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Investigating the Measurement of Physical Activity and Associated Factors in Youth and Adults with Cystic Fibrosis

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Dedication

In dedication to my precious family, Ryan, Elza, Mariangela and Fatima

for your loving support and encouragement.

"If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health."

Hippocrates, 450 B.C.

Abstract

Cystic Fibrosis (CF) is a multisystemic condition that affects almost every organ in the body, but especially the lungs. Regular physical activity (PA) can significantly slow disease progression and has become a crucial part of CF care. Previous research evaluating PA in CF has been hindered by the use of cut-points developed for healthy populations and the investigation of collinear movement behaviours as independent entities, both of which are likely to have confounded their findings and any subsequent inferences regarding associated health outcomes. Therefore, the overall aim of this thesis was to investigate the measurement and analysis of PA in those with CF.

An initial systematic review provided recommendations for research calibrating accelerometry in paediatric clinical populations, highlighting that the pathophysiology of the condition must be accounted for and that the protocol should include a broad range of activities varying in intensity (**Chapter 4**). Subsequently, **Chapter 5** developed and cross-validated raw acceleration CF-specific cut-points in youth which were then further assessed in **Chapter 6,** demonstrating that the CF-specific thresholds were associated with higher levels of moderate-to-vigorous physical activity (MVPA) and sedentary time (SED) and lower levels of light PA compared to generic cut-points. Furthermore, lung function was associated with light PA when using condition-specific thresholds. Further investigation of the relationship between PA and health in **Chapter 7** found that reallocating time from sedentary to any other behaviour was beneficial for lung function, with the greatest improvements observed when SED was reallocated to sleep or MVPA. Finally, **Chapter 8** developed and validated machine learning algorithms that achieved excellent accuracy to classify PA types and intensities in youth with CF.

In conclusion, these findings significantly advance the assessment of PA, enhancing our understanding of the relationship between PA and health in CF and informing future condition-specific PA guidelines, care strategies and interventions.

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Declaration and Statements

Statement 1 I, Mayara Silveira Bianchim, declare that this work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

Statement 2 I, Mayara Silveira Bianchim, state that this thesis is the result of my own investigations.

Statement 3 I, Mayara Silveira Bianchim, declare that I give my consent for the thesis, if accepted, to be made available online in the University's Open Access Repository and for inter-library loan, and for the title and summary to be made available to outside organisations.

Signed: _[redacted]_ (candidate)

Date: 22 / 01 / 2021

Contents

Glossary of Terms and Abbreviations

ANOVA	Analysis of Variance
AUC	Area under the curve
AG	ActiGraph
BMC	Bone Mineral Content
BMD	Bone Mineral Density
BMI	Body Mass Index
zBMI	z-score Body Mass Index
CF	Cystic Fibrosis
CHAQ	Childhood Health Assessment Questionnaire
CHD	Congenital Heart Disease
CI	Confidence Interval
Cl^-	Chloride
CO_2	Carbon Dioxide
CP	Cerebral Palsy
CPET	Cardiopulmonary Exercise Test
CSA	Computer Science Application
CFQ	Cystic Fibrosis Questionnaire
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator (gene)
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator (protein)
CFRD	Cystic Fibrosis Related Diabetes
DIOS	Distal Intestinal Obstruction Syndrome
ECG	Electrocardiogram
EE	Energy Expenditure
ENMO	Euclidean Norm Minus One
FVC	Forced Vital Capacity
$FEV_1\%_{predicted}$	Forced Expiratory Volume in one Second Predicted
GE	GENEActiv
GET	Gas Exchange Threshold
GMFCS	Gross Motor Function Classification System
HE	Haemophilia
HR	Heart Rate

HREC	Human Research Ethics Committee
Ilr	Isometric Log-ratio
IMD	Idiopathic Muscular Dystrophies
IPAQ	International Physical Activity Questionnaire
JIA	Juvenile Idiopathic Arthritis
k-NN	k-Nearest Neighbour
LOA	Limits of Agreement
LOOCV	Leave-one-out Cross-validation
LPA	Light Physical Activity
MAD	Mean Amplitude Deviation
MIX REG	Linear Mixed Model Regression
MS	Multiple Sclerosis
MSE	Mean Squared Error
MET	Metabolic Equivalent of Task
MPA	Moderate Physical Activity
MVPA	Moderate-to-Vigorous Physical Activity
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
O_2	Oxygen
OLR	Ordinary Linear Regression
PA	Physical Activity
PAR	Physical Activity Recall
PD	Parkinson's Disease
PedsQL	Pediatric Quality of Life Inventory
PHV	Peak Height Velocity
PICO	Population Intervention Comparison Outcome
QoL	Quality of Life
RMR	Resting Metabolic Rate
ROC	Receiver Operating Characteristics Analysis
RT3	Research Tracker Accelerometer
SD	Standard Deviation
SRC	Strategic Research Centre
Se	Sensitivity

SED	Sedentary Time
Sp	Specificity
SpO_2	Oxygen Saturation
UK	United Kingdom
USA	United States of America
VA	Vertical Axis
VM	Vector Magnitude
VPA	Vigorous Physical Activity
$\dot{V}O_2$	Oxygen Uptake
$\dot{V}O_{2peak}$	Peak Oxygen Uptake
$V_E/\dot{V}O_2$	Ventilatory equivalents for oxygen uptake
WHO	World Health Organisation
XGBoost	eXtreme Gradient Boost

Units and Symbols

counts·min^{-1}	Counts per minute
counts·15 s^{-1}	Counts per fifteen seconds
cm	Centimetres
cm^{3}	Cubic centimetre
deg·sec^{-1}	Degrees per seconds
g	Grams
g	Gravity
G	Gravitational Constant
mg	Milligravity
mg	Miligram
mm	Milimetre
g·cm^{-2}	Grams per centimetre squared
h	Hour
Hz	Hertz
kg	Kilogram
kg·m^{-2}	Kilogram per meter squared
L	Litres
L·min^{-1}	Litres per minute
min	Minutes
mmol·L^{-1}	Milimolar per litre
ml·kg^{-1}	Millilitre per kilogram
ml·min^{-1}·kg^{-1}	Millilitre per minute per kilogram
mg·dL^{-1}	Milligrams per decilitre
m·s^{-2}	Metre per second squared
s	Second
%	Percentage

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Equation 3.1 BMI = body mass (kg) / stature (m^2)

Equation 3.2 z-score (or SD-score) = (observed value - median value of the reference population) / standard deviation value of reference population

Equation 3.3 Boys: *Maturity offset (years)* = - 9.236 + (0.0002708*(leg length*sitting height)) + (−0.001663*(age*leg length)) + (0.007216*(age*sitting height)) + (0.02292*(weight ÷ height*100))

Equation 3.4 Girls: *Maturity offset (years)* = - 9.376 + (0.0001882*(leg length*sitting height)) + (0.0022*(age*leg length)) + (0.005841*(age*sitting height)) + (- 0.002658*(age*weight)) + (0.07693*(weight ÷ height*100))

Equation 3.5 $RMR = 1.44(3.94 \cdot \dot{V}O_2 + 1.11 \cdot \dot{V}CO_2)$

Equation 3.6 *J* = maximum (sensitivity(c) + specificity(c) – 1)

Equation 3.7 $$z_i = \sqrt{\frac{D-i}{D-i+1}}\ ln\frac{xi}{\sqrt[D-i]{\Pi_j^D = i+\ 1^{x_j}}}, for\ i = 1, \dots, D-1$$

Equation 6.1

$$\left\{(X^1, \ldots, X^D) \in \mathbb{R}^D : \sum_{j=1}^{D} X^j = 1, X^j > 0 \; for \; j = 1, \ldots, D\right\}$$

where

$$D = d + 1$$

Equation 6.2

$$z_i = \sqrt{\frac{D-i}{D-i+1}}\; ln \frac{xi}{\sqrt[D-i]{\Pi_j^D = i + 1^{x_j}}}, for \; i = 1, \ldots, D-1$$

CHAPTER 1

Introduction

Cystic Fibrosis (CF) is an autosomal recessive condition more prevalent in the Caucasian population, currently affecting more than 100,000 individuals worldwide and 10,500 people in the United Kingdom (UK; Cystic Fibrosis Trust, 2018). Whilst a cure is yet to be found, life expectancy has increased progressively to a median survival age of 48 and 44 years for males and females, respectively, due to a broader understanding of the condition and advancements in treatments (Keogh & Stanojevic, 2018). Cystic Fibrosis is caused by a single mutation in the long arm of chromosome seven that translates to a chloride channel protein. The result is a chloride channel with abnormal function that causes a disruption in the homeostasis of electrolytes throughout the whole body, but particularly in the lungs and pancreas (Hull, 2012). Consequently, CF is characterised, amongst other things, by progressive lung disease and malnutrition, with the most common cause of death being respiratory failure (Elborn, 2016; Radtke et al., 2017).

Physical activity (PA) is a broad term describing any bodily movement produced by skeletal muscles that requires energy expenditure, and encompasses activities including, but not limited to, leisure, household, transport, sport and exercise (Caspersen et al., 1985). Among many other benefits, in those with CF, regular PA maintains pulmonary function, reduces the number of hospitalisations and improves overall health (Hebestreit et al., 2014). More specifically, exercise, a sub-component of PA, in those with CF improves blood glucose control (Foster et al., 2018), bone mineral density (Selvadurai et al., 2002), pulmonary clearance (Cox et al., 2018), quality of life (QoL; Hebestreit et al., 2014) and aerobic capacity independent of lung function, age or gender (Cox et al., 2018). Therefore, regular PA is vital to the maintenance of lung function, enhancing prognosis, survival and quality of life in those with CF (Paranjape et al., 2012; Schneiderman et al., 2013). Despite the crucial importance of PA, children and adolescents with CF, become less physically active with age (Bacil et al., 2015). However, whilst age-related declines are similarly reported in healthy children as they approach maturation (Bacil et al., 2015), the declines appear to be greater, and possibly from a lower baseline, in those with CF (Nixon et al., 2001). Of concern, physical inactivity has serious implications for those with CF, such as decreased aerobic capacity, reduced life expectancy and accelerated disease progression (Radtke et al., 2017).

Despite the recognised benefits associated with regular PA for children with CF, there is still a dearth of research objectively assessing PA levels in those populations (Kilbride et al., 2012; Mackintosh et al., 2018; Selvadurai et al., 2004). Consequently, there is little consensus on PA levels in paediatric CF populations, which is particularly concerning given the contribution of physical inactivity in accelerating disease progression (Troosters et al., 2009). Indeed, Aznar et al. (2014) reported that as little as 2.1% of children with CF achieved the recommended 60 minutes of moderate-to-vigorous physical activity (MVPA) daily (Department of Health and Social Care, 2019), but engaged in more total PA, largely accumulated from lower intensities, in comparison with their healthy peers. In contrast, Selvadurai et al. (2004) reported that no significant differences in PA levels were found between children with and without CF. These inconsistent findings may be due to inter-study methodological discrepancies, not least the reduction of raw accelerometer data to arbitrary 'counts', which are associated with major limitations, such as the loss of key information for PA classification (Schmiedek et al., 2016). Indeed, the use of machine learning and/or cut-points developed from raw acceleration metrics have been shown to provide superior accuracy in comparison to counts in healthy children (Schmiedek et al., 2016).

The interpretation of earlier studies reporting PA levels in those with CF is limited by their reliance on cut-points developed for healthy populations, which fail to account for the greater nutritional and energetic demands engendered by the condition (Brage et al., 2019). Specifically, chronic respiratory diseases, such as CF, are often associated with higher energetic demands due to the high cost of breathing and reduced exercise tolerance (Lipert & Jegier, 2017). These demands are likely to translate to a greater relative intensity of a given activity or accelerometry signal, potentially leading to the misclassification of PA intensities, and thus overall PA levels, in those with CF. These issues may be further exacerbated by the delayed onset of puberty (Aswani et al., 2003), as well as a slower rate of progression (Landon & Rosenfeld, 1987), suggested in youth with CF, although these remain controversial (Goldsweig et al., 2019). Indeed, PA levels are likely to change after the onset of puberty in those with CF (Selvadurai et al., 2004). Therefore, the establishment of specific guidance regarding the type, intensity and frequency of PA and exercise that is prescribed is not only required, but would greatly benefit children and adolescents with CF (Cox et al., 2018). It is imperative to ascertain the optimal dose of PA and exercise required to confer health benefits for those with CF.

Regular PA can elicit acute and chronic physiological changes which might vary according to the frequency, duration, intensity and type of the activity. Accelerometers are currently the most widely used method to measure PA among a wide array of available techniques (Lipert & Jegier, 2017; Patterson et al., 2018). Accelerometers are wearable devices able to detect velocity over time, which can be translated into PA patterns and intensities by using cut-points, prediction equations or, more recently, machine learning models (Farrahi et al., 2019; Welk, 2005). Specifically, accelerometers allow the objective measurement of PA intensities, such as light physical activity (LPA) and MVPA, as well as sedentary time (SED). However, an important limitation of using prediction equations and cut-points to derive time spent in the respective intensity domains is that they are highly specific to the population from which they were derived. When such cut-points are applied to other populations or activities other than those on which they were developed, they can significantly over- or underestimate energy expenditure (EE; Serra et al., 2017; Stephens et al., 2016). Indeed, cut-points and predictive equations developed for healthy populations will not account for the altered resting metabolic rate and higher EE demands that are typical in individuals with chronic conditions, such as CF (Bandini et al., 1991; Epstein et al., 1989; Ramsey et al., 1992).

Recently, considerable attention has focussed on machine learning approaches to estimate EE from accelerometer data, with suggestions that this may be the most accurate method for PA classification, providing 99.8% accuracy when applied to free-living behaviours in healthy children (Ahmadi, Chowdhury, et al., 2020; Fergus et al., 2015) and adults (Bonomi, Plasqui, et al., 2009; Doherty et al., 2018; Staudenmayer et al., 2015; Staudenmayer et al., 2009). Furthermore, machine learning has been used in clinical populations, such as Cerebral Palsy (Ahmadi et al., 2018; Trost et al., 2016), demonstrating higher accuracy (> 80%) in comparison with traditional methods (~60%). The detail that can be achieved with machine learning algorithms has the potential to facilitate a greater understanding of the relationship between different PA behaviours and health outcomes.

It is well known that less SED and more time being physically active are associated with multiple health benefits, and therefore, are the targets of the majority of interventions. However, it is pertinent to note the finite nature of PA behaviours, such that any reallocations of behaviour must have reciprocal effects (Aitchison, 1982; Dumuid et al., 2018). Compositional analysis has been suggested to produce more reliable results when compared to traditional approaches, such as regression models. Interestingly, Chastin et al. (2015) found that compositional analysis resulted in different associations between PA and cardiometabolic

health markers in comparison with traditional approaches. This raises important questions as to the most appropriate way to analyse accelerometer data, with little consideration to date of the application of such methods to clinical populations. A more integrated approach that includes all daily activity behaviours could provide crucial information for future PA recommendations (Dumuid et al., 2018); disease-specific measures of PA levels in CF are paramount to advancing our understanding of the association between PA and health outcomes, enabling the tailoring of interventions and recommendations for those with CF.

1.1 Thesis Aims

The overall aim of this thesis was to investigate the PA levels in those with CF. Specifically, the thesis sought to develop CF-specific cut-points for youth, accounting for relevant factors, such as maturity stage and disease severity. A further aim was to use these cut-points to investigate how PA was accumulated in youth with CF. Specifically, this thesis sought to:

Chapter 4 (Study 1) – Provide a thorough systematic review of the literature and draw recommendations for the calibration and cross-validation of accelerometry in children and adolescents with chronic conditions.

Chapter 5 (Study 2) – Develop and cross-validate disease-specific cut-points for the measurement of sedentary, moderate and vigorous activities in children and adolescents with CF and investigate how these thresholds vary according to accelerometer placement and brand.

Chapter 6 (Study 3) – Determine the PA levels in children and adolescents with CF using disease-specific cut-points in order to **(i)** assess whether the PA guidelines for health are being met; and **(ii)** to investigate the association between PA levels and lung function.

Chapter 7 (Study 4) – Use compositional analyses to investigate the association between time spent in sleep, SED, LPA and MVPA with lung function in children and adolescents with CF.

Chapter 8 (Study 5) – Develop and cross-validate machine learning models to predict different activities and intensities in children and adolescents with CF, across different accelerometer brands and placements.

CHAPTER 2

Literature Review

2.1 History of Cystic Fibrosis

The first account of Cystic Fibrosis (CF) was in the 1930s, prior to it even being recognised as a disease when Blackfan and Wolbach (1933) described the condition as a pathology of the pancreas, as well as a lung disease, caused by Vitamin A deficiency. Later, Andersen (1938) defined the condition as 'the cystic fibrosis of the pancreas' (pp. 344 - 396). Thus, the condition was originally considered as originating from a pancreatic failure, leading to malnutrition, growth impairment and pulmonary infection (Davis, 2006). Ten years later, during the heat wave in New York, it was first discovered that some of the infants presenting heat prostration had elevated levels of sodium and chloride in their sweat, which is now a key characteristic of CF diagnosis (Di Sant'Agnese et al., 1953). However, it was not until 1989 that the cause of CF was discovered to be a genetic mutation (Dodge, 2015; Ratjen et al., 2015).

2.2 Pathogenesis of Cystic Fibrosis

Cystic Fibrosis is caused by a mutation in the gene responsible for the transcription of the Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) and is the most common, fatal, hereditary disorder worldwide (Hector et al., 2015). More than 2,000 gene variations are related to CF, but only 150 cause CFTR malfunction. The *CFTR* gene translates to the CFTR chloride channel protein which also has a fundamental role in the secretion of bicarbonate and inhibition of sodium transport. Thus, mutations not only have an impact on the synthesis of CFTR protein, but also on its function, quantity, placement and stability in the cell membrane, which can lead to a broad range of manifestations of the disease, even for individuals with the same genotype (Elborn, 2016; Hector et al., 2015; Ratjen et al., 2015).

Cystic Fibrosis is typically characterised by progressive deterioration in lung function and exocrine pancreatic insufficiency (Somayaji et al., 2017). Indeed, chronic obstructive lung disease, from viscous mucus accumulation, airway inflammation and bacterial infection, is the major cause of morbidity and mortality in CF (Mall & Hartl, 2014). Furthermore, pancreatic

insufficiency results in gastrointestinal malabsorption and malnutrition, which are associated with decreased fat stores, muscle wasting and impaired growth. Whilst single organ manifestations can be present in individuals with residual CFTR function and are considered mild mutations, 'severe mutations' are usually associated with multiple manifestations (Elborn, 2016). Moreover, individuals with CF may also present with secondary manifestations, such as distal intestinal obstruction syndrome (DIOS), CF-related liver disease, oesophageal varices, bone disease, joint and abdominal pain and CF-related diabetes (CFRD; Ratjen et al., 2015).

2.2.1 Cystic Fibrosis Transmembrane Regulator

CFTR mutations are categorised into six classes according to their impact on function; classes I, II and III are considered severe, with no residual function of the CFTR channel, while classes IV, V and VI have some CFTR residual function and are associated with a mild phenotype. Whilst clinically relevant, this classification system is not without problems. Indeed, one class does not always explain the phenotype as one mutation can fall into more than one class (Cutting, 2014). For example, the *Phe508del* is the most common *CFTR* mutation in northern Europeans and is mainly categorised as class II with a misfolded CFTR. However, some small amount of the CFTR protein is transported to the membrane and still functions albeit at severely reduced levels, placing the mutation into classes III and VI (Cutting, 2014; Sosnay et al., 2013; Wilschanski et al., 1995).

2.3 Pathophysiology of Lung Disease in Cystic Fibrosis

Airway disease is of particular importance as the main cause of mortality and morbidity in CF, and is hypothesised to result from an intricate process involving mucus accumulation (Ratjen, 2009). Whilst the pathophysiology of lung disease in CF is yet to be fully understood, the study of CFTR function has provided some understanding of the complex disease manifestations. Specifically, the faulty epithelial CFTR leads to an abnormal transportation of chloride, sodium and bicarbonate, resulting in diminished airway surface hydration in the lungs (Henderson et al., 2014). This inadequate hydration and osmolality causes ciliary instability and collapse, subsequently hindering mucociliary clearance which, in turn, leads to mucus

accumulation (Ratjen, 2009). Diminished hydration of the airway surface also contributes to the impaired transportation of this mucus and may help to explain the changes in the physical properties and adhesion of mucus. Furthermore, the disruption in CFTR function may impair the transportation of bicarbonate, leading to key changes in pH levels that culminate in an increased mucus viscosity and an impaired innate immunity (Elborn, 2016). The accumulation and alteration in the properties of mucus increase the predisposition to infection and airway injury, ultimately leading to loss of airway functionality, and respiratory failure (Ratjen, 2009).

As CFTR regulates the inflammatory response by interacting with integral membrane proteins, it is directly associated with the high number of exacerbations observed in those with CF. Specifically, evidence suggests that the mutation of CFTR causes epithelial cells to become pro-inflammatory compared to healthy cells (Elborn, 2016). The reason for the pro-inflammatory response in CF may be the interaction between the mutated *CFTR* and leukocytes cells. Evidence suggests that the mutated *CFTR* has a direct effect on neutrophil degranulation (Pohl et al., 2014) and on the inflammatory response of macrophages (Bruscia & Bonfield, 2016). Indeed, neutrophilic inflammation releases factors, such as neutrophil elastase, which exacerbate the airway dehydration, increase mucus production and cause significant damage (Elborn, 2016; Ratjen, 2009). In addition, deficiency of CFTR is also linked to abnormal regulatory T cell response (Hector et al., 2015). Despite this, it is currently unknown whether the infection of the airway must precede inflammation to initiate the respiratory disease in CF (Elborn, 2016; Ratjen, 2009). *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Aspergillus* species are among the most common pathogens affecting those with CF and are associated with frequent exacerbations (Bhatt, 2013). Infection control is therefore imperative to avoid tissue damage and subsequent respiratory failure.

2.4 Clinical Manifestations of Cystic Fibrosis Lung Disease

Lung disease in CF is progressive, with a broad range of clinical manifestations that usually involve dyspnea, sputum production and chronic cough (Davies et al. 2007). The onset of CF lung disease consists of air trapping, bronchial wall thickening and bronchiolitis. Subsequent obstructive pulmonary disease occurs as a result of inflammation combined with viscous mucus blockage of the airways and hyperventilation (Somayaji et al., 2017). Persistent inflammation and infections in the airway can cause irreversible damage and bronchiectasis,

which is characterised by structural impairment of the airways (i.e. thickening, dilatation, and herniation). Specifically, bronchiectasis compromises clearance of mucus and leads to further inflammation and infection, which contributes to the vicious cycle of recurrent and persistent pulmonary exacerbations. Subsequently, as a result of lung disease progression, respiratory failure results in hypoxemia and hypoventilation (Don Hayes et al., 2014). In extreme cases, a complex process involving alveolar hypoxia stimulates pulmonary vasoconstriction, which can progress to pulmonary hypertension and cor pulmonale (Don Hayes et al., 2014; Evans et al., 2011).

Objective measures of disease progression are extremely important in chronic conditions, such as CF, in order to tailor treatment and maintenance of the condition. Spirometry is the most common technique to measure pulmonary function in individuals with CF (Scholz et al., 2017; Vilozni et al., 2007). Specifically, forced expiratory volume in the first second (FEV_1) is the main outcome measure derived from spirometry, and is directly associated with survival (Kerem et al., 1992; Taylor-Robinson et al., 2012). Importantly, FEV_1, commonly expressed as percentage of the predicted value ($FEV_1\%_{predicted}$), is also used to grade disease severity as mild (> 70%), moderate (40 - 69%) or severe (< 40%; Davies & Alton, 2009). Diminished FEV_1 rates can indicate an exacerbation and/or poor treatment response, and is used to inform critical clinical decisions in those with CF, such as referral for lung transplant. Therefore, it is vital to distinguish changes in $FEV_1\%_{predicted}$ due to measurement error or normal daily-fluctuations from important clinical alterations related to the progression of airway disease (Taylor-Robinson et al., 2012). It is therefore recommended that additional measures are considered when interpreting any potential changes in lung function. For example, forced vital capacity (FVC), also measured by spirometry, can also indicate obstruction and dynamic collapse of the airways during a forced expiratory manoeuvre (Quanjer & Weiner, 2014).

2.5 Extrapulmonary Manifestations of Cystic Fibrosis

2.5.1 Gastrointestinal Disorders

The impairment of CFTR might also have important consequences to the gastrointestinal tract, specifically involving the pancreas, intestines and liver (Haack et al.,

2013; Somayaji et al., 2017). Indeed, evidence suggests that those with CF present chronic inflammation of the gastrointestinal tract (Somayaji et al., 2017). In the pancreas, the lack of CFTR will result in reduced water content of pancreatic secretions and a decreased in pH level, leading to pancreatic insufficiency in 60 - 80% of individuals with CF (Castellani & Assael, 2017). Pancreatic insufficiency occurs due to the obstructive viscosity of the luminal content, which subsequently progresses to inflammation and fibrosis of the organ. Malnutrition and poor growth are consequences of fat malabsorption due to pancreatic exocrine insufficiency. Ultimately, later in life, the loss of pancreatic function can lead to CFRD, which is associated with a poor prognosis (Moran, Becker, et al., 2010).

2.5.2 Endocrine Comorbidities

As CFTR is expressed in epithelial cells and functions as an important regulator in multiple physiological processes, endocrine comorbidities are common in those with CF. The most common endocrine comorbidity in CF is CFRD due to pancreatic fibrosis, affecting 40-50% of older patients (Castellani & Assael, 2017). Fibrosis of the pancreas is progressive and occasionally affects the insulae, causing reduced insulin secretion (Kayani et al., 2018). Despite showing similar features as type 1 and type 2 diabetes, CFRD is considered as distinct clinical entity, and it is related with worsening of lung disease and increased mortality (Moran, Brunzell, et al., 2010). For example, Okoniewski et al. (2020) found that children with CFRD and poor glycaemic control show lower FEV_1 recovery during acute pulmonary exacerbations. In accordance, improvement in hyperglycaemia control reduces respiratory exacerbations and delay lung disease progression (Castellani & Assael, 2017).

A complex variety of factors contributes to bone disease in CF, such as malnutrition, lung disease severity, poor mobility, steroid use, systemic inflammation, and increased bone turnover. In the late stages of the disease, 50% of individuals with CF are at risk of developing osteopenia, osteoporosis, and consequently, bone fractures. Furthermore, CFTR is also expressed in bone cells and might play an important role on bone metabolism (Castellani & Assael, 2017). Reduced growth velocity is another important endocrine alteration that is often present in CF children and adolescents (Wong et al., 2016). Such delayed growth has been attributed to a diminished pituitary secretion of growth hormone, coupled with chronic inflammation and suboptimal nutrition (Castellani & Assael, 2017; Wong et al., 2016).

Importantly, short stature, specifically height below the 5th United States National Centre for Health Statistics (NCHS) percentile for age, is an independent predictor of mortality and directly associated with disease severity, as an indicator of malnutrition or frequent pulmonary exacerbations (Beker et al., 2001; Vieni et al., 2013; Wong et al., 2016). The implications of delayed growth are a lower lung reserve and delayed skeletal maturation, and it often precedes the onset of CFRD (Wong et al., 2016).

2.6 Epidemiology: Incidence and Mortality of Cystic Fibrosis in the UK

Whilst CF was first described in 1938 as a deadly disease affecting early childhood, the majority of deaths currently occur in adulthood, with CF now considered an adult disorder (Elborn, 2016). Following advances in our understanding of the condition, which enabled more effective therapies, predicted survival has increased from 18 years in 1976 to 47.3 years in 2018 (Figure 2.1; Davis, 2006; Keogh & Stanojevic, 2018). However, CF still poses a significant challenge for the health-care systems as a multi-organ disease that requires multidisciplinary care and age-specific expertise (Elborn, 2016).

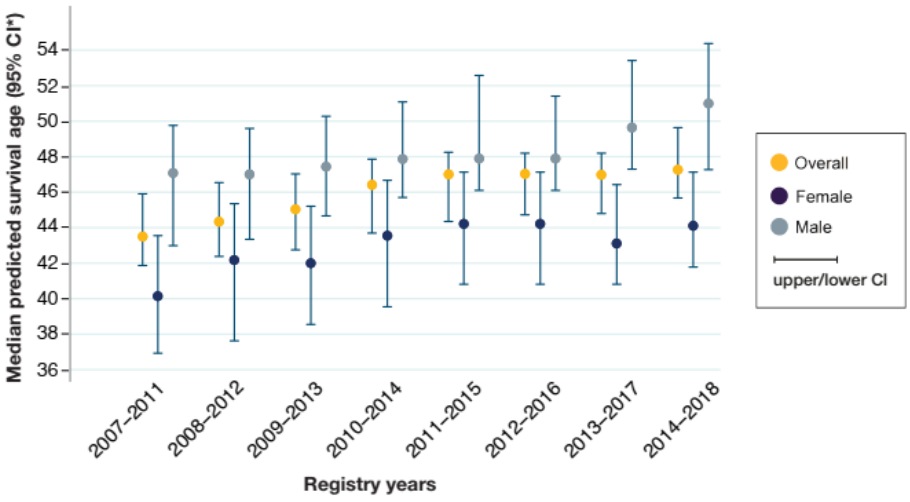


Figure 2.1 Median Predicted Survival age in Cystic Fibrosis

Image adapted from Cystic Fibrosis Trust (2018)

Individuals with CF are recommended daily treatment, which varies according to disease severity but usually involves keeping their lungs free of mucus to avoid infections.

Physiotherapy is one of the foundation treatments, with the techniques used drastically advancing in recent decades. Initially, in the early 1980s, physiotherapy for those with CF comprised solely of airway clearance techniques, and children were recommended to refrain from moderate-to-vigorous physical activity (MVPA). In contrast, the regular practice of physical activity (PA) and exercise are now an integral part of the care for those with CF to counter lung function decline, assist in airway clearance, and improve and maintain bone mineral density, muscle strength and cardiovascular fitness (Cosulich et al., 2017; Lannefors, 2012). Given that regular PA and exercise are key to delay the decline in $FEV_1\%_{predicted}$ (Figure 2.2) and reduce the number of exacerbations, they are also considered as important prognostic indicators (Lannefors, 2012).

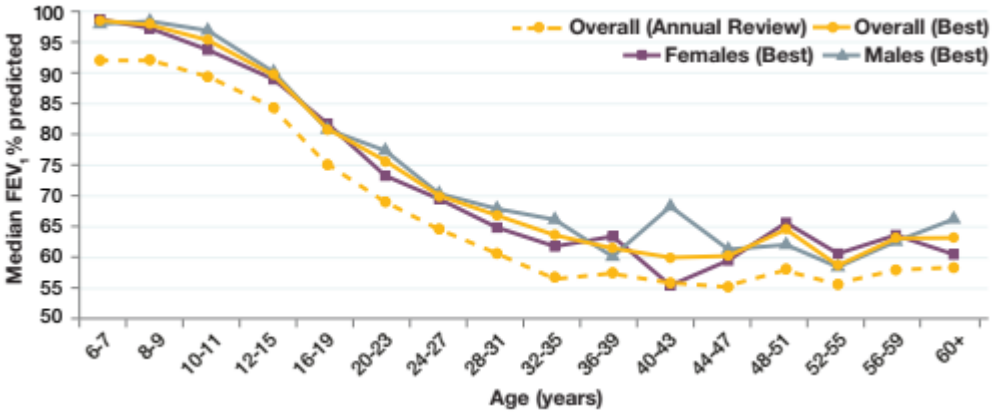


Figure 2.2 Lung Function ($FEV_1\%_{predicted}$) Decline in Cystic Fibrosis

Image adapted from Cystic Fibrosis Trust (2018). Annual review refers to the multidisciplinary yearly assessment conducted in specialist Cystic Fibrosis Centres.

Despite recent efforts to consolidate PA and exercise in the therapeutic routine (Cosulich et al., 2017), those with CF face numerous disease-specific barriers, such as exercise intolerance, in addition to the barriers typically faced by their healthy peers. For example, Denford et al. (2020) identified the lack of enjoyment of PA and family's sedentary lifestyles as barriers to PA that were common to those with and without CF. In contrast, unstable health and a perception of limited control over the condition were barriers to PA exclusive to youth and young adults with CF. Rand and Prasad (2012) also reported that treatment burden is an important factor limiting regular PA in CF populations. The pathophysiological alterations in CF are also the source of exercise intolerance, therefore hindering PA accumulation, which

subsequently reduces the tolerance to exercise even further in a vicious cycle (Wilkes et al., 2009).

2.7 Factors Limiting Exercise Tolerance in Cystic Fibrosis

In addition to constituting one of the barriers to PA, exercise intolerance also has important implications to the measurement of PA in CF. Specifically, the pathologic exercise intolerance is one of the main justifications for the enhanced energetic cost of daily-life activities for those with CF in comparison with their healthy counterparts (Matel & Milla, 2009). Consequently, device-based measures of PA in CF are likely to be misclassified, since those methods are usually calibrated using the energy expenditure (EE) of healthy populations as a reference (Troosters et al., 2009). Exercise intolerance in CF is multifactorial, but particularly occurs due to pulmonary disease, malnutrition and chronic inflammation (Pastré et al., 2014). Additionally, hemodynamic dysfunction and low oxidative efficiency may also contribute to the reduced exercise tolerance in CF. Fielding et al. (2015) found that aerobic performance during maximum cardiopulmonary exercise test (CPET) was significantly lower in CF in comparison with healthy controls. Exercise capacity is usually determined with a CPET and expressed as peak oxygen uptake ($\dot{V}O_{2peak}$), which is defined as the maximum ability to generate energy through aerobic metabolism (Nichols et al., 2015; Vendrusculo et al., 2019). Most importantly, $\dot{V}O_{2peak}$, maximal work rate, and ventilatory equivalents for oxygen uptake ($V_E/\dot{V}O_2$), measured during a CPET, all predict survival in CF (Savi et al., 2013).

2.7.1 Pulmonary Factors

Progressive airway disease with subsequent decreases in FEV_1 are the main pulmonary factors contributing to exercise intolerance in CF. Specifically, those factors culminate in airflow limitation, increased physiological dead space, carbon dioxide retention and static hyperinflation (Bongers et al., 2014; Paolo et al., 2019). The increase in dead space is also exacerbated during exercise, causing a deficit in the ventilatory reserve and ventilatory capacity. Indeed, children and adults with CF often show an increased maximal voluntary ventilation during vigorous activities as a compensation mechanism (Sovtic et al., 2013; Stein et al., 2003). However, this compensation mechanism often results in hyperinflation,

hypoxemia and the premature fatigue of respiratory muscles (de Jong et al., 1997). In particular, exercise induced hypoxemia is a key determinant of exercise intolerance in CF, and it is defined as a reduction of > 4% from the oxygen saturation at rest in children (Narang et al., 2003).

2.7.2 Cardiovascular Factors

As lung disease progresses in CF, pulmonary hypertension and cor pulmonale might affect the structure of the heart, particularly with regard to the right ventricle. Specifically, dilation of the right ventricle causes the heart to assume an abnormal shape, such as a concave curvature with posterior dislocation of the interventricular septum. Consequently, these anatomical abnormalities lead to dysfunctional contraction of the cardiomyocytes and subsequent reductions in stroke volume. Indeed, Van Iterson et al. (2018) showed that those with mild-to-moderate CF had a reduced stroke volume and lower cardiac output during a submaximal exercise test compared to healthy controls. Whilst the cardiomyopathy secondary to lung disease in severe CF is well described in the literature (Sayyid & Sellers, 2017), studies using echocardiography also demonstrated decreased ventricular strain even in those with preserved lung function (Sayyid & Sellers, 2017; Sellers et al., 2015). This is suggested to be due to the effect of the abnormal CFTR on the cardiomyocytes (Sellers et al., 2015), which results in impaired cardiac function. Indeed, Van Iterson et al. (2016) demonstrated that the abnormal cardiac function was strongly related to exercise intolerance during CPET in those with moderate CF.

2.7.3 Nutritional and Metabolic Factors

Nutrition has been reported to be related with longitudinal changes in exercise capacity (Klijn et al., 2003) and skeletal muscle function in CF. Essentially, malnutrition and prolonged nutritional deficits can cause muscle wasting and reductions in fat free mass (Lands et al., 1992; Papalexopoulou et al., 2018). Most importantly, the systematic reduction of peripheral muscle negatively affects lung function and exercise tolerance in CF. Initially, mitochondrial dysfunction was considered as the main cause for the pathophysiological changes in skeletal peripheral muscles in CF (de Meer et al., 1995). However, studies measuring muscle

metabolism during exercise in CF have shown a slower recovery and reduced concentration of substrates in skeletal muscles. In addition, evidence suggests that the peripheral muscle weakness in CF might also result from factors such as calcium dysregulation, systemic inflammation, hypoxemia and enhanced energetic demands (Jaffé & Montgomery, 2005; Selvadurai et al., 2003). It is noteworthy that the exercise intolerance is likely to lead to physical inactivity and consequently further aggravate the systemic muscle weakness (Dupont et al., 2009). Finally, whilst inactivity is not the main cause for muscle weakness, PA plays a crucial role in exercise tolerance and muscle strength in CF (Dupont et al., 2009).

2.8 Physical Activity and Sedentary Behaviour

Defined as *"any bodily movement produced by skeletal muscles that results in energy expenditure above resting"* (Caspersen et al., 1985; page 126), PA is usually classified according to activity intensity, specifically light (LPA), moderate (MPA) and vigorous (VPA) physical activity. Additionally, as PA is habitual, it can also be categorised as occupational, household, transport and sports, for example. Exercise, a subcomponent of PA, is planned and structured with a focus on maintaining or improving fitness (Caspersen et al., 1985). The recommendation that children and adolescents should accumulate at least 60 minutes of MVPA per day across the week are in place for non-clinical populations (Chief Medical Officers, 2019).

The Sedentary Behaviour Research Network defined sedentary behaviour as any waking behaviour eliciting an enery expenditure (EE) below 1.5 metabolic equivalents of task (METs) whilst in a sitting, reclining or lying posture; and sedentary time (SED) as the time spent in sedentary behaviour (Tremblay et al., 2017). It is noteworthy that sedentary behaviour and physical inactivity are not synonyms (Pate et al., 2008). More specifically, physical inactivity is a well recognised risk factor accounting for 9% of premature mortality worldwide (Lee et al., 2012), and it is defined as insufficient PA levels to meet the current guidelines (Tremblay et al., 2017). Indeed, van der Ploeg and Melvyn (2017) highlighted that it is possible to accumulate large amounts of both MVPA and SED in the course of a day. Most importantly, the accurate estimation of SED and MVPA in CF is vital in order to establish their impact on health, and, subsequently, inform strategies and guidelines in this population.

2.9 The Impact of Physical Activity on Health in those with Cystic Fibrosis

The benefits of PA and exercise in healthy populations are well established, particularly those associated with MVPA (Warburton et al., 2010); regular PA and exercise provide protective effects and are directly associated with a healthy cardiometabolic profile across the life span. In those with CF, PA is positively correlated with lung function, aerobic capacity, exercise tolerance, nutritional status and quality of life (QoL) in both children (Hebestreit et al., 2006; Hebestreit et al., 2014; Schneiderman et al., 2014) and adults (Savi, Di Paolo, et al., 2015; Shelley et al., 2019). Furthermore, regular PA increases airway clearance and leads to a reduction in exacerbations and hospitalisations (Savi et al., 2013; Swisher & Erickson, 2008). Consequently, the National Institute for Health and Care Excellence (NICE) guidelines advise the use of PA and exercise as part of the management of CF, to maintain respiratory function or slow respiratory function decline, facilitate sputum clearance, improve bone density, and benefit the musculoskeletal system (Cosulich et al., 2017).

2.9.1 Physical Activity and Exercise Capacity

When exercise was first investigated as a possible therapeutic tool for people with CF (Godfrey & Mearns, 1971), aerobic training was considered to be more beneficial than anaerobic training. Subsequently, regular aerobic exercise training has been evidenced to slow lung function decline and increase exercise tolerance in children with CF (Schneiderman-Walker et al. 2000; Swisher et al. 2015). Additionally, regular PA seems to be related with the maintenance of increased aerobic capacity following an exercise intervention even during exacerbations (Selvadurai et al., 2002). Specifically, Selvadurai et al. (2002) developed a randomised controlled intervention to assess the impact of performing aerobic and resistance training in children with CF, during a hospital admission as a result of an acute exacerbation. The aerobic group showed significantly better peak aerobic capacity and PA levels in comparison with no training or resistance training, which were maintained four weeks after the intervention (Selvadurai et al., 2002). It is hypothesised that the increased PA is likely to explain the maintained aerobic capacity following intervention cessation. This is congruent with previous research which suggests that PA promotion has a positive impact on aerobic capacity in those with CF, although it is noteworthy that causality cannot be established given

their cross-sectional design (Hebestreit et al., 2006; Savi, Di Paolo, et al., 2015; Troosters et al., 2009). In addition, regular PA, particularly MPA and VPA, are a significant predictor of exercise capacity in CF, even after adjusting for confounders such as body size, sex, lung function, and muscle-power (Hebestreit et al., 2006). Improvements in PA levels and aerobic capacity were also shown at the six- to eight-week follow-up of a four-week home-based behavioural program to increase PA in children with CF (Light et al., 1998). However, the small sample size, subjective assessment of PA and short intervention duration warrants caution when interpreting these results.

2.9.2 Physical Activity and Lung Function

Several studies have demonstrated the benefits of PA and exercise for the maintenance (Hebestreit et al., 2010; Schneiderman-Walker et al., 2000) or improvement (Paranjape et al., 2012) of lung function. Specifically, exercise programs have been shown to be effective at delaying lung function decline in children and adolescents with CF (Hebestreit et al., 2010; Schneiderman-Walker et al., 2000). However, a few studies found that exercise interventions only improved FVC (Moorcroft et al., 2004; Schneiderman-Walker et al., 2000), with no effect on FEV_1 (Klijn et al., 2004; Kriemler et al., 2016). One possible explanation is that long-term regular PA is important for lung function maintenance and therefore short intervention durations would not be sufficient to confer such benefits. Indeed, a longitudinal study following children and adolescents with CF for nine years demonstrated that those with high levels of self-reported PA had a reduced FEV_1 decline in comparison to those who had lower PA levels (Schneiderman et al., 2013). Furthermore, an increased PA was also associated with a reduced decline in FEV_1, even at low intensities (Schneiderman et al., 2013). Nonetheless, research investigating the association, or effect, of PA with lung function in CF remains sparse, and have often relied on subjective measures of PA, which are associated with inherent problems such as recall bias (Celis-Morales et al., 2012).

Currently, there is a dearth of research and a lack of consensus regarding the PA levels in children and adolescents with CF. The scarcity of research and discrepancy regarding PA levels in CF affects the understanding of the relationship between PA and lung function. For example, Mackintosh et al. (2018) found that LPA was associated with lung function in children with CF, whereas Cox et al. (2018) found that 30 minutes of MVPA daily was

associated with lung function in adults with CF. While Savi, Simmonds, et al. (2015) suggested that lower PA levels were associated with more exacerbations in adults with CF, this association was not sustained after adjusting for age, lung function, sex and genotype. Most importantly, much debate has been given to the mechanisms underpinning the therapeutic effects of exercise and PA on lung function. It is hypothesised that decreased respiratory muscle strength, particularly expiratory muscles, diminishes lung function and exercise tolerance (Sovtic et al., 2018). Alternatively, regular aerobic exercise has been shown to help maintain higher indices of respiratory muscle strength in CF patients, which might partially explain its therapeutic effect on lung function (Dassios et al., 2013). In addition, exercise enhances mucociliary clearance (Dwyer et al., 2017; Radtke et al., 2018), potentially through the generation of increased ventilation and shear force (Prasad & Ammani, 2014).

Tucker et al. (2017) found improvements in lung function after a single bout of MVPA. Specifically, following acute exercise, an improvement in the lung clearance index was reported, which provides a functional index of lung obstruction. It was suggested that an increase in the tension of respiratory muscles, coupled with the greater mucous clearance, during exercise might facilitate the expansion of lower airways, thereby relieving air trapping and increasing ventilatory reserve (Tucker et al., 2017). Moreover, exercise-related immunological responses may play a key role in delaying lung function decline in CF. A single exercise session has been shown to increase leukocytes and the systemic release of immune-modulatory peptides, such as interleukins, which are related with immune activation (van de Weert-van Leeuwen et al., 2013; van de Weert-van Leeuwen et al., 2012). In addition, regular MPA is associated with a reduction in infection susceptibility (van de Weert-van Leeuwen et al., 2013). Given that chronic infections and exacerbations are pivotal to the progression of airway disease in CF, the importance of exercise in reducing infection, thereby maintaining lung health, cannot be underestimated.

2.9.3 Physical Activity and Quality of Life

Self-reported PA and aerobic capacity are associated with increased QoL in children and adolescents with mild and moderate CF (Hebestreit et al., 2014). Furthermore, long-term improvements in QoL were demonstrated in children with CF after a home-based, partially supervised exercise intervention (Hebestreit et al., 2010). In accord, Schneiderman-Walker et al. (2000) reported health-related QoL benefits measured with the revised CF questionnaire

(CFQR; Quittner et al., 2012), such as less chest congestion and higher energy levels, following a three-year home-based exercise intervention in children and adolescents with CF. Evidence also suggests that exercise interventions are beneficial to enhance self-perception and general self-worth (Gulmans et al., 1999). However, similar benefits were not reported in shorter duration interventions, corroborating the notion that long-term regular PA and exercise are needed to enhance QoL in children and adolescents with CF.

2.10 The Measurement of Physical Activity

Physical activity is a complex concept that includes different contexts, making it particularly challenging to assess (Matthews et al., 2012). Essentially, PA can be measured objectively or subjectively. Subjective methods consist of questionnaires and records that usually require recalling recent activities, and are common in large cohorts given their greater feasibility. In contrast, objective methods are capable of measuring the movement or the energy expended (Ainsworth, 2009; Matthews et al., 2012; Sylvia et al., 2014). Examples of objective assessments of PA are pedometers, accelerometers and doubly labelled water. Whilst objective methods to assess PA are reliable and accurate, they require equipment and expertise which reduces their feasibility in clinical settings (Matthews et al., 2012; Sylvia et al., 2014). Intervention and observational studies often use objective assessment tools, more recently referred to as device-based measures due to the associated subjective processing techniques (Bassett, 2012), to obtain a more accurate measure of PA (Matthews et al., 2012; Troiano et al., 2014). Accelerometers are able to estimate the intensity, duration and energy cost of different activities in an accurate and reliable manner (Welk, 2005). Despite this, additional consideration must be given when measuring PA in clinical populations, such as CF (Stephens et al., 2016). For example, accelerometry might not account for systemic pathophysiological alterations, such as exercise intolerance, and the consequent enhanced metabolic cost of daily-life activities in comparison to healthy populations (Bell et al., 2001).

a. Questionnaires and Log-books

Self-report questionnaires are broadly used in epidemiological research given their low cost and practicality (Ainsworth, 2009; Sylvia et al., 2014). This method relies on the participants' ability to recall past activities and can vary greatly regarding the parameters

measured (i.e. PA type, intensity and duration). For example, whilst global questionnaires investigate general PA levels without providing much detail about specific PA types and patterns, recall questionnaires are tailored to identify the frequency, duration and type of the activities performed (Ainsworth, 2009). Additionally, recall questionnaires can be designed to investigate different domains of PA, such as leisure activities, daily-life activities and activities related to specific health-guidelines. The International Physical Activity Questionnaire (IPAQ; Craig et al., 2003) and the 7-day Physical Activity Recall (PAR; Sallis et al., 1993) are examples of frequently used questionnaires for PA assessment. Despite this, self-report methods are susceptible to recall bias and have low validity when compared to doubly labelled water or accelerometers (Pierce et al., 2006; Rangul et al., 2008; Richardson et al., 2001). Questionnaires in particular often have low accuracy to measure different intensities of PA, as well as EE, and are limited by social factors such as age and complexity of questions (Pierce et al., 2006; Rangul et al., 2008; Richardson et al., 2001). Alternatively, diaries and log-books have been shown to provide more detailed information as they require immediate records of PA. Thus, log books are also used alongside accelerometers to provide additional information, which is also important to contextualise non-wear data (Matthews et al., 2012; O'Donoghue et al., 2018).

b. Direct Observation

Direct observation utilises a trained independent observer recording PA in an assigned space and population (Honas et al., 2008). This method is more accurate and reliable than subjective questionnaires, particularly in young children and older adults as they might have difficulties recalling past activities (MacDonald et al., 2012; Pate et al., 2010). The downsides of direct observation are the high cost, lack of direct EE measures, and limited applicability to a free-living environment. Additionally, participants might react differently with the knowledge that they are being observed (Sylvia et al., 2014).

c. Motion Sensors

Currently, there are two types of motion sensors for PA measurement, pedometers and accelerometers (Ainsworth, 2009). Pedometers are able to measure movement in the horizontal axis, providing a measure of steps taken. They operate by a spring-suspended lever arm that is triggered during vertical acceleration and are usually worn around the waist or ankle. Despite

the low cost and ease of application, pedometers can only provide a measure of PA volume and is limited to activities such as walking and running. As pedometers promote PA reactivity in participants, it is commonly used as a PA intervention tool (Bravata et al., 2007). Alternatively, accelerometers have the ability to record large amounts of PA data that can be translated into EE or PA intensities (Sylvia et al., 2014). Indeed, given their reliability and accuracy, accelerometers are the most popular instrument to assess PA across the lifespan and clinical status (Arvidsson, Fridolfsson, & Börjesson, 2019; Matthews et al., 2012).

2.10.1 Accelerometers for Physical Activity Assessment

Accelerometers are small electronic devices designed to measure acceleration, which can be expressed as counts per unit of time, or more recently, as raw acceleration data (Troiano et al., 2014). Raw acceleration data or counts are then used to quantify the intensity and duration of movements. In addition, accelerometers can also be used to estimate EE with specifically developed algorithms and equations (Pischon & Steinbrecher, 2016).

Most accelerometers are 'cantilever beam', which means that they have a piezoelectric element that bends in response to acceleration. This allows the accelerometer to translate mechanical motion into a voltage signal at a determined sampling frequency, which is then stored in the device memory as raw acceleration signal over a user-specified time-sampling interval denominated epoch (Mathie et al., 2004). Little consensus exists regarding the use of different epoch lengths (i.e. from one second to one minute) for the analysis of the acceleration data, with longer epochs potentially resulting in the loss of important information. Indeed, the selection of epoch length affects the outcomes, with higher epoch lengths resulting in less predicted MVPA and LPA and more SED in healthy children (Colley et al., 2014). In accord, it has been postulated that shorter epoch lengths are more appropriate for children and adolescents, whose PA is characterised by short sporadic bursts (Colley et al., 2014; McClain et al., 2008). The sampling frequency is the rate at which the accelerometer collects acceleration data, and it is usually defined at 30 – 100 Hz for the measurement of PA (Arvidsson, Fridolfsson, & Börjesson, 2019). Specifically, recent research has advised the use of a sampling frequency rate of at least 30 Hz to guarantee that all movement will be included in the measurement (Arvidsson, Fridolfsson, & Börjesson, 2019).

Accelerometers have evolved to become smaller, more reliable, and provide additional physiological measures such as heart rate (Nichols et al., 2010). Several brands, and indeed models, of accelerometers are currently available, with ActiGraph and GENEActiv being the most popular choices, not least as they are able to provide unfiltered raw acceleration data. The difference between accelerometer brands generally lies in the sampling rate, ranging from 20 to 100 Hz, varied filtering options and the dynamic measurement range of the sensor (Ainsworth, 2009). Most importantly, a systematic review of the literature indicated that triaxial accelerometers, calibrated using EE measured by indirect calorimetry, are able to accurately classify SED and PA levels in healthy children (Lynch et al., 2019). Beyond providing detailed information regarding PA intensity, duration and volume (Syed et al., 2020), accelerometers can also be used to estimate SED (Carlson et al., 2019) and sleep patterns (van Hees et al., 2018). In addition, accelerometers offer minimal burden to participants at a relative lower cost (Bassett, 2012; Bassett et al., 2012). Whilst the use of accelerometers has clear advantages, it is not without limitations. For example, accelerometers are not able to measure isometric muscle contractions such as carrying or lifting weights, or consider variabilities of terrain such as incline, or account for specific non-locomotor activities (i.e., cycling). Consequently, accelerometers have been shown to provide low accuracy to classify cycling (Robertson et al., 2010) and strength-based activities (Skender et al., 2016). Additionally, data collection is highly dependent on participants' compliance (Matthews et al., 2012). Essentially, accelerometers should be worn for a minimum number of days in order to be representative of the individual's habitual PA (Bassett, 2012; Bassett et al., 2012). Finally, it is important to consider whether wearing an accelerometer might increase the participant's motivation to be more physically active and, subsequently, the associated bias (Napolitano et al., 2010). For example, Dössegger et al. (2014) demonstrated that the awareness of being measured introduced significant bias to the PA outcomes in healthy children and adolescents, particularly during the first day of the measurement. Consequently, this reactivity effect leads to an overestimation of the PA levels in these populations, which could subsequently impact the association between PA levels and health outcomes.

The accelerometer placement varies according to the research question and the activity being measured, though common sites are the waist, wrist and thigh. Earlier studies adopted the waist as the preferred site due to its proximity to the body's centre of gravity, which favours the measurement of ambulatory activities, such as walking and running (Freedson et al., 2005).

However, in addition to providing limited accuracy for assessing SED, this placement site is known to result in poor compliance during free-living measurements (Fairclough et al., 2016; Rowlands et al., 2014). Subsequently, research has shifted towards using a wrist-worn device to avoid misclassification and bias associated with low compliance (Rowlands et al., 2014).

2.10.2 Accelerometer reliability

Reliability, the degree to which a method is able to produce stable and consistent results, is instrumental for the assessment of PA and SED, particularly in clinical populations. There are distinct approaches to assess inter- and intra-accelerometer reliability; intra-monitor reliability is assessed through mechanical shakers, with inter-monitor reliability examined during a lab-based activity protocol or in free-living settings.

The ActiGraph has been extensively tested for intra- and inter-monitor reliability. Whilst previous models of ActiGraph yielded good to excellent reliability in clinical and healthy paediatric populations (O'Neil et al., 2014; Wood et al., 2008), the ActiGraph GT9X accelerometer has mostly been tested in healthy adults since it was first released in 2014 (Metcalf et al., 2018; Valkenet & Veenhof, 2019; Yang et al., 2018). Kim and Lochbaum (2018) demonstrated that the GT9X showed greater correlations with EE than the Polar Active watch and a previous model of ActiGraph (GT3X+) during unstructured activities in healthy children. Similarly, Yang et al. (2018) demonstrated that the GT9X yielded low errors and low coefficient of variation for detecting different PA types and intensities in healthy adults. Although the GENEActiv has not been as widely tested for reliability as the ActiGraph, some data is available in healthy adults. Specifically, Esliger et al. (2011) found high intra- and inter-monitor reliability when compared to a mechanical shaker and the ActiGraph (GT1M), respectively, independent of placement.

2.11 Calibration of Accelerometry

Accelerometer raw data is meaningless without a context and therefore requires the use of thresholds or cut-points to be translated into intensity-based metrics. However, obtaining the true measure of PA requires careful consideration of the populations' context, such as age and

clinical status (Watson et al., 2014). As such, accelerometry calibration is performed in order to generate population-specific cut-points. As a result, numerous calibration studies derived accelerometer-based prediction equations and population-specific cut-points (Freedson et al., 2005; Troiano et al., 2008). Calibration is performed for a particular accelerometer model and analyses the accelerometer data against a reference criterion during a determined PA protocol.

Janz (1994) published the first study developing thresholds to estimate PA in children (7 - 15 years) from the distribution of counts per minute derived from the CSA (Computer Science Application) accelerometer. Subsequently, Freedson et al. (1998) derived cut-points from accelerometer counts to measure PA intensities and EE, using the uniaxial CSA (7164 accelerometer). Freedson et al. (1998) utilised a laboratory-based protocol to record accelerometer counts from a hip-worn accelerometer and EE during walking, jogging, and running. A linear regression was employed to predict EE from the accelerometer counts and, subsequently, cut-points were calculated to classify PA into LPA, MPA, hard and very hard. Subsequently, numerous studies have sought to develop cut-points for classifying PA in children (Evenson et al., 2008; Freedson et al., 2005; Mackintosh et al., 2012; Mattocks et al., 2007).

Earlier calibration studies have mainly utilised laboratory-based protocols, usually encompassing highly structured activities such as walking and running (Nichols et al., 1999; Swan et al., 1997; Trost et al., 1998). Due to an inherent lack of ecological validity, such laboratory-derived thresholds typically result in substantial misclassifications of EE and PA intensities when applied to habitual data (Basset et al., 2000; Hendelman et al., 2000). Hendelman et al. (2000) first demonstrated this concept by comparing regression equations to predict EE from accelerometer counts that were developed from two different types of protocols: one from a walking protocol and one from a daily-life protocol (windows washing, dusting, vacuuming, lawn mowing, planting shrubs). Hendelman et al. (2000) concluded that the regression equations were highly dependent on the type of activities involved in the calibration protocol; the equation derived from the walking protocol underestimated EE by 30.5 - 56.8% when applied to activities from the daily-life protocol. Consequently, calibration protocols have now progressed to incorporate a broad range of activities and a variety of intensities in order to mimic daily life (Evenson et al., 2008; Freedson et al., 2005; Mackintosh et al., 2012; Puyau et al., 2002).

Although the adoption of a structured protocol including activities varying in intensity enhanced PA prediction in comparison with previous approaches (Crouter et al., 2013), the majority of the cut-points and equations still yielded large individual prediction errors (Kim et al., 2012). It is important to acknowledge, however, that the comparison of cut-points and equations derived from different calibrations protocols is challenging. Specifically, comparability is compromised by the wide variation in accelerometer characteristics (i.e. number of axes, brand, and model) and settings (i.e. epoch, frequency). Additionally, cut-points can be developed using a broad range of criterion references (e.g. EE, direct observation, HR) and protocols (laboratory-based, daily-life, free-living). Lastly, the statistical approach utilised to derive cut-points impacts the validity and performance of the thresholds (Welk, 2005).

A further concern in deriving cut-points is the statistical approach employed to translate the accelerometer raw metrics into intensity thresholds. Whilst earlier studies have utilised linear regression (Puyau et al., 2002; Trost et al., 1998), this approach was shown to provide limited accuracy when classifying activity intensities or predicting EE (Freedson et al., 2005; Trost et al., 1998). Specifically, both EE and PA are generally non-linear, particularly when approaching more strenuous activities (Brage et al., 2003). By using linear regression, researchers are assuming homoscedasticity of the values. It is therefore presumed that the error of the prediction is consistent across all values, which is not always true when working with different PA intensities (Jago et al., 2007). Other studies attempted to circumvent these limitations by applying non-linear regression (Pate et al., 2006), with no significant improvement in prediction accuracy. Subsequently, the receiver operating characteristic (ROC) curve was proposed to overcome the limitations of regression methods, given its ability to quantify sensitivity and specificity with continuous outcomes, while including all possible decision thresholds (Jago et al., 2007). Consequently, a wide range of studies have employed ROC curve methods to develop cut-points in healthy children and adolescents (Chandler et al., 2016a; Sirard et al., 2005; van Cauwenberghe et al., 2011). In addition, cut-points that were recently developed from raw acceleration data in healthy children have also employed ROC, achieving moderate-to-excellent accuracy (Crotti et al., 2020; Evenson et al., 2008; Mackintosh et al., 2012).

Recent research identified the use of accelerometer counts as an important factor limiting prediction accuracy (Kühnhausen et al., 2017). Specifically, vital information for PA classification is lost in the process of converting raw acceleration data to accelerometer counts (Kühnhausen et al., 2017). In contrast, the use of raw acceleration metrics broaden the control

over data processing and facilitate comparisons between accelerometer brands and placements (Fairclough et al., 2016). In 2013, the use of raw accelerometer data was greatly facilitated with the development of an open-source tool to process and analyse unfiltered acceleration data (Migueles, Rowlands, et al., 2019; van Hees et al., 2014; van Hees et al., 2015) Consequently, calibration studies started to develop cut-points from raw acceleration data metrics, such as Euclidean Norm Minus One (ENMO) and Mean Amplitude Deviation (MAD; Aittasalo et al., 2015; Hildebrand et al., 2014). Whilst research is embracing raw acceleration thresholds, no research to date has developed raw metric cut-points in clinical populations.

The vast majority of the cut-points developed have been derived from healthy populations, with little consideration given to their applicability to those with clinical conditions, such as CF. Specifically, CF pathophysiological alterations suggests that a higher EE is likely to be demanded for a given activity relative to their healthy peers, which consequently impacts the performance of cut-points (Stephens et al., 2016). In accord, Mackintosh et al. (2018) hypothesised that the high-LPA accumulation observed in children and adolescents with CF was likely a result of using generic cut-points, consequently underestimating the PA levels in a CF population. Indeed, Stephens et al. (2016) found that current prediction equations to transform accelerometer counts into EE developed in healthy children are not accurate for paediatric clinical populations, including CF. Subsequently, Stephens et al. (2016) developed disease-specific prediction equations and cut-points, which both achieved higher accuracy when compared to non-specific approaches. Nonetheless, the newly predicted cut-points and equations still yielded a significantly high standard error (0.47 – 0.76), which may be attributed to protocol characteristics, such as the use of accelerometer counts instead of raw metrics (Stephens et al., 2016). Thus, further accelerometry calibration in CF is warranted in order to enhance prediction accuracy, and therefore, accurately inform future studies tailoring exercise interventions and clinical-specific PA guidelines.

2.12 Physical Activity Levels in Cystic Fibrosis

There is a dearth of research investigating device-measured PA levels in CF, with the limited information available largely equivocal and, consequently, understanding regarding the potential health outcomes associated with different PA levels remains sparse. Specifically, whilst Nixon et al. (2001) reported that children and adolescents with CF accumulated less

vigorous activities than their healthy peers, Selvadurai et al. (2004) found no significant differences. In accord with Nixon et al. (2001), recent studies have also reported that children and adolescents with CF engaged in less strenuous activities in comparison with sex- and age-matched controls (Aznar et al., 2014; Jantzen et al., 2016; Mackintosh et al., 2018). Interestingly, Aznar et al. (2014) reported that although children with CF engaged in less vigorous activities, they accumulated a greater volume of PA overall when compared to their healthy counterparts. Such discrepancies may be due, at least in part, to methodological inconsistences, particularly the use of generic cut-points (Mackintosh et al., 2018). Indeed, PA levels previously reported are potentially not representative of the true volume of PA accumulated by those with CF given the lack of CF-specific cut-points, which therefore hinders further conclusions regarding associated health outcomes. In addition, it is noteworthy that the use of traditional approaches, such as linear regression or accelerometer count cut-points, may also limit the accuracy of PA prediction. Recent technological advancements have allowed accelerometers to measure three-dimensional, unfiltered, raw acceleration data, and, subsequently, the development of novel processing methods, all of which seek to overcome the limitations associated with device-based measurements of PA.

The PA levels in people with CF are impacted by sex and maturation, with girls significantly reducing their PA levels after the onset of puberty (Selvadurai et al., 2004). In addition, evidence suggests that the PA levels of pre-pubertal children with CF are comparable to their healthy peers until the onset of puberty when it starts to decline (Aznar et al., 2014; Jantzen et al., 2016). This sex disparity may explain the greater annual decline in FEV_1 observed in girls compared to boys, and consequently, the poor survival of females with CF (Schneiderman-Walker et al., 2005). Savi, Di Paolo, et al. (2015) showed that this sex disparity continues into adulthood, with women with CF showing significantly lower PA levels in comparison with their male peers, even when adjusted by age, BMI, $FEV_1\%_{predicted}$, infection with *Pseudomonas aeruginosa*, genotype, diabetes and pancreatic insufficiency. Despite the important impact of sex and maturity on PA levels in individuals with CF, most studies investigating PA in CF have not accounted for these factors (Aznar et al., 2014; Jantzen et al., 2016; Nixon et al., 2001), which might have led to erroneous conclusions. Another important factor that warrants attention when evaluating PA levels in CF is disease severity. Indeed, Nixon et al. (2001) showed that children with moderate-to-severe CF engage in significantly less VPA than their healthy counterparts. Moreover, Nixon et al. (2001) hypothesised that such a discrepancy was likely to be related with reduced exercise capacity in CF. In accord, adults

with CF have also been shown to have lower PA levels than their healthy peers, which has been associated with increased disease severity, and consequently, reduction in exercise tolerance (Rasekaba et al., 2013).

It is noteworthy that longitudinal research demonstrated an association between low socioeconomic status and greater disease severity and prognosis (Swartz et al., 2003; Taylor-Robinson et al., 2013). Of interest, Schechter et al. (2009) found that the poor health outcomes observed in people with CF with a lower socioeconomic status was not explained by differential health services or prescription of chronic therapy. Robust research found that lower socioeconomic status is associated with lower PA across the lifespan in healthy individuals (O'Donoghue et al., 2018), and it might help to explain the poorer prognosis in those with CF with lower socioeconomic status. Finally, important cross-national disparities in PA levels were found in a large survey (Guthold et al., 2020) including 168 countries and 1.9 million participants. Although the effect of cross-national differences to PA levels in CF has not been evaluated to date, this factor is relevant to the analyses and interpretation of PA, and therefore, should be considered.

2.13 Novel Approaches to Assess and Analyse Physical Activity

Whilst the development of condition-specific cut-points is likely to enhance PA prediction accuracy, previous studies investigating PA levels and lung function in CF have mainly employed traditional approaches, such as the use of linear regression, which is associated with significant error (Pedišić, 2014). Alternatively, novel approaches such as compositional analysis and machine learning algorithms are promising methods to advance PA research.

2.13.1 Compositional Analysis

In order to study the impact of different PA intensities to health outcomes, it is crucial to first understand what composes a typical day, which consists of different PA behaviours, SED and sleep. Given that the amount of time available in a day is finite, any increase in one of these components will result in a reduction or displacement of the others (Dumuid et al., 2018; Olds et al., 2017). Traditional linear approaches are not designed to account for the

collinearity between different PA intensities as observed by Pedišić (2014). This implies that the majority of studies investigating PA levels in CF, and associated health factors, have only analysed each of these behaviours in isolation without considering their compositional nature or accounting for the displacement of time (Hebestreit et al., 2014; Schneiderman et al., 2014). Unsurprisingly, the association between the different PA intensities and health outcomes in those with CF remains equivocal (Collaco et al., 2014; Cox et al., 2016; Mackintosh et al., 2018).

Pedišić (2014) was the first to propose the use of compositional analysis as the best statistical framework (VIRTUE) to analyse and understand PA behaviours as time-use data, which has furthered our understanding of how the relationship between sleep, PA and SED impacts health outcomes (Chaput et al., 2014; Chaput et al., 2017; Štefelová et al., 2018). Specifically, compositional data lives in the compositional sample space (*d*-simplex) where it is constrained by its own relative nature. A key step in compositional analysis is the performance of normalisation methods, such as the transformation of the relative information into a set of log-ratios (Chastin et al., 2015). Briefly, normalisation methods are applied in order to transpose the compositional data from the *d*-simplex into the real sample space, where traditional statistics (i.e., linear regression) can be performed (Aitchison, 1982; Dumuid et al., 2018; Pawlowsky-Glahn et al., 2015).

