....5
Hardly any of the time.....6
None of the time..... 7

3. I have pain in my throat (P/Th)

(circle one)

All of the time.....1
Most of the time.....2
A good bit of the time..... 3
Some of the time.....4
A little of the time.....5
Hardly any of the time.....6
None of the time..... 7

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE_____/_____/_____	VISIT_____

4. I have a sensation of something stuck in my throat (O)

(circle one)

All of the time.....1
Most of the time.....2
A good bit of the time..... 3
Some of the time.....4
A little of the time.....5
Hardly any of the time.....6
None of the time..... 7

5. My throat is blocked. (O)

(circle one)

All of the time.....1
Most of the time.....2
A good bit of the time..... 3
Some of the time.....4
A little of the time.....5
Hardly any of the time.....6
None of the time..... 7

6. My throat feels tight. (O)

(circle one)

All of the time.....1
Most of the time.....2
A good bit of the time..... 3
Some of the time.....4
A little of the time.....5
Hardly any of the time.....6
None of the time..... 7

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

7. There is an irritation in my throat. (O)

(circle one)

All of the time.....1
Most of the time.....2
A good bit of the time..... 3
Some of the time.....4
A little of the time.....5
Hardly any of the time.....6
None of the time..... 7

8. I have a sensation of something pushing on my chest. (P/Th)

(circle one)

All of the time.....1
Most of the time.....2
A good bit of the time..... 3
Some of the time.....4
A little of the time.....5
Hardly any of the time.....6
None of the time..... 7

9. I have a sensation of something pressing on my throat (O)

(circle one)

All of the time.....1
Most of the time.....2
A good bit of the time..... 3
Some of the time.....4
A little of the time.....5
Hardly any of the time.....6
None of the time..... 7

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE_____/_____/_____	VISIT_____

10. There is a feeling of constriction as though needing to inhale a large amount of air. (O)

(circle one)

All of the time.....1
Most of the time.....2
A good bit of the time..... 3
Some of the time.....4
A little of the time.....5
Hardly any of the time.....6
None of the time..... 7

11. Food catches when I eat or drink. (O)

(circle one)

All of the time.....1
Most of the time.....2
A good bit of the time..... 3
Some of the time.....4
A little of the time.....5
Hardly any of the time.....6
None of the time..... 7

12. There is a tickle in my throat. (TT)

(circle one)

All of the time.....1
Most of the time.....2
A good bit of the time..... 3
Some of the time.....4
A little of the time.....5
Hardly any of the time.....6
None of the time..... 7

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

13. There is an itch in my throat. (TT)

(circle one)

All of the time.....1
Most of the time.....2
A good bit of the time..... 3
Some of the time.....4
A little of the time.....5
Hardly any of the time.....6
None of the time..... 7

14. I have a hot or burning sensation in my throat (P/Th)

(circle one)

All of the time.....1
Most of the time.....2
A good bit of the time..... 3
Some of the time.....4
A little of the time.....5
Hardly any of the time.....6
None of the time..... 7

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE_____/_____/_____	VISIT_____

NUTRITION

Weight_____kg

Height_____cm

BMI = weight (kg) ÷ height² (m) BMI = _____

- **BMI>27 OR waist circumference >94cm (males) or >80cm (females):** Overweight/Obese (refer to Dietitian)
- **BMI 20-25 AND 25-27 if waist circumference <94cm (males) and <80cm (females):** Acceptable weight range- refer to Dietitian if in intervention group
- **BMI <20** Malnourished or at risk of malnutrition (refer to Dietitian)

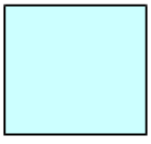
Malnutrition Universal Screening Tool

1. Have you/the patient lost weight recently without trying?

No	0
Unsure	2
Yes, How much (kg)?	
1-5	1
6-10	2
11-15	3
>15	4
Unsure	2

2. Have you /the patient been eating poorly because of a decreased appetite?

No	0
Yes	1

Malnutrition Universal Screening Tool - Total Score 

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE _____/_____/_____	VISIT_____

Epworth Sleepiness Scale

How likely are you to dose off or fall asleep in the following situations, in contrast to feeling tired? Using the following scale circle a number to score each of the questions with regard to the last week.

0 **Never doze** **1** **Slight chance of dozing** **2** **Moderate chance of dozing** **3** **High chance of dozing**

How likely are you to doze off or fall asleep **(please circle your answer)**

1.	While sitting and reading?	**0**	**1**	**2**	**3**
2.	While watching TV?	**0**	**1**	**2**	**3**
3.	While sitting inactive in a public place (eg theatre, meeting)?	**0**	**1**	**2**	**3**
4.	While a passenger in a car for an hour without a break?	**0**	**1**	**2**	**3**
5.	While lying down to rest in the afternoon when circumstances permit?	**0**	**1**	**2**	**3**
6.	While sitting and talking to someone?	**0**	**1**	**2**	**3**
7.	While sitting quietly after lunch without alcohol?	**0**	**1**	**2**	**3**
8.	While in a car stopped for a few minutes in traffic?	**0**	**1**	**2**	**3**

Total Score

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

Smoking Module

Do you currently smoke? Yes / No

If yes, time since last cigarette _____(hours)

Have you ever smoked? Yes / No

If yes, how old were you when you began smoking?_____(years)

If yes, how old were you when you gave up smoking? _____(years)

How many cigarettes per day did/do you smoke? _____

Pack years = (Number of cigarettes/20) x years smoked =

Calculation assumes 1 pack has 20 cigarettes. 1 pack year = 20 cigarettes per day for one year

Exhaled carbon monoxide level _____**ppm (Pico meter)**

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

Exercise Tolerance

Predicted HRmax (220-age):_____

Bronchodilator pre treatment Salbutamol 400mcg given? Yes/No Time given: _____

Date _____ Time_____

Bronchodilator time since last dose_____

BP	RR	Supplemental Oxygen?	Gait Aid?

Time (min)	SpO_2	HR	Dyspnoea (BORG)	Rests
Rest				
1				
2				
3				
4				
5				
6				
Recovery 1				**Total rests**
2				

Post RR **(at 6 minutes)**_____

Limiting factor to the test: Low SpO_2 ☐ Leg fatigue ☐ Other: _____

40	200	360	520
80	240	400	560
120	280	440	600
160	320	480	+/-
TOTAL WALK DISTANCE			**METRES**

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE_____/_____/_____	VISIT_____

BRONCHODILATOR REVERSIBILITY AND SPUTUM INDUCTION

Please refer to sputum induction flowchart for safety guidelines. If FEV1 < 40% call physician.
Pre medicate all IPBM participants with ventolin (400mcg).

Asthma medication and time last taken	1. 2. 3.
Has the patient rinsed their mouth? (initial)	
Nebuliser make	Spirometer make
Predicted FEV_1	Predicted FVC
Post B_2 FEV_1 % predicted Post B_2 FEV_1 / Predicted FEV_1 x 100 _____ / _____ = _____%	Post B_2 FEV_1/FVC (actual) Post B_2 FEV_1/Post B_2 FVC=% _____ / _____ = _____%
B_2 dose and time	15% fall from Baseline FEV_1 FEV_1: _____ x 0.85 =_____
Agent used (circle) 4.5% saline 0.9% saline	Nebuliser Output Pre weight - Post weight / cumulative time _____ - _____ / _____ =

Saline nebulised time	FEV_1 effort			% fall from baseline FEV_1	Sputum produced (yes or no)	B_2 required? Dose Time paused	Recovery FEV_1 (post B_2)
	1	2	3				
Post B_2					SS		
30 sec					SP		
1 min					SP		
2 min					SP		
4 min					SP		
4 min					SP		
4 min					SP		

Pre B_2 FEV_1 / FVC _____/_____ _____/_____ _____/_____

Baseline (Post B_2) FEV_1 / FVC _____/_____ _____/_____ _____/_____

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE_____/_____/_____	VISIT_____

COMMON COLD QUESTIONNAIRE (COMPLETE ONLY IF THERE IS A SUSPECTED VIRUS)

SUBJECT No:_____Date:_____INITIALS:_____

In the past two days have you experienced any of the following:

	NONE	MILD	MODERATE	SEVERE
A General Symptoms:				
1. Fevers	☐	☐	☐	☐
2. Chills	☐	☐	☐	☐
3. Muscle pains	☐	☐	☐	☐
B. Nasal Symptoms:				
1. Watery eyes	☐	☐	☐	☐
2. Runny nose	☐	☐	☐	☐
3. Sneezing	☐	☐	☐	☐
C. Throat Symptoms:				
1. Sore throat	☐	☐	☐	☐
D. Chest Symptoms:				
1. Cough	☐	☐	☐	☐
2. Chest pain	☐	☐	☐	☐
E. Photophobia:	☐	☐	☐	☐

- A probable viral infection is where there are moderate symptoms noted in at least two of the above four categories or mild symptoms noted in three or more categories.
- A possible viral infection is where mild symptoms are noted in one category plus a cough.

Probable Viral: **Yes** ☐ **No** ☐

Possible Viral: **Yes** ☐ **No** ☐

Infected Controls must have a probable or possible infection
All other subjects must have none of the symptoms listed with the exception of cough ***- IF RETURN A POSITIVE RESPONSE PLEASE RE-BOOK FOR FOUR WEEKS TIME***

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE _____/_____/_____	VISIT_____

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA
VISIT 1 PART B

VISIT 1 CHECKLIST	Sign Initials
Date of Visit 1 Part B_____/_____/_____	
Inclusion/Exclusion criteria	
Anxiety and Depression assessments	
Dysfunctional breathing (Nijmegen)	
SGRQ	
ACQ	
AQLQ	
Allergy Skin Prick Test	
FENO	
Body Composition (DXA)	
Bioelectrical Impedance Analysis (BIA)	
Trunk strength Tests	
Respitrace	
Saline Challenge	
Monitored	

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

Bloods

1x9ml red serum tube for IgE _____ (initial)

ECG

ECG completed (initial)_____

Feno (use Niox)

Sample 1 _____ppb

Sample 2_____ppb

Sample 3_____ppb

Average_____ppb

Ambient eNO_____

Last oral intake_____hours

Last bronchodilator_____hours

HR QOL - SGRQ

Scored on - IPBM Laptop Vanessa's laptop (please circle)

Remind patient to answer the questions relating the answers to the last month, not the last year.

Symptoms	
Activity	
Impacts	
Total	

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE _____/_____/_____	VISIT_____

HOSPITAL ANXIETY AND DEPRESSION SCALE

I feel tense or 'wound up:	**A**	**I feel as if I am slowed down:**	**D**
Most of the time	3	Nearly all the time	3
A lot of the time	2	Very often	2
Time to time, occasionally	1	Sometimes	1
Not at all	0	Not at all	0
I still enjoy the things I used to enjoy:	**D**	**I get a sort of frightened feeling like 'butterflies in the stomach':**	**A**
Definitely as much	0	Not at all	0
Not quite so much	1	Occasionally	1
Only a little	2	Quite often	2
Not at all	3	Very often	3
I get a sort of frightened feeling as if something awful is about to happen:	**A**	**I have lost interest in my appearance:**	**D**
Very definitely and quite badly	3	Definitely	3
Yes, but not too badly	2	I don't take as much care as I should	2
A little, but it doesn't worry me	1	I may not take quite as much care	1
Not at all	0	I take just as much care as ever	0
I can laugh and see the funny side of things:	**D**	**I feel restless as if I have to be on the move:**	**A**
As much as I always could	0	Very much indeed	3
Not quite as much now	1	Quite a lot	2
Definitely not so much now	2	Not very much	1
Not at all	3	Not at all	0
Worrying thoughts go through my mind:	**A**	**I look forward with enjoyment to things:**	**D**
A great deal of the time	3	As much as I ever did	0
A lot of the time	2	Rather less than I used to	1
From time to time but not too often	1	Definitely less than I used to	2
Only occasionally	0	Hardly at all	3
I feel cheerful:	**D**	**I get sudden feelings of panic:**	**A**
Not at all	3	Very often	3
Not often	2	Quite often	2
Sometimes	1	Not very often	1
Most of the time	0	Not at all	0
I can sit at ease and feel relaxed:	**A**	**I can enjoy a good book or radio or TV programme:**	**D**
Definitely	0	Often	0
Usually	1	Sometimes	1
Not often	2	Not often	2
Not at all	3	Very seldom	3

A=
D=
TOTAL =

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE_____/_____/_____	VISIT_____

DYSFUNCTIONAL BREATHING

NIJMEGEN QUESTIONNAIRE ***Patient to complete***

We would like you to think about your breathing symptoms. Please circle the score that best describes the frequency with which you experience the symptoms listed below:

	Never	Seldom	Sometimes	Often	Very Often
Chest pain	0	1	2	3	4
Feeling tense	0	1	2	3	4
Blurred vision	0	1	2	3	4
Dizziness	0	1	2	3	4
Confusion or loss of touch with reality	0	1	2	3	4
Fast or deep breathing	0	1	2	3	4
Shortness of breath	0	1	2	3	4
Tightness across chest	0	1	2	3	4
Bloated sensation in stomach	0	1	2	3	4
Tingling in fingers and hands	0	1	2	3	4
Difficulty in breathing or taking a deep breath	0	1	2	3	4
Stiffness or cramps in fingers and hands	0	1	2	3	4
Tightness around the mouth	0	1	2	3	4
Cold hands or feet	0	1	2	3	4
Palpitations in the chest	0	1	2	3	4
Anxiety	0	1	2	3	4
Total					

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE_____/_____/_____	VISIT_____

ALLERGY HISTORY

Do you or have you had any of the following conditions?