While rethinking PA behaviours in a compositional way might solve a methodological issue, it also helps to create a broader understanding of PA. Indeed, by adopting a compositional perspective of different PA behaviours, one is tasked with recognising how the different behaviours interact with each other throughout the day. Recently, research using compositional analysis has shown that PA behaviours, SED and sleep can affect health in a direct manner, but also by displacing the time available for other behaviours (Chastin et al., 2015). In accord, Chastin et al. (2015) demonstrated that the relationship between health outcomes and each behaviour varies according to the amount of time spent in the other behaviours. There is growing interested in how the reallocation of PA behaviours, sleep and SED might affect health outcomes, particularly in clinical populations such as CF. For example, recent studies using compositional analysis indicated that increasing MVPA by displacing time available for SED was beneficial to reduce mortality risk (McGregor, Palarea-Albaladejo, Dall, Del Pozo Cruz, et al., 2019), cardiometabolic biomarkers (McGregor, Palarea-Albaladejo, Dall, Stamatakis, et al., 2019) and diabetes markers (Swindell et al., 2020). Despite this, no research to date has applied compositional analysis to investigate the impact

of displacing different movement behaviours to health outcomes in CF. Finally, the use of compositional analysis is fundamental to inform interventions targeting all PA domains, SED and sleep, synergistically.

2.13.2 Machine Learning

Whilst the use of cut-points and linear equations constituted an important first step in PA research, these methods have been criticised for poor prediction accuracy and large error (Bassett, 2012; Bassett et al., 2012; Trost et al., 2012). It is noteworthy that the previous methodological approaches reflected the accelerometry capabilities at that point in time; recent technological advances engender the potential for applying superior analysis to PA data. Specifically, machine learning techniques can distinguish activity types, and predict EE, PA intensities and SED from accelerometry data (Preece et al., 2009). Machine learning encompasses an array of complex algorithms with the specific trait of recognising and learning from different patterns. Unsurprisingly, research in healthy children has started to shift towards machine learning modelling approaches given their promising potential in enhancing PA prediction (de Vries et al., 2011; Ruch et al., 2011; Trost et al., 2018), though the majority of research still utilises cut-points. Specifically, PA modelling approaches usually utilises accelerometer counts or raw acceleration data in the algorithms, which subsequently derives the outputs as EE or activity type. Algorithms are usually designed to extract pre-defined time- and/or frequency-domain features from the input data (i.e. mean, standard deviation or root mean square error), which are subsequently used to distinguish between activity intensities and EE (Preece et al., 2009).

Amongst the four machine learning algorithms branches (supervised learning, semi-supervised, reinforcement learning and unsupervised learning), PA research heavily relies on the supervised learning strategy. Specifically, this type of algorithm is designed to learn from a training dataset (i.e. accelerometry outputs) in order to generate outputs (i.e. PA types and EE). Briefly, two main sub-types of algorithms can be distinguished within supervised learning according to the type of outcome produced: regression algorithms for continuous variables and classification algorithms for categorical variables (see Figure 2.3). However, some algorithms alternate between both groups depending on the type of outcome produced (i.e. Random Forest). Earlier studies employing machine learning in PA research have mainly utilised

artificial neural networks (Freedson et al., 2011; Staudenmayer et al., 2009) and decision trees (Bonomi, Goris, et al., 2009). Given the lack of consensus regarding which technique yields the highest accuracy for PA assessment, recent validation studies in children have employed multiple machine learning algorithms (Ahmadi et al., 2018; Ahmadi, Chowdhury, et al., 2020; Chowdhury et al., 2017; Steenbock et al., 2019; Trost et al., 2018), reporting that Random Forest classifiers achieved significantly higher overall classification accuracy than other algorithms (Ahmadi et al., 2018; Chowdhury et al., 2017; Steenbock et al., 2019).

The Random Forest (Breiman et al., 1984) is an ensemble classifier that generates multiple decision tress in order to train a model. Decision trees are similar to a flowchart with multiple internal nodes and are built using randomly selected values from the training dataset. The internal nodes correspond to a test on one of the generated features from the sample. The tree branches correspond to the test results and the leaf nodes to a class label (Kuhn et al., 2013). The final outcome is produced by assembling the decisions of multiple trees and based on a majority vote. It is noteworthy that the Random Forest classifier has numerous advantages over other machine learning approaches. Specifically, these models are able to directly operate on both continuous and categorical variables, producing highly accurate classifiers. The Random Forest is also designed to generate unbiased estimates of the generalisation error whilst the classifier operates (Krzywinski & Altman, 2017). Recent studies have increasingly adopted this classifier as an alternative to cut-point methods, resulting in highly accurate predictions, even in clinical populations (79 – 95.7%; Ahmadi et al., 2018; Ahmadi, Chowdhury, et al., 2020; Chowdhury et al., 2017; Steenbock et al., 2019). Indeed, Trost et al. (2018) demonstrated that Random Forest classifiers significantly outperformed (74 – 84%) traditional cut-point methods (49 – 65%).

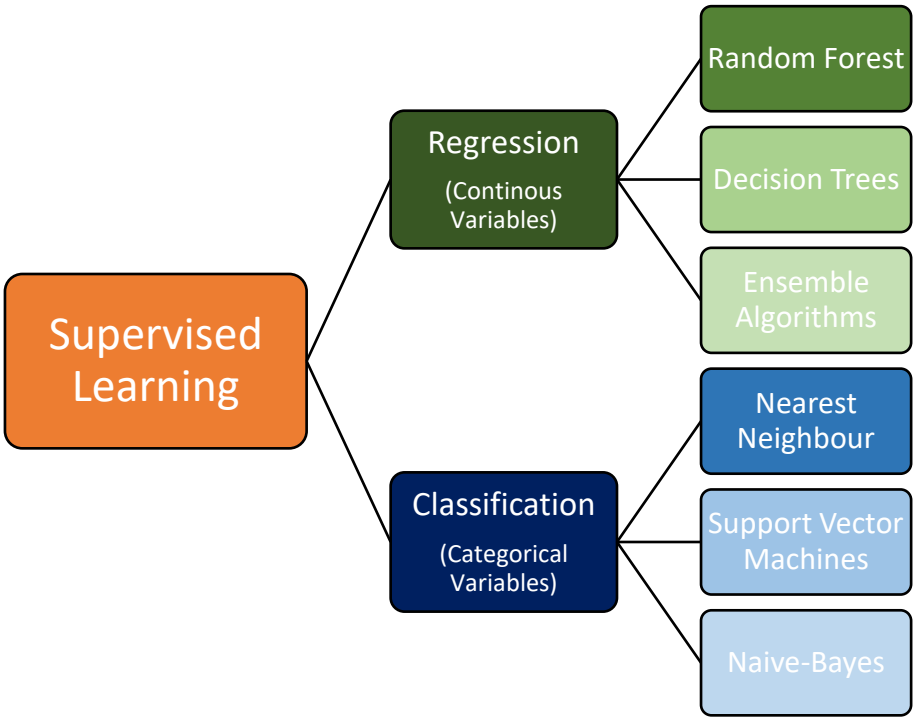


Figure 2. 3 Types of Machine Learning Supervised Algorithms

The k-Nearest Neighbours (k-NN; Patrick & Fischer, 1970) is considered as a direct classifier as it does not have a learning process and works directly with the whole dataset. This algorithm employs the similarity principle by examining the class labels of the nearest neighbours in the training set. According to the neighbours labels, the training sample is classified by votes, with the class most frequently represented receiving the maximum votes and assigned as the predicted class (i.e. PA intensities). Any ties between classes are solved by favouring the class with the minimum average distance to the training sample (Kataria & Singh, 2013). Specifically, the distances between neighbours is obtained using the similarity measure (i.e. Euclidean distance). Despite the simplicity and efficacy of this algorithm, only a few studies have utilised this approach, primarily in healthy adults (Attal et al., 2015; Bao & Intille, 2004). Nonetheless, the k-NN was reported as the second most accurate algorithm for activity recognition in adults (89.3%), only being outperformed by the Random Forest (> 90%; Bao & Intille, 2004). Moreover, when comparing different machine learning classifiers to perform activity recognition, Attal et al. (2015) found that k-NN outperformed other classifiers providing the best accuracy (96.5%), F-measure, recall and precision, followed by Random Forest models (94.8%).

The extreme Gradient Boosting (XGBoost) is a type of ensemble algorithm designed to boost the prediction of classifiers, such as decision trees, by learning from the weak predictions and correcting possible errors (Chen & Guestrin, 2016). Specifically, this algorithm incorporates a compilation of models and functions by using the weighted averages of results generated from previous models to minimise loss function (Friedman, 2001). As such, each new model will display a more accurate fit, and consequently, improve overall accuracy. Whilst the use of this type of algorithm has yielded excellent accuracy (84 – 99%) in recent studies classifying PA types in adults (Guo et al., 2019; Rahman et al., 2020; Zhang et al., 2019), a similar approach has not been studied in children. Interestingly, using data from a smartphone to recognise five types of activities (walking, stillness, climbing stairs, escalator and elevator taking), Zhang et al. (2019) found that placement had a major impact in the accuracy of the predictions, with thigh-worn showing the best results.

Irrespective of the algorithm utilised, machine learning still requires a calibration protocol accounting for variables such as placement and reference criterion, in order to classify PA. Consequently, errors and misclassification can still arise from the variability in data processing, monitor positioning and brand, which can also impact adherence to the protocol (Fairclough et al., 2016). Consequently, research investigating the performance of machine learning algorithms using data from different accelerometer placements for PA assessment in healthy children remains sparse (de Vries et al., 2011; Mackintosh et al., 2016; Montoye et al., 2019; Trost et al., 2018; Trost et al., 2014). Consequently, there is a lack of consensus regarding the optimal placement, with some evidence indicating that machine learning yields acceptable classification accuracy irrespective of placement (Mackintosh et al., 2016; Trost et al., 2014), whist others reported that models utilising data from waist placement outperformed wrist in healthy children (Montoye et al., 2019; Trost et al., 2018).

It is noteworthy that the use of accelerometer count data is a major factor limiting machine learning performance to classify PA types and intensities in children. For example, whilst Trost et al. (2012) achieved an overall activity classification accuracy of 80 - 86% when applying machine learning to accelerometer counts, Ahmadi, Pfeiffer, et al. (2020) reported an overall accuracy of 87.5 - 99.6% when applying the activity recognition algorithms to raw acceleration data. Despite the low accuracy associated with this approach (57 - 86%), count-based data is still broadly used by the majority of studies in healthy children, irrespective of machine learning approach, to predict PA types (de Vries et al., 2011; Ruch et al., 2011; Trost et al., 2012). This discrepancy is attributed to the loss of vital information during the process

of converting raw accelerometer data into counts (Kühnhausen et al., 2017). Additionally, this approach is generally performed using proprietary algorithms, which hinders the comparison across different accelerometry brands. The use of accelerometry brands such as GENEActiv and ActiGraph (GT3X+ and GT9X) facilitates the use of raw, unfiltered, acceleration data and may play a key role in further enhancing the PA accuracy prediction (Schmiedek et al., 2016; Trost et al., 2020; Trost et al., 2018). Finally, algorithms should be validated to overcome confounding factors arising from the calibration protocol in order to accurately identify activities intensities in populations other than those from which the models were initially derived.

2.14 Summary

Physical activity is well established as vital to the health and wellbeing of those with CF, though fundamental questions remain regarding the accurate measurement, and thus classification, of PA in those with CF. Specifically, whilst accelerometers are currently the preferred method to assess PA intensities (Hagstromer et al., 2007; Matthews et al., 2012; Troiano et al., 2008). they are unable to account for the increased RMR, exercise intolerance and the high cost of breathing, which are key characteristics of people with CF (Stephens et al., 2016). Consequently, it is hypothesised that accelerometry underestimates PA levels when utilised to assess PA in children and adolescents with CF (Mackintosh et al., 2018). Alternatively, accelerometer calibration can be performed to generate cut-points that are true to the physiological context of youth with CF. Thus, the development of specific cut-points to measure PA in CF is warranted in order to enhance PA prediction, and as a result, enable more informed clinical-specific PA guidelines to be developed. Most importantly, no research to date has employed CF-specific cut-points to evaluate PA levels in those with CF, which hinders the understanding of the relationship between PA and health outcomes in these populations. Furthermore, the subsequent misclassification of PA levels following the use of generic cut-points might help to explain the lack of consensus on research evaluating PA levels in youth with CF (Aznar et al., 2014; Kilbride et al., 2012; Mackintosh et al., 2018; Selvadurai et al., 2004). For example, whilst some studies described that youth with CF engaged in less in strenuous activities than their healthy peers (Aznar et al., 2014; Mackintosh et al., 2018; Nixon et al., 2001), others reported no significant differences (Selvadurai et al., 2004).

Novel methods, such as the use of machine learning, have received considerable attention given their ability to generate highly accurate predictions. Machine learning algorithms, in particular, have great potential to enhance PA prediction, thereby, advancing the study of the relationship between different PA intensities and health outcomes. Indeed, machine learning has been shown to predict PA types and EE from accelerometer data with high accuracy (Ahmadi, Chowdhury, et al., 2020; Fergus et al., 2015). As such, machine learning models have been used to predict PA in healthy and clinical paediatric populations (Ahmadi et al., 2018; de Vries et al., 2011; Ruch et al., 2011; Trost et al., 2018), though no research to date has utilised machine learning to predict PA intensities in children with CF.

Earlier studies investigating the relationship between PA levels and lung function in CF have mainly utilised traditional approaches (i.e. linear regressions), which are associated with significant error when applied to relative data (Pedišić, 2014). Alternatively, novel statistical analyses, such as compositional analysis, might be more appropriate to analyse PA intensities. Specifically, PA domains, SED and sleep are considered time-use data, and therefore, relative in nature as proportions of a complete day (Dumuid et al., 2018; Olds et al., 2017). Indeed, the use of compositional analysis can identify whether, and indeed how, different PA intensities might be related to health outcomes in CF, which is essential to inform interventions for this population.

CHAPTER 3

General Methods

3.1 Overview of Design

This Chapter provides a detailed description of the data collection methods used to investigate the measurement of physical activity (PA) in Cystic Fibrosis (CF). Initially, a systematic review of the literature (**Chapter 4**) was conducted in order to inform the protocol design of **Chapters 5 and 7**. Subsequently, three testing sessions were conducted and the data from those sessions were utilised in four cross-sectional studies (**Chapters 5 to 8**; Figure 3.1). The initial session incorporated clinical assessments including lung function, resting metabolic rate (RMR) and anthropometric measurements. The second session took place after a week and included a daily-life activity protocol, with the last session, consisting of a treadmill protocol for assessment of aerobic capacity, took place at least 48-hours later. In addition, baseline data from the Strategic Research Centre (SRC): Youth Activity Unlimited was included in **Chapters 6 and 7**. This SRC is dedicated to developing resources to support clinical practitioners to prescribe PA in CF, and it includes five research sites: Swansea University (United Kingdom), the University of Exeter (United Kingdom), University College London (United Kingdom), La Trobe University (Australia) and the University of Toronto (Canada).

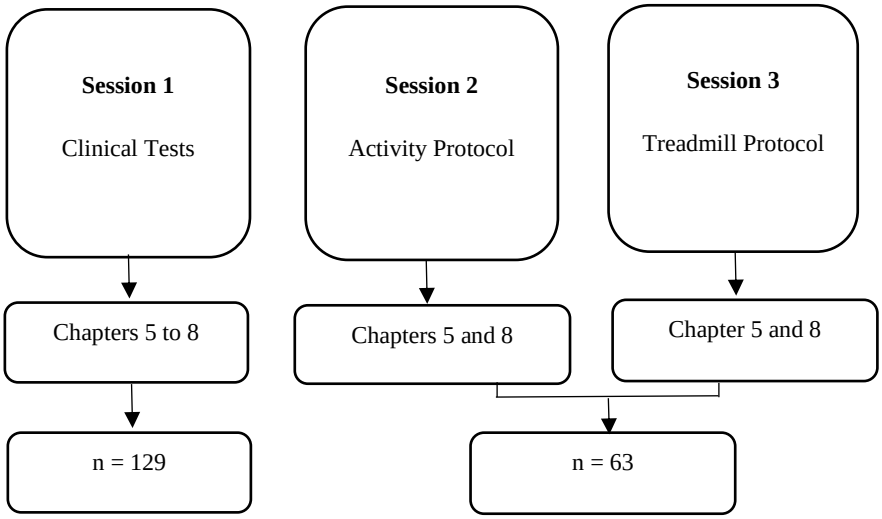


Figure 3.1 Distribution of Testing Session Data within Studies

3.2 Scientific Review and Ethics Approval

The Joint Study Review Committee initially assessed and approved the protocols for **Chapter 5 to 8** (Appendix D1). Subsequently, ethics approval was sought from the National Health Service Research Ethics Committees (**Chapter 5 to 8**; 18/WS/0032; Appendix D2) and the Alfred Health Human Research Ethics Committee (**Chapter 6 to 7**; HREC/16/Alfred/188; Project 7/17; Appendix D4).

3.3 Study Participants

Children and adolescents (7 – 18 years) were recruited from paediatric CF outpatient clinics in South Wales. The primary respiratory consultant confirmed the suitability of each patient prior to recruitment. For **Chapters 6 and 7**, the baseline data from participants with CF from the SRC were included. Specifically, the participants included from the SRC were children and adults (12 – 35 years) admitted for a respiratory cause and recruited from five hospitals in Australia (Victoria, Tasmania, New South Wales and South Australia), as part of a randomised controlled trial (Cox et al., 2019). Healthy controls were recruited from Swansea University and via friends and family of the CF participants. The supportive written document that was provided to all participants and their parents/guardians was specifically tailored for different age groups and health status using appropriate language (Appendix E). Potential participants were provided with 48-hours to review the study information sheets, after which they were contacted to inquire whether they were willing to participate and, if so, their availability. Fully informed consent (Appendix F1) and assent (Appendix F2) were obtained from parents/guardians and participants, respectively. Participant sample numbers are shown in Figure 3.2.

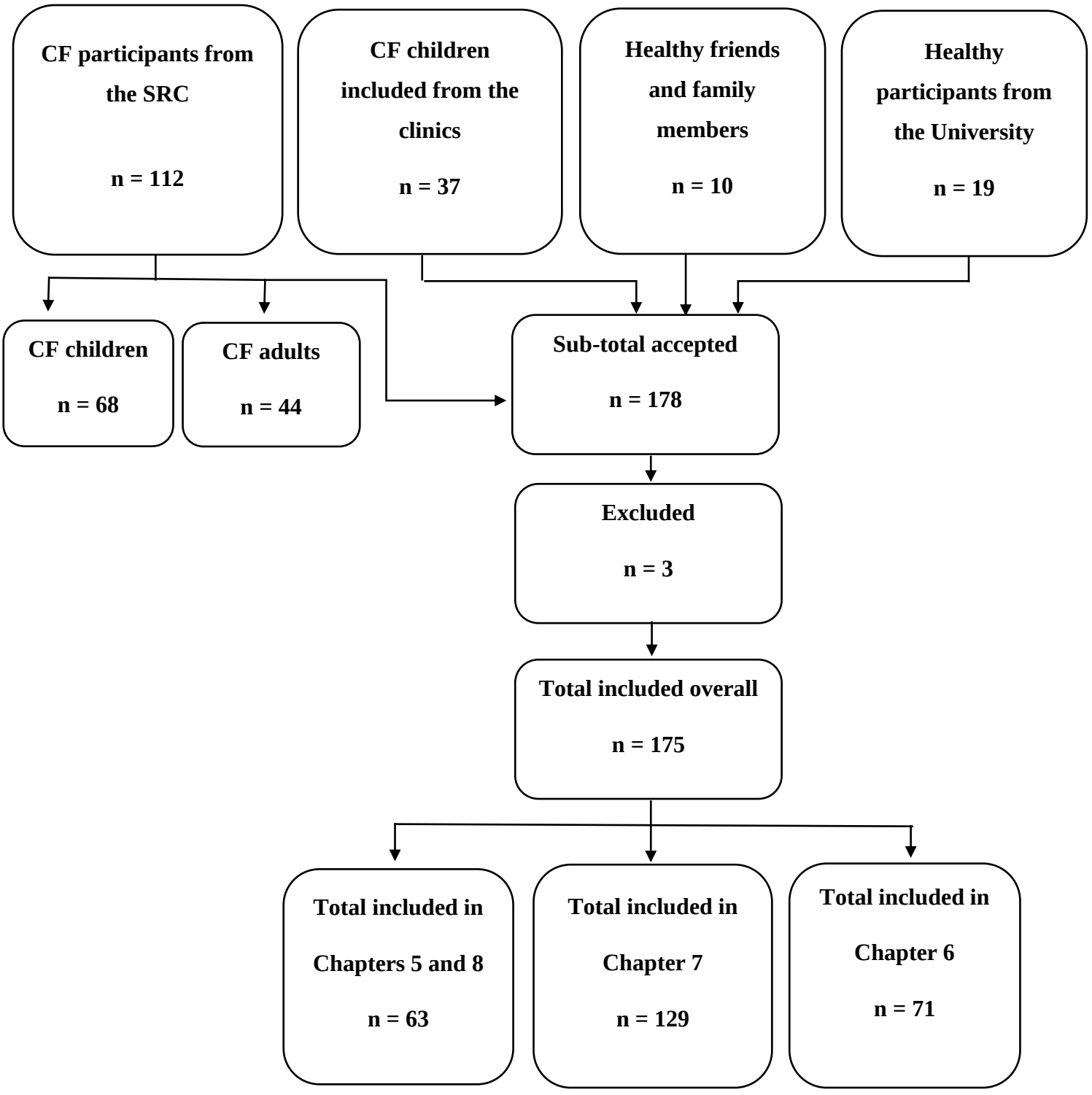


Figure 3.2 Flow Chart Describing Participant Numbers

3.4 Participant Inclusion and Exclusion Criteria

3.4.1 Cystic Fibrosis Group

Participants with a diagnosis of CF according to a newborn screening test, or using CF-typical symptoms and either two pathological sweat tests (sweat Cl^- > 60 $mmol \cdot L^{-1}$ sweat), or a diagnostic genotype, were included. The medical records were consulted in order to extract information regarding participants medication. Participants were excluded if they had other medical conditions, such as cardiovascular or musculoskeletal issues that could compromise their ability to undertake PA. In addition, those with multi-resistant bacteria (*Burkholderia Cepacia* and nontuberculous mycobacteria), an acute exacerbation at the time of the assessments (**Chapters 5 and 8**) or awaiting a transplant were excluded from the study.

3.4.2 Healthy Controls

Children and adolescents were recruited to compose the age- and sex-matched control group. Children and adolescents with pulmonary conditions or any conditions affecting the ability to exercise, such as cardiovascular or musculoskeletal impairments, were excluded. The health status of the control group was confirmed by a short clinical anamnesis where the participants were asked if they have any clinical conditions or diseases and whether they were taking any medication(s) for health purposes.

3.5 Age

Decimal age was obtained to the nearest 0.1 year during the first session of each experimental study.

3.6 Anthropometry

Anthropometric measures were obtained during the first session. The same researcher performed the measurements, and participants were instructed to wear light clothes and have their footwear removed during the assessments.

3.6.1 Body Mass

Body mass was assessed using electronic weighing scales (Seca 876, Hamberg, Germany) to the nearest 0.1 kg.

3.6.2 Stature

Stature was obtained to the nearest 0.1 cm using a stadiometer (Holtain Stadiomerter 603VR, Holtain Ltd, UK). During the procedure, participants were instructed to stand upright and look forward whilst positioning their heels against the stadiometer. Sitting stature was obtained to the nearest 0.1 cm using a sitting height stadiometer (Holtain Sitting Height Stadiometer 607VR, Holtain Ltd, UK).

3.6.3 Body Mass Index

Stature and body mass were used to assess body mass index as follows:

Equation 3.1

$$\text{BMI} = \text{body mass (kg)} / \text{stature}^2 \text{ (m}^2\text{)}$$

Body mass index z-scores (zBMI) were estimated using the World Health Organisation (WHO) reference data (de Onis et al., 2004). Specifically, this approach generates measures of relative weight adjusted by age and sex through the z-score system, which expresses the anthropometric variables as a number of standard deviations (i.e. z-scores) below or above the reference mean or median value. The zBMI is fundamental to allow comparisons across different age ranges within samples including children and adolescents. The formula used to estimate the z-score was:

Equation 3.2

z-score (or SD-score) = (observed value - median value of the reference population) / standard deviation value of reference population

3.7 Maturity Status

The peak height velocity (PHV) is the period during adolescence with the maximum rate of growth. The estimated age at the PHV can be calculated using a maturity offset prediction equation. Specifically, maturity offset is the difference in years from age at PHV, with negative values indicating the number of years prior to PHV and positive values indicating number of years since PHV. The sex-specific equations developed by Mirwald et al. (2002) were used to predict the age at PHV, as follows:

Equation 3.3

Boys: *Maturity offset (years)* = - 9.236 + (0.0002708*(leg length*sitting height)) + (−0.001663*(age*leg length)) + (0.007216* (age*sitting height)) + (0.02292*(weight ÷ height*100))

Equation 3.4

Girls: *Maturity offset (years)* = - 9.376 + (0.0001882*(leg length*sitting height)) + (0.0022*(age*leg length)) + (0.005841*(age*sitting height)) + (- 0.002658*(age*weight)) + (0.07693*(weight ÷ height*100))

The leg length was estimated by subtracting sitting height from standing height. The prediction equation developed by Mirwald et al. (2002) was validated against skeletal age, and it was reported to have an error of estimate of approximately 0.49 and 0.50 for boys and girls, respectively. Subsequently, the age at the PHV was used to estimate the pubertal stages with pre-pubertal considered > -1 years from PHV, pubertal as -1 to +1 years and post-pubertal as > +1 years post PHV.

3.8 Metabolic Gas Analysis

Figure 3.3 MetaMax Cortex 3B Gas Analyser

Consent for photography and publication was obtained from the participant and parents/guardians.

The metabolic system MetaMax Cortex 3B (Figure 3.3; CORTEX Biophysik GmbH, Germany) was used in **Chapters 5 and 8** to assess oxygen uptake ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) measured breath-by-breath and averaged every five seconds using the MetaSoft® Studio Software (CORTEX Biophysik GmbH, Germany). The same gas analyser was also used in **Chapters 5 to 6** to assess lung function and RMR, to ensure consistency within the measurements. The MetaMax 3B is a portable metabolic system composed of two parts, a measurement module and a battery module, both of the same size (120 x 110 x 45 mm). This system was designed to be worn on the chest with a harness, and weighs 1.40 kg in total. The metabolic system measures volume through a turbine attached to flexible face mask (Hans Rudolph, Kansas City, MO). A sampling tube, connected to the turbine, to capture expired air to the metabolic system. Standard metabolic algorithms are used to calculate $\dot{V}O_2$ and $\dot{V}CO_2$ through the Haldane transformation (Wasserman et al., 1999). Finally, concentration and volume signals were time-aligned to account for the delay in the capillary gas transit and analyser rise time (McNarry et al., 2017).

The analyser was calibrated according to the manufacture guidelines prior to each measurement. Specifically, this involves calibrating the analyser using gases of known concentrations (16% O_2, 5% CO_2; Viasys, Hoechberg, Germany) and subsequently, calibrating against ambient air. Then, a volume calibration is performed using a standardised three litre

syringe (5530 series, Hans Rudolph, Inc., USA). Previous studies investigating the reliability and validity of the MetaMax Cortex 3B reported stable and reliable (i.e. precision) results for field-based assessments in healthy and clinical populations (Compagnat et al., 2020; Macfarlane & Wong, 2012; Vogler et al., 2010). For example, in a validation study, Compagnat et al. (2020) compared the performance of the MetaMax 3B with an automated Douglas bag system during exercise, demonstrating that $\dot{V}O_2$ and $\dot{V}CO_2$ were over-estimated by approximately 3 - 4% and 5 - 7%, respectively, when using the metabolic system. The MetaMax 3B demonstrated excellent reproducibility yielding errors of < 2% (Macfarlane & Wong, 2012).

3.9 Pulmonary Function

A forced vital capacity (FVC) manoeuvre was utilised to determine forced expiratory volume in one second (FEV_1). Subsequently, the predicted FEV_1 ($FEV_1\%_{predicted}$) was estimated according to a reference equation (Quanjer et al., 2012) for age, sex and body mass, and used to categorise disease severity as mild (> 70%), moderate (40 – 69%) or severe (< 40%; Davies & Alton, 2009). The spirometry was assessed in accordance with American Thoracic Society and European Respiratory Society standards (ATS/ERS; Graham et al., 2019; Moore, 2012).

The manoeuvre was performed with the participant sitting in an upright position whilst maintaining the neck in a fixed neutral position and verbal encouragement was provided during all stages (McCormack et al., 2019). Specifically, participants were instructed to initiate the test following three initial resting breaths, breathing as deeply as possible, with a subsequent exhalation, which should be performed forcefully and fast, until no further air remained in the lungs. Participants were asked to repeat the manoeuvre until three consistent (< 5% variability) measures were obtained, up to a maximum of eight repeats (Jat, 2013). In order to be accepted, curves had to display a rapid and clear rise reaching the peak flow and a prolonged expiratory curve which gradually decreased in flow (Figure 3.4).

Variation in spirometry might occur due to inter-participant variables, such as age, sex, stature, or an underlying respiratory condition, or other factors, such as cough, leakage, effort or the number of manoeuvres (Belzer & Lewis, 2019; Künzli et al., 1995). Indeed, mean error for FVC and FEV_1 has been reported to range from 1.7 – 3.1% when measured using 17 spirometers in primary care (Hegewald et al., 2016). It is noteworthy, however, that the clinics

included in this thesis did not perform the flow calibration as recommended by the ATS/ERS (Graham et al., 2019; Moore, 2012), which might have impacted the accuracy of the results. Previous research reported intra-person inter-test variability ranging from 1.8 – 4.9% for FVC and 2.3 – 4.7% for FEV_1 (Belzer & Lewis, 2019). The age- and height-based Quanjer et al. (2012) prediction equation yielded -0.3% and -0.4% error for FEV_1 in boys and girls (6 to 19 years), respectively. Finally, whilst the likely cumulative error is unknown, it is important to consider the associated implications and need for further research.

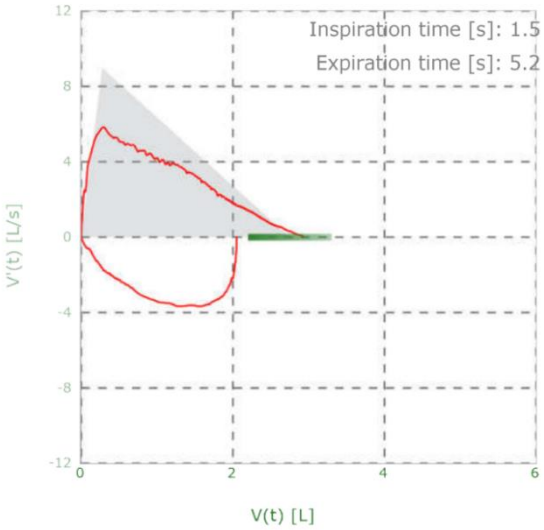


Figure 3.4 Maximum Flow-volume Loop

3.10 Resting Metabolic Rate

Participants were instructed to arrive in a two-hour dietary fasting state and having avoided caffeine and extraneous exercises in the previous 24-hours. Resting metabolic rate was measured using the gas analyser (Metamax 3B, Cortex Biophysik GmbH, Germany) over a 20-minute period whilst participants were resting in the supine position avoiding any conversation or movements. The measurement started following at least 10 minutes at rest, and participants were required to stay awake throughout the test, with noise kept to a minimum. In order to calculate RMR, the first five and the last two and a half minutes were removed from the

analysis, with the remaining values of $\dot{V}O_2$ and $\dot{V}CO_2$ averaged (Cooper et al., 2009; Jackson et al., 2007). Whilst currently no CF-specific equation is available to calculate RMR, the Weir (1949) equation has been broadly used in this population (Hollander-Kraaijeveld et al., 2020; O'Rawe et al., 1992; Richards et al., 2001). Therefore, the RMR was calculated according to the equation developed by Weir (1949), as follows:

Equation 3.5

$$RMR = 1.44(3.94 \cdot \dot{V}O_2 + 1.11 \cdot \dot{V}CO_2)$$

3.11 Aerobic Function

Figure 3.5 Cardiopulmonary Exercise Test

Consent for photography and publication was obtained from all participants and their parents/guardians

Participants had their aerobic function assessed during an incremental treadmill test to volitional exhaustion using calibrated treadmills at a laboratory (Pulsar®3p, h/p/Cosmos®, Germany) and hospital (TrackMaster, FullVision Inc, USA). All participants were equipped with a safety harness attached to the treadmill and provided with a screen displaying a virtual run to encourage looking forward (Figure 3.5). All CF participants performed this test at the hospital, unless their parent/guardians requested to attend the university laboratories instead,

with all healthy participants undertaking the exercise test at the university. Participants were required to first familiarise themselves with walking and running on the treadmill at different speeds, with adjustments made to the harness for each participant. Participants were instructed to avoid caffeinated drinks and heavy meals at least two hours prior to the test and arrive in a rested and hydrated state.

The standard Bruce protocol (Bruce et al., 1973) involving three-minute stages to volitional exhaustion was used to assess peak oxygen uptake ($\dot{V}O_{2peak}$) at the highest 10 s moving average (Table 3.1). This protocol is the most widely used treadmill exercise test (Klijn et al., 2003; van der Cammen-van Zijp, Ijsselstijn, et al., 2010; van der Cammen-van Zijp, van den Berg-Emons, et al., 2010) due to its great reliability in healthy children (0.94; Cumming et al., 1978). Moreover, this protocol is recommended to assess aerobic capacity in CF populations (Hebestreit et al., 2015). During the test, gas exchange variables were measured on a breath-by-breath basis (MetaMax 3B, Cortex Biophysik GmbH, Germany), and oxygen saturation and heart rate and rhythm were assessed throughout using a pulse oximeter (Nonin® WristOx® Model 3150, Nonin® Medical Inc., USA) and a three-lead electrocardiogram (ECG; Custo Guard ECG, custo med GmbH, Germany), respectively. During the final 30 s of each exercise stage, the participant's perceived exertion and breathlessness were assessed using the modified Borg scale of perceived exertion (0 - 10; Borg, 1982). Criteria to stop the test included severe desaturation ($\leq$ 80% SpO_2) accompanied by symptoms and signs of hypoxemia, chest pain, signs of respiratory failure, haemoptysis, sudden pallor, loss of co-ordination, mental confusion, dizziness or faintness, and complex cardiac ectopy (Hebestreit et al., 2015).

Table 3.1 Stages of Bruce Protocol (Bruce et al., 1973)

Stage	Minutes	MPH	Grade (%)
1	3	1.7	10
2	3	2.5	12
3	3	3.4	14
4	3	4.2	16
5	3	5	18
6	3	5.5	20
7	3	6	22

3.12 Accelerometry

ActiGraph GT9X Link (ActiGraph, Pensacola, FL) and GENEActiv (ActivInsights Ltd., Cambridge, UK) accelerometers were used to measure raw acceleration at 100 Hz. Participants were requested to wear three GT9X (writs and right waist) and two GENEActiv (both wrists) monitors during the daily-life activity protocol, as well as for seven consecutive days for the assessment of habitual PA levels.

3.12.1 ActiGraph

The ActiGraph GT9X Link (Figure 3.6; ActiGraph, Pensacola, USA) is a small triaxial micro-electro-mechanical system (MEMs) accelerometer (~ 8 G; size: 3.5 x 3.5 x 1 cm; mass: 14 grams) combined with a gyroscope (approximate max range of -2,000 deg·sec^{-1}), magnetometer and a secondary triaxial sensor (approximate max range of 16 G) to record movement, rotation and body position. The sample rate ranges from 30 to 100 Hz and the filtering size can be selected from 1 to 60-s epochs.

3.12.2 GENEActiv

The GENEActiv (Figure 3.6; Activinsights Ltd., Cambridgeshire, UK) is waveform triaxial MEMs accelerometer (~ 8 G; size: 43 mm x 40 mm x 13 mm; mass: 16 grams) including light and temperature sensors. Sample rate can be selected from 10 to 100 Hz, and epoch options vary from 1 to 60-s.

a **b**

Figure 3.6 Accelerometers used in the Studies

a. ActiGraph GT9X Link. b GENEActiv.

3.12.3 Accelerometer Data Reduction and Analysis

For the purpose of all the studies within this thesis, the raw acceleration data was extracted at 100 Hz as .gt3x and .bin files for ActiGraph GT9X (ActiLife V 6.10.2) and GENEActiv, (GENEActiv PC software V2.2), respectively. Specifically, the GGIR package (V 1.2 – 0; Migueles, Rowlands, et al., 2019) was used to auto-calibrate and extract raw acceleration data from all monitors. As such, all .gt3x files were converted to time-stamp free .csv files and subsequently exported along with the .bin files into R statistical software (V3.1.2; R Foundation for Statistical Computing, Vienna, Austria) for subsequent pre-processing using GGIR. The package was then utilised to extract the raw data from all three axes (x, z and y), and calculate the Euclidean Norm Minus One (ENMO) and the Mean Amplitude Deviation (MAD) metrics (Migueles, Rowlands, et al., 2019; van Hees et al., 2014). The ENMO metric is computed by adjusting the vector magnitude (VM) for gravity by subtracting one gravitational unit (1 g = 9.81 $m \cdot s^{-2}$) from the three raw acceleration signals at each time point (i.e. Euclidean Norm). The MAD metric is calculated by removing the static component from the measured orthogonal acceleration resultant vector (Bakrania et al., 2016). Following the signal pre-processing in R, all values were converted from gravity-based acceleration units (g to milligravitational; *mg*) units and calculated over 5-s epochs (Matthews et al., 2012; Vähä-Ypyä et al., 2015).

3.13 Estimation and Investigation of Physical Activity in Cystic Fibrosis

3.13.1 Methods to Estimate Physical Activity in Cystic Fibrosis

Figure 3.7 Daily-life Protocol

Consent for photography and publication was obtained from the participant and parents/guardians

This thesis developed two different approaches to predict PA in children with and without CF: cut-points and machine learning algorithms. A daily-life activity protocol was designed following recommendation from a systematic review (**Chapter 4**) and used in **Chapter 5** to develop raw acceleration cut-points and in **Chapter 8** to generate machine learning algorithms.

The daily-life calibration protocol (Figure 3.7) was carefully designed to include activities replicating the participant's daily lives using public and patient involvement (PPI). Specifically, five participants with CF selected by the physiotherapist, including both children and adolescents (7 to 17 years), were invited to complete a survey of common activities from the compendium of physical activities (Appendix G1; Ainsworth et al., 2011) and asked to select any that they would typically do during their normal routine. The PPI group was representative of the final study sample. Fifty-six healthy children and adolescents attending a science festival in South Wales also completed the survey. Participants were encouraged to suggest any additional activities that were not listed. The six activities with the highest votes, stratified by intensity and behaviour type, were selected to be included in the daily-life protocol: watching a video, playing on a handheld device (i.e. tablet), colouring/writing, walking, playing self-selected games, and stairs (Table 3.2). For the activity of walking, all participants received the same instruction to walk at a comfortable pace in the provided space. The space consisted of a

spacious laboratory and participants covered 200 to 400 m in five minutes. The activity of playing self-selected games included a variety of options and was incorporated to the protocol in order to simulate the free-living environment. In total, the protocol lasted approximately 50 minutes, with all activities being performed in a random order, varying from three to ten minutes, with a three-minute rest in between. The stairs activity was performed across three flights of stairs and consisted of both climbing and descending the stairs. Participants were instructed to continuously climb and descend at a comfortable pace, which resulted in a range of four to six climbs and descents. The participants wore five accelerometers (three GT9X on both wrists and waist, and two GENEActiv on both wrists), the metabolic system and the pulse oximeter throughout the whole duration of testing, including the rest periods. All five monitors and the metabolic system (MetaMax Cortex 3B) were synchronised to an external clock to allow comparability across the outputs.

Table 3.2 Activities Included in the Daily-life protocol

Activity	**Description**
Watching a video	Watching a video in a seated position for 10 minutes
Colouring/writing	Colouring or writing in a seated position for 6 minutes
Playing on a handheld device	Playing games on the handheld device in a seated position for 6 minutes
Playing self-selected games	Playing a variety of self-selected games including football, hula hoops, tennis, badminton, rugby, skipping and mini bowling for 6 minutes
Self-paced walking	Walking continuously at a self-selected comfortable pace for 5 minutes
Stairs	Climbing and descending stairs continuously at a self-selected comfortable pace for 3 minutes

The energy expenditure (EE) was obtained as metabolic equivalent of task (MET) values for each activity by dividing the $\dot{V}O_2$ measured for each activity by the resting $\dot{V}O_2$ (McMurray et al., 2015). The MET values were then used as the reference criterion to label the 5-s raw accelerometer data (ENMO, MAD and three axes) as sedentary time (SED; ≤ 1.5 MET), moderate physical activity (MPA; 4 - 6.9 METS) or vigorous physical activity (VPA;

≥ 7 METS; Troiano et al., 2008). In order to avoid transitional movements, accelerometry and MET data from the first and last minute of each activity were excluded. Lastly, for the final analyses, at least two minutes of data for each activity were included. Subsequently, two different approaches were utilised for generating cut-points and machine learning models. Specifically, cut-points were developed from the labelled ENMO and MAD metrics, whereas machine learning models were generated with the labelled data from the three axes.

a) Cut-points

The receiver operating characteristics (ROC) analysis (Figure 3.8) method was employed to generate cut-points for SED, MPA and VPA. This method was first developed during World War II in order to facilitate recognising signal from noise in the radar detection (Lusted, 1971). Briefly, ROC curve is simply a plot of sensitivity (*y* axis) against 1-specificity (*x* axis) for different cut-point values. In general, the cut-points are a product of a trade-off between sensitivity, representing true positives, and specificity, representing false positives. Whilst there are many different approaches for identifying the optimal threshold, the Youden index is the most common method adopted for this task (Perkins & Schisterman, 2005). Specifically, this method identifies the optimal cut-point as the point maximising the Youden function, which is defined as following:

Equation 3.6

$$J = \text{maximum}\,(\text{sensitivity}(c) + \text{specificity}(c) - 1)$$

The overall classification accuracy is represented by the ROC area under the curve (AUC), with a value equal to 0.5 indicating random chance or absence of classification accuracy, and a value of 1 suggesting perfect classification accuracy. As such, AUC values are usually used to indicate whether a classification achieved excellent (≥ 0.90), good (0.80 – 0.90), fair (0.70 – 0.80) or poor (< 0.70) accuracy. Intensity cut-points were developed through the Youden index for SED, MPA and VPA for both the healthy and CF groups. As such, the MET values were transformed into binary codes according to the different relative intensities (see section 3.10.1) and used as the dependent variable for the ROC curve. The final step consisted of cross-validating the cut-points to ensure their applicability to populations other than the one from which they were developed. This process was performed through an iterative leave-one-out approach, from which the mean squared error (MSE) was calculated. Specifically, cut-points

were generated on a loop of n-1 participants and the MSE was obtained from subtracting the thresholds and averaging the results (Unal, 2017).

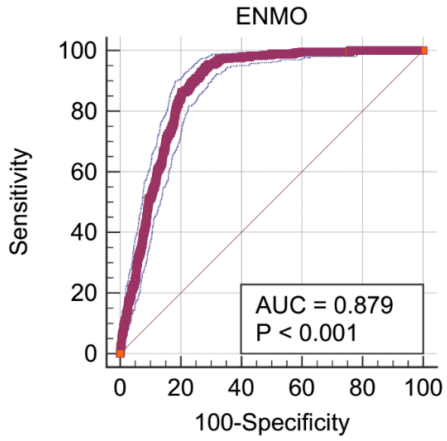


Figure 3.8 Receiver Operating Characteristics Analysis

b) Machine Learning

Machine learning evolved from the study of pattern recognition and computational learning theory to become a subfield in computer science, with wide applicability in other fields. Machine learning can be defined as the compilation of methods and algorithms that allow computers to automate multiple functions through systematic recognition of patterns (Dhall et al., 2019). Although machine learning can be classified in different ways, the most common is the use of three broad categories designed according to the nature of the learning outputs. Briefly, machine learning algorithms can fall into the categories of supervised, unsupervised or reinforcement learning. Unsupervised learning occurs when the algorithm is provided with unlabelled data, and thereby, it is left to recognise patterns and 'meaning' on its own. Reinforcement learning happens when the algorithm interacts with a dynamic environment in order to achieve a determinate goal (i.e. driving a vehicle, playing a game). Supervised learning, which is the category broadly utilised in PA recognition, occurs when the algorithm is presented with labelled data and instructions regarding the desired output. Sometimes the fourth category of semi-supervised is also acknowledged, with the use of an incomplete training set, for example (Dhall et al., 2019). The category of supervised learning can be further divided into two main types of algorithms according to the output produced as

regression algorithms (continuous variables) and classification algorithms (categorical variables).

Research applying machine learning to classify PA generally uses supervised algorithms with training data sets from accelerometer signals labelled with activity type or EE (METs). Windowing is common practice amongst classification algorithms, and is performed in order to segment the acceleration signal into smaller windows (Preece et al., 2009). Subsequently, machine learning algorithms can be applied separately to each segment, and then combined to provide the desired output. Preece et al. (2009) defined three windowing techniques commonly applied to activity monitoring: sliding, event-defined and activity-defined windows. The sliding method is characterised by a static width (i.e. 0.25 – 6.7 s) and is the most used amongst the three types. Following the segmentation of the signal, a range of different parameters, known as 'features' are generated and used as inputs. More specifically, time-domain features are calculated directly from a window as statistical measures, and frequency-domain features are derived from data transformed through a Fast Fourier Transform (Preece et al., 2009).

The selection of features is a crucial step in analyses and greatly affects the accuracy of the classifications (Ellis et al., 2014; Kiani et al., 1997). Essentially, including a large number of features in the model can increase the risk of overfitting, particularly when working with small samples of data. In addition, the inclusion of a large number of features hinders the clustering of the data, due to, at least in part, the creation of too many dimensions. Subsequently, the large number of dimensions results in every observation generated from the data to seem equidistant from all the others in a phenomenon known as the curse of dimensionality (Altman & Martin, 2018). In accord, when testing machine learning algorithms to predict PA intensities, Montoye, Bradford, et al. (2018) found that including frequency-domain features did not improve the performance of the models, and even reduced the accuracy in some cases. Ellis et al. (2016) demonstrated similar findings when using a random forest algorithm to predict PA in a free-living setting. Following the careful selection of the feature set from the sensor data, a classifier is then utilised to identify PA types or intensities. Currently, there is a wide range of classifiers varying in complexity, but the most common in PA research are Random Forest, Artificial Neural Networks and Support Vector Machines (Farrahi et al., 2019).

The Random Forest classifier combines outputs from multiple decision trees trained independently on a random subset of data (Figure 3.9; Breiman et al., 1984). Each tree has multiple internal nodes that are split by selecting the best randomly selected features as their final prediction (Winham et al., 2013). Subsequently, the final predictions of all trees are aggregated and a final prediction (i.e. PA intensity) is defined by a majority vote (Figure 3.9). In addition, the Random Forest outperformed other classifiers in previous models designed to predict PA types and intensities (Ellis et al., 2014)

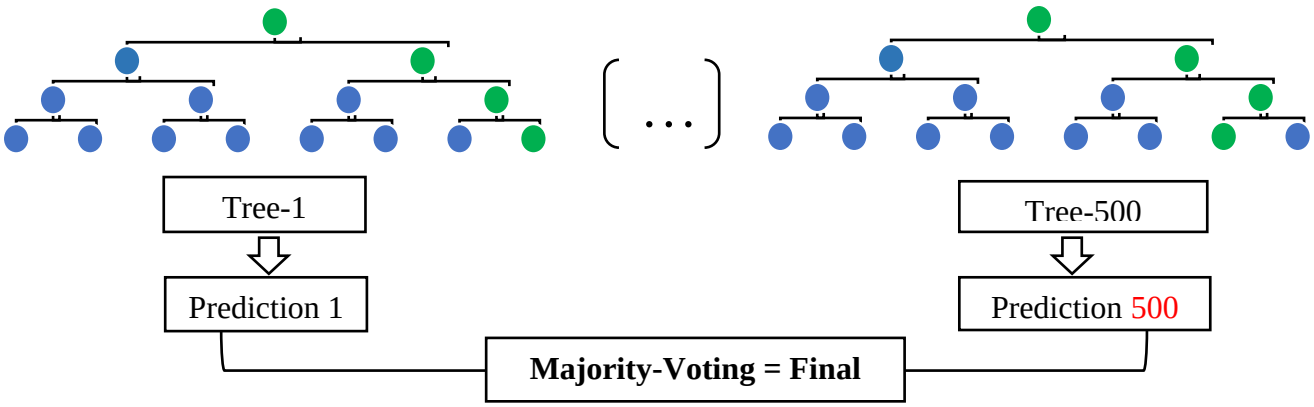


Figure 3.9 Simplified Random Forest Classifier

The Extreme Gradient Boosting classifier (XGBoost) is a type of boosting algorithm that builds a prediction model from other algorithms, most commonly from decision trees (Chen & Guestrin, 2016). Unlike the Random Forest classifier that builds its prediction models randomly, the XGBoost builds each individual model by allocating weight to instances with wrong predictions and high errors. This design allows the algorithm to 'learn' from past mistakes as the most difficult predictions will be highlighted during the prediction process. As such, highlighted 'weak' predictions from the decision trees are compared to the reference criteria (i.e. EE, activity type), and the distance between these parameters represents the error rate of the model (i.e. loss of function). The XGBoost differs from other types of boosting classifiers since it is designed to provide second derivative of loss function, which is essential to provide further information regarding the efficiency of the model (Chen & Guestrin, 2016).

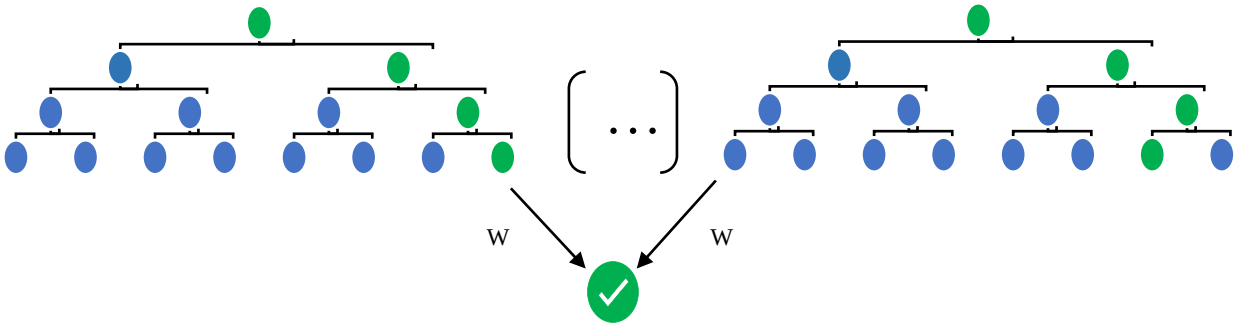


Figure 3.10 Simplified Extreme Gradient Boosting Decision Trees

W represented the weighted averages

The weighted k-nearest neighbours classifier (k-NN; Dudani, 1976) is a modified version of the k-NN classifier, designed to overcome the limitations associated with the probabilistic type of classification of the first version. Essentially, the k-NN is designed to identify k training samples that are closest to the reference criteria (i.e. EE, activity type), and subsequently, assign the classification category according to their distances. The weighted k-NN allocates weight to each of the neighbours according to their distance to the reference point, instead of only adopting the distances as classification criteria. Finally, the points with greater weight are located nearest to the reference. The advantage of this classifier is that the Euclidean distance is relatively simple to compute. In addition, the use of weighted distances make this classifier robust to noisy training data (Cost & Salzberg, 1993).

Cross-validation is used in machine learning to test the validity whilst preventing overfitting. More specifically, cross-validation is a great indication of model overfit due to its robust approach and design. For example, a *k*-fold cross-validation is designed to randomly split the training set into *k* equally sized smaller segments, and then train the model *k* times using all the *k* segments minus one until all the segments are processed. A common approach is the use of a 10-fold cross validation, which will ensure that each model is trained and validated 10 times using 10 unique sets of data. The measure of the final accuracy of the model is subsequently obtained by averaging the results of each model.

3.13.2 Compositional Analysis to Investigate Physical Activity in Cystic Fibrosis

The existence of compositional data was first acknowledged in geological sciences, after Pearson (1897) described the presence of *spurious correlations* that affected any data measuring proportions of a whole. Whilst studying methods to circumvent the issue associated with the spurious correlations, Atchison and Shen (1980) formulated some of the foundations of compositional data analysis (Aitchison, 1983, 1992). Compositional data is defined as relative variables that are proportions of a whole, including time-use movement behaviours, such as PA intensities, SED and sleep (Dumuid et al., 2019; Pedišić, 2014). As such, compositional data are interrelated and can only convey relative rather than absolute information, which implies that they are only meaningful when interpreted collectively. This type of data is constrained to a specific sample space, denominated *d*-simplex, which can be represented in a ternary diagram when accounting for three variables (Figure 3.11). Data living in the '*d*-simplex' are expressed as ratios rather than absolute values, and consequently, they cannot be described using arithmetic means and standard deviation. Indeed, Pawlowsky-Glahn and Egozcue (2002) demonstrated that the geometric mean is optimal to describe compositional data, as it reflects the relative scale of data. Specifically, geometric mean is defined as the n^{th} root of the product of n numbers.

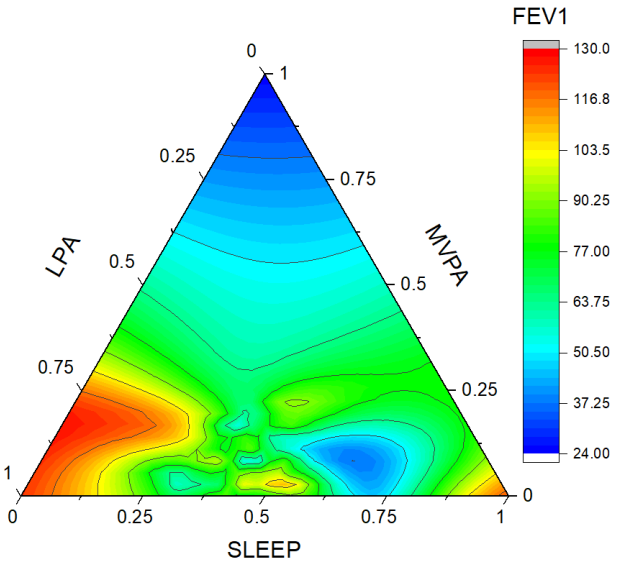


Figure 3.11 Ternary Plot

The use of standard statistical methods (i.e. linear regression) with compositional data might lead to erroneous findings, since these approaches were tailored to absolute data living

in the 'real space'. To overcome this issue, Aitchison (1992) proposed the use of a log-ratio transformation to normalise the constrained compositional data, thereby allowing the application of traditional statistical approaches. However, evidence suggests that the log-ratio transformation is asymmetric and non-isometric, and therefore, not suitable for compositional analysis of time-use data such as PA (Dumuid et al., 2018). Different approaches to normalise compositional data have been proposed since Aitchison's log-ratio transformation (Egozcue & J, 2005; Pawlowsky-Glahn & Egozcue, 2019; Pawlowsky-Glahn et al., 2015). For example, Egozcue et al. (2005) proposed the use of an isometric log-ratio (*ilr)* to transform compositional data, as follows for a D-part composition x, with a transformation of $z = (z_1, \ldots, z_{D-1}) = ilr(x)$:

Equation 3.7

$$z_i = \sqrt{\frac{D-i}{D-i+1}}\ ln\frac{xi}{\sqrt[D-i]{\Pi_{j=i+1}^{D} x_j}}, for\ i = 1, \ldots, D-1$$

The use of *ilr* transformation produces a set of coordinates that can be used to describe the total variance of the composition. Additionally, traditional statistical approaches (i.e. multiple regression) can be applied to the *ilr* coordinates to investigate the relationship between compositional data (i.e. movement behaviours) with health outcomes. The coordinates on their own are hard to interpret, hence, a sequential binary partition can be used to further explore the data (Pawlowsky-Glahn & Egozcue, 2016). The sequential binary partition is used to group the composition into separate parts, and it can be applied to investigate the nature and interaction of different movement behaviours. Essentially, this approach splits the full composition into smaller groups including a numerator and a denominator, which can be specifically tailored to address the research question. For example, in order to study the impact of a sedentary-lifestyle on health in relation to the other movement behaviours, the partition can be design to include inactivity-related components as the numerator, and activity-related components as the denominators (Carson, Hunter, et al., 2016; Chastin et al., 2015; Dumuid et al., 2018). Most importantly, the implications of compositional analyses to advance the understanding of how movement behaviours are related to health are promising. For example, Gupta et al. (2018) compared the use of compositional analyses with *ilr* transformations to a multivariate model in order to assess how movement behaviours impact health outcomes. Gupta et al. (2018) showed that the inferences regarding time spent sedentary and in PA were significantly different with compositional analyses, which indicates that this method has the potential to change the findings, and therefore, the core message of a study.

CHAPTER 4

Study One: Calibration and Validation of Accelerometry using cut-points to Assess Physical Activity in Paediatric Clinical Groups: A Systematic Review

Abstract

Regular physical activity is associated with physiological and psychosocial benefits in both healthy and clinical populations. However, little is known about tailoring the analysis of physical activity using accelerometers to the specific characteristics of chronic conditions. Whilst accelerometry is broadly used to assess physical activity, recommendations on calibration in paediatric clinical groups are warranted. The aim of this systematic review was to provide a critical overview of protocols used to calibrate accelerometry in children and adolescents with clinical conditions, as well as to develop recommendations for calibration and validation of accelerometry in such populations. The search was performed between March to July 2017 using text words and subject headings in six databases. Studies had to develop moderate-to-vigorous intensity physical activity (MVPA) cut-points for paediatric clinical populations to be included. Risk of bias was assessed using a specific checklist for calibration studies. A total of 540,630 titles were identified, with 323 full-text articles assessed. Five studies involving 347 participants aged 9 to 15 years were included. Twenty-four MVPA cut-points were reported for seven clinical conditions, 16 of which were developed for different models of ActiGraph, seven for Actical and one for Tritrac-R3D. Statistical approaches included mixed regression, machine learning and receiver operating characteristic analyses. Disease-specific MVPA cut-points ranged from 152 to 735 counts·15 s^{-1}, with lower cut-points found for juvenile arthritis (152 counts·15 s^{-1}), juvenile dermatomyositis (166 counts·15 s^{-1}) and inherited muscle disease (297 counts·15 s^{-1}), and higher cut-points associated with cerebral palsy (735 counts·15 s^{-1}) and intellectual disabilities (652 counts·15 s^{-1}). The lower MVPA cut-points for diseases characterised by both ambulatory and metabolic impairments likely reflect the higher energetic demands associated with those conditions.

4.1 Introduction

Regular physical activity (PA) is recommended for children and adolescents to promote health and well-being (WHO, 2020), irrespective of disease status. However, PA plays a particularly potent role in youth with chronic conditions and is associated with slowing disease progression in conditions such as cerebral palsy (CP; Keawutan et al., 2017; Verschuren et al., 2016). A common issue for children and adolescents with chronic conditions, is the tendency to become less physically active with age and disease progression, which can lead to deconditioning and the initiation of a vicious negative spiral involving subsequent reductions in the ability to perform PA (Durstine et al., 2013; Torpy et al., 2018).

Careful consideration should be given when recommending PA to children and adolescents with some chronic conditions due to the enhanced nutritional, metabolic and energetic requirements associated with the condition or structural disability (West et al., 2019). Children and adolescents with chronic conditions would, therefore, benefit from a greater understanding of the dose-response relationship between PA and health benefits in order to balance this with the potential negative sequalae that could ensue (Riner & Sellhorst, 2013). However, the current recommendation that children aged 5 to 18 years should accumulate on average at least 60 minutes of moderate-to-vigorous physical activity (MVPA) per day weekly (WHO, 2020) has been developed for non-clinical populations, and therefore, are likely to have limited applicability to clinical populations. Indeed, a specific clinical guideline would warrant a higher degree of specificity and a cautious assessment of particular risks and benefits for each condition. It is therefore imperative to account for condition-specific factors that could be associated with exercise intolerance and/or an altered physiological response to exercise/physical activity (Wells et al., 2019). PA recommendations tailored for children and adolescents with clinical conditions, however, remain sparse (Morris, 2008).

Objective methods used to assess PA, such as accelerometers, are appropriate for clinical settings due to the low participant burden and relatively low cost (Trost & O'Neil, 2014). Accelerometers are capable of detecting patterns of PA accumulation, as well as information on PA frequency and intensity, such as sedentary time (SED), light physical activity (LPA) and MVPA (Welk, 2005). Specifically, accelerometry measures velocity over a period of time which can be translated into intensities of PA by using cut-points (Welk, 2005). However, the generation of these cut-points is highly challenging, for example, even within

one type of accelerometer, the MVPA cut-point in healthy youth varies from 400 to 3,600 counts·min^{-1} (Cain et al., 2013). Whilst the accurate assessment of PA levels is particularly important in chronic conditions, inaccurate cut-points can result in over- or underestimated predictions. Additionally, it is also important to consider the limitations associated with the use of accelerometry. For example, while accelerometry can accurately assess sedentary time, it is not able to differentiate between various sedentary activities (Hurter et al., 2018). Moreover, factors such as brand and placement are likely to have an impact on the prediction of both sedentary time and time spent in different PA intensities (Godfrey et al., 2008).

Amongst the challenges of calibrating accelerometry are the different methods to translate (e.g., physical activity protocols and criterion method) and interpret (e.g., statistical approach) the accelerometer raw signals into biological and behavioural outcomes (e.g., cut-points). Indeed, a recent systematic review summarising different accelerometry calibration studies in healthy populations acknowledged the lack of cut-points that account for individual characteristics such as demographic and physiological variations (de Almeida Mendes et al., 2018). A key limitation of generalising cut-points developed for healthy populations to clinical populations is that they will not consider the altered resting metabolic rate (RMR) and higher energy expenditure (EE) for a given activity often evident in youth with chronic conditions (Bandini et al., 1991; Epstein et al., 1989; Ramsey et al., 1992). Whilst some research has sought to calibrate accelerometry in paediatric clinical conditions (Stephens et al., 2016; Trost et al., 2015), the lack of standardisation, wide variability in protocol designs and lack of healthy matched controls limits interpretation (Logan et al., 2016). Indeed, this systematic review can contribute by providing recommendations regarding the most appropriate criterion references, types of activities and statistical analyses to calibrate and cross-validate the cut-points.

The aim of this systematic review was to provide a critical overview of the protocols used to calibrate and validate accelerometer-derived MVPA cut-points in children and adolescents with clinical conditions and identify key parameters and considerations for future research.

4.2 Methods

This review was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis statement (Liberati et al., 2009; Moher et al., 2015) and

is registered on the International Prospective Register of Systematic Review (PROSPERO registration ID: CRD42016053880).

4.2.1 Search Methods

The search was performed between March and July of 2017 using six databases (PubMed, SPORTDiscus, ScienceDirect, Scopus, ISI Web of Knowledge, Wiley Online Library). A Population Intervention Comparison Outcome (PICO) framework was adopted to build and structure the search; a detailed description of the search protocol is available in the Appendix C. The protocol and search strategy were reviewed by an experienced librarian and a pilot was performed to ensure the suitability of the criteria and search terms. The search terms were in accordance with the 2017 Medical Subject Headings and were inserted as keywords to all the databases and platforms. The search terms were: acceleromet*; acceleromet* AND (validation OR calibration); acceleromet* AND physical activity; wearable monitors AND (calibration OR validation); physical activity AND (calibration OR validation); acceleromet* cut-points; energy expenditure AND acceleromet*; and classification AND physical activity intensities. The reference lists of relevant reviews and of all the studies included therein were examined for studies matching the inclusion criteria.

4.2.2 Eligibility Criteria

Studies published in English from the year 2000 which generated MVPA accelerometry cut-points in children and adolescents (5 to 18 years) with any chronic clinical condition (disease of long duration and slow progression; Goodman et al., 2013) were included. Only studies published after the year 2000 were included in order to avoid the inclusion of outdated accelerometer models, such as the Computer Science Application (CSA). Specifically, whilst the first accelerometer was developed in 1980 (Montoye et al., 1983), the use of this new technology was highly limited due to the high cost and poor reliability (Troiano et al., 2014). Furthermore, these devices have limited comparability to modern accelerometer models, particularly after the advent of triaxial devices and the option to extract raw acceleration data (Freedson et al., 2012). Non-English, non-human and unpublished studies, book chapters,

theses, monographs, dissertations and abstracts were not included. In addition, studies using accelerometers along with additional technologies such as a microcontroller were not excluded. Studies in adults, or calibrating for healthy populations, sedentary behaviour or wheelchair users were excluded. It is noteworthy that all studies calibrating accelerometry in adult clinical populations constituted another systematic review (Bianchim et al., 2019; Appendix A). This sample of studies were investigated and synthesised separately given the different nature of calibration protocols for children and adults.

4.2.3 Data Extraction and Management

An EndNote X7 (Clarivate Analytics, USA) database was created with potential studies, and all the titles and abstracts were initially screening by one author for selection of full-texts. All full-texts selected were then subsequently screened by three authors according to the pre-established inclusion criteria. Supplementary information for each study was consulted when available. In the case of missing information or variables required for completion of the extraction sheet, study authors were contacted, however, no additional data was provided. Data was extracted from the included full-texts by one author and reviewed by two authors (Table 4.1). Any discrepancies were discussed by the three authors until a consensus was reached.

Table 4.1 Summary of the Data Extracted from the Included Studies

Data extraction field	**Information extracted**
Context and participants	The author, year and sample size of the study; participant characteristics such as age, health status, height, weight, BMI, ethnicity; and covariates measured such as self-report questionnaire data and health scales related to disease assessments were extracted.
Study design and methods used	Any information related to the accelerometer, such as accelerometer model (e.g., number of axes); accelerometer placement (e.g., wrist [dominant/non-

	dominant], hip, chest); accelerometer settings (e.g., epoch, sampling frequency, use of low frequency filter); and data processing decisions (e.g., wear-time criteria) were extracted. Additionally, any information related to the calibration protocol, such as protocol design (e.g., laboratory-based, field-based, daily-life protocol); duration of the protocol; adjustment of specific variables (e.g., age, body mass); performance of individual calibration; criterion measure (e.g., energy expenditure, direct observation, heart rate); resting metabolic rate assessment; statistical approach (e.g., ROC-curve analyses, linear regression, machine learning); validation method (e.g., validation, cross-validation leave-one-out, cross-validation *k*-fold); and assessment for agreement (e.g., Kappa, Bland-Altman) were also extracted.
Findings	The extracted outcomes were protocol design and cut-points. All the extracted protocols were classified in four categories: laboratory-based (walking or running, over-ground or on a treadmill), free-living (assessment of participant routine), daily-life (daily-life activities performed at the research site), and mixed (at least two of laboratory-based, free-living and daily-life) protocols.
Quality of the study	Quality assessment specifically created for calibration studies (checklist sheet).

The risk of bias was assessed independently by two authors using a specific checklist (Table 4.2) created according to previous recommendations for calibration protocols (Bassett, 2012; Bassett et al., 2012; Welk, 2005). This checklist considers six elements of the calibration protocol (sample characteristics, accelerometer settings, criterion measure, statistical approach for calibration, and statistical approach for validation) to rate studies as good, fair or poor according to the criteria described in Table 4.2. The inter-rater reliability was calculated using Kappa scores with 0.8 as the minimum acceptable inter-rater agreement (McHugh, 2012). Where any discrepancies arose following the risk assessment, all three authors involved in the screening and data extraction discussed these until a consensus was reached.

Table 4.2 Quality and Risk Assessment Criteria According to Descriptive Variables and Study Design

Standard	**Poor**	**Fair**	**Good**
1. Sample Characteristics	Study did not include any descriptive variables other than age and sex.	Study included height, weight, body mass index and variables specific to the clinical condition.	Study included height, weight, body mass index, ethnicity, resting metabolic rate, maturity stages and variables specific to the clinical condition.
2. Accelerometer Settings	Study described accelerometer model.	Study included accelerometer model, number of axes and placement position.	Study included accelerometer model, number of axes, placement, sampling frequency, epoch length and any filtering techniques.
3. Protocol Design	Calibration protocol composed by walking or treadmill test.	Calibration used a mixed protocol (daily-life activities and a treadmill test).	Mixed protocol combining daily-life activities, laboratory protocol test on a treadmill and free-living assessments.
4. Criterion	Speed or direct observation.	Heart rate or metabolic equivalent.	Energy expenditure (including resting metabolic rate estimation*).
5. Statistical Approach for Calibration	Linear regression or Individual linear regression.	ROC curve analyses.	Machine learning techniques, hierarchical models or multilevel modelling, adjusting for factors related to participant's characteristics and to the pathophysiology of the clinical condition to develop the cut-point.
6. Statistical Approach for Validation	No validation assessment.	Leave-one-out cross-validation and agreement assessment using Bland-Altman or kappa score.	*K*-fold cross-validation using different samples and activities. Agreement assessment using Bland-Altman or Kappa score, and estimates the intra-class correlation coefficient, and/or limits of agreement.

ROC: receiver operating characteristic. *The criteria for a valid resting metabolic rate estimation was a minimum of 15 min of steady state, preferably adopting the formula of de Weir (Weir, 1948)

A narrative synthesis of the studies was performed due to the heterogeneity of calibration protocols encountered, covering the topics of the protocol design, description of, and adjustment for, disease-specific factors, accelerometer brand and settings, criterion measure and the statistical approach for generating and validating the cut-points. All cut-points in counts·min^{-1} were reintegrated to counts·15 s^{-1} epochs, which is commonly used in youth, to allow inter-study comparability.

4.3 Results

A total of 543,741 titles were found across all databases, with 540,630 titles remaining following the removal of duplicates. Following initial screening of titles and abstract, 619 articles were selected according to the inclusion criteria by the main author for full-text assessment. In total, 614 studies were subsequently excluded, primarily due to being in a healthy population (279 studies; Figure 4.4). Five studies (Clanchy et al., 2011; McGarty et al., 2016; Ryan et al., 2014; Stephens et al., 2016; Trost et al., 2015), including 347 9 – 15-year-old participants, with a total of 24 generated MVPA cut-points for seven clinical conditions, were included in the final synthesis. The clinical conditions were: CP, intellectual disabilities, CF, congenital heart diseases (CHD), haemophilia (HE), idiopathic muscular dystrophies (IMD), juvenile idiopathic arthritis (JIA; Appendix B).

The inter-rater Kappa score for risk of bias was 0.80, with authors disagreeing regarding accelerometer settings. Discrepancies were regarding the ‘Accelerometer Settings’ scores and were resolved after two authors discussed each point resulting in a Kappa score of 1. Most studies (n = 4) were classified as fair for sample characteristics, with only one study scoring as good. One study scored as fair, and four as good, for accelerometer settings, with three and two studies classified as fair and good, respectively, for protocol design. For criterion measure, one scored as good, three as fair and one as poor. The majority (n = 4) of the studies scored as fair for statistical approach for calibration, with only one scoring as good. Finally, regarding the statistical approach for validation, three studies scored as fair and two as poor (Table 4.3).

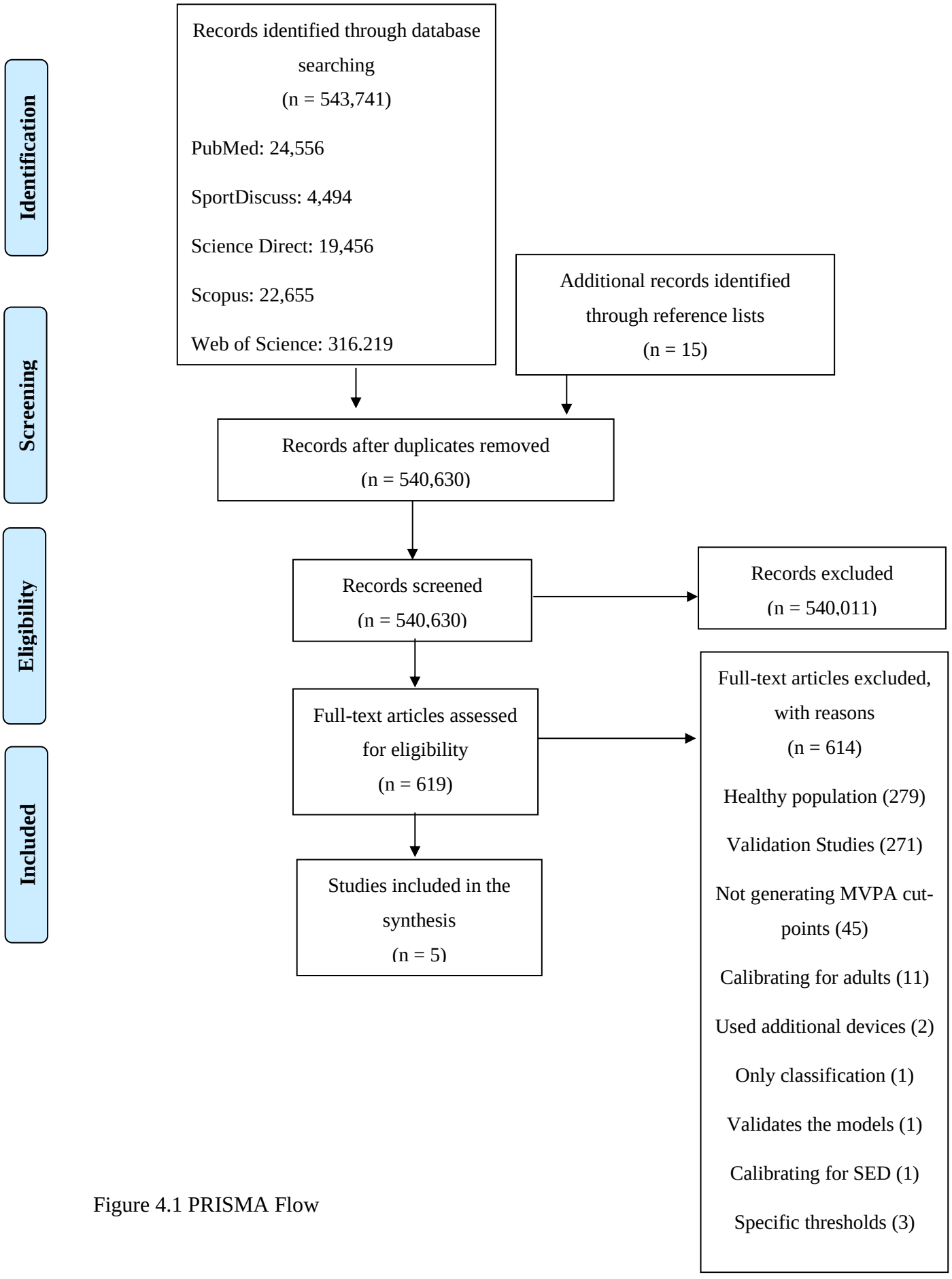


Figure 4.1 PRISMA Flow

Table 4.3 Risk of Bias Assessment Results (Checklist sheet)

Study	Sample Characteristics	Accelerometer Settings	Protocol Design	Criterion	Statistical Approach for Calibrations	Statistical Approach for Validations
Clanchy et al. 2011	Fair	Fair	Poor	Fair	Fair	Poor
Ryan et al. 2014	Fair	Good	Fair	Poor	Fair	Fair
Trot et al. 2015	Fair	Good	Fair	Fair	Good	Fair
McGarty et al. 2016	Fair	Good	Poor	Fair	Fair	Poor
Stephens et al., 2016	Good	Good	Fair	Good	Fair	Fair

Quality of life (Varni et al., 2004), maturity status (Emmanuel & Bokor, 2017; Stephens et al., 2016) and results from a generic health questionnaire (Feldman et al., 1995; Huber et al., 2001) were used as co-variates. Additionally, three studies (Clanchy et al., 2011; Ryan et al., 2014; Trost et al., 2015) used the specific classification system for CP (Gross Motor Function Classification System - GMFCS). Whilst covariates were considered by most of the included studies, only one study (Stephens et al., 2016) adjusted for disease-specific factors when generating the cut-points, although no formal description was provided regarding the variables included in the model. None of the studies investigated whether the disease-specific factors and participant demographics impacted on the developed cut-points.

4.3.1 Accelerometers

Sixteen of the included MVPA cut-points were developed for different ActiGraph models (McGarty et al., 2016; Ryan et al., 2014; Stephens et al., 2016; Trost et al., 2015), seven for Actical (Stephens et al., 2016) and one for Tritrac-R3D (RT3; Table 4.4; Ryan et al., 2014). This translates to 15 MVPA cut-points derived from the vertical axis (VA; Clanchy et al., 2011; Stephens et al., 2016) and nine from the vector magnitude (VM; McGarty et al., 2016; Ryan et al., 2014; Trost et al., 2015). Three studies utilised hip-worn accelerometry on the right side (McGarty et al., 2016; Stephens et al., 2016; Trost et al., 2015) and two studies calibrating for CP placed the accelerometer on the least affected side of the body (Clanchy et al., 2011; Ryan

et al., 2014). The sample frequency varied between 1 to 32 Hz, with one study (Clanchy et al., 2011) not specifying this information. Two studies used an epoch of 15-s (Stephens et al., 2016; Trost et al., 2015), with others using 1-s (Clanchy et al., 2011), 10-s (McGarty et al., 2016) and 60-s (Ryan et al., 2014).

Table 4.4 Summary of the Accelerometer Models used by the Included Studies

Name / Model	Manufacturer	Weight and Size	Memory Capacity	Axis	Frequency Sampling
ActiGraph 7164 (CSA)	ActiGraph LLC Pensacola, FL	45.5 g 5.1 x 4.1 x 1.5 cm	22 days of data with 60-s epoch	Uniaxial	10 Hz
ActiGraph GT3X	ActiGraph LLC Pensacola, FL	27 g 3.8 x 3.7 x 1.8 cm	378 days using 60-s epoch	Triaxial	30 Hz
ActiGraph wGT3X+	ActiGraph LLC Pensacola, FL	19 g 4.6 x 3.3 1.5 cm	38 days 100 Hz	Triaxial	30 – 100 Hz
Actical	Mini-Mitter Sunriver, OR	17.5 g 2.8 x 2.7 x 1.0 cm	45d using 60-s epoch	Uniaxial	32 Hz
Research Tracker accelerometer (RT3)	StayHealthy, Inc; Monrovia, California	71.5 g 71 x 56 x 28 mm	30 days using 60-s epoch	Triaxial	0.017 – 1 Hz

4.3.2 Calibration Protocol Settings

A daily-life calibration protocol was the most commonly used (n = 3), generating 22 MVPA cut-points, with only two studies utilising a laboratory-based protocol (Clanchy et al., 2011; Ryan et al., 2014). Indirect calorimetry was the most common physiological criterion used for calibration (Clanchy et al., 2011; Ryan et al., 2014; Stephens et al., 2016; Trost et al., 2015), with one study using direct observation (McGarty et al., 2016). The protocol duration

varied from 35 to 240 minutes. Resting metabolic rate was estimated by Stephens et al. (2016) using the Weir equation, whereas Clancy et al. (2011) and Trost et al. (2015) used the Schofield equation (Schofield, 1985) and Ryan et al. (2014) the Oxford equation (Henry, 2005). As McGarty et al. (2016) developed cut-points through direct observation, a RMR estimation was not required. All included studies performed a group calibration rather than individual calibrations.

4.3.3 Statistical Approach

Fourteen MVPA cut-points were developed through mixed regression models (Stephens et al., 2016), six using machine learning (regressing trees; Trost et al., 2015), and four through Receiver Operating Characteristic (ROC) analysis (Clanchy et al., 2011; McGarty et al., 2016; Ryan et al., 2014; Stephens et al., 2016). Only one study did not perform any kind of validation (Clanchy et al., 2011), with all other validations performed using leave-one-out cross-validations. No studies utilised independent samples or a different set of activities to cross-validate. Eighteen (Clanchy et al., 2011; Ryan et al., 2014; Stephens et al., 2016; Trost et al., 2015) of the generated cut-points were validated through comparison of previously established cut-points developed for healthy populations (Evenson et al., 2006; Puyau et al., 2002; Rowlands et al., 2004; Vanhelst et al., 2010). Three studies (McGarty et al., 2016; Ryan et al., 2014; Trost et al., 2015) utilised the Kappa score for agreement assessment, whereas two studies (Clanchy et al., 2011; Stephens et al., 2016) performed ANOVA. A description of the statistical methods used in each included study is provided in Appendix B.

4.3.4 Outcome

The disease-specific MVPA cut-points ranged from 152 to 724 counts·15 s^{-1}, with 19 MVPA cut-points presented in counts·15 s^{-1}, and four presented in counts·min^{-1} (Table 4.5). The sensitivity of the cut-points ranged from 37 to 91%, and the specificity ranged from 85 to 97%. Cerebral palsy was the mostly widely studied clinical condition, with eight cut-points developed across three studies (Clanchy et al., 2011; McMurray et al., 2015; Ryan et al., 2014). Trost et al. (2015) generated cut-points for different degrees of CP severity, with fair to excellent accuracy, demonstrating better accuracy (lower rates of misclassification, particularly

for GMFCS III and for LPA classification) than Evenson et al. (2006) cut-points. In contrast, Ryan et al. (2014) and Clanchy et al. (2011) did not develop specific cut-points for different GMFCS levels or perform a leave-one-out cross validation, using specificity and sensitivity as a measure of validation. Clanchy et al. (2011) cut-points showed no significant improvement in PA classification accuracy compared to healthy population cut-points, whilst the MVPA cut-points of Ryan et al. (2014) demonstrated moderate classification agreement (Evenson et al., 2006; Rowlands et al., 2004; Vanhelst et al., 2010). Similarly, Stephens et al (2016) also applied healthy population cut-points (Evenson et al., 2006) to their participants with various chronic conditions (CF, IMD, JIA, HE and CHD), which resulted in poor-to-moderate sensitivity in PA classification. Most of the disease-specific cut-points developed were below the previously established MVPA cut-points for healthy populations (e.g., 2,020 to 8,199 counts·min^{-1}).

Table 4.5 Summary and Validity of the Clinical-specific Moderate-to-vigorous Cut-points

Conditions (n)	**Study**	**Reason for split**	**Cut-points MVPA (original)**	**Cut-points MVPA converted to counts·15 s^{-1}**	**Criterion Validity**
Cerebral palsy **(7)**	Trost et al. 2015	GMFCS I / VA	535 (counts·15 s^{-1})	N/A	LOOCV – 81.1%
	Trost et al. 2015	GMFCS II / VA	333 (counts·15 s^{-1})	N/A	LOOCV – 76.7%
	Trost et al. 2015	GMFCS III/VA	200 (counts·15 s^{-1})	N/A	LOOCV – 82.9%
	Trost et al. 2015	GMFCS I / VM	724 (counts·15 s^{-1})	N/A	LOOCV – 80.5%
	Trost et al. 2015	GMFCS II / VM	685 (counts·15 s^{-1})	N/A	LOOCV – 75.6%
	Trost et al. 2015	GMFCS III / VM	669 (counts·15 s^{-1})	N/A	LOOCV – 84.2%
	Ryan et al. 2014	N/A	689.3 (counts·min^{-1})	172.3	Se – 86.7% / Sp – 91.9%
	Clanchy et al. 2011	N/A	2942 (counts·min^{-1})	735.5	Se – 91.4% / Sp – 86.2%
Intellectual disability **(2)**	McGarty et al. 2016	VA	1008 (counts·min^{-1})	252	LOOCV – 93% Se – 91% / Sp – 95%

	McGarty et al. 2016	VM	2610 (counts·min^{-1})	652	LOOCV – 87% Se – 91% / 84%
Cystic fibrosis **(2)**	Stephens et al. 2016	CF / ActiGraph 7164	487 (counts·15 s^{-1})	N/A	Se – 71% / Sp – 85%
	Stephens et al. 2016	CF / Actical 7164	368 (counts·15 s^{-1})	N/A	Se – 51% / Sp – 91%
Chronic heart disease **(2)**	Stephens et al. 2016	CHD / ActiGraph 7164	349 (counts·15 s^{-1})	N/A	Se – 42% / Sp – 85%
	Stephens et al. 2016	CHD / Actical	349 (counts·15 s^{-1})	N/A	Se – 41 / Sp – 94%
Inherited muscle disease **(2)**	Stephens et al. 2016	IMD / ActiGraph 7164	663 (counts·15 s^{-1})	N/A	Se – 81% / Sp – 90%
	Stephens et al. 2016	IMD / Actical	297 (counts·15 s^{-1})	N/A	Se – 47% / Sp – 96%
Juvenile dermatomyositis **(2)**	Stephens et al. 2016	JDM /ActiGraph 7164	172 (counts·15 s^{-1})	N/A	Se – 41% / Sp – 90%
	Stephens et al. 2016	JDM / Actical	166 (counts·15 s^{-1})	N/A	Se – 37% / Sp – 94%
Haemophilia (2)	Stephens et al. 2016	HE / Actical	306 (counts·15 s^{-1})	N/A	Se – 49% / Sp – 92%
	Stephens et al. 2016	HE / ActiGraph 7164	432 (counts·15 s^{-1})	N/A	Se – 53% / Sp – 92%
Juvenile arthritis **(2)**	Stephens et al. 2016	JIA / Actical	152 (counts·15 s^{-1})	N/A	Se – 49% / Sp – 94%
	Stephens et al. 2016	JIA / ActiGraph 7164	255 (counts·15 s^{-1})	N/A	Se – 41% / Sp – 90%
Overall (CF, JA, HE, CHD, JDM, IMD) **(2)**	Stephens et al. 2016	Overall Diseases / Actical	289 (counts·15 s^{-1})	N/A	Se – 77% / Se – 97%
	Stephens et al. 2016	Overall Diseases / ActiGraph 7164	426 (counts·15 s^{-1})	N/A	Se – 78% / Sp – 94%

MVPA: moderate-to-vigorous physical activity; GMFCS: gross motor function classification system; VA: vector axial, VM: vector magnitude; LOOCV: leave-one-out cross-validation; Se: sensitivity; Sp: specificity; CF: Cystic Fibrosis; CHD: Congenital Heart Disease; IMD: Inherited Muscle Disease; JMD: Juvenile Dermatomyositis; HE: Haemophilia; JA: Duvenile Arthritis.

4.4 Discussion

Twenty-four MVPA cut-points were extracted from five studies across seven different paediatric clinical groups. Overall, the review revealed little consensus with regards to MVPA cut-points, due to, at least in part, the relatively low number of calibration studies and broad range of protocol designs and accelerometer settings used in the studies, thereby limiting inter-study comparisons. Nonetheless, despite this, a thorough methodological quality assessment of the included studies was performed, which contributed to a higher transparency and aided the interpretation of the outcomes. Moreover, this review presented a critical analysis of the methodological challenges faced when developing cut-points for clinical paediatric populations, providing recommendations for future studies.

4.4.1 Calibration Protocol for Paediatric Clinical Populations

The majority of the included studies utilised daily-life (McGarty et al., 2016) or mixed (Stephens et al., 2016; Trost et al., 2015) protocols composed of daily-life and laboratory protocols. To accommodate different disease and disability levels, Stephens et al. (2016) adjusted their laboratory-based protocol by performing two different treadmill tests based on 6-min walking test performance. Whilst the protocol can greatly impact the PA classification, the physiological criterion adopted is equally important. For example, both Trost et al. (2015) and Stephens et al. (2016) utilised indirect calorimetry as criterion, which therefore considers the higher energetic demand associated with a given activity in some chronic conditions (Walker et al., 2015). Specifically, diseases associated with chronic inflammation (e.g., CF, obesity) and musculoskeletal adaptations (e.g., CP, JIA, IMD) can reduce exercise tolerance, leading to chronic deconditioning and a higher EE demand for a given activity (Mehta, 2015).

It is well known that the majority of paediatric clinical conditions are associated with altered cardiometabolic demands (Bar-Or & Rowland, 2004). Thus, studies calibrating

accelerometry for these populations should adopt EE as their criterion method. Another important consideration is that RMR changes dramatically according to maturity, disease and health parameters (McErlane et al., 2017), such as chronic inflammation and reductions in PA (Buchdahl et al., 1988; Eisenstein & Berkun, 2014). Specifically, individuals with CF often have a greater RMR, which can be explained to some extent by pulmonary impairment (Dorlöchter et al., 2002) and increased cost of breathing (Bell et al., 1996; Frankenfield et al., 2017). Conversely, children with certain types of CP have a reduced RMR due to a lower energetic requirement at rest and altered body composition (e.g., reduced fat free mass and lean body mass) (Bandini et al., 1995; Bandini et al., 1991; Stallings et al., 1993). Consequently, condition-specific calibration protocols adopting EE as the criterion should measure RMR. Despite using indirect calorimetry in their protocols, some of the included studies utilised Schofield and Oxford equations (Clanchy et al., 2011) to determine RMR. Whilst such equations may provide a low-cost estimation of RMR, they are based on chronological, rather than biological, age (McMurray et al., 2015), and do not account for sex or health status. This may lead to an inaccurate estimation of RMR, and consequently of EE, in clinical populations (De Wit et al., 2010; Fuster et al., 2007). Therefore, the measurement of oxygen uptake at rest should be utilised to provide a precise estimation of RMR, and consequently enhance the accuracy of the disease-specific cut-points in youth with chronic conditions (Stephens et al., 2016).

It is also important to consider the influence of disease severity within a condition, which is likely to affect the relative energetic demand, as might differences in the treatment and medication strategies between patients (Walker et al., 2015). Indeed, Ryan et al. (2014) and Clanchy et al. (2011) did not stratify their sample by the GMFCS scale, resulting in large heterogeneity of CP-severity across participants, with some children not able to finish the protocol. In contrast, Trost et al. (2015) demonstrated that the relationship between EE and activity counts changed significantly according to GMFCS level, with children classified as level III having greater EE during locomotion when compared to levels I and II.

4.4.2 Statistical Approach

The statistical approach chosen is highly influential in the translation of the physiological criterion into cut-points. Linear regression, which was initially one of the most commonly used methods for calibration, cannot account for the non-linear relationship between

PA and EE (Freedson et al., 2005; Welk, 2005). Consequently, most of the studies included in this review utilised ROC analyses to develop their cut-points. Whilst ROC is more accurate than linear regression (Welk, 2005), it is dependent on the number of participants and does not allow adjustment of disease-specific factors (Staudenmayer et al., 2009).

Alternatively, mixed regression modelling is an exploratory analysis, particularly useful due to its flexible nature that allows the inclusion of disease-specific factors (Freedson et al., 2005; Welk, 2005). Stephens et al. (2016) utilised mixed regression modelling to control for disease-specific factors to generate predictive equations for children and adolescents with CF, HE, JIA, CHD and IDM (Aadland & Steene-Johannessen, 2012; Lopes et al., 2009), reporting that heart rate improved the model and lowered the standard error associated with the prediction. These findings agree with those in healthy populations (Altini et al., 2014), with the improvements in standard error likely to be attributable to the reduction of the inter-individual variability caused by the adjustment of physiological signals. It is noteworthy that whilst a certain degree of accuracy can be achieved with cut-points, recent PA research has moved towards using machine learning. Indeed, more complex machine learning analysis have provided a higher degree of accuracy in comparison with traditional cut-points (Bonomi, Plasqui, et al., 2009; Staudenmayer et al., 2015; Staudenmayer et al., 2009; Welk, 2005). Despite this, a calibration protocol is still required even when using those techniques. Indeed, machine learning can also be used to develop cut-points, for example, Trost et al. (2015) used Binary Decision Trees to generate CP-specific cut-points. Whilst machine learning provides high accuracy, evidence suggests that considerable bias can arise from using a small sample size (Combrisson & Jerbi, 2015). Alternatively, approaches such as using different testing and training data sets, and testing algorithm performance (i.e. nested cross-validation), can provide unbiased performance estimates even with small sample sizes (Vabalas et al., 2019).

A cross-validation analysis of the cut-points evaluates the predictive models to ensure validity and avoid over-fitting, and it can be performed through different methods such as the *k*-fold or leave-one-out cross-validation. Specifically, considering that the developed cut-points might be biased to the sample characteristics or to the calibration protocol design, the use of an independent sample with a different set of activities for cross-validating the cut-points is recommended (Welk, 2005). Stephens et al. (2016) and Trost et al. (2015) applied a leave-one-out cross-validation, identified as the most appropriate approach when working with smaller samples (Welk et al., 2003), or to lessen the burden on the participants. It is further recommended that the disease-specific cut-points should also be validated against a healthy

matched control group to ensure that potential cut-point discrepancies are a result of the pathophysiology rather than from the protocol design. Further to the cross-validation, agreement measures, such as Kappa score and Bland-Altman, indicate whether two methods can be used concomitantly or interchangeably, thereby facilitating inter-study comparisons (Bland & Altman, 1986). Alternatively, recent research has used a statistical equivalence test to measure agreement, which has been shown to be more appropriate for highlighting similarities between methods (Dixon et al., 2018; Kim et al., 2016). Particularly, the performance of agreement measures between activity counts and the criterion measures in a calibration protocol ensures that both measurements are comparable, and therefore, it prevents potential errors when developing cut-points (Welk, 2005).

4.4.3 Outcome: Cut-points

Cross-validation identified moderate to excellent accuracy for most of the disease-specific cut-points. Considerable inter-study discrepancies were found when comparisons were made between the disease-specific and previously established healthy population cut-points. For example, whilst Trost et al. (2015) found that applying cut-points developed for healthy populations (Evenson et al., 2006) to CP children resulted in poor accuracy and misclassification, Ryan et al. (2014) and Clanchy et al. (2011) demonstrated fair to moderate accuracy (Rowlands et al., 2004; Vanhelst et al., 2010). Indeed, converse to Ryan et al. (2014) and Clanchy et al. (2011), Trost et al. (2015) calibrated for each level of the GMFCS instead of performing an overall calibration, and applied machine learning techniques to generate the CP cut-points, presenting higher specificity than the cut-points developed for healthy populations. Furthermore, Stephens et al. (2016) also found that their disease-specific cut-points (CF, CHD, HE, JIA and IMD) had improved accuracy when compared with standard cut-points, thereby supporting the notion that specific cut-points are necessary for clinical populations.

Given that SED is mainly classified based on stationary activities and therefore does not consider musculoskeletal disabilities, it is unsurprising that some studies (Clanchy et al., 2011; Ryan et al., 2014; Trost et al., 2015) demonstrated fair to excellent accuracy when utilising healthy population-based SED cut-points for children with less severe CP. Despite this, poor classification of LPA may affect specific clinical populations, such as CP

(Verschuren et al., 2014), who may not be able to engage in MVPA activities, and would therefore greatly benefit from a reduction in SED (Ryan et al., 2015). Specifically, considering that daily PA is a composite measure, an increase in LPA could be associated with a reduction in SED and enhancement on the total volume of PA (Bassett et al., 2017). Indeed, estimation of LPA for children with CP through standard cut-points, such as Evenson et al. (2006) and Vanhelst et al. (2010), presented poor to fair classification accuracy (Clanchy et al., 2011; Ryan et al., 2014; Trost et al., 2015). Additionally, the lack of standardisation regarding protocol design and statistical approach hinders the applicability of the cut-points, which might explain the variability found between cut-points developed for the same clinical condition. Consequently, age- and sex-matched healthy control groups are essential to elucidate whether the differences observed in the disease-specific protocol are due to the disease severity or to protocol discrepancies. However, only one study (Stephens et al., 2016) included a control group although this was only used for baseline comparisons.

4.4.4 Strengths and Limitations

The present systematic review is associated with numerous strengths. Firstly, an experienced librarian was consulted to revise the initial protocol and a pilot search was conducted to minimise errors, leading to changes in the eligibility of participants, outcomes, risk of bias assessment and analysis. Moreover, the initial search terms were adapted following advice from the librarian. The pilot search generated a large number of studies for participants across the lifespan and health continuum, therefore, the inclusion criteria for participants were limited to only children and adolescents with clinical conditions. Nevertheless, the literature was initially screened to capture all calibration studies for healthy and clinical populations. Whilst this strategy resulted in an extensive search, it also minimised the possibility of missing studies calibrating for a clinical condition. However, this strategy is not without limitations, as it required having only one author screen all the titles and abstracts. Nonetheless, different approaches were adopted to minimise error. Specifically, an EndNote library was created, and the same search strategy was used for all databases. Whilst double data entry was not performed, a data extraction sheet was created and checked by two authors, and subsequently made available to all authors during the extraction process.

A qualitative data synthesis was performed due the heterogeneity of calibration protocols and the calculation of cut-point effect sizes not being possible, thereby precluding a meta-analysis from being performed. The heterogeneity of the protocols can partially be explained by the inclusion of a broad range of clinical conditions. However, whilst the comparison of numerous clinical conditions of a different nature may be questioned, the primary aim of the review was to investigate the structure of different calibration protocols and how they accounted for the pathophysiology of the respective conditions. Despite the varying nature of the conditions included, only a small range of studies calibrated accelerometry in clinical populations, which hinders further conclusions regarding the optimal protocol.

4.5 Conclusion

Overall, this systematic review highlights the broad range of protocol designs and accelerometer settings of studies developing MVPA cut-points for children and adolescents with clinical conditions. Research seeking to develop disease-specific paediatric cut-points should consider the pathophysiology of the disease and seek to include a measure of EE, an accurately assessed RMR and a healthy comparison group. Moreover, all cut-points developed should be cross-validated. In summary, studies calibrating accelerometry in paediatric clinical populations are urgently required to establish an optimal calibration protocol. Subsequently, the enhancement in the assessment and surveillance of PA for clinical populations could lead to the development of more informed clinically specific PA guidelines.

4.6 Practical Implications

A systematic review of the literature resulted in five studies which generated PA cut-points for seven conditions in youth. Specific recommendations for future studies calibrating accelerometry in paediatric clinical groups were developed:

- To account for the pathophysiology of the disease in the calibration protocol.
- To integrate a measurement of energy expenditure to the calibration protocol.
- To move towards using machine learning techniques.

- To include a control group.
- To cross-validate the cut-points.

CHAPTER 5

Study Two: Developing and Evaluating Raw Acceleration Thresholds for Children and Adolescents with Cystic Fibrosis compared to Healthy Youth

Abstract

Introduction: Regular physical activity (PA) is recommended as part of Cystic Fibrosis (CF) treatment. Currently, available cut-points to classify PA intensity have primarily been generated and validated in healthy populations and are likely to misclassify PA in this those with CF. Therefore, the aim of this study was to develop raw acceleration, condition-specific PA cut-points for children and adolescents with CF and to investigate how these cut-points vary according to accelerometer placement and brand and compared to healthy controls.

Methods: Thirty-five children and adolescents with CF (15 girls; 11.6 ± 2.8 years) and 28 healthy controls (16 girls; 12.2 ± 2.7 years) participated. Energy expenditure and triaxial acceleration were measured during six typical daily activities of varying intensities and a cardiopulmonary exercise test to exhaustion. The metrics Euclidean Norm Minus One (ENMO) and Mean Amplitude Deviation (MAD) were extracted from the raw acceleration data measured using a GENEActiv (both wrists) and ActiGraph GT9X (both wrists and right waist) accelerometers. Receiver Operator Characteristic (ROC) curves were used to determine healthy and CF-specific cut-points for sedentary time (SED), moderate physical activity (MPA) and vigorous physical activity (VPA).

Results: Irrespective of intensity, the cut-points were generally lower in those with CF than their healthy peers for both ENMO (60.2 – 73.1 vs. 63.5 – 86.8) and MAD (58.9 – 85.2 vs. 75.9 – 93.7). The accuracy of the CF-specific ENMO and MAD cut-points varied from fair to excellent for both brands and across all placements, with the leave-one-out cross-validation demonstrating greater accuracy for SED (73 – 98%) and VPA (66 – 99%), than MPA (66 – 87%). A significant difference in raw acceleration data was observed between placements within a device brand, with waist and non-dominant wrist showing lower outputs particularly during VPA. A three-way interaction between accelerometer brand, placement and activity was found for ENMO, independent of health status ($p < 0.0001$). Waist-worn ActiGraph GT9X yielded lower outputs, whereas the dominant wrist-worn GENEActiv produced higher outputs during free-games, stairs and playing on a handheld device.

Conclusion: Whilst this study found significant inconsistencies between placements and accelerometer brands, the non-dominant wrist placement is recommended to ensure standardisation across studies. It is pertinent to note the substantial differences observed between the cut-points developed for those with CF and healthy populations, raising questions regarding the accuracy of previous studies comparing PA levels between those with CF and their healthy counterparts using generic cut-points. Therefore, the current cut-points have the potential to greatly influence our understanding of PA levels in children and adolescents with CF and their association with physical and mental health and wellbeing.

5.1 Introduction

Physical activity (PA) reduces exacerbations, improves life expectancy and enhances quality of life in those with Cystic Fibrosis (CF; Hebestreit et al., 2014; Savi, Di Paolo, et al., 2015). Structured PA is associated with enhanced aerobic capacity, bone mineral density, and a reduced decline in lung function in children and adolescents with CF (Hebestreit et al., 2006; Schneiderman et al., 2013; Tejero et al., 2016). PA is also associated with improved regulation of chloride secretion and reduced sodium conductance, which leads to lower sputum viscosity (Hebestreit et al., 2001; Wheatley et al., 2015).

Accelerometry is used as a device-based measure of PA levels in children, providing accurate estimates of PA (Brage et al., 2019; De Vries et al., 2009; Lynch et al., 2019; Trost et al., 2005) with a higher validity and reliability compared to self-report approaches (Hidding et al., 2018; LeBlanc & Janssen, 2010; Trost et al., 2005). Accelerometers measure velocity over time, which can subsequently be translated into PA intensities by using prediction equations, cut-points, and, more recently, machine learning models (Arvidsson, Fridolfsson, & Börjesson, 2019). However, the inappropriate selection of cut-points or prediction equations, such as the application of cut-points developed for healthy populations to those with chronic conditions, such as CF, may lead to inaccurate PA estimations (Gába et al., 2016; Mackintosh et al., 2018). Indeed, previous research using moderate-to-vigorous physical activity (MVPA) cut-points developed for healthy populations were found to underestimate PA in youth with CF (Stephens et al., 2016). Such discrepancies may be related to the pathophysiology of the disease itself, with children and adolescents with CF shown to have a higher resting metabolic rate (RMR) and energy expenditure (EE) for a given task compared to their healthy peers (Moudiou et al.,

2007; O'Rawe et al., 1992). Consequently, the cut-points used to assess PA in children with CF may need to be specifically tailored to account for these alterations in EE in order to provide accurate estimations of PA levels, and thus enable the appropriate delineation of the dose-response relationship.

To develop CF-specific cut-points, accelerometers need to be calibrated using a protocol comprising of a range of activities that span the intensity spectrum and are representative of daily life (Trost et al., 2005; Welk, 2005). In healthy populations, calibration studies have typically utilised either laboratory-based or free-living protocols (Welk, 2005). Whilst highly structured activities, such as walking or running on a treadmill, included in laboratory-based protocols are generally associated with superior predictive accuracy, they lack ecological validity (Farrahi et al., 2019; Freedson et al., 2005; Welk, 2005). Consequently, free-living protocols are widely recommended to generate cut-points reflecting the unique, sporadic nature of children's PA patterns (Mackintosh et al., 2012). However, despite the associated advantages, a free-living protocol precludes the measurement of a biological reference criteria, such as EE, which is pivotal when calibrating accelerometry, especially in clinical populations (Mackintosh et al., 2012). Indeed, **Chapter 4** found that while the type of protocol greatly impacts PA classification, studies calibrating accelerometry in paediatric clinical cohorts should account for the pathophysiology of the disease and integrate EE measurements, including an appropriate estimation of RMR, in the protocol.

Earlier studies developing cut-points in healthy children have utilised waist-worn accelerometers due to the proximity of this location to the body's centre of gravity (Freedson et al., 2005). Whilst the waist is known to provide accurate estimations of whole-body movement, this placement is associated with poor compliance during habitual assessments, which can lead to misclassification and bias (Fairclough et al., 2016; Rowlands et al., 2014). Consequently, research has increasingly adopted the wrist as the placement site to improve participant compliance (Rowlands et al., 2014). However, although recent evidence suggests that accelerometer measures derived from the waist and wrist are similar in healthy children (Mackintosh et al., 2016; Rowlands et al., 2014), the optimal accelerometer placement to estimate PA in children with CF remains to be elucidated. Similarly, there is no consensus regarding the ideal accelerometer brand to derive PA levels in children and adolescents with CF, though recent studies developing cut-points for healthy children have relied on brands that provide raw, unfiltered acceleration data, such as the GENEActiv and ActiGraph (GT3X+ and GT9X; Aittasalo et al., 2015; Hildebrand et al., 2014; Hurter et al., 2018).

The aims of this study were to develop healthy and disease-specific cut-points for children and adolescents with CF and to consider how these cut-points vary according to health status, and accelerometer placement (wrist and waist) and brand (GENEActiv and ActiGraph).

5.2 Methods

5.2.1 Participants

Thirty-five children with CF (15 girls) and 28 healthy controls (16 girls), aged 7 – 17 years participated in the study. Those with CF were recruited from Paediatric CF Clinics in South Wales and had been diagnosed as having CF according to a newborn screening test, and/or presenting with CF-typical symptoms and either two pathological sweat tests or the identification of two CF-relevant mutations. Those with multi-resistant bacteria (*Burkholderia Cepacia* and nontuberculous mycobacteria), an acute exacerbation at the time of the assessments, co-morbidities such as cardiovascular or musculoskeletal issues that compromise exercise performance, or who were less than two weeks post antibiotic treatment for an exacerbation or awaiting a transplant, were excluded from the study. The majority of the CF participants were homozygous (55%) for the *ΔF508* mutation and had a relatively mild disease severity, with an average forced expiratory volume in the first second (FEV_1) of 94 ± 19% predicted ($FEV_1\%_{predicted}$; range 50 - 130%). More specifically, amongst the participants in the CF group, 28 presented with mild and 7 with moderate lung disease. On average, those with CF were taking 10 ± 3 (range 5 - 16) medications, daily. Healthy participants were recruited through a University in Wales and from the friends and families of the CF participants. The health status of the healthy control group was confirmed by a short clinical anamnesis in which the participants were asked if they have any clinical conditions or diseases and whether they were taking any medication(s) for health purposes. During the clinical anamnesis, parents/guardians were consulted whenever necessary. Written informed consent was obtained from parent/guardians and assent from the participants prior to the study commencement. Ethics approval was obtained from the National Health Service (NHS) Research Ethics Committee (18/WS/0032; Appendix D2).

5.2.2 Protocol

Participants were asked to attend the laboratory on three occasions, with the first two visits separated by seven days. The first visit involved baseline measures of anthropometry, RMR and lung function. The second and third visits consisted of the daily-life activity protocol and a treadmill-based exercise test, respectively. Participants were asked to arrive at least two hours postprandial and to have avoided caffeine and vigorous exercise for 24-hours. For participants with CF, information regarding medication, any associated comorbidities, and the frequency of exacerbations was extracted from their medical records.

5.2.3 Measurements

a. Anthropometry

Body mass (Seca 876, Hamberg, Germany), stature (Holtain Stadiomerter 603VR, Holtain Ltd, UK) and sitting height (Holtain Sitting Height Stadiometer 607VR, Holtain Ltd, UK) were measured to the nearest 0.1 kg, 0.1 cm and 0.1 cm, respectively. Body mass index (BMI) and age- and sex-specific z-scores were determined according to the World Health Organisation reference data (de Onis et al., 2004). Finally, pubertal stage was estimated according to time pre or post peak height velocity (PHV; Mirwald et al., 2002), with pre-pubertal considered > -1 years from PHV, pubertal as -1 to +1 years and post-pubertal as > +1 years post PHV.

b. Resting Metabolic Rate

Following at least 10 minutes at rest, participants were instructed to lie in the supine position for 20 minutes for the assessment of RMR via indirect calorimetry using a facemask (MetaMax Cortex 3B, CORTEX Biophysik GmbH, Germany). This measure was performed in a quiet room and all participants were instructed to remain in the supine position for the duration of the test, avoiding talking and/or sleeping. Prior to this analysis, the analyser was calibrated with gases of known concentration and the volume calibrated using a three-litre syringe (5530 series, Hans Rudolph, Inc., USA). Concentration and volume signals were time-aligned to account for the delay in the capillary gas transit and analyser rise time (McNarry et

al., 2017). To calculate RMR, the first five minutes and the last two and a half minutes were removed from the analysis, with the remaining values of oxygen uptake ($\dot{V}O_2$) and carbon dioxide output ($\dot{V}CO_2$) averaged (Cooper et al., 2009; Jackson et al., 2007). Subsequently, RMR was calculated according to the Weir equation (Weir, 1949).

c. Aerobic Capacity

A standard Bruce protocol involving incremental three-minute stages to volitional exhaustion was used to assess peak oxygen uptake ($\dot{V}O_{2peak}$). Gas exchange variables were measured on a breath-by-breath basis (Metamax 3B, Cortex Biophysik GmbH, Germany). Oxygen saturation and heart rate were measured throughout using a pulse oximeter (Nonin® WristOx® Model 3150, Nonin® Medical Inc., USA) and a three-lead electrocardiogram (ECG; Custo Guard ECG, custo med GmbH, Germany), respectively. During the final 30-s of each exercise stage, the participant's rating of perceived exertion and breathlessness were assessed using the modified Borg scale of perceived exertion (0 - 10; Borg, 1982). Peak oxygen uptake was defined as the highest 10-s moving average during the exercise test.

d. Lung Function

All participants were asked to complete a standard spirometry assessment, at the start of the session, using a forced vital capacity manoeuvre to determine FEV_1 (Metamax 3B, Cortex Biophysik GmbH, Germany). The manoeuvre was performed with the participant sitting in an upright position whilst maintaining the neck in a fixed neutral position (McCormack et al., 2019). Participants were asked to repeat the manoeuvre until three consistent (< 5% variability) measures were obtained. Participants were allowed to repeat the test for a maximum of eight times (Jat, 2013). In order to be accepted, curves had to display a rapid and clear rise reaching the peak flow and a prolonged expiratory curve which gradually decreased in flow. A face mask, which provides similar validity and intra-class reliability in comparison with a cylindrical mouthpiece, was used to complete the manoeuvres as it is easier to use, particularly in children (McCormack et al., 2019; Wohlgemuth et al., 2003). For those with CF who were prescribed a salbutamol inhaler, spirometry was completed prior to and following at least 10 minutes of bronchodilator administration to determine the reversibility of airway obstruction (Sim et al. 2015). The $FEV_1\%_{predicted}$ was estimated using a reference

equation (Quanjer et al., 2012) for age, sex and body weight, and used to categorise disease severity as mild (> 70%), moderate (40 – 69%) or severe (< 40%; Davies & Alton, 2009).

e. Accelerometry

The ActiGraph GT9X Link (ActiGraph, Pensacola, FL) and GENEActiv (ActivInsights Ltd., Cambridge, UK) were used to measure raw acceleration. In total, five monitors were used, including three ActiGraph GT9X Link monitors placed on both wrists and the right waist, and two GENEActiv placed on both wrists. Specifically, the wrist monitors were placed beside one another and varied in position in a randomised order across participants. All monitors were initialised to sample at 100 Hz, with the ActiGraph filter (low frequency extension) activated, when available.

5.2.4 Daily-life Calibration Protocol

The daily-life calibration protocol consisted of activities mimicking the participant's daily lives. During their first laboratory visit, participants were given a spreadsheet of common activities from the compendium of physical activities (Ainsworth et al., 2011) and asked to select any that they would typically do at least once a day. Suggestions of additional activities were also integrated, with the six most commonly selected activities, stratified by behaviour type (i.e., sedentary), chosen to be integrated into the daily-life protocol (Table 5.1). Over a duration of 50 minutes, participants performed the six activities for three to ten minutes each, in a randomised order, interspersed by three minutes rest, whilst wearing the accelerometers, metabolic system and the pulse oximeter. All accelerometers and the metabolic system were synchronised to an external clock.

Table 5.1 Six Activities Included in the Daily-life Protocol

Activity	Description
Video	Watching a video in a seated position for ten minutes
Colouring/writing	Colouring or writing in a seated position for six minutes
Playing on a handheld device	Playing games on a handheld device on a seated position for six minutes
Free-games	Playing a variety of games, including football, tennis, badminton, rugby, skipping and mini-bowling for five minutes
Walking	Walking continuously at a self-selected comfortable pace for five minutes
Stairs	Climbing and descending stairs continuously at a self-selected comfortable pace for three minutes

5.2.5 Data Reduction

The raw acceleration data were extracted as .gt3x files and .bin files at 100 Hz using ActiLife V 6.10.2, and GENEActiv PC software V2.2, respectively. All .gt3x files were converted to time-stamp free .csv files and subsequently exported along with the .bin files into R statistical software (V3.1.2; R Foundation for Statistical Computing, Vienna, Austria) for the extraction of raw acceleration data. Specifically, the GGIR package (V 1.2 – 0; Migueles, Rowlands, et al., 2019) was used to auto-calibrate and extract the Euclidean Norm Minus One (ENMO) and Mean Amplitude Deviation (MAD) metrics (Migueles, Rowlands, et al., 2019; van Hees et al., 2014). The values resulting from the signal processing in R are expressed in gravity-based acceleration units (g = 9.81 $m \cdot s^{-2}$), which were subsequently converted to milligravitational (*mg*) units and calculated over 5-s epochs, according to previous recommendations (Matthews et al., 2012; Vähä-Ypyä et al., 2015).

Metabolic equivalent of task (MET) values for each activity were calculated by dividing the $\dot{V}O_2$ ($ml \cdot min^{-1} \cdot kg^{-1}$) for each activity by the measured resting $\dot{V}O_2$ in accord with previous recommendations (McMurray et al., 2015). Data from the first and last minute of each activity were excluded to avoid transitional movements, resulting in the inclusion of at least one (i.e. stairs) to two minutes of data for each activity in the final analysis. Subsequently, MET values were paired with the ENMO and MAD metrics for each activity. MET values were then used

to code the corresponding 5 s raw accelerometer data as sedentary (≤ 1.5 MET), moderate (4 - 6.9 METS) or vigorous (≥ 7 METS; Troiano et al., 2008).

5.2.6 Statistical Analyses

Descriptive analyses were performed with data presented as mean ± standard deviation (SD) or frequencies for continuous and categorical variables, respectively. Data was tested for normality using the Shapiro-Wilk test, and sphericity using the Mauchly's test of sphericity. A two-way ANOVA and Kruskal-Wallis test were utilised for parametric and non-parametric data, respectively, to investigate inter-group comparisons of participant demographics, accelerometer outputs and EE data. A three-factorial, repeated-measures ANOVA test was used to investigate the effect of activity type, accelerometer placement and accelerometer brand, and their interaction in two distinct steps. Initially, this analysis was applied to healthy and CF participants separately, and subsequently included health status as one of the factors. The conservative Greenhouse-Geisser-corrected values were used whenever the assumption of sphericity was violated. Finally, a Bonferroni *post hoc* was utilised to further explore and interpret the findings from the multifactorial repeated-measures ANOVA.

Cut-points for SED, MPA and VPA were generated using the receiver operating characteristics analysis (ROC) with its respective area under the curve (AUC). The ROC analyses were interpreted according to the sensitivity (the number of true positives), and specificity (the number of false positives). For the ROC-AUC, a value of 1 represents a perfect classification, whereas an area of 0.5 represents a complete absence of classification accuracy; ROC-AUC values of ≥ 0.90 were considered excellent, 0.80 – 0.90 good, 0.70 – 0.80 fair, and < 0.70 poor. Separate cut-points were generated for SED, MPA and VPA for the healthy and CF groups. The code generated from the MET (view section 5.5) values, for each intensity, was used as the dependent variable for the ROC curve, with the cut-points generated selected to optimise both sensitivity and specificity. An iterative leave-one-out approach was used to cross-validate the cut-points. Specifically, cut-points were generated on a loop using data from n-1 participants (until data from all participants were used) and the mean squared error (MSE) was determined by subtracting the cut-points and the final result was produced by averaging all the MSE values (Unal, 2017). Bland-Altman plots were used to assess the mean bias and limits of agreement between monitors for each placement in both groups (Bland & Altman,

1986). Significance was accepted at $p \leq 0.05$. The descriptive statistics and inter-group comparisons were performed using SPSS Statistics, version 23.0 (IBM Corp., USA), whereas the ROC analyses and the leave-one-out cross-validation were performed using MedCalc, version 19.2.1 (MedCalc Software, Ostend, Belgium) and R, respectively.

5.3 Results

From the initial 64 participants that were screened, one participant was unable to attend the second visit and was therefore excluded from further analysis. Therefore, in total, the study included 63 children, 35 with CF and 28 healthy controls (Table 5.2). The two-way ANOVA revealed that those with CF had significantly lower body mass ($p = 0.02$) and lower zBMI ($p = 0.006$) than the healthy participants. No significant differences were encountered between the CF and healthy groups in terms of age, stature, RMR, lung function or $\dot{V}O_{2peak}$. The majority of the participants (38 participants; 23 CF) were classified as pre-pubertal, with 10 (8 CF) pubertal and 15 (4 CF) post-pubertal.

Table 5.2 Participant Characteristics

	Cystic Fibrosis			Healthy		
	Total (n = 35)	**Girls (n = 15)**	**Boys (n = 20)**	**Total (n = 28)**	**Girls (n = 16)**	**Boys (n = 12)**
Age (years)	11.6 ± 2.8	11.3 ± 2.7	11.8 ± 2.9	12.2 ± 2.7	12.6 ± 2.6	11.5 ± 2.8
Height (cm)	1.46 ± 0.15	1.44 ± 0.12	1.47 ± 0.17	1.53 ± 0.16	1.54 ± 0.10	1.50 ± 0.21$^{\times}$
Body mass (kg)	39.13 ± 12.0^{+}	37.3 ± 10.2	40.4 ± 14.2	47.1 ± 15.0	50.1 ± 12.7	43.0 ± 12.2
BMI ($kg \cdot m^{-2}$)	18.0 ± 4.2	17.5 ± 18.2	18.4 ± 5.3	19.6 ± 3.5	20.6 ± 3.3	18.2 ± 3.5
zBMI	-0.31 ± 1.10^{+}	-0.12 ± 0.78	-0.47 ± 1.28	0.41 ± 0.80	0.57 ± 0.62	0.19 ± 1.00
RMR ($ml \cdot kg^{-1} \cdot min^{-1}$)	6.21 ± 1.31	5.86 ± 1.26	6.45 ± 1.24	5.35 ± 1.54	4.51 ± 0.89	6.47 ± 1.51
$\dot{V}O_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	41.23 ± 11.61	37.22 ± 10.81	44.76 ± 10.47	41.62 ± 12.33	36.42 ± 9.24	47.68 ± 13.56
FEV_1 (L)	2.0 ± 0.7	1.9 ± 0.4	2.2 ± 0.9*	2.4 ± 0.8	2.4 ± 0.8	2.4 ± 0.9
$FEV_1\%_{predicted}$ (%)	94 ± 19	92 ± 20	94 ± 19	99 ± 21	99 ± 22	100 ± 14
FEV_1 (z-score)	-0.21 ± 1.44	-0.07 ± 1.46	-0.21 ± 1.44	0.14 ± 1.88	0.14 ± 1.93	0.03 ± 1.26

Data are presented as mean ± SD

CF: Cystic Fibrosis, RMR: resting metabolic rate, $\dot{V}O_{2peak}$: peak oxygen uptake, FEV_1: forced expiratory volume in one second, $FEV_1\%_{predicted}$: forced expiratory volume in one second, BMI: body mass index, zBMI: z-scores body mass index. $^{+}$indicates significant difference between healthy and CF participant; $^{\times}$ indicates significant difference between boys and girls in the healthy group; *indicates significant difference between boys and girls in the CF group ($p \leq 0.05$).

Participants with CF had a higher EE than the healthy group whilst watching television, with the healthy group expending more energy during the free-games, although both failed to reach significance ($p = 0.052$ and 0.055, respectively). Furthermore, during walking at a comfortable pace, the CF group had significantly higher accelerometer outputs in comparison to the healthy group for both ENMO ($p = 0.04$) and MAD ($p = 0.05$), but no difference in EE (Table 5.3). Tables 5.4 and 5.5 present the cut-points derived from ENMO and MAD, respectively. The cross-validation data for each cut-point are presented in Appendix G2.

Table 5.3 Mean Energy Expenditure (METs) and ENMO and MAD (*mg*) During each Activity within the Daily-life protocol

	METs		**ENMO**		**MAD**	
	CF	**Healthy**	**CF**	**Healthy**	**CF**	**Healthy**
Video	1.20 (0.66 - 2.03)	1.03 (0.51 - 2.06)	9 (3 - 150)	10 (2 - 60)	10 (2 - 190)	10 (1 - 80)
Colouring	1.32 (0.85 - 2.86)	1.27 (0.58 - 2.47)	10 (0.08 - 50)	10 (1 - 50)	20 (3 - 81)	20 (7 - 80)
Handheld Device	1.13 (0.72 - 2.47)	1.00 (0.44 - 2.13)	5 (0. 02 - 34)	7 (0. 08 - 34)	10 (4 - 50)	10 (6 - 50)
Free-games	3.86 (1.46 - 10.27)	3.81 (1.46 - 10.13)	150 (30 - 740)	140 (1 - 360)	220 (60 - 700)	200 (10 - 400)
Walking	2.35 (1.80 - 4.32)	2.34 (1.13 - 9.43)	110* (30 - 330)	80 (10 - 530)	170* (50 - 380)	140 (40 - 306)
Stairs	4.49 (3.11 - 9.93)	4.97 (3.71 - 7.41)	180 (50 - 630)	180 (50 - 600)	250 (60 - 590)	270 (90 - 590)

Data are presented as median (range)

CF: Cystic Fibrosis, MET: metabolic equivalent. *indicates significant difference between groups ($p \leq 0.05$).

Table 5.4 Cut-points Derived from ENMO Accelerometer Raw data in *mg*

Placement	Intensity	CF				Healthy			
		ENMO cut-point	**AUC (95%CI)**	**Sensitivity (%)**	**Specificity (%)**	**ENMO cut-point**	**AUC (95%CI)**	**Sensitivity (%)**	**Specificity (%)**
					ActiGraph				
Dominant wrist	SED	55.5	85.8 (84.6 – 86.9)	93.6	69.9	51.4	81.3 (79.9 – 82.7)	91.4	60.9
	MPA	63.0	83.2 (86.6 – 89.1)	87.8	68.7	63.5	87.9 (86.6 – 89.1)	94.2	71.9
	VPA	177.9	90.8 (89.8 – 91.7)	83.6	86.3	103.3	87.0 (85.7 – 88.2)	99.0	72.1
Non-dominant wrist	SED	38.4	88.5 (87.4 – 89.6)	89.7	76.2	30.8	82.3 (80.8 – 83.8)	80.8	74.1
	MPA	60.2	81.4 (80.1 – 82.7)	85.4	66.6	65.9	86.2 (84.7 – 87.5)	84.2	73.5
	VPA	115.3	88.0 (86.8 – 89.0)	90.0	74.2	128.4	82.1 (80.6 – 83.6)	86.5	57.6
Waist	SED	61.3	82.3 (81.0 – 83.6)	97.5	59.7	37.3	83.3 (81.7 – 84.8)	89.4	69.6
	MPA	73.1	83.4 (82.1 – 84.7)	81.8	75.0	66.8	90.0 (88.7 – 91.1)	95.4	74.7
	VPA	133.1	92.3 (91.3 – 93.2)	89.3	84.7	83.6	87.5 (86.1 – 88.8)	93.6	70.0
					GENEActiv				
Dominant wrist	SED	44.8	87.7 (86.7 – 88.7)	94.5	72.3	38.3	87.4 (85.9 – 88.7)	92.9	73.1
	MPA	74.8	81.2 (80.0 – 82.4)	82.2	71.7	86.8	88.8 (87.5 – 90.1)	86.3	78.1

	VPA	156.8	93.9 (93.2 – 94.6)	92.0	84.7	127.8	88.4 (87.0 – 89.7)	96.6	74.4
Non-dominant wrist	SED	43.9	87.2 (86.2 – 88.2)	96.8	71.8	39.0	86.9 (85.4 – 88.3)	91.3	75.3
	MPA	64.3	88.0 (87.0 – 88.9)	96.2	72.3	84.7	91.0 (89.7 – 92.2)	89.3	78.9
	VPA	165.6	94.0 (93.2 – 94.7)	92.5	86.2	100.2	84.6 (83.1 – 86.1)	98.0	70.8

CF: Cystic Fibrosis, ENMO: Euclidean norm minus one, AUC: area under the curve, CI: confidence interval; SED: sedentary; MPA: moderate activity; VPA: vigorous activity.

Table 5.5 Cut-points Derived from MAD Accelerometer raw data in *mg*

		CF				Healthy			
Placement	**Intensity**	**MAD cut-point**	**AUC (95%CI)**	**Sensitivity (%)**	**Specificity (%)**	**MAD cut-point**	**AUC (95%CI)**	**Sensitivity (%)**	**Specificity (%)**
					ActiGraph				
Dominant wrist	SED	74.2	89.0 (88.0 – 90.1)	92.0	75.6	76.1	83.2 (81.7 – 84.5)	89.0	65.1
	MPA	82.5	83.5 (82.2 – 84.7)	92.3	63.5	113.5	87.6 (86.3 – 88.8)	93.7	72.3
	VPA	262.7	90.5 (89.5 – 91.5)	83.6	86.6	220.4	90.0 (88.8 – 91.1)	97.5	79.1
Non-dominant wrist	SED	51.2	87.3 (86.1 – 88.4)	89.4	77.0	73.4	82.9 (81.3 – 84.4)	86.3	71.9
	MPA	73.1	82.1 (80.8 – 83.4)	90.1	63.3	149	84.0 (82.5 – 85.4)	75.8	79.2
	VPA	260.8	87.2 (86.1 – 88.3)	76.5	85.4	214.2	81.2 (79.6 – 82.7)	76.1	80.4
Waist	SED	55.3	88.9 (87.7 – 89.9)	92.0	75.8	43.5	86.9 (85.5 – 88.3)	95.4	70.2
	MPA	58.9	85.8 (84.5 – 86.9)	92.9	66.7	109.2	90.3 (89.0 – 91.5)	95.9	76.2
	VPA	92.4	92.4 (91.4 – 93.3)	92.0	80.9	170	88.9 (87.6 – 90.2)	93.3	73.5
					GENEActiv				
Dominant wrist	SED	74.6	87.7 (86.7 – 88.6)	94.0	72.1	61.5	88.8 (87.4 – 90.0)	91.6	74.4
	MPA	85.3	83.8 (82.6 – 84.8)	91.7	66.8	94.5	88.6 (87.2 – 89.8)	92.3	70.7

	VPA	222.5	94.0 (93.2 – 94.6)	94.1	83.3	186.4	88.1 (86.7 – 89.4)	93.5	73.6
Non-dominant wrist	SED	70.9	86.2 (85.2 – 87.2)	96.6	71.4	73.5	86.6 (85.1 – 88.0)	92.8	74.1
	MPA	85.2	88.1 (87.1 – 89.1)	98.0	70.7	129.4	91.0 (89.8 – 92.2)	90.8	76.7
	VPA	224.5	94.1 (93.4 – 94.8)	93.6	84.4	186.9	84.8 (83.3 – 86.3)	95.4	77.6

CF: Cystic Fibrosis, AUC: area under the curve, CI: confidence interval, MAD: mean amplitude deviation, SED: sedentary; MPA: moderate activity; VPA: vigorous activity.

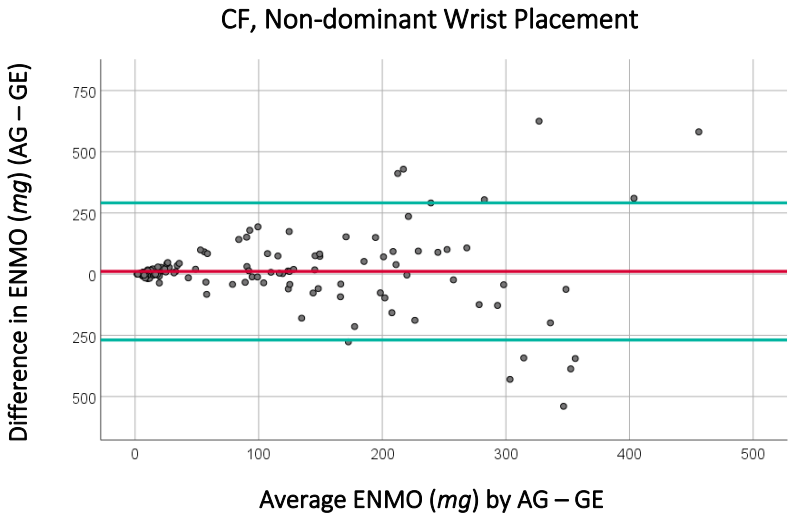
The factorial ANOVA analysis including health status as one of the factors only showed a significant effect of activity type on both ENMO and MAD ($F_{5,8}$ = 107.75, $F_{5,8}$ = 141.54, respectively, both $p < 0.0001$), with the highest outputs from free-games and stairs. The factorial ANOVA considering the groups separately, also showed a significant effect of activity type on both ENMO and MAD ($F_{2.58,82.74}$ = 64.30, $F_{3.24,103.77}$ = 161.96, respectively, both $p < 0.0001$) with similar activity results as the four-factorial model. Whilst no significant main effect was observed for placement ($F_{1,32}$ = 0.30, p = 0.58), there was a significant effect of brand for MAD metrics in both CF ($F_{1,32}$ = 6.17, $p < 0.05$) and healthy participants ($F_{1,32}$ = 6.17, $p < 0.05$), with significantly higher outputs from GENEActiv. Significant two-way interactions were observed for activity*brand ($F_{2.53,81.18}$ = 5.47, $p < 0.0001$) and brand*placement ($F_{1,32}$ = 4.35, $p < 0.05$) for ENMO. Specifically, the ENMO output from the wrist-worn GENEActiv was higher in comparison with the waist-worn ActiGraph GT9X, particularly during vigorous activities. Furthermore, there was a significant interaction between activity*placement for both ENMO and MAD ($F_{3.04,97.41}$ = 11.51, $F_{1,120}$ = 7.13, respectively, both $p < 0.05$), with significantly lower outputs for waist-worn monitors during intense activities.

A significant three-way interaction of activity*placement*accelerometer brand was observed for ENMO ($F_{2.49,79.72}$ = 15.27, $p < 0.0001$). *Post hoc* analyses showed a significant effect of brand during stairs and colouring, with GENEActiv producing higher outputs than the ActiGraph GT9X for both ENMO and MAD ($F_{1,32}$ = 14.51, $F_{1,32}$ = 5.96, respectively, both $p < 0.05$). Finally, wrist- and waist-worn monitors showed a significant effect for playing on a handheld device ($F_{5,28}$ = 31.66; $F_{5,28}$ = 98.24, $p < 0.0001$), free-games ($F_{5,28}$ = 98.24; $F_{5,28}$ = 43.30, $p < 0.0001$) and stairs ($F_{5,28}$ = 52.99; $F_{5,28}$ = 75.23, $p < 0.0001$) for ENMO and MAD, respectively. Specifically, ActiGraph GT9X yielded lower outputs when placed at the waist, whilst GENEActiv produced higher outputs when placed on the dominant wrist, particularly during these three activities.

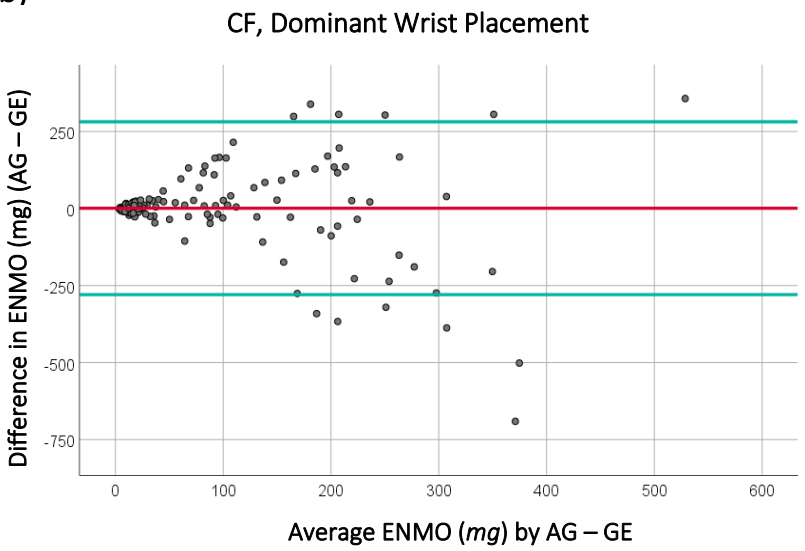
A visual inspection of the Bland-Altman plots showed heteroscedasticity for ENMO and MAD metrics, irrespective of placement, in the CF group (Figure 5.1). Similarly, heteroscedasticity was found, regardless of placement, for MAD in the healthy group, but only in the dominant wrist for ENMO. A visual analysis of dispersion of the plots indicated high agreement between the dominant wrist and waist for MAD in the CF group. In the healthy children, ENMO from the non-dominant wrist and waist displayed the best agreement. A negative correlation was found between the average ENMO values and the difference in values

for waist-worn devices (-0.24, $p = 0.003$) in the CF group. Moreover, a negative correlation was found between the average raw acceleration values and the difference in values for both ENMO and MAD from the dominant wrist in the healthy group (-0.42, -0.45, respectively, both $p < 0.0001$).