	NEVER	*CURRENT*	*PAST*	**NOTES:**
Persistent cough (>3/12 of last 12)				
Hayfever				
Eczema				
Allergic conjunctivitis				
Nasal polyps				

Breathing Assessment and Respitrace

Does patient have a pacemaker? If yes do not complete respitrace.

Respiratory rate.....

O2 Saturation.....

Contribution of upper chest to tidal volume.....%

Contribution of lower ribcage/abdomen to tidal volume.....%

Nasal or mouth breathing (circle)? Nasal Mouth

Posture (circle) Normal

Head forward

Increased thoracic kyphosis

Reduced lumbar lordosis

Increased lumbar lordosis

Thoracic ROM (circle) Reduced Normal

Accessory muscle use (circle) Yes No

General observations.....

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

ALLERGY SKIN PRICK TEST

Has the participant taken Antihistamines within the past 5 days? **Yes No**
(Hismanal 6 weeks)
*If **yes** provide details do not continue test and reschedule test.*
How long since last antihistamine taken?

_____
_____

ALLERGY SKIN PRICK TEST

Has the participant taken Antihistamines within the past 5 days? ☐ Yes ☐ No
(Hismanal 6 weeks)

*If **yes** provide details do not continue test and reschedule appointment.*
How long since last antihistamine taken?

_____

_____

Start Time:_____

_____Test	Weal Size (mm) x (mm)
CONTROLS	
Positive Control ***(measure at 10 mins)***	X
Negative Control (***measure at 15 mins)***	X
ALLERGENS (*measure at 15 mins)*	
Aspergillus mix	X
Alternata	X
Dust mite (DP)	X
Cockroach mix	X
5 grasses	X

ATOPY positive if (any allergen weal ≥ 3mm) **Yes** ☐ **No** ☐

Performed By:_____

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE _____/_____/_____	VISIT_____

Asthma Control Questionnaire

Date..... .....
Please answer questions 1-6.
Circle the number of the response that best describes how you have been during the past week.

1 On average, during the past week, how often were you woken by your asthma during the night?
0 Never
1 Hardly ever
2 A few minutes
3 Several times
4 Many times
5 A great many times
6 Unable to sleep because of

2. On average, during the past week, how bad were your asthma symptoms when you work up in the morning?
0 No symptoms
1 Very mild symptoms
2 Mild symptoms
3 Moderate symptoms
4 Quite severe symptoms
5 Severe symptoms
6 Very severe symptoms

3 In general, during the past week, how limited were you in your activities because of your asthma?
0 Not limited at all
1 Very slightly limited
2 Slightly limited
3 Moderately limited
4 Very limited
5 Extremely limited
6 Totally limited

4 In general, during the past week, how much shortness of breath did you experience because of your asthma?
0 None
1 Very little
2 A little
3 A moderate amount
4 Quite a lot
5 A great deal
6 A very great deal

5 In general, during the past week, how much of the time did you wheeze?
0 Not at all
1 Hardly any of the time
2 A little of the time
3 A moderate amount of the time
4 A lot of the time
5 Most of the time
6 All the time

6. On average, during the past week, how many puffs of short-acting bronchodilator (eg Ventolin) Have you used each day?
0 None
1 1-2 puffs most days
2 3-4 puffs most days
3 5-8 puffs most days
4 9-12 puffs most days
5 13-16 puffs most days
6 More than 16 puffs most days

To be completed by a member of the clinic staff

7 FEV_1 pre-bronchodilator .....
FEV_1 predicted.....
FEV_1 % predicted.....
(Record actual values on the dotted lines and score the FEV_1 % predicted in the next column)

0 > 95% predicted
1 95-90%
2 89 –80%
3 79-70%
4 69-60%
5 59-50%
6 <50% predicted

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE_____/_____/_____	VISIT_____

Juniper Asthma Quality of Life Questionnaire (AQLQ) (Standardised)

1. Please indicate how much you have been limited by your asthma in strenuous activities (such as hurrying, exercising, running up stairs, sport) during the last 2 weeks. **Green card** ☐

2. Please indicate how much you have been limited by your asthma in moderate activities (such as walking, housework, gardening, shopping, climbing stairs) during the last 2 weeks. **Green card** ☐

3. Please indicate how much you have been limited by your asthma in social activities (such as talking, playing with pets/children, visiting friends/relatives) during the last 2 weeks. **Green card** ☐

4. Please indicate how much you have been limited by your asthma in work related activities (such as tasks that you have to do at work) during the last 2 weeks. **Green card** ☐

5. Please indicate how much you have been limited by your asthma in sleeping during the last 2 we **Green card** ☐

6. How much discomfort or distress have you felt over the last 2 weeks as a result of chest tightness **Red card** ☐

7. In general how often during the last 2 weeks have you felt concerned about having asthma? **Blue card** ☐

8. How often during the last 2 weeks did you feel short of breath as a result of your asthma? **Blue card** ☐

9. How often during the last 2 weeks did you experience asthma symptoms as a result of being exposed to cigarette smoke? **Blue card** ☐

10. How often during the last 2 weeks did you experience a wheeze in your chest? **Blue card** ☐

11. How often during the past 2 weeks did you feel you had to avoid a situation or an environment because of cigarette smoke? **Blue card** ☐

12. How much discomfort or distress have you felt over these 2 past weeks as a result of coughing? **Red card** ☐

13. How often during the past 2 weeks did you feel frustrated as a result of your asthma? **Blue card** ☐

14. How often during the past 2 weeks did you experience a feeling of chest heaviness? **Blue card** ☐

15. How often during the past 2 weeks did you feel concerned about the need to take medications for your asthma? **Blue card** ☐

16. How often during the past 2 weeks did you feel the need to clear your throat? **Blue card** ☐

17. How often during the past 2 weeks did you experience asthma symptoms as a result of being exposed to dust? **Blue card** ☐

Continued on next page.

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE_____/_____/_____	VISIT_____

18. How often during the past 2 weeks did you experience difficulty breathing out as a result your asthma? **Blue card** ☐

19. How often during the past 2 weeks did you feel you had to avoid a situation or an environment because of dust? **Blue card** ☐

20. How often during the past 2 weeks did you wake up in the morning with asthma symptoms? **Blue card** ☐

21. How often during the past 2 weeks did you feel afraid of not having your asthma medication available?
Blue card ☐

22. How often during the past 2 weeks were you bothered by heavy breathing? **Blue card** ☐

23. How often during the past 2 weeks did you experience asthma symptoms as a result of the weather
or air pollution outside? **Blue card** ☐

24. How often during the past 2 weeks have you been woken at night by your asthma? **Blue card** ☐

25. How often during the past 2 weeks have you had to avoid or limit going outside because of the weather or air pollution? **Blue card** ☐

26. How often during the past 2 weeks did you experience asthma symptoms as a result of being exposed to strong smells or perfume? **Blue card** ☐

27. How often during the past 2 weeks did you feel afraid of getting out of breath? **Blue card** ☐

28. How often during the past 2 weeks did you feel you had to avoid a situation or environment because of strong smells or perfume? **Blue card** ☐

29. How often during the past 2 weeks has your asthma interfered with getting a good night sleep? **Blue card** ☐

30. How often during the past 2 weeks have you had the feeling of fighting for air? **Blue card** ☐

31. Think of the overall range of activities that you would have liked to have done during the past 2 weeks.
How much has your range of activities been limited by your asthma? **Yellow card** ☐

32. Overall, among all the activities that you have done during the past 2 weeks,
how limited have you been by your asthma? **Green card** ☐

Thank you for completing this questionnaire.

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE _____/_____/_____	VISIT_____

Dexa pre-test questionnaire

PRIOR TO SCAN

Waist Circumference (cm):

The participant should empty their bladder, remove all jewellery, hairpins, glasses, underwire bras and put on a gown

Previous Bone Density or Body Composition Scan:		**Yes**		**No**	
When:			Result:		
Previous Medical History:					
Fractures:		**Yes**		**No**	
Details/Cause:					
Previous lumber spine x-ray?		**Yes**		**No**	
Date:			Result:		
Kidney disease:	**Yes**	**No**	Liver Disease:	**Yes**	**No**
Overactive Thyroid	**Yes**	**No**	Arthritis	**Yes**	**No**
Parathyroid disease	**Yes**	**No**	Malabsorption (Coeliac Disease)	**Yes**	**No**
Other Medical Illness or Major operation?		**Yes**		**No**	
Have you had an X-ray or CT scan with contrast material such as barium in the last 7 days?		**Yes**		**No**	
(If 'Yes' delay DEXA scan for at least 72hrs, see DEXA SOP Appendix 2 for minimum delay times)					
Have you had any nuclear medicine scans in the past 3 days?		**Yes**		**No**	
(If 'Yes' delay DEXA scan for at least 48hrs, see DEXA SOP Appendix 2 for minimum delay times)					
Have you ever fractured your hip, had a hip replacement, or do you have a pin in your hip?		**Yes – Both / Right / Left**		No	
(If bilateral hip replacement, pins or screws present do not perform femur measurement, if unilateral hip metal surgical implant present scan other hip)					
Do you have any lumbar spine implants, pins or have		**Yes**		**No**	

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE_____/_____/_____	VISIT_____

pins, a pacemaker or defibrillator?		
If 'Yes' List:		
(DEXA is safe for permanent pacemakers or implantable defibrillators)		
Have you been on oral steroid treatment?	**Yes**	**No**
What treatment:	Dose:	Duration:
Are you on treatment for Osteoporosis?	**Yes**	**No**
What treatment:	Year commenced:	
Do you take Calcium Supplements?	**Yes**	**No**
(If yes, have they taken any in the last 24hrs, if yes delay scan for 24hrs)		
Menopausal?	**Yes**	**No**
Age of menopause:	LMP:	
Are you or could you be pregnant?	**Yes**	**No**
(If 'Yes', do not scan, subject not eligible)		

BIA

Has participant exercised / or showered in the past 2 hours?_____ If yes, postpone for at least 2 hours
Has participant eaten in the last 2 hours?_____ If yes, postpone for at least 2 hours
Has participant emptied bladder prior to test?_____ If no, perform now
Has participant wiped hands and feet with wipes?_____If no, perform now
Does participant have a pacemaker or other implanted electrical or metal devices?
_____Do not perform test.
Remind participant to remove all jewellery, extra clothing, stockings and empty pockets.

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

DEXA – TOTAL BODY SCAN

BMI (kg/m²): _____

Classification: _____

Total Tissue % Fat: _____

Trunk Tissue % Fat: _____

Android Tissue % Fat: _____

Gynoid Tissue % Fat: _____

Total Tissue (g): _____

Total Fat (g): _____

Total Lean (g): _____

Total BMC (g): _____

Fat Free (g): _____

Fat Free Mass Index :

$$\frac{\text{total body lean soft tissue + bone mineral content in Kg}}{\text{Height (m)}^2} = \square$$

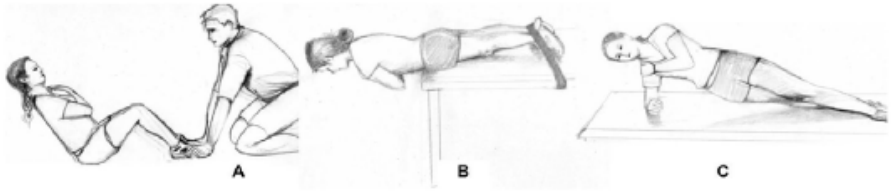
Appendicular Skeletal Muscle Mass Index :

$$\frac{\text{lean soft tissue both arms+ lean soft tissue both legs in Kg}}{\text{Height (m)}^2} = \square$$

Sarcopenia (Men: ≤7.26Kg/m^2) (Women: ≤5.45Kg/m^2) **Yes** ☐ **No** ☐

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

Core Strength Tests



A) **Flexion endurance test:** Patient is positioned as if commencing a sit up. Patient is instructed to raise upper body off plinth but to keep spine in neutral position. Patient is instructed to hold up as long as possible. Maximal endurance is timed, recorded and compared to normative data.