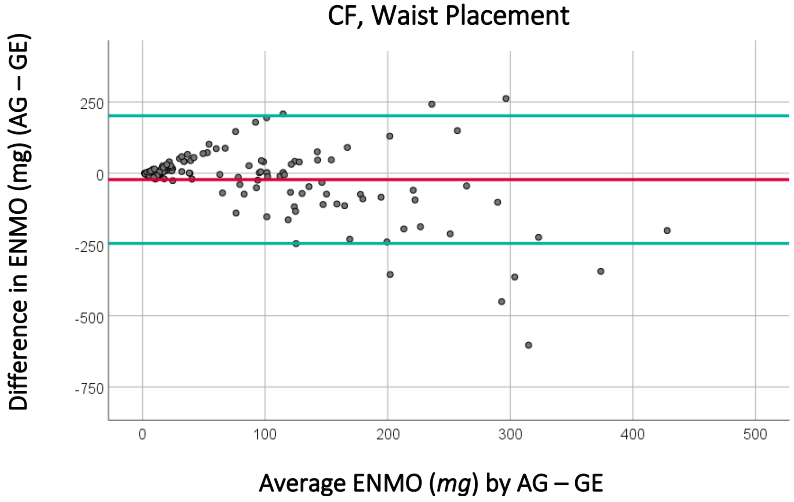
a)


CF, Non-dominant Wrist Placement
Difference in ENMO (mg) (AG – GE)
750
500
250
0
250
500
0
100
200
300
400
500
Average ENMO (mg) by AG – GE

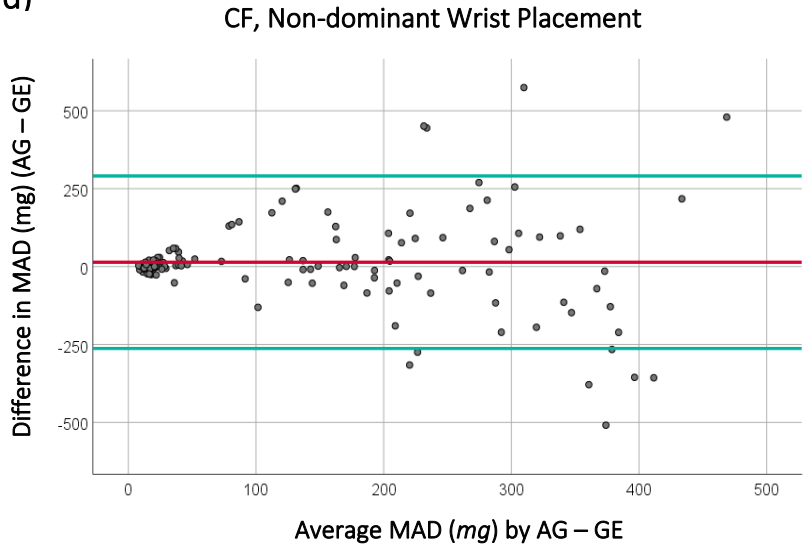
b)


CF, Dominant Wrist Placement
Difference in ENMO (mg) (AG – GE)
250
0
-250
-500
-750
0
100
200
300
400
500
600
Average ENMO (mg) by AG – GE

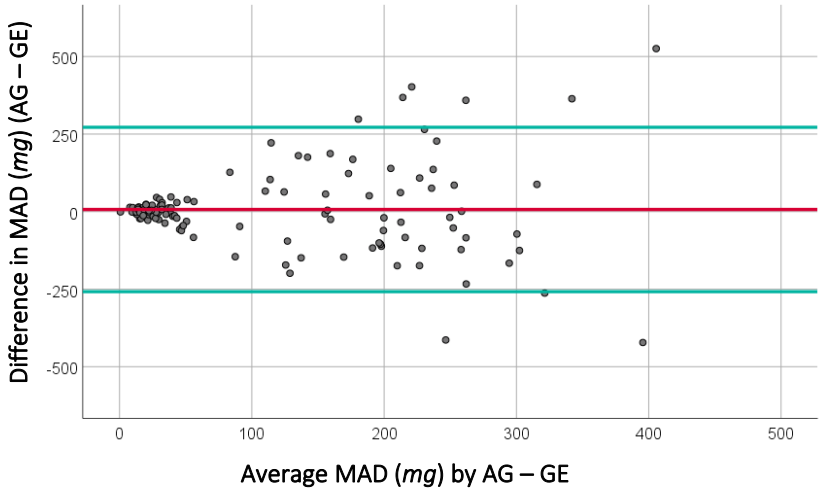
c)


CF, Waist Placement
Difference in ENMO (mg) (AG – GE)
250
0
-250
-500
-750
0
100
200
300
400
500
Average ENMO (mg) by AG – GE

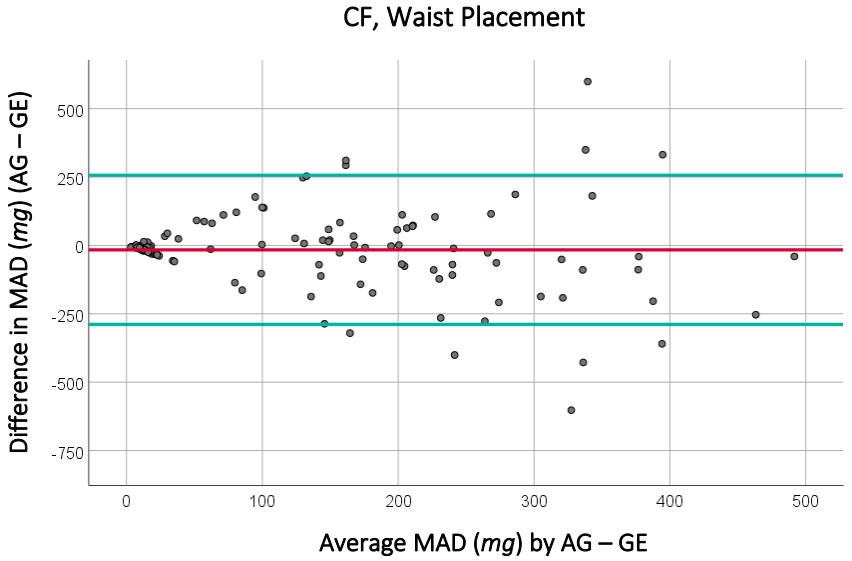
d)


CF, Non-dominant Wrist Placement
Difference in MAD (mg) (AG – GE)
500
250
0
-250
-500
0
100
200
300
400
500
Average MAD (mg) by AG – GE

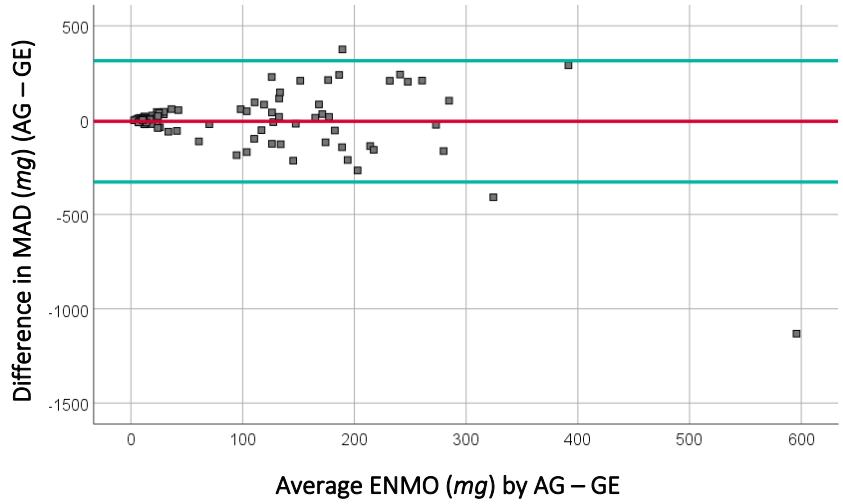
e)


CF, Dominant Wrist Placement
Difference in MAD (mg) (AG – GE)
500
250
0
-250
-500
0
100
200
300
400
500
Average MAD (mg) by AG – GE

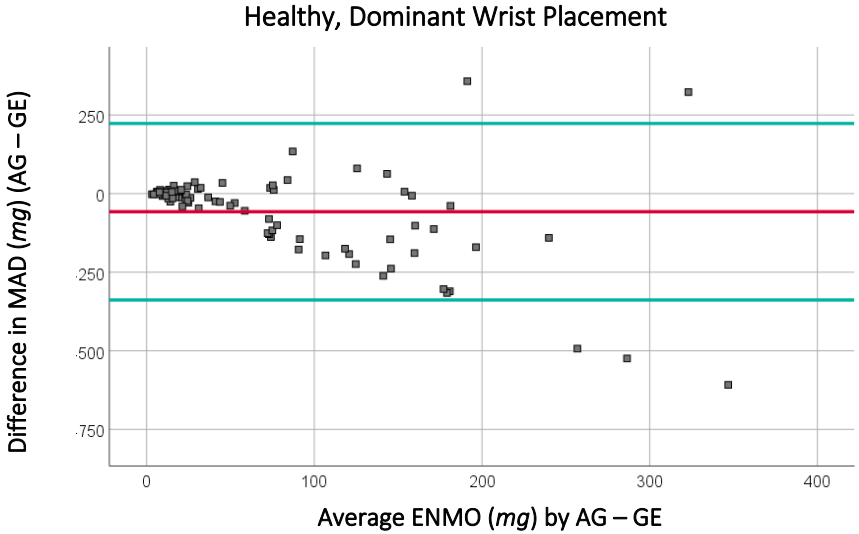
f)


CF, Waist Placement
Difference in MAD (mg) (AG – GE)
500
250
0
-250
-500
-750
0
100
200
300
400
500
Average MAD (mg) by AG – GE

g)


Healthy, Non-dominant Wrist Placement
Difference in MAD (mg) (AG – GE)
500
0
-500
-1000
-1500
0
100
200
300
400
500
600
Average ENMO (mg) by AG – GE

h)


Healthy, Dominant Wrist Placement
Difference in MAD (mg) (AG – GE)
250
0
-250
-500
-750
0
100
200
300
400
Average ENMO (mg) by AG – GE

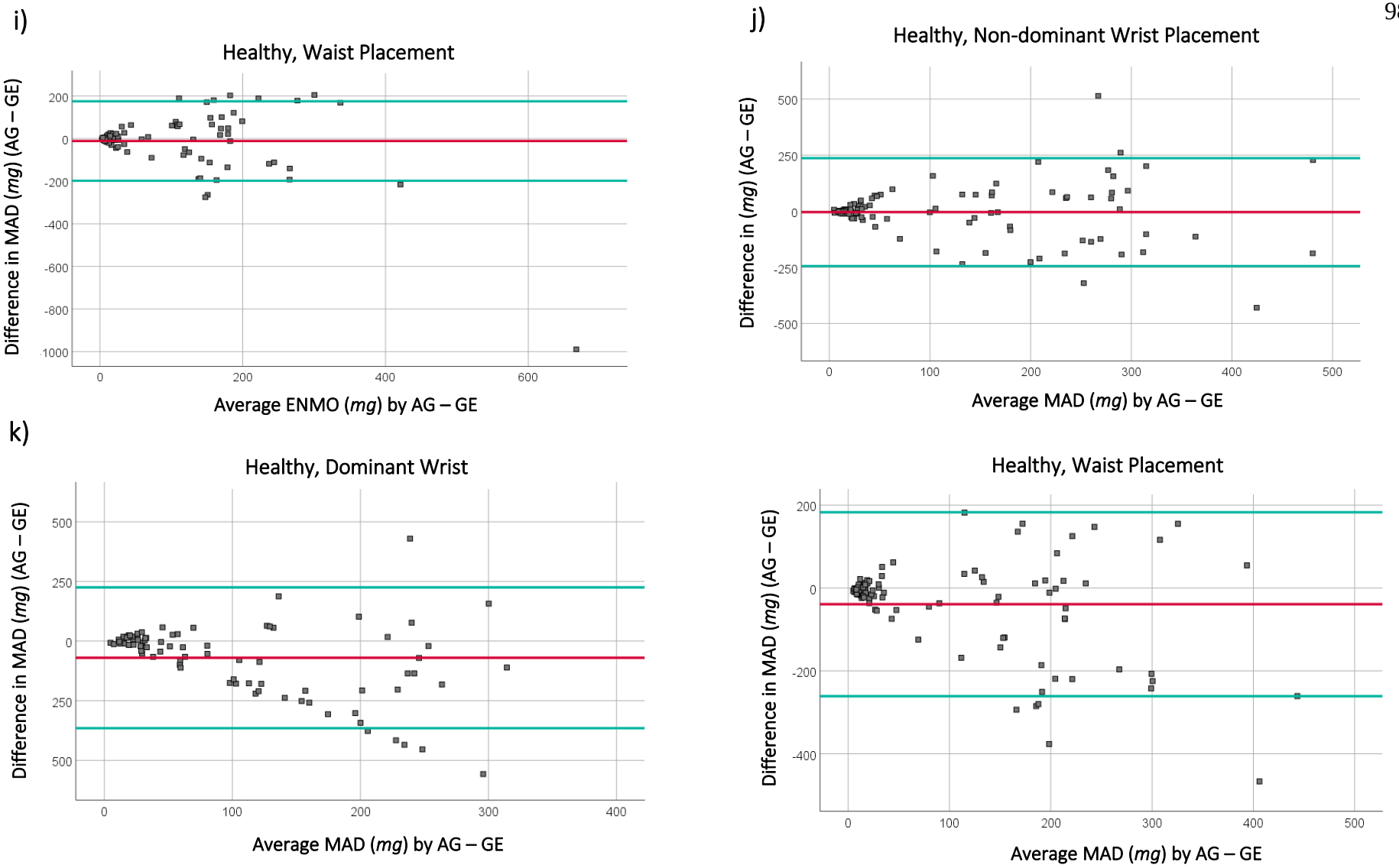


Figure 5.1 Bland-Altman Plots Assessing Agreement between Raw Accelerometer Output by Placement

Green lines represent 95% limits of agreement (±1.96 SD). CF: Cystic Fibrosis, ENMO: Euclidean norm minus one, MAD: mean amplitude deviation, AG: ActiGraph, GE: GENEActiv

5.4 Discussion

This study developed raw acceleration SED, MPA and VPA cut-points from ActiGraph GT9X and GENEActiv accelerometers placed at the waist and wrist in children and adolescents with and without CF. All cut-points demonstrated fair to excellent accuracy, sensitivity and specificity, and low error. Overall, the GENEActiv provided significantly higher outputs, in comparison with ActiGraph, irrespective of placement and condition.

Evidence shows that the use of count-based cut-points is responsible for misclassifying PA intensities approximately 33 - 68% of the time (Trost et al., 2010). Consequently, more recent calibration studies have utilised raw acceleration metrics, such as ENMO and MAD (de Almeida Mendes et al., 2018). However, the majority of studies developing cut-points from raw acceleration metrics have focused on adults, with few generating thresholds for children (Bakrania et al., 2016; Hildebrand et al., 2014; Migueles, Cadenas-Sanchez, et al., 2019). Hildebrand et al. (2014) developed ENMO cut-points for MPA and VPA from wrist-worn ActiGraph and GENEActiv monitors in healthy children using a protocol composed of eight structured activities, whilst Aittasalo et al. (2015) developed MAD MPA and VPA cut-points from waist-worn ActiGraph GT3X monitors in healthy adolescents (13 to 15 years). Importantly, whilst our study found that the MPA and VPA cut-points developed for healthy children were largely comparable to these earlier studies, the MPA and VPA CF-specific cut-points were substantially lower. Such discrepancies may be due to the ventilatory and muscular impairments associated with the pathophysiology of CF (Stephens et al., 2016). Specifically, given the enhanced cost of breathing and the pathologic exercise intolerance associated with the condition, daily-life activities are likely to be more energetically costly for those with CF in comparison with their healthy counterparts (Matel & Milla, 2009). As such, it is expected that those with CF will have higher EE at lower raw accelerations than healthy participants during given activities. Notably, participants in the CF group expended more energy during all the sedentary tasks (colouring, watching TV, and playing on a handheld device), and had significantly higher accelerometer outputs and EE during walking, in comparison to those without CF. It is also noteworthy that the healthy participants in the present study had, on average, lower aerobic capacity in comparison to normal age-specific reference data (Takken et al., 2017). As such, these differences observed during walking might be related to the altered muscle function and metabolic adaptations observed even in children and adolescents with mild

CF (Erickson et al., 2015; Johnson et al., 2006), therefore reinforcing the crucial need for condition-specific cut-points in these populations.

Whilst this study corroborates previous research indicating the need for CF-specific MVPA cut-points (Mackintosh et al., 2018; Stephens et al., 2016), our SED thresholds were generally comparable to those developed in earlier studies in healthy youth. For example, Hurter et al. (2018) developed ENMO cut-points from wrist- and waist-worn ActiGraph (GT9X and GT3X) and GENEActiv accelerometers that were similar to the CF-specific thresholds, except for the waist-worn threshold which was higher in the present study. Furthermore, the SED cut-point for wrist-worn ActiGraph GT3X+ reported by Hildebrand et al. (2017) is also similar to the healthy participants and CF-specific thresholds developed in the current study for the same brand and placement. Interestingly, the authors acknowledged that the wrist-worn ActiGraph cut-points were the only ones that did not over-estimate SED across placements and brands (Hildebrand et al., 2017). Similarly, the SED cut-points that were developed in this study for the CF and healthy children and adolescents were generally comparable, except for the waist-worn cut-points, which were lower in the healthy group. However, it is noteworthy that participants with CF demonstrated higher EE during sedentary activities, without substantially impacting on the associated cut-points. Whilst the increased EE at rest is expected given the CF airway disease, the performance of sedentary activities is not greatly affected as it is comprised of stationary activities. Thus, this explains the similarities between the newly developed CF-specific SED cut-points with those previously developed in healthy children despite the pathophysiological alterations.

A unique aspect of this study was the comparison of outputs from two different accelerometer brands, across wrist and waist placements. Overall, GENEActiv generated higher values for both ENMO and MAD across all placements and participants, in accord with previous studies (Ekblom et al., 2012; Hildebrand et al., 2014; Hurter et al., 2018; Phillips et al., 2013). Such inter-brand differences could be attributed to multiple factors including, but not limited to, a difference in the magnitude of acceleration signals, proprietary filters, signal to noise ratios, and data resolution (Hildebrand et al., 2014). It is well known that ActiGraph has an inbuilt low-pass filter of an unknown cut-off frequency, which is considered proprietary information (John et al., 2012). Moreover, research using an orbital shaker has identified a lower magnitude of acceleration from the ActiGraph in comparison with another commercially available accelerometer (John et al., 2013). Nonetheless, it is important to reiterate that both

brands performed equally well, regardless of health status, and are suitable to be used in future studies assessing PA levels in youth with CF.

Intra-brand comparisons showed that the dominant wrist-worn GENEActiv yielded higher ENMO and MAD values, particularly during free-games. This is particularly important considering that this activity was designed to replicate the free-living environment, and therefore may be more representative of the children's normal daily-life routines. Moreover, only marginal differences were observed between the outputs from both wrist-worn ActiGraph accelerometers, though the waist-worn ActiGraph generated significantly lower outcomes overall. It is, however, pertinent to note that there was no significant effect of placement, irrespective of population, across brands. In contrast, significant interactions between placement, accelerometer brand and activities were identified for both groups. Indeed, in accord with research in healthy children (Hildebrand et al., 2014), the agreement between placements across brands varied greatly by activity, with more pronounced differences shown for colouring, playing on a handheld device, free-games and stairs. Interestingly, Hildebrand et al. (2014) did not find such differences in adults, which could be indicative of the sporadic nature of children's PA. Notably, cut-point performance also varied according to placement, with ENMO cut-points developed from the waist and non-dominant wrist-worn accelerometers performing better than the ones developed from the dominant wrist, irrespective of population. Of importance, accelerometer placement impacted performance differently according to health status, with MPA cut-points from the dominant wrist performing slightly better amongst all placements in CF. In contrast, MPA cut-points from the non-dominant wrist and waist performed better in healthy participants. Indeed, research in healthy children recommended that the non-dominant wrist should be the placement of choice in order to prioritise compliance (Chandler et al., 2018; Fairclough et al., 2016; Hildebrand et al., 2014; Lisa et al., 2013). Given that, in general, both wrists performed well, and in order to allow for greater standardisation across studies, the non-dominant wrist placement is also the recommended option in youth with CF.

The cross-validation found that the cut-points developed in children and adolescents accurately classified SED, MVPA and VPA most of the time, irrespective of condition, brand and placement. In particular, cut-points derived from ENMO achieved superior accuracy for all placements and brands, in comparison with MAD, independent of health status. Nonetheless, further validation of the CF-specific cut-points is warranted to ensure validity in free-living conditions (Mackintosh et al., 2012). Another important consideration is that

research developing cut-points from raw acceleration metrics in children is still in its infancy, and, therefore, it is of paramount importance to ensure a certain degree of standardisation to allow inter-study comparisons in the future. It is noteworthy that new evidence has emerged challenging whether the estimation of EE from indirect calorimetry provides sufficient rigour to serve as the criterion measure for accelerometry calibration (Arvidsson, Fridolfsson, Buck, et al., 2019). Indeed, the limitations associated with the normalisation of EE for body mass, such as the ratio scaling of $\dot{V}O_2$, are well known and may contribute to bias in the cut-points (McMurray et al., 2015). In light of that, McMurray et al. (2015) compared different approaches to normalise the EE of children and adolescents, concluding that, whilst all metrics had limitations, the most favourable for the estimation of PA intensities was derived by dividing the $\dot{V}O_2$ of the activity by the estimated RMR converted to $\dot{V}O_2$ (Harrell et al., 2005). This approach is particularly important in clinical populations, such as CF, given the pathological alterations in RMR as a result of pulmonary impairment (Dorlöchter et al., 2002).

Overall, the disparity in the cut-points developed for youth with CF, relative to an apparently healthy population, both in the present study and in previous literature (Stephens et al., 2016), further supports the contention that cut-points developed in healthy children and adolescents are not suitable to estimate PA levels in youth with CF (Bianchim et al., 2020). Most importantly, earlier studies estimating PA levels in paediatric CF cohorts from non-specific cut-points have potentially underestimated total MVPA in these populations. Further research comparing the use of healthy and CF-specific cut-points is warranted in order to evaluate the practical implications of such discrepancy. Indeed, previous research using accelerometry in children and adolescents have reported that those with CF spent less time in MVPA and more in LPA when compared with healthy participants (Aznar et al., 2014; Nixon et al., 2001; Selvadurai et al., 2004). As such, whilst previous research found that children with CF do not engage in as much strenuous PA as their healthy peers (Jantzen et al., 2016; Mackintosh et al., 2018), the present research suggests that such findings may have been due to the cut-points applied, and subsequently a misclassification of PA. Therefore, the potential implications of utilising these CF-specific cut-points cannot be understated.

There are several strengths to this study. This was the first study to develop CF-specific cut-points, using raw acceleration data, for three different placements across two popular brands of accelerometers. More specifically, EE was used as a criterion measure to calibrate the raw accelerometer data, akin to previous recommendations for both healthy (Welk et al.,

2019) and clinical (Bianchim et al., 2019) populations. In accord with previous recommendations, EE was calculated from resting $\dot{V}O_2$ (McMurray et al., 2015). This study advances previous research, using a leave-one-out cross-validation of the cut-points, which is particularly important to ensure the applicability of the thresholds. Indeed, only one (Hildebrand et al., 2014) amongst the three (Aittasalo et al., 2015; Hildebrand et al., 2014; Hurter et al., 2018) most recent studies developing raw acceleration metrics have utilised this approach. Furthermore, individual measures of RMR were used to accurately estimate MET values for all the activities. Finally, it is pertinent to note that participants selected the activities that were involved in the daily-life protocol, leading to a more ecologically valid approach.

It is important to acknowledge the complexity of developing cut-points for a progressive chronic condition, such as CF (Ratjen et al., 2015). In addition, CF manifestations vary considerably according to the type of mutation and treatment. Most importantly, this might raise questions regarding the applicability of methods such as cut-points rather than individual assessment. Whilst individual assessment might be ideal in the clinical environment, it is not feasible in research, particularly when working with large cohorts, such as in epidemiological studies. Specifically, individual assessment in a research scenario would imply that accelerometers should be continuously re-calibrate for each individual and as the condition progresses. Alternatively, the cross-validation of the thresholds allows greater generalisability to samples other than the one from which they were derived and might help to overcome this issue. In addition, research also requires a certain degree of standardisation in order to ensure reliability and validity of the method.

Despite numerous strengths, this study is not without its limitations. Our sample consisted of children and adolescents with mild CF and might not represent those with a more severe condition. Additionally, due to the COVID-19 lockdown, it was not possible to recruit as many healthy volunteers as in the CF group. Finally, it is paramount to recognise that the statistical approach used to develop the cut-points can greatly impact the prediction accuracy (Bassett, 2012; Bassett et al., 2012; Welk et al., 2019). Specifically, whilst ROC curve analyses presents advantages in relation to linear-models (Bianchim et al., 2020), it may not be optimal for clinical populations, where adjusting for health-related confounding factors may enhance accuracy and account for inter-patient variability. Given the complexity and non-linear nature of PA, future research should consider using machine learning to further enhance the accuracy for PA classification in those with CF (Farrahi et al., 2019).

5.5 Conclusion

This is the first study to calibrate and cross-validate cut-points from raw accelerometer data for children and adolescents with CF. The newly developed CF-specific cut-points demonstrated high sensitivity and specificity, fair to excellent accuracy, and a low error. Most importantly, the majority of the CF-specific cut-points, particularly MPA and VPA, were lower than those developed for healthy controls and previously reported cut-points. This disparity might originate from PA misclassification, and explain previous evidence showing that those with CF do not engage in as much strenuous PA as their healthy peers. Therefore, the newly developed CF-specific cut-points have the potential to greatly re-evaluate research investigating PA levels and associated health outcomes in children and adolescents with CF.

5.6 Practical Implications

A calibration protocol was performed in order to develop CF-specific cut-points for the assessment of PA. Specifically, **this Chapter** found that:

- GENEActiv monitors provided higher values for both ENMO and MAD in comparison to ActiGraph GT9X monitors.
- The non-dominant wrist placement is recommended in order to maintain consistency between studies calibrating clinical and healthy populations.
- The CF-specific cut-points varied greatly from previous thresholds developed in healthy populations, except for the SED cut-point.

CHAPTER 6

Study Three: Comparing Condition-specific and Generic Cut-points to Assess Sleep, Sedentary Time and Physical Activity Levels in Children and Adolescents with Cystic Fibrosis

Abstract

Introduction: Regular physical activity (PA) is recognised as an essential part of Cystic Fibrosis (CF) care. Pivotal to identifying the dose-response relationship in those with CF is the accurate classification of time spent in PA intensities. However, previous research reporting PA levels in CF have relied on cut-points developed for healthy populations, and few studies have accounted for key factors such as sex and type of day. Therefore, the aim of this study was to compare the use of generic and condition-specific cut-points to assess PA levels in children and adolescents with CF.

Methods: Physical activity was assessed for seven consecutive days using a non-dominant wrist-worn ActiGraph GT9X in 71 children and adolescents (36 girls; 13.5 ± 2.9 years) with mild CF. Subsequently, CF-specific and generic Euclidean Norm Minus One (ENMO) cut-points were used to determine sedentary time (SED), time spent asleep, and in moderate physical activity (MPA) and vigorous physical activity (VPA). The effect of threshold selection on the relationship between PA intensities and lung function was subsequently determined.

Results: Physical activity levels differed significantly according to the cut-point used, with the CF-specific cut-points resulting in more SED ($p < 0.0001$) and MVPA ($p < 0.0001$) and less LPA ($p < 0.0001$) than the generic thresholds. Lung function and LPA were only related when using the CF-specific cut-points ($p = 0.04$). Irrespective of the thresholds used, the type of day and sex were found to significantly affect sleep and PA intensities, with male sex and weekdays generally associated with higher MVPA and lower LPA.

Conclusion: The present study demonstrated that thresholds developed for healthy populations misclassified PA levels and SED in children and adolescents with CF. This discrepancy affected the relationship between lung function and PA, which was only apparent when using the CF-specific cut-points. Promoting LPA seems a promising strategy to enhance lung function in children and adolescents with CF, though future interventions should stratify by week and weekend days, and target girls and boys separately.

6.1 Introduction

Cystic Fibrosis (CF) is the most common autosomal inherited condition in the Caucasian population, affecting 70,000 people worldwide (CF Trust, 2018). Progressive lung impairment is one of the most important features of this systemic condition, which often culminates in respiratory failure. Whilst exercise intolerance in CF is multifactorial, involving chronic inflammation, poor nutritional status and muscle weakness, the main factor is the progressive airway disease with subsequent abnormal ventilatory response to exercise (Gruet et al., 2017; Pastré et al., 2014; van de Weert-van Leeuwen et al., 2013; van de Weert-van Leeuwen et al., 2012). Limited exercise tolerance often leads to physical inactivity and the adoption of a sedentary lifestyle, which is associated with negative health implications (González et al., 2017; Owen et al., 2010; Troosters et al., 2009). In contrast, physical activity (PA), particularly moderate-to-vigorous physical activity (MVPA), is considered a key element in CF care, and is associated with multiple benefits. Specifically, regular MVPA has been shown to slow lung function decline and improve aerobic fitness, both of which are correlated with survival in CF (Hebestreit et al., 2006; Kriemler S, 2013). Moreover, evidence suggests that habitual PA is also beneficial in terms of enhancing quality of life, reducing hospital admissions and improving nutritional and bone density statuses in those with CF (Cox et al., 2016; Dwyer et al., 2011; Hebestreit et al., 2014; Neri et al., 2008; Schneiderman-Walker et al., 2000; Selvadurai et al., 2004; Tejero et al., 2016).

There is still a dearth of research assessing PA in children and adolescents with CF using accelerometers (Aznar et al., 2014; Jantzen et al., 2016; Kilbride et al., 2012; Mackintosh et al., 2018; Selvadurai et al., 2004). Indeed, in addition to contradictory findings regarding the total volume of PA in those with CF compared to their healthy peers, there is also no consensus regarding the intensity distribution, with some studies reporting that children and adolescents with CF accumulated less vigorous activities in relation to their healthy peers (Aznar et al., 2014; Nixon et al., 2001; Troosters et al., 2009), whereas Selvadurai et al. (2004) and Mackintosh et al. (2018) reported no significant difference in vigorous PA. The equivocal findings regarding PA levels in youth with CF may be related to inter-study differences in the composition of the study population and protocols. Specifically, evidence suggests that age (Shei et al., 2019; Swisher & Erickson, 2008), sex (Selvadurai et al., 2004) and type of day (i.e. weekdays and weekend days; Mackintosh et al., 2018) all affect the PA levels of children and

adolescents with CF but the majority of previous studies have not accounted for these factors (Jantzen et al., 2016; Nixon et al., 2001).

The lack of consensus regarding PA levels in those with CF may also be due to methodological limitations associated with earlier studies, such as the use of generic cut-points (Mackintosh et al., 2018). Specifically, the use of cut-points previously developed for healthy populations might be associated with the misclassification of PA intensities when applied to clinical populations, such as CF (Mackintosh et al., 2018; Stephens et al., 2016). Indeed, children with CF expend more energy for a given activity than their healthy peers due to impaired metabolic and ventilatory response (Hirsch et al., 1989; Johnson et al., 2006). Research to date is therefore likely to have misclassified PA intensities in those with CF, potentially over-estimating time spent in LPA and underestimating time spent in MVPA, which is likely to have led to erroneous conclusions regarding the relationship of PA with health. Such misclassifications of PA intensities may therefore explain the higher LPA and lower MVPA that has been reported in children with CF relative to their healthy counterparts (Aznar et al., 2014; Nixon et al., 2001). Potential misclassifications may have been further compounded by the reliance on count-based cut-points in previous studies assessing PA in children and adolescents with CF, the limitations of which are widely recognised. Specifically, Schmiedek et al. (2016) highlighted that vital information for classifying PA may be lost during the data reduction process involved in converting raw accelerometer data to counts. In accord with this, the use of cut-points developed from raw acceleration metrics, such as Euclidean Norm Minus One (ENMO), provides superior accuracy in comparison to counts (Schmiedek et al., 2016). Therefore, the use of CF-specific raw acceleration cut-points has significant potential to advance our current knowledge of the PA levels of children and adolescents with CF, and, importantly, the impact of these PA levels on associated health outcomes.

The relationship between PA levels and health in those with CF largely remains to be elucidated; whilst adherence to the Chief Medical Officer guidelines (Chief Medical Officers, 2019) is generally promoted by multidisciplinary care teams, there is little evidence regarding the applicability of these guidelines to those with CF. Although higher PA levels are generally accepted to be associated with a slower decline in lung function in children with CF (Schneiderman et al., 2013), the evidence regarding the optimal intensity remains equivocal. Specifically, Mackintosh et al. (2018) reported that ‘high’ light physical activity (LPA) was the only predictor of lung function but, in stark contrast, others reported that vigorous physical activity (VPA) was primarily associated with lung function in children with CF (Jantzen et al.,

2016; Nixon et al., 2001). The aim of this study was therefore to ascertain whether these discrepancies are attributable to the misclassification of PA and/or to a failure to account for key factors such as age, sex and type of day. The secondary aim of this study was to determine the influence of threshold selection on the relationship between PA and health in those with CF.

6.2 Methods

6.2.1 Participants

A total of 93 participants with CF (36 girls; 13.5 ± 2.9 years) participated in the study, of which 42% were homozygous for *ΔF508* mutation [*p.Phe508del (c.1521_1523delCTT)]* and 20% had Cystic Fibrosis Related Diabetes. Participants were recruited from hospitals in Australia (n = 58) and from Paediatric CF Clinics in South Wales (n = 35). Participants from Australia constituted the baseline of a randomised controlled trial intervention, more details of this sample are provided elsewhere (Cox et al., 2019). Participants aged 7 – 18 years previously diagnosed as having CF through a new-born screening test, and/or those presenting CF-typical symptoms and either two pathological sweat tests or the identification of two CF-relevant mutations, were included. Exclusion criteria were the presence of multi-resistant bacteria (*Burkholderia Cepacia* and nontuberculous mycobacteria), an acute exacerbation at the time of the assessments, having received less than two weeks of antibiotic treatment following an exacerbation, or being on the transplant list. Written informed assent and consent were obtained from all the participants and their parents/guardians, respectively. Ethics approval was obtained from the National Health Service (NHS) Research Ethics Committee (18/WS/0032; Appendix D2) and from the Human Research Ethics Committee at Alfred Health in Australia (HREC/16/Alfred/188; Project 7/17).

6.2.2 Measurements

Lung function was assessed through standard spirometry (Metamax 3B, Cortex Biophysik GmbH, Germany) using a forced vital capacity manoeuvre. Participants were

instructed to repeat the manoeuvre until three repeatable measures were achieved (< 5% variability), and the best among those three was recorded. Criteria for acceptance of the curve included: a rapid and clear rise reaching peak flow and a gradual, prolonged expiratory curve decreasing in flow. The forced expiratory volume in the first second (FEV_1) was determined (McCormack et al., 2019) and percentage of predicted values ($FEV_1\%_{predicted}$) estimated using age, sex and weight-specific equations (Quanjer et al., 2012), which were subsequently used to classify disease severity as mild (> 70%), moderate (40 – 69%), or severe (< 40%; Davies & Alton, 2009). Body mass (Seca 876, Hamberg, Germany) and stature (Holtain Stadiomerter 603VR, Holtain Ltd, UK) were measured to the nearest 0.1 kg and 0.1 cm, respectively, and body mass index (BMI) was calculated, with BMI z-scores determined using the World Health Organisation reference data (de Onis et al., 2004).

d. Acceletometry

Habitual PA was measured using the ActiGraph GT9X Link (ActiGraph, Pensacola, FL) worn on the non-dominant wrist for seven consecutive days. Participants were instructed to wear the monitors at all times, including during sleep. Accelerometer data were downloaded as 100 Hz .gt3x files using ActiLife V 6.10.2 software, and subsequently converted to time-stamp free .csv files for data processing using the GGIR package (V 1.2 – 0; van Hees et al., 2013) in R statistical software (R V3.1.2 Foundation for Statistical Computing, Vienna, Austria). The GGIR package was designed to auto-calibrate the data, detect abnormal values and non-wear time, and extract the ENMO. Specifically, the ENMO was calculated from the vector magnitude (VM) and adjusted for gravity by subtracting one. Subsequently, the ENMO values, expressed as *mg*, were further reduced to 5-s epochs over the monitoring period (Matthews et al., 2012; Vähä-Ypyä et al., 2015).

All files with a post-calibration error greater than 0.02 *g* or less than three valid days, including one weekend day, were excluded from subsequent analyses (da Silva et al., 2014). At least 16-hours of wear-time per day was required to be considered valid (van Hees et al., 2013; van Hees et al., 2011). The non-wear detection is described in detail in Van Hees et al. (2013), but briefly, the estimation was calculated according to the standard deviation and range of each axis over a 60-minute sliding window with 15-minute increments. Time accumulated in sedentary, MPA and VPA was calculated using CF-specific ENMO cut-points developed for ActiGraph GT9X Link monitors (38.4 *mg*, 60.2 *mg* and 115.3 *mg*, respectively; Bianchim

et al., 2020) and a generic cut-point (35.6 *mg*; 201.4 *mg*, 707.0 *mg*; Hildebrand et al., 2017; Hildebrand et al., 2014).

The integrated algorithm for sleep analysis developed by van Hees et al. (2015) and incorporated into GGIR was used to estimate sleep. Essentially, sleep time was estimated as any period of sustained inactivity with no change of more than five degrees in the monitor angle during a nocturnal sleep window, identified using the van Hees et al. (2018) heuristic algorithm for wrist-worn accelerometers. Briefly, the algorithm estimates the z-angle from the raw acceleration signal over a 5-s epoch, and the rolling variance over time within these epochs (van Hees et al., 2018). The sleep period time window was identified as the longest block of time (i.e. over 30 minutes from noon to noon) that included few postural changes. Any awake period in the nocturnal window lasting longer than 60 minutes was treated as a sleep episode. The data were then visually inspected to confirm that the nocturnal sleep pattern was correctly estimated (van Hees et al., 2015).

6.2.3 Statistical Analysis

Descriptive statistics (mean ± SD) and Shapiro-Wilks were utilised to confirm gaussian distribution. An ANOVA was used to assess sex differences in descriptive characteristics. A three-factorial, repeated-measures ANOVA was employed to investigate the effect of cut-point, sex and type of day (week and weekend days), and their interaction, on PA levels. The conservative Greenhouse-Geisser-corrected values were used whenever the assumption of sphericity was violated. A Bonferroni *post hoc* test was subsequently performed as necessary to identify the specific location of significant differences. A stepwise linear regression explored the association between FEV_1 and time spent in different PA intensities, adjusting for key cofounding factors (age, sex, BMI, genotype, wear-time). Finally, a chi-square test was conducted to compare the impact of the cut-points in determining whether participants met the PA guidelines. All analyses were performed using SPSS version 23.0 (IBM Corp., USA). Statistical significance was accepted when $p \leq 0.05$.

6.3 Results

In total, 71 participants (Table 6.1) were included in the final analysis after excluding those that did not meet the wear-time criteria. No significant differences were found in demographic, anthropometric or lung function characteristics for those included or excluded from the analysis. Shapiro-Wilk revealed that most of the data did not follow the normal gaussian distribution, except for the descriptive data (demographic, anthropometric and lung function). According to the ANOVA, boys were taller and had a higher absolute FEV_1 than girls ($p = 0.02$).

Table 6.1 Participants Characteristics and Lung Function by Sex

Characteristics	**Total (n = 71)**	**Girls (n = 36)**	**Boys (n = 35)**
Age (years)	13.5 ± 2.9	13.5 ± 2.9	13.5 ± 2.8
Height (cm)	154.1 ± 14.9	151.7 ± 14.0	156.5 ± 15.7*
Body mass (kg)	46.2 ± 14.6	44.9 ± 12.9	47.5 ± 16.2
BMI ($kg \cdot m^{-2}$)	19.0 ± 3.9	19.1 ± 2.9	18.9 ± 4.7
zBMI	-0.2 ± 1.0	-0.04 ± 0.8	-0.4 ± 1.14
FEV_1 (L)	2.3 ± 0.8	2.1 ± 0.7	2.5 ± 0.8*
$FEV_1\%_{predicted}$ (%)	84 ± 21	83 ± 25	86 ± 18

Data are presented as mean ± SD

FEV_1: forced expiratory volume in one second, $FEV_1\%_{predicted}$: forced expiratory volume in one second predicted, BMI: body mass index, zBMI: z-scores body mass index.

*Significant sex difference ($p \leq 0.05$).

The PA levels according to sex and cut-points are presented in Table 6.2. Children achieved 4.5 ± 0.9 valid weekdays and 1.8 ± 0.4 valid weekend days. The factorial ANOVA revealed a significant main effect for type of day ($F_{2,64} = 26.78$, $p < 0.0001$), cut-point ($F_{1,65} = 50.50$, $p < 0.0001$) and intensity ($F_{5,61} = 148.3$, $p < 0.0001$) on PA levels across all intensities. A comparison between PA intensities across thresholds demonstrated that the CF-specific cut-points (Bianchim et al. 2020) elicited significantly higher SED ($p < 0.0001$), MPA ($p < 0.0001$), VPA ($p = 0.002$) and MVPA ($p < 0.0001$) than Hildebrand et al. (2014) thresholds, independent of type of day. There was an interaction between intensity and sex ($F_{5,61} = 3.11$, $p = 0.01$), with higher SED, MPA and VPA levels in boys but lower LPA and sleep. A significant three-way interaction was also observed between cut-point, intensity and sex ($F_{5,61} = 2.60$, $p = 0.03$), indicating that this difference varied according to cut-points used. Specifically, according to the CF-specific cut-points (Bianchim et al. 2020), boys spent significantly more time asleep (p

= 0.01), and in VPA (p = 0.009) and MVPA (p = 0.007), and less in LPA than girls (p = 0.02). Similarly, Hildebrand et al. (2014) thresholds showed that boys spent significantly more time asleep (p = 0.05), but, in contrast, no differences were found across PA intensities between boys and girls. Additionally, an interaction between type of day and sex was found ($F_{2,64}$ = 4.12, p = 0.02), along with an interaction between type of day, cut-point and intensity ($F_{10,56}$ = 3.91, p < 0.0001). This interaction reflected the greater accumulation of MPA and MVPA during week than weekend days in boys when using CF-specific cut-points (Bianchim et al. 2020), whilst girls spent less time asleep and more time sedentary on week days, in comparison to weekend days according to the Hildebrand et al. (2014) thresholds. Finally, a significant interaction between type of day and cut-point ($F_{2,64}$ = 7.23, p = 0.01) indicated that each set of cut-points yielded different PA levels across week and weekend days.

Table 6.2 Physical Activity Levels Across Week Days, Weekend Days and Overall by Sex and Cut-point

	Generic			**CF-Specific**		
	Hildebrand et al. (2014)			*Bianchim et al. (2020)*		
Overall	**Overall**	**Boys**	**Girls**	**Overall**	**Boys**	**Girls**
Sleep	529.8 ± 86.9	525.8 ± 102.2	533.5 ± 69.5	501.6 ± 94.1	590.2 ± 117.05	507.4 ± 60.2
SED	384.8 ± 213.1	395.5 ± 223.8	375.0 ± 202.5	555.3 ± 150.8$^{\#}$	576.4 ± 176.5$^{\#}$	533.2 ± 129.3$^{\#}$
LPA	414.8 ± 259.2	407.0 ± 273.4	422.1 ± 245.6	206.4 ± 73.5$^{\#}$	188.1 ± 76.7$^{\#+}$	226.2 ± 65.3$^{\#}$
MPA	74.6 ± 59.6	75.8 ± 58.7	73.5 ± 60.4	126.3 ± 47.6$^{\#}$	121.4 ± 50.3$^{\#}$	131.7 ± 47.3$^{\#}$
VPA	31.6 ± 37.9	35.7 ± 43.5	27.8 ± 31.4	50.2 ± 31.6$^{\#}$	59.0 ± 36.2$^{\#+}$	41.2 ± 25.4$^{\#}$
MVPA	105.9 ± 91.5	111.5 ± 94.9	100.6 ± 88.4	176.5 ± 66.3$^{\#}$	180.4 ± 73.1$^{\#}$	172.9 ± 63.1$^{\#}$
Week days						
Sleep	521.3 ± 153.2	556.9 ± 195.7	486.3 ± 93.1^{+*}	554.8 ± 129.4	594.5 ± 157.7^{+}	514.9 ± 88.5
SED	451.6 ± 148.7	428.9 ± 136.5	474.1 ± 163.0^{+*}	543.6 ± 144.6$^{\#}$	532.5 ± 161.4$^{\#}$	554.4 ± 136.6$^{\#}$
LPA	387.7 ± 221.1	373.6 ± 240.7	400.5 ± 206.9	215.5 ± 82.9$^{\#}$	194.5 ± 87.0$^{\#+}$	236.7 ± 78.7$^{\#}$
MPA	77.5 ± 59.4	78.4 ± 57.1	77.7 ± 63.6	127.3 ± 49.6$^{\#}$	124.2 ± 50.2$^{\#*}$	130.9 ± 51.7$^{\#}$
VPA	30.1 ± 36.7	35.6 ± 41.3	25.0 ± 29.6	49.1 ± 31.6$^{\#}$	59.2 ± 36.3^{+}	38.9 ± 24.8$^{\#}$
MVPA	107.7 ± 92.3	114.0 ± 96.2	102.8 ± 91.2	176.5 ± 72.1$^{\#}$	183.5 ± 77.4^{*+}	169.8 ± 70.8$^{\#}$
Weekend days						
Sleep	579.4 ± 133.4	563.0 ± 153.7	594.1 ± 110.9	580.5 ± 157.5	590.2 ± 182.6	569.9 ± 120.7
SED	354.6 ± 197.5*	380.2 ± 208.0	329.1 ± 191.2	509.3 ± 151.4$^{\#*}$	525.0 ± 173.2$^{\#}$	492.0 ± 133.4$^{\#}$

LPA	405.5 ± 265.0[*]	399.9 ± 293.8	405.7 ± 241.2	192.3 ± 98.4[#*]	176.7 ± 105.7[#]	206.2 ± 70.8[#]
MPA	73.0 ± 60.9[*]	70.3 ± 51.1	76.9 ± 70.8	114.9 ± 51.5[#*]	97.9 ± 47.4[#+]	131.8 ± 52.7[#]
VPA	27.2 ± 35.5[*]	26.3 ± 35.4	27.4 ± 34.8	44.1 ± 32.2[#*]	45.3 ± 34.4[#]	41.9 ± 29.9[#]
MVPA	98.9 ± 91.5[*]	93.8 ± 82.1	104.4 ± 101.0	159.1 ± 72.9[#*]	143.2 ± 73.1[#]	173.8 ± 72.8[#]

Data are presented as mean ± SD

CF: Cystic Fibrosis, SED: sedentary time, LPA: light physical activity, MPA: moderate physical activity, VPA: vigorous physical activity, MVPA: moderate-to-vigorous physical activity. [*]Significant difference between week and weekend days. [#]Significant difference between cut-points ($p \leq 0.05$). [+]Significant sex difference ($p \leq 0.05$).

In total, 33 (46.5%) met the PA guidelines (WHO, 2020), when using Hildebrand et al. (2014) cut-points, whereas 64 (90%) participants met the recommendations when using CF-specific cut-points (Bianchim et al 2020). Age emerged as an important predictor of FEV_1 across regression models, independent of the cut-points utilised. When using CF-specific cut-points, only LPA was associated with FEV_1 ($r = 0.52$, $\beta = -0.25$, $p = 0.04$) after adjusting for key cofounders. In the unadjusted model, SED was associated with FEV_1 ($r = 0.41$, $\beta = 0.41$, $p = 0.03$), but this relationship was ameliorated when age, BMI, wear-time, genotype and sex were accounted for. No significant association was found between FEV_1 and PA when using Hildebrand et al. (2014) cut-points. Finally, an association between FEV_1 and sleep ($r = 0.29$, $\beta = -0.29$, $P < 0.038$) was found for both thresholds, but it was not sustained after adjusting the model.

6.4 Discussion

This study sought to compare the use of generic raw accelerometry cut-points and CF-specific cut-points on the PA levels of children and adolescents with CF. The CF-specific cut-points yielded significantly different PA levels in comparison to the generic thresholds; the condition-specific thresholds resulted in significantly more time spent in MPA, VPA, MVPA and sedentary and less time asleep and in LPA. The relationship between lung function and PA was only apparent with the condition-specific thresholds, whereby FEV_1 was dependent on LPA. The current findings also highlight that sex and type of day significantly influence PA levels in youth with CF.

The significant discrepancies observed between cut-points has important implications regarding the interpretation of previous research that utilised generic thresholds to estimate PA

levels in children and adolescents with CF. Specifically, the use of a generic cut-point appears to underestimate SED and MPA and VPA levels, whilst over-estimating LPA. These findings are in agreement with the hypothesis proposed by Mackintosh et al. (2018), suggesting that divergences in PA levels previously reported in CF resulted, at least in part, from the inappropriate use of generic cut-points and subsequent misclassification of MVPA as LPA. It is noteworthy that such misclassification may have affected previous comparisons between the relative PA levels of those with CF and healthy populations. Indeed, whilst some evidence showed that children with CF did not accumulate as much MVPA as their healthy peers (Aznar et al., 2014; Jantzen et al., 2016; Nixon et al., 2001), others found no differences (Mackintosh et al., 2018). The misclassification of MVPA also impacts research that seeks to identify whether children and adolescents are meeting the recommended PA guidelines. Indeed, the present study demonstrated that only 46.5% of children met the guidelines when using the generic thresholds, in comparison to 90% when using the CF-specific cut-points. However, the present study challenges the applicability of current PA guidelines that were developed based on healthy populations to those with CF (Department of Health and Social Care, 2019; WHO, 2015). This is a critical question that remains to be addressed, given the pivotal role of PA in CF care and it highlights the need for CF-specific recommendations regarding the optimal combination of PA intensities, frequency and duration.

The children with CF included in the present study were substantially more active in comparison with healthy UK and Australian counterparts, independent of the cut-points used (Gomes et al., 2017). Specifically, Gomes et al. (2017) showed that compliance with the PA guidelines in Australia and the UK varied from 10 and 39% in healthy children. It is noteworthy that the percentage of children and adolescents meeting the current PA guidelines is significantly impacted by the method used to process and analyse the accelerometer data (Ekelund et al., 2011). For example, Kim et al. (2017) found that 0% of children achieved the 60-minute target of MVPA when using GGIR, irrespective of age and sex. In contrast, Kim et al. (2017) also demonstrated that using other methods of analyses instead of GGIR significantly increased the percentage of children meeting the guidelines, for both boys and girls, to 43.5% to 69.0% using the Crouter method (Crouter et al., 2015) and 6.2% to 23.2% using the Chandler method (Chandler et al., 2016b). In addition, the reactivity to accelerometer measurement is associated with an overestimation of children and adolescents PA levels of approximately 5% on the first day of measurement (Dössegger et al., 2014), which may have contributed to the high level of PA observed in the present study.

Whilst the appropriate selection of cut-points is a major factor for accurately assessing PA in CF, this study also highlighted the importance of sex and type of day. Selvadurai et al. (2004) similarly found that PA levels in CF are affected by sex and maturation, with girls significantly decreasing their PA levels after the onset of puberty. In accord, the present study showed that age is a key predictor across all PA intensities, and it should be considered when assessing PA levels in CF. It is important to acknowledge, however, that chronological and biological age are not equivalent, and consequently, individuals with the same chronological age can significantly differ regarding biological maturity (Lloyd et al., 2014). Therefore, further work is warranted to estimate the impact of biological age on PA levels in youth with CF. Furthermore, in accord with the current findings, previous studies have reported differences in how children and adolescents with CF accumulate PA levels during week and weekend days (Aznar et al., 2014; Mackintosh et al., 2018). However, discordant with the present study, Mackintosh et al. (2018) reported that children spent more time being sedentary and less time in MPA and LPA on weekend days. In contrast, but in agreement with the present study, Aznar et al. (2014) found that children and adolescents with CF accumulated more SED and MVPA during week days than weekend days. This discrepancy could be attributed to cut-point misclassification or a failure to account for sex in earlier studies. More specifically, the present study showed that the amount of time accrued during week and weekend days varied according to sex and cut-points, with boys accumulating more MPA and MVPA during the week with CF-specific thresholds (Bianchim et al. 2020), and girls accumulating less sleep and more SED during the week for Hildebrand et al. (2014) cut-points. In addition to highlighting the importance of the population-specific cut-points, these findings also indicate that PA interventions should be stratified by sex and type of day, given that boys and girls had significantly different PA across week and weekend days.

This study confirmed that the use of generic thresholds significantly misclassifies PA levels in children and adolescents with CF. It is therefore postulated that previously reported associations between PA and lung function may subsequently be inaccurate. Whilst some evidence suggested, to a certain extent, a relationship between MVPA and FEV_1 in children with CF (Jantzen et al., 2016; Nixon et al., 2001), such findings were not corroborated by others (Boucher et al., 1997; Selvadurai et al., 2004). It is noteworthy that the majority of previous research has not investigated the full spectrum of PA intensities, focusing solely on the relationship between MVPA and health (Boucher et al., 1997; Britto et al., 2000; Nixon et al.,

2001). Additionally, the use of self-reported measures, as commonly utilised in studies investigating PA levels in those with CF, is also likely to affect the association with health outcomes. The limited research that has investigated the relationship between health and PA across the intensity spectrum similarly reported that LPA was significantly associated with FEV_1 in children with CF (Mackintosh et al., 2018), although it is important to acknowledge that these previous findings were based on count-based cut-points developed in healthy populations. While the present study findings endorse that LPA was the most influential behaviour in terms of lung function, there is a growing body of evidence showing that both volume and intensity of weekly PA are important for health (Saint-Maurice et al., 2018). Therefore, despite the abundant evidence associating LPA with health (Füzéki et al., 2017; Kwon et al., 2011; Poitras et al., 2016), further work investigating the optimal weekly volume, frequency and duration that is associated with such benefits in CF is warranted.

The finding that CF-specific thresholds (Bianchim et al. 2020) yielded significantly higher levels of SED in comparison with Hildebrand et al. (2014) cut-points warrants attention given the important role of this behaviour as an independent risk factor of all-cause mortality (Patterson et al., 2018). Specifically, this finding reflects the higher energetic demands for a given sedentary task that is associated with the pathophysiological alterations in CF, as described in **Chapter 5**, and it raises relevant questions regarding the definition of sedentary behaviour in this population. In particular, since the definition of sedentary behaviour is centred around an energetic cost threshold (i.e. < 1.5 MET; Tremblay et al., 2017), it could be hypothesised that this threshold should be higher in those with CF to account for the physiological limitations of this condition. Whilst it is beyond the scope of the present study to explore this contention, future research focused on SED in those with CF is warranted. Indeed, there is a concerning lack of research investigating the relationship between SED and disease severity in those with CF, with the limited evidence available demonstrating contradictory findings (Aznar et al., 2014; Mackintosh et al., 2018). Specifically, Aznar et al. (2014) reported that children with CF spent less time sedentary than their healthy peers, whereas Mackintosh et al. (2018) found no differences. Interestingly, despite the challenges associated with inter-study comparisons, the SED reported by Aznar et al. (2014) in those with CF was comparable to those elicited with Hildebrand et al. (2014) cut-points in the present study, despite the different processing choices. Specifically, whilst Aznar et al. (2014) used count-based cut-points and a 15-s epoch, the present study utilised raw accelerometer data at 5-s epochs. The present study demonstrated that SED was associated with FEV_1, although this relationship was

not sustained following adjustment for sex, BMI, genotype and wear-time. Future research should investigate the relationship between SED and lung function, stratifying their samples by sex and disease severity, whilst accounting for accelerometer wear-time. Indeed, the detrimental effects of prolonged SED to health are well documented in healthy children (Bélair et al., 2018; Carson, Hunter, et al., 2016; Tremblay et al., 2011), although some evidence suggests that not all types of SED are associated with such risks (Shakir et al., 2018). Finally, recent research using compositional analyses to investigate the interactions between SED and PA intensities and their impact on lung function (Chapter 7), found that populations with CF may benefit from interventions targeting the reduction of SED whilst increasing MVPA and LPA.

It is important to acknowledge that inter-study discrepancies in PA levels could be attributed to methodological differences, such as the use of count-based cut-points and epoch length. Specifically, the use of counts is known to hinder PA classification given that the process to transform raw acceleration to counts is associated with loss of vital information (Kühnhausen et al., 2017). For example, the use of generic raw acceleration cut-points (Hildebrand et al., 2014) yielded higher levels of LPA and MVPA in comparison with previous research using count-based thresholds in children and adolescents with CF (Aznar et al., 2014). Another key factor contributing to error and bias in PA assessment is the use of inappropriate epochs, with shorter durations being more indicative of the sporadic nature of children and adolescents PA. Future studies are therefore advised to utilise raw acceleration thresholds with a 5-s epoch, akin to previous recommendations (Matthews et al., 2012; Vähä-Ypyä et al., 2015), in order to ensure inter-study comparability.

The present study had numerous strengths. This is the first study to assess PA using raw acceleration, CF-specific, cut-points. Furthermore, given that previous research indicated that PA is likely to differ across the week, the present study investigated total PA and SED across the week, as well as on week and weekend days (Aznar et al., 2014). However, it is important to acknowledge the limitations, not least the lack of an age- and sex-matched healthy control group, which precluded inter-study comparisons. It is also pertinent to note that the children and adolescents included in this study were categorised as having mild CF and are unlikely to represent those with a more severe form of the condition. Moreover, this study adopted a cross-sectional design, and therefore, no causal inferences can be established.

6.5 Conclusions

In conclusion, the present study revealed that previous research is likely to have misclassified PA levels in children and adolescents with CF, resulting in an underestimation of the percentage of those with CF who meet the current PA guidelines. This misrepresentation of PA levels in children with CF could have affected condition-specific PA recommendations and the design of interventions for this population. Future interventions should seek to promote LPA to increase lung function through a stratified approach according to sex and type of day.

6.6 Practical Implications

This Chapter investigated the impact of using a CF-specific cut-points in comparison with generic cut-points on PA outcomes in children and adolescents with CF. Some highlights and recommendations are:

- CF-specific cut-points elicited significantly more time in MVPA and SED and significantly less time in LPA in comparison to generic thresholds.
- LPA was associated with lung function, independent of age, sex, BMI, genotype and accelerometer wear-time.
- Future PA interventions should stratify approaches by sex and type of day (i.e., week or weekend day).
- Future studies should target interventions to reduce SED and increase LPA in children with CF.

CHAPTER 7

Study Four: A Compositional Analysis of Movement Behaviours and Associated Health Outcomes in Children and Adults with Cystic Fibrosis

Abstract

Introduction: Regular physical activity (PA), sedentary time (SED) and sleep are associated with lung function and other health markers in those with Cystic Fibrosis (CF). Previous research has investigated the association between these movement behaviours and health in isolation, without accounting for their collinear and interactive nature. Therefore, this study sought to use compositional analysis to investigate the association between sleep, SED, light physical activity (LPA) and moderate-to-vigorous physical activity (MVPA) with lung function in children and adults with CF.

Methods: In total, 147 people with CF participated, with a final sample of 86 children (41 girls; 13.6 ± 2.8 years) and 43 adults (21 females CF; 13.5 ± 2.8 years; 24.6 ± 4.7 years) with CF included in the analyses. Spirometry using a forced vital capacity manoeuvre yielded a forced expiratory volume in the first second predicted ($FEV_1\%_{predicted}$) of 86 ± 21% and 63 ± 21% for children and adults, respectively. Seven-day wrist-worn accelerometry was used to assess PA, SED and sleep. Compositional linear regression models were conducted following normalisation via isometric log-ratio transformations. Subsequently, sequential binary partitioning was applied for all possible combinations of behaviours (including sleep, SED, LPA and MVPA) to investigate the impact of reallocating 10 to 30 minutes of each behaviour to $FEV_1\%_{predicted}$.

Results: Compositional analyses, adjusting for age, sex and genotype, revealed that an estimated decline in lung function was observed with the reallocation of 30 minutes from MVPA to SED and LPA (-0.01 – -2.22%) or sleep to any other behaviour (-1.03 – -3.58%). Conversely, favourable improvements in lung function were observed when increasing 30 minutes in MVPA from LPA and SED (0.12 – 2.10%) and sleep from any other behaviour (0.23 – 3.58%). Finally, reallocating 30 minutes of SED to LPA also estimated a modest improvement in lung function (0.35 – 1.29%).

Conclusion: This study further supports the importance of MVPA and sleep for lung function in people with CF, irrespective of age, sex and genotype. Additionally, increments in LPA with

time reallocated from SED was also beneficial to $FEV_1\%_{predicted}$. Finally, these findings reinforce the inclusion of sleep and PA across the intensity spectrum as promising strategies to maintain, improve or slow the rate of decline of estimated $FEV_1\%_{predicted}$.

7.1 Introduction

Cystic fibrosis (CF) is the most prevalent life-shortening inherited disorder affecting over 10,500 people in the United Kingdom (UK ; Cystic Fibrosis Trust, 2018). The condition originates from a mutation in the Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) gene, resulting in malfunctioning or absent CFTR proteins and ultimately leading to the dysfunctional regulation of electrolytes and water content at the mucosal surfaces (Cutting, 2005). Cystic Fibrosis is characterised by a systemic accumulation of viscous sticky mucus, particularly detrimental to the lungs and the digestive system (Davies et al., 2007). Respiratory dysfunction manifests in early childhood and recurrent infections lead to the development of bronchiectasis, culminating into progressive lung function impairment (Hulzebos et al., 2013). Regular physical activity (PA) is an important component of CF care and is associated with multiple benefits, such as a reduction in lung function decline and improved nutritional status and bone mineral density (Beekman et al., 2013; Hebestreit et al., 2014; Ratjen et al., 2014). Importantly, PA is associated with better quality of life and prolonged life expectancy (Hebestreit et al., 2006; Reimers et al., 2012; Wilkes et al., 2009).

Research investigating the association between PA and health outcomes in people with CF have reported equivocal findings (Collaco et al., 2014; Cox et al., 2016; Mackintosh et al., 2018; Savi, Simmonds, et al., 2015). Specifically, whilst a few studies reported that vigorous physical activity (VPA) was associated with forced expiratory volume in the first second, in both absolute (FEV_1) and predicted ($FEV_1\%_{predicted}$) terms, in children with CF (Jantzen et al., 2016; Mackintosh et al., 2018; Nixon et al., 2001) found that light physical activity (LPA), but not VPA, was shown to predict FEV_1 in this population. Similar discrepancies were also observed in adults with CF (Cox et al., 2016; Savi, Di Paolo, et al., 2015). For example, whilst a few studies (Cox et al., 2016; Savi, Simmonds, et al., 2015) found that regular moderate-to-vigorous physical activity (MVPA) was associated with lung function in adults with CF, such an association was not found by Savi, Di Paolo, et al. (2015). Furthermore, longitudinal studies have shown that higher self-reported PA levels are positively associated with a slower decline

in lung function in both children and adults with CF (Collaco et al., 2014; Schneiderman et al., 2013). Such discrepancies may be due to, at least in part, the failure to account for the compositional nature of PA. Specifically, movement behaviours, such as sleep, sedentary time (SED), LPA and MVPA, are relative portions of a complete day, and should therefore not be analysed as independent entities. Thus, health outcomes may not be attributed to one behaviour in isolation (i.e. MVPA), but as a product of the overall composition of PA and the interactions between behaviours. Indeed, this is reflected in more recent PA recommendations, which considers all movement behaviours over a 24-hour period (Kuzik et al., 2017; Waters et al., 2017; WHO, 2020).

Recent improvements in accelerometer devices and processing techniques, such as machine learning, have substantially advanced the field of PA research (Farrahi et al., 2019). However, the majority of statistical analyses of PA data still employ traditional linear approaches (i.e. linear regression), therefore failing to account for the collinearity between the PA behaviours (Cox et al., 2018; Radtke et al., 2017; Ratjen et al., 2014). PA data are inherently compositional by nature; each intensity represents a proportion of the total waking time (Carson, Hunter, et al., 2016). Thus, the amount of time allocated to one daily behaviour will directly affect the time available for all others, with any change in time in one behaviour requiring a concomitant change in other behaviour(s) (Chastin et al., 2015). Ideally, analyses of PA should not be conducted on intensities in isolation (Carson, Tremblay, et al., 2016). PA research has increasingly recognised the value of integrating all movement behaviours, including sleep, through the use of compositional analyses (Carson, Hunter, et al., 2016; Chastin et al., 2015; Dumuid et al., 2018). Compositional data analysis accounts for the collinearity of PA data by expressing the relative information as a set of log-ratios (Chastin et al., 2015), which can be transposed from the compositional sample space (*d*-simplex), and analysed with traditional models (i.e., linear regression). The use of compositional analysis has enabled researchers to explore the effects of increasing MVPA at the expense of SED to reduce mortality risk (McGregor, Palarea-Albaladejo, Dall, Del Pozo Cruz, et al., 2019), cardiometabolic biomarkers (McGregor, Palarea-Albaladejo, Dall, Stamatakis, et al., 2019) and diabetes (Swindell et al., 2020). Such findings are crucial to inform the design of interventions and clinical guidelines, providing an indication of the amount of time that needs to be displaced from each behaviour in order to elicit CF health outcomes. However, to date, no research has utilised compositional analysis to ascertain the relationship between PA and the primary CF-associated health outcome, $FEV_1\%_{predicted}$.

For people with CF, it remains unclear how the displacement of time in different movement behaviours, including sleep, SED, LPA, and MVPA, might impact health outcomes. Therefore, the aim of this study was to use compositional analysis to investigate the association between time spent in sleep, sedentary, LPA, MVPA and $FEV_1\%_{predicted}$ in children and adults with CF.

7.2 Methods

7.1.1 Participants

In total, 147 individuals (93 children, 48 girls, 13.5 ± 2.8 years; 54 adults, 27 females, 21.4 ± 3.4 years) with a confirmed diagnosis of CF aged 7 to 35 years participated in the study, with adulthood being defined as 18+ years. Amongst these, 42% were homozygous for *ΔF508* mutation [*p.Phe508del (c.1521_1523delCTT)*] and 25% had Cystic Fibrosis Related Diabetes (CFRD). Participants were recruited from Paediatric CF Clinics in South Wales (n = 35) and from those admitted to hospital for a respiratory cause in Australia (n = 112). Participants from Australia constituted the baseline of a randomised controlled trial intervention, more details of this sample are provided elsewhere (Cox et al., 2019). Individuals had to have a CF diagnosis through new-born screening, and/or be presenting CF-typical symptoms and either two pathological sweat tests or two CF-relevant mutations to be included. Those with multi-resistant bacteria (*Burkholderia Cepacia* and nontuberculous mycobacteria), co-morbidities that might compromise being physically active (i.e. cardiovascular and musculoskeletal), an acute exacerbation at the time of the assessments or were awaiting a transplant, were excluded from the study. Prior to study commencement, parents/guardians and participants signed a written informed consent and assent, respectively. Ethics approval was obtained from the National Health Service (NHS) Research Ethics Committee (18/WS/0032; Appendix D2) in the United Kingdom and from the Human Research Ethics Committee at Alfred Health in Australia (HREC/16/Alfred/188; Project 7/17; Appendix D4).

7.2.1 Measurements

Movement Behaviours: Physical Activity, Sedentary Time and Sleep

Habitual PA was assessed by two different accelerometers, ActiGraph GT9X Link (n = 105; ActiGraph, Pensacola, FL) and GENEActiv (n = 42; ActivInsights Ltd., Cambridge, UK), secured on the non-dominant wrist for seven consecutive days. Participants were instructed to wear the monitors at all times. Raw accelerometer data were extracted at 100 Hz as .gt3x and .bin files using ActiLife V 6.10.2 and GENEActiv PC software V2.2, for ActiGraph GT9X Link and GENEActiv monitors, respectively. All .gt3x files were converted to time-stamp free .csv files and then imported along with the .bin files into R statistical software (V3.1.2; R Foundation for Statistical Computing, Vienna, Austria). The GGIR package (V1.2–0; http://cran.r-project.org; Migueles, Rowlands, et al., 2019) was used to auto-calibrate the data, detect abnormal values, and detect non-wear time. Subsequently, the Euclidean Norm Minus One (ENMO) was determined from the vector magnitude by subtracting one gravitational unit from the three raw acceleration signals at each time-stamp. Only those with at least four days and three nights of valid accelerometer data, with ≥ 16-hours of wear-time in each day, were included in the final analyses (Haszard et al., 2020). The procedure utilised to detect non-wear time is described in detail elsewhere (van Hees et al., 2013). Briefly, the procedure of non-wear detection developed by van Hees et al. (2013) used a 60-minute time overlapping windows. Were classified as non-wear any periods of less than 30% of the combined duration of their bordering non-wear periods within less than six hours. Additionally, periods which formed less than 80% of their bordering non-wear periods within less than three hours were also classified as non-wear. Hildebrand et al. (2014) age- and brand-specific cut-points were used to estimate time accumulated in sedentary, LPA and MVPA in 5-s epochs (Hildebrand et al., 2014).

Sleep was assessed using a validated algorithm, which is integrated within the GGIR package (van Hees et al., 2015; van Hees et al., 2018). Briefly, the algorithm detects sleep time as any period of sustained inactivity that is defined as no change of more than five degrees in the monitor angle during a nocturnal sleep window (van Hees et al., 2015). For the present study, the nocturnal window was identified using the heuristic algorithm developed by van Hees et al. (2018) for wrist-worn accelerometers. Essentially, this algorithm calculates the z-angle over a 5-s epoch from the raw acceleration signal. Subsequently, the algorithm estimates the rolling variance over time within these epochs, and the 10^{th} percentile of this output, over the period of an individual day, is multiplied by 15 and used as an individual night threshold. This individual night threshold is used to differentiate between periods of time containing according to the frequency of postural changes. The sleep period time window is then identified

as the longest block of time (from noon to noon) including few postural changes over periods longer than 30 minutes. Additionally, any awake period (in the nocturnal window) lasting longer than 60 minutes is treated as two distinct sleep episodes. Finally, all data were visually inspected to ensure that this was in accord with the nocturnal sleep pattern for this specific sample population (van Hees et al., 2015).

Body mass (Seca 876, Hamberg, Germany) and stature (Holtain Stadiomerter 603VR, Holtain Ltd, UK) were measured to the nearest 0.1 kg and 0.1 cm, respectively, and body mass index (BMI) was calculated. Subsequently, BMI z-scores were calculated for children and adolescents according to the World Health Organisation reference data (de Onis et al., 2004). A standard spirometry (Metamax 3B, Cortex Biophysik GmbH, Germany) assessment using a forced vital capacity manoeuvre was performed to determine lung function (McCormack et al., 2019). Spirometry was assessed in accordance with American Thoracic Society and European Respiratory Society standards (Graham et al., 2019; Moore, 2012). Forced expiratory volume in one second was obtained, and $FEV_1\%_{predicted}$ was estimated using a reference equation (Quanjer et al., 2012), and subsequently utilised to indicate disease severity as mild (> 70%), moderate (40 – 69%) or severe (< 40%; Davies & Alton, 2009). Genotype and the presence of CFRD were extracted from the medical records.

7.2.2 Statistical Analysis

Descriptive statistics (mean ± standard deviation (SD)) and frequencies (%) were calculated for continuous and categorical variables, respectively, and an independent t-test was utilised for inter- and intra-group comparisons, using SPSS Statistics, version 23.0 (IBM Corp., USA). Statistical significance was accepted at $p \leq 0.05$. Compositional analysis was performed in R using the 'compositions' and 'robCompositions' packages (Chastin et al., 2015). Initially, all data sets were screened to ensure that no zero values would be included in the composition, given that the presence of zeros impairs the process of normalisation of the time-use data. No zero values were encountered in our data set. Subsequently, the compositional mean of each behaviour (sleep, SED, LPA, MVPA) was computed across an average of all valid days. Then, a variation matrix was calculated for logs of all possible pair-wise ratios between the movement behaviours, with all pairs achieving values close to zero considered as presenting high proportionality. The relative data including all movement behaviours were presented as

isometric log-ratio (*ilr*) coordinates. This is important as compositional data consists of vectors of positive components in a constrained unit-sum (Aitchison, 1982; van de Boogaart & Tolosana-Delgado, 2008). It is generally accepted that the standard simplex (*d*-simplex) is the sample space designated for compositional data, which was previously described (Pawlowsky-Glahn et al., 2015) as:

Equation 6.1

$$\left\{ (X^1, \ldots, X^D) \in \mathbb{R}^D : \sum_{j=1}^{D} X^j = 1, X^j > 0 \; for \; j = 1, \ldots, D \right\}$$

where

$$D = d + 1$$

This definition describes the *d*-simplex for a composition of D parts, which lies within a (D – 2) sample space, for which the sums of its proportions must result in one (i.e. one day; Pawlowsky-Glahn et al., 2015). As such, a crucial step in compositional analysis is the normalisation of the compositional data using methods such as *ilr* transformation. These methods allow the transposition of compositional data from the *d*-simplex into the real sample space, where it is unconstrained and traditional statistics can be performed (Aitchison, 1982; Dumuid et al., 2018; Pawlowsky-Glahn et al., 2015). A detailed description of different approaches to normalise compositional data have been described elsewhere (Pawlowsky-Glahn et al., 2015), but the most common method is the family of one-to-one log-ratio transformation, as described by Aitchison et al (1986). Whilst Aitchison's additive log-ratio co-ordinate brought advancements to compositional computations, this approach is asymmetric and non-isometric, hence, inappropriate for compositional analysis of PA data (Dumuid et al., 2018). Alternatively, the present study utilised the *ilr* transformation described by Egozcue et al. (2005), as follows for a D-part composition x, with a transformation of $z = (z_1, \ldots, z_{D-1}) = ilr(x)$:

Equation 6.2

$$z_i = \sqrt{\frac{D-i}{D-i+1}} \; ln \frac{xi}{\sqrt[D-i]{\prod_j^D = i + \; 1^{x_j}}}, for \; i = 1, \ldots, D-1$$

Egozcue et al. (2005) also introduced the use of *ilr* coordination under a construct of sequential binary partitions, which has been broadly adopted by research employing

compositional analysis to analyse PA behaviours (Dumuid et al., 2018; Stevens et al., 2020). Indeed, the use of binary partitions is particularly useful to investigate the nature of different behaviour components. Specifically, by splitting the full composition into two sub-groups comprised of a numerator and a denominator, it can then be further split to include the remaining coordinates. In order to investigate the relationship of all movement behaviours (sleep, SED, LPA and MVPA) with lung function, this study initially designed the numerator to comprise of inactivity-related components, such as sleep and SED, and the denominators of activity-related components, such as LPA and MVPA. Subsequently, a partition including sleep as the numerator and SED as the denominator was created. Finally, LPA was designated as a numerator and MVPA as the denominator, thereby composing the last partition (Carson, Tremblay, et al., 2016; Chastin et al., 2015; Dumuid et al., 2018).

Multiple linear regression, with the *ilr* coordinates as the explanatory variables, was used to explore the relationship between each behaviour and $FEV_1\%_{predicted}$ (Dumuid et al., 2018). Specifically, this study used four sets of *ilr*-coordinate systems, sleep, SED, LPA and MVPA. Initially, a model consisting of the four behaviours as *ilr* coordinates and $FEV_1\%_{predicted}$ as the continuous dependent variable was performed. A second model to predict $FEV_1\%_{predicted}$ was then performed adjusting for age, sex and genotype. As such, sex and genotype were inputted to the model as categorical variables using binary code. All covariates were selected according to clinical relevance and relevance to PA levels (Stevens et al., 2020). In order to estimate how the reallocation of each behaviour impacts $FEV_1\%_{predicted}$, the difference between each estimated outcome at the reference composition and at a new composition was estimated as described by Dumuid et al. (2017). The reference composition comprised of the averages of all behaviours linearly scaled to add to one (i.e. one day, 24-hours in terms of the behaviour data), and the reallocation of time between different behaviours from the reference constituted the new composition (i.e. LPA to MVPA; Dumuid et al., 2018). Lastly, the approach of binary partitioning, described above, was applied to estimate how the reallocation of time from each behaviour, in relation to the reference composition, affects $FEV_1\%_{predicted}$ (Dumuid et al., 2018; Pawlowsky-Glahn et al., 2015). This approach was repeated until all possible combinations of behaviours were analysed, with time reallocation ranging between increments of 10 to 30 minutes from the averages for each PA intensity (Carson, Hunter, et al., 2016; Chastin et al., 2015; Dumuid et al., 2018; Pawlowsky-Glahn et al., 2015). Specifically, increments of 10, 20 and 30 minutes from the averages were applied to each PA intensity in the non-adjusted models, whilst increments of 30 minutes were applied to each PA intensity in the adjusted models.

Finally, ternary plots displaying the relationship between all movement behaviours were created to allow the visualisation of the *d*-simplex.

7.3 Results

Following the exclusion of 18 participants who did not meet the inclusion wear-time criteria, 129 participants, including 43 adults (21 females; 24.6 ± 4.7 years) and 86 children (41 girls; 13.6 ± 2.8 years), were included in the analyses. Descriptive characteristics and lung function data are presented in Table 7.1. Seventy-one participants had mild lung disease, 53 had moderate lung disease and a minority had severe lung disease (n = 5). Independent t-tests revealed significant inter-group differences in BMI ($p = 0.007$), stature and $FEV_1\%_{predicted}$ ($p = 0.004$) with children having significantly lower MVPA ($p < 0.0001$) and longer sleep ($p = 0.04$), in comparison with adults. Intra-group comparisons identified that girls and females had lower FEV_1 than boys and males ($p = 0.01$), respectively. In addition, girls accumulated less MVPA than boys ($p = 0.02$); and females accrued less LPA ($p = 0.04$) and more SED ($p = 0.05$) than males. There were no significant differences in demographic and anthropometric characteristics and lung function for those included and excluded from the analysis ($p > 0.05$).

Table 7.1 Participants Characteristics, Physical Activity Levels and Lung Function for Children and Adults by Sex

	Children (n = 86)	**Girls (n = 41)**	**Boys (n = 45)**	**Adults (n = 43)**	**Females (n = 21)**	**Males (n = 22)**
Age (years)	13.6 ± 2.8	13.7 ± 2.7	13.5 ± 2.8	24.6 ± 4.7	23.6 ± 3.5	25.5 ± 5.5
Height (cm)	154.2 ± 14.9*	152.5 ± 13.1	155. ± 16.13	166.0 ± 28.7	153.2 ± 35.6+	178.1 ± 10.0
Body Mass (kg)	46.5 ± 14.3*	45.2 ± 12.0	47.7 ± 16. 1	61.8 ± 17.2	51.6 ± 14.3	71.5 ± 13.8
BMI ($kg \cdot m^{-2}$)	18.7 ± 3.4*	18.8 ± 2.5	18.6 ± 4.1	21.2 ± 4.4	20.0 ± 5.3	22.4 ± 2.9
zBMI	-0.2 ± 0.9	-0.1 ± 0.8	-0.3 ± 1.1	-	-	-
FEV_1 (L)	2.3 ± 0.8	2.1 ± 0.7+	2.5 ± 0. 7	2.4 ± 1.0	1.9 ± 0.7+	2.9 ± 1.0
$FEV_1\%_{predicted}$ (%)	86 ± 21*	84 ± 24	88 ± 18	63 ± 21	62 ± 1	64 ± 21
Sleep (min)	479.3 ± 70.6*	471.2 ± 63.4	487.0 ± 77.5	453. 3 ± 64.5	452.1 ± 68.0	454.5 ± 62.6
SED (min)	344.8 ± 165.7	382.1 ± 196.0	313.7 ± 123.1	341.5 ± 116.0	381.3 ± 122.9+	303 ± 97.1

LPA (min)	562.0 ± 140.5	543.7 ± 167.9	574.6 ± 105.5	529.6 ± 121.1	491.3 ± 125.7[+]	566.3 ± 106.8
MVPA (min)	53.7 ± 115.3[*]	42.8 ± 32.0[+]	64.5 ± 53.0	115.3 ± 83.6	115.1 ± 68.6	115.5 ± 97.5

Data are presented as mean ± SD

FEV_1: forced expiratory volume in one second, $FEV_1\%_{predicted}$: Forced expiratory volume in the first second predicted, BMI: body mass index. [*]Significant difference between children and adults ($p \leq 0.05$). [+]Significant difference between sex within the age groups ($p \leq 0.05$).

The standard and compositional means describing the accumulation of time spent in each behaviour, along with the variation matrix of movement, are shown in Table 7.2. The results from the variation matrix indicated SED and LPA were the most highly co-dependent pairs, whilst SED and MVPA represented the least co-dependent pair.

Table 7.2 Unadjusted (mean ± SD) and Compositional Means and Variation Matrix of Movement Behaviours in Children and Adults with Cystic Fibrosis

	Sleep	**SED**	**LPA**	**MVPA**
Unadjusted (min)	470.6 ± 69.2	343.7 ± 149.8	551.1 ± 134.2	74.4 ± 66.8
Compositional	0.34	0.23	0.38	0.03
Sleep		0.06	0.04	-0.19
SED	0.06		-0.02	-0.32
LPA	0.04	-0.02		-0.15
MVPA	-0.19	-0.32	-0.15	

SED: sedentary time, LPA: light physical activity, MVPA: moderate-to-vigorous physical activity

The linear regression models including the *ilr*-coordinates as explanatory variables to predict lung function are presented in Table 7.3. All adjusted models resulted in a multiple R^2 of 0.25, an adjusted R^2 of 0.20 and a p value of < 0.001. For non-adjusted models, the multiple R^2 was 0.09, with an adjusted R^2 of 0.06, and a p value of 0.01. In the adjusted analyses, age was significant across all models ($p < 0.001$), whereas sex was only significant in the model retaining LPA ($p < 0.01$). In addition, the adjusted models designed to retain MVPA and SED were positively associated with sleep and negatively associated with all other behaviours. In contrast, the non-adjusted analyses showed that both models retaining sleep and SED as *ilr*-coordinates were negatively related with MVPA. Interestingly, the adjusted model retaining LPA was positively associated with both MPVA and sleep, and negatively associated with SED. In contrast, the model retaining LPA did not elicit similar positive associations with MVPA in the non-adjusted analyses.

Table 7.3 Regression Coefficients, Standard Errors, and p-values for each Retained *ilr*-coordinate for $FEV_1\%_{predicted}$

		Non-adjusted			Adjusted		
Retained *ilr*-coordinate	**Clinical Covariates**	**Regression Coefficient**	**Standard Error**	**p-value**	**Regression Coefficient**	**Standard Error**	**p-value**
MVPA	Sleep	11.36	4.41	0.01*	8.53	4.31	< 0.001*
	SED	-3.78	1.75	0.03*	-3.42	1.17	0.05*
	LPA	-0.20	2.12	0.92	-1.86	2.09	0.05*
	Sex	NA	NA	NA	3.25	4.43	0.42
	Age	NA	NA	NA	23.36	5.08	< 0.001*
	Genotype	NA	NA	NA	3.07	4.42	0.46
Sleep	SED	-7.35	2.38	0.002*	-6.07	2.35	0.01*
	LPA	-4.89	3.56	0.17	-5.06	3.44	0.14
	MVPA	-8.08	2.93	0.006*	-5.05	2.92	0.08
	Sex	NA	NA	NA	3.25	4.43	0.46
	Age	NA	NA	NA	23.36	5.08	< 0.001*
	Genotype	NA	NA	NA	3.07	4.42	0.48
SED	LPA	-2.16	3.11	0.48	-2.75	3.01	0.36
	MVPA	-2.71	1.47	0.06*	-0.66	1.49	0.65
	Sleep	11.46	3.89	0.003*	8.94	3.82	0.02*
	Sex	NA	NA	NA	3.25	4.43	0.42
	Age	NA	NA	NA	23.36	5.08	< 0.001*
	Genotype	NA	NA	NA	3.07	4.42	0.46
LPA	MVPA	-1.84	1.10	0.09	0.28	1.17	0.80
	Sleep	11.40	4.59	0.01*	9.10	4.47	0.04*
	SED	-3.17	2.16	0.14	-2.03	2.13	0.34
	Sex	NA	NA	NA	-8.93	3.50	< 0.01*

Age	NA	NA	NA	23.70	3.72	< 0.001*
Genotype	NA	NA	NA	-2.67	3.29	0.41

$FEV_1\%_{predicted}$: forced expiratory volume in the first second predicted, SED: sedentary time, LPA: light physical activity, MVPA: moderate-to-vigorous physical activity. *Statistically significant ($p \leq 0.05$).

7.3.1 Sequential binary partitioning

The estimated changes in $FEV_1\%_{predicted}$ with the non-adjusted and adjusted analyses are shown in Table 7.4 and 7.5, respectively. Children and heterozygous males had significantly higher $FEV_1\%_{predicted}$ ($p < 0.05$) in comparison to the rest of the sample. For both non-adjusted and adjusted analyses, all reallocations from sleep to other behaviours (i.e. SED, LPA and MVPA) resulted in a reduction in estimated lung function, whilst time displaced from all movement behaviours to sleep increased the estimated lung function. In the non-adjusted analyses, LPA displaced to SED and MVPA resulted in a reduced $FEV_1\%_{predicted}$. In contrast, the adjusted analyses showed that LPA displaced to MVPA resulted in an increased $FEV_1\%_{predicted}$, whilst the displacement of LPA to SED resulted in reduced $FEV_1\%_{predicted.}$ In addition, whilst the non-adjusted analyses indicated that time displaced from SED to LPA, but not MVPA, increased $FEV_1\%_{predicted}$, the adjusted model showed estimated increments in $FEV_1\%_{predicted}$ with time displaced from SED to all movement behaviours, including MVPA. Finally, stratifying groups according to age, sex and genotype revealed that time reallocated from MVPA to SED and LPA reduced lung function, irrespective of age, genotype or sex.

Table 7.4 Percentage Changes Values of $FEV_1\%_{predicted}$ when Reallocating Time Amongst Different Movement Behaviours in Children and Adults with Cystic Fibrosis

	Non-adjusted Model		
Reallocation	*10 min*	*20 min*	*30 min*
Sleep to SED	-1.17	-2.32	-3.47
Sleep to LPA	-0.83	-1.55	-2.30
Sleep to MVPA	-1.22	-2.38	-3.49
SED to Sleep	1.16	2.31	3.48
SED to LPA	0.45	0.92	1.40
SED to MVPA	-0.04	0.00	0.12
LPA to Sleep	0.70	1.40	2.09
LPA to SED	-0.45	-0.85	-1.26
LPA to MVPA	-0.50	-0.92	-1.29
MVPA to Sleep	1.27	2.66	4.19
MVPA to SED	0.13	0.41	0.84
MVPA to LPA	0.56	1.26	2.11

SED: sedentary time, LPA: light physical activity, MVPA: moderate-to-vigorous physical activity, $FEV_1\%_{predicted}$: Forced expiratory volume in the first second predicted

Table 7.5 Percentage Change Values of $FEV_1\%_{predicted}$ when Reallocating 30 minutes Amongst Different Movement Behaviours, Stratified by Sex, Genotype and Age

	Children				**Adults**			
	Homozygous		**Heterozygous**		**Homozygous**		**Heterozygous**	
Reallocation	**Girls (n = 27)**	**Boys (n = 22)**	**Girls (n = 14)**	**Boys (n = 23)**	**Females (n = 9)**	**Males (n = 11)**	**Females (n = 12)**	**Males (n = 11)**
Sleep to SED	-2.44	-2.46	-3.04	-2.38	-3.58	-3.24	-3.40	-3.24
Sleep to LPA	-1.59	-1.64	1.29	-1.59	-2.39	-2.10	-2.27	-2.16
Sleep to MVPA	-1.11	-1.07	-1.66	-1.03	-1.56	-1.98	-1.48	-1.41
SED to Sleep	2.56	2.46	1.87	2.38	3.58	3.40	3.24	3.24
SED to LPA	0.98	0.94	0.35	0.91	1.37	1.29	1.13	1.23
SED to MVPA	0.73	0.59	0.12	0.57	0.85	0.97	0.81	0.77
LPA to Sleep	1.71	1.53	0.94	1.47	2.22	2.10	2.11	2.00
LPA to SED	-0.73	-0.82	-1.40	-0.79	-1.19	-1.13	-1.13	-1.08
LPA to MVPA	1.59	1.53	0.94	1.36	2.05	2.10	1.94	2.00
MVPA to Sleep	0.98	0.82	0.23	0.79	1.19	1.29	1.13	1.08
MVPA to SED	-1.47	-1.53	-2.11	-1.47	-2.22	-1.94	-2.11	-2.00
MVPA to LPA	-0.005	-0.006	-0.011	-0.006	-0.006	-0.005	-0.006	-0.006

SED: sedentary time, LPA: light physical activity, MVPA: moderate-to-vigorous physical activity, $FEV_1\%_{predicted}$: forced expiratory volume in the first second predicted

Ternary diagrams to visualise the *d*-simplex sample space for all movement behaviours have been produced for the distribution of the sample compositions showing 75%, 95% and 99% probability regions (Figure 7.1).

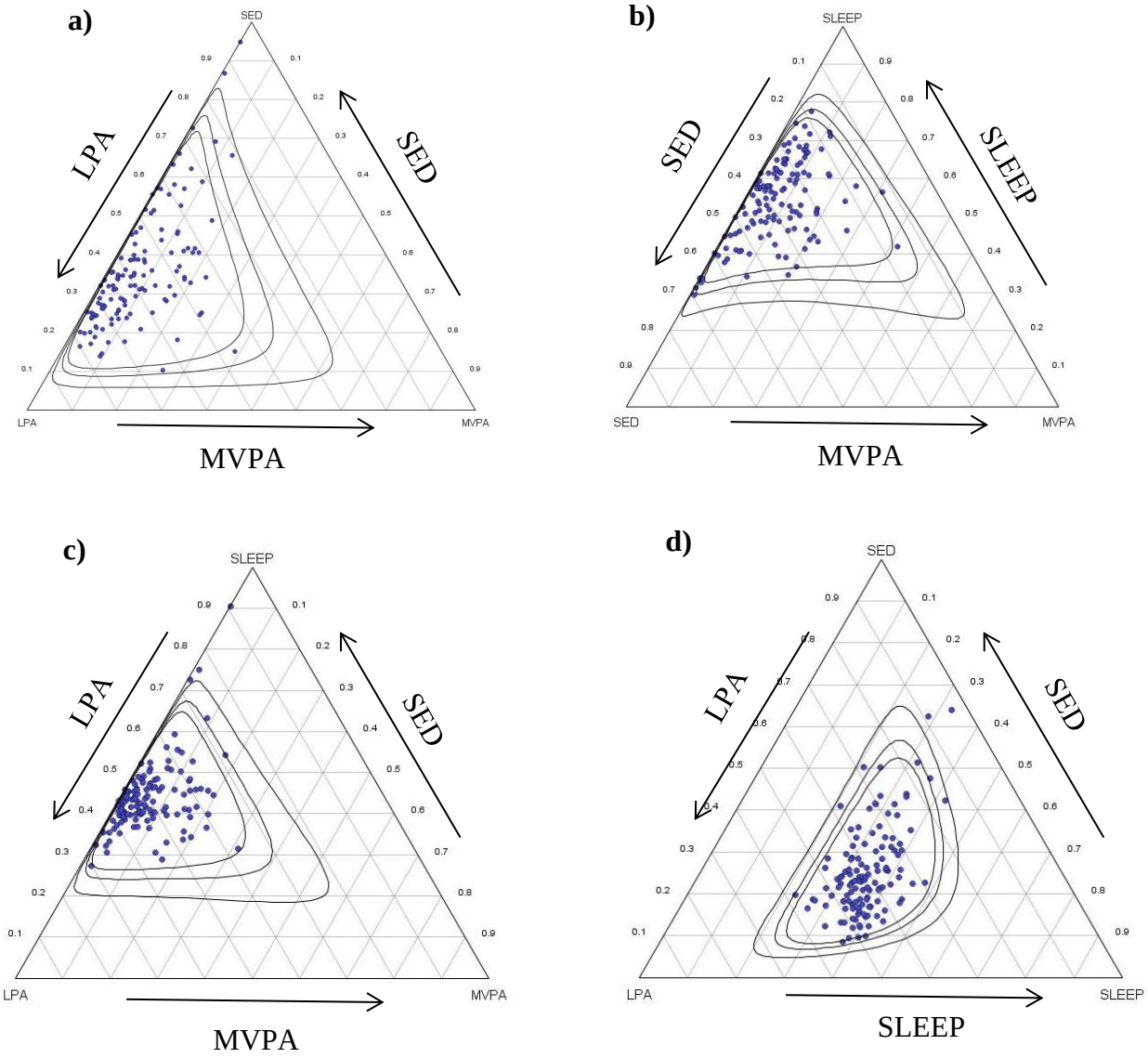


Figure 7.1 Ternary Plots Displaying the Composition of Movement Behaviours in Children and Adults with Cystic Fibrosis

Each plot displays the relationship between three behaviours. a) Sedentary time, light physical activity and moderate-to-vigorous activity. b) Sleep, sedentary time and moderate-to-vigorous physical activity. c) Sleep, light physical activity and moderate-to-vigorous physical activity. d) sedentary time, light physical activity and sleep. Probability regions structured as 75%, 95% and 99%, are represented as circles (i.e. smaller circle: 75% and larger circle: 99%) around the composition centre. SED: sedentary time, LPA: light physical activity, MVPA: moderate-to-vigorous physical activity.

Figures 7.2 and 7.3 display ternary diagrams accounting for $FEV_1\%_{predicted}$ in children and adults, respectively. Specifically, the accumulation of MVPA and sleep favoured $FEV_1\%_{predicted}$ in both children and adults. In addition, the accumulation of LPA and SED are associated with lower $FEV_1\%_{predicted}$ in children, whereas only more SED was associated with reduced lung function in adults.

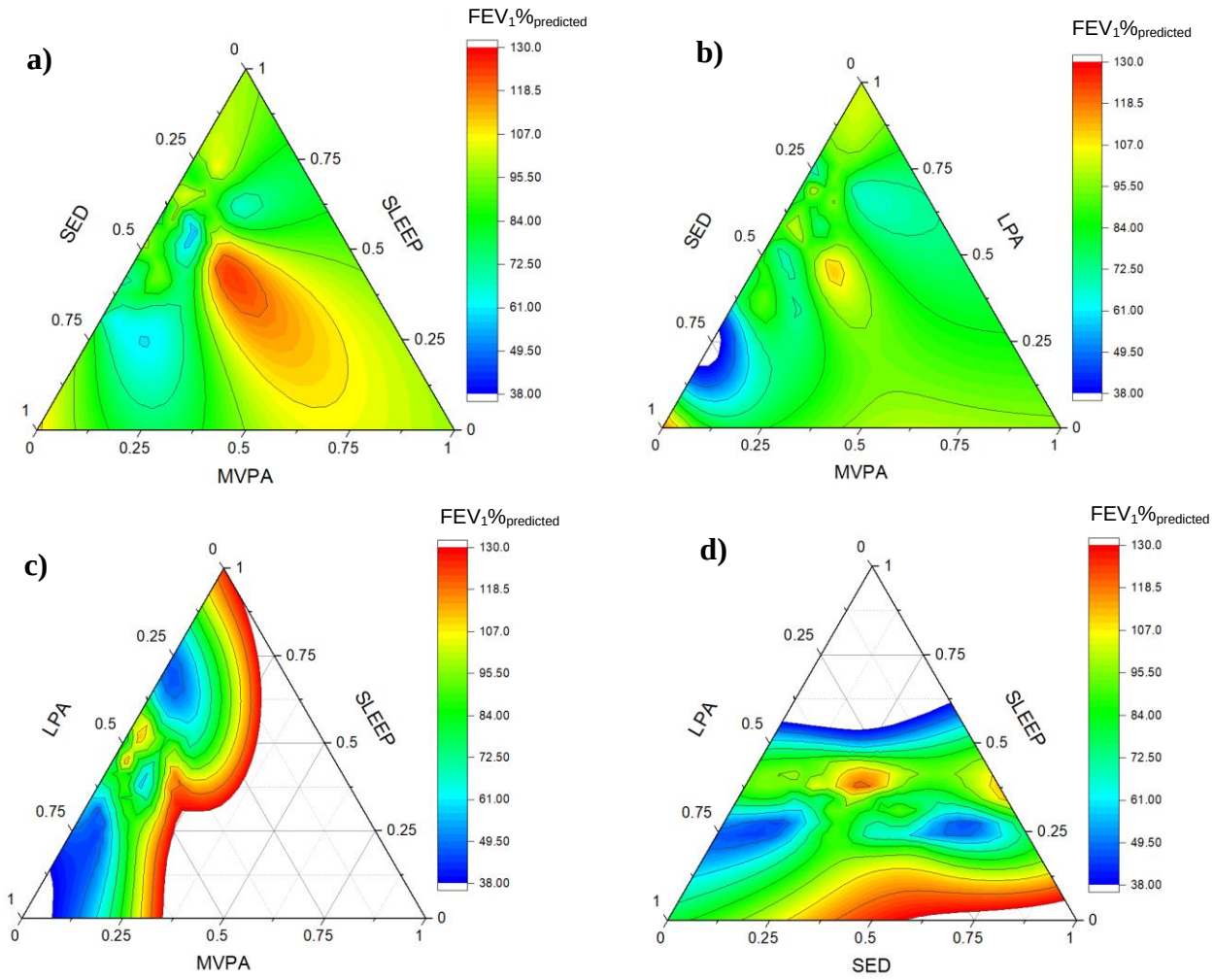


Figure 7.2 Ternary Plots displaying how the Movement Behaviours are Associated with $FEV_1\%_{predicted}$ in Children with Cystic Fibrosis

Each plot displays the relationship between three behaviours. The heat map represents the distribution of data points, with difference in colours indicating changes in $FEV_1\%_{predicted}$. a) Sedentary time, sleep and moderate-to-vigorous activity. b) sedentary time, light physical activity and moderate-to-vigorous physical activity. c) light physical activity, sleep and moderate-to-vigorous physical activity. d) light physical activity, sleep and sedentary time. SED: sedentary time, LPA: light physical activity, MVPA: moderate-to-vigorous physical activity, $FEV_1\%_{predicted}$: forced expiratory volume in the first second predicted

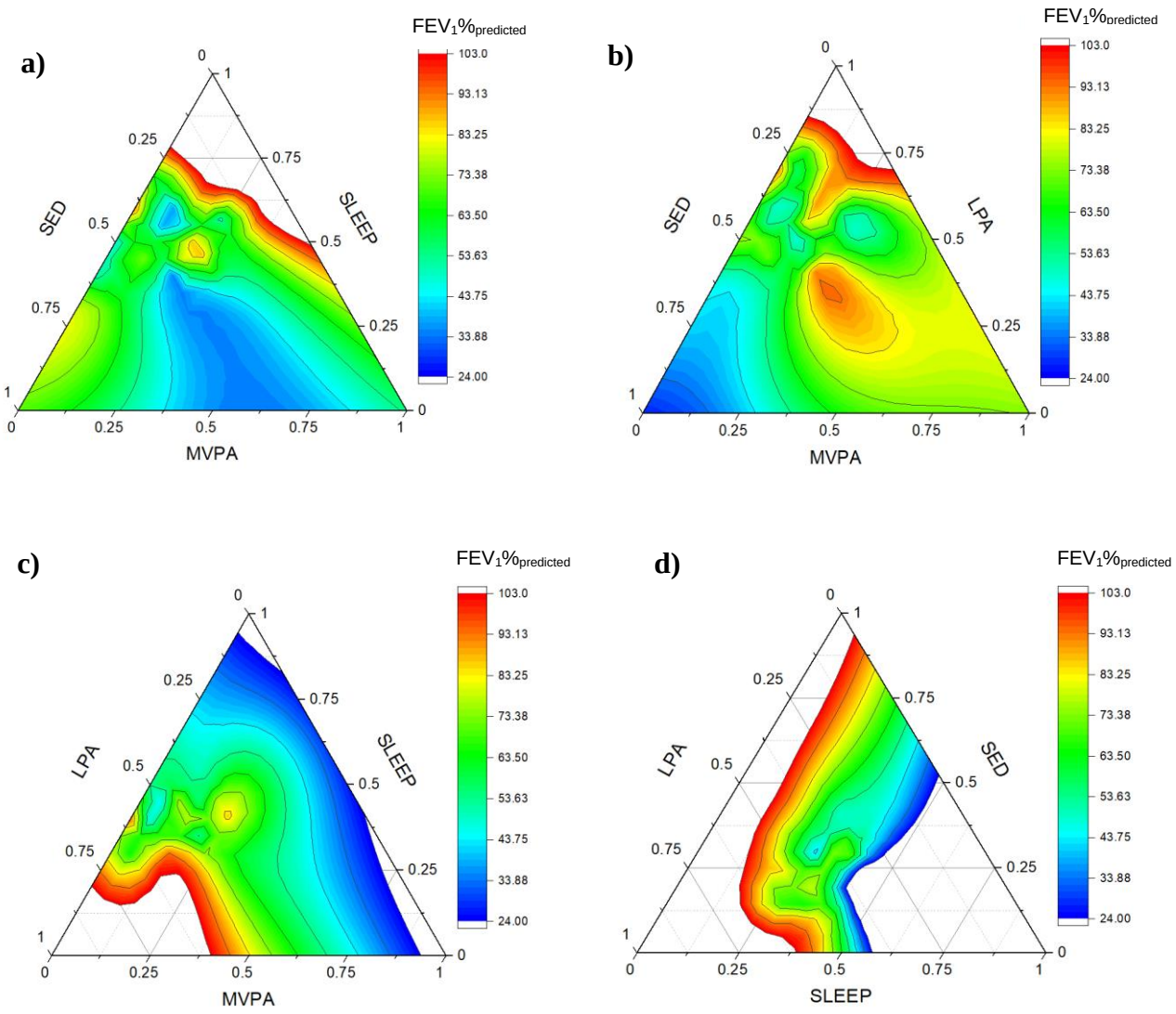


Figure 7.3 Ternary Plots displaying how the Movement Behaviours are Associated with $FEV_1\%_{predicted}$ in Adults with Cystic Fibrosis

Each plot displays the relationship between three behaviours. The heat map represents the distribution of data points, with difference in colours indicating changes in $FEV_1\%_{predicted}$. A. Sedentary time, sleep and moderate-to-vigorous activity. B. sedentary time, light physical activity and moderate-to-vigorous physical activity. C. light physical activity, sleep and moderate-to-vigorous physical activity. D. light physical activity, sleep and sedentary time. SED: sedentary time, LPA: light physical activity, MVPA: moderate-to-vigorous physical activity, $FEV_1\%_{predicted}$ forced expiratory volume in the first second predicted

7.4 Discussion

This study sought to investigate the association between time spent in sleep, sedentary, LPA, MVPA and $FEV_1\%_{predicted}$ in children and adults with CF. Overall, this study found that SED and LPA demonstrated the greatest co-dependency, which is in accordance with research in healthy populations (Carson, Hunter, et al., 2016; Štefelová et al., 2018). Specifically, this indicates that individuals who accumulated high amounts of SED also accrued a high proportion of time in LPA. Age was the only factor associated with all movement behaviours; children had high levels of LPA while older participants spent more time in MVPA. There was a significant positive association between MVPA and sleep with lung function ($FEV_1\%_{predicted}$), irrespective of age. The reallocation of 30 minutes of SED to sleep was associated with the greatest increase in percentage in lung function after adjusting for sex, age and genotype. The second greatest increase in percentage in lung function was associated with the reallocation of 30 minutes of LPA to MVPA, after adjusting for sex, age and genotype.

The present study found that the reallocation of 30 minutes from LPA and SED to MVPA, and from all movement behaviours to sleep, estimated an improvement of up to 3.66% in $FEV_1\%_{predicted}$. It is noteworthy that the clinical significance of a change in FEV_1 might vary according to disease severity, with more severe cases benefiting greatly from even small improvements. Despite this, it is also important to note that the mean error associated with the $FEV_1\%_{predicted}$ measurement is reported to range between 1.7% to 3.1% in spirometers utilised in primary care (Hegewald et al., 2016). However, it is noteworthy that, in the present study, the spirometers were carefully calibrated prior to the assessments and all the ATS/ERS (Graham et al., 2019; Moore, 2012) recommendations were strictly followed to minimise error. Nonetheless, given that $FEV_1\%_{predicted}$ declines from 1.0 to 3.1% per year in children and adults with CF (De Boeck & Zolin, 2017; Liou et al., 2010), achieving up to 3.6% increase in $FEV_1\%_{predicted}$ from the reallocation of different movement behaviours may have substantial clinical benefit. In addition, the magnitude of change in $FEV_1\%_{predicted}$ with increasing MVPA and sleep, shown in the present analysis is akin to the percentage changes reported in studies evaluating the effect of medications for maintenance of lung health in CF (Elkins et al., 2006; Mogayzel et al., 2013; Wainwright et al., 2015). For example, results from a large randomised trial including children and adults with CF, indicated that the mean absolute improvement in the percentage of $FEV_1\%_{predicted}$ ranged from 2.6 to 4.0% with the use of a Cystic Fibrosis transmembrane conductance regulator corrector (lumacaftor) in combination with a potentiator

(ivacaftor; Wainwright et al., 2015). The present study, therefore, contributes to the emerging literature suggesting that an integrated approach to PA promotion and behaviour change may be more beneficial than emphasis on isolated PA behaviours (Carson et al., 2019).

Congruent with earlier studies investigating different health markers (Carson, Hunter, et al., 2016; Carson et al., 2019; Dumuid et al., 2018), the present study demonstrated that prioritising sleep, in comparison to SED, LPA and MVPA, was associated with the best estimated outcome. More specifically, the present study found that even a 30-minute reduction in sleep was associated with detrimental effects on lung function (-1.03 – -3.58%). A recent systematic review and meta-analysis reported a direct correlation between $FEV_1\%_{predicted}$ and fragmentation of sleep in children and adults with CF, suggesting such disturbances were also associated with an increased frequency of exacerbation and a deterioration in nutritional status and quality of life (Shakkottai et al., 2018). Moreover, Shakkottai et al. (2018) found that sleep disorders and nocturnal hypoxemia are prevalent in children and adolescents with CF, and are associated with worse clinical score and higher morbidity in this population. Sleep disorders are also associated with exercise intolerance and increased SED in children with CF (Barbosa, Coelho, et al., 2020). Additionally, research utilising traditional statistical methods (non-compositional) reported that sleep fragmentation is related to reduced MVPA in adults with CF (Cox et al., 2019). Similarly, habitual PA, particularly at higher intensities, is associated with better sleep in children and adults with CF (Dietz-Terjung et al., 2020). These findings suggest that whilst sleep and PA seem to influence each other, they also mutually affect lung function, and disease progression. As such, future studies developing PA recommendations or interventions in people with CF are strongly advised to account for sleep, in line with the Canadian 24-hour movement guidelines (Tremblay et al., 2016).

Research investigating the relationship between PA and clinical outcomes in CF remains sparse and has mainly focused on individual movement behaviours (Cox et al., 2019). Nonetheless, longitudinal investigations have reported a slower decline in FEV_1 with regular PA in paediatric (Schneiderman et al., 2013) and adult cohorts (Collaco et al., 2014; Cox et al., 2018). Amongst these studies, the only one that used accelerometry to measure PA showed that accumulating 30 minutes of MVPA daily is associated with slower FEV_1 decline in adults with CF (Cox et al., 2018). However, whilst MVPA is well recognised as fundamental to health promotion and maintenance, particularly in people with CF, evidence regarding the association between lung function and PA remains controversial (Radtke et al., 2017; Shelley et al., 2019). Specifically, Cox et al. (2016) found that adults with CF that accumulated more than 30 minutes

of MVPA per day had better lung function than their peers. In accord, Savi, Simmonds, et al. (2015) found that MVPA was associated with $FEV_1\%_{predicted}$ but not with the frequency of pulmonary exacerbations in adults with CF. In contrast, in another study by Savi, Di Paolo, et al. (2015), that included a smaller sample of adults with CF, no associations between $FEV_1\%_{predicted}$ and MVPA were found. Furthermore, Mackintosh et al. (2018) found that LPA, but not MVPA, was related to FEV_1 in children with CF. These discordant findings may have emerged from the confounding effect of the collinear nature of movement behaviours. Importantly, the use of compositional analysis demonstrated that MVPA only resulted in enhanced estimates of lung function when the time was reallocated from LPA and SED, but not from sleep. Additionally, the association between MVPA and $FEV_1\%_{predicted}$ was only evident after stratifying by age, sex and genotype. These findings clearly illustrate the importance of accounting for all relative movement behaviours.

An important consideration is that lung function predictions, resulting from reallocating the composition, were asymmetrical for all movement behaviours, with the exception of sleep (except for heterozygous girls). Previous studies utilising compositional analysis have also found asymmetrical relationships between movement behaviours and other outcomes in healthy (Biddle et al., 2018; Štefelová et al., 2018; Tlučáková et al., 2020) and pre-diabetic (Swindell et al., 2020) populations. Essentially, asymmetry is observed when the alteration in a certain movement behaviour does not predict the exact same magnitude of change with the reverse reallocation. For example, reductions in MVPA in the present study were associated with a greater magnitude of deleterious change in $FEV_1\%_{predicted}$ (-0.01 – -2.22%) than to the estimated benefit following the proportional increase in MVPA. This finding has important clinical implications given that $FEV_1\%_{predicted}$ is related to survival in CF (Diggle et al., 2012). Therefore, encouraging the maintenance of daily MVPA while reducing SED is paramount, irrespective of age, sex or genotype. Finally, whilst the finding that sleep was symmetrical for most PA reallocations has not been previously reported in the literature, it is congruent with evidence suggesting that those behaviours are mutually correlated (Cox et al., 2019; Dietz-Terjung et al., 2020).

Despite previous research showing that LPA is associated with reduced inflammatory markers (Carson, Hunter, et al., 2016), there is still a lack of research investigating the clinical benefits of LPA in people with CF. Mackintosh et al. (2018) reported that FEV_1 was associated with LPA in children with CF. In agreement, the present study demonstrated that the reallocation of 30 minutes of SED to LPA resulted in improved estimations of lung function in

both children and adults with CF (0.35 – 1.37%). This finding holds important clinical implications, even if those improvements were modest in comparison to the benefits associated with increasing sleep or MVPA. Specifically, those with CF spend less time in MVPA in relation to their healthy peers (Aznar et al., 2014; Troosters et al., 2009), which has been attributed to exercise intolerance associated with the condition (Arikan et al., 2015). Therefore, large reallocations of time to LPA from SED are particularly important in moderate and severe cases of the condition, which are characterised by exercise intolerance and muscle weakness (Troosters et al., 2009). It is also noteworthy that LPA was the only behaviour affected by sex in the adjusted model, with males, irrespective of age, demonstrating higher levels of LPA and higher $FEV_1\%_{predicted}$ than females. This finding corroborates previous research, reinforcing the importance of accounting for sex when investigating PA and its relationship with lung function in CF (Schneiderman-Walker et al., 2005; Selvadurai et al., 2004).

This study demonstrated that the displacement of SED resulted in improved estimates of $FEV_1\%_{predicted}$, regardless of the behaviour being reallocated to. Specifically, the reallocation of 30 minutes of SED to sleep resulted in the greatest increase in $FEV_1\%_{predicted}$ (1.87 – 3.58%), whilst the reallocation to MVPA resulted in the lowest (0.12 – 0.97%). Surprisingly, the displacement of 30 minutes from SED to LPA resulted in marginally greater estimates of $FEV_1\%_{predicted}$ (0.35 – 1.37%) in comparison to the same amount of time reallocated to MVPA. Nonetheless, it is notable that the reduction of SED might have meaningful implications for people with CF. For example, Polito et al. (2019) reported that adults with CF who spent longer being sedentary had an increase in inflammatory markers, in comparison to those who engaged in more PA. In addition, SED is broadly recognised as a major risk factor for disease and is associated with metabolic markers in healthy children (Owen et al., 2010) and adults (González et al., 2017). This is especially relevant given that SED increases with age (Ortega et al., 2013), in parallel with the complexity of the exercise intolerance and airway disease due to the progressive nature of CF (Shei et al., 2019). Therefore, it is not surprising that age had a fundamental role as predictor of all movement behaviours in the present study, akin to previous research (de Gracia et al., 2005; Harness-Brumley et al., 2014; Schneiderman-Walker et al., 2005; Shei et al., 2019). Finally, the use of compositional analysis indicated that while increasing MVPA appears to be one of the most optimal stimuli to enhance lung function, this should not be achieved at the expense of sleep. However, in scenarios where it is not possible to increase MVPA, due to disease severity for example, large increments in LPA with time reallocated from SED may provide similar benefit to $FEV_1\%_{predicted}$.

It is noteworthy that even those with mild CF lung disease have higher metabolic demands to perform the same activities as their healthy peers (Bell et al., 2001). This is particularly challenging for studies using accelerometry reliant on cut-points to assess PA. Specifically, the use of cut-points that were developed based on healthy populations might underestimate the relative intensity of a count rate or raw metric when applied to CF (Bianchim et al. 2020). It could therefore be postulated that the high LPA levels previously reported in those with CF, and confirmed in this study, might be the result of misclassification. Furthermore, the lack of CF-specific cut-points, and consequently, misclassification of MVPA as LPA (Mackintosh et al., 2018), might help to explain some of the contradictory findings in the present study. For example, this study found that reallocations from SED to LPA, but not MVPA, and to MVPA from LPA, but not SED, resulted in marginally greater estimates of $FEV_1\%_{predicted}$ in the adjusted model. Therefore, further research is required to investigate the relative intensity for those with CF, as well as the associated implications on health, and specifically lung function.

Overall, this study was associated with numerous strengths, not least the use of compositional analysis using device-measured SED and PA, whilst accounting for factors such as age, sex and genotype. The utilisation of cut-points from raw metrics, as opposed to count-based cut-points, is important given that count-based thresholds have been associated with low accuracy and high error (Kühnhausen et al., 2017). Finally, a large sample was utilised, including a broad range of age and disease severity.

Regardless of the strengths, there are limitations that need to be considered. First, this study utilised a cross-sectional approach, precluding causality to be established. As such, any changes observed in $FEV_1\%_{predicted}$ arising from the reallocation of each behaviour warrants careful interpretation. Future longitudinal research is warranted to confirm these findings. In addition, two different monitor brands were utilised in this study which might generate some variability in the PA estimations. Moreover, whilst CF-specific cut-points for children and adolescents were recently developed, similar condition-specific thresholds are not currently available for adults. Therefore, age- and accelerometer brand-specific cut-points (Hildebrand et al., 2014) were utilised for children and adults in order to maintain consistence across age groups, despite the potential bias associated with this approach. Another important consideration is the heterogeneity of the sample. This study included participants across the age and disease severity spectrum from two different countries. Whilst this heterogeneity might help to generalise the study findings, it also might affect the estimation of PA. The implementation of 30-minute reallocations, particularly the increment of 30 minutes of MVPA from LPA and

SED in future interventions, or indeed recommending in standard clinical care, might not be feasible and inherently challenging. Finally, it is noteworthy that the participants included in the present study had relatively high MVPA, which might have affected the results, and consequently, the generalisability of these findings to less physically active people with CF.

7.5 Conclusion

This was the first study to use compositional analysis to investigate the impact of reallocating different movement behaviours on lung function in children and adults with CF. The estimated improvements in $FEV_1\%_{predicted}$ of 1.87 – 3.58% and 0.94 – 2.10% were associated with reallocating 30 minutes from SED to sleep, and from LPA to MVPA, respectively. Importantly, these results were irrespective of age, sex and genotype, though age was an important factor for all movement behaviours. Overall, these findings reinforce the importance of accounting for the full spectrum of movement behaviours, and are imperative to inform future studies tailoring PA interventions, providing important information regarding the amount of time and the direction of the reallocation warranted to enhance lung function for people with CF.

7.6 Practical Implications

The development of a compositional approach to assess PA in CF populations resulted in the following outcomes and recommendations:

- Increasing 30 minutes of either MVPA (from SED and LPA) and sleep (from all other behaviours) can benefit $FEV_1\%_{predicted}$ in people with CF when accounting for age, sex and genotype.
- Reducing SED by largely increasing LPA can benefit $FEV_1\%_{predicted}$ in people with CF.
- The maintenance of MVPA is as important as its promotion.
- Age was associated with all movement behaviours (sleep, SED, LPA and MVPA).

- Future research promoting PA in those with CF should consider accounting for age, sex and genotype.

CHAPTER 8

Study Five: A Machine Learning Approach for Activity Recognition in Children and Adolescents with Cystic Fibrosis

Abstract

Introduction: Habitual physical activity (PA) is associated with a slower rate of decline in lung function and better quality of life in youth with CF. Whilst the current threshold-reliant methods to assess PA are associated with significant error, machine learning models are able to classify complex PA patterns with minimal accuracy loss. Therefore, this study aimed to develop and validate machine learning models to predict PA types and intensities in children and adolescents with CF across different accelerometer brands and placements.

Methods: Thirty-five CF (11.6 ± 2.8 years; 15 girls) and 28 healthy (12.2 ± 2.7 years; 16 girls) children and adolescents participated in the study. Participants performed six activities varying in intensity and a cardiopulmonary exercise test whilst wearing two GENEActivs (both wrists), three ActiGraphs GT9X (both wrists and waist) and a portable metabolic system. Three supervised learning classifiers (K-Nearest Neighbour, Random Forest and eXtreme Gradient Boosted Decision Tree) were used to identify the input signal pattern for each physical activity type and intensity. A 10-fold cross-validation was utilised to assess the performance of the classifiers.

Results: ActiGraph GT9X on the dominant wrist and waist and GENEActiv on the dominant wrist failed to classify vigorous activities. All other models, for all activity types and intensities, exceeded 97% accuracy, with a sensitivity and specificity of greater than 99%, irrespective of accelerometer brand, placement or health status.

Conclusion: Machine learning provided an accurate method to identify different types and intensities of PA from ActiGraph GT9X and GENEActiv accelerometers in children and adolescents with CF. The models developed in this study demonstrated excellent accuracy which was comparable to or higher than previous algorithms applied in healthy children and adolescents. These highly accurate newly developed machine learning models will impact future studies investigating PA patterns in those with CF and advance our understanding of PA and health outcomes in these populations.

8.1 Introduction

Cystic Fibrosis (CF) is the most common life-limiting autosomal recessive disorder, affecting over 10,500 individuals in the United Kingdom (UK; CF Trust, 2018). CF is a multi-systemic condition characterised by pronounced progressive lung function impairment that ultimately culminates in respiratory failure. Habitual physical activity (PA) has been associated with a slower rate of decline in lung function, prolonged life expectancy and a better quality of life in children and adolescents with CF (Beekman et al., 2013; Hebestreit et al., 2014; Ratjen et al., 2014). More specifically, moderate-to-vigorous physical activity (MVPA) is associated with the prevention of CF-related diabetes and bone disease, and has been recommended as part of CF care (Rand & Prasad, 2012). However, it is important to note that the traditionally derived cut points on which these conclusions are based are associated with limited predictive accuracy and are prone to the misclassification of PA intensities, particularly in clinical populations (Bianchim et al., 2020).

Previous research has relied on accelerometer cut-points or prediction equations to assess PA intensities due, at least in part, to the practicality and simplicity of this method (Trost, 2007). However, cut-points and equations are highly specific to the population, activities, and accelerometer device and settings on which they were developed (Bassett, 2012; Bassett et al., 2012). Indeed, it is speculated that cut-points developed in healthy children and adolescents are likely to underestimate PA levels in those with CF (Mackintosh et al., 2018; Stephens et al., 2016).

Traditionally, cut-points have been developed using linear methods, resulting in poor predictions when applied to estimate non-linear data, such as PA (Bassett, 2012; Trost et al., 2012). Recent technological advances have facilitated the application of machine learning to non-linear accelerometer data, enabling the analysis of complex accelerometer patterns to identify activity types or PA intensities. Machine learning is increasingly used in healthy children due to its enhanced prediction accuracy (de Vries et al., 2011; Ruch et al., 2011; Trost et al., 2018). For example, Trost et al. (2012) applied artificial neural networks to count-based data, achieving an overall activity classification accuracy of 80 - 86% in healthy children. However, whether machine learning approaches can also enhance the prediction of PA and sedentary time (SED) in children and adolescents with clinical conditions, such as CF in which

a higher energy expenditure (EE) is likely to be engendered for a given activity relative to their healthy peers, largely remains to be elucidated.

Whilst machine learning has improved the accuracy of estimating PA, the impact of different methodological approaches, such as accelerometer brand and placement, on EE prediction remains unclear, particularly in clinical populations. Research investigating the optimal accelerometer placement for PA assessment remains equivocal, with some evidence that machine learning enhances the prediction of EE compared to previous traditional approaches (i.e. cut-points), irrespective of placement (Mackintosh et al., 2016; Trost et al., 2014). Other research has found that the wrist placement provides higher accuracy when using machine learning to assess PA in healthy children (Mackintosh et al., 2016; Montoye, Bradford, et al., 2018; Trost et al., 2014). In addition, Fairclough et al. (2016) demonstrated that PA predictions varied significantly across accelerometer brands. Indeed, brands such as GENEActiv and ActiGraph (GT3X+ and GT9X) enable the use of raw unfiltered acceleration data, which may further enhance the accuracy of PA prediction (Schmiedek et al., 2016; Trost et al., 2020; Trost et al., 2018). More recently, Ahmadi, Pfeiffer, et al. (2020) demonstrated that two machine learning classifiers derived from raw accelerometer data achieved an overall accuracy of 87.5 - 99.6%, and were superior to the models trained using accelerometer counts. However, the majority of studies in healthy children using different classifiers to predict PA types still rely on count-based data despite the low accuracy associated with this approach (57 - 86%; de Vries et al., 2011; Ruch et al., 2011; Trost et al., 2012).

Therefore, the primary aim of this study was to develop and validate machine learning models to predict PA types and intensities (SED, light physical activity (LPA), moderate physical activity (MPA) and vigorous physical activity (VPA)) in children and adolescents with CF. The secondary aim was to investigate how these predictions vary according to accelerometer brand and placement.

8.2 Methods

8.2.1 Participants

Sixty-four children and adolescents (35 with CF) participated in the study. Participants with CF were mainly homozygous (55%) for *ΔF508* mutation and had an average intake of 10 ± 3 medications daily. Participants were classified as having CF through newborn screening, or/and if they presented with CF-typical symptoms and had either two pathological sweat tests or the identification of two CF-relevant mutations. Exclusion criteria were: infection with multi-resistant bacteria (*Burkholderia Cepacia* and nontuberculous mycobacteria), an acute exacerbation at the time of the tests, participants being less than two weeks post antibiotic treatment following an exacerbation, those with cardiovascular or musculoskeletal issues that would compromise exercise performance, or those currently awaiting a transplant. Participants in the apparently healthy group had their health status confirmed by a short clinical evaluation to identify the presence of any clinical conditions or medications. Written parental consent and child assent were obtained from all parents/guardians and participants, respectively. This study received ethics approval through the National Health Service (NHS) Research Ethics Committee (18/WS/0032).

8.2.2 Protocol

Participants completed six activities across three separate visits, with the first two visits separated by seven days. The first visit consisted of the assessment of anthropometric outcomes and health indicators. The second and third visits comprised of a simulated free-living protocol performed in a laboratory setting, and a treadmill-based exercise test, respectively. Participants were advised to avoid caffeine and vigorous exercise 24-hours prior to all visits and to arrive at least two hours post-postprandial.

8.2.3 Measurements

a. Anthropometry

Body mass (Seca 876, Hamberg, Germany), stature (Holtain Stadiomerter 603VR, Holtain Ltd, UK) and sitting stature (Holtain Sitting Height Stadiometer 607VR, Holtain Ltd, UK) were determined to the nearest 0.1 kg, 0.1 cm and 0.1 cm, respectively. Subsequently, body mass index (BMI) was calculated, and z-scores for BMI were estimated according to the World

Health Organisation reference data (de Onis et al., 2004). Finally, the age at peak height velocity was used to estimate pubertal stages as pre-pubertal, pubertal or post-pubertal (Mirwald et al., 2002).

b. Resting Metabolic Rate

Resting metabolic rate (RMR) was assessed with participants lying down and remaining in the supine position for 20 minutes using an online gas analyser (MetaMax Cortex 3B, CORTEX Biophysik GmbH, Germany). All participants were instructed to avoid talking and/or sleeping for the duration of the test, which was performed in a quiet room following at least 10 minutes of rest. The analyser was calibrated according to the manufacture's guidelines prior to each measurement. Specifically, the flow volume was calibrated using a three-litre syringe (5530 series, Hans Rudolph, Inc., USA) and gas calibration was performed using gases of known concentrations. The first five minutes and the last two and a half minutes of the recording were discarded, with remaining breath by breath values of oxygen uptake ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) included in the analyses (Cooper et al., 2009). The Weir equation was then used to calculate the RMR (Weir, 1949).

c. Lung Function

Lung function was assessed by standard spirometry (MetaMax 3B, Cortex Biophysik GmbH, Germany) using a forced vital capacity manoeuvre. During the test, participants were in an upright sitting position maintaining their neck in a neutral fixed position (McCormack et al., 2019). A face mask was used for the manoeuvre as it is easier to use, particularly in children, and provides a similar validity and intra-class reliability in comparison with a cylindrical mouthpiece (McCormack et al., 2019; Wohlgemuth et al., 2003). The manoeuvre was repeated a maximum of seven times until three consistent (i.e. repeatable) measures were obtained (Sim et al., 2017). Acceptable curves displayed a rapid and clear rise reaching the peak flow and a prolonged expiratory curve that gradually decreased in flow (Sim et al., 2017). Lung function was assessed according to forced expiratory volume in one second (FEV_1) in absolute and relative ($FEV_1\%_{predicted}$) to age, sex and weight specific reference data (Quanjer et al., 2012). Disease severity was subsequently classed according to $FEV_1\%_{predicted}$ as mild (> 70%), moderate (40 – 69%), or severe (< 40%; Davies & Alton, 2009).

d. Aerobic Capacity

A standard or modified Bruce protocol composed of three minutes stages to volitional exhaustion was used to assess exercise capacity (Mead, 1979). An online gas analyser (MetaMax 3B, CORTEX Biophysik GmbH, Germany) was utilised to measure gas exchange on a breath-by-breath basis and oxygen saturation (Nonin® WristOx® Model 3150, Nonin® Medical Inc., USA) and heart rate and rhythm (Custo Guard electrocardiogram, custo med GmbH, Germany) were assessed throughout the test. Participants' perceived exertion and breathlessness were assessed using the modified Borg scale of perceived exertion during the final 30 s of each exercise stage (0 - 10; Borg, 1982). Finally, the highest 10 s stationary average during the exercise test was used to determine the peak oxygen uptake ($\dot{V}O_{2peak}$).

e. Accelerometry

In total, five monitors were used during the activities; three ActiGraph GT9X monitors positioned on both wrists and the right hip, and two GENEActiv monitors, one on each wrist. A sampling frequency of 100 Hz was used, with a low-frequency extension activated when available.

8.2.4 Activity protocol

The protocol included six activities of daily living selected by participants from a survey based on the PA compendium (Ainsworth et al., 2011). Each activity was conducted for three to ten minutes (see Table 8.1), with at least three minutes rest separating activities. All activities were performed in a randomised order whilst wearing the accelerometers, a metabolic analyser and a pulse oximeter. The online gas analyser and all accelerometers were synchronised to an external clock.

Table 8.1 Activities Included in The Activity Protocol

Activity	**Duration (min)**	**Description**
Video	10	Watching a video whist sitting

Colouring/ writing	6	Colouring or writing whist sitting
Handheld device	6	Playing games on the handheld device whist sitting
Games	6	Playing a variety of self-selected games including football, tennis, badminton, rugby, skipping and mini bowling
Walking	5	Walking continuously at a self-selected comfortable pace
Stairs	3	Climbing and descending stairs continuously at a self-selected comfortable pace

8.2.5 Data Processing and Feature Extraction

Data from all five accelerometers were processed in the same manner. The raw accelerometer data was extracted at 100 Hz as .gt3x files and .bin files for ActiGraph GT9X (ActiLife V 6.10.2) and GENEActiv (GENEActiv PC software V2.2), respectively. All .gt3x files were converted to time-stamp-free .csv files using the ActiLife software, and then imported with the .bin files into R statistical software (V3.1.2; R Foundation for Statistical Computing, Vienna, Austria), which was used for all subsequent analyses. Raw accelerometer data were then auto-calibrated and the x, y and z axes extracted in 5-s epochs using the GGIR package (V 1.2 – 0; Matthews et al., 2012; Migueles, Rowlands, et al., 2019; Vähä-Ypyä et al., 2015). Visual screening tools, such as plots and histograms, were utilised to identify any traits or missing data, and features were extracted from the vector magnitude. Specifically, sliding windows of 1.5 s were created and the components were split into low- and high-frequency using a cut-off of 6 Hz, according to previous recommendations (Zalewski et al., 2020). This is particularly important given the dynamic nature of the signal extracted from the accelerometer. Subsequently, nine time-domain components were calculated for each window using data from the three axes. The features extracted were: mean, standard deviation, peak-to-peak value, root mean squared value, kurtosis, skewness, crest factor, root mean square velocity and signal entropy. Metabolic equivalent of task (MET) values were calculated for each activity by dividing the mean relative $\dot{V}O_2$ ($ml \cdot kg^{-1} \cdot min^{-1}$) by the resting $\dot{V}O_2$ derived from the RMR assessment. The first and last minutes of each activity were excluded to avoid transitional movements. MET values were subsequently aligned with the raw accelerometer

data and used to classify PA intensities as sedentary (≤ 1.5 MET), moderate (4 - 6.9 METS) or vigorous (≥ 7 METS; Troiano et al., 2008).

8.2.6 Machine Learning Modelling

Three supervised learning classifiers, K-Nearest Neighbour (k-NN), Random Forest and eXtreme Gradient Boosted Decision Tree (XGBoost Decision Trees), were used to identify the input signal pattern for each PA type and intensity (Friedman, 2001; Kuhn et al., 2013; Patrick & Fischer, 1970; Zertuche, 2014). All models were trained and cross-validated using the following packages within R: "caret", "randomForest", "xboost", "entropy", "signal" and "knn". Initially, models were used to classify different activities and, subsequently, to identify different PA intensities from EE (METs).

The random forest classifier of 500 trees was trained using the data from all nine features. Specifically, the features were randomly sampled into training and test sets and the whole process was repeated 1,000 times. An internal out of bag approach (Winham et al., 2013) was then used to test the accuracy of the model. Specifically, (Breiman, 1996) defined as "out-of-bag" sample the 1/3 of the instances in the original training set that are not part of a single bootstrap sample in bagging (i.e. bootstrap sampling theory). The out of bag approach is commonly applied to measure model performance given its advantage of also utilising the complete original sample for constructing the classifier and for error estimation (Zhang et al., 2010). Indeed, a decision tree learns from a subset of the data, enabling the remaining data to be used to evaluate the performance of the model (Winham et al., 2013). For the XGBoost model, the data set was randomly split into two, with 80% of data used for training and 20% for testing. XGBoost is a type of boosting algorithm designed to learn from previous poor predictions in order to use this information to enhance future predictions (Chen & Guestrin, 2016). Specifically, each new tree is generated whilst reducing the residual (differences between the actual and predicted values) of the previous model. As such, this model evaluates the performance of each round of classification instead of assessing the overall performance of the training set (Chen & Guestrin, 2016). For this model, 15 consecutive rounds of classification decline were determined prior to halting the learning, with the last best score used as the final outcome. Finally, the weighted k-NN was performed using a kernel function to weight the neighbours of a data point using the distance as a parameter (Zhang, 2016).

A 10-fold cross-validation was utilised to assess the performance of the classifiers. Specifically, the original data set was randomly split into 10 subsamples of the same size, with one of the sections used to validate the model and the remaining nine as training data. Subsequently, the process was repeated 10 times until all subsamples served as validation data. The average of the results was then used to indicate the accuracy of the model. In addition, the percentage agreement with 95% confidence intervals were also calculated and Kappa scores were determined for each classifier. The sensitivity and specificity, along with the balanced accuracy (calculated as the average of the proportion corrects of each class individually), were also calculated for each model.

8.2.7 Statistical Analyses

Descriptive data were presented as mean ± standard deviation (SD), and a two-way ANOVA test was performed to identify inter-group differences, between CF and healthy participants, and intra-group differences between boys and girls.

8.3 Results

One participant was excluded from the analysis for not attending visit two, resulting in a total of 63 (35 CF) participants being included in the analyses. Cystic Fibrosis was classified as mild for all participants, with an $FEV_1\%_{predicted}$ of 94 ± 19%. According to the age at peak height velocity, 38 (23 CF) of the participants were pre-pubertal, 15 (4 CF) were post-pubertal, and 10 were (8 CF) pubertal (Table 8.2; Mirwald et al., 2002). Participants with CF had significantly lower body mass ($p = 0.02$) and lower zBMI ($p = 0.006$) than the healthy group. Despite this, no significant differences in age, height, RMR or $\dot{V}O_{2peak}$ were encountered between the mild CF and healthy participants.

XGBoost and k-NN algorithms were reported as one outcome; they both achieved the same performance and provided the same classification values. Confusion matrices for classification (rows are indicating actual observations and columns represent predicted classifications using the time-domain features selected by each model), according to activity

types and intensities are provided as supplementary material for Random Forest (Appendix H, see Tables H8.1 and H8.2) and XGBoost/k-NN models (Appendix H, see Tables H8.3 and H8.4), respectively. Models using features extracted from ActiGraph GT9X worn on the dominant wrist and waist and GENEActiv worn on the dominant wrist failed to classify VPA in those with CF, whilst the GENEActiv on the non-dominant wrist also failed to recognise patterns related to vigorous intensity in healthy children. Visual inspection of the data indicated that that the models failed to classify VPA in healthy participants due to the scarcity of data points associated with this intensity. In contrast, participants with CF had a considerable amount of data points associated with VPA.

Table 8.3 shows the differences in EE between CF and healthy participants. Specifically, t-tests identified that those with CF had higher EE than healthy participants while watching television and stairs. The healthy group did not reach vigorous intensity (≥ 7 METs) for any activity.

Table 8.2 Participants Characteristics

	CF			**Healthy**		
	Total (n = 35)	**Girls (n = 15)**	**Boys (n = 20)**	**Total (n = 28)**	**Girls (n = 16)**	**Boys (n = 12)**
Age (years)	11.6 ± 2.8	11.3 ± 2.7	11.8 ± 2.9	12.2 ± 2.7	12.6 ± 2.6	11.5 ± 2.8
Height (cm)	1.46 ± 0.15	1.44 ± 0.12	1.47 ± 0.17	1.53 ± 0.16	1.54 ± 0.10	1.50 ± 0.21$^{\times}$
Body mass (kg)	39.1 ± 12.0^{+}	37.3 ± 10.2	40.4 ± 14.2	47.1 ± 15.0	50.1 ± 12.7	43.0 ± 12.2
BMI ($kg \cdot m^{-2}$)	18.0 ± 4.2	17.5 ± 2.0	18.4 ± 5.3	19.6 ± 3.5	20.6 ± 3.3	18.2 ± 3.5
zBMI	-0.31 ± 1.10^{+}	-0.12 ± 0.78	-0.47 ± 1.28	0.41 ± 0.8	0.57 ± 0.62	0.19 ± 1.00
RMR ($ml \cdot kg^{-1} \cdot min^{-1}$)	6.21 ± 1.31	5.86 ± 1.26	6.45 ± 1.24	5.35 ± 1.54	4.51 ± 0.89	6.47 ± 1.51
$\dot{V}O_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	41.2 ± 11.6	37.2 ± 10.8	44.7 ± 10.4	41.6 ± 12.3	36.4 ± 9.2	47.6 ± 13.5
FVC (L)	2.5 ± 1.0	2.5 ± 1.0	2.5 ± 1.0*	2.8 ± 1.0	2.8 ± 1.0	2.9 ± 1.2$^{\times}$
FVC predicted (%)	99 ± 21	97 ± 20	99 ± 21	105 ± 26	105 ± 26	106 ± 18
FEV_1 (L)	2.0 ± 0.7	1.9 ± 0.4	2.2 ± 0.9*	2.4 ± 0.8	2.4 ± 0.8	2.4 ± 0.9
$FEV_1\%_{predicted}$	94 ± 19	92 ± 20	94 ± 19	99 ± 21	99 ± 22	100 ± 14

Data are presented as mean ± SD

CF: Cystic Fibrosis, BMI: body mass index, zBMI: z-score BMI, RMR: resting metabolic rate, $\dot{V}O_{2peak:}$ peak oxygen uptake, FVC: forced vital capacity, FEV_1: forced expiratory volume in one second. *indicates significant difference between boys and girls in the CF group and ˟ indicates significant difference between boys and girls in the healthy group ($p \leq 0.05$).

Table 8.3 Mean Energy Expenditure (METs) During each Activity

	METs	
	CF (n = 35)	**Healthy (n = 28)**
Video	1.3* ± 0.9	1.0 ± 0.3
Colouring/writing	1.3 ± 0.3	1.2 ± 0.5
Handheld device	1.1 ± 0.3	1.1 ± 0.4
Free-games	4.1 ± 2.0	4.2 ± 1.8
Walking	2.9 ± 1.3	2.5 ± 1.1
Stairs	5.1* ± 2.0	4.7 ± 0.7

Data are presented as mean ± SD.

CF: Cystic Fibrosis, MET: metabolic equivalent. *indicates significant difference between groups ($p \leq 0.05$).

Details regarding the cross-validation are provided in the appendix for Random Forest) and XGBoost/k-NN, respectively. All models provided excellent accuracy (97 - 100%) and low error to classify activities types and intensities (Appendix H, Tables H8.5 and H8.6). The highest accuracy was observed for XGBoost and k-NN in both CF and healthy participants. Overall, GENEActiv achieved marginally higher (100%) accuracy in comparison with ActiGraph (99%) in both groups. Finally, all classifications presented a sensitivity and specificity higher than 97%, independent of accelerometer brand, placement and health status for all models performed in this study.