Time held:.....

B) **Sorgenson test:** Patient prone with trunk off the edge of the plinth. Patient instructed to lift trunk so that the body is level with the plinth and legs and hold the position in neutral for as long as possible. Maximal endurance is timed, recorded and compared to normative data.

Time Held:.....

C) **Side bridge endurance test:** Patient is positioned in the side bridge position and is instructed to raise hips off plinth and hold as long as possible. Maximal endurance is timed, recorded and compared to normative data.

Time Held:.....

Dynamometry (Shoulder) **Push _____** **Dynamometry (Leg)**

Attempt 1_____

Pull_____

Attempt 2_____

Termination criteria and Contraindications for trunk endurance tests

- Subject no longer able to sustain position
- Subject unable to assume position on practice trial
- Subject terminates the test
- Subject reports pain- staff are to terminate the test immediately and document the time held until pain commenced.
- Subject refuses to attempt test
- Signs of poor perfusion
- Heart rate exceeds pre defined HR maximum (220-age)
- Onset of angina or angina symptoms
- SpO2<88% at rest
- Test will not be performed if there are any contraindications to exercise. This will be screened prior to walk test. Contraindications include HR>125 bpm at rest, SpO2<88% prior to test, physical disability preventing safe performance, acute/unstable angina, RR excessive or BORG >4 at rest.

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE_____/_____/_____	VISIT_____

The 3 Incontinence Questions (3IQ) Assessment Tool

The 3IQ is a patient questionnaire that helps your doctor distinguish urgency incontinence from stress incontinence. It should take no more than a couple of minutes. Complete the quiz and bring it to your next appointment.

1. During the last 3 months, have you leaked urine (even a small amount)?

☐ Yes ☐ No (if this response is marked, the 3IQ test is complete)

2. During the last 3 months, did you leak urine (check all that apply):

☐ When you were performing some physical activity, such as coughing, sneezing, lifting, or exercising?

☐ When you had the urge or the feeling that you needed to empty your bladder, but you could not get to the toilet fast enough?

☐ Without physical activity and without sense of urgency?

3. During the last 3 months, did you leak urine most often (check only one):

☐ When you were performing some physical activity, such as coughing, sneezing, lifting, or exercising?

☐ When you had the urge or the feeling that you needed to empty your bladder, but you could not get to the toilet fast enough?

☐ Without physical activity and without a sense of urgency?

☐ About equally as often with physical activity as with a sense of urgency?

Definitions of type of urinary incontinence are based on responses to question 3.

Response to Question 3	Type of Incontinence
Most often with physical activity	Stress only or stress predominant
Most often with the urge to empty the bladder	Urgency only or urgency predominant
Without physical activity or sense of urgency	Other cause only or other cause predominant
About equally with physical activity and sense of urgency	Mixed

PHENOTYPE BASED MANAGEMENT OF SEVERE PERSISTENT ASTHMA THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE_____/_____/_____	VISIT_____

SALINE CHALLENGE (IF V1 post bronchodilator FEV_1>.5L Date: _____

Asthma medication and time last taken		1. 2. 3.
Has the patient rinsed their mouth? (initial)		
Nebuliser make		Spirometer make
Predicted FEV_1	Predicted FVC	15% fall from FEV_1
Agent used (circle) 4.5% saline 0.9% saline		Pre weight – Post weight = Provocation dose
		<u>If 15% Drop:</u> Provocation Dose/Total Time = Saline dose/min. Saline dose/min x Saline neb time (pre-drop) = drop dose

Saline nebulised time	FEV_1 1	2	3	% fall from baseline FEV_1	Sputum produced (yes or no)	B_2 required? Dose Time paused	Recovery FEV_1 (post B_2)
Baseline (Pre B_2)					SS		
30 sec					SS		
1 min					SP		
2 min					SP		
4 min					SP		
4 min					SP		
4 min					SP		

Time	FEV_1	% fall from baseline
5 mins		
10 mins		
15 mins		
30 mins		

Monitor Recovery (All patients)
400 mcg Ventolin given: (time)_____

COMMON COLD QUESTIONNAIRE (<u>COMPLETE ONLY IF THERE IS A</u>

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (August 2002)

SHORT LAST 7 DAYS SELF-ADMINISTERED FORMAT

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health–related physical activity.

Background on IPAQ
The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Using IPAQ
Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation
Translation from English is supported to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

Further Developments of IPAQ
International collaboration on IPAQ is on-going and an ***International Physical Activity Prevalence Study*** is in progress. For further information see the IPAQ website.

More Information
More detailed information on the IPAQ process and the research methods used in the development of IPAQ instruments is available at www.ipaq.ki.se and Booth, M.L. (2000). *Assessment of Physical Activity: An International Perspective*. Research Quarterly for Exercise and Sport, 71 (2): s114-20. Other scientific publications and presentations on the use of IPAQ are summarized on the website.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities → ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   _____ **hours per day**

   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

   _____ **days per week**

   ☐ No moderate physical activities → ***Skip to question 5***

SHORT LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised August 2002.

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐ No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

This is the end of the questionnaire, thank you for participating.

SHORT LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised August 2002.

Supplemental Digital Content 1

Past-day Adults' Sedentary Time (PAST) Questionnaire

Section 2 Sedentary Time

Next I will ask you about particular activities you did yesterday while sitting down or lying down. Please note that this does not include sleeping, either in bed or if you fell asleep while doing another activity, for example watching television.

Interviewer: Record yesterday's date

Yesterday's date: _____

We are going to ask you about different times when you may be sitting or lying down: when working, travelling, watching TV, using the computer, and when doing other activities. For each of these, only count the time when this was your main activity. For example, if you watched TV and ate dinner at the same time, this might be TV or meal time, but not both. Your answers can be given in hours and minutes. Try to report only the time you spent sitting or lying down and not time you spent getting up for breaks (e.g. coffee, bathroom).

ST 1. The next question is about sitting for work. Did you work in a paid position yesterday?

☐ Yes
☐ No

Interviewer: if participant did not work yesterday, skip to ST 4. If they did work yesterday continue to ST 2.

Time spent for work

ST 2. How long **in total** did you spend at your workplace or working from home yesterday, including meal and snack breaks?

☐☐ hours ☐☐ minutes

Sitting for work

ST 3. **How long** were you **sitting** at your workplace or working from home yesterday, including during meal and snack breaks?

		hours			minutes

Interviewer: if the respondent has difficulty, you can reassure them that their best estimate will be OK.

***Interviewer Check: the time for ST3 cannot be longer than ST2. If ST3 is exactly the same as ST2 (they say they sat for the whole time at work) prompt 'So, can I confirm that you sat for the whole time at work without getting up?'*

Sitting for Transport

ST 4. Thinking again of yesterday, please estimate the **total** time that you spent **sitting** to travel from one place to another. Please include sitting and waiting for transport. Do **not** include any time you were standing up while travelling or waiting.

		hours			minutes

Interviewer clarification: transport includes public and private, waiting for any type of transport and travel to all locations. This would not include time spent travelling as part of work which was reported in ST3 e.g. taxi driver

Television Viewing

ST 5. Please estimate the **total time** you spent sitting or lying down to watch TV or DVDs or play games on the TV, such as play station yesterday? This includes if you watch TV in bed.

Remember, your answer can be given in hours and/or minutes.

		hours			minutes

Computer, Internet, Electronic Games

ST 6. Please estimate the total time yesterday that you spent sitting or lying down and using the computer. For example, include time spent playing games, internet activities.

		hours			minutes

Interviewer: if the respondent reported working include the prompt 'Do not include time spent doing paid work on the computer as this should have been included in the previous question about sitting for work.'

Reading

ST 7. Please estimate the total time yesterday that you spent sitting or lying down while reading during your leisure time. Include reading in bed but do not include time spent reading for paid work.

		hours			minutes

Hobbies

ST 8. Please estimate the total time yesterday that you spent sitting or lying down for hobbies. For example, doing art, craft or cross words.

		hours			minutes

Sitting/lying for other purposes

ST 9. We are interested in any other sitting or lying down that you may have done that you have not already told us. For example this could include socializing with friends or family including time on the telephone; eating meals; or listening to music.

Again thinking of yesterday, please estimate the **total time** that you spent sitting or lying down **NOT** including time that you have told us about in the previous answers.

		hours			minutes

Interviewer: if the respondent has difficulty, you can reassure them that their best estimate will be OK.

That's all the questions we have for you about the time you spent sitting or lying down yesterday. Thinking back on your answers, is there anything you would like to change?

Interviewer: This will give the participant an opportunity to confirm that they have given an accurate response to each question. Please change responses as required.

If the participant has reported sitting for over 16 hours in the day prompt them to consider their answers by saying 'I've got here that you spent ..... sitting yesterday. Are there any times where you might have over-estimated or doubled up on reporting sitting time?'

APPENDIX X: Case Record File for bronchiectasis and healthy control participants

INVESTIGATING BRONCHIECTASIS – EVALUATING PHENOTYPES (iBEEP) THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

PARTICIPANT DEMOGRAPHICS

PARTICIPANT ID: _____ MRN:_____

Surname: _____ First Name:_____

Middle Name: _____

Contact Details:

Street Address:_____

Suburb:_____ Post Code:_____

Phone Home:_____ Work:_____

Mobile:_____ Email:_____

Sex: Male ☐ Female ☐

Date of Birth: __ __ /__ __/__ __ __ __

GP Name and

Address:_____

_____

_____

☛**REMOVE THIS SHEET FROM CRF**

FILE IN SUBJECT DEMOGRAPHICS FOLDER

INVESTIGATING BRONCHIECTASIS – EVALUATING PHENOTYPES (IBEEP) THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE _____/_____/_____	VISIT_____

INVESTIGATING BRONCHIECTASIS – EVALUATING PHENOTYPES (IBEEP)
VISIT 1 PART A

VISIT 1 CHECKLIST	Sign Initials
Date of Visit 1 Part A _____/_____/_____	
Demographics	
Inclusion/Exclusion	
Clinical Data	
Other Medications	
Exacerbation History	
Mucus Hyper-secretion	
Inhaler technique	
Smoking (ExCO collected)	
Allergy Skin Prick Test	
Vital Signs	
Spirometry	
Saline Challenge	
Body Composition (DXA & BIA)	
Systemic Inflammation (blood collected and POC)	
Physical Activity Monitor	
Book HRCT Scan (if Not Done in the past 12months)	
Adherence	
International Physical Activity Questionnaire	
Dyspnoea	
Laryngeal Dysfunction Questionnaire	
Nutrition	
Sleep	
Patient Experience & Patient related problems	
Monitored	

INVESTIGATING BRONCHIECTASIS – EVALUATING PHENOTYPES (iBEEP) THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

PARTICIPANT DEMOGRAPHICS --- VISIT 1

SUBJECT ID:_____ SUBJECT INITIALS: _____

** See Subject demographics file for contact details.

Sex: Male ☐ Female ☐

Date of Birth:__ __ /__ __/__ __ __ __

Age of bronchiectasis onset :

Measure height twice. Ask the subject to take a deep breath in while performing the measurement so they get to their full height. Both measures must be within 0.5cm of each other, if not repeat a third time. Then record the average of the 2 measures; this is the measure you will report

Height (without shoes): ☐☐☐•☐ cm

Height (without shoes): ☐☐☐•☐ cm

Average: ☐☐☐•☐ cm

Weight (without shoes): kg

BMI: ☐☐☐•☐☐ kg/m2

Entry Spirometry:

	Litres	% predicted
Pre BD FEV1		
Pre BD FVC		
Pre FER (decimal place not %)		

INVESTIGATING BRONCHIECTASIS – EVALUATING PHENOTYPES (IBEEP) THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

INCLUSION CRITERIA *Subjects must fulfil **ALL** of the following to be included in the study.*	**YES**	**NO**	**EXCLUSION CRITERIA** *Subjects with **any** of the following will **not** be included in the study.*	**YES**	**NO**
Able to provide informed written consent (file signed consent)	☐	☐	Inability to attend study visits	☐	☐
Confirmed diagnosis of bronchiectasis OR healthy control participant (please circle)	☐	☐	Diagnosed with a respiratory disease other than asthma or COPD (e.g. active tuberculosis, pulmonary fibrosis)	☐	☐
Aged ≥18 years.	☐	☐	Aged < 18 years	☐	☐

INVESTIGATING BRONCHIECTASIS – EVALUATING PHENOTYPES (IBEEP) THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE _____/_____/_____	VISIT_____

MEDICAL HISTORY/COMORBIDITIES

Area	Yes	No	Specify: Condition / Procedure (Year)
Ear, nose and throat Allergic Rhinitis, nasal polyps, hearing loss			
Eye Glasses, cataracts, eye surgery etc.			
Respiratory Asthma, persistent cough, pulmonary fibrosis, lung cancer, bronchiectasis, interstitial lung disease			
Cardiovascular BP issues, high cholesterol, MI, angina, coronary heart disease, congestive heart failure, atrial fibrillation/ flutter			
Gastrointestinal IBS, intolerances, lap band, GORD, gastric/duodenal ulcers, oesophageal cancer			
Hepatobiliary / Pancreas Hepatitis, cirrhosis, bile disorders, pancreatic cancer			
Urology Kidney/bladder issues, UTIs, prostate, incontinence			
Reproduction Hysterectomy, fertility problems, caesarian sections, breast cancer, is patient still menstruating?			
Neurology Stroke, chronic headaches, MS.			
Blood and Lymphatic Haemachromatosis (iron overload), lymph node removal, anaemias.			
Endocrine and Metabolic Diabetes, hormonal issues.			
Musculoskeletal Muscles, bones, joints, arthritis, broken bones.			
Skin Eczema, dermatitis, psoriasis, burns.			
Psychiatry Mental health issues. Depression/anxiety			
Non – site specific Viral illness such as measles, chicken pox.			
Drug Allergies? Known or possible drug allergies			
All other cancers			
Any other illnesses			

CHARLESON (CCI)	BODE

INVESTIGATING BRONCHIECTASIS – EVALUATING PHENOTYPES (IBEEP) THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

CLINICAL DATA: RESPIRATORY MEDICATIONS

Please circle and indicate specific device*, unit dose, puffs per occasion and occasions per day **in numbers not abbreviations**.	Current?
Short acting β_2-agonist: (E.g. Ventolin, Asmol, Airomir)	Yes/ No
Long acting β_2-agonists: (E.g. Serevent, Foradile, Oxis, Onbrez)	Yes/ No
Leukotriene modifier: (E.g. Singulair)	Yes/ No
Short acting anti-cholinergic: (E.g. Atrovent)	Yes/ No
Long acting anti-cholinergic: (E.g. Spiriva, Seebri, Bretaris)	Yes/ No
Long acting β_2-agonists/ Long acting anti-cholinergic (E.g. Ultibro, Anoro)	Yes/ No
Nasal Steroids:	Yes/ No
Theophylline: (Eg. Austyn, Neulin, Theo-Dur)	Yes/ No
Oral Steroids (Eg. Prednisone, Panafcort, Solone) Type: Dose: Reducing Dose?	Yes/ No
Inhaled Corticosteroids: (E.g. Qvar, Pulmicort, Flixotide, Alvesco) Type: Device: Dose *(strength, puffs, frequency):* *e.g. Flixotide 250mcg, 2 puffs bd=250 x 2 x 2=1000mcg TDD*	Yes/ No
Seretide / Symbicort / Breo / Flutiform (circle one) Dose *(strength, puffs, frequency)*: Device	Yes/ No
How many days in the last week did you use your reliever medication? **How many times on those days did you use your reliever?**	/7
Other respiratory medications *(Device, Drug, strength, dose, frequency)* _____	Yes/No

* Device: Pressurised Metered Dose Inhaler (MDI); Turbuhaler (Turb); Autohaler (Auto); Nebuliser (Neb); Accuhaler (Acc); Aeroliser (Aero); Handihaler (Hand); Breezehaler; Genuair; Ellipta; Rapihaler; Spacer; Oxygen/Concentrator.

INVESTIGATING BRONCHIECTASIS – EVALUATING PHENOTYPES (IBEEP) THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE _____/_____/_____	VISIT_____

OTHER MEDICATIONS

☛Check that new medications do not appear on list of prohibited concomitant medications.

Drug	Route and *dosage form	Total Daily Dose (units) (=Unit dose * dose per occasion * occasion per day)	Indication	Start date/Stop date/comments

* **Dosage form**: **Oral** (tablets/capsule, liquids); **Topical** (creams, ointments); **Eye, ear & nose** (eye drops, ear drops, nasal spray); **Inhalation** (MDI, Turb, Neb, Acc, Aero, Hand, Breezehaler, Genuair, Ellipta, Rapihaler, Spacer, Oxygen/ concentrator); **Others** (injections, suppositories, pessaries).

INVESTIGATING BRONCHIECTASIS – EVALUATING PHENOTYPES (IBEEP) THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE _____/_____/_____	VISIT_____

EXACERBATION MODULE

Questions apply to the 12 months up to, and including today and relate to your breathing / chest only. (Participant to answer each question directly, symptom diary can be used to help complete the module if required)

Date Completed: ___ / ___ / _____ (dd/mm/yyyy)

	In the last 12 MONTHS have you...	YES (✓)	NO (✓)	# of courses +occasions?	Start Date (for each event)	Stop Date (for each event)
1	Visited the Emergency Department for your chest / breathing? *(Not including those that led to hospital admission)*					
2	Been admitted to hospital for your chest / breathing?					
3	Taken oral corticosteroids for chest / breathing (>10mg for ≥ 3 days)?					
4	Taken antibiotics for chest / breathing?					
5	Had an unscheduled visit to a GP for your chest / breathing? *Ie. Unplanned visit due to worsening symptoms. Not including those episodes that resulted in hospital admisison or ED visit.*					
6	Taken oral corticosteroids ≥3 days or antibiotics for chest / breathing, as a result of the Written Action Plan being initiated? *Ie. Community treated exacerbations, without having consulted GP or attending ED/hospital.*					
7	Increased your chest / breathing medication for ≥ 2 days? *IF YES, complete 6 A and B*					
	6A. Increased reliever?					
	6B. Increased preventer?					
8	Total number of exacerbations in 12 months					

Update other medications log where required.

	Increased symptoms in the last 4 weeks:	YES (✓)	NO (✓)	For how many days since your last visit did you have an increase in these symptoms?
7	Cough			
8	Wheezing			
9	Dyspnoea			
10	Chest Tightness			
11	Produce Phlegm			
12	How much phlegm to you produce each day? (circle)			Teaspoon 1 tblspoon 2 tblspoons ½ cup 1cup
13	What colour is it? (circle)			Clear White Yellow Green Blood-stained
14	Other *If Yes*, please details			

IBEEP CRF V1 VERSION 10 OF 10 PAGE 9 OF 47

INVESTIGATING BRONCHIECTASIS – EVALUATING PHENOTYPES (iBEEP) THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE_____/_____/_____	VISIT_____

EXACERBATION MANAGEMENT

Have you been prescribed a written action plan? Yes / No

Do you use your WAP? Yes / No

If not why not?_____

How many times have you used you WAP in the last 6 months_____

Note to researcher: Please ask for a copy of the WAP. If the participant has undergone an education programme within the last 12 months please also ask for a copy of their action plan prior to enrolment in the education programme.

Mucous Hypersecretion

1. When you don't have a cold, do you usually bring up phlegm from your chest OR have phlegm on your chest that is difficult to bring up? **Yes / No**

If ***Yes:***,1A. How many days in the past week have you coughed up sputum/phlegm? /7

2A. Are there months in which you have this phlegm on most days? **Yes / No**

NB: "this phlegm" refers to phlegm that is brought up AND/OR phlegm that is stuck in the chest.

If Yes, ask both Questions 2B & 2C; If No, skip to Dyspnea]

2B. Do you bring up this phlegm on most days for as much as three months each year? **Yes / No**

2C. For how many years have you had this phlegm? (Circle)

Less than 2 years **2-5 years** **More than 5 years**

3. Have you produced sputum/phlegm for more than 3 consecutive months for 2 consecutive years? **Yes / No**

4. How much sputum/phlegm do you cough up in the course of a day?

< Teaspoon Teaspoon 1 tblspoon 2 tblspoons ½ cup 1 cup

5. What part in the day do you cough up the most sputum/phlegm?

Morning afternoon evening all day am and pm

6. What colour is your sputum/phlegm at the most productive time?

clear / white / yellow / green / blood stained

7. What colour is your sputum/phlegm for the rest of the time?

INVESTIGATING BRONCHIECTASIS – EVALUATING PHENOTYPES (IBEEP) THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

clear / white / yellow / green / blood stained

Inhaler Technique

Please assess inhaler technique today.

Please use placebo devices. Each box must be entered using the following choices;

I = inadequate A = adequate O = optimal NU – Not Used

pMDI		Accuhaler		Handihaler	
Spacer		Autohaler		Nebuliser	
Turbuhaler		Aerolizer		Other device (specify)	

Number of devices used (peak flow *not* included)

Note to researcher: refer to AMS inhaler device assessment sheet

Smoking Module

Do you currently smoke? Yes / No

If yes, time since last cigarette _____(hours)

Have you ever smoked? Yes / No

If yes, how old were you when you began smoking?_____(years)

If yes, how old were you when you gave up smoking? _____(years)

How many cigarettes per day did/do you smoke? _____

Pack years = (Number of cigarettes/20) x years smoked =

Calculation assumes 1 pack has 20 cigarettes. 1 pack year = 20 cigarettes per day for one year

Exhaled carbon monoxide level _____**ppm (Pico meter)**

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ALLERGY HISTORY

Do you or have you had any of the following conditions?

	NEVER	*CURRENT*	*PAST*	NOTES:
Persistent cough (>3/12 of last 12)	☐	☐	☐	
Hayfever	☐	☐	☐	
Eczema	☐	☐	☐	
Allergic conjunctivitis	☐	☐	☐	
Nasal polyps	☐	☐	☐	

ALLERGY SKIN PRICK TEST

Has the participant taken Antihistamines within the past 5 days? (Hismanal 6 weeks) ☐ Yes ☐ No

*If **yes** provide details do not continue test and reschedule appointment.*
How long since last antihistamine taken?

_____

_____

Start Time:_____

Test	Weal Size (mm) x (mm)
CONTROLS	
Positive Control ***(measure at 10 mins)***	X
Negative Control ***(measure at 15 mins)***	X
ALLERGENS (*measure at 15 mins*)	
Aspergillus mix	X
Alternata	X
Dust mite (DP)	X
Cockroach mix	X
5 Grasses	X

ATOPY positive if (any allergen weal ≥ 3mm) **Yes** ☐ **No** ☐

Performed By:_____

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VITAL SIGNS (Perform prior to spirometry)

Blood pressure (after resting for 5 mins): ___ ___ ___/___ ___ ___mmHg
Systolic Diastolic

Pulse (Heart Rate): ..... bpm

Pulse Oximetry: ..... %spO_2

Temperature (tympanic): .....°C

Respiration rate: ..... breaths per minute

SPIROMETRY – Visit 1a *(Participant required to withhold medications according to Section 5.2.1 Table 2 of Protocol)*					
Spirometer Make:				**Assessor:**	
Asthma Medications Withheld? Yes ☐ No ☐		Medication Name:			
		Date & Time last taken:			
	Predicted:	**FEV_1 (L):**			
		FVC (L):			

PRE-BRONCHODILATOR SPIROMETRY EFFORTS								
	1	2	3	4	5	6	7	8
FEV_1 (L)								
FVC (L)								
Comment								

		BEST	% Predicted (xx.x)	Comment
BEST Pre-B_2	**FEV_1 (L)**			
	FVC (L)			

☞ ***If FEV_1 < 1.0L OR < 40% Predicted,*** STOP Do not Continue- Contact supervisor re 0.9% Saline. Get Permission First!

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SALINE CHALLENE AND INDUCTION

***Please refer to sputum challenge + induction flowchart for safety guidelines** (Protocol Appendix C)*

☐ Not Performed. Reason: _____

Saline Challenge + Induction

(ie. no documented evidence of VAO in last 10 years)
NB: DO NOT give bronchodilator prior to saline challenge.

Antihistamines Withheld? ☐ N/A (according to Section 5.2.1 Table 3 of Protocol)	☐ Yes (Continue) ☐ No (continue test, if included, repeat challenge at v2 + withhold antihist.)