8.4 Discussion

This study sought to ascertain the suitability of using three machine learning classifiers with raw accelerometer data to classify PA types and intensities in children and adolescents with CF. Overall, the use of machine learning seems to yield high accuracy (> 97%) to classify different PA types and intensities when trained on time-domain features, irrespective of accelerometer brand or placement. Indeed, the current overall classification accuracy is

superior to traditional approaches used to predict PA in children with CF (Chapter V; Stephens et al., 2016). Therefore, based on this study, it is recommended that future research evaluating PA levels in CF use raw accelerometer data with machine learning algorithms.

Despite major limitations, such as the lack of generalisability across different accelerometer brands, previous research using pattern recognition to predict PA has relied on accelerometer counts (Kühnhausen et al., 2017). Specifically, previous studies in children using different classifiers to predict PA types from accelerometer counts have achieved an accuracy of 57 - 86% (de Vries et al., 2011; Ruch et al., 2011; Trost et al., 2012). Of importance, and akin to previous studies using machine learning on raw accelerometer data (Ahmadi, Pfeiffer, et al., 2020; Kühnhausen et al., 2017), all three classifiers trained and tested in this study outperformed previous models trained on accelerometer counts. For example, using Random Forest and regularised logistic regression classifiers to predict activity type from waist-worn ActiGraph raw data in children, Ahmadi et al. (2020) achieved an overall accuracy of 90% and 87 - 99%, respectively. Although it is well known that differences in the protocol, such as activity types and accelerometer brand and settings, can impact the classifiers performance, the use of accelerometer counts seems to be associated with low PA classification accuracy, irrespective of such factors. Indeed, Kühnhausen et al. (2017) found a significantly higher accuracy (92%) for predicting PA in healthy children using machine learning models (support vector machines) developed from raw accelerometer data in comparison to those using counts (70 – 71%). Such discrepancies may be due to the elimination of vital information during the data reduction process to transform raw accelerometer data into counts (Schmiedek et al., 2016).

Whilst the three activity classifiers tested in the present study demonstrated similar overall performance, the XGBoost and k-NN achieved marginally higher classification accuracy. Specifically, the Random Forest demonstrated slightly low accuracy to predict four of the activities (TV, colouring/writing, walk and stairs) and sedentary and LPA intensities, independent of health status. This is contradictory to previous studies in healthy children which found that Random Forest performed marginally better to predict ambulatory activities in comparison with SED and LPA (Ahmadi, Pfeiffer, et al., 2020). This discrepancy during ambulatory activities may reflect pathological metabolic and muscle function adaptations that could impact the predictions of EE in those with CF (Erickson et al., 2015; Johnson et al., 2006). Indeed, higher accelerometer raw outputs were observed for those with CF in comparison with healthy participants during walking (Chapter 5). In the current study, Random

Forest models were enhanced by XGBoost, independent of activity type or intensity. This finding is corroborated by previous research demonstrating that Gradient Boosting classifiers perform better compared to other types of boosting classifiers for PA classification (Rahman et al., 2020). However, the differences between all three classifiers utilised in this study were not significant, suggesting that any of these models could be used to predict PA in children with CF, or indeed, healthy children. Similar findings were reported in studies using different activity classifiers in both healthy children (Ahmadi, Pfeiffer, et al., 2020; Park, 2013; Trost et al., 2018) and youth with cerebral palsy (Ahmadi et al., 2018), with only marginal differences found between different machine learning models.

All three placements yielded comparable overall accuracy across classifiers, in line with previous research in healthy children (Mackintosh et al., 2016). Nonetheless, the ActiGraph GT9X placed on the dominant wrist and waist and the GENEActiv placed on the dominant wrist failed to classify VPA in those with CF. Similar results were found for models using features extracted from the GENEActiv placed on the non-dominant wrist in healthy children. Visual inspection of the data suggested that whilst the models failed to classify VPA in healthy participants due to the scarcity of data points associated with this intensity, a similar explanation is not applicable to those with CF. Irrespective, this discrepancy indicates that although intended vigorous components of the protocol, such as the activity of stairs, were classified as moderate intensity for healthy participants, this was classified as vigorous for the majority of the CF group. This not only reiterates the need for CF-specific approaches to evaluate PA, but questions the ability of the machine learning models to predict VPA from ActiGraph GT9X and GENEActiv placed on the dominant-wrist and waist in children and adolescents with CF.

Amongst all models developed to classify PA intensities, waist-worn ActiGraph GT9X monitors achieved marginally less accuracy for both SED and LPA, in contrast to other placements in the CF group. One possible explanation is that the metabolic demand did not match the intensity of the waist-worn accelerometer signals for both SED and LPA, which comprised of seated activities (i.e. video, colouring). Indeed, children and adolescents with CF are known to require higher EE during rest due to the enhanced cost of breathing and higher RMR in comparison with their healthy peers (Tomezsko et al., 1994). Despite this, it is noteworthy that no differences regarding RMR and $\dot{V}O_{2peak}$ were found between mild CF and healthy participants in the present study. While this might raise the question of whether a

specific model is warranted in mild CF, it is important to acknowledge that other factors associated with exercise intolerance, such as chronic inflammation and impaired muscle metabolism, were not controlled for.

Whilst waist-worn ActiGraph GT9X provided marginally lower accuracy to classify activity intensities in CF, this site yielded excellent accuracy across all placements in healthy participants. This finding corroborates previous research (Ellis et al., 2016; Trost et al., 2018) reporting that Random Forest models achieved marginally higher activity classification accuracy when the ActiGraph GT3X+ was placed at the waist in comparison with wrist in healthy children and adults. Interestingly, the waist-worn ActiGraph GT9X also performed marginally better than the wrist to classify PA in children with cerebral palsy using different machine learning models (Binary Decision Trees, Random Forest and Support Vector Machine; Ahmadi et al., 2018). Converse to CF, those with cerebral palsy are likely to present normal EE levels during rest, with increases only anticipated during activities (Bell et al., 2020). However, it is important to highlight that all placements demonstrated excellent accuracy to predict PA types and intensities. Nevertheless, wrist-worn accelerometer protocols are associated with enhanced compliance (Fairclough et al., 2016), which is extremely important in studies assessing PA in free-living conditions.

This study demonstrated the feasibility of using machine learning models to accurately predict SED, LPA, MPA and VPA from EE in youth with CF. Notably, these findings have significant importance for clinical practice, not least because PA guidelines are tailored around intensities. Specifically, clinicians and health professionals could receive better guidance regarding which exercise or PA intensity would be most suitable to generate health outcomes in different circumstances such as, exacerbations and varies disease severities. It is well known that PA, particularly of moderate intensity, is recognised as a valued component of CF treatment (Rand & Prasad, 2012). Despite this, few studies have used machine learning to develop models to predict PA intensities from EE (Staudenmayer et al., 2009; Trost et al., 2012), with the vast majority classifying different activities types instead (Kühnhausen et al., 2016; Trost et al., 2014). Alternatively, machine learning algorithms could be used to identify daily patterns of PA in children and adolescents with CF. For example, Willetts et al. (2018) developed a balanced Random Forest with a Hidden Markov Model to assess free-living accelerometer data in healthy adults, achieving an 87% accuracy to classify PA and sleep behaviours. This could significantly advance research investigating the association between daily behaviours (PA and sleep patterns) and health outcomes (Doherty et al., 2018). This

study, therefore, has the potential to contribute to further advancements in research investigating the PA profiles of children and adolescents with CF, which is paramount to the design of PA interventions and specific recommendations for this population.

This study has numerous strengths. Specifically, this is the first study to utilise machine learning models to identify PA types and intensities using raw accelerometer data from both wrist- and waist-worn accelerometers in children and adolescents with CF. Moreover, all activities incorporated in the study protocol were selected by the participants through an initial survey. This provided a more ecologically valid approach, including activities that were representative of the participants' daily routine. In addition, this study included participants with a broad age range (7 – 17 years) in accord with previous recommendations (Freedson et al., 2005). Given that previous research has suggested that the leave-one-out cross-validation approach may not be appropriate to determine the accuracy of machine learning models developed for activity classification (Montoye, Bradford, et al., 2018), this study employed a 10-fold cross-validation. Additionally, comparisons between models and features across multiple accelerometer placements and brands were made.

There were, however, limitations to this study. First, all models were trained using data collected from activities performed in a structured laboratory setting and might not be representative of free-living conditions. Second, this study has not sought to investigate how other processing choices might affect the accuracy of the PA prediction, such as employing different windowing techniques or the use of different filtering approaches. Third, it was not possible to develop a model to classify sleep due to the design of the current study. This is particularly important for future studies given the recent shift towards 24-hour movement guidelines (Kuzik et al., 2017; Waters et al., 2017; WHO, 2020). As such, future research evaluating the performance of machine learning models in free-living conditions should account for sleep as one of the key daily behaviours. Fourth, whilst this study has not included frequency domain features in accord with previous recommendations (Ellis et al., 2016; Montoye, Bradford, et al., 2018), this omission might arguably hinder inter-study comparisons. Despite that, previous research has demonstrated that the inclusion of frequency domain features in the activity models does not improve the overall accuracy of the predictions and can lead to overfitting (Ellis et al., 2016; Montoye, Bradford, et al., 2018). Another important consideration is regarding the sensitivity and specificity values, which were high for all models, and might indicate a degree of overtraining. Future studies could use nested cross-validation (Vabalas et al., 2019) to identify the optimal features that should be included in the models,

thereby reducing the total number of features included and, consequently, diminishing the issue of dimensionality. However, it is noteworthy that any correlated features were excluded from the models and cross-validation was performed to minimise overfitting. Finally, this study included children and adolescents with mild CF and, therefore, might not be representative of those with more severe forms of the condition.

8.5 Conclusion

In conclusion, this study demonstrated the feasibility of using three different machine learning classifiers to estimate different types of PA and intensities from waist- and wrist-mounted ActiGraph GT9X and GENEActiv accelerometers in children and adolescents with CF. The accuracy achieved in this study was comparable or higher than studies in healthy children and adolescents using various machine learning classifiers. Thus, this study provides support for the use of machine learning to predict complex pattern variables such as PA in children and adolescents with CF. Future studies assessing PA levels in those with CF are advised to use raw accelerometer data with machine learning algorithms to enhance prediction accuracy.

8.6 Practical Implications

Overall, **Chapter 8** developed and validated machine learning models to recognise activity type and intensities in children and adolescents with and without CF. The key findings were:

- All predictions achieved excellent accuracy, irrespective of accelerometer model or placement.
- Models can be applied to research investigating PA patterns and its association with health outcomes in those with and without CF.

CHAPTER 9

Synthesis

The primary aim of this thesis was to investigate the measurement and analysis of physical activity (PA) in individuals with Cystic Fibrosis (CF) and to thereby provide more accurate insights into the PA levels of those with CF and the relationship of PA with key health outcomes. The experimental chapters within this thesis provide key information for the future development of PA interventions and recommendations in CF. This chapter provides a synthesis of the overall findings and identifies future research directions whilst acknowledging the overarching strengths and limitations of the current work.

9.1 Overview

9.1.1 Physical Activity Assessment in Children and Adolescents with Cystic Fibrosis

Whilst accelerometry has been broadly used in clinical and epidemiological research, the methods used to investigate the association between PA and health to date are associated with significant limitations. Specifically, a reliance on accelerometer counts and linear statistical approaches in many earlier studies is now well accepted to be associated with error and low accuracy in PA prediction (Arvidsson, Fridolfsson, & Börjesson, 2019). Furthermore, accelerometry in clinical contexts warrants specific calibration and validation in order to reflect the characteristics of that particular population (**Chapter 4**; Bianchim et al., 2020). Indeed, the systematic review provided in **Chapter 4** highlighted that protocols developed to calibrate accelerometry in paediatric clinical populations should be specifically tailored to account for the pathophysiology of the condition and include a control group. The importance of this tailored approach was supported by the findings of **Chapters 5** and **8** in which the superiority of CF-specific raw acceleration thresholds and algorithms was clearly demonstrated. Furthermore, the findings from **Chapter 6** revealed that the use of generic cut-points previously developed in healthy populations significantly underestimated PA predictions when applied to assess PA in children and adolescents with CF. These findings therefore question the validity of the PA levels reported in previous studies that have used such generic thresholds

but also the applicability of the current PA recommendations proposing that children should accrue 60 minutes of daily moderate-to-vigorous activities to those with CF (MVPA; Department of Health and Social Care, 2019).

Overall, the findings from **Chapters 5** and **6** highlight that cut-points tailored specifically for children and adolescents with CF improved the assessment of PA levels, and might be fundamental to advance our understanding of the relationship between PA and health. For example, the use of CF-specific cut-points to estimate PA revealed that light physical activity (LPA) was the only predictor of lung function, across the full spectrum of PA intensities, after adjusting for sex, age, genotype, BMI and accelerometer wear-time (**Chapter 6**). This is in accord with previous research utilising generic count-based cut-points to evaluate PA in children with CF (Mackintosh et al., 2018). Whilst this finding emphasises the potential importance of LPA in CF care, it is important to acknowledge that all PA behaviours are inherently inter-related, highly collinear and, ultimately, constrained within a 24-hour period (Carson, Tremblay, et al., 2016; Dumuid et al., 2019; Dumuid et al., 2018; Tlučáková et al., 2020), such that any increases in LPA occur at a cost to another PA or sleep behaviour. It is therefore vital that the optimal composition of daily PA for health is considered rather than continuing to pursue the traditional, isolated approach.

Of interest, and contrasting findings described in **Chapter 6,** the use of a compositional approach in **Chapter 7** found that LPA was not the most relevant movement behaviour for lung function. Instead, **Chapter 7** showed that sleep and MVPA elicited greater estimated increments in lung function amongst all movement behaviours across the lifespan in CF. Whilst these findings may have only been revealed as a result of the compositional approach, this discrepancy may have also arisen from the large volume of LPA observed in children and adolescents in previous research (Mackintosh et al., 2018). Specifically, recent studies highlighted the importance of accounting for the contribution of a given intensity (i.e. LPA) to total PA volume when investigating associated health outcomes (Carlson et al., 2019; Hnatiuk et al., 2019; Saint-Maurice et al., 2018; Verswijveren et al., 2018). As such, the promotion of a greater increase in LPA amongst those accumulating less MVPA might be a more feasible and achievable approach for future PA interventions in CF. Additionally, **Chapter 7** showed that the reallocation of sedentary time (SED) to other PA intensities and sleep also increased lung function. Although this is the first study to utilise compositional analyses in CF populations, these findings are congruent with previous research in healthy and clinical populations that also report favourable associations between MVPA and sleep for

cardiometabolic risk markers (Carson, Tremblay, et al., 2016; Carson et al., 2019), and obesity indicators (Dumuid et al., 2018).

Whilst spirometry-assessed forced expiratory volume in one second (FEV_1) is the most commonly used indicator of disease progression and lung function (Jantzen et al., 2016; Mackintosh et al., 2018; Schneiderman-Walker et al., 2005; Szczesniak et al., 2017), it is important to acknowledge the limitations associated with this approach. Specifically, evidence suggests that spirometry cannot assess damage in small airways (Fretzayas et al., 2019), which are an important indicator of early lung impairment. This is particularly important since new therapies have considerably attenuated lung damage (Edmondson & Davies, 2016; Ridley & Condren, 2020), which implies that spirometry might no longer provide sufficient sensitivity to monitor and detect disease progression. Indeed, individuals with CF seem to present stable FEV_1 throughout childhood and early adulthood (**Chapters 5 to 8**), despite robust evidence of structural damage (Horsley et al., 2013). Research suggests that the lung clearance index (LCI) is more sensitive to detect airway disease than spirometry (Singer et al., 2013), and might be a better alternative to indicate lung function and disease progression. Although it was not possible to implement this approach in this thesis due to feasibility given the multi-site design, future research is advised to integrate a measure of LCI when investigating the impact of PA levels to lung function in CF.

9.1.2 Condition-specific Approaches to Assess Physical Activity Levels in Children and Adolescents with Cystic Fibrosis

Chapter 5 sought to develop CF-specific cut-points in order to enhance the accuracy of PA assessment for children and adolescents with CF. The use of metrics directly extracted from raw accelerometer data demonstrated excellent accuracy and low error in comparison with CF-specific cut-points previously developed from accelerometer counts (Stephens et al., 2016). Given the disease aetiology of CF, **Chapter 5** theorised that the newly developed CF-specific cut-points would vary significantly from those previously developed from healthy children. Indeed, the CF-specific moderate physical activity (MPA) cut-points were lower in comparison to those developed for the healthy controls and those previously published for healthy children (Aittasalo et al., 2015; Hildebrand et al., 2014). These findings are also in accordance with **Chapter 4**, which suggests that cut-points developed in healthy children and

adolescents are not suitable for youth with chronic conditions. Such findings have significant implications, not least as previous research assessing PA levels in CF have utilised cut-points that were developed in healthy populations, therefore potentially hindering our understanding of the association between PA levels and clinical outcomes in youth with CF. Most importantly, **Chapter 5** theorised that the discrepancy in condition-specific and generic cut-points, may have potentially led to previous studies underestimating the amount of MVPA in children and adolescents with CF. Notably, there is no consensus regarding overall PA levels in children and adolescents with CF, with a few studies reporting that children with CF spend less time in MPVA and more time in LPA (Aznar et al., 2014; Nixon et al., 2001), whilst others found no difference in comparison to healthy counterparts (Boucher et al., 1997; Selvadurai et al., 2004). Indeed, this theory was corroborated in **Chapter 6,** with the CF-specific cut-points eliciting higher SED and MVPA and lower LPA than Hildebrand et al. (2014) cut-points. Therefore, future studies are advised to utilise CF-specific approaches to assess PA in children and adolescents with CF in order to ensure the validity of their findings, and consequently, inform strategies to promote PA in this population.

Whilst CF-specific cut-points were shown to enhance the prediction of PA (**Chapter 6**), more complex computational methods, such as machine learning, have demonstrated higher rates of success to classify PA activities and intensities (Farrahi et al., 2019). Therefore**, Chapter 8** sought to develop machine learning algorithms to classify PA types and intensities from raw acceleration data in children and adolescents with CF. More specifically, **Chapter 8** investigated whether the use of pattern recognition approaches could also enhance the prediction of PA in those with CF. Indeed, all the algorithms tested achieved excellent accuracy for classifying different PA types and intensities when trained on time-domain features extracted from raw acceleration data. Machine learning models achieved excellent accuracy to predict SED and PA intensities from energy expenditure (EE) in youth with CF, which is particularly important given that the pathophysiological alterations associated with the condition underpin the need for CF-specific cut-points and algorithms. Indeed, those with CF are likely to expend more energy undertaking a certain activity in comparison with their healthy peers as a result of the enhanced cost of breathing and exercise intolerance associated with the condition (Matel & Milla, 2009). Therefore, the availability of validated machine learning models and cut-points is paramount to research assessing PA levels in CF to inform disease-specific PA guidelines and interventions.

9.1.3 Impact of Specific Approaches to Assess Physical Activity in Cystic Fibrosis

This thesis centred around the concept that the physiological complexity associated with CF is likely to affect the measurement of PA, and therefore, the estimation of PA levels and any subsequent association with lung function (predicted forced expiratory volume in the first second; $FEV_1\%_{predicted}$). Indeed, **Chapter 6** found that the use of generic cut-points significantly underestimated MVPA and SED and over-estimated LPA in children and adolescents with CF. This misclassification is associated with CF-specific pathophysiological alterations and could explain previous reports that children and adolescents with CF have lower MVPA and higher LPA levels than their healthy peers (Aznar et al., 2014; Nixon et al., 2001). In addition, another important limitation of previous research investigating PA levels in CF, is the failure to account for the composition of the movement behaviours. Indeed, the use of compositional analyses in **Chapter 7** revealed that improvements in lung function were only achieved when accounting for the interaction of movement behaviours. For example, increments in MVPA were only beneficial to lung function when LPA and SED were displaced, with 30-minute reallocations from sleep to MVPA resulting in up to a 2.0% decrease in $FEV_1\%_{predicted}$ instead. In contrast, reallocating 30 minutes of other movement behaviours to MVPA or sleep estimated an improvement of up to 2.1% and 3.6% in $FEV_1\%_{predicted}$, respectively, after adjusting for age, sex and genotype. Most importantly, given that $FEV_1\%_{predicted}$ declines approximately 1.0 to 3.0% annually, the uninformed reallocation of movement behaviours can either delay or accentuate the progressive airway disease in CF. Therefore, the abovementioned limitations are particularly concerning given that the accurate assessment and analyses of PA and SED in those with CF are fundamental to the appropriate development of PA interventions and clinical decisions.

It is pertinent to note that no research to date has designed, or indeed implemented, interventions targeting the reduction of SED in paediatric populations with CF. This may be due, at least in part, to the assumption that children and adolescents with CF spend little time being sedentary and a significant portion of their time accruing LPA instead (Aznar et al., 2014). This misconception, and subsequent lack of research, carries important health implications due to the possible independent detrimental effects associated with prolonged SED (Bélair et al., 2018; Carson, Hunter, et al., 2016; Tremblay et al., 2011). In accord, the results from **Chapter 7** indicated that the displacement of SED to sleep resulted in the best estimated improvement in $FEV_1\%_{predicted}$ (3.6%). Whilst this finding suggests that replacing

SED with sleep might be a feasible and simple strategy to enhance, or slow the decline in, lung function, it is important to highlight that SED and LPA showed the highest co-dependency across all the behaviours assessed. Specifically, reductions in SED are likely to be accompanied by a decrease in LPA, which might counteract the desired outcomes for lung function. As such, future interventions targeting the reduction of SED should account for both LPA and sleep in order to obtain the best outcome. It is noteworthy that **Chapters 5 and 6** found that those with CF have a higher EE for a given sedentary task in comparison to their healthy peers. This finding has important repercussions, such as the misclassification of SED as LPA when using generic cut-points, as demonstrated in **Chapter 6**. Additionally, this discrepant energetic demand raises even deeper questions regarding the applicability of the definition of sedentary behaviour, which is centred around an energetic cost threshold (i.e. <1.5 MET; Tremblay et al., 2017), to those with CF. Specifically, it seems appropriate that this energetic threshold defining sedentary behaviour should be altered to accommodate the physiological alterations associated with the condition.

It is noteworthy that sleep quality, quantity and timing were found to be key determinants of PA in healthy populations (Kline, 2014). Although further investigation is warranted, research also suggests a bidirectional relationship between those variables in children and adults, independent of health status (Ávila-García et al., 2020; Kline, 2014; Master et al., 2019). Sleep quality is also crucial to both physical and mental wellbeing, with sleep duration recommendations available for the healthy population (Paruthi et al.; Watson et al.). Nevertheless, sleep behaviour drastically varies with age and in the presence of clinical conditions (Borbely et al., 2017). Research shows that sleep disturbance are particularly harmful for those with chronic disorders as it aggravates the condition and hinders treatment (Strine & Chapman, 2005). Indeed, recent studies (Barbosa, Coelho, et al., 2020; Shakkottai et al., 2018) corroborates findings from **Chapters 6 and 7** regarding the important relationship between sleep and PA and their impact on associated health outcomes. Specifically in CF, poor sleep duration, which is common in children with CF (Jankelowitz et al., 2005), has been associated with neurocognitive, cardiovascular and metabolic abnormalities (Hanly et al., 2002; Katz, 2014), an increase in SED (Barbosa, Coelho, et al., 2020), and nocturnal hypoxemia (Shakkottai et al., 2018). Of importance, nocturnal hypoxaemia is considered a major cause of chronic sleep loss in CF and it is associated with early mortality (Hanly et al., 2002; Katz, 2014; Ramos et al., 2013). Therefore, precise guidelines for identifying sleep

disturbances earlier is essential for the maintenance of health and promotion of PA in those with CF.

An important contribution of **Chapter 6** was the re-evaluation of the relationship between PA, across the intensity spectrum, SED and lung function in CF. One of the major implications of the findings from **Chapters 4 to 6** is the associated issues of using PA recommendations developed based on healthy populations, to those with CF. However, in order to tailor CF-specific PA recommendations, it is essential to initially determine what duration and direction of change (i.e. the reallocation from one intensity to another) in the spectrum of PA intensities that is associated with improved health outcomes. For example, according to findings from **Chapter 7**, it could be postulated that increases in SED, likely displaced from MVPA and sleep, might further accelerate the disease progression. Therefore, intervention studies are advised to focus on increasing MVPA and sleep, through reducing SED and LPA, the latter of which would mean increasing the intensity of activities, in order to slow airway disease. In addition, further details regarding the manner in which PA is accumulated (i.e., PA patterns) across the activity spectrum are also crucial to designing effective population-specific recommendations. For example, Barkin et al. (2018) found sex differences in how children accrue the PA recommendations. Specifically, Barkin et al. (2018) found that girls accumulated greater spontaneous bursts of MVPA, whilst boys accrued more sustained MVPA. This is particularly interesting given that Mackintosh et al. (2016) found no differences in how children with and without CF accrued their PA levels regarding frequency or duration of bouts. Whilst this thesis did not investigate PA patterns, **Chapter 6** did find significant sex differences in PA levels in children and adolescents with CF, with boys spending significantly more time asleep and in VPA and MVPA, and less in LPA than girls. In addition, **Chapter 6** also found sex differences in PA levels depending on the type of day, with boys accumulating greater MPA and MVPA on week days, in comparison to weekend days. This finding is in accord with studies in CF (Aznar et al., 2014; Mackintosh et al., 2018) and healthy children (Fairclough et al., 2015), and indicates the importance of investigating both week and weekend day patterns of PA to inform more efficient interventions. Therefore, children and adolescents with CF might benefit from PA interventions focusing on boys and girls, and weekdays and weekend days, separately.

9.2 Strengths and Limitations

This thesis has numerous strengths, not least the progressive and novel application of PA measurements and analyses. Indeed, **Chapters 5, 7** and **8** are the first to develop raw accelerometry cut-points, machine learning algorithms and use compositional analyses to assess PA in CF, respectively. Additionally, **Chapters 5 and 8** were informed by a systematic review of the literature, thereby enhancing the robustness of the methodology utilised. Specifically, **Chapter 4** recommended that accelerometry calibration protocols in paediatric clinical cohorts should account for the pathophysiology of the disease and integrate a measure of EE into their protocol. To further ensure methodological rigour, metabolic equivalent of task (MET) values were determined by dividing the $\dot{V}O_2$ obtained from the activities by individual measures of resting metabolic rate (RMR), which is in accord to previous recommendations in clinical (Bianchim et al., 2020) and healthy populations (McMurray et al., 2015). Conversely, a limitation of **Chapters 5 and 8** was the use of activities performed in a structured laboratory setting, which might not be representative of free-living conditions. However, a free-living protocol precludes integrating a measure of EE. Therefore, **Chapters 5 and 6** consisted of a field-based protocol encompassing free-play activities that children and adolescents commonly engage in. It is also important to acknowledge that, to maximise ecological validity, the protocol utilised in **Chapters 5 and 8** was designed based on information extracted from randomly selected participants. However, it is pertinent to note that there was not a fully age- and sex-matched control group in **Chapter 5 and 8**, or any age- and sex-matched control group in **Chapter 6** as the COVID-19 lockdown prematurely curtailed data collection. Nonetheless, **Chapter 6** included a large CF cohort and was the first study to compare the application of CF-specific and generic cut-points to estimate PA levels in CF.

A key strength to all current studies was the adoption of raw accelerometer data to quantify PA instead of using accelerometer counts. Indeed, Trost et al. (2010) reported that count-based cut-points are responsible for 33 to 68% of misclassifications of PA. More specifically, Kühnhausen et al. (2017) reported that the bias originates from the loss of vital information during the process of converting accelerometer raw signal to counts. In accord, the CF-specific raw cut-points yielded higher accuracy and less error than previous CF-specific count-based thresholds (Stephens et al., 2016). In addition, to further reduce misclassification and bias, and to ensure the generalisability of the cut-points and algorithms, previous research recommended that a cross-validation should be performed (Bianchim et al., 2020; Montoye,

Bradford, et al., 2018). Therefore, another strength of **Chapters 5 and 8** was the cross-validation of the newly developed cut-points and algorithms. Further methodological rigour was demonstrated in the selection of the cross-validation approach, with the use of a leave-one-out approach in **Chapter 5** and a 10-fold cross-validation in **Chapter 8**. Whilst previous research has suggested that the leave-one-out approach is the most appropriate for the cross-validation of thresholds generated from a modest number of participants (Bianchim et al., 2020), this method is not appropriate to assess the accuracy of machine learning models (Montoye, Bradford, et al., 2018). Finally, **Chapters 5 and 8** generated outcomes for different accelerometer brands and placements to enable inter-study comparability and key recommendations.

A common limitation in **Chapters 6 and 7** was the cross-sectional design adopted which meant that inferences regarding causality and directionality cannot be made. Despite this, both studies included a large number of participants with a broad age range, which contributes to the generalisability of the findings. Specifically, **Chapter 7** included both children and adults, and drew comparisons between the different age groups, according to sex and genotype, therefore providing valuable insight regarding how PA impacts lung function in CF across the age and severity spectrum. Despite the strengths associated with the inclusion of participants across the lifespan, a limitation associated with this design is the lack of CF-specific cut-points to assess PA in adults. As such, generic cut-points that were age- and accelerometer brand-specific (Hildebrand et al., 2014) were utilised to assess PA in children and adults in **Chapter 7** to ensure consistency across age groups. The implication of applying cut-points that were developed based on healthy populations to those with CF was theorised in **Chapters 4 and 5** and empirically tested in **Chapter 6**. Specifically, generic cut-points underestimated PA in those with CF in comparison with their healthy counterparts given the exercise intolerance and consequent elevated metabolic demands associated with the condition (Bell et al., 2001).

A key strength of the thesis was the development and validation of CF-specific machine learning algorithms to classify activity types and intensities in **Chapter 8**. Indeed, Freedson et al. (2012) recommended the use of machine learning with raw acceleration data to estimate PA in order to reduce misclassification and prediction error. In accord, **Chapter 8** developed algorithms from time-domain features extracted from the raw acceleration signal to recognise PA intensities in CF. Nonetheless, **Chapter 8** did not include frequency-domain features, which consequently limits inter-study comparisons. Despite this, Montoye, Bradford, et al.

(2018) showed that the inclusion of frequency-domain features can lead to overfitting, in addition to not improving the overall accuracy of the predictions. It is also noteworthy that **Chapter 7** did not assess the impact of different data processing choices, such as windowing techniques and filtering approaches, which have been shown to affect PA predictions (Allahbakhshi et al., 2019; Preece et al., 2009). Finally, given the protocol design, it was not feasible to develop a model or cut-point to classify sleep in **Chapters 5 and 8**. This is a particularly important limitation given the importance of considering the interaction across all movement behaviours demonstrated in **Chapter 7**. In accordance, PA guidelines have recently adopted a 24-hour design to account for the interaction between movement behaviours including PA, SED and sleep (Kuzik et al., 2017; Waters et al., 2017; WHO, 2020). Therefore, future research should fully support the development of more efficient approaches to evaluate sleep in children and adolescents with CF.

9.3 Recommendations for Future Research

9.3.1 Informed Decisions for Designing a Calibration Protocol in Cystic Fibrosis

Chapter 4 made several recommendations for future research calibrating accelerometry in paediatric clinical populations. Essentially, a calibration protocol in children with chronic conditions should include a broad range of activities seeking to mimic daily-life whilst accounting for condition-specific factors, such as exercise intolerance and altered physiological response to exercise. Therefore, it is imperative to adopt a physiological reference criterion, such as EE, to label the accelerometer data. Also, **Chapters 4 and 5** reinforced the importance of individually estimating RMR in children with CF to account for possible pathophysiological alterations from pulmonary impairment and increased cost of breathing. Congruent with McMurray et al. (2015), **Chapters 4 and 5** indicated that disease-specific cut-points in children with chronic conditions should be developed with a precise measurement of RMR and oxygen uptake to account for pathological alterations. Moreover, findings from the systematic search performed in **Chapter 4** indicated that the statistical approach adopted to generate the cut-points impacts the accuracy of the classification of PA. Specifically, the least recommended approach for accelerometry calibration is linear regression, with the most desirable being the use of machine learning algorithms. The use of

approaches such as receiver operator curve (ROC) and mixed modelling regression might also provide alternatives for developing cut-points and have been successfully utilised in paediatric clinical cohorts (McGarty AM, 2016; Stephens et al., 2016).

The cross-validation of cut-points, to ensure the validity and generalisability, is important for future research calibrating accelerometry in paediatric clinical cohorts. This recommendation is akin to previous work by Welk (2005), suggesting that cross-validation should be performed using a different set of activities and participants than those from which the cut-points were derived. **Chapter 4** also demonstrated that, when working with smaller samples, the use of a leave-one-out cross-validation is also appropriate and reduces the participant burden. Despite this, amongst the most recent research developing raw accelerometry thresholds (Aittasalo et al., 2015; Hildebrand et al., 2014; Hurter et al., 2018), only one (Hildebrand et al., 2014) performed a cross-validation. Therefore, future research should ensure a cross-validation strategy is incorporated within their protocol to verify the applicability of their outcomes. Another important addition to the calibration protocol is the use of a measure of agreement, such as Kappa score or Bland-Altman plots (Bland & Altman, 1986). Finally, **Chapter 4** recommends that, in addition to the cross-validation, all disease-specific cut-points should be compared against a healthy matched control group. Specifically, this practice is essential to ensure that any apparent cut-point discrepancies are associated with pathophysiological alterations.

9.3.2 Recommendations for the Measurement of Physical Activity in Children and Adolescents with Cystic Fibrosis

The findings from **Chapter 6** clearly illustrate the importance of using a condition-specific approach when evaluating PA in a CF population, with the use of a generic cut-point significantly underestimating SED and MVPA in these populations. Therefore, **Chapter 5** provided CF-specific cut-points that can be used in future research estimating PA levels in CF, subsequently minimising PA misclassification. There is increasing recognition regarding the impact of the choice of data processing, study design and statistical methods on the accuracy of PA measurement and the relationship with health in clinical populations (Arvidsson, Fridolfsson, & Börjesson, 2019). Therefore, **Chapter 5** generated CF-specific cut-points from two different raw acceleration metrics for three placements from two accelerometer brands.

This strategy not only ensured comparability across different accelerometer placements and brands, but provides future research with a broad range of options for the measurement of PA in children and adolescents with CF. No recommendations were made regarding the optimal acceleration brand given that both accelerometers utilised (GENEActiv and ActiGraph GT9X) performed equally well in both CF and healthy participants. Although waist-worn accelerometer cut-points were developed for the ActiGraph GT9X, future studies assessing PA levels in CF are advised to adopt the non-dominant wrist placement in order to maintain consistency and allow inter-study comparisons across clinical and healthy populations. Indeed, wrist-worn accelerometers have become increasingly popular for the assessment of PA given the higher compliance achieved with this placement (Fairclough et al., 2016) and following the recent integration of 24-hour protocols in PA assessments. In addition, in contrast to hip-worn monitors, wrist-worn accelerometers were shown to provide valid measures of sleep against the gold standard for sleep assessment (i.e. polysomnography; Full et al., 2018).

Whilst the development of condition-specific cut-points is fundamental for the perpetuation of PA research in CF, this approach is not without limitations (Freedson et al., 2005). Alternatively, the use of machine learning algorithms to classify PA has been highly recommended due to its ability to generate highly accurate predictions (Freedson et al., 2012; Freedson et al., 2005). As such, **Chapter 8** machine learning models were developed for different accelerometer brand and placements, and therefore, allowing for higher applicability and comparison. Future research measuring PA levels in paediatric populations with CF are recommended to use raw acceleration data with machine learning algorithms to enhance prediction accuracy. Finally, and most importantly, the models developed in **Chapter 8** can be employed by studies measuring PA, and ultimately, elucidate the association between PA and health in those with and without CF.

9.3.3 Physical Activity Guidelines for those with Cystic Fibrosis

This thesis was centred around investigating and developing new approaches to improve PA predictions in CF. Essentially, the precise measurement of PA in CF is fundamental to inform PA guidelines and interventions specifically tailored to the condition. For example, the development (**Chapter 5**) and application of a CF-specific cut-point (**Chapter 4**) suggests that previous research may have underestimated PA levels in paediatric

CF populations, and consequently questions previously identified associations between PA levels and lung function in those with CF. Most importantly, the findings of **Chapter 4** suggest that the current guidelines might need to be revisited in order to elucidate the PA levels associated with health benefits in those with CF (Department of Health and Social Care, 2019; WHO, 2015). Indeed, Williams and Stevens (2013) questioned the applicability of the PA guidelines previously developed for healthy populations to those with CF. Williams and Stevens (2013) also highlighted the scarcity of evidence to support the creation of CF-specific PA recommendations in paediatric CF populations. Specifically, more research is warranted to elucidate the optimal PA duration and intensity to elicit health benefits in children and adolescents with CF. It is noteworthy that the pattern of how PA is accumulated seems to be more closely related to health outcomes than absolute PA levels (Mark & Janssen, 2009; Stone et al., 2009), and therefore, should also be considered when tailoring CF-specific PA interventions and recommendations. More specifically, PA is accumulated in bouts of different frequencies, durations and intensities (Tremblay et al., 2017), and it varies across the age spectrum, with children displaying more intermittent and sporadic bouts than adults (Pangrazi, 2000). Whilst investigating PA patterns in healthy children, Willis et al. (2015) found that the accumulation of higher percentage of short and medium-to-short bouts of MVPA was associated with better outcomes. Despite this, the investigation of how those with CF accrue their PA patterns and associated implications to health outcomes is a key gap in our understanding that needs to be addressed by future research. Finally, there is increasing recognition regarding the importance of integrating all movement behaviours, with recent PA guidelines tailored over a 24-hour period in healthy children (Kuzik et al., 2017; Waters et al., 2017; WHO, 2020). Similar guidance would be extremely useful to those with CF given the vital implications of PA and sleep on health in this population. As such, this thesis developed a compositional framework to analyse the impact of the interaction between movement behaviours (sleep, SED, LPA and MVPA) on lung function.

9.3.4 Impact of Physical Activity for Health in Cystic Fibrosis and Associated Factors

In addition to drawing recommendations regarding the approaches utilised to measure PA, this thesis also investigated how we analyse PA data in people with CF. As a result, a key recommendation from **Chapter 7** is that future research investigating the relationship between

PA and lung function should account for all PA intensities, sleep and SED. Specifically, future interventions aiming to increase lung function should consider targeting an increase of 30 minutes MVPA, with time displaced from SED and LPA, and 30 minutes increase in sleep, with time displaced from any other behaviour. In addition, **Chapter 7** suggested that replacing SED with LPA can be a promising strategy to maintain, and/or increase, lung function, though future research is warranted to verify this. Notably, Mackintosh et al. (2018) also acknowledged the potential of LPA for designing effective strategies to increase PA, and thereby lung function. Although previous research corroborated some of these findings (Cox et al., 2016), no guidance was available regarding the important interaction between all movement behaviours and their effect on lung function. Alternatively, **Chapter 7** elucidated the importance of maintaining elevated MVPA and LPA levels and reduced SED, given their asymmetric relationship with lung function. As such, alterations in MVPA, LPA and SED did not elicit the same magnitude of change in lung function when the reallocation was reversed. Whilst previous studies have also demonstrated the asymmetrical relationship between PA intensities and SED with other outcomes (Biddle et al., 2018; Štefelová et al., 2018; Swindell et al., 2020; Tlučáková et al., 2020), **Chapter 7** was the first to demonstrate a symmetrical relationship between sleep and lung function for most PA reallocations. Recent research has suggested that sleep disorders are associated with exercise intolerance, increased SED and elevated morbidity in CF (Barbosa, Coelho, et al., 2020; Barbosa, Liberato, et al., 2020). In accord, this thesis demonstrated the crucial role of sleep for lung function, with time displaced from sleep to any other behaviour costing up to 3.6% $FEV_1\%_{predicted.}$ Therefore, sleep should be acknowledged as an important component of movement behaviours with valuable impact on lung function.

9.3.5 Final Recommendations and Future Research Directions

This thesis highlighted factors such as age, sex, maturity and genotype as areas for careful consideration in future studies investigating PA levels and associated health outcomes in children and adolescents with CF. It is well known that lung function decreases with age and is dependent on sex, with females showing steeper declines annually (De Boeck & Zolin, 2017; Liou et al., 2010). In agreement, **Chapters 6 and 8** demonstrated that age was associated with all movement behaviours and their relationship with lung function. Interestingly, **Chapter 7** found that, in comparison to children and adolescents, adults with CF had higher magnitudes

of change, irrespective of direction, with the reallocation of different behaviours. It is pertinent to note that the relationship between MVPA and lung function was only evident after stratifying by age, sex and genotype, illustrating the need to account for such factors in future research. Of importance, females with CF are expected to live approximately 4 years less than their male counterparts, even after adjusting by CF-related comorbidities (Harness-Brumley et al., 2014; Keogh & Stanojevic, 2018). It is noteworthy that girls with CF are significantly less active than their male peers (Selvadurai et al., 2004), which appears to track into adulthood (Savi, Di Paolo, et al., 2015). Indeed, this lower survival rate in females has been attributed to the disparity in PA levels between males and females (Schneiderman-Walker et al., 2005). This suggests that future research should implement sex-specific interventions and strategies to counteract or/and slow the rate annual decline in $FEV_1\%_{predicted}$, which is particularly important during early adulthood (De Boeck & Zolin, 2017; Liou et al., 2010). Despite this, it is important to acknowledge the importance of focussing on biological, rather than chronological age. The increase in biological age is associated with a reduction in PA in healthy populations, irrespective of sex (Bacil et al., 2015), whereas in CF this association was only observed in girls (Selvadurai et al., 2004). This finding might explain, at least in part, the increased rate of pulmonary exacerbations in female post-puberty, compared to their male counterparts (Sutton et al., 2014). Finally, sex hormones, such as oestrogen and progesterone, which have been shown to play a vital role in widening the gender disparities in CF post-puberty, cannot be ignored (Sutton et al., 2014). Future research should therefore investigate the effect of biological age on PA, and consequently lung function, to enhance CF treatment and survival.

The challenges associated with assessing PA and informing strategies and recommendations in a condition with broad clinical variability, such as CF, cannot be underestimated. This condition can be originated from more than 2,000 mutations generating a broad range of clinical manifestations varying in severity (de Gracia et al., 2005). Indeed, **Chapter 7** demonstrated that males heterozygous for *ΔF508* mutation had significantly higher $FEV_1\%_{predicted}$, in addition to showing a higher increase in lung function with the PA reallocations than homozygous participants. Despite this, it is important to acknowledge that male heterozygous participants also showed the worst estimated decline in lung function when the PA reallocations were inverted. Most importantly, heterozygous for *ΔF508* mutation were shown to have worst aerobic capacity, anaerobic power and BMI (Selvadurai et al., 2002), and develop more severe lung disease than those with homozygous mutations (Geborek & Hjelte, 2011). Therefore, future studies are advised to further investigate the impact of PA

accumulation to health outcomes in heterozygous in order to promote strategies to delay the rapid decline in $FEV_1\%_{predicted}$ observed in this group (Dahl et al., 2001).

It is important to highlight that some of the breakthrough drug therapies developed to treat CF to date are genotype-specific (Thursfield & Jane, 2013). Therefore, we can expect an even larger gap across disease severities in individuals with CF, which will require careful investigation prior to the formulation of population-specific PA guidelines. For example, the triple-combination therapy *Kaftrio* (tezacaftor*elexacaftor* ivacaftor) is only currently available in those older than 12 years with at least one *ΔF508* mutation. Despite this, the development of the triple-combination therapy represents a monumental advancement in the treatment of CF with significant improvements in $FEV_1\%_{predicted}$ and quality of life (Heijerman et al., 2019; Ridley & Condren, 2020). Specifically, robust randomised controlled clinical trials demonstrated that the treatment with *Kaftrio* improved $FEV_1\%_{predicted}$ in 10% in homozygous (Ridley & Condren, 2020) and 14% in heterozygous (Middleton et al., 2019). To highlight the significance of this achievement, such increments in lung function have resulted in the removal of CF patients from the lung transplant list (Volkova et al., 2020). Of importance, the prolonged use of the *Kaftrio* is likely to have an impact on the survival rates in CF. In particular, comorbidities associated with lifestyle, such as cardiometabolic conditions, that were not commonly encountered in those with CF might start to arise in this population. Given the pathophysiological alterations, people with CF are already prone to the development of associated comorbidities including, cardiopathies, osteoporosis and cystic fibrosis related diabetes. Most importantly, regular PA is associated with a reduced risk of developing noncommunicable diseases (Anderson & Durstine, 2019) and is key to prevent the genesis of multi-comorbidities in people with CF. Finally, future PA interventions should focus on adopting methods to increase adherence, such as using remote-based approaches, in order to ultimately integrate regular PA into CF routine care.

9.4 Final Conclusions

This thesis investigated and developed novel approaches to measure and analyse PA in children and adolescents with CF. The results from **Chapter 4** informed and consolidated the methodology applied in **Chapters 5 and 8**, to develop CF-specific cut-points and machine learning algorithms, respectively, to assess PA. Notably, findings from **Chapter 6** corroborated the need for CF-specific cut-points, with the significant misclassification of PA in children and

adolescents with CF when generic thresholds were used. It was also highlighted that sex and day type were key factors determining PA levels in this population. The compositional framework adopted in **Chapter 7** to account for the interaction between PA behaviours highlighted the potential for PA to delay disease progression across the lifespan in CF, highlighting that 30 minutes displaced to MVPA (from SED and LPA) and to sleep (from all movement behaviours) was associated with up of up to 2.1% and 3.6% in $FEV_1\%_{predicted}$, respectively. Overall, the findings of **Chapters 4 to 8** provide a foundation for future research seeking to design PA interventions and clinical guidelines. Future studies are advised to adopt condition-specific approaches to assess PA in CF and to account for the relative nature of movement behaviours when drawing associations with health outcomes. Additionally, PA interventions in CF should consider the differences in how boys and girls accrue their PA levels during the week and weekend days whilst targeting to increase sleep with time reallocated from all behaviours and MVPA from time spent sedentary and on LPA. Finally, it is noteworthy that PA plays a pivotal role in the lifelong health of people with CF, and it is one of the few lifestyle factors which relevance is not likely to be surpassed with the advent of *Kaftrio*.

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Appendices

Appendix A: Calibration and Validation of Accelerometry to Measure Physical Activity in Adult Clinical Groups: A Systematic Review

1.1 Introduction

Physical activity (PA) is defined as any bodily movement that requires an energy expenditure above resting (Caspersen et al., 1985). Regular PA has been associated with the prevention and treatment of a range of diseases, such as cardiovascular disease (Li et al., 2013), type II diabetes (Colberg et al., 2010), osteoporosis (McMillan et al., 2017; Senderovich et al., 2017) and breast cancer (Goncalves et al., 2014). However, 31% of adults are inactive, making physical inactivity a major international public health concern (Hallal et al., 2012).

Although accelerometers are capable of measuring raw acceleration at high sampling frequencies, the majority of studies rely on cut-points to classify PA intensities. Consequently, a growing body of calibration studies has led to a range of cut-points to classify PA intensities in adults (Freedson et al., 1998; Troiano et al., 2008), with little consensus as to the optimal cut-points or their applicability to populations other than those in which they were developed. Indeed, inter-study comparisons and cut-point generalisability are limited by a lack of standardisation of methodologies. Specifically, considerable variation in calibration protocols has arisen due, at least in part, to the progression from uniaxial to triaxial accelerometry, the growing range of accelerometer models available and the broad range of configuration options (e.g., epoch, frequency). Furthermore, inter-study discrepancies in moderate-to-vigorous physical activity (MVPA) cut-points may also be attributable to variations in the criterion measures adopted and to the specific calibration protocol utilised; calibration protocols may range from a laboratory-based treadmill or walking protocol (Freedson et al., 2011) to a field-based protocol (Payey et al., 2017), or a combination of both (Midorikawa et al., 2017). Finally, the statistical approach used to translate activity counts into thresholds aligned with the criterion varies considerably between studies, with little evidence currently available regarding the comparability of different statistical methods.

A key question that remains to be addressed is the applicability of current calibration protocols to clinical populations. Specifically, physiological and biomechanical differences, common in many chronic conditions such as Chronic Obstructive Pulmonary Disease and Parkinson's Disease (PD), may result in a higher cost of breathing or daily living activities and altered resting metabolic rate (RMR) demands (Bell et al., 1996; Goldstein et al., 1987; Levi et al., 1990; Psota & Chen, 2013; Sandroff, Klaren, et al., 2014; Serra et al., 2016). Subsequently, cut-points developed for healthy populations are unlikely to appropriately reflect the activity levels of those with such diseases (McGinley et al., 2015; Serra et al., 2017) and population-specific cut-points, accounting for condition-specific energy expenditure (EE), are warranted. For example, applying cut-points developed on healthy populations was shown to be inappropriate for some clinical conditions, such as chronic stroke (Serra et al., 2017) and type II diabetes (McGinley et al., 2015). However, whilst accelerometry seems to be valid for some clinical conditions (Clarke, 2016), the development of population-specific cut-points was shown to improve the accuracy of the PA measurement in multiple sclerosis (MS) and in obese populations (Valenti et al., 2014). Given this lack of consensus, a synthesis of currently available cut-points, and calibration protocols, in clinical populations could afford valuable information for future clinical physical activity research.

Therefore, the aim of this systematic review was to describe current protocols utilised for the calibration of accelerometry to estimate MVPA thresholds for adult clinical populations. Secondly, the purpose was to provide recommendations for future studies seeking to calibrate accelerometers for clinical conditions in adults.

2.1 Methods

This review was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis statement (Liberati et al., 2009; Moher et al., 2015), and registered on the International Prospective Register of Systematic Review (PROSPERO registration ID: CRD42016053880).

2.1.1 Search Methods

The search was performed between March and July 2017 using six databases (PubMed, SPORTDiscus, ScienceDirect, Scopus, ISI Web of Knowledge, Wiley Online Library). Further details regarding the full search can be found on the Appendix C. The protocol was revised by an experienced librarian and a pilot was performed to assure feasibility. The search terms were in accordance with the 2017 Medical Subject Headings and were inserted as keywords to all the databases as follows: acceleromet*; acceleromet* AND (validation OR calibration); acceleromet* AND physical activity; wearable monitors AND (calibration OR validation); physical activity AND (calibration OR validation); acceleromet* thresholds; acceleromet* (cut-points OR cut-points); energy expenditure AND acceleromet*; and classification AND physical activity intensities. To check for any further studies meeting the inclusion criteria, the reference list of all the included studies and any systematic reviews on a similar topic were examined.

2.1.2 Eligibility Criteria

In order to be included, studies needed to be published in or after the year 2000 in English and generate MVPA cut-points for accelerometry in adults with any chronic clinical condition. Chronic conditions were considered any long-term disease with slow progression (Goodman et al., 2013). Book chapters, theses, monographs, dissertations, abstracts, non-human, unpublished and non-English studies were not included. Studies using accelerometers associated with other technologies (e.g. microcontroller), calibrating for healthy population, sedentary behaviour or conditions that required a dispositive for gait (e.g. wheelchair), were excluded.

2.1.3 Data Extraction and Management

Following the creation of an EndNote X7 (Clarivate Analytics, US) database of potential studies, the lead author screened all the studies based on their titles and abstracts. Where any discrepancies on paper inclusion arose, a second author was available to consult to reach a consensus. All full texts were subsequently independently screened by two authors (MAM and KAM) according to the pre-established criteria. Studies that generated more than

one MVPA cut-point were analysed as separate studies since protocols using multiple accelerometers or calibrations in different populations (e.g., different diseases) might lead to different MVPA thresholds. Supplementary information for each study was consulted when available or necessary for data extraction. No additional data was provided after consulting the authors. Data was extracted by the first author (MSB) and cross-checked by two co-authors (KAM and MAM). Further details of the data extraction are presented in Table A1. The risk of bias in individual studies was assessed by two authors (MSB and MAM), independently, using a checklist that was specifically tailored for calibration of accelerometry protocols (Table A2) based on previous literature (Freedson et al., 2005; Lyden et al., 2014; Welk, 2005). This checklist rates studies as good, fair or poor for six elements of the calibration protocol (sample characteristics, accelerometry settings, criterion, statistical approach for calibration, and statistical approach for validation). Studies scoring poor for all the sections were excluded in order to prevent potentially biased and skewed results (Kane et al., 2017). Inter-rater reliability was determined by using Kappa scores and 0.8 was the minimum acceptable inter-rater agreement (McHugh, 2012). Following the risk assessment, all three authors discussed any discrepancies until a consensus had been reached.

Table A1 Summary of the Data Extracted from the Included Studies

Data extraction field	**Information extracted**
Context and participants	The author, year and sample size of the study; participant characteristics such as, age, health status, height, weight, BMI, ethnicity; and covariates measured such as, self-report questionnaire data, health scales related to disease assessments were extracted.

Study design and methods used	Any information related to the accelerometer, such as accelerometer model (e.g., number of axes); accelerometer placement (e.g., wrist [dominant/non-dominant], hip, chest); accelerometer settings (e.g., epoch, sampling frequency, use of low frequency filter); and data processing decisions (e.g., wear-time criteria) were extracted. Additionally, any information related to the calibration protocol, such as protocol design (e.g., laboratory-based, field-based, daily-life protocol); duration of the protocol; adjustment of specific variables (e.g., age, body mass); performance of individual calibration; criterion anchoring (e.g., energy expenditure, direct observation, heart rate); resting metabolic rate assessment; statistical approach (e.g., ROC-curve analyses, linear regression, machine learning); validation method (e.g., validation, cross-validation leave-one-out, cross-validation *k*-fold); and assessment for agreement (e.g., Kappa, Bland-Altman) were also extracted.
Findings	The extracted outcomes were protocol design and cut-points. All the extracted protocols were classified in four categories: laboratory-based (walking or running, over-ground or on a treadmill), free-living (assessment of participant routine), daily-life (daily-life activities performed at the research site) and mixed (at least two of laboratory-based, free-living and daily-life) protocols.
Quality of the study	Checklist rating for performing calibration for accelerometry in clinical adult population.

Table A2 Guideline Rating for Performing Calibration for Accelerometry in Clinical Adult Population (checklist)

Standard	Poor	Fair	Good
1. Sample Characteristics	Calibration study that do not provide any descriptive variables other than age and sex.	Calibration study that assess descriptive variables such as height, weight, body mass index and specific to the clinical condition.	Calibration study that assess descriptive variables such as height, weight, body mass index, ethnicity, resting metabolic rate and specific to the clinical condition.
2. Accelerometry Settings	Study just describes the accelerometer model.	Study describes the accelerometer model, number of axes and placement.	Study describes the accelerometer model, number of axes, placement, wear-time criteria (in case of free-living protocols), sampling frequency, epoch length and filtering procedures.
3. Protocol Design	Study performs the calibration using a laboratory-based protocol composed only by walking or treadmill test.	Study uses a mixed protocol combining daily-life activities with a laboratory protocol test on a treadmill.	Study uses a mixed protocol combining daily-life activities with a laboratory protocol test on a treadmill and free-living assessments.
4. Criterion	Uses speed or direct observation to anchor the accelerometer counts.	Uses heart rate or metabolic equivalent to anchor the accelerometer counts.	Uses energy expenditure measures, considering resting metabolic rate* estimation, to anchor the accelerometer counts.
5. Statistical Approach for Calibration	Study uses group linear regression or Individual linear regression to develop the cut-points.	Study uses ROC curve analyses to develop the cut-points.	Study uses machine learning techniques, hierarchical models or multilevel modelling, adjusting for factors related to participants characteristics and to the pathophysiology of the clinical condition to develop the cut-point.
6. Statistical Approach for Validation	Study do not perform a validation of the cut-points.	Study performs a leave-one-out cross-validation of the cut-points and agreement assessment using Bland-Altman or kappa score.	Study performs a *k*-fold cross-validation using different samples and activities, determine agreement assessment using Bland-Altman or Kapa score, and estimates the intra-class correlation coefficient, and / or limits of agreement.

ROC: receiver operating characteristic. *The criteria for a valid resting metabolic rate estimation was a minimum of 15 min of steady state, preferably adopting the formula of de Weir (Weir, 1948)

A narrative synthesis was performed covering each area of the protocol design: participant information; inclusion of disease-specific factors; accelerometer model and settings; protocol design; criterion; statistical approach for generating and validating cut-points and MVPA cut-points.

3.1 Results

A total of 543,741 titles were identified from all databases, with 540,630 titles remaining after the removal of duplicates. Subsequently, the main author applied the eligibility criteria to all 540,630 titles and abstracts, which resulted in 619 articles remaining for full-text assessment. In total, 608 studies were excluded, primarily due the inclusion of healthy populations (279 studies), resulting in 11 studies involving a total of 488 participants aged 24 to 73 years being included in this review. Descriptive characteristics of the study samples are provided in Table A3. Twenty-three disease-specific MVPA thresholds for six different clinical conditions were identified. For the final synthesis, the six clinical conditions were stratified into either metabolic (n = 4; obesity, type II diabetes mellitus) or neuromusculoskeletal diseases (n = 7; MS, PD, down syndrome, chronic stroke).

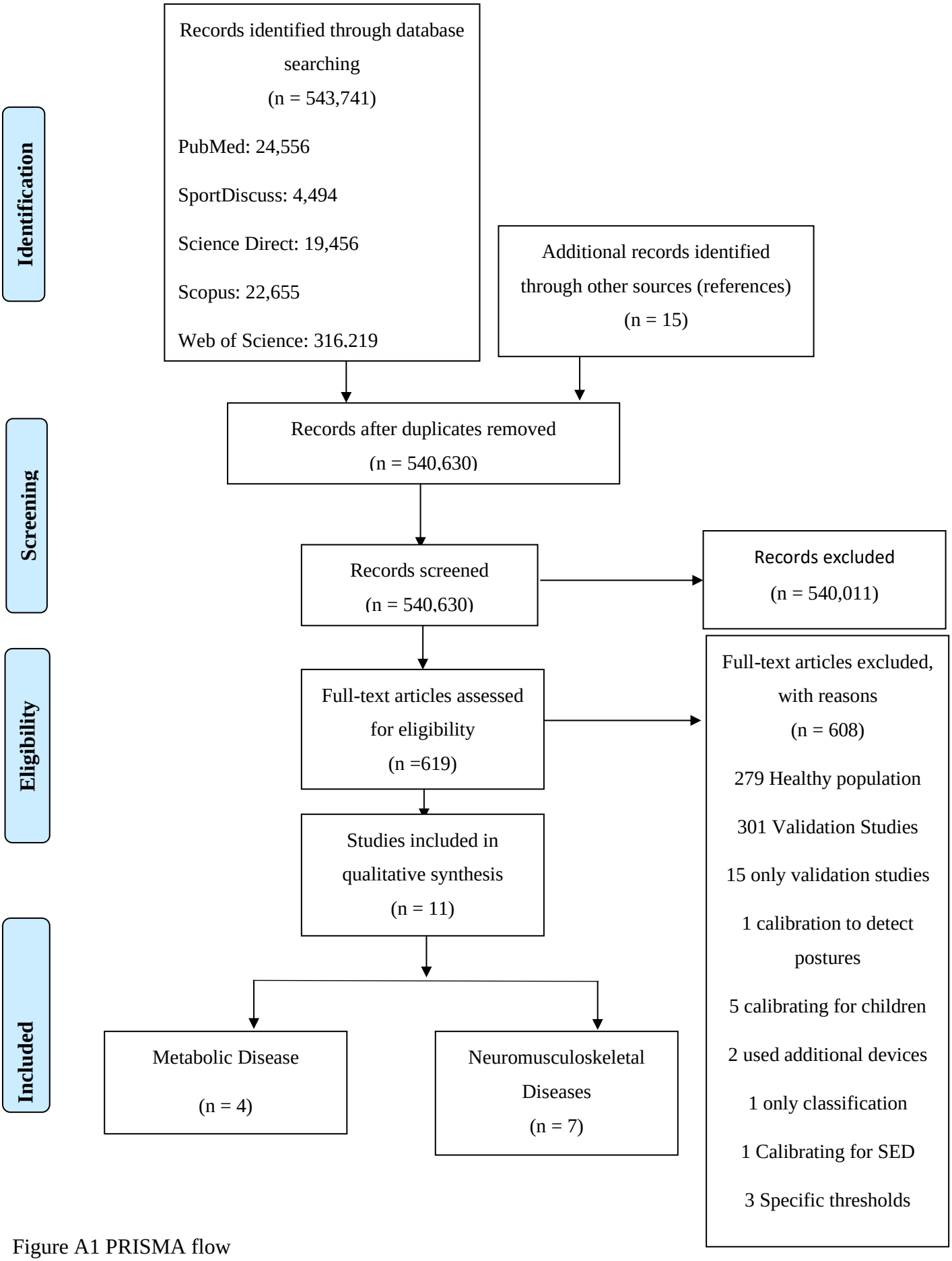


Figure A1 PRISMA flow

Table A3 Summary of the Included Studies Characteristics

Studies	**Participants**	**Accelerometer**	**Calibration Protocol**	**Statistical Approach**	**Outcome**
Author, year	***Sample size (n)*** ***Sex (male/female)*** ***Health status*** ***Control Group*** ***Age (range or mean ± SD)*** ***Height (mean ± SD)*** ***Weight (range or mean ± SD)*** ***BMI (range or mean ± SD)*** ***Ethnicity*** ***Covariates***	***Device Model*** ***Number of axes*** ***Placement*** ***Sampling frequency*** ***Filter*** ***Epoch*** ***Monitoring period*** ***Wear-time***	***Physiological/ Observational*** ***EE estimation*** ***RMR estimation*** ***Individual calibration*** ***Protocol type*** ***Duration***	***Calibration*** ***Validation*** ***Agreement***	***Cut-Points***
Molt et al., 2009	n = 48 40 females and 8 males Multiple Sclerosis (n = 24) Control (n = 24) 43.5 ± 12.2 years 167.0 ± 11.6 cm 76.7 ±19.2 kg Demographic scale Patient Determined Disease Steps Scale	ActiGraph Uniaxial Right hip Epoch: 30-s	Physiological: $\dot{V}O_2$ RMR: 3.5 $ml.kg^{-1}$ Individual calibration: no Protocol type: laboratory Duration: 30 min	Calibration: linear regression Validation: none Agreement: none	Cut-points ($counts \cdot min^{-1}$): Multiple Sclerosis: LPA: < 591 MPA: 591-6,460 VPA: > 6,460 Control: LPA: < 1,289 MPA: 1,289-7,694 VPA: > 7,694

Lopes et al., 2009	n = 26 15 females and 11 males Overweight/obese/ Type 2 Diabetes Mellitus Control = no 62.6 ± 6.5 years *Calibration group (n: 14):* Male: 168.07 ± 5.18 cm Female: 151.49 ± 8.54 cm Male: 80.32 ± 7.21 kg Female: 77.05 ± 21.03 kg 31 ± 5.17 $kg \cdot m^{-2}$ Obese: 57.1% Overweight: 42.9 % Caucasians HBA1c: 7.2 ± 1.8 % Insulin: 9.6 ± 4.41 $mg \cdot dL^{-1}$ HOMA-IR: 1.59 ± 0.71 *Validation group (n = 12):* Male: 162.63 ± 3.54 cm Female: 155.1 ± 7.99 cm Male: 75.9 ± 16.03 kg Female: 72.19 ± 17.58 kg 29.33 ± 4.85 $kg \cdot m^{-2}$ Obese: 41.7 % Overweight: 58.3 %	ActiGraph Right hip Epoch: 60-s	Physiological: $\dot{V}O_2$ and HR RMR: 15 min rest Individual calibration: none Protocol type: laboratory Duration: 30 min	Calibration: Hierarchal Model for equation and ROC for cut-points Validation: cross-validation for the regression Agreement: concordance correlation coefficient	Cut-points ($counts \cdot min^{-1}$): SED / LPA: 200 LPA / MPA: 1,240 MPA / VPA: 2,400

	Caucasians HBA1c: 7.34 ± 1.81 % Insulin: 9.25 ± 4.47 $mg \cdot dL^{-1}$ HOMA-IR: 1.53 ± 0.72				
Weikert et al., 2011	N = 24 20 females and 4 males Multiple Sclerosis Group with gait disability (n = 10) Group without gait disability (n= 14) Control: no 42.0 ±11.7 years 20 Caucasian 18 graduated from college Patient-Determined Disease Steps - 1 (0-4) Multiple Sclerosis Walking Scale	ActiGraph (7164) Uniaxial Waist nondominant hip 10 Hz Epoch: 1-s	Physiological: $\dot{V}O_2$ Individual calibration: none Protocol type: laboratory Duration: 16 min	Calibration: linear regression Validation: none Agreement: none	Cut-points ($counts \cdot min^{-1}$): Overall: MPVA 2371 ± 847 gait disability: 1,886 ± 739 without gait disability: 2,717 ± 763
Aadland and Anderssen, 2012	n = 42 31 females and 11 males Obesity Control: no 43.2 ± 9.2 years 172.2 ± 9.1 cm 118.2 ± 18.2 kg 39.8 ± 5.7 $kg \cdot m^{-2}$	ActiGraph (GT1M) Uniaxial Right hip Normal Filtering Epoch: 10-s	Physiological: $\dot{V}O_2$ and HR RMR: 1 h fast – 10 min in rest Individual calibration: yes Protocol type: laboratory Duration: 40 min	Calibration: linear regression, linear mixed model and 1. ROC curve with high sensitivity and specificity and 2. ROC with high accuracy. Validation: cross-validation Agreement: none	Cut-points ($counts \cdot min^{-1}$): Linear regression: 3 METS: 720 Linear mixed model: 3 METS: 612 ROC 1: 3 METS: 1,646 ROC2: 3 METS: 1,310

	Waist circumference: 127.6 ± 13.2 cm				Linear regression: 6 METs: 5,779 Linear mixed model: 6 METs: 4,980 ROC1: 6 METs: 3,061 ROC2: 6 METs: 7,220
Aadland and Steene-Johannessen et al., 2012	n = 42 31 females and 11 males Obesity Control: no 43.2 ± 9.2 years 172.2 ± 9.1 cm 118.2 ± 18.2 kg 39.8 ± 5.7 kg·m^{-2} Waist circumference: 127.6 ± 13.2 cm	ActiGraph (GT1M) Uniaxial Right hip and left hip (n: 22) Normal Filtering Epoch: 10-s	Physiological: $\dot{V}O_2$ and HR RMR: 1 h fast – 10 min in rest Individual calibration: yes Protocol type: laboratory Duration: 40 min	Calibration: Linear regression (individual calibration) and mixed model (group calibration). Validation: none Agreement: Bland-Altman	Cut-points (counts·min^{-1}): Individual calibration: Right hip: MPVA: 1,078 Left hip: MPVA: 1,095
Agiovlasitis et al., 2012	n = 38 21 females and 27 males Control 26.3 ± 5.2 years 171.1 ± 8.2 cm 73.4 ± 22.6 kg 24.9 ± 7.4 kg·m^{-2} n= 17	ActiGraph (7164) Uniaxial Right wrist Epoch: 30-s	Physiological: $\dot{V}O_2$ RMR: 3 h fast – 6 min rest in sitting position. Individual calibration: none Protocol type: laboratory Duration: 30 min	Calibration: multilevel modelling. Validation: none Agreement: Bland-Altman	Cut-points (counts·min^{-1}): Control: self-paced walking: 2,758 ± 1,373 0.5 m/s: 714 ± 279 0.75 m/s: 1036 ± 420; 1 m/s: 1,992 ± 669 1.25 m/s: 2,743 ± 1,140 1.5 m/s: 3,185 ± 1568 3 METs: 1,526

	Down Syndrome 9 females 24.7 ± 6.9 years 154 ± 79 cm 76.9 ± 16.8 kg 32.6 ± 7.7 $kg \cdot m^{-2}$				Down Syndrome: self-paced walking: 2888 ± 1468 0.5 m/s: 862 ± 443 0.75 m/s: 1,712 ± 747 1 m/s: 2,708 ± 1,013 1.25 m/s: 4,052 ± 1862 1.5 m/s: 5,768 ± 2808 3 METs: 1,137 6 METs: 4,525
Giffuni et al., 2012	n = 29 17 females and 12 males Obese / overweight 31.9 ± 9.0 years 169.1 ± 8.3 cm 100.8 ± 23.3 kg 35.2 ± 7.6 $kg \cdot m^{-2}$ VO_2: 29.1 ± 11.5 $ml \cdot kg^{-1} \cdot min^{-1}$ n= 25 Control 13 males 26.1 ± 9.4 years 174.3 ± 8.7 cm 70 ± 10 kg 23 ±2.2 $kg \cdot m^{-2}$ $\dot{V}O_2$: 40.8 ± 10.2 $ml \cdot kg^{-1} \cdot min^{-1}$	Actical Uniaxial Midline of the right tight Epoch: 60-s	Physiological: $\dot{V}O_2$ RMR: 2 min rest Individual calibration: yes Protocol type: laboratory Duration: 45 min	Calibration: Linear regression. Validation: none Agreement: none	Cut-points ($counts \cdot min^{-1}$): Obese: 3 METs: 1,923 6 METs: 4,032 Control: 3MET: 1,726 6MET: 4,117

Sandroff et al., 2012	n = 86 76 females and 10 males Control 46.5 ± 10.0 years 168.5 ± 8.9 cm 75.4 ± 16.2 kg n = 43 Multiple Sclerosis 47.2 ± 9.1 years 168.2 ± 8.3 cm 75.7 ± 19.4 kg Demographic and exercise history questionnaires 7DPAR 26ft GAITRite mat Patient-Determined Steps 12-item MS walking scale	ActiGraph (7164, GT3X) Uniaxial and triaxial Non-dominant hip 30 Hz Epoch: 15-s	Physiological: $\dot{V}O_2$ Individual calibration: yes Protocol type: laboratory Duration: 20 min	Calibration: linear regression Validation: none Agreement: none	Cut-points (counts·min^{-1}): Multiple Sclerosis: MVPA: 1,723 ± 732 Control: MVPA: 2,017 ± 801 *GT3X:* Multiple Sclerosis: MVPA: 1,584 ± 697 Control: 1,950 ± 852
Sandroff et al., 2014b	n = 54 45 females and 9 males Multiple Sclerosis Control: no 50.9 ± 9.2 years 168.3 ± 7.6 cm 82.3 ± 23 kg	ActiGraph (GT3X+) Triaxial Filter: Low frequency extension Epoch: 60-s	Physiological: $\dot{V}O_2$ RMR: 10 – 15 min rest Individual calibration: yes Protocol type: laboratory Duration:	Calibration: individual regression Validation: none Agreement: none	Cut-points (counts·min^{-1}): Vertical axis: Overall sample: MVPA: 1,754 Mild and moderate disability: MVPA: 1,980 Severe disability: MVPA: 1,185

Nero et al., 2016	n = 30 13 females and 17 males Parkinson disease Control: no 73.0 ± 5.4 years 24.6 ± 3.3 kg·m^{-2} Unified Parkinson's Disease Rating Scale part II Freezing of Gait Questionnaire Borg and Perceived Exertion Scale	ActiGraph (GT3X+) Triaxial Waist 30 Hz Filter: normal Epoch: 15-s	Physiological: HR and speeds RMR Individual calibration Protocol type: laboratory Duration: 9 min	Calibration: ROC curve Validation: leave-one-out cross-validation Agreement: Cohen's Kappa	Cut-points (counts·15 s): Vertical Axis: < 1 ms: < 328 > 1.3 m/s: > 730 Vector Magnitude: < 1 ms: < 470 > 1.3 m/s: > 851
Serra et al., 2017	n = 28 10 females and 18 males Chronic Stroke - chronic hemiparetic gait Control: no 60.4 ± 1.6 (47 – 83) years 31.5 ± 1.1 (19-48) kg·m^{-2} 43% Caucasian 56% African-american 6MWT Lean mass (kg)	Actical Uniaxial non-paretic hip	Physiological: $\dot{V}O_2$, HR, karvonen formula (HR reserve). RMR: 10 min rest Individual calibration: none Protocol type: mixed Duration: 60 min	Calibration: Regression analysis Validation: none Agreement: non	Cut-points (counts·min^{-1}): SED/LPA: 125 LPA/MPA: 667 MPA/VPA: 1,546

SED: sedentary time, LPA: light physical activity, MPA: moderate physical activity, VPA: vigorous physical activity, MVPA: moderate to vigorous physical activity, RMR: resting metabolic rate, $\dot{V}O_2$: oxygen uptake, HR: heart rate, ROC: receiver operating characteristic, ROC 1: ROC with best sensitivity and specificity, ROC 2: ROC with best accuracy definition, MET: metabolic equivalent of Task.