Mouth rinsed (x3) with water? ☐ Yes ☐ No		Nebuliser Make/Name:		
Asthma medications withheld prior to visit? ☐ Yes ☐ No		Saline Used: ☐ 4.5% saline ☐ 0.9% saline		
Is the **baseline best FEV_1 (L) >1.0L AND ≥ 40% predicted?** ☐ Yes (continue) ☐ No (STOP Do not Continue- Contact supervisor re0.9% sal.) Get Permission First		**Calculate Safety Stop:** **15% fall from baseline FEV_1 (L)** = 85% x baseline FEV_1 (L)		
Nebuliser Cup Weight (with saline + tubing)	Pre Weight (g)	Post Weight (g)	**Nebulised dose (g)**	**Provocation dose (g)/PD15**

Spontaneous Sputum Sample Collected? ☐ Yes (label 'SS', store in fridge, start new specimen jar for SIS) ☐ No

Saline nebulised time *(adjust intervals if required up to a total of 15.5mins)*	**FEV_1 (L) efforts** 1	2 optional	3 optional	**% fall from baseline FEV_1**	**Saline Induced Sputum (SIS) produced (Y/N)**	**B_2 required?** Y/N	Dose (µg)	Pause (mins)	**Recovery FEV_1, L (post B_2)**
Baseline Best FEV_1 (L) (pre B_2 – chall.; post B_2 – Ind. only)									
30 sec									
1 min									
2 min									
4 min									
4 min									
4 min									

Cumulative Induction Time (mins): (total time on nebuliser)		Sputum Collected? ☐ Yes ☐ No Time sputum collected (24hr):	

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BIA

Has participant exercised / or showered in the past 2 hours?_____ If yes, postpone for at least 2 hours
Has participant eaten in the last 2 hours?_____ If yes, postpone for at least 2 hours
Has participant emptied bladder prior to test?_____ If no, perform now
Has participant wiped hands and feet with wipes?_____If no, perform now
Does participant have a pacemaker or other implanted electrical devices (such as a defibrillator or nerve stimulator)? _____Do not perform test.
Does participant have any metal implants (eg pins/plates, knee replacement)?
This is only a contraindication when the metal is in the hands/feet (when close to the electrodes). However may potentially affect results.
Is the participant breastfeeding or currently pregnant? _____
BIA is contraindicated during the first 12 weeks of pregnancy. Do not perform test on pregnant women regardless of gestation. Breastfeeding may affect the fluid levels and caution should be taken interpreting results.
Has the participant had any radiographic contrast material (Barium) injected in the last 72 hours? Do not perform the test as results would not be valid. Postpone test.
Do not perform if the participant has an amputation.
Remind participant to remove all jewellery, extra clothing, stockings and empty pockets.

Dexa pre-test questionnaire

PRIOR TO SCAN

Waist Circumference (cm):

The participant should empty their bladder, remove all jewellery, hairpins, glasses, underwire bras and put on a gown

Previous Bone Density or Body Composition Scan:		Yes		No	
When:			Result:		
Previous Medical History:					
Fractures:		Yes		No	
Details/Cause:					
Previous lumber spine x-ray?		Yes		No	
Date:			Result:		
Kidney disease:	Yes	No	Liver Disease:	Yes	No
Overactive Thyroid	Yes	No	Arthritis	Yes	No
Parathyroid disease	Yes	No	Malabsorption (Coeliac Disease)	Yes	No
Other Medical Illness or Major operation?		Yes		No	

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Have you had an X-ray or CT scan with contrast material such as barium in the last 7 days?	Yes	No
(If 'Yes' delay DEXA scan for at least 72hrs, see DEXA SOP Appendix 2 for minimum delay times)		
Have you had any nuclear medicine scans in the past 3 days?	Yes	No
(If 'Yes' delay DEXA scan for at least 48hrs, see DEXA SOP Appendix 2 for minimum delay times)		
Have you ever fractured your hip, had a hip replacement, or do you have a pin in your hip?	Yes – Both / Right / Left	No
(If bilateral hip replacement, pins or screws present do not perform femur measurement, if unilateral hip metal surgical implant present scan other hip)		
Do you have any lumbar spine implants, pins or have you had spinal fusion?	Yes	No
(If metallic rods or spinal fusion devices present in lumbar spine, do not perform lumbar spine scan)		
Do you have any other surgical implants, surgical pins, a pacemaker or defibrillator?	Yes	No
If 'Yes' List:		
(DEXA is safe for permanent pacemakers or implantable defibrillators)		
Have you been on oral steroid treatment?	Yes	No
What treatment:	Dose:	Duration:
Are you on treatment for Osteoporosis?	Yes	No
What treatment:	Year commenced:	
Do you take Calcium Supplements?	Yes	No
(If yes, have they taken any in the last 24hrs, if yes delay scan for 24hrs)		
Menopausal?	Yes	No
Age of menopause:	LMP:	
Are you or could you be pregnant?	Yes	No
(If 'Yes', do not scan, subject not eligible)		
Comments		

DEXA – TOTAL BODY SCAN

BMI (kg/m^2): _____

Classification: _____

Total Tissue % Fat: _____

Trunk Tissue % Fat: _____

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ID_____	INITIALS_____	DATE ____/____/____	VISIT____

Android Tissue % Fat: _____

Gynoid Tissue % Fat: _____

Total Tissue (g): _____

Total Fat (g): _____

Total Lean (g): _____

Total BMC (g): _____

Fat Free (g): _____

Fat Free Mass Index :

total body lean soft tissue + bone mineral content in Kg = ☐

Height $(m)^2$

Appendicular Skeletal Muscle Mass Index :

lean soft tissue both arms+ lean soft tissue both legs in Kg= ☐

Height $(m)^2$

Sarcopenia (Men: ≤7.26Kg/m^2) **Yes** ☐ **No** ☐

(Women: ≤5.45Kg/m^2)

Blood & Sputum Biomarkers

Blood collected for: FBC, CRP, RNA, IgE, serum, plasma. (initial)_____Time of collection: _____

Tube required:

1 x 4mL EDTA blood (purple top)

1 x 9ml EDTA (purple top)

1 x 4ml Lithium heparin (green)

2 x 6ml serum (red) – 1x 6ml Serum to go to HAPS for IgE (No IgE for healthy controls)

POC-CRP

HS-CRP: Measurement: _____ Initial: _____

Haemoglobin: Measurement: _____ Initial: _____

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PHYSICAL ACTIVITY

Activity monitors x 2 given: Yes / No

Care instructions & Wear log given Yes / No

Activity monitor number: ☐

Activpal number: ☐

HRCT Scan Chest (Not applicable for healthy controls)

Has the subject had a HRCT scan of the Chest in the past 12months?

Yes ☐ Date performed: _____ No ☐ (Please arrange)

Date and time HRCT Booked: _____

Booked by:_____

Adherence

Medication use over the last three months

Please circle the answer:

In the last three month;

Have you at times been careless about using your inhaler? **Y/N**
Comment – ie .Describe how many missed doses in the last week

Have you ever forgotten to use your inhaler? **Y/N**
Comment

Have you ever stopped using your inhaler because you felt better? **Y/N**
Comment

Have you ever stopped using your inhaler because you felt worse? **Y/N**
Comment

Have you ever used your inhaler less than the doctor prescribed because you felt better? **Y/N**
Comment

Have you ever used your inhaler more than the doctor prescribed because you felt you were having an attack?
Comment **Y/N**

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International Physical Activity Questionnaire

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days. Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

_____ **days per week**

☐ No vigorous physical activities → **Skip to question 3**

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

_____ **hours per day**
_____ **minutes per day**

☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

_____ **days per week**

☐ No moderate physical activities → **Skip to question 5**

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**
_____ **minutes per day**

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐ No walking → **Skip to question 7**

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**
_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**
_____ **minutes per day**

☐ Don't know/Not sure

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ID_____	INITIALS_____	DATE _____/_____/_____	VISIT_____

DYSPNOEA

Modified Medical Research Council Dyspnoea Scale

"We would like to assess your level of breathlessness"

Grade/Circle

0 "I only get breathless with strenuous exercise"

1 "I get short of breath when hurrying on the level or walking up a slight hill"

2 "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level"

3 "I stop for breath after walking about 100 yards or after a few minutes on the level"

4 "I am too breathless to leave the house" or "I am breathless when dressing"

Note to researcher: This is the modified MRC scale that uses the same descriptors as the original MRC scale in which the descriptors are numbered 1-5. The modified MRC scale (0-4) is used for calculation of BODE index.

Laryngeal Dysfunction Questionnaire

1. Where do you feel the tightness?

   Neck ☐ jugular notch ☐ upper chest ☐ lower chest ☐ N/A ☐

2. Is it harder to breathe in than out? Y/N
(if answers to Q1 and Q2 are N/A and No then move onto Q7).

3. How quickly do your symptoms come on?
   (ie, tightness, breathing difficulty)
   Seconds
   < 3 minutes
   > 3 minutes

4. When the attack stops, (including after treatment), how quickly do your symptoms go away?

   Seconds
   < 5 minutes
   > 5 minutes

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5. What triggers your symptoms? (eg: exercise, heart burn, pnd, pollution, cold air, talking)

6. Do asthma medications give you relief?

No
Yes (if Y within how many minutes?) _____ minutes
N/A

7. Does your voice get hoarse or do you lose your voice? Y/N

8. Do you feel a lump in your throat? Y/N

9. Do you feel like you are choking or suffocating? Y/N

10. Do you have pins and needles around the lips or the fingertips? Y/N

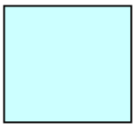
Malnutrition Universal Screening Tool

1. Have you/the patient lost weight recently without trying?

No	0
Unsure	2
Yes, How much (kg)?	
1-5	1
6-10	2
11-15	3
>15	4
Unsure	2

2. Have you /the patient been eating poorly because of a decreased appetite?

No	0
Yes	1

Malnutrition Universal Screening Tool - Total Score 

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ID_____	INITIALS_____	DATE ____/____/____	VISIT____

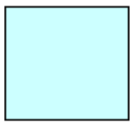
Epworth Sleepiness Scale

How likely are you to dose off or fall asleep in the following situations, in contrast to feeling tired? Using the following scale circle a number to score each of the questions with regard to the last week.

0 Never doze **1** Slight chance of dozing **2** Moderate chance of dozing **3** High chance of dozing

How likely are you to doze off or fall asleep **(please circle your answer)**

1.	While sitting and reading?	**0**	**1**	**2**	**3**
2.	While watching TV?	**0**	**1**	**2**	**3**
3.	While sitting inactive in a public place (eg theatre, meeting)?	**0**	**1**	**2**	**3**
4.	While a passenger in a car for an hour without a break?	**0**	**1**	**2**	**3**
5.	While lying down to rest in the afternoon when circumstances permit?	**0**	**1**	**2**	**3**
6.	While sitting and talking to someone?	**0**	**1**	**2**	**3**
7.	While sitting quietly after lunch without alcohol?	**0**	**1**	**2**	**3**
8.	While in a car stopped for a few minutes in traffic?	**0**	**1**	**2**	**3**



Total Score

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ID_____	INITIALS_____	DATE ____/____/____	VISIT____

Short Assessment of Patient Satisfaction (SAPS) with Instructions

(Not applicable for healthy controls)

Instructions: After reading each question, circle the answer that best describes your situation. We know that sometimes answers may not describe you exactly, so please pick the answer that *most closely describes you*.

When you have finished, please check that you have answered all questions.

Q1. How happy are you with the effect of your treatment?

Very happy.....0
Happy.....1
Neither happy nor unhappy.....2
Unhappy.....3
Very unhappy.....4

Q2. How satisfied are you with the explanations the {doctor/other health professional} has given you about the results of your treatment?

Very dissatisfied.....0
Dissatisfied.....1
Neither satisfied nor dissatisfied.....2
Satisfied.....3
Very satisfied.....4

Q3. The {doctor/other health professional} was very careful to check everything when examining you.

Strongly agree.....0
Agree.....1
Not sure.....2
Disagree.....3
Strongly disagree.....4

Q4. How satisfied were you with the choices you had in decisions affecting your health care?

Very dissatisfied.....0
Dissatisfied.....1
Neither satisfied nor dissatisfied.....2
Satisfied.....3
Very satisfied.....4

Q5. How much of the time did you feel respected by the {doctor/other health professional}?

All of the time.....0
Most of the time.....1
About half the time.....2
Some of the time.....3
None of the time.....4

Q6. The time you had with the {doctor/other health professional} was not long enough.

Strongly agree.....0
Agree.....1
Not sure.....2
Disagree.....3
Strongly disagree.....4

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ID_____	INITIALS_____	DATE _____/_____/_____	VISIT_____

Q7. Are you happy with the care you received in the {hospital/clinic}?

Very happy.....0
Happy.....1
Neither happy nor unhappy.....2
Unhappy.....3
Very unhappy.....4

Total

Scoring the SAPS:
1. Reverse the scores for #1, #3, #5, #7
2. Sum all scores. The score range is from 0 (extremely dissatisfied) to 28 (extremely satisfied)

Patient Related Problems

What is/are the biggest problem/s you experience as a result of your breathing problem?

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ID_____	INITIALS_____	DATE ____/____/____	VISIT____

Common cold questionnaire (complete only if there is a suspected virus)

SUBJECT No:_____ **Date:**_____ **INITIALS:**_____

In the past two days have you experienced any of the following:

	NONE	MILD	MODERATE	SEVERE
A General Symptoms:				
1. Fevers	☐	☐	☐	☐
2. Chills	☐	☐	☐	☐
3. Muscle pains	☐	☐	☐	☐
B. Nasal Symptoms:				
1. Watery eyes	☐	☐	☐	☐
2. Runny nose	☐	☐	☐	☐
3. Sneezing	☐	☐	☐	☐
C. Throat Symptoms:				
1. Sore throat	☐	☐	☐	☐
D. Chest Symptoms:				
1. Cough	☐	☐	☐	☐
2. Chest pain	☐	☐	☐	☐
E. Photophobia:	☐	☐	☐	☐

- A probable viral infection is where there are moderate symptoms noted in at least two of the above four categories or mild symptoms noted in three or more categories.
- A possible viral infection is where mild symptoms are noted in one category plus a cough.

Probable Viral: **Yes** ☐ **No** ☐

Possible Viral: **Yes** ☐ **No** ☐

Infected Controls must have a probable or possible infection
All other subjects must have none of the symptoms listed with the exception of cough ***- IF RETURN A POSITIVE RESPONSE PLEASE RE-BOOK FOR FOUR WEEKS TIME***

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ID_____	INITIALS_____	DATE_____/_____/_____	VISIT_____

INVESTIGATING BRONCHIECTASIS – EVALUATING PHENOTYPES (IBEEP) VISIT 1 PART B

VISIT 1B CHECKLIST	Sign Initials
Date of Visit 1 Part B_____/_____/_____	
ECG	
FENO	
Spirometry (Pre and Post)	
Potential Sputum Induction	
Exercise Tolerance (6MWT)	
Trunk strength Tests (core/upper body/lower body)	
Physical Activity Monitors Returned	
SGRQ (bronchiectasis participants only)	
COPD Assessment Test (CAT)	
SF36	
Anxiety and Depression assessments	
Dysfunctional breathing (Nijmegen)	
Past-day Adults' Sedentary Time (PAST) Questionnaire	
3IQ	
QOL B	
Monitored	

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ID_____	INITIALS_____	DATE _____/_____/_____	VISIT_____

ECG

ECG completed (initial)_____

FeNO

Sample 1 _____ppb

Sample 2_____ppb

Sample 3_____ppb

Average_____ppb

Ambient eNO_____

Last oral intake_____hours

Last bronchodilator_____hours

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ID_____	INITIALS_____	DATE ____/____/____	VISIT____

SPIROMETRY *(Participant required to withhold medications according to Section 5.2.1 Table 2 of Protocol)*				
Spirometer Make:			**Assessor:**	
Asthma Medications Withheld? **Yes** ☐ **No** ☐	Medication Name:			
	Date & Time last taken:			
	Predicted:	**FEV_1 (L):**		
		FVC (L):		

PRE-BRONCHODILATOR EFFORTS								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
FEV_1 (L)								
FVC (L)								
Comment								

		BEST	**Comments**
BEST Pre-B_2	**FEV_1 (L)**		
	FVC (L)		

Bronchodilator Administration:

400µg (4 puffs) Salbutamol given via spacer? ☐Yes ☐No Comment: _____

Time B_2 Given (24hr): _____ Time Paused (15mins): _____(mins)

POST-BRONCHODILATOR EFFORTS								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
FEV_1 (L)								
FVC (L)								
Comment								

		BEST	**Comments**
BEST Post-B_2	**FEV_1 (L)**		
	FVC (L)		

INVESTIGATING BRONCHIECTASIS – EVALUATING PHENOTYPES (IBEEP) THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

SPUTUM INDUCTION (COMPLETE if NO Sputum was obtained at Visit A OR if either cell counts or micro data was not obtained from the visit A sample)

Please refer to sputum induction flowchart for safety guidelines (Protocol Appendix C)

☐ Not Performed. Reason: _____

Mouth rinsed (x3) with water? ☐ Yes ☐ No		Nebuliser Make/Name:	
Asthma medications withheld prior to visit? ☐ Yes ☐ No		Saline Used: ☐ 4.5% saline ☐ 0.9% saline	
Is the best Post B2 FEV_1 (L) ≥ 40% predicted? ☐ Yes (continue) ☐ No (STOP discuss with supervisor, ? 0.9% sal.)		**Calculate Safety Stop:** **15% fall from baseline FEV_1 (L)** = 85% x baseline FEV_1 (L)	
Nebuliser Cup Weight (with saline + tubing)	Pre Weight (g)	Post Weight (g)	**Delivered dose (g)**

Spontaneous Sputum Sample Collected? ☐ Yes (label 'SS', store in fridge, **start new specimen jar** for SIS) ☐ No

Saline nebulised time *(adjust intervals if required up to a total of 15.5mins)*	**FEV_1 (L) efforts** 1	2 optional	3 optional	**% fall from baseline FEV_1**	**Saline Induced Sputum (SIS) produced (Y/N)**	**B_2 required?** Y/N	Dose (µg)	Pause (mins)	**Recovery FEV_1, L (post B_2)**
Baseline Best FEV_1 (L) (post B2)									
30 sec									
1 min									
2 min									
4 min									
4 min									
4 min									

Cumulative Induction Time (mins)#: (total time on nebuliser)		Sputum Sample Collected? ☐ Yes ☐ No	
		Time sputum collected (24hr):	

Comments/Notes:

Attempt a **full 15.5 minute induction** regardless of total time on nebuliser at visit 1.

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Exercise Tolerance

Predicted HRmax (220-age):_____

Bronchodilator pre treatment Salbutamol given? Yes/No Time given: _____

NOTE:1. Healthy controls do not receive bronchodilator pre treatment
2. If 6MWT done < 20 minutes after Pre/Post spirometry this can count as pre treatment
3. If 6MWT done after Pre/Post Spirometry but > 20 minutes after, pre treat with 200mcg
4. If 6MWT done before Pre/Post spirometry pre treat with 400mcg

Date _____ Time_____

Bronchodilator time since last dose_____

BP	RR	Supplemental Oxygen?	Gait Aid?
Manual HR			

Time (min)	SpO_2	HR	Dyspnoea (BORG)	Rests
Rest				
1				
2				
3				
4				
5				
6				
Recovery 1				**Total rests**
2				

Post RR **(at 6 minutes)**_____

Limiting factor to the test: Low SpO_2 ☐ Leg fatigue ☐ Other: _____

40	200	360	520
80	240	400	560
120	280	440	600
160	320	480	+/-
TOTAL WALK DISTANCE			**METRES**

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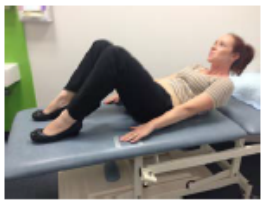
Core Strength Tests:

Past Injury / Surgical History: _____

_____

_____



A) Static ¼ sit-up: Patient in crook lying with arms by side. Adhere tape at finger tips and 12 cm from the first strip (8cm if the pt. over 40 yrs old). Instruct patient to raise head & shoulders by sliding palms forward to second strip and hold.

Time held:.....**Classification (percentile range):**.....

B) Sorenson test: Patient prone with trunk off the edge of the plinth and arms resting on the chair. Patient instructed to lift trunk until level with the plinth and hold. If horizontality broken, once = correct, twice = stop test.

Time Held:.....**Classification:**.....

C) Side bridge endurance test: Patient in side bridge position (top foot in front of lower foot on plinth) and instructed to raise hips off plinth and hold.

Time Held:.....**Classification Left:**.....**Classification right:**.....

Termination criteria and Contraindications for trunk endurance tests

- Subject no longer able to sustain position
- Subject unable to assume position on practice trial
- Subject terminates the test
- Subject reports pain- staff are to terminate the test immediately and document the time held until pain commenced.
- Subject refuses to attempt test
- Signs of poor perfusion
- Heart rate exceeds pre defined HR maximum (220-age)
- Onset of angina or angina symptoms
- SpO2<88% at rest
- Test will not be performed if there are any contraindications to exercise. This will be screened prior to walk test. Contraindications include HR>125 bpm at rest, SpO2<88% prior to test, physical disability preventing safe performance, acute/unstable angina, RR excessive or BORG >4 at rest.

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Upper & Lower Body Strength Tests:

Dynamometry (Shoulder) Push _____ **Dynamometry (Leg)** Attempt 1_____

Pull _____ Attempt 2_____

Activity monitor and heart rate monitor returned (should be worn for 6MWT) ☐

Wear log returned ☐

HR QOL - SGRQ
(Not applicable for healthy controls)

Remind patient to answer the questions relating the answers to the last month, not the last year.

Symptoms	
Activity	
Impacts	
Total	

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How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	**I cough all the time**	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	**My chest is completely full of phlegm (mucus)**	
My chest does not feel tight at all	0 1 2 3 4 5	**My chest feels very tight**	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	**When I walk up a hill or one flight of stairs I am very breathless**	
I am not limited doing any activities at home	0 1 2 3 4 5	**I am very limited doing activities at home**	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	**I am not at all confident leaving my home because of my lung condition**	
I sleep soundly	0 1 2 3 4 5	**I don't sleep soundly because of my lung condition**	
I have lots of energy	0 1 2 3 4 5	**I have no energy at all**	
		TOTAL SCORE	

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QUALITY OF LIFE – SF36 Health Survey

Patient to complete: This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question please give the best answer you can.

1. In general, would you say your health is: (Please tick **one** box.)
   - Excellent (1) ☐
   - Very Good (2) ☐
   - Good (3) ☐
   - Fair (4) ☐
   - Poor (5) ☐

2. Compared to one year ago, how would you rate your health in general now? (Please tick **one** box).
   - Much better than one year ago (1) ☐
   - Somewhat better now than one year ago (2) ☐
   - About the same as one year ago (3) ☐
   - Somewhat worse now than one year ago (4) ☐
   - Much worse now than one year ago (5) ☐

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? **(Please circle one number on each line.)**

	Activities	**Yes, Limited A Lot**	**Yes, Limited A Little**	**Not Limited At All**
3(a)	**Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
3(b)	**Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	1	2	3
3(c)	Lifting or carrying groceries	1	2	3
3(d)	Climbing **several** flights of stairs	1	2	3
3(e)	Climbing **one** flight of stairs	1	2	3
3(f)	Bending, kneeling, or stooping	1	2	3
3(g)	Walking **more than a mile**	1	2	3
3(h)	Walking **several blocks**	1	2	3
3(i)	Walking **one block**	1	2	3
3(j)	Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	(Please circle one number on each line.)	**Yes**	**No**
4(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
4(b)	Accomplished less than you would like	1	2
4(c)	Were **limited** in the **kind** of work or other activities	1	2
4(d)	Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (e.g. feeling depressed or anxious)?

	(Please circle one number on each line.)	**Yes**	**No**
5(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
5(b)	Accomplished less than you would like	1	2
5(c)	Didn't do work or other activities as **carefully** as usual	1	2

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6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups? (Please tick one box.)

- Not at all (1) ☐
- Slightly (2) ☐
- Moderately (3) ☐
- Quite a bit (4) ☐
- Extremely (5) ☐

7. How much physical pain have you had during the past 4 weeks? (Please tick one box.)

- None (1) ☐
- Very mild (2) ☐
- Mild (3) ☐
- Moderate (4) ☐
- Severe (5) ☐
- Very Severe (6) ☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Please tick one box.)

- Not at all (1) ☐
- A little bit (2) ☐
- Moderately (3) ☐
- Quite a bit (4) ☐
- Extremely (5) ☐

9. These questions are about how you feel and how things have been with you during the past 4 weeks. Please give one answer that is closest to the way you have been feeling for each item,

	(Please circle one number on each line)	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the time
9(a)	Did you feel full of life?	1	2	3	4	5	6
9(b)	Have you been a very nervous person?	1	2	3	4	5	6
9(c)	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
9(d)	Have you felt calm and peaceful?	1	2	3	4	5	6
9(e)	Did you have a lot of energy?	1	2	3	4	5	6
9(f)	Have you felt downhearted and blue?	1	2	3	4	5	6
9(g)	Did you feel worn out?	1	2	3	4	5	6
9(h)	Have you been a happy person?	1	2	3	4	5	6
9(i)	Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc.) (Please tick one box.)

- All of the time (1) ☐
- Most of the time (2) ☐
- Some of the time (3) ☐
- A little of the time (4) ☐
- None of the time (5) ☐

11. How TRUE or FALSE is each of the following statements for you?

	(Please circle one number on each line.)	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
11(a)	I seem to get sick a little easier than other people	1	2	3	4	5
11(b)	I am as healthy as anybody I know	1	2	3	4	5
11(c)	I expect my health to get worse	1	2	3	4	5
11(d)	My health is excellent	1	2	3	4	5

Thank You!