Initially the reviewers achieved an inter-rater kappa score of 0.716 for the risk of bias assessment, with the criteria utilised to define RMR as one of the main reasons for disagreement. Subsequently, MSB and MAM resolved discrepancies by discussing each point which resulted in a kappa score of 1. Thus, the criteria to define RMR was specified in the checklist. The majority of the studies had high scores for sample characteristics and accelerometer settings (Table A4), with 5 studies classified as good, five as fair and two as poor for both criteria. Similar results were not found for protocol design, with 10 studies scoring as poor and one as fair. For physiological criterion, 9 studies were classified as fair, 1 as good and 1 as poor. Only two studies scored as good for statistical approach for calibration, with the majority classified as poor (n = 5) and fair (n = 4). Almost all studies were poor (n = 8) for statistical approach for validation, with only 3 studies classified as fair.

Table A4 Checklist Risk of Bias Assessment Results

Study	**Sample Characteristics**	**Accelerometer Settings**	**Protocol Design**	**Criterion**	**Statistical Approach for Calibrations**	**Statistical Approach for Validations**
Molt et al., 2009	Fair	Fair	Poor	Fair	Poor	Poor
Weikert et al., 2011	Poor	Fair	Poor	Fair	Poor	Poor
Sandroff et al., 2012	Good	Good	Poor	Fair	Poor	Poor

Sandroff et al., 2014b	Fair	Good	Poor	Fair	Poor	Poor
Lopes et al., 2009	Good	Poor	Poor	Fair	Fair	Fair
Giffuni et al., 2012	Fair	Fair	Poor	Fair	Fair	Poor
Aadland & Anderseen et al., 2012	Good	Good	Poor	Fair	Good	Fair
Aadland & Steene-Johannessen et al., 2012	Good	Good	Poor	Fair	Fair	Poor
Agiovlasitis et al., 2012	Fair	Fair	Poor	Good	Good	Poor
Nero et al., 2016	Fair	Good	Poor	Poor	Fair	Fair

Serra et al., 201	Good	Fair	Fair	Fair	Poor	Poor

Indirect calorimetry was the most common method (n = 10) used to estimate the physiological criterion (e.g. EE, METs or $\dot{V}O_2$). Covariates were considered by nine studies, five of which utilised disease-specific assessments (e.g., Multiple Sclerosis Walking Scale). Among the studies including covariates, four either included disease-related factors in the analysis or investigated whether the inclusion of those variables would improve the model adopted for calibration. Four studies also included demographic factors in the analysis. Two studies investigated the relationship of the covariates through correlations with accelerometer derived counts·min^{-1}.

3.1.2 Accelerometers

Thresholds were developed for 6 different accelerometers (Table A5); the majority were different models of ActiGraph (n = 9; Aadland & Anderssen, 2012; Aadland & Steene-Johannessen, 2012; Agiovlasitis et al., 2012; Lopes et al., 2009; Motl et al., 2009; Nero et al., 2015; Sandroff et al.; Sandroff, Riskin, et al., 2014; Weikert et al., 2011) with the others using Actical (Giffuni et al., 2012; Serra et al., 2017). Seventeen of the MVPA cut-points were developed using a uniaxial accelerometer and six using a triaxial accelerometer. The hip was the most common placement, adopted by nine studies to develop 22 MVPA cut-points. Nine of the MVPA cut-points were developed with the accelerometer placed on the right hip (Aadland & Anderssen, 2012; Aadland & Steene-Johannessen, 2012; Giffuni et al., 2012; Lopes et al., 2009; Motl et al., 2009), seven on non-dominant hip (Sandroff et al.; Sandroff, Riskin, et al., 2014), one on non-paretic hip (Serra et al., 2017), one on both hips (Aadland & Steene-Johannessen, 2012), two on the left hip (Aadland & Steene-Johannessen, 2012). One study placed the accelerometer on the right wrist (Agiovlasitis et al., 2012) and one did not specify the side (Nero et al., 2015). Reported sampling frequency varied from 10 Hz (Weikert et al., 2011) to 30 Hz (Nero et al., 2015; Sandroff et al.), although eight studies did not report

the sampling frequency used (Aadland & Anderssen, 2012; Aadland & Steene-Johannessen, 2012; Agiovlasitis et al., 2012; Giffuni et al., 2012; Lopes et al., 2009; Motl et al., 2009; Sandroff, Riskin, et al., 2014; Serra et al., 2017). Furthermore, only four studies described how they filtered the accelerometer data, with three (Aadland & Anderssen, 2012; Aadland & Steene-Johannessen, 2012; Nero et al., 2015) using the standard filtering provided by the accelerometer software and one (Sandroff, Riskin, et al., 2014) applying the low-filtering extension provided by ActiLife software. A wide variety of epoch lengths were used to develop the MVPA cut-points, with five studies using 60-s epochs (Giffuni et al., 2012; Lopes et al., 2009; Sandroff, Riskin, et al., 2014; Serra et al., 2017; Weikert et al., 2011), followed by one using 10-s (Aadland & Steene-Johannessen, 2012), two studies using 15-s (Nero et al., 2015; Sandroff et al.) and two using 30-s epochs (Agiovlasitis et al., 2012; Motl et al., 2009). The epoch length was extracted from MVPA cut-point unit (i.e. counts·min^{-1}, counts per 15-s) when not specified in the methodology (Nero et al., 2015).

Table A5 Summary of Accelerometer Models Calibrated in the Included Studies

Name / Model	Manufacturer	Dimensions (Weight and Size)	Memory Capacity	Axis	Frequency Sampling
ActiGraph 7164 (CSA)	ActiGraph LLC Pensacola, FL	45,5g 5.1 x 4.1 x 1.5 cm	22 days of data with 60-s epoch	Uniaxial	10 Hz
GT1M ActiGraph	ActiGraph LLC Pensacola, FL	27g 3.8 x 3.7 x 1.8 cm	378 days using 60-s epoch	Biaxial	30 Hz
ActiGraph GT3X	ActiGraph LLC Pensacola, FL	27g 3.8 x 3.7 x 1.8 cm	378 days using 60-s epoch	Triaxial	30 Hz
ActiGraph GT3X+	ActiGraph LLC Pensacola, FL	19g 4.6 x 3.3 1.5 cm	38 days using 100 Hz	Triaxial	30 – 100 Hz
ActiGraph wGT3X+	ActiGraph LLC Pensacola, FL	19g 4.6 x 3.3 1.5 cm	38 days 100 Hz	Triaxial	30 – 100 Hz
Actical	Mini-Mitter Sunriver, OR	17.5g 2.8 x 2.7 x 1.0 cm	45d using 60-s epoch	Uniaxial	32 z

3.1.3 Calibration Protocol Settings

Laboratory-based protocols were utilised in 10 studies (Aadland & Anderssen, 2012; Aadland & Steene-Johannessen, 2012; Agiovlasitis et al., 2012; Giffuni et al., 2012; Lopes et al., 2009; Motl et al., 2009; Sandroff et al.; Sandroff, Riskin, et al., 2014; Weikert et al., 2011), with only one study (Lopes et al., 2009) applying a mixed protocol. Indirect calorimetry was performed by 10 (Aadland & Anderssen, 2012; Aadland & Steene-Johannessen, 2012; Agiovlasitis et al., 2012; Giffuni et al., 2012; Lopes et al., 2009; Motl et al., 2009; Sandroff et al.; Sandroff, Riskin, et al., 2014; Serra et al., 2017; Weikert et al., 2011) of the studies, with one study (Nero et al., 2015; Serra et al., 2017) using both indirect calorimetry and HR and another using speed (Nero et al., 2015) and the duration of the protocol varied from 9 to 60 minutes. Indirect calorimetry was utilised as the physiological criterion by the majority of studies (n =10). Specifically, six studies derived Metabolic Equivalents of Task (MET) from oxygen uptake ($\dot{V}O_2$), whereas four studies used the $\dot{V}O_2$ itself to determine the relationship with accelerometer counts. Four studies performed an individual calibration (Aadland & Steene-Johannessen, 2012; Giffuni et al., 2012; Sandroff et al.; Sandroff, Riskin, et al., 2014), five performed a group calibration (Lopes et al., 2009; Motl et al., 2009; Nero et al., 2015; Serra et al., 2017; Weikert et al., 2011) and one study performed both (Aadland & Steene-Johannessen, 2012).

3.1.4 Statistical Approach

Linear regression was the most common technique employed to generate eight MVPA cut-points in adult clinical populations (Aadland & Anderssen, 2012; Aadland & Steene-Johannessen, 2012; Motl et al., 2009; Sandroff et al.; Sandroff, Riskin, et al., 2014; Serra et al., 2017; Weikert et al., 2011; Weikert et al., 2012), followed by hierarchical modelling, generating four MVPA cut-points (Aadland & Anderssen, 2012; Aadland & Steene-Johannessen, 2012; Agiovlasitis et al., 2012; Lopes et al., 2009), and receiver operating characteristic (ROC) analysis, developing five MVPA cut-points (Aadland & Anderssen, 2012; Giffuni et al., 2012; Nero et al., 2015). Thus, one study (Aadland & Anderssen, 2012) applied two different ROC models; the first model prioritized higher sensitivity (true positives/total positives) and specificity (true negatives/total negatives), whilst the second model used overall

accuracy (true positives and true negatives/total positives and negatives).Ten studies (Aadland & Anderssen, 2012; Aadland & Steene-Johannessen, 2012; Agiovlasitis et al., 2012; Giffuni et al., 2012; Lopes et al., 2009; Motl et al., 2009; Sandroff et al.; Sandroff, Riskin, et al., 2014; Weikert et al., 2011) did not perform any kind of validation and one performed a leave-one-out cross validation (Nero et al., 2015). Furthermore, most of the studies did not perform any agreement assessment (n = 8) (Aadland & Anderssen, 2012; Aadland & Steene-Johannessen, 2012; Lopes et al., 2009; Motl et al., 2009; Sandroff et al.; Sandroff, Riskin, et al., 2014; Serra et al., 2017; Weikert et al., 2011); one study performed Bland-Altman (Agiovlasitis et al., 2012) and one calculated the Kappa Score (Nero et al., 2015).

3.1.5 Outcome

All the disease-specific MVPA cut-points extracted from the included studies were integrated to a 60-s epoch to allow comparison between thresholds when not available in this format (Table A6). Most studies presented their cut-points in counts·min^{-1}, despite using different epoch lengths for processing the activity counts. Disease-specific cut-points of MVPA varied from a minimum of 612 counts·min^{-1} to a maximum of 6,460 counts·min^{-1}.

Table A6 Summary of Moderate-to-vigorous Disease-specific Cut-points

Disease (n*)	**Study**	**Reason for split**	**Cut-points MVPA (original)**	**Cut-points MVPA converted to counts.min^{-1}[a]**	**Criterion Validity**
	Molt et al., 2009	N/A	6460 (counts.min^{-1})	N/A	N/A
	Weikert et al., 2011	No Gait-disability Group	2717 (counts·min^{-1})	N/A	N/A
	Weikert et al., 2011	Overall Group (gait and non-gait-disability)	2371 (counts·min^{-1})	N/A	N/A
	Weikert et al., 2011	Gait-disability Group	1886 (counts·min^{-1})	N/A	N/A

Multiple Sclerosis **(7)**	Sandroff et al., 2012	ActiGraph 7164	1723 (counts·min^{-1})	N/A	N/A
	Sandroff et al., 2012	ActiGraphGT3X	1584 (counts·min^{-1})	N/A	N/A
	Sandroff et al., 2014b	Overall Group (gait and non-gait-disability)	1745 (counts·min^{-1})	N/A	N/A
	Sandroff et al., 2014b	Gait-disability Group	1185 (counts·min^{-1})	N/A	N/A
	Sandroff et al., 2014b	No Gait-disability Group	1980 (counts·min^{-1})	N/A	N/A
	Lopes et al., 2009	N/A	2400 (counts·min^{-1})	N/A	Concordance Correlation Coefficient: 0.8
	Giffuni et al., 2012	N/A	4032 (counts·min^{-1})	N/A	N/A
	Aadland and Anderssen et al., 2012	ROC 1	1646 (counts·min^{-1})	N/A	N/A
	Aadland and Anderssen et al., 2012	ROC 2	1310 (counts·min^{-1})	N/A	N/A
	Aadland and Steene-Johannessen et al., 2012	Individual Calibration / Linear Regression	1151 (counts·min^{-1})	N/A	Bland-Altman / LOA
Overweight/obesity/ Type 2 Diabetes Mellitus **(10)**	Aadland and Steene-Johannessen et al., 2012	Linear Regression / Left Hip	1095 (counts·min^{-1})	N/A	Bland-Altman / LOA
	Aadland and Steene-Johannessen et al., 2012	Linear Regression / Right Hip	1078 (counts·min^{-1})	N/A	Bland-Altman / LOA
	Aadland and Anderssen et al., 2012	OLR / Right Hip	720 (counts·min^{-1})	N/A	N/A
	Aadland and Anderssen et al., 2012	MIX REG / Left Hip	685 (counts·min^{-1})	N/A	Bland-Altman / LOA

	Aadland and Anderssen et al., 2012	MIX REG / Right Hip	612 (counts·min^{-1})	N/A	N/A
Down Syndrome **(1)**	Agiovlasitis et al., 2012	N/A	1137 (counts·min^{-1})	N/A	Bland-Altman / LOA
	Nero et al., 2016	N/A	730 (counts·15 s^{-1})	2980	Cross-validation: 74% - 64% of agreement; Kappa Score: 0.79 for y axis and kappa score: 0.69 for VM.
Parkinson disease **(2)**					
	Nero et al., 2016		851 (counts·15 s^{-1})	3404	
Chronic Stroke **(1)**	Serra et al., 2017	N/A	1546 (counts·min^{-1})	N/A	N/A

ROC: receiver operating characteristic, ROC 1: Roc with best sensitivity and specificity, ROC 2: ROC with better accuracy definition, OLR: Ordinary Linear Regression, MIX REG: Linear Mixed Model Regression. LOA: limits of agreement

[a]Converted when not available.

4.1 Discussion

In total, 11 studies generating 23 MVPA cut-points in clinical conditions revealed a broad range of MVPA cut-points. Key recommendations for future studies are to include a variety of free-living activities that are applicable to the specific disease-population, of various intensities, and to ensure that a robust measure of EE and precise estimation of RMR are included to account for disease related alterations.

4.1.1 Calibration Protocol for Clinical Populations

Numerous factors should be considered in the development of a calibration protocol for clinical populations, including the inclusion of participant demographics and disease-related factors. Another key consideration in the development of cut-points for clinical populations is the addition of a physiological criterion to the calibration protocol, particularly related to energetic cost. Specifically, some conditions might be associated with an alteration in the daily

total EE. This variation is likely to occur due to many factors, including impaired biomechanics (e.g., neuromusculoskeletal disorders), higher energetic cost of breathing (e.g., respiratory conditions) and disease severity and treatments (e.g., medications; (Bell et al., 1996; Psota & Chen, 2013; Sandroff, Klaren, et al., 2014; Serra et al., 2016). Thus, numerous factors in addition to PA contributes to total EE, such as the thermal effect of food intake and RMR. Indeed, indirect calorimetry was shown to overestimate EE when the RMR was not properly assessed (Fares et al., 2008). Therefore, RMR estimation is highly recommended to avoid bias, particularly as it was shown to be altered in many clinical conditions (Agiovlasitis et al., 2012; Alawad et al., 2013; Gajewski et al., 2017; Mahler et al., 2012; Montaurier et al., 2007; Nawata et al., 2004; Serra et al., 2015; Wens et al., 2014). Alternatively, MET can be used to estimate EE; Serra et al. (Serra et al., 2017) found METs to be the strongest predictor of activity counts, despite explaining only 65% of the accelerometer activity counts. Thus, most of the included studies derived MET values from a measure of oxygen uptake, which arguably would encompass any possible alteration in energetic cost arising from the disease. However, careful consideration must be given when using METs due to the controversial nature of this method and its failure to represent clinical subgroups (McMurray et al., 2014). Indeed, the standard MET value of 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$ was developed based on healthy populations and therefore does not reflect pathological, biomechanical, metabolic and respiratory adaptations which are common in many clinical conditions (Byrne et al., 2005).

4.1.2 Accelerometer Setting and Analysis Description

Whilst hip was the most popular choice among the included studies (Aadland & Anderssen, 2012; Aadland & Steene-Johannessen, 2012; Giffuni et al., 2012; Lopes et al., 2009; Motl et al., 2009; Sandroff et al.; Sandroff, Riskin, et al., 2014; Serra et al., 2017), the best location for monitor placement in clinical populations is unclear. Indeed, comparisons of hip- and wrist-generated thresholds demonstrated great variability which may be explained by biomechanical differences related to dominance (Aadland & Steene-Johannessen, 2012) or functional adaptations due to clinical conditions (Lerner et al., 2014; Ling et al., 2012). For example, in PD, freezing of gait can lead to a rapid trembling in the legs, which would be more efficiently measured by an accelerometer placed on the lower limb (Suzuki et al., 2017). Similarly, other conditions affecting the gait biomechanics might benefit from hip or lower

limb placements, as demonstrated under a free-living protocol for chronic stroke and MS patients (Rand et al., 2009; Sparaco et al., 2018).

The choice of accelerometer settings and signal processing should be described in the calibration protocol to allow comparability between studies and generalisability of the developed cut-points (Brond & Arvidsson, 2016). Nonetheless, five of the included studies did not report the sampling frequency and filtering methods used (Agiovlasitis et al., 2012; Giffuni et al., 2012; Lopes et al., 2009; Motl et al., 2009; Serra et al., 2017). The most popular choice of epoch was 60-s (Giffuni et al., 2012; Lopes et al., 2009; Sandroff et al.; Sandroff, Riskin, et al., 2014; Serra et al., 2017; Weikert et al., 2011), with the majority of studies presenting MVPA in counts·min^{-1}. Alternatively, the choice of 1 or 5-s epochs is appropriate to capture short bursts of activities and could be a suitable choice for free-living protocols or for analyses utilising pattern recognition (Gabriel et al., 2010; Staudenmayer et al., 2009). Whilst counts·min^{-1} are commonly used, the units are somewhat arbitrary and lack direct practical meaning and transparency due to their proprietary nature (Kozey et al. 2011; Sievanan et al. 2017). Indeed, the brand-specific units limit inter-study comparisons. In contrast, the use of raw acceleration signals allow more complex analyses and, consequently, higher prediction accuracy (Montoye, Nelson, et al., 2018).

4.1.3 Protocol Design

The calibration protocols were classified into four categories: laboratory-based protocols that involved walking or running on a treadmill; free-living protocols that assessed participants during their daily routines; daily-life protocols that involved daily-life activities in the laboratory and mixed protocols that utilised more than one of the previously described protocols. A free-living protocol is widely considered the most appropriate for calibration as it determines the relationship between EE and PA in an ecologically valid manner (Mackintosh et al., 2012). Despite that, almost all the studies in the neuromusculoskeletal disease group (Agiovlasitis et al., 2012; Motl et al., 2009; Nero et al., 2015; Sandroff et al.; Sandroff, Riskin, et al., 2014; Weikert et al., 2011) utilised over-ground walking protocols. Likewise, almost all of the studies in metabolic disease populations (Aadland & Anderssen, 2012; Aadland & Steene-Johannessen, 2012; Giffuni et al., 2012; Lopes et al., 2009) performed treadmill walking protocols, with only one study encompassing jogging. A limitation of such walking

protocols is that they are unlikely to provide a fair classification of activities beyond those of locomotion (Crouter et al., 2006). In addition, studies suggest that individuals with chronic stroke and PD are more prone to adopt a different strategy to increase gait speed when walking on the treadmill (Lamontagne et al., 2016; Warlop et al., 2018). During treadmill ambulation, the lack of visual cues and a moving floor results in a cautious gait, with individuals adopting slower speeds and increased stride length compared to overground walking (Lamontagne et al., 2016; Warlop et al., 2018). As such, the use of treadmill to calibrate for such populations may result in a misrepresentation of their gait during daily-life and should be considered with caution. Alternatively, a free-living protocol would be the ideal framework to provide a more ecologically valid measure of PA (Welk, 2005) in clinical populations.

4.1.4 Statistical Approach

The statistical approach adopted to translate activity counts and EE into cut-points could substantially impact the derived thresholds. For example, whilst linear regression has been most widely used (Aadland & Anderssen, 2012; Aadland & Steene-Johannessen, 2012; Motl et al., 2009; Sandroff et al.; Sandroff, Riskin, et al., 2014; Serra et al., 2017; Weikert et al., 2011), it assumes that the relationship between activity counts and metabolic data (i.e. $\dot{V}O_2$, METs) is linear. To address this issue, recent calibration studies have incorporated more flexible statistical methods, such as ROC analysis, hierarchical models, and machine learning (Crouter et al., 2011; Freedson et al., 2005; Montoye et al., 2017). However, in the context of clinical populations, it is pertinent to note that ROC analysis does not allow adjustment for clinical factors and may therefore not be an optimal approach.

Machine learning and pattern recognition have been identified as the optimal methods for classifying PA (Bonomi, Plasqui, et al., 2009; Staudenmayer et al., 2015; Staudenmayer et al., 2009; Welk, 2005). A recent systematic review highlighted the high predictive accuracy of laboratory-calibrated protocols using machine learning models (Farrahi et al., 2019), with Hidden Markov models (Pober et al., 2006), decision trees (Mathie et al., 2004) and artificial neural networks (Staudenmayer et al., 2009) the most common models used to estimate PA from raw acceleration signals. Indeed, the use of such models improved PA prediction, overcoming the inherent limitations of using static epoch lengths (Montoye, Bradford, et al., 2018). Whilst promising, the use of machine learning to estimate PA from raw accelerations is

still in the early phases of development. Specifically, the reproducibility of machine learning approaches in free-living settings requires further investigation (Kerr et al., 2016). Additionally, machine learning models often require considerably sized training data sets, particularly deep learning, which might be a challenge when using indirect calorimetry (Mannini & Sabatini, 2010). Future studies calibrating accelerometry for clinical populations should consider using machine learning in order to achieve higher prediction accuracy and promote advancements in the field. However, it is noteworthy that even complex statistical approaches such as pattern recognition would still require an optimised calibration protocol in order to ensure high prediction accuracy. In addition, other statistical approaches should also be considered, such as probability analysis which has been employed to translate activity counts into PA behavioural data in mental illness patients (Chapman et al., 2017).

Cross-validation establishes the validity of the developed cut-points and verifies that the thresholds are applicable across any participant of similar age and health status to the sample it was generated from. Whilst it is recommended that a cross-validation should be conducted utilising an independent sample and different activities (Welk, 2005), the use of a leave-one-out-approach can also be considered. For example, Nero et al. (2015) used a leave-one-out approach to cross-calibrate the specific PD cut-points. Additionally, a measure of agreement should be performed in addition to a cross validation (Lopes et al., 2009), and the cross-validation should be applied after developing the thresholds and not as a robustness check prior to the analysis (Aadland & Anderssen, 2012). Future studies should continue to cross-validate the disease-specific thresholds to ensure their reliability and validity across different protocols and clinical stages.

4.1.5 Outcome: MVPA Cut-points

Disease-specific cut-points are essential in understanding and promoting PA in clinical populations. The majority of the MVPA cut-points developed for clinical populations were different to those previously developed for healthy adults (Freedson et al., 1998); disease-specific MVPA cut-points varied greatly, from 612 counts·min^{-1} to 6,460 counts·min^{-1}, even within the same condition. Indeed, (Serra et al., 2017) developed Actical MVPA cut-points for stroke patients that were equivalent to LPA cut-points for general population. This large variability can be attributed to the occurrence of gait impairment at advanced stages of the

disease, in addition to differences in treatments and medications. However, a control group is warranted in order to ascertain whether any variation in the cut-points is caused by the pathophysiology of the disease or differences in the calibration protocol. Indeed, whilst a control group is highly beneficial in the interpretation of the findings of each study, cut-points previously established for general populations could be used when necessary to investigate whether the use of the disease-specific cut-points enhances the predictive accuracy (Janssen et al., 2015; Trost et al., 2015).

4.1.6 Strengths and Limitations

It is important to acknowledge that the search protocol was developed with a subject-specific librarian, following a rigorous iterative process. Specifically, initial pilot searches were conducted to assess the feasibility of the initial criteria and search terms. Revisions were subsequently made to the outcomes, risk of bias assessment and final analyses. Moreover, extensive screening was performed by the first author to capture all calibration studies, irrespective of healthy or clinical status, to ensure that no clinical calibration studies were missed. Whilst this review is associated with numerous strengths, there are, nonetheless, limitations. Firstly, only studies generating MVPA cut-points were included; whilst cut-points are still widely used in PA research, major limitations associated with this practice should be acknowledged. The large variability of intensity-related cut-points also occurs among general population (Reilly et al., 2008), causing what Trost et al. (2007) described as the ‘cut-point conundrum’. This discrepancy is multifactorial, arising in part from the lack of standardization of calibration protocols and broad range of statistical approaches applied to reduce accelerometer data to cut-points. It is also important to acknowledge the high risk of bias encountered within the included studies which limits our conclusions. Finally, it is noteworthy that the present recommendations were based on a relatively small range of clinical conditions, further demonstrating the need for more population-specific calibration protocols.

5.1 Conclusion

This systematic review highlights the large variability in MVPA cut-points developed for clinical populations. Indeed, a lack of standardisation in the protocol design, as well as the statistical approach, makes it impossible to compare disease-specific cut-points to those generated for healthy populations. To ensure ecological validity, future calibration protocols should incorporate a large variety of free-living activities, of various intensities, instead of protocols composed predominantly of walking. Moreover, future research should ensure a robust measure of EE is adopted as the criterion measure for accelerometry, as well as a precise estimation of RMR. Studies incorporating a control group and utilising cross-validation of the developed clinical thresholds are warranted. Finally, whilst standardization is necessary, it is highly recommended that future studies consider the pathophysiology of the disease when designing the protocol.

6.1 Practical Implications

- To incorporate the pathophysiology of the disease to the calibration protocol.
- To use a daily-life or free-living protocols mimicking the routine of the participants.
- To include a control group.
- To shift towards machine learning models as a statistical approach.
- To cross-validate the cut-points.

Appendix B: Chapter 4 - Summary of Included Studies Calibrating Accelerometry in Paediatric Clinical Group

Studies	**Participants**	**Accelerometer**	**Calibration Protocol**	**Statistical Approach**	**Outcome**
Author, year	Sample size (n) Health status Control Group Sex (boy/girl) Age (range or mean ± SD) Height (mean ± SD) Weight (range or mean ± SD) BMI (range or mean ± SD) Ethnicity Covariates	Device Model Number of axes Placement Sampling frequency Filter Epoch Sampling duration Wear-time	Physiological/ Observational EE estimation RMR estimation Individual calibration Protocol type Duration	Calibration Validation Agreement	Cut-Points/ Equation
Trost et al. 2015	n = 51 Cerebral Palsy GMFCS I (27) GMFCS II (12) GMFCS III (12) Control: 0 28 girls 12.0 ± 3.0 years 147.0 ± 16.5 cm 46.8 ± 19.0 kg GMFCS	ActiGraph GT3X Triaxial Right hip 30 Hz Epoch: 1-s	Physiological: $\dot{V}O_2$ Resting $\dot{V}O_2$: Schofield Individual calibration: no Protocol type: Mixed – daily-life and walking Duration: 120 min	Calibration: Binary DT Validation: LOOCV Agreement: Kappa and ROC	Cut-points (counts·15 s^{-1}) All levels: LPA: < 72 GMFCS I MVPA: 724 GMFSC II MVPA: 685 GMFCS III MVPA: 669

Ryan et al. 2014	n = 18 Cerebral Palsy Control: no 11.4 ± 3.2 years 147.0 ± 18.5 cm 44.6 ± 16.9 kg BMI: 20 ± 4.5 kg·m^{-2} GMFCS	RT3 Right hip Epoch: 60-s	Physiological: $\dot{V}O_2$ RMR: Oxford equation Individual calibration: none Protocol type: laboratory Duration: 36 min	Calibration: ROC curve Validation: none Agreement: Kappa score	Cut-points (counts·min^{-1}): LPA: 52 MVPA: 689.3
Clanchy et al. 2011	n = 29 Cerebral palsy Control: no 13 girls 12.5 ± 2.0 years 156.6 ± 11.0 cm 47.7 ± 16.1 kg GMFCS	ActiGraph (7164) Uniaxial Least affected hip 10 Hz Epoch: 1-s	Physiological: $\dot{V}O_2$ RMR: Schofield equation Individual calibration: none Protocol type: laboratory Duration: 60 min	Calibration: ROC curve Validation: none Agreement: none	Cut-points (counts·min^{-1}): LPA: 1627.3 MVPA: 2942.1 VPA: 4683.6

McGarty et al. 2016	n = 50 Validation: 36 Intellectual disabilities Control: no 37 girls 9.5 ± 1.1 years 143 ± 0.9 cm 39.33 ± 10.28 kg BMI: 19.9 ± 3.8 kg·m^{-2}	ActiGraph Wgt3X+ Triaxial Right hip 30 Hz Epoch: 10-s	Physiological: Direct Observation Individual calibration: none Protocol type: Daily-life Duration: 45 min	Calibration: ROC Validation: LOOCV Agreement: Kappa score	Cut-points (counts·min^{-1}): VA: SED: 507 MPA: 1008 – 2300 VPA: 2301 MVPA: 1008 VM: SED: 1863 MPA: 2610 – 4214 VPA: 4215 MVPA: 2610
Stephens et al. 2016	n = 195 Control: n = 29 13 girls 13.1 ± 2.8 years 162 ± 16 cm 57.6 ± 20 kg	ActiGraph (7164) and Actical Uniaxial Right hip 10 HZ / 32 Hz Epoch: 15-s	Physiological: $\dot{V}O_2$ and HR RMR: 2 h fasting – 20 min in rest Individual calibration: no Protocol type: Mixed: laboratory and daily-life	Calibration: Mixed regression models for equation, ROC curve for cut-points. Validation: LOOCV Agreement: none	Chronic disease (combined) – ActiGraph SED: 10 LPA: 10 – 426 MVPA: 426 – 785 Chronic disease (combined) – Actical

Skinfold: 38 ± 17 Tanner stages: 30 % (stages 1-2), 70 % (stage 3) CHAQ: 0.15 ± 0,26 PedsQL: 83 ± 9	Duration: 240 min	SED: 10 LPA: 17 - 288 MVPA: 289 - 570
Cystic fibrosis (n = 32) 14 girls 12.8 ± 2.9 years 156 ± 16 cm 45 ± 14 kg Skinfold: 31 ± 13 Tanner stage: 19 % (stages 1-2), 81% (stage 3) CHAQ: 0.27 ±0.3 PedsQL: 78 ± 12		Cystic fibrosis - ActiGraph SED: 10 LPA: 10 - 487 MVPA: 487 – 852
		Cystic fibrosis - Actical SED: 5 LPA: 5 – 368 MVPA: 368 – 1025
Congenital heart disease (n = 15) 5 girls		Congenital heart disease - ActiGraph SED: 10 LPA: 10 - 349 MVPA: 349 - 785
		Congenital heart disease - Actical

13.6 ± 3.3 years 161 ± 17 cm 54 ± 17 kg Skinfold: 42 ± 15.5 Tanner Stage: 38 % (stages 1 - 2), 62 % (stage 3) CHAQ: 0.17 ± 0.3 PedsQL: 72 ± 12	SED: 9 LPA: 9 - 349 MVPA: 349 – 633
Haemophilia (n= 28) 0 girls 12.4 ± 3.3 years 156 ± 19 cm 53 ± 20.7 kg Skinfold: 40 ± 20 Tanner Stage: 27 % (stages 1-2), 73 % (stage 3) CHAQ: 0.25 ± 0.4 PedsQL: 82 ± 16	Haemophilia - ActiGraph SED: 17 LPA: 17 - 432 MVPA: 432 - 788
	Haemophilia - Actical SED: 19 LPA: 19 - 306 MVPA: 306 - 1114
	Inherited muscle disease - ActiGraph SED: 37 LPA: 37 - 663 MVPA: 663 - 972
	Inherited muscle disease - Actical

Idiopathic muscular dystrophies (n= 30) 8 girls 12.0 ± 3.4 years 146 ± 22 cm 41 ± 14 kg Skinfold: 41 ± 18 Tanner stage: 70 % (stages 1-2) 30 % (stage 3) CHAQ: 0.8 ± 0.7 PedsQL: 68 ± 17	SED: 14 LPA: 14 - 297 MVPA: 297 - 523
Juvenile dermatomyositis (n = 31) 20 girls 13.4 ± 2.3 years 159 ± 11 cm 52 ± 14 kg Skinfold: 48 ± 17	Juvenile dermatomyositis- ActiGraph SED: 14 LPA: 14 - 172 MVPA: 172 - 543 Juvenile dermatomyositis - Actical SED: 18 LPA: 10 -166 MVPA: 166 - 601 Juvenile arthritis - ActiGraph SED: 25 LPA: 25 - 255 MVPA: 255 - 771 Juvenile arthritis - Actical

Tanner stage: 27 % (stages 1 - 2), 73 % (stage 3) CHAQ: 0.4 ± 0.6 PedsQL: 77 ± 15	SED: 19 LPA: 19 - 152 MVPA: 152 - 542
Juvenile arthritis (n = 31) 23 girls 12.7 ± 2.6 years 154 ± 12 cm 47 ± 14 kg Skinfold: 46 ± 22 Tanner stage: 32 (stages 1 -2), 68 % (stage 3) CHAQ: 0.5 ± 0.5 PedQL: 72 ± 13	

SD: standard deviation; BMI: body mass index; EE: energy expenditure; RMR: resting metabolic rate; GMFCS: gross motor function classification system; $\dot{V}O_2$: oxygen uptake, LOOV: leave-one-out cross-validation; ROC: receiver operating characteristic; SED: sedentary time, LPA: light physical activity; MVPA: moderate-to-vigorous physical activity; VPA: vigorous activity; CHAQ: childhood health assessment questionnaire; PedsQL: pediatric quality of life inventory

Appendix C: Chapter 4 - Literature Search Details

Sources searched: The search was performed between March and July 2017 in four databases (PubMed, SPORTDiscus, ScienceDirect, Scopus), the Web of Science platform, which is composed of 6 electronic databases (Web of Science Core Collection, BIOSIS Citation Index, KCI-Korean Journal Database, MEDLINE, Russian Science Citation Index, SciELO Citation Index), and the Wiley Online Library

Dates searched: 2000 onwards

Criteria: Cross-sectional studies; English language only

One search strategy was adopted for all databases and included the terms: physical activity, accelerometry, calibration, wearable monitors, thresholds, cut-points, validation, classification, energy expenditure and physical activity intensities.

All findings according to database:

PubMed search

Searched online 3rd April 2017

1. acceleromet* 7.365
2. acceleromet* AND (validation OR calibration): 823
3. acceleromet* AND physical activity: 5.099
4. wearable monitors AND (calibration OR validation): 17
5. physical activity AND (calibration OR validation): 5.026
6. acceleromet* thresholds: 127
7. acceleromet* cut-points: 133
8. energy expenditure AND acceleromet*: 825
9. classification AND physical activity intensities: 42

Science Direct

Searched online 26 of April 2017

1. **acceleromet*:** 37
2. Acceleromet* AND (validation OR calibration): 1281
3. Acceleromet* AND physical activity: 2560
4. wearable monitors AND (calibration OR validation): 685
5. physical activity AND (calibration OR validation): 5677
6. acceleromet* thresholds: 3464
7. acceleromet* cut-points: 955
8. energy expenditure AND acceleromet*: 2482
9. classification AND physical activity intensities: 2315

SportDiscuss

Searched online 05 of May 2017

1. **acceleromet*:** 1740
2. Acceleromet* AND (validation OR calibration): 155
3. Acceleromet* AND physical activity: 1228
4. wearable monitors AND (calibration OR validation): 3
5. physical activity AND (calibration OR validation): 374
6. acceleromet* thresholds: 23
7. acceleromet* cut-points: 133
8. energy expenditure AND acceleromet*: 825
9. classification AND physical activity intensities: 13

Scopus

Searched online 17 of May 2017

1. **acceleromet*:** 9569
2. Acceleromet* AND (validation OR calibration): 1035
3. Acceleromet* AND physical activity: 5871
4. wearable monitors AND (calibration OR validation): 54
5. physical activity AND (calibration OR validation): 3979

6. acceleromet* thresholds: 664
7. acceleromet* cut-points: 196
8. energy expenditure AND acceleromet*: 949
9. classification AND physical activity intensities: 338

Wiley

Searched online 20 of June 2017

1. **acceleromet*:** 10482
2. Acceleromet* AND (validation OR calibration): 3955
3. Acceleromet* AND physical activity: 5393
4. wearable monitors AND (calibration OR validation): 601
5. physical activity AND (calibration OR validation): 97285
6. acceleromet* thresholds: 3836
7. acceleromet* cut-points: 551
8. energy expenditure AND acceleromet*: 1792
9. classification AND physical activity intensities: 32466

ISIS Web of Science

Searched online 03 of July

1. **acceleromet*:** 301087
2. Acceleromet* AND (validation OR calibration): 986
3. Acceleromet* AND physical activity: 3207
4. wearable monitors AND (calibration OR validation): 387
5. physical activity AND (calibration OR validation): 7004
6. acceleromet* thresholds: 849
7. acceleromet* cut-points: 249
8. energy expenditure AND acceleromet*: 2062
9. classification AND physical activity intensities: 388

Database	Results	Selected papers	After deduplication
PubMed	**24,556**	**671**	**175**
SportDiscuss	4,494	139	48
Scopus	22,655	207	95
Wiley	156,361	34	14
Science Direct	19,456	74	30
ISIS Web of Science	316,219	692	242

604 results saved to EndNote X7 library

Appendix D: Ethics Approval

1. Chapters 5 to 8 – Joint Study Review Committee Approval Letter

in terms of convenience for attendance if you asked for review by **Wales REC 6 based in Swansea**.

Note: Applications processed via the Proportionate Review Service will automatically be booked to the next available agenda slot in the UK.

All forms created in IRAS for submission to NHS RECs (except notices of substantial amendment) are now submitted electronically form IRAS. All forms must be authorised using the electronic authorisation functionality in IRAS, which must be completed in advance of booking. Please contact the Sponsor representative to arrange signature of Part D2 "Declaration by the Sponsor Representative'.

R&D Submission (IRAS R&D form)

The IRAS forms may be submitted in parallel to your REC application but many researchers choose to submit to REC first, this is your decision. To submit for Health Board R&D approval, you will be required to complete a Site Specific Information (SSI) form in addition to the previously generated IRAS form. To generate the SSI form you will notice a tab at the top of the online grid for the IRAS form. For advice on the number of SSI forms required for your study, please ring the R&D team on 01792-530888.

Once you have completed your IRAS forms and the associated SSI forms, you will be required to download from IRAS in XML format. Please then email both forms, along with the full dataset to the Health and Care Research Wales, Research Permissions at: Research-permissions@wales.nhs.uk

Upon receipt of a valid application, the study details will be transferred to the applicable Health Boards for internal R&D Governance review.

JSRC Approval Conditions

As part of the conditions of JSRC approval, you will be required to provide 6 monthly progress reports to the Committee. These progress reports will be an opportunity for you to highlight your study development and showcase the study progress to the Committee and equally highlight any concerns or difficulties which may have arisen in the study for advice from members.

May I take this opportunity to wish you well with your study.

Yours sincerely

Professor Rhys Williams
Chair, Joint Study Review Committee

GIG CYMRU NHS WALES
Bwrdd Iechyd Prifysgol Abertawe Bro Morgannwg University Health Board

R&D RESEARCH & DEVELOPMENT
Abertawe Bro Morgannwg University Health Board

Dyddiad/Date: 11 December 2017

☎ 01792 704056
Fax: 01792 545774
Jemma.Hughes@wales.nhs.uk
Abm.rd@wales.nhs.uk

Dr Melitta McNarry
Senior Lecturer
Applied Sports Science Technology and Medicine Research Centre | Canolfan Ymchwil Technoleg Chwaraeon Cymhwysol, Ymarfer a Meddygaeth (A-STEM)
College of Engineering | Coleg Peirianneg
[redacted]|104 Perianneg Dwyrain
Bay Campus| Campws y Bae
Swansea University | Prifysgol Abertawe
Fabian Way | Ffordd Fabian
Swansea | Abertawe
SA1 8EN

Dear Dr McNarry

Re: Study Title: Calibration and Cross-Validation of Accelerometry in Youth and Adults with Cystic Fibrosis: A cross-sectional Study

Thank you for submitting your revised protocol as requested by the Joint Study Review Committee (JSRC) that met on 6 September 2017, 1 November 2017 and 6 December 2017. Having read the revised protocol I am happy that the specific points raised have been addressed satisfactorily and on this basis I can approve the study by Chairman's action.

The next stage is to submit your JSRC approved protocol for Ethical and R&D approval. Please note, you are unable to commence the study until all relevant approvals are in place.

Ethical and R&D Submission
For submission to Ethics & R&D, please register with the Integrated Research Application System (IRAS) at www.myresearchproject.org.uk. At login, you will be required to complete a project filter page; this will result in the appropriate forms being generated for your type of study.

Ethics (IRAS REC form)
Once you have finalised the IRAS forms, you should contract the Central Booking Service (CBS) which covers all bookings for RECs in the UK (0161 625 7836 9:30am – 4:00pm weekdays).

During the call you will need to provide your IRAS project ID, answer a series of questions about your study and confirm you are ready to submit on the same day. This will enable to the operator to check that your study is ready for review, that you are booked to an appropriate REC and that electronic submission is enabled in IRAS.

When booking, you will be offered the first available agenda slot within the UK. You may, however, request review by a named committee and it would be distinctly to your advantage

2. Chapters 5 to 8 – NHS Research Ethics Committee Approval

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

West of Scotland REC 5
West of Scotland Research Ethics Service
West Glasgow Ambulatory Care Hospital
Dalnair Street
Glasgow
G3 8SJ

Date 16 May 2018

Direct line 0141 232 1809
E-mail WoSREC5@ggc.scot.nhs.uk

Dr Melitta McNarry
Swansea University
College of Engineering
Bay Campus
SA1 8EN

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

Dear Dr McNarry

Study title:	**Calibration and Cross-Validation of Accelerometry in youth and adults with Cystic Fibrosis**
REC reference:	**18/WS/0032**
Protocol number:	**RIO 019-17**
IRAS project ID:	**220354**

Thank you for your email of 14 May 2018, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a Sub-Committee of the REC. A list of the Sub-Committee members is attached. They thank you for your rapid response to their queries.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System, at www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Indemnity]		15 July 2017
GP/consultant information sheets or letters [GP letter]	1.2	17 October 2017
Instructions for use of medical device [Monitor Instructions 12-18 Years]	1.2	17 October 2017
Instructions for use of medical device [Monitor Instructions Adult]	1.2	17 October 2017
Instructions for use of medical device [Monitor Instructions Parental Guardian]	1.2	17 October 2017
Instructions for use of medical device [Monitor Instructions Under 12 Years]	1.2	17 October 2017
Letters of invitation to participant [Recruitment Email]	1.2	17 October 2017
Other [Clarification re buddy system]		
Other [Response to REC]		
Participant consent form [Participant Consent Form]	1.3	07 March 2018
Participant consent form [Participant Assent Form]	1.3	07 March 2018
Participant consent form [Parent_Guardian Consent Form]	1.3	07 March 2018
Participant information sheet (PIS) [Adult Information Sheet_Llandough]	1.3	07 March 2018
Participant information sheet (PIS) [Parent_Guardian Information Sheet_Llandough]	1.3	07 March 2018
Participant information sheet (PIS) [12-18 Years Old Information Sheet_Llandough]	1.3	07 March 2018
Participant information sheet (PIS) [Under 12 Information Sheets_Llandough]	1.3	07 March 2018
Participant information sheet (PIS) [12-18 Years Old Information Sheet_Royal Devon]	1.3	07 March 2018
Participant information sheet (PIS) [Adult Information Sheet_Royal Devon]	1.3	07 March 2018
Participant information sheet (PIS) [Parent_Guardian Information Sheet_Royal Devon]	1.3	07 March 2018
Participant information sheet (PIS) [Under 12 Information Sheets]	1.3	07 March 2018
Participant information sheet (PIS) [12-18 Years Old Control Information Sheet_Morriston_DXA]	1.3	07 March 2018
Participant information sheet (PIS) [12-18 Years Old Information Sheet_Morriston]	1.3	07 March 2018
Participant information sheet (PIS) [Adult Control Information Sheet_Morriston_DXA]	1.3	07 March 2018
Participant information sheet (PIS) [Adult Information Sheet_Morriston]	1.3	07 March 2018
Participant information sheet (PIS) [Parent_Guardian Control Information Sheet_Morriston_DXA]	1.3	07 March 2018
Participant information sheet (PIS) [Parent_Guardian Information Sheet_Morriston]	1.3	07 March 2018
Participant information sheet (PIS) [Under 12 Control Information Sheets_Morriston_DXA]	1.3	07 March 2018
Participant information sheet (PIS) [Under 12 Information Sheets_Morriston]	1.3	07 March 2018
REC Application Form [REC_Form_06022018]		06 February 2018
Research protocol or project proposal [Exercise Protocol]	1.4	06 December 2017
Research protocol or project proposal [Exercise Protocol]	1.5	28 February 2018

Research protocol or project proposal	1.6	12 May 2018
Response to Request for Further Information [Email]		07 May 2018
Response to Request for Further Information [Email]		14 May 2018
Summary CV for Chief Investigator (CI) [McNarry Melitta CV]		10 August 2017
Summary CV for student [Silveira Mayara CV]		29 June 2017
Summary CV for supervisor (student research) [Mackintosh Kelly CV]		27 July 2017
Validated questionnaire [7daypar_survey]		
Validated questionnaire [All Versions English-UK CFQ-R FINAL]		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

18/WS/0032	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

Dr Stewart Campbell
Chair

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

"After ethical review – guidance for researchers"

Copy to: Dr Jeanette Hewitt, Swansea University
Anne-Claire Owen, Abertawe Bro Morgannwg University Health Board

West of Scotland REC 5

Attendance at Sub-Committee of the REC meeting

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Stewart Campbell	Consultant Physician & Gastroenterologist (CHAIR)	Yes	
Professor Eddie McKenzie	Statistician	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Mrs Sharon Macgregor	REC Manager

3. Chapters 5 to 8 – Health Research Authority Approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Melitta McNarry
Swansea University
College of Engineering
Bay Campus
SA1 8EN

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

05 June 2018

Dear Dr McNarry,

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Calibration and Cross-Validation of Accelerometry in youth and adults with Cystic Fibrosis**
IRAS project ID:	**220354**
Protocol number:	**RIO 019-17**
REC reference:	**18/WS/0032**
Sponsor:	**Swansea University**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales*, as well as any documentation that has been updated as a result of the assessment.

*'In flight studies' which have already started an SSI (Site Specific Information) application for NHS organisations in Wales will continue to use this route. Until 10 June 2018, applications on either documentation will be accepted in Wales, but after this date all local information packs should be shared with NHS organisations in Wales using the Statement of Activities/Schedule of Events for non-commercial studies and template agreement/ Industry costing template for commercial studies.

Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of

IRAS project ID	220354

capacity and capability (e.g. provision by you of a 'green light' email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: Dr Jeanette Hewitt
Tel: [redacted]
Email: researchcontracts@swansea.ac.uk

IRAS project ID	220354

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **220354**. Please quote this on all correspondence.

Yours sincerely,

Emma Stoica
Senior Assessor

Email: hra.approval@nhs.net

Copy to: *Dr Jeanette Hewitt, Swansea University [sponsor contact]*
Anne-Claire Owen, Abertawe Bro Morgannwg University Health Board [lead NHS R&D contact]
Research-permissions@wales.nhs.uk

IRAS project ID	220354

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Indemnity]		15 July 2017
GP/consultant information sheets or letters [GP letter]	1.2	17 October 2017
HRA Schedule of Events	2	05 June 2018
HRA Statement of Activities	1	23 May 2018
Instructions for use of medical device [Monitor Instructions 12-18 Years]	1.2	17 October 2017
Instructions for use of medical device [Monitor Instructions Adult]	1.2	17 October 2017
Instructions for use of medical device [Monitor Instructions Parental Guardian]	1.2	17 October 2017
Instructions for use of medical device [Monitor Instructions Under 12 Years]	1.2	17 October 2017
Letter from funder [confirmation of PhD Studentship funding]		01 September 2016
Letter from funder [programme funding]		23 February 2016
Letter from sponsor [SU-Sponsor-Application V1]		25 August 2017
Other [Clarification re buddy system]		
Other [Response to REC]		
Participant consent form [Participant Consent Form]	1.3	07 March 2018
Participant consent form [Participant Assent Form]	1.3	07 March 2018
Participant consent form [Parent_Guardian Consent Form]	1.3	07 March 2018
Participant information sheet (PIS) [Parent_Guardian Information Sheet_Royal Devon]	1.3	07 March 2018
Participant information sheet (PIS) [12-18 Years Old Information Sheet_Royal Devon]	1.3	07 March 2018
Participant information sheet (PIS) [Adult Information Sheet_Royal Devon]	1.3	07 March 2018
Participant information sheet (PIS) [Under 12 Information Sheets]	1.3	07 March 2018
REC Application Form [REC_Form_06022018]		06 February 2018
Referee's report or other scientific critique report [McNarry jsrc apprvl lttr 12.1.18 cross valid CF]		11 December 2017
Research protocol or project proposal	1.6	12 May 2018
Response to Request for Further Information [Email]		07 May 2018
Response to Request for Further Information [Email]		14 May 2018
Summary CV for Chief Investigator (CI) [McNarry Melitta CV]		10 August 2017
Summary CV for student [Silveira Mayara CV]		29 June 2017
Summary CV for supervisor (student research) [Mackintosh Kelly CV]		27 July 2017
Validated questionnaire [7daypar_survey]		
Validated questionnaire [All Versions English-UK CFQ-R FINAL]		

IRAS project ID	220354

Summary of assessment

The following information provides assurance to you, the sponsor and the NHS in England and Wales that the study, as assessed for HRA and HCRW Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England and Wales to assist in assessing, arranging and confirming capacity and capability.

Assessment criteria

Section	Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and process	Yes	No comments
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	A Statement of Activities and a Schedule of Events have been provided to aid the set-up of the study at the participating NHS sites. The Statement is intended to form the agreement of the NHS sites to participate.
4.2	Insurance/indemnity arrangements assessed	Yes	No comments
4.3	Financial arrangements assessed	Yes	There is no funding for the participating NHS sites but all equipment required to conduct the testing will be provided by the sponsor.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments

IRAS project ID	220354

Section	Assessment Criteria	Compliant with Standards	Comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England and Wales

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
There is one type of participating NHS organisation in the study. The research activities to be undertaken at the NHS sites are listed in the Schedule of Events provided by the sponsor. Some participants will also be recruited outside the NHS. HRA approval does not cover activity outside the NHS. Before recruiting outside the NHS the research team must follow the procedures and governance arrangements of responsible organisations. The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England and Wales in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. Where applicable, the local LCRN contact should also be copied into this correspondence. If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England and Wales which are not provided in IRAS, the HRA or HCRW websites, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net or HCRW at Research-permissions@wales.nhs.uk. We will work with these organisations to achieve a consistent approach to information provision.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and Wales, and the minimum expectations for education, training and experience that PIs should meet (where applicable).
A Local Collaborator should be in place at the NHS sites participating in the study, to identify potential participants and to support practical arrangements for access for members of the central

IRAS project ID	220354

research team coming on NHS premises to undertake research activities.

GCP training is not a generic training expectation, in line with the HRA/HCRW/MHRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken

No additional arrangements are required for local staff helping with identifying and approaching potential participants.

Should prior contractual arrangements with the host NHS sites not be in place, the external researchers undertaking research activities at the NHS trusts would be expected to obtain Letters of Access on the basis of Research Passports if University employed, or NHS to NHS confirmation of pre-engagement checks letters if they are NHS employed, or have already Honorary Research Contracts. Enhances DBS checks and occupational health clearance would be appropriate.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales to aid study set-up.

The applicant has indicated that they intend to apply for inclusion on the NIHR CRN Portfolio.

4. Chapters 6 and 7 – Human Research Ethics Committee at Alfred Health in Australia

ETHICS COMMITTEE CERTIFICATE OF APPROVAL

This is to certify that

Project Number: HREC/16/Alfred/188 (Local Reference: Project 7/17)

Project Title: A randomised controlled trial of a novel web-based intervention to promote physical activity participation in people with Cystic Fibrosis

Coordinating Principal Investigator: Professor Anne Holland

*was considered under the Victorian Streamlined Ethical Review Process (SERP) by the Ethics Committee on **2-Feb-2017**, meets the requirements of the National Statement on Ethical Conduct in Human Research (2007) and was **APPROVED** on **3-Feb-2017**.*

It is the Coordinating Principal Investigator's responsibility to ensure that all researchers associated with this project are aware of the conditions of approval and which documents have been approved.

The Coordinating Principal Investigator is required to notify the Secretary of the Ethics Committee, via amendment or progress report, of

- Any significant change to the project and the reason for that change, including an indication of ethical implications (if any);
- Serious adverse effects on participants and the action taken to address those effects;
- Any other unforeseen events or unexpected developments that merit notification;
- The inability of the Coordinating Principal Investigator to continue in that role, or any other change in research personnel involved in the project;
- Any expiry of the insurance coverage provided with respect to sponsored clinical trials and proof of re-insurance;
- A delay of more than 12 months in the commencement of the project; and,
- Termination or closure of the project.

Additionally, the Coordinating Principal Investigator is required to submit

- A Progress Report on the anniversary of approval and on completion of the project.

The Ethics Committee may conduct an audit at any time.

All research subject to the Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).

The Alfred Hospital Ethics Committee is a properly constituted Human Research Ethics Committee in accordance with the National Statement on Ethical Conduct in Human Research (2007).

SPECIAL CONDITIONS

None

5. Chapters 5 to 8 – Human Research Ethics Committee at Alfred Health in Australia Approval of Amendments

TheAlfred

Ethics Committee

Certificate of Approval of Amendments

This is to certify that amendments to

Project: **HREC/16/Alfred/188** (Local reference: **7/17**)
A randomised controlled trial of a novel web-based intervention to promote physical activity participation in people with Cystic Fibrosis

Coordinating Principal Researcher:
Professor Anne Holland

Amendment:
Sharing of physical activity data with UK collaborators

have been approved under the Victorian Streamlined Ethics Review Process (SERP) in accordance with your amendment request dated **22-May-2018** on the understanding that you observe the National Statement on Ethical Conduct in Human Research.

It is now your responsibility to ensure that all people associated with this particular research project are made aware of what has actually been approved and any caveats specified in correspondence with the Ethics Committee. Any further change to the application which is likely to have a significant impact on the ethical considerations of this project will require approval from the Ethics Committee.

[redacted]

Professor John J. McNeil
Chair, Ethics Committee

Date: **30-May-2018**

All research subject to Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).

The Alfred Ethics Committee is a properly constituted Human Research Ethics Committee operating in accordance with the National Statement on Ethical Conduct in Human Research (2007).

Appendix E: Information Sheets for Participants and Parents/Guardians

1. Chapters 5 to 8 – Control 12-18 years old Information Sheet

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

School of Sport and Exercise Sciences, College of Engineering

CONTROL INFORMATION SHEET (12 - 18 YEARS OLD)

(Version 1.3, Date 07/03/2018)

Project Title: Calibration and Cross-Validation of Accelerometry in Youth and Adults with Cystic Fibrosis: A cross-sectional Study

Contact Details:

Dr Melitta McNarry

Email: [redacted]

Telephone: [redacted]

Mayara Silveira Bianchim

Email: [redacted]

Telephone: [redacted]

Dr Kelly Mackintosh

Email: [redacted]

Telephone: [redacted]

Dr Jeanette Hewitt (Independent contact)

Email: [redacted]

Telephone: [redacted]

1. Invitation Paragraph

Thank you for being interested in our project. Please read this information sheet very carefully, and think if you are happy to take part. If you are happy to, thank you. If you don't want to take part, that is absolutely fine.

2. What is the purpose of this study?

For those with CF, physical activity and exercise are really important to staying as well as possible. However, we don't know how much physical activity should be recommended to those with CF. Therefore, the purpose of this study is to see how difficult daily tasks like walking and playing games are for those with Cystic Fibrosis compared to their healthy friends and family. This will mean we can make specific recommendations for those with Cystic Fibrosis about the amount of physical activity they should do.

3. Why have you been chosen?

You have been asked if you would like to take part because you are aged between 12 and 18 years of age and are free from any injuries or other illnesses.

4. What will happen to you if you take part?

You will be invited to attend 3 sessions that will take place at Swansea University (Bay Campus):

Before the visits it would be great if you can avoid any intense physical activities (for example: playing sports or running for a long time), and avoid drinking caffeine (e.g. tea, coffee, coke) on the day before. Also, please don't eat in the two hours before your sessions.

Visit 1

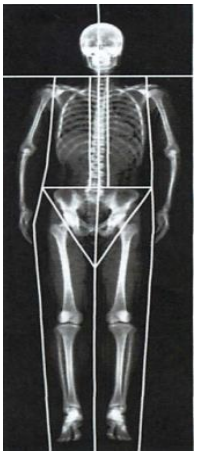
- Step 1 – First, we will measure your height, sitting height, weight and waist size.

- Step 2 – Then, you will answer a questionnaire about your physical activity routine. There are no right or wrong answers, we are just interested in what you normally do.

- Step 3 – We also need to know how mature you are so we will ask you to look at some pictures and tick which picture is most like you. You will do this on your own and no one else will see what you have ticked until you have finished the study when only the researcher will see. There is no right or wrong answer and no one minds which picture you tick. If you don't want to do this bit, you don't have to.

- Step 4 – Next, we will measure your lung function by breathing out as hard as possible into a mouthpiece then we will ask you to lie down for 30 mins and breathe through a different mouthpiece so we can see how much energy you use while you are just lying down.

- Step 5 – After this, we will take a picture of your skeleton and muscles using a machine called a DEXA machine. This will take about 5-10 minutes and you will be asked to lie on a bed and a very sensitive scan will be taken that gives us an image of your skeleton and allows us to see how thick and how old your bones are. We will take three different scans, one of your hand, one of your spine and another one of your whole skeleton. These scans use a very small dose of x-rays but much less than the type of x-ray you get at a hospital when they think you have broken a bone. The x-rays are the same amount as you get on a short-distance flight.



- Step 6 – Finally, we will give you six physical activity monitors to wear continuously for 7 days, even when you sleep. These monitors are Physical Activity Trackers. They are like 'FitBits', and will record every movement you make, they are called accelerometers. This way we will be able to tell exactly how active you are. As you can see in the pictures below, four of these will be worn on your wrists, one around your waist and one will be stuck to your chest using sticky plasters which will also measure your heart rate. We are giving you six so we can see how they differ and what effect where you wear them has on how good they are at sensing your movements. It's really important that when you are wearing these monitors, you do not do anything differently. We just want you to do whatever you would normally do each day. You do not need to take them off to do anything in water, like swimming or showering, because they are completely water proof. They can stay on all

the time. If you do take them off, we will give you a diary to note down when you did so and why so we can understand the data when we get the monitors back. On this diary, we would also like you to write down what time you went to sleep and woke up and how well you think you slept.




Visit 2

- Step 7 – One week later, we will ask you to come back and to do a variety of activities that you typically do at home, like watching TV, playing videogames and playing games outside. You will be asked to do all of the activities with a face mask on to measure how much oxygen you are breathing in and out, and a small clip on your index finger that will tell us how much oxygen you have in your blood. At the end of this visit, we will take off all of the physical activity monitors that you have been wearing for the last 7 days.

Visit 3

- Step 8 – On this last visit we will ask you to walk and then run on a treadmill while wearing the face mask and also all six of the monitors again. You will also be asked to wear a small clip on your index finger that will tell us how much oxygen you have in your blood. This test will only last as long as you are happy for it to last and we will not make

you run faster than you are happy with or normally do.

We can cover reasonable travel expenses to help you attend these sessions.

5. What are the possible disadvantages of taking part?

The exercise on the treadmill may make you feel tired and the mask may feel a little uncomfortable, but you will soon feel less tired when you stop exercising and people generally forget about the mask after the first few minutes. We will give you lots of time to rest and make sure there is water if you need a drink. We know that we are asking for a lot of your time but we will try and fit these sessions in at the best times for you. Finally, the physical activity monitors might seem quite bulky when we first give them to you but they are just like wearing a watch or a belt and you will soon forget about them. For the one on your chest, you might find this itchy so we will give you some spare plasters so you can change them if you want to.

6. How much radiation will I receive and what is the associated risk?

If you take part in this study, we will ask you to do a scan of your bones and all the tissues in your body, like your muscles. This will mean you get a very small dose of radiation which can harm cells in your body. Lots of radiation can increase your risk of diseases later in life. This sounds scary but the amount of radiation through this scan is really small, the same as you get every 20 hours by just living in the UK. To put it in numbers, we estimate the exposure you will receive from the testing to be 2.5µSv which is a lot less than the limit recommended for those under 18 years of 10µSv/year.

7. What are the possible benefits of taking part?

The information gained from this study may mean we can try to help those with Cystic Fibrosis by giving them much better advice on how to stay healthy for as long as possible.

8. What happens if something goes wrong?

We don't expect any problems, but, if something does go wrong during the study, you will be asked to stop. We will then get doctors to check you to make sure you are ok and whether you can continue or not. The study and all the protocols within it are covered by Swansea University's indemnity policy.

9. Will my taking part in the study be kept confidential?

Your GP will be notified of your participation for safety reasons. However, all personal information collected will be kept completely private. That is, only members of the research team will have access to it. You will be given a unique number so that no one knows who your results belong to and your name will not be linked to your data. After the study is finished, all private information will be deleted.

10.What if I have any questions?

If you have any questions, please contact us on the details at the beginning of this sheet. You can also ask one of the researchers when you come in to see us. It is never too late to ask more questions.

11.What will happen with all the information collected?

If you allow it, all the collected data will be used for this research and potentially for other studies in the future in an anonymous way, which means that no one will know it's your information. We would also like to take some photos of you during the activities if you are ok with that, but you don't have to agree. These photos would be used to show others what the study was like but we can make it so no one can recognise you.

This study is organised by Swansea University and funded by the Cystic Fibrosis Trust.

2. Chapters 5 to 8 – 12-18 years old Information Sheet

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

School of Sport and Exercise Sciences, College of Engineering

INFORMATION SHEET (12 - 18 YEARS OLD)

(Version 1.4, Date 17/01/2019)

Project Title: Calibration and Cross-Validation of Accelerometry in Youth and Adults with Cystic Fibrosis: A cross-sectional Study

Contact Details:

Dr Melitta McNarry

Email: [redacted]

Telephone: [redacted]

Mayara Silveira Bianchim

Email: [redacted]

Telephone: [redacted]

Dr Kelly Mackintosh

Email: [redacted]

Telephone: [redacted]

Dr Jeanette Hewitt (Independent contact)

Email: [redacted]k

Telephone: [redacted]

1. Invitation Paragraph

Thank you for being interested in our project. Please read this information sheet very carefully, and think if you are happy to take part. If you are happy to, thank you. If you don't want to take part, that is absolutely fine.