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Hospital Anxiety and Depression Scale

I feel tense or 'wound up:	**A**	**I feel as if I am slowed down:**	**D**
Most of the time	3	Nearly all the time	3
A lot of the time	2	Very often	2
Time to time, occasionally	1	Sometimes	1
Not at all	0	Not at all	0
I still enjoy the things I used to enjoy:	**D**	**I get a sort of frightened feeling like 'butterflies in the stomach':**	**A**
Definitely as much	0	Not at all	0
Not quite so much	1	Occasionally	1
Only a little	2	Quite often	2
Not at all	3	Very often	3
I get a sort of frightened feeling as if something awful is about to happen:	**A**	**I have lost interest in my appearance:**	**D**
Very definitely and quite badly	3	Definitely	3
Yes, but not too badly	2	I don't take as much care as I should	2
A little, but it doesn't worry me	1	I may not take quite as much care	1
Not at all	0	I take just as much care as ever	0
I can laugh and see the funny side of things:	**D**	**I feel restless as if I have to be on the move:**	**A**
As much as I always could	0	Very much indeed	3
Not quite as much now	1	Quite a lot	2
Definitely not so much now	2	Not very much	1
Not at all	3	Not at all	0
Worrying thoughts go through my mind:	**A**	**I look forward with enjoyment to things:**	**D**
A great deal of the time	3	As much as I ever did	0
A lot of the time	2	Rather less than I used to	1
From time to time but not too often	1	Definitely less than I used to	2
Only occasionally	0	Hardly at all	3
I feel cheerful:	**D**	**I get sudden feelings of panic:**	**A**
Not at all	3	Very often	3
Not often	2	Quite often	2
Sometimes	1	Not very often	1
Most of the time	0	Not at all	0
I can sit at ease and feel relaxed:	**A**	**I can enjoy a good book or radio or TV programme:**	**D**
Definitely	0	Often	0
Usually	1	Sometimes	1
Not often	2	Not often	2
Not at all	3	Very seldom	3

A=
D=
Total =

IBEEP CRF V1 VERSION 10 OF 10

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Dysfunctional Breathing

Nijmegen Questionnaire ***PATIENT TO COMPLETE***

We would like you to think about your breathing symptoms. Please circle the score that best describes the frequency with which you experience the symptoms listed below:

	Never	Seldom	Sometimes	Often	Very Often
Chest pain	0	1	2	3	4
Feeling tense	0	1	2	3	4
Blurred vision	0	1	2	3	4
Dizziness	0	1	2	3	4
Confusion or loss of touch with reality	0	1	2	3	4
Fast or deep breathing	0	1	2	3	4
Shortness of breath	0	1	2	3	4
Tightness across chest	0	1	2	3	4
Bloated sensation in stomach	0	1	2	3	4
Tingling in fingers and hands	0	1	2	3	4
Difficulty in breathing or taking a deep breath	0	1	2	3	4
Stiffness or cramps in fingers and hands	0	1	2	3	4
Tightness around the mouth	0	1	2	3	4
Cold hands or feet	0	1	2	3	4
Palpitations in the chest	0	1	2	3	4
Anxiety	0	1	2	3	4
Total					

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Past-day Adults' Sedentary Time (PAST) Questionnaire

Next I will ask you about particular activities you did yesterday while sitting down or lying down. Please note that this does not include sleeping, either in bed or if you fell asleep while doing another activity, for example watching television.

Interviewer: Record yesterday's date

Yesterday's date: _____

We are going to ask you about different times when you may be sitting or lying down: when working, travelling, watching TV, using the computer, and when doing other activities. For each of these, only count the time when this was your main activity. For example, if you watched TV and ate dinner at the same time, this might be TV or meal time, but not both. Your answers can be given in hours and minutes. Try to report only the time you spent sitting or lying down and not time you spent getting up for breaks (e.g. coffee, bathroom).

ST 1. The next question is about sitting for work. Did you work in a paid position yesterday?

☐ Yes
☐ No

Interviewer: if participant did not work yesterday, skip to ST 4. If they did work yesterday continue to ST 2.

Time spent for work

ST 2. How long **in total** did you spend at your workplace or working from home yesterday, including meal and snack breaks?

☐☐ hours ☐☐ minutes

Sitting for work

ST 3. **How long** were you **sitting** at your workplace or working from home yesterday, including during meal and snack breaks?

☐☐ hours ☐☐ minutes

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Interviewer: if the respondent has difficulty, you can reassure them that their best estimate will be OK.

***Interviewer Check: the time for ST3 cannot be longer than ST2. If ST3 is exactly the same as ST2 (they say they sat for the whole time at work) prompt 'So, can I confirm that you sat for the whole time at work without getting up?'*

Sitting for Transport

ST 4. Thinking again of yesterday, please estimate the **total** time that you spent **sitting** to travel from one place to another. Please include sitting and waiting for transport. Do **not** include any time you were standing up while travelling or waiting.

☐☐ hours ☐☐ minutes

Interviewer clarification: transport includes public and private, waiting for any type of transport and travel to all locations. This would not include time spent travelling as part of work which was reported in ST3 e.g. taxi driver

Television Viewing

ST 5. Please estimate the **total time** you spent sitting or lying down to watch TV or DVDs or play games on the TV, such as play station yesterday? This includes if you watch TV in bed.

Remember, your answer can be given in hours and/or minutes.

☐☐ hours ☐☐ minutes

Computer, Internet, Electronic Games

ST 6. Please estimate the total time yesterday that you spent sitting or lying down and using the computer. For example, include time spent playing games, internet activities.

☐☐ hours ☐☐ minutes

Interviewer: if the respondent reported working include the prompt 'Do not include time spent doing paid work on the computer as this should have been included in the previous question about sitting for work.'

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Reading

ST 7. Please estimate the total time yesterday that you spent sitting or lying down while reading during your leisure time. Include reading in bed but do not include time spent reading for paid work.

☐☐ hours ☐☐ minutes

Hobbies

ST 8. Please estimate the total time yesterday that you spent sitting or lying down for hobbies. For example, doing art, craft or cross words.

☐☐ hours ☐☐ minutes

Sitting/lying for other purposes

ST 9. We are interested in any other sitting or lying down that you may have done that you have not already told us. For example this could include socializing with friends or family including time on the telephone; eating meals; or listening to music.

Again thinking of yesterday, please estimate the **total time** that you spent sitting or lying down **NOT** including time that you have told us about in the previous answers.

☐☐ hours ☐☐ minutes

Interviewer: if the respondent has difficulty, you can reassure them that their best estimate will be OK.

That's all the questions we have for you about the time you spent sitting or lying down yesterday. Thinking back on your answers, is there anything you would like to change?

Interviewer: This will give the participant an opportunity to confirm that they have given an accurate response to each question. Please change responses as required.

If the participant has reported sitting for over 16 hours in the day prompt them to consider their answers by saying 'I've got here that you spent ….. sitting yesterday. Are there any times where you might have over-estimated or doubled up on reporting sitting time?'

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The 3 Incontinence Questions (3IQ) Assessment Tool

The 3IQ is a patient questionnaire that helps your doctor distinguish urgency incontinence from stress incontinence. It should take no more than a couple of minutes. Complete the quiz and bring it to your next appointment.

1. During the last 3 months, have you leaked urine (even a small amount)?

☐ Yes ☐ No (if this response is marked, the 3IQ test is complete)

2. During the last 3 months, did you leak urine (check all that apply):

☐ When you were performing some physical activity, such as coughing, sneezing, lifting, or exercising?

☐ When you had the urge or the feeling that you needed to empty your bladder, but you could not get to the toilet fast enough?

☐ Without physical activity and without sense of urgency?

3. During the last 3 months, did you leak urine most often (check only one):

☐ When you were performing some physical activity, such as coughing, sneezing, lifting, or exercising?

☐ When you had the urge or the feeling that you needed to empty your bladder, but you could not get to the toilet fast enough?

☐ Without physical activity and without a sense of urgency?

☐ About equally as often with physical activity as with a sense of urgency?

Definitions of type of urinary incontinence are based on responses to question 3.

Response to Question 3	Type of Incontinence
Most often with physical activity	Stress only or stress predominant
Most often with the urge to empty the bladder	Urgency only or urgency predominant
Without physical activity or sense of urgency	Other cause only or other cause predominant
About equally with physical activity and sense of urgency	Mixed

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QOL-B QUALITY OF LIFE QUESTIONNAIRE – BRONCHIECTASIS

Understanding the impact of your illness and treatments on your everyday life can help your doctor monitor your health and adjust your treatments. For this reason, we have developed a quality of life questionnaire specifically for people who have bronchiectasis. Thank you for your willingness to complete this questionnaire.

Instructions: The following questions are about the current state of your health, as you perceive it. This information will allow us to better understand how you feel in your everyday life.

Please answer all the questions. There are **no** right or wrong answers! If you are not sure how to answer, choose the response that seems closest to your situation.

Demographics

Please fill in the information or tick the box indicating your answer.

A. What is your date of birth?
Date ☐☐/☐☐/☐☐☐☐
Day Month Year

B. What is your gender?
☐ Male ☐ Female

C. During the **past week**, have you been on holidays or not studying or working for reasons **NOT** related to your health?
☐ Yes ☐ No

D. What is your current marital status?
☐ Single/never married
☐ Married
☐ Widowed
☐ Divorced
☐ Separated
☐ Remarried
☐ With a partner

E. Which of the following best describes your ethnic group?
☐ Caucasian
☐ Asian
☐ Australian Aboriginal or Torres Strait Islander
☐ Other (please describe) _____
☐ Prefer not to answer this question

F. What is the highest level of education you have achieved?
☐ Year 11 or below
☐ Year 12
☐ Advanced Diploma and Diploma
☐ Certificate III/IV
☐ Bachelor Degree
☐ Graduate Diploma and Graduate Certificate
☐ Postgraduate Degree

G. Which of the following best describes your current employment or study status?
☐ Studying outside the home
☐ Studying by distance education
☐ Seeking work
☐ Working full-time or part-time (either outside the home or at a home-based business)
☐ Domestic duties
☐ Not studying or working due to my health
☐ Not working for other reasons/Retired

Continue to Next Page

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QOL-B QUALITY OF LIFE QUESTIONNAIRE – BRONCHIECTASIS

Section I. Quality of Life *Please tick the box indicating your answer.*

During the past week, to what extent have you had difficulty:	A lot of difficulty	Moderate difficulty	A little difficulty	No difficulty
1. Performing vigorous activities, such as gardening or exercising	☐	☐	☐	☐
2. Walking as fast as others (family, friends, etc.)	☐	☐	☐	☐
3. Carrying heavy things, such as books, groceries, or shopping bags	☐	☐	☐	☐
4. Climbing one flight of stairs	☐	☐	☐	☐

During the past week, indicate how often:	Always	Often	Sometimes	Never
5. You felt well	☐	☐	☐	☐
6. You felt tired	☐	☐	☐	☐
7. You felt anxious	☐	☐	☐	☐
8. You felt energetic	☐	☐	☐	☐
9. You felt exhausted	☐	☐	☐	☐
10. You felt sad	☐	☐	☐	☐
11. You felt depressed	☐	☐	☐	☐

Are you currently on any treatments (such as oral or inhaled medications, a PEP, Flutter® or Acapella® device, chest physiotherapy, or Vest) for bronchiectasis?

☐ Yes ☐ No (Go to Question 15 on the next page)

Please circle the number indicating your answer. Please choose only one answer for each question.

12. To what extent do your treatments for bronchiectasis make your daily life more difficult?
    1. Not at all
    2. A little
    3. Moderately
    4. A lot

13. How much time do you currently spend each day on your treatments for bronchiectasis?
    1. A lot
    2. A moderate amount
    3. A little
    4. Almost none

14. How difficult is it for you to fit in your treatments for bronchiectasis each day?
    1. Not at all
    2. A little
    3. Moderately
    4. Very

Continue to Next Page

INVESTIGATING BRONCHIECTASIS – EVALUATING PHENOTYPES (IBEEP) THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

QOL-B QUALITY OF LIFE QUESTIONNAIRE – BRONCHIECTASIS

Please circle the number indicating your answer. Please choose only one answer for each question.

15. How do you think your health is now?
1. Excellent
2. Good
3. Fair
4. Poor

Please tick a box to indicate your answer.
Thinking about your health during the past week, indicate the extent to which each sentence is true for you.

	Completely true	Mostly true	A little true	Not at all true	
16. I have to limit vigorous activities, such as walking or exercising	☐	☐	☐	☐	
17. I have to stay at home more than I want to	☐	☐	☐	☐	
18. I am worried about being exposed to others who are sick	☐	☐	☐	☐	Doesn't apply
19. It is difficult to be intimate with a partner (kissing, hugging, sexual activity)	☐	☐	☐	☐	☐
20. I lead a normal life	☐	☐	☐	☐	
21. I am concerned that my health will get worse	☐	☐	☐	☐	
22. I think my coughing bothers others	☐	☐	☐	☐	
23. I often feel lonely	☐	☐	☐	☐	
24. I feel healthy	☐	☐	☐	☐	
25. It is difficult to make plans for the future (holidays, attending family events, etc.)	☐	☐	☐	☐	
26. I feel embarrassed when I am coughing	☐	☐	☐	☐	

Please circle the number or tick the box indicating your answer.

During the past week:

27. To what extent did you have trouble keeping up with your job, housework, or other daily activities?
1. You have had no trouble keeping up
2. You have managed to keep up but it's been difficult
3. You have been behind
4. You have not been able to do these activities at all

	Always	Often	Sometimes	Never
28. How often does having bronchiectasis get in the way of meeting your work, household, family, or personal goals?	☐	☐	☐	☐

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INVESTIGATING BRONCHIECTASIS – EVALUATING PHENOTYPES (IBEEP) THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

QOL-B QUALITY OF LIFE QUESTIONNAIRE – BRONCHIECTASIS

Section II. Respiratory Symptoms

Please tick the box indicating your answer.

Indicate how you have been feeling during the past week:	A lot	A moderate amount	A little	Not at all
29. Have you felt congestion in your chest?	☐	☐	☐	☐
30. Have you been coughing during the day?	☐	☐	☐	☐
31. Have you had to cough up mucus?	☐	☐	☐	☐

32. Has your sputum been mostly:
☐ Clear ☐ Clear to yellow ☐ Yellowish-green
☐ Brownish to dark ☐ Green with traces of blood ☐ Don't know

How often during the past week:	Always	Often	Sometimes	Never
33. Have you had shortness of breath with greater activity, such as housework or gardening?	☐	☐	☐	☐
34. Have you been wheezing?	☐	☐	☐	☐
35. Have you had chest pain?	☐	☐	☐	☐
36. Have you had shortness of breath when talking?	☐	☐	☐	☐
37. Have you woken up during the night because you were coughing?	☐	☐	☐	☐

Please make sure you have answered all the questions.

THANK YOU FOR YOUR COOPERATION!

INVESTIGATING BRONCHIECTASIS – EVALUATING PHENOTYPES (IBEEP) THE UNIVERSITY OF NEWCASTLE HUNTER NEW ENGLAND AREA HEALTH SERVICE			
ID_____	INITIALS_____	DATE ____/____/____	VISIT____

Common cold questionnaire (complete only if there is a suspected virus)

SUBJECT No:_____**Date:**_____**INITIALS:**_____

In the past two days have you experienced any of the following:

	NONE	MILD	MODERATE	SEVERE
A General Symptoms:				
4. Fevers	☐	☐	☐	☐
5. Chills	☐	☐	☐	☐
6. Muscle pains	☐	☐	☐	☐
B. Nasal Symptoms:				
4. Watery eyes	☐	☐	☐	☐
5. Runny nose	☐	☐	☐	☐
6. Sneezing	☐	☐	☐	☐
C. Throat Symptoms:				
2. Sore throat	☐	☐	☐	☐
E. Chest Symptoms:				
3. Cough	☐	☐	☐	☐
4. Chest pain	☐	☐	☐	☐
E. Photophobia:	☐	☐	☐	☐

- A probable viral infection is where there are moderate symptoms noted in at least two of the above four categories or mild symptoms noted in three or more categories.
- A possible viral infection is where mild symptoms are noted in one category plus a cough.

Probable Viral: **Yes** ☐ **No** ☐

Possible Viral: **Yes** ☐ **No** ☐

Infected Controls must have a probable or possible infection
All other subjects must have none of the symptoms listed with the exception of cough ***- IF RETURN A POSITIVE RESPONSE PLEASE RE-BOOK FOR FOUR WEEKS TIME***

APPENDIX XI: PHYSICAL ACTIVITY DIARY

Participant logbook

Participant ID:	
ID number Actigraph:	
ID number activPAL:	
Start date:	/ /
End date:	/ /

If you have any questions about this diary, please contact:

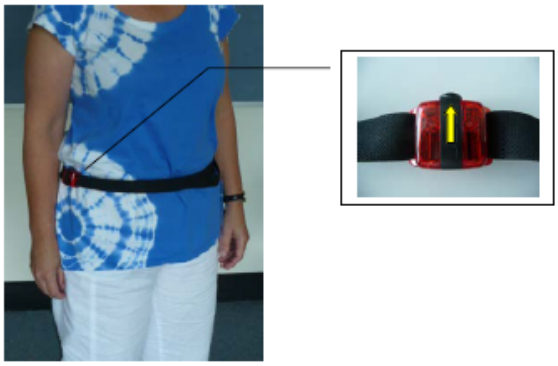
Name:_____ **Tel:**_____

email:_____

How to wear your activity monitors

Activity monitor around the waist (Actigraph monitor)

The red activity monitor that is attached to the belt can be worn either above or below clothing. It is not necessary for this monitor to make contact with the skin. However, the monitor must be held snugly against the body to collect optimal data. Some people find it helpful to loop the belt through the belt loops of trousers to keep it in place. The elastic runs through the back of the device, this side should be against your body/clothing, with the 'front' facing out and black button facing up. Please wear the monitor on your _____hip and keep the placement consistent over the fourteen days. See picture for an example of how to put the belt on.



If you are having problems with the monitors, the instructions below will help you further:

- The belt doesn't stay in position:
  - It may help if you tighten the belt
- The monitor fell in the toilet/water:
  - Please take the monitor out of the water as quickly as possible and contact one of our staff
- Your skin shows a rash or becomes very itchy:
  - Try wearing the belt over clothing.

How to wash the belt

If you need to wash the belt of a monitor, **remove the monitor** before hand-washing the belt in warm soapy water. Hang them out to dry completely. Reassemble and wear the monitor again ASAP. Do NOT machine wash or dry or iron them.

1

Activity monitor on the thigh (AcitvPAL monitor)
HMRI staff will apply the thigh monitor at your study appointment. Please check your monitor every day as per the following:

1. **Check the skin around the dressing every day**. Look for signs of skin reaction: redness, itchiness, irritation or discomfort. If there is a reaction, remove the white dressing and reattach the monitor to your thigh away from the reaction. (See **How to reapply your activPAL monitor**).

2. **Check the stickiness of your white dressing every day.** If the dressing starts to peel off, remove the dressing and reattach the monitor to your thigh with a new white dressing (**See How to reapply your activPAL monitor**)

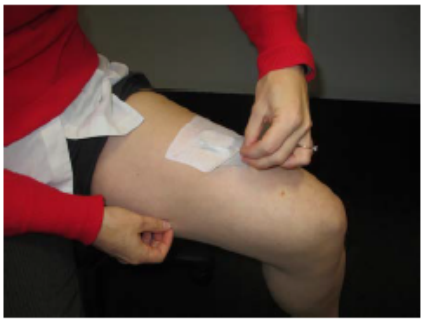
3. **Remove the white dressing and reattach the monitor with a fresh dressing after 3-4 days** if you have not already done this because of stickiness or skin reaction (**See How to reapply your activPAL monitor**)

4. If a skin reaction does not subside and you cannot tolerate the monitor, please remove it and contact HMRI (use the phone number on the front page). Please record this in this logbook.

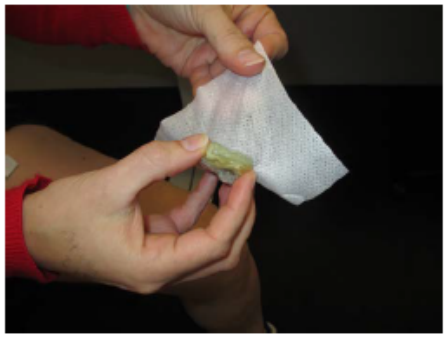
5. If you accidently drop the monitor in water please dry it as quickly as possible and contact HMRI (use the phone number on the front page).

How to reapply your activPAL monitor

1. **Sit down.** This makes sure the skin on your thigh is stretched.
2. Gently peel the white dressing off your skin. It will be more comfortable if you peel in the same direction as the hair growth.

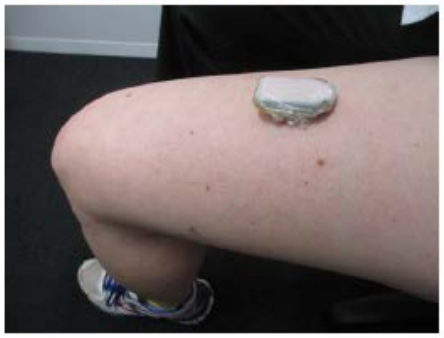


3. Remove the wrapped monitor from the white dressing and throw out the white dressing. **Please DO NOT remove the clear cover on from the monitor.**

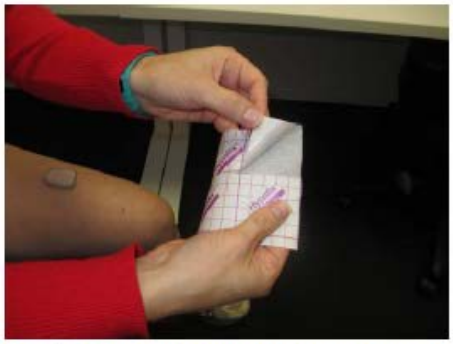


4. Get a fresh 8x10cm piece of white dressing
5. Dry your thigh completely

6. Place the monitor on the ***front of your thigh*** with the ***rounded edge pointing towards your hip***. Place it on away from the skin you have just removed it from.



7. Peel the paper off the fresh white dressing



8. Stick the monitor to your thigh using the fresh white dressing. Try to avoid any creases in the dressing.

4

For a reliable measurement, we ask you to wear the two monitors every day and every night for 14 days (even when you are sleeping). The waist monitor is not waterproof and must be taken off when showering, bathing or swimming. The thigh monitor is waterproof if kept in the clear waterproof cover; however you may choose to replace the white dressing after getting it wet (See **How to reapply your thigh monitor**). Please record the times you did not wear the monitors in this logbook. Store the monitor in a dry, cool, safe place while you are not wearing it

How to complete your activity logbook

Please complete this logbook **every day for 14 consecutive days starting with tomorrow**.

- General information about your day: date, day of the week, the time that you woke up in the morning, and the time you went to bed that night.
- Any time you did not wear your monitor/s during the day, for example to go swimming or take a shower.
- Anything else you want to tell us about your day - did anything unusual happen during the day?

5

DAY 1

Date: ...../...../..... Mon / Tue / Wed / Thurs / Fri / Sat / Sun

Time you **woke up** : AM/PM

Time you **went to bed** : AM/PM

Were there any points in the day that you took the **waist monitor** off?

O No

O Yes → please tell us when you did not wear the **waist monitor**

Time taken off : AM/PM Time put on again : AM/PM

Reason not worn: _____

Time taken off : AM/PM Time put on again : AM/PM

Reason not worn: _____

Were there any points in the day that you took the **thigh monitor** off?

O No

O Yes → please tell us when you did not wear the **thigh monitor**

Time taken off : AM/PM Time put on again : AM/PM

Reason not worn: _____

Time taken off : AM/PM Time put on again : AM/PM

Reason not worn: _____

Any nap? _____ start nap time: _____ finish nap time: _____

Is there any other information you would like to tell us about your activities today?

_____

6

DAY 14

Date: ...../...../..... Mon / Tue / Wed / Thurs / Fri / Sat / Sun

Time you **woke up** : AM/PM

Time you **went to bed** : AM/PM

Were there any points in the day that you took the **waist monitor** off?

O No

O Yes → please tell us when you did not wear the **waist monitor**

Time taken off : AM/PM Time put on again : AM/PM

Reason not worn: _____

Time taken off : AM/PM Time put on again : AM/PM

Reason not worn: _____

Were there any points in the day that you took the **thigh monitor** off?

O No

O Yes → please tell us when you did not wear the **thigh monitor**

Time taken off : AM/PM Time put on again : AM/PM

Reason not worn: _____

Time taken off : AM/PM Time put on again : AM/PM

Reason not worn: _____

Any nap? _____ start nap time: _____ finish nap time: _____

Is there any other information you would like to tell us about your activities today?

_____

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You have now completed this logbook. Please hand it over to us the next time we visit you.

Thank you very much

we appreciate your time and effort

Acknowledgements and thanks to Paul Gardiner and Geeske Peeters from University of Queensland for their assistance with this log book.