2. What is the purpose of this study?

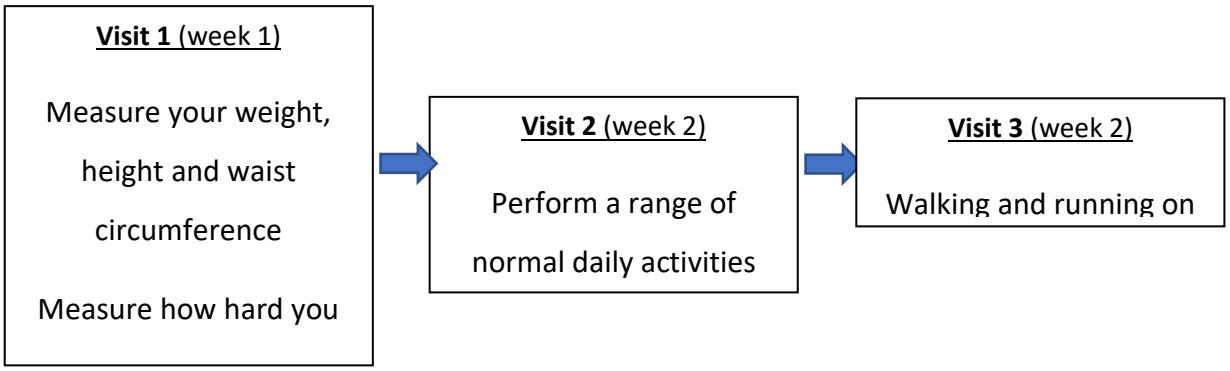
For those with CF, physical activity and exercise are really important to staying as well as possible. However, we don't know how much physical activity should be recommended to those with CF. Therefore, the purpose of this study is to see how difficult daily tasks like walking and playing games are for those with Cystic Fibrosis compared to their healthy friends and family. This will mean we can make specific recommendations for those with Cystic Fibrosis about the amount of physical activity they should do.

3. Why have you been chosen?

You have been asked if you would like to take part because you are aged between 12 and 18 years of age, have Cystic Fibrosis, and are free from any other injuries or other illnesses.

4. What will happen to you if you take part?

You will be invited to attend 3 sessions that will take place at Swansea University (Bay Campus) or Morriston Hospital



Before the visits it would be great if you can avoid any intense physical activities (for example: playing sports or running for a long time), and avoid drinking caffeine (e.g. tea, coffee, coke) on the day before. Also, please don't eat in the two hours before your sessions.

Visit 1 (Swansea University, Bay Campus)

- Step 1 – First, we will measure your height, sitting height, weight and waist size.

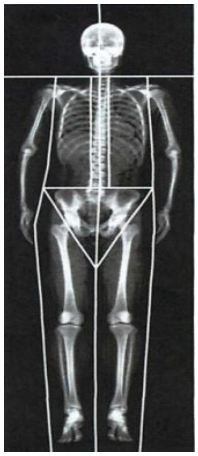
- Step 2 – Then, you will answer a questionnaire about your physical activity routine. There are no right or wrong answers, we are just interested in what you normally do.

- Step 3 – We also need to know how mature you are so we will

ask you to look at some pictures and tick which picture is most like you. You will do this on your own and no one else will see what you have ticked until you have finished the study when only the researcher will see. There is no right or wrong answer and no one minds which picture you tick. If you don't want to do this bit, you don't have to.

- Step 4 – Next, we will measure your lung function by breathing out as hard as possible into a mouthpiece then we will ask you to lie down for 30 mins and breathe through a different mouthpiece so we can see how much energy you use while you are just lying down.

- Step 5 – After this, we will take a picture of your skeleton and muscles using a machine called a DEXA machine. This will take about 5-10 minutes and you will be asked to lie on a bed and a very sensitive scan will be taken that gives us an image of your skeleton and allows us to see how thick and how old your bones are. We will take three different scans, one of your hand, one of your spine and another one of your whole skeleton. These scans use a very small dose of x-rays but much less than the type of x-ray you get at a hospital when they think you have broken a bone. The x-rays are the same amount as you get on a short-distance flight.



- Step 6 – Finally, we will give you six physical activity monitors to wear continuously for 7 days, even when you sleep. These monitors are Physical Activity Trackers. They are like 'FitBits', and will record every movement you make, they are called accelerometers. This way we will be able to tell exactly how active you are. As you can see in the pictures below, four of these will be worn on your wrists, one around your waist and one will be stuck to your chest using sticky plasters which will also measure your heart rate. We are giving you six so we can see how they differ and what effect where you wear them has on how good they are at sensing your movements. It's really important that when you are wearing these monitors, you do not do anything differently. We just want you to do whatever you would normally do each day. You do not need to take them off to do anything in water, like swimming

or showering, because they are completely water proof. They can stay on all the time. If you do take them off, we will give you a diary to note down when you did so and why so we can understand the data when we get the monitors back. On this diary, we would also like you to write down what time you went to sleep and woke up and how well you think you slept.

Visit 2 (Morriston Hospital or Swansea University – Bay Campus)

- Step 7 – For our next session, one week later, you will be able to choose whether you would like to attend the visit at Morriston Hospital or at Bay Campus to do a variety of activities that you typically do at home, like watching TV, playing videogames and playing games outside. You will be asked to do all of the activities with a face mask on to measure how much oxygen you are breathing in and out, and a small clip on your index finger that will tell us how much oxygen you have in your blood. At the end of this visit, we will take off all of the physical activity monitors that you have been wearing for the last 7 days.

Visit 3 (Morriston Hospital or Swansea University – Bay Campus)

- Step 8 – You also will be able to choose whether you would like to attend the last visit at Morriston Hospital or at Bay Campus. We will ask you to walk and then run on a treadmill

while wearing the face mask and also all six of the monitors again. You will also be asked to wear a small clip on your index finger that will tell us how much oxygen you have in your blood. This test will only last as long as you are happy for it to last and we will not make you run faster than you are happy with or normally do.

We can cover reasonable travel expenses to help you attend these sessions.

5. What are the possible disadvantages of taking part?

The exercise on the treadmill may make you feel tired and the mask may feel a little uncomfortable, but you will soon feel less tired when you stop exercising and people generally forget about the mask after the first few minutes. We will give you lots of time to rest and make sure there is water if you need a drink. We know that we are asking for a lot of your time but we will try and fit these sessions in at the best times for you. Finally, the physical activity monitors might seem quite bulky when we first give them to you but they are just like wearing a watch or a belt and you will soon forget about them. For the one on your chest, you might find this itchy so we will give you some spare plasters so you can change them if you want to.

6. How much radiation will I receive and what is the associated risk?

If you take part in this study, we will ask you to do a scan of your bones and all the tissues in your body, like your muscles. This will mean you get a very small dose of radiation which can harm cells in your body. Lots of radiation can increase your risk of diseases later in life. This sounds scary but the amount of radiation through this scan is really small, the same as you get every 20 hours by just living in the UK. To put it in numbers, we estimate the exposure you will receive from the testing to be 2.5µSv which is a lot less than the limit recommended for those under 18 years of 10µSv/year.

7. What are the possible benefits of taking part?

The information gained from this study may mean we can try to help those with Cystic Fibrosis by giving them much better advice on how to stay healthy for as long as possible.

8. What happens if something goes wrong?

We don't expect any problems, but, if something does go wrong during the study, you will be asked to stop. We will then get doctors to check you to make sure you are ok and whether you can continue or not. The study and all the protocols within it are covered by Swansea University's indemnity policy.

9. Will my taking part in the study be kept confidential?

Your GP will be notified of your participation for safety reasons. However, all personal information collected will be kept completely private. That is, only members of the research team will have access to it. You will be given a unique number so that no one knows who your results belong to and your name will not be linked to your data. After the study is finished, all private information will be deleted.

10. What if I have any questions?

If you have any questions, please contact us on the details at the beginning of this sheet. You can also ask one of the researchers when you come in to see us. It is never too late to ask more questions.

11. What will happen with all the information collected?

If you allow it, all the collected data will be used for this research and potentially for other studies in the future in an anonymous way, which means that no one will know it's your information. We would also like to take some photos of you during the activities if you are ok with that, but you don't have to agree. These

photos would be used to show others what the study was like but we can make it so no one can recognise you.

This study is organised by Swansea University and funded by the Cystic Fibrosis Trust.

3. Chapters 5 to 8 – Control Parent/Guardian Information Sheet

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

School of Sport and Exercise Sciences, College of Engineering

CONTROL INFORMATION SHEET (PARENT/GUARDIAN)

(Version 1.3, Date 07/03/2018)

Project Title: Calibration and Cross-Validation of Accelerometry in Youth and Adults with Cystic Fibrosis: A cross-sectional Study

Contact Details:

Dr Melitta McNarry

Email: [redacted]

Telephone: [redacted]

Mayara Silveira Bianchim

Email: [redacted]k

Telephone: [redacted]

Dr Kelly Mackintosh

Email: [redacted]

Telephone: [redacted]

Dr Jeanette Hewitt (Independent contact)

Email: [redacted]

[redacted]

1. Invitation Paragraph

Thank you for being interested in your child taking part in our project. Please read this information sheet very carefully, and think if you are happy for them to take part. If you are happy for them to, thank you! If you don't want them to take part, that is absolutely fine!

2. What is the purpose of this study?

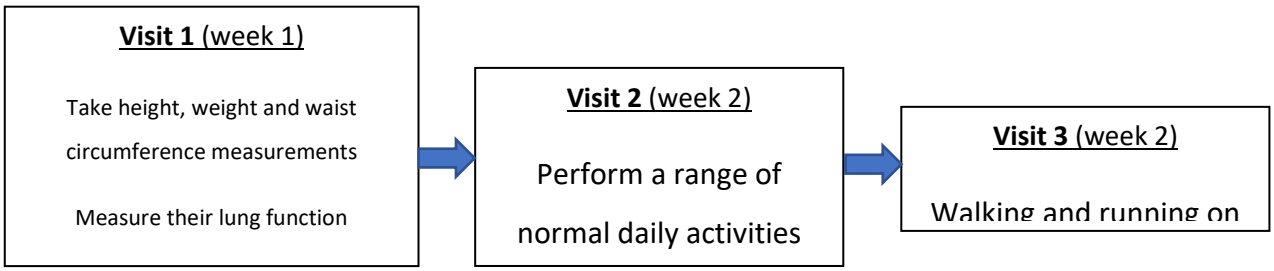
For those with CF, physical activity and exercise are key to staying as well as possible. However, we don't know how much physical activity should be recommended to those with CF. Therefore, the purpose of this study is to see how difficult daily tasks like walking and playing games are for those with CF compared to their healthy friends and family. This will mean we can make specific recommendations for those with CF about the amount of physical activity they should do.

3. Why has my child been chosen?

Your child has been asked if they would like to take part because they are under 18 years of age, and are free from any injuries or illnesses.

4. What will happen to my child if they take part?

Your child will be invited to attend 3 sessions that will take place at Swansea University (Bay Campus):



Before the visits it would be great if your child can avoid any intense physical activities, such as running or playing sports, and avoid drinking caffeine (e.g. tea, coffee, coke) on the day before. Also, please don't let them eat in the two hours before their sessions.

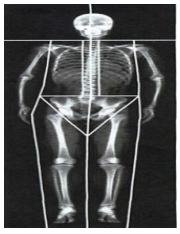
Visit 1

- Step 1 - Take their height, weight and waist circumference measurements.

- Step 2 – Complete a physical activity questionnaire so we can determine their current levels. There are no right or wrong answers, we are just interested in what they normally do.

- Step 3 – We will measure their lung function by getting them to breathe out as hard as possible into a mouthpiece. Following this, will ask them to lie down for 30 mins and breathe through a different mouthpiece so we can see how much energy they use while they are resting.

- Step 4 – We will then ask them to lie down for approximately 5-10 minutes to have a DEXA scan of their body. This will allow us to measure the strength of their bones as well as their body composition. We will take three different scans, one of their hand, one of their spine and another one of their whole skeleton. These scans use a very small dose of x-rays but much less than the average x-ray machine. The x-rays are the same amount as they'd get on a short-distance flight.



- Step 5 – Finally, we will give your child six physical activity monitors to wear continuously for 7 days, even when they sleep! These are Physical Activity Trackers, also known as accelerometer. It works by recording the acceleration and rotational forces when you move. We will use this equipment to tell exactly how active your child is. Four of these will be worn on their wrists (two on each wrist), one around their waist and one will be attached to their chest using sticky pads (electrodes), which will also measure their heart rate. We are giving them six so we can see how they differ and what effect where you wear them has on how good they are at sensing their movements. It's really important that when they are wearing these monitors, they do not do anything differently. We just want them to do whatever they would normally do each day. All

monitors are completely waterproof so they can be worn at all times, even when swimming. However, if they do take them off, we will give them a log sheet to note down the time they took them off and put them back on. This will help us understand the data once they return the monitors. On the log sheet, we would also like them to write down what time they went to sleep and woke up and how well they think they slept.



Visit 2

- Step 6 – One week later, we will ask them to come back and to do a variety of activities that they typically do at home, like watching TV or playing games. They will be asked to do all of the activities with a face mask on to measure how much oxygen they are breathing in and out, and a small clip on their index finger that will tell us how much oxygen they have in their blood. At the end of this visit, they will take off all of the physical activity monitors that they have been wearing for the last 7 days.

Visit 3

- Step 7 – On this last visit we will ask them to walk and then run on a treadmill while wearing the face mask and all six of the monitors again. They will also be asked to wear a small clip on your index finger that will tell us how much oxygen they have in your blood. This test will only last as long as they are happy for it to last and we will not make them run faster than they are happy with or normally do.

We can cover reasonable travel expenses to help you attend these sessions.

5. What are the possible disadvantages of my child taking part?

The exercise on the treadmill may be tiring and the mask may feel a little uncomfortable, but people generally forget about the mask after the first few minutes! We will give your child lots of time to rest and make sure there is water if they need a drink. We know that we are asking for a lot of your child's time but we will try and fit these sessions in at the best times for them. Finally, the physical activity monitors might seem quite bulky when we first give them to your child, but they are just like wearing

a watch or a belt and they will soon forget about them. For the one on their chest, they might find this itchy so we will give them some spare electrodes (sticky pads) so they can change them if they want to.

6. How much radiation will my child receive and what is the associated risk?

If your child takes part in this study, we will ask them to do a body scan (bones, muscle and tissue). This will mean they get a very small dose of radiation which can harm cells in their body. Lots of radiation can increase their risk of diseases later in life. Although this might sound frightening, the amount of radiation through this scan is really small, the same as your child would get every 20 hours by just living in the UK. To put it in numbers, we estimate the exposure your child will receive from the testing to be 2.5µSv, and the radiation exposure in addition to background levels for minors (under the age of 18 years) is limited to 10µSv/year.

7. What are the possible benefits of my child taking part?

The information gained from this study may help us to help those with Cystic Fibrosis by being able to give them much better advice on how to stay healthy for as long as possible.

8. What happens if something goes wrong?

We don't expect any problems, but, if something does go wrong during the study, your child will be asked to stop. We will then get doctors to check you to make sure they are ok and whether they can continue or not. The study and all the protocols within it are covered by Swansea University's indemnity policy.

9. Will my child taking part in the study be kept confidential?

Your child's GP will be notified of their participation for safety reasons. However, all personal information collected will be kept completely confidential. Only members of the research team will have access to it. Your child will be given a unique identification number so that no one knows who their results belong to and their name will not be linked to your data. After the study is complete, all private information will be deleted.

10. What if my child or I have any questions?

If you have any questions, please contact us on the details provided above. You can also ask one of the researchers when you come in to visit the Clinic.

11. What will happen with all the information collected?

If you allow it, all the collected data will be used for this research and potentially for other studies in the future in an anonymous way, which means that no one will know it's your child's information. If you allow, we would like to take some photos during the tests to use to promote the study in Science

Festivals and Scientific Conferences. These photos will only be taken with your consent and your child can be kept anonymous if you prefer.

This study is organised by Swansea University and funded by the Cystic Fibrosis Trust.

4. Chapters 5 to 8 – Parent/Guardian Information Sheet

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

School of Sport and Exercise Sciences, College of Engineering

INFORMATION SHEET (PARENT/GUARDIAN)

(Version 1.4, Date 17/01/2019)

Project Title: Calibration and Cross-Validation of Accelerometry in Youth and Adults with Cystic Fibrosis: A cross-sectional Study

Contact Details:

Dr Melitta McNarry

Email: [redacted]

Telephone: [redacted]

Mayara Silveira Bianchim

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Telephone: [redacted]

Dr Kelly Mackintosh

Email: [redacted]

Telephone: [redacted]

Dr Jeanette Hewitt (Independent contact)

Email: [redacted]

Telephone: [redacted]

1. Invitation Paragraph

Thank you for being interested in your child taking part in our project. Please read this information sheet very carefully, and think if you are happy for them to take part. If you are happy for them to, thank you! If you don't want them to take part, that is absolutely fine!

2. What is the purpose of this study?

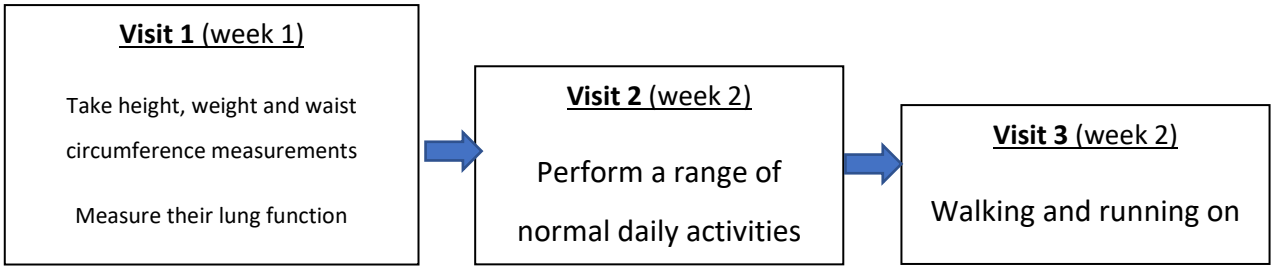
For those with CF, physical activity and exercise are key to staying as well as possible. However, we don't know how much physical activity should be recommended to those with CF. Therefore, the purpose of this study is to see how difficult daily tasks like walking and playing games are for those with CF compared to their healthy friends and family. This will mean we can make specific recommendations for those with CF about the amount of physical activity they should do.

3. Why has my child been chosen?

Your child has been asked if they would like to take part because they are under 18 years of age, have Cystic Fibrosis, and are free from any injuries or other illnesses.

4. What will happen to my child if they take part?

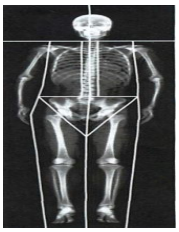
Your child will be invited to attend 3 sessions that will take place at Swansea University (Bay Campus) or Morriston Hospital:



Before the visits it would be great if your child can avoid any intense physical activities, such as running or playing sports, and avoid drinking caffeine (e.g. tea, coffee, coke) on the day before. Also, please don't let them eat in the two hours before their sessions.

Visit 1 (Swansea University, Bay Campus)

- Step 1 - Take their height, weight and waist circumference measurements.
- Step 2 – Complete a physical activity questionnaire so we can determine their current levels. There are no right or wrong answers, we are just interested in what they normally do.
- Step 3 – We will measure their lung function by getting them to breathe out as hard as possible into a mouthpiece. Following this, will ask them to lie down for 30 mins and breathe through a different mouthpiece so we can see how much energy they use while they are resting.
- Step 4 – We will then ask them to lie down for approximately 5-10 minutes to have a DEXA scan of their body. This will allow us to measure the strength of their bones as well as their body composition. We will take three different scans, one of their hand, one of their spine and another one of their whole skeleton. These scans use a very small dose of x-rays but much less than the average x-ray machine. The x-rays are the same amount as they'd get on a short-distance flight.



- Step 5 – Finally, we will give your child six physical activity monitors to wear continuously for 7 days, even when they sleep! These are Physical Activity Trackers, also known as accelerometer. It works by recording the acceleration and rotational forces when you move. We will use this equipment to tell exactly how active your child is. Four of these will be worn on their wrists (two on each wrist), one around their waist and one will be attached to their chest using sticky pads

(electrodes), which will also measure their heart rate. We are giving them six so we can see how they differ and what effect where you wear them has on how good they are at sensing their movements. It's really important that when they are wearing these monitors, they do not do anything differently. We just want them to do whatever they would normally do each day. All monitors are completely waterproof so they can be worn at all times, even when swimming. However, if they do take them off, we will give them a log sheet to note down the time they took them off and put them back on. This will help us understand the data once they return the monitors. On the log sheet, we would also like them to write down what time they went to sleep and woke up and how well they think they slept.




Visit 2 (Morriston Hospital or Swansea University – Bay Campus)

- Step 6 – For our next session, one week later, they will be able to choose whether they would like to attend the visit at Morriston Hospital or at Bay Campus to do a variety of activities that they typically do at home, like watching TV or playing games. They will be asked to do all of the activities with a face mask on to measure how much oxygen they are breathing in and out, and a small clip on their index finger that will tell us how much oxygen they have in their blood. At the end of this visit, they will take off all of the physical activity monitors that they have been wearing for the last 7 days.

Visit 3 (Morriston Hospital or Swansea University – Bay Campus)

- Step 7 – They will also be able to choose whether they would like to attend the last visit at Morriston Hospital or at Bay Campus. We will ask them to walk and then run on a treadmill while wearing the face mask and all six of the monitors again. They will also be asked to wear a small clip on your index finger that will tell us how much oxygen they have in your blood. This test will only last as long as they are happy for it to last and we will not make them run faster than they are happy with or normally do.

We can cover reasonable travel expenses to help you attend these sessions.

5. What are the possible disadvantages of my child taking part?

The exercise on the treadmill may be tiring and the mask may feel a little uncomfortable, but people generally forget about the mask after the first few minutes! We will give your child lots of time to rest and make sure there is water if they need a drink. We know that we are asking for a lot of your child's time but we will try and fit these sessions in at the best times for them. Finally, the physical activity monitors might seem quite bulky when we first give them to your child, but they are just like wearing a watch or a belt and they will soon forget about them. For the one on their chest, they might find this itchy so we will give them some spare electrodes (sticky pads) so they can change them if they want to.

6. How much radiation will my child receive and what is the associated risk?

If your child takes part in this study, we will ask them to do a body scan (bones, muscle and tissue). This will mean they get a very small dose of radiation which can harm cells in their body. Lots of radiation can increase their risk of diseases later in life. Although this might sound frightening, the amount of radiation through this scan is really small, the same as your child would get every 20 hours by just living in the UK. To put it in numbers, we estimate the exposure your child will receive from the testing to be 2.5µSv, and the radiation exposure in addition to background levels for minors (under the age of 18 years) is limited to 10µSv/year.

7. What are the possible benefits of my child taking part?

The information gained from this study will help us to help those with Cystic Fibrosis by being able to give them much better advice on how to stay healthy for as long as possible.

8. What happens if something goes wrong?

We don't expect any problems, but, if something does go wrong during the study, your child will be asked to stop. We will then get doctors to check you to make sure they are ok and whether they can continue or not. The study and all the protocols within it are covered by Swansea University's indemnity policy.

9. Will my child taking part in the study be kept confidential?

Your child's GP will be notified of their participation for safety reasons. However, all personal information collected will be kept completely confidential. Only members of the research team will have access to it. Your child will be given a unique identification number so that no one knows who their results belong to and their name will not be linked to your data. After the study is complete, all private information will be deleted.

10. What if my child or I have any questions?

If you have any questions, please contact us on the details provided above. You can also ask one of the researchers when you come in to visit the Clinic.

11. What will happen with all the information collected?

If you allow it, all the collected data will be used for this research and potentially for other studies in the future in an anonymous way, which means that no one will know it's your child's information. If you allow, we would like to take some photos during the tests to use to promote the study in Science Festivals and Scientific Conferences. These photos will only be taken with your consent and your child can be kept anonymous if you prefer.

This study is organised by Swansea University and funded by the Cystic Fibrosis Trust.

5. Chapters 5 to 8 – Under 12 years Information Sheet

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

School of Sport and Exercise Sciences, College of Engineering

INFORMATION SHEET (UNDER 12 YEARS)

(Version 1.4, Date 17/01/2019)

Project Title: Calibration and Cross-Validation of Accelerometry in Youth and Adults with Cystic Fibrosis: A cross-sectional Study

Contact Details:

Dr Melitta McNarry
Email: [redacted]
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Dr Kelly Mackintosh
Email: [redacted]
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Mayara Silveira Bianchim
Email: [redacted]
Telephone: [redacted]

Dr Jeanette Hewitt (Independent contact)
Email: [redacted]
Telephone: [redacted]

1. Invitation Paragraph

Thank you for being interested in our project. Please read this sheet very carefully. If you are happy to take part, thank you. If you don't want to take part, that is no problem.

2. What is the purpose of this study?

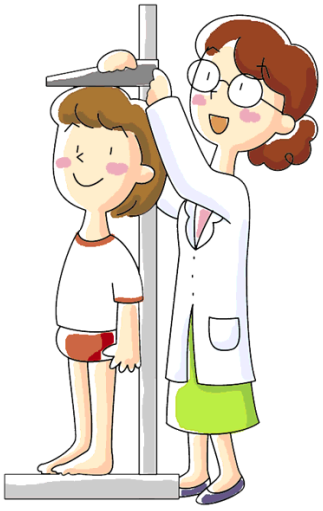
Moving around is good for health. We would like to know more about how much you move. To do this, we need to use special little monitors. We want to make sure that we are good at measuring your movements.

3. Why have you been chosen?

You have been asked if you would like to take part because you are aged between 8 and 12 years of age, have Cystic Fibrosis, and do not have any injuries or other illnesses.

4. What will happen to you if you take part?

You will be invited to come in 3 times, once to Swansea University (Bay Campus) and twice to Morriston Hospital. This will be whenever is easy for you. We can pay for you to travel there and back.



Picture 1

Visit 1

Ask any questions

Get to know the equipment

Take height and weight (Pictures 1 and 2)

Answer the questionnaire

Get to know the mask, and use the mask for a few minutes

Picture 2

Visit 2

Play and exercise. (Picture 4)

Visit 3

Walk on a treadmill with the mask (Picture 5)

Picture 3

Picture 4

Picture 5

Before the visits we will ask you to have an easy day. Try not to do hard physical activities, like running a lot or playing sport with impact.

Each visit will take about 45 minutes to 1.5 hours. We will show you all the equipment being used during the project. You can ask any questions you have.

The first visit will be at Swansea University (Bay Campus). We will ask you not to eat or drink anything 2 hours before arriving. You can only have water. First of all we will ask you to lie down for 30 minutes. We will use a mask to measure how much you breathe. We will then see how tall you are when you are standing and sitting down. Then we will see how much you weigh. We will also see how far round your waist it is and how your lungs are working. We will also take a picture of your bones. Then we will ask you to complete a few questions about how much you move and how grown up you are. There are no right or wrong answers, we are just interested in what you do on a normal day.

You can see the monitors (special devices) in the pictures. These monitors are Physical Activity Trackers. These monitors are similar to 'FitBits', and will record every movement you make. This way we will be able to tell exactly how active you are. You will wear them for a week. You can wear them all day, every day, even when you sleep or go swimming. They can get completely wet. You will wear some on your wrists, one on your right hip, and one stuck to your chest using sticky patches. The chest monitor can measure your heart beating as well. So, you will be wearing six special devices in total. You do not have to change anything about your week. Just do what you would normally do. We will give you a diary to note down if you do take the

monitors off and why. You can also write down when you went to bed and woke up each day. We will ask you how well you think you slept. ‘1’ would be not very well at all. ‘10’ would be really well.

A week later, you will be asked to come to see us again at Morriston Hospital or at Bay Campus, according to your preference. You will then do some activities that you normally do at home. This would be things like watching TV or playing games. You would be wearing the mask again to measure how much you breathe. We will ask you to use a clip on your finger. This will tell us about how much oxygen you have in your blood. After this, you can take off all six of the special devices.

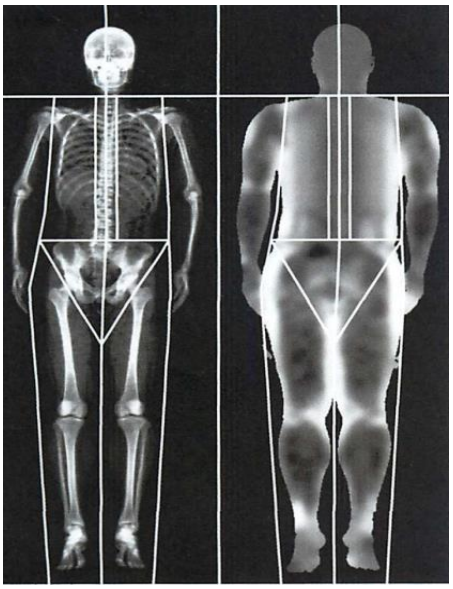
After two days, we will ask you to come back again to Morriston Hospital or at Bay Campus, according to your preference. We will ask you to walk and then run on a treadmill. You will be asked to wear the mask and monitors again. The walk and run will only last for as long as you are happy to. We will not make you run faster than you are want to.

12. What are the possible disadvantages of taking part?

You may feel tired after doing the activities. The mask may feel a little strange, but it won't make it hard to breath. The sticky pads may be a little uncomfortable when taken off. It's a bit like removing a sticky plaster, but they will come off in warm water.

13.How much radiation will I receive from the Bone Scan?

If you are happy to take part, we will take three pictures of your bones, tissues and muscles. First, we will take a picture of your whole skeleton. This will look like the picture below (picture 6). Then, we will take a picture of the skeleton of your hand and another one of your spine. You can use your normal clothes to do this test. This uses an X-Ray machine, like in hospitals if you think you've broken your arm or leg, but it is much less strong. This will mean you get a very small dose of radiation (X-Rays), which can harm cells in your body. This sounds scary but the amount of radiation through this scan is really small. It is the same as you get every 20 hours by just living in the UK.



Picture 6

14. What are the possible benefits of taking part?

You will find out how fit you are and how much you move in a week.

15. What happens if something goes wrong?

We don't think there will be anything that goes wrong. If it does, we will ask you to stop straight away. The doctors will check to see if you are OK. They can say if you can keep taking part in the project.

16. Will my taking part in the study be kept secret?

Your GP will be notified of your participation for safety reasons. However, all personal information collected will be kept completely secret. That is, only members of the research team will be able to see it. You will be given a special number so that no one knows who your results belong to and your name will not be linked to your data. After the study is finished, all private information will be deleted.

17. What if I have any questions?

If you have any questions you can ask an adult to ask us. Our phone number and email addresses are at the top of this information. You can also ask one of the people on the project when you come in to see us.

18. What will happen with all the information collected?

If you are happy we want to look at all your information to see if we can help to measure how much other children move. We can see if it will help their health. We will give you a special code so no-one will know it is your information. We would also like to take some photos of you during the activities if you are ok with that, but you don't have

to agree. These photos would be used to show others what the study was like but we can make it so no one can recognise you.

This study is organised by Swansea University and funded by the Cystic Fibrosis Trust.

6. Chapters 5 to 8 – Control under 12 years Information Sheet

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

School of Sport and Exercise Sciences, College of Engineering

CONTROL INFORMATION SHEET (UNDER 12 YEARS)

(Version 1.3, Date 07/03/2018)

Project Title: Calibration and Cross-Validation of Accelerometry in Youth and Adults with Cystic Fibrosis: A cross-sectional Study

Contact Details:

Dr Melitta McNarry
Email: [redacted]
Telephone: [redacted]

Dr Kelly Mackintosh
Email: [redacted]
Telephone: [redacted]

Mayara Silveira Bianchim
Email: [redacted]
Telephone: [redacted]

Dr Jeanette Hewitt (Independent contact)
Email: [redacted]
Telephone: [redacted]

1. Invitation Paragraph

Thank you for being interested in our project. Please read this sheet very carefully. If you are happy to take part, thank you. If you don't want to take part, that is no problem.

2. What is the purpose of this study?

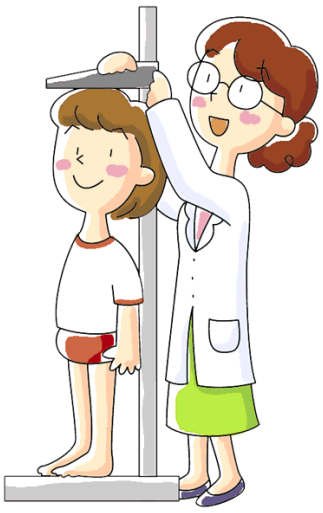
Moving around is good for health. We would like to know more about how much you move. To do this, we need to use special little monitors. We want to make sure that we are good at measuring your movements. This will help us see if we can help children with Cystic Fibrosis to live life to the full.

3. Why have you been chosen?

You have been asked if you would like to take part because you are aged between 8 and 12 years of age, and do not have any injuries or illnesses.

4. What will happen to you if you take part?

You will be invited to come in 3 times to Swansea University (Bay Campus). This will be whenever is easy for you. We can pay for you to travel there and back.



Picture 1

Visit 1

Ask any questions

Get to know the equipment

Take height and weight (Pictures 1 and 2)

Answer the questionnaire

Get to know the mask, and use the mask for a few minutes

Picture 2

Visit 2

Play and exercise. (Picture 4)

Visit 3

Walk on a treadmill with the mask (Picture 5)

Picture 3

Picture 4

Picture 5

Before the visits we will ask you to have an easy day. Try not to do hard physical activities, like running a lot or playing sport with impact.

Each visit will take about 45 minutes to 1.5 hours. We will show you all the equipment being used during the project. You can ask any questions you have.

For the first visit, we will ask you not to eat or drink anything 2 hours before arriving. You can only have water. First of all we will ask you to lie down for 30 minutes. We will use a mask to measure how much you breathe. We will then see how tall you are when you are standing and sitting down. Then we will see how much you weigh. We will also see how far round your waist it is and how your lungs are working. We will also take a picture of your bones. Then we will ask you to complete a few questions about how much you move and how grown up you are. There are no right or wrong answers, we are just interested in what you do on a normal day.

You can see the monitors (special devices) in the pictures. These monitors are Physical Activity Trackers. These monitors are similar to 'FitBits', and will record every movement you make. This way we will be able to tell exactly how active you are. You will wear them for a week. You can wear them all day, every day, even when you sleep or go swimming. They can get completely wet. You will wear some on your wrists, one on your right hip, and one stuck to your chest using sticky patches. The chest monitor can measure your heart beating as well. So, you will be wearing six special devices in total. You do not have to change anything about your week. Just do what you would normally do. We will give you a diary to note down if you do take the

monitors off and why. You can also write down when you went to bed and woke up each day. We will ask you how well you think you slept. ‘1’ would be not very well at all. ‘10’ would be really really well.

A week later, you will be asked to come to see us again. You will then do some activities that you normally do at home. This would be things like watching TV or playing games. You would be wearing the mask again to measure how much you breathe. We will ask you to use a clip on your finger. This will tell us about how much oxygen you have in your blood. After this, you can take off all six of the special devices.

After two days, we will ask you to come back again. We will ask you to walk and then run on a treadmill. You will be asked to wear the mask and monitors again. The walk and run will only last for as long as you are happy to. We will not make you run faster than you are want to.

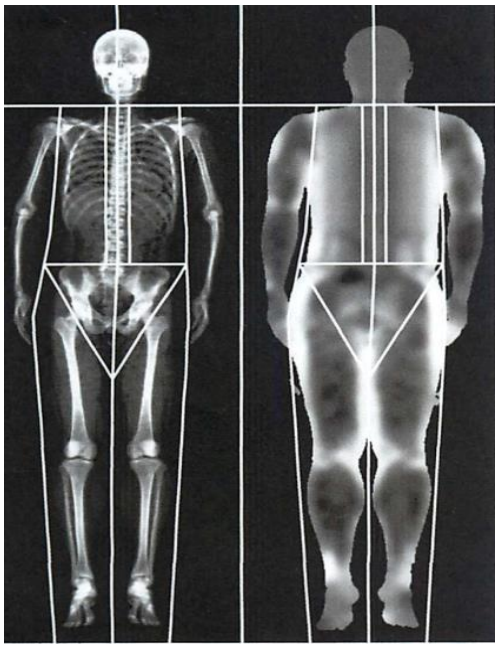
5. What are the possible disadvantages of taking part?

You may feel tired after doing the activities. The mask may feel a little strange, but it won’t make it hard to breath. The sticky pads may be a

little uncomfortable when taken off. It's a bit like removing a sticky plaster, but they will come off in warm water.

6. How much radiation will I receive from the Bone Scan?

If you are happy to take part, we will take three pictures of your bones, tissues and muscles. First, we will take a picture of your whole skeleton. This will look like the picture below (picture 6). Then, we will take a picture of the skeleton of your hand and another one of your spine. You can use your normal clothes to do this test. This uses an X-Ray machine, like in hospitals if you think you've broken your arm or leg, but it is much less strong. This will mean you get a very small dose of radiation (X-Rays), which can harm cells in your body. This sounds scary but the amount of radiation through this scan is really small. It is the same as you get every 20 hours by just living in the UK.



Picture 6

7. What are the possible benefits of taking part?

You will find out how fit you are and how much you move in a week.

8. What happens if something goes wrong?

We don't think there will be anything that goes wrong. If it does, we will ask you to stop straight away. The doctors will check to see if you are OK. They can say if you can keep taking part in the project.

9. Will my taking part in the study be kept secret?

Your GP will be notified of your participation for safety reasons. However, all personal information collected will be kept completely secret. That is, only members of the research team will be able to see it. You will be given a special number so that no one knows who your results belong to and your name will not be linked to your data. After the study is finished, all private information will be deleted.

10. What if I have any questions?

If you have any questions you can ask an adult to ask us. Our phone number and email addresses are at the top of this information. You can also ask one of the people on the project when you come in to see us.

11. What will happen with all the information collected?

If you are happy we want to look at all your information to see if we can help to measure how much other children move. We can see if it will help their health. We will give you a special code so no-one will know it is your information. We would also like to take some photos of you during the activities if you are ok with that, but you don't have

to agree. These photos would be used to show others what the study was like but we can make it so no one can recognise you.

This study is organised by Swansea University and funded by the Cystic Fibrosis Trust.

Cystic Fibrosis Trust

Fighting for a Life Unlimited

Appendix F: Consent and Assent Forms

1. Chapters 5 to 8 – Parent/Guardian Consent Form

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

School of Sport and Exercise Sciences, College of Engineering

PARENT/GUARDIAN CONSENT FORM

(Version 1.3, Date: 07/03/2018)

Project Title: Calibration and Cross-Validation of Accelerometry in Youth and Adults with Cystic Fibrosis: A cross-sectional Study

Contact Details:

Dr Melitta McNarry

Email: [redacted]

Telephone: [redacted]

Dr Kelly Mackintosh

Email: [redacted]

Telephone: [redacted]

Mayara Silveira Bianchim

Email: [redacted]

Telephone: [redacted]

Dr Jeanette Hewitt (Independent contact)

Email: [redacted]

Telephone: [redacted]

Please initial box

1. I confirm that I have read and understood the information sheet dated 07/03/2018 (version number 1.3) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my child's participation is voluntary and that they are free to withdraw at any time, without giving any reason and without their medical care, school work or legal rights being affected. ☐

3. I understand that sections of any of data obtained may be looked at by responsible individuals from the Swansea University or from regulatory ☐

authorities where it is relevant to my child taking part in research. I give permission for these individuals to have access to these records.

4. I am happy for photos of my child to be taken and used to promote the project and share the findings. ☐
5. I am happy for my child's information to be used anonymously in future research ☐
6. I am happy for my child's GP to be informed of their participation in this study. ☐
7. I agree for my child to take part in the above study. ☐

_____	_____	_____
Name of Parent/Guardian	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature
_____	_____	_____
Researcher	Date	Signature

2. Chapters 5 to 8 – Participant Assent Form

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

School of Sport and Exercise Sciences, College of Engineering

PARTICIPANT ASSENT FORM

(Version 1.3, Date: 07/03/2018)

Project Title: Calibration and Cross-Validation of Accelerometry in Youth and Adults with Cystic Fibrosis: A cross-sectional Study

Contact Details:

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Email: [redacted]

Telephone: [redacted]

Dr Kelly Mackintosh

Email: [redacted]

Telephone: [redacted]

Mayara Silveira Bianchim

Email: [redacted]

Telephone: [redacted]

Dr Jeanette Hewitt (Independent contact)

[redacted]

Telephone: [redacted]

Please initial box

1. I have read and understood the information sheet for this study and have been able to ask any questions I have. ☐

2. I know that it is my choice to take part and that I can stop doing so at any time, without giving any reason, and without any problems. ☐

3. I understand that some of the information I give may be looked at by people at Swansea University or the hospital. I am happy for these people to see my results. ☐

☐

4. I am happy for my photos to be taken and shown to people interested in the project. ☐
5. I am happy for my information to be used anonymously in future research ☐
6. I am happy for my GP to be informed that I am doing this study. ☐
7. I agree to take part in the above study. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Appendix G: Chapter 5 – Supplementary Material

1. Activity Survey

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

Swansea University
Prifysgol Abertawe

Swansea University
Prifysgol Abertawe

List of Daily Life Physical Activity

We would like to ask for you to think carefully about the activities you usually do at home, school and during transport, and then mark a X on the boxes of those activities you recognize that you would usually perform.

- ☐ Continuous running.
- ☐ Walking with a backpack.
- ☐ Arts and crafts.
- ☐ Hopscotch.
- ☐ Wii (or Kinect) games.
- ☐ Board games.
- ☐ Rope Jumping.
- ☐ Climbing stairs.
- ☐ Playground games.
- ☐ Gymnastics.
- ☐ Stretching.
- ☐ Stop and go.
- ☐ Capture the flag.
- ☐ Cleaning your room.
- ☐ Frisbee
- ☐ Basketball.

- ☐ Football.
- ☐ Tennis.
- ☐ Watching TV / Playing video games
- ☐ Computer use / Mobile phone
- ☐ Another activity: _____

2. Leave-one-out Cross-validation of Cut-points

Table G5.1 Leave-one-out Cross-validation of Cut-points

Placement	Intensity	CF						Healthy					
		ENMO cut-point	MSE	Accuracy (%)	MAD cut-point	MSE	Accuracy (%)	ENMO cut-point	MSE	Accuracy (%)	MAD cut-point	MSE	Accuracy (%)
						ActiGraph							
Dominant wrist	SED	55.5	0.01	73	74.2	0.01	84	51.4	0.05	80	76.1	0.05	67
	MPA	63.0	0.01	87	82.5	0.1	83	63.5	0.04	71	113.5	0.05	67
	VPA	177.9	0.01	82	262.7	0.01	88	103.3	0.03	98	220.4	0.02	77
Non-dominant wrist	SED	38.4	0.01	73	51.2	0.01	77	30.8	0.05	78	73.4	0.04	77
	MPA	60.2	0.01	70	73.1	0.02	85	65.9	0.05	81	149	0.03	80
	VPA	115.3	0.01	96	260.8	0.01	86	128.4	0.02	82	214.2	0.02	81
Waist	SED	61.3	0.005	98	55.3	0.009	77	37.3	0.01	78	43.5	0.03	83
	MPA	73.1	0.005	71	58.9	0.02	72	66.8	0.01	91	109.2	0.03	81
	VPA	133.1	0.004	78	92.4	0.008	66	83.6	0.01	94	170	0.01	78

		GENEActiv											
Dominant wrist	SED	44.8	0.01	77	74.6	0.009	77	38.3	0.02	93	61.5	0.03	89
	MPA	74.8	0.01	81	85.3	0.01	66	86.8	0.03	91	94.5	0.03	76
	VPA	156.8	0.007	99	222.5	0.006	99	127.8	0.01	98	186.4	0.01	86
Non-dominant wrist	SED	43.9	0.01	85	70.9	0.01	98	39.0	0.01	92	73.5	0.01	86
	MPA	64.3	0.01	73	85.2	0.01	66	84.7	0.01	95	129.4	0.01	89
	VPA	165.6	0.01	98	224.5	0.01	99	100.2	0.0008	95	186.9	0.008	99

CF: Cystic Fibrosis, ENMO: Euclidean norm minus one, MAD: mean amplitude deviation, SED: sedentary; MPA: moderate activity; VPA: vigorous activity, MSE: mean squared error.

Appendix H: Chapter 8 – Matrices and Cross-Validation

1. Confusion Matrices of Random Forest to Classify Activity Type

Table H8.1 Confusion Matrices of Random Forest to Classify Different Activities for each Placement and Accelerometer Brand

		CF						Healthy					
Brand / Placement	**Activities**	**TV**	**Colouring/ writing**	**Handheld device**	**Games**	**Walk**	**Stairs**	**TV**	**Colouring/ writing**	**Handheld device**	**Games**	**Walk**	**Stairs**
GE non-dominant wrist	**TV**	283	0	0	0	0	0	120	0	0	0	0	0
	Colouring/ writing	0	239	0	0	0	0	0	120	0	0	0	0
	Handheld device	0	0	193	0	0	0	0	0	223	0	0	0
	Games	0	0	0	195	0	0	0	0	0	105	0	0
	Walk	0	0	0	0	118	0	0	0	0	0	150	0
	Stairs	0	0	0	0	0	59	0	0	0	0	0	105
GE dominant wrist	**TV**	299	0	0	0	0	0	135	0	0	0	0	0
	Colouring/ writing	0	312	0	0	0	0	0	45	0	0	0	0

	Handheld device	0	0	135	0	0	0	0	0	120	0	0	0
	Games	0	0	0	165	0	0	0	0	0	105	0	0
	Walk	0	0	0	0	282	0	0	0	0	0	105	0
	Stairs	0	0	0	0	0	210	0	0	0	0	0	45
AG non-dominant wrist	**TV**	388	0	0	0	0	0	299	0	0	0	0	0
	Colouring/ writing	0	285	0	0	0	0	0	312	0	0	0	0
	Handheld device	0	0	405	0	0	0	0	0	135	0	0	0
	Games	0	0	0	315	0	0	0	0	0	165	0	0
	Walk	0	0	0	0	375	0	0	0	0	0	282	0
	Stairs	0	0	0	0	0	409	1	0	0	0	0	210
AG dominant wrist	**TV**	313	0	0	0	0	0	253	0	0	0	0	0
	Colouring/ writing	0	255	0	0	0	0	0	298	0	0	0	0

	Handheld device	0	0	405	0	0	0	0	0	135	0	0	0
	Games	0	0	0	15	0	0	0	0	0	254	0	0
	Walk	0	0	0	0	690	0	0	0	0	0	195	0
	Stairs	0	0	0	0	0	330	0	0	0	0	0	195
AG waist	**TV**	225	0	0	0	0	0	209	0	0	0	0	0
	Colouring/ writing	0	255	0	0	0	0	0	207	0	0	0	0
	Handheld device	0	0	270	0	0	0	0	0	90	0	0	0
	Games	0	0	0	300	0	0	0	0	0	180	0	0
	Walk	0	0	0	0	284	0	0	0	0	0	165	0
	Stairs	0	0	0	0	0	270	0	0	0	0	0	163

CF: Cystic Fibrosis, GE: GENEActiv, AG: ActiGraph

2. Confusion Matrices of Random Forest to Classify Activity Intensity

Table H8.2 Confusion Matrices of Random Forest to Classify Physical Activity Intensities for each Placement and Accelerometer Brand

		CF				Healthy			
Brand / Placement	**Activities**	**SED**	**LPA**	**MPA**	**VPA**	**SED**	**LPA**	**MPA**	**VPA**
GE non-dominant wrist	**SED**	1767	0	0	0	252	0	0	N/A
	LPA	0	1436	0	0	0	280	0	N/A
	MPA	0	0	179	0	0	0	60	N/A
	VPA	0	0	0	15	N/A	N/A	N/A	N/A
GE dominant wrist	**SED**	584	1	0	0	685	0	0	0
	LPA	0	533	0	0	1	823	0	0
	MPA	0	0	44	0	0	0	118	0
	VPA	0	0	0	15	0	0	0	15
AG non-dominant wrist	**SED**	1185	0	0	0	897	0	0	0
	LPA	0	1210	0	0	1	583	0	0
	MPA	0	0	389	0	0	0	298	0

	VPA	0	0	0	14	0	0	0	15
AG dominant wrist	**SED**	771	0	0	NA	685	0	0	0
	LPA	0	895	0	NA	1	823	0	0
	MPA	0	0	186	NA	0	0	118	0
	VPA	NA	NA	NA	NA	0	0	0	15
AG waist	**SED**	296	0	0	0	928	0	0	0
	LPA	0	N/A	0	0	1	599	0	0
	MPA	0	0	580	0	0	0	330	0
	VPA	0	0	0	45	0	0	0	30

CF: Cystic Fibrosis, GE: GENEActiv, AG: ActiGraph, SED: sedentary time, LPA: light physical activity, MPA: moderate physical activity, VPA: vigorous physical activity.

3. Confusion Matrices of Extreme Gradient Boosting Tree and k-Nearest Neighbour to Classify Activity Type

Table H8.3 Confusion Matrices of XGBoost and k-NN to Classify Different Activities for each Placement and Accelerometer Brand

		CF						Healthy					
Brand / Placement	**Activities**	**TV**	**Colouring/ writing**	**Handheld device**	**Games**	**Walk**	**Stairs**	**TV**	**Colouring/ writing**	**Handheld device**	**Games**	**Walk**	**Stairs**
GE non-dominant wrist	**TV**	42	0	0	0	0	0	42	0	0	0	0	0
	Colouring/ writing	0	35	0	0	0	0	0	35	0	0	0	0
	Handheld device	0	0	28	0	0	0	0	0	28	0	0	0
	Games	0	0	0	29	0	0	0	0	0	29	0	0
	Walk	0	0	0	0	17	0	0	0	0	0	17	0
	Stairs	0	0	0	0	0	8	0	0	0	0	0	8
GE dominant wrist	**TV**	44	0	0	0	0	0	20	0	0	0	0	0
	Colouring/ writing	0	47	0	0	0	0	0	6	0	0	0	0

	Handheld device	0	0	20	0	0	0	0	0	18	0	0	0
	Games	0	0	0	24	0	0	0	0	0	15	0	0
	Walk	0	0	0	0	42	0	0	0	0	0	15	0
	Stairs	0	0	0	0	0	31	0	0	0	0	0	6
AG non-dominant wrist	**TV**	58	0	0	0	0	0	44	0	0	0	0	0
	Colouring/ writing	0	42	0	0	0	0	0	46	0	0	1	0
	Handheld device	0	0	60	0	0	0	0	0	20	0	0	0
	Games	0	0	0	47	0	0	0	0	0	24	0	0
	Walk	0	0	0	0	56	0	0	0	0	0	42	0
	Stairs	0	0	0	0	0	60	0	0	0	0	0	31
AG dominant wrist	**TV**	46	0	0	0	0	0	37	0	0	0	0	0
	Colouring/ writing	0	38	0	0	0	0	0	44	0	0	0	0

	Handheld device	0	0	60	0	0	0	0	0	20	0	0	0
	Games	0	0	0	2	0	0	0	0	0	38	0	0
	Walk	0	0	0	0	103	0	0	0	0	0	29	0
	Stairs	0	0	0	0	0	49	0	0	0	0	0	29
AG waist	**TV**	33	0	0	0	0	0	31	0	0	0	0	0
	Colouring/ writing	0	38	0	0	0	0	0	31	0	0	0	0
	Handheld device	0	0	40	0	0	0	0	0	13	0	0	0
	Games	0	0	0	45	0	0	0	0	0	27	0	0
	Walk	0	0	0	0	42	0	0	0	0	0	24	0
	Stairs	0	0	0	0	0	40	0	0	0	0	0	24

CF: Cystic Fibrosis, GE: GENEActiv, AG: ActiGraph; XGBoost: eXtreme Gradient Boosting Trees; k-NN: k-Nearest Neighbour.

4. Confusion Matrices of Extreme Gradient Boosting Tree and k-Nearest Neighbour to Classify Activity Intensity

Table H8.4 Confusion Matrices of XGBoost and k-NN to Classify Physical Activity Intensities for each Placement and Accelerometer Brand

		CF				Healthy			
Brand / Placement	**Activities**	**SED**	**LPA**	**MPA**	**VPA**	**SED**	**LPA**	**MPA**	**VPA**
GE non-dominant wrist	**SED**	265	0	0	0	143	0	0	0
	LPA	0	215	0	0	0	93	0	0
	MPA	0	0	26	0	0	0	42	0
	VPA	0	0	0	2	0	0	0	0
GE dominant wrist	**SED**	211	0	0	N/A	102	0	0	0
	LPA	0	212	0	N/A	0	123	0	0
	MPA	0	0	36	N/A	0	0	17	0
	VPA	N/A	N/A	N/A	N/A	0	0	0	2

AG non-dominant wrist	**SED**	177	0	0	0	134	0	0	0
	LPA	0	181	0	0	0	87	0	0
	MPA	0	0	58	0	0	0	44	0
	VPA	0	0	0	2	0	0	0	2
AG dominant wrist	**SED**	184	0	0	N/A	102	0	0	0
	LPA	0	172	0	N/A	0	123	0	0
	MPA	0	0	36	N/A	0	0	17	0
	VPA	N/A	N/A	N/A	N/A	0	0	0	2
AG waist	**SED**	179	0	0	N/A	139	0	0	0
	LPA	0	170	0	N/A	0	89	0	0
	MPA	0	0	54	N/A	0	0	49	0
	VPA	N/A	N/A	N/A	N/A	0	0	0	4

CF: Cystic Fibrosis, GE: GENEActiv, AG: ActiGraph, SED: sedentary time, LPA: light physical activity, MPA: moderate physical activity, VPA: vigorous physical activity. XGBoost: eXtreme Gradient Boosting Trees; k-NN: k-Nearest Neighbour.

5. Cross-validation Results for Random Forest, Extreme Gradient Boosting and k-Nearest Neighbour to Classify Physical Activity Types

Table H8.5 Predictive Accuracy (%) of Different Models to Classify Different Activities

		CF				Healthy			
	Placement	**Sensitivity**	**Specificity**	**Accuracy**	**Detection Rate**	**Sensitivity**	**Specificity**	**Accuracy**	**Detection Rate**
Random Forest									
TV	*GE non-dominant wrist*	100	100	100	0.26	100	100	100	0.14
	GE dominant wrist	99.67	100	99.83	0.21	100	100	100	0.24
	AG non-dominant wrist	100	100	100	0.17	99.67	100	99.83	0.21
	AG dominant wrist	100	100	100	0.15	100	100	100	0.19
	AG waist	100	100	100	0.14	100	100	100	0.20
Colouring/writing	*GE non-dominant wrist*	100	100	100	0.21	100	100	100	0.14
	GE dominant wrist	100	99.82	99.91	0.22	100	100	100	0.08
	AG non-dominant wrist	100	100	100	0.13	100	99.82	99.91	0.22
	AG dominant wrist	100	100	100	0.12	100	100	100	0.22
	AG waist	100	100	100	0.15	100	100	100	0.20
Handheld device	*GE non-dominant wrist*	100	100	100	0.17	100	100	100	0.27
	GE dominant wrist	100	100	100	0.09	100	100	100	0.21
	AG non-dominant wrist	100	100	100	0.18	100	100	100	0.09

	AG dominant wrist	100	100	100	0.20	100	100	100	0.10
	AG waist	100	100	100	0.16	100	100	100	0.08
Games	*GE non-dominant wrist*	100	100	100	0.17	100	100	100	0.12
	GE dominant wrist	100	100	100	0.11	100	100	100	0.18
	AG non-dominant wrist	100	100	100	0.14	100	100	100	0.11
	AG dominant wrist	100	100	100	0.007	100	100	100	0.19
	AG waist	100	100	100	0.18	100	100	100	0.17
Walk	*GE non-dominant wrist*	100	100	100	0.10	100	100	100	0.18
	GE dominant wrist	99.30	100	99.65	0.20	100	100	100	0.18
	AG non-dominant wrist	100	100	100	0.17	99.30	100	99.65	0.20
	AG dominant wrist	100	100	100	0.34	100	100	100	0.14
	AG waist	100	100	100	0.17	100	100	100	0.16
Handheld device	*GE non-dominant wrist*	100	100	100	0.05	100	100	100	0.12
	GE dominant wrist	100	99.92	99.96	0.14	100	100	100	0.08
	AG non-dominant wrist	100	100	100	0.18	100	99.92	99.96	0.14
	AG dominant wrist	100	100	100	0.16	100	100	100	0.14
	AG waist	100	100	100	0.16	100	100	100	0.16
XGBoost / k-NN									
TV	*GE non-dominant wrist*	100	100	100	0.26	100	100	100	0.14
	GE dominant wrist	100	100	100	0.21	100	100	100	0.25
	AG non-dominant wrist	100	100	100	0.18	100	100	100	0.21

	AG dominant wrist	100	100	100	0.15	100	100	100	0.18
	AG waist	100	100	100	0.13	100	100	100	0.20
Colouring/writing	*GE non-dominant wrist*	100	100	100	0.22	100	100	100	0.14
	GE dominant wrist	100	100	100	0.22	100	100	100	0.07
	AG non-dominant wrist	100	100	100	0.13	100	99.38	99.69	0.22
	AG dominant wrist	100	100	100	0.12	100	100	100	0.22
	AG waist	100	100	100	0.13	100	100	100	0.20
Handheld device	*GE non-dominant wrist*	100	100	100	0.17	100	100	100	0.27
	GE dominant wrist	100	100	100	0.09	100	100	100	0.22
	AG non-dominant wrist	100	100	100	0.18	100	100	100	0.09
	AG dominant wrist	100	100	100	0.20	100	100	100	0.10
	AG waist	100	100	100	0.13	100	100	100	0.08
Games	*GE non-dominant wrist*	100	100	100	0.18	100	100	100	0.12
	GE dominant wrist	100	100	100	0.11	100	100	100	0.18
	AG non-dominant wrist	100	100	100	0.14	100	100	100	0.11
	AG dominant wrist	100	100	100	0.006	100	100	100	0.19
	AG waist	100	100	100	0.13	100	100	100	0.18
Walk	*GE non-dominant wrist*	100	100	100	0.10	100	100	100	0.18
	GE dominant wrist	100	100	100	0.20	100	100	100	0.18
	AG non-dominant wrist	100	100	100	0.17	97.67	100	98.84	0.20
	AG dominant wrist	100	100	100	0.34	100	100	100	0.14

	AG waist	100	100	100	0.13	100	100	100	0.16
Stairs	*GE non-dominant wrist*	100	100	100	0.05	100	100	100	0.12
	GE dominant wrist	100	100	100	0.14	100	100	100	0.07
	AG non-dominant wrist	100	100	100	0.18	100	100	100	0.14
	AG dominant wrist	100	100	100	0.16	100	100	100	0.14
	AG waist	100	100	100	0.13	100	100	100	0.16

CF: Cystic Fibrosis, GE: GENEActiv, AG: ActiGraph, XGBoost: eXtreme Gradient Boosting Trees; k-NN: k-Nearest Neighbour.

6. Cross-validation Results for Random Forest, Extreme Gradient Boosting and k-Nearest Neighbour to Classify Physical Activity Intensities

Table H8.6 Predictive Accuracy (%) of Different Models to Classify Physical Activity Intensities

		CF				Healthy			
	Placement	**Sensitivity**	**Specificity**	**Accuracy**	**Detection Rate**	**Sensitivity**	**Specificity**	**Accuracy**	**Detection Rate**
Random Forest									
SED	*GE non-dominant wrist*	100	100	100	0.52	NA	NA	NA	NA
	GE dominant wrist	100	100	100	0.45	100	100	100	0.41
	AG non-dominant wrist	100	100	100	0.42	99.89	100	99.94	0.50
	AG dominant wrist	100	100	100	0.41	100	100	100	0.39
	AG waist	99.66	100	99.85	0.32	100	100	100	0.49
LPA	*GE non-dominant wrist*	100	100	100	0.42	NA	NA	NA	NA
	GE dominant wrist	100	100	100	0.46	100	100	100	0.50
	AG non-dominant wrist	100	100	100	0.43	100	100	99.96	0.32
	AG dominant wrist	100	100	100	0.48	100	100	100	0.45
	AG waist	100	99.82	99.85	0.62	100	100	100	0.31
MPA	*GE non-dominant wrist*	100	100	100	0.05	NA	NA	NA	NA
	GE dominant wrist	100	100	100	0.07	100	100	100	0.07
	AG non-dominant wrist	100	100	100	0.13	100	100	100	0.16

	AG dominant wrist	100	100	100	0.10	100	100	100	0.11
	AG waist	100	100	100	0.04	100	100	100	0.17
VPA	*GE non-dominant wrist*	100	100	100	0.004	NA	NA	NA	NA
	GE dominant wrist	100	100	100	0.01	100	100	100	0.009
	AG non-dominant wrist	100	100	100	0.005	100	100	100	0.008
	AG dominant wrist	NA	NA	NA	NA	100	100	100	0.03
	AG waist	NA	NA	NA	NA	100	100	100	0.01
XGBoost / k-NN									
SED	*GE non-dominant wrist*	100	100	100	0.52	100	100	100	0.51
	GE dominant wrist	100	100	100	0.45	100	100	100	0.41
	AG non-dominant wrist	100	100	100	0.42	100	100	100	0.50
	AG dominant wrist	100	100	100	0.46	100	100	100	0.39
	AG waist	100	100	100	0.44	100	100	100	0.49
LPA	*GE non-dominant wrist*	100	100	100	0.42	100	100	100	0.51
	GE dominant wrist	100	100	100	0.46	100	100	100	0.50
	AG non-dominant wrist	100	100	100	0.43	100	100	100	0.32
	AG dominant wrist	100	100	100	0.43	100	100	100	0.46
	AG waist	100	100	100	0.42	100	100	100	0.31
MPA	*GE non-dominant wrist*	100	100	100	0.05	100	100	100	0.33
	GE dominant wrist	100	100	100	0.07	100	100	100	0.06
	AG non-dominant wrist	100	100	100	0.13	100	100	100	0.16

	AG dominant wrist	100	100	100	0.09	100	100	100	0.11
	AG waist	100	100	100	0.13	100	100	100	0.17
VPA	*GE non-dominant wrist*	100	100	100	0.003	100	100	100	0.15
	GE dominant wrist	NA	NA	NA	NA	100	100	100	0.008
	AG non-dominant wrist	100	100	100	0.004	100	100	100	0.007
	AG dominant wrist	NA	NA	NA	NA	100	100	100	0.03
	AG waist	NA	NA	NA	NA	100	100	100	0.01

CF: Cystic Fibrosis, GE: GENEActiv, AG: ActiGraph, SED: sedentary time, LPA: light physical activity, MPA: moderate physical activity, VPA: vigorous physical activity, XGBoost: eXtreme Gradient Boosting Trees; k-NN: k-Nearest Neighbour.

Appendix I: Accelerometry Procedures

1. Chapters 5 to 8 – Accelerometry Instructions for 12 to 18 years

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

Swansea University
Prifysgol Abertawe

School of Sport and Exercise Sciences, College of Engineering

Instructions on How to Use the Monitors (12 – 18 years)

(Version 1.2, Date 17/10/2017)

This is a Physical Activity Tracker! These monitors are like fancier '*FitBits',* and will record every movement you make, they are called accelerometers! This way we will be able to tell exactly how active you really are.

All the monitors can get wet and can be worn at all times. You can wear them whilst sleeping or for water-based activities, like swimming. You do not need to change anything about your week; we want to know how much you usually move.

Wrist Monitors:

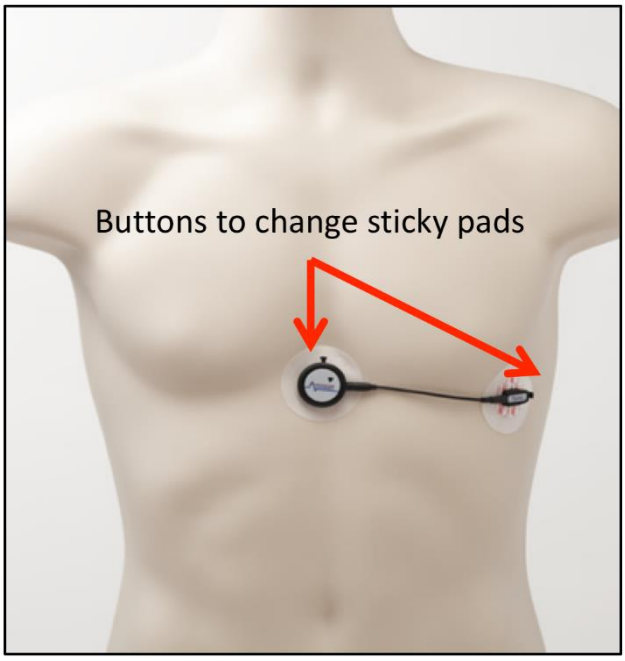
You can wear the monitors on your wrist just like a watch. The monitors will be fully charged and the battery will last the full week. Don't worry if the screens are blank - the monitors will be working! The monitors can get wet, so you don't need to take them off, even for swimming or having a shower. Please make sure that they do not move around on your wrist, but are not too tight that they are uncomfortable. You can change the strap length, just like on a watch.

Wear the hip monitor like a belt, just above your **right** hipbone. You can wear it underneath or on top of your clothing. At first the belt may feel slightly funny, but after a few hours you will probably forget about it. Please wear the monitor so that the writing is facing the right way up (see picture below). **The monitor should not move around when you are active.** You can tighten it by pulling the ends of the straps. To loosen it, push more of the strap through the loop.

The hip monitor will be fully charged. You do not need to worry about charging it. Don't worry if the screen doesn't have anything on it – the monitor will be working! The monitor can get wet, but you might want to take it off to go swimming or when having a bath or shower so the belt doesn't get wet. Please make sure you put it back on as soon as you can. Make sure you write in the log sheet we have given you the times the monitor was taken off and put back on.

Chest Monitor:

The monitor on your chest is attached using two sticky pads (see the picture below). You need to make sure that the cable is in a straight line. You might not need to change the pads, but will we give you some spare ones if you need to. They might come off if you get very hot or do a lot of swimming. The monitor can get wet, so you can wear it in the shower or bath, or to go swimming. The monitor will be fully charged, so the battery will last the full week.



What should I do if I need to change the sticky pads on my chest?

First of all, you need to clean the skin where the sticky pad was. After cleaning the skin, make sure it's dry before you attempt to stick on a new pad. The sticky pad in the middle should be placed two palms from your belly button (in the middle of your chest). The other one should be placed in line with it, as far round as the monitor will comfortably reach. It is best to stick the new pads where the old ones were. To attach the monitor to the metal spike on the sticky pads, you will need to press in and hold each of the buttons (shown in the picture above).

If you have any trouble replacing the sticky pads, or any kind of problems with the monitors, feel free to contact us at any time!

Please don't forget to keep a track of every time you take the monitors off and put them back. You can do this on the log sheet given to you.

Please remember to wear the monitors every day (including during the weekend and whilst sleeping) for the next week. If you do take them off for any reason, please put them back on as soon as you can. Do NOT let anyone else wear your monitors.

Please take care of the monitors. Each one broken or damaged will cost us the same as an Xbox or PS3 to replace.

If you have any questions or if something happens to your monitor please contact:

Mayara Silveira Bianchim

[redacted]

Alternatively, you can contact:

Dr Melitta McNarry

[redacted]

[redacted]

2. Chapters 5 to 8 – Accelerometry Instructions for Parents/Guardian

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

School of Sport and Exercise Sciences, College of Engineering

Swansea University
Prifysgol Abertawe

Instructions on How to Use the Monitors (Parental/Guardian)

(Version 1.2, Date 17/10/2017)

This is a Physical Activity Tracker, also known as accelerometer. It works by reading and recording the acceleration and rotational forces when you move. We will use this equipment to tell exactly how active your child really is.

All monitors are fully waterproof and can be worn at all times, including sleeping and water-based activities. Your child does not need to change anything about their week; we want to know their usual physical activity levels.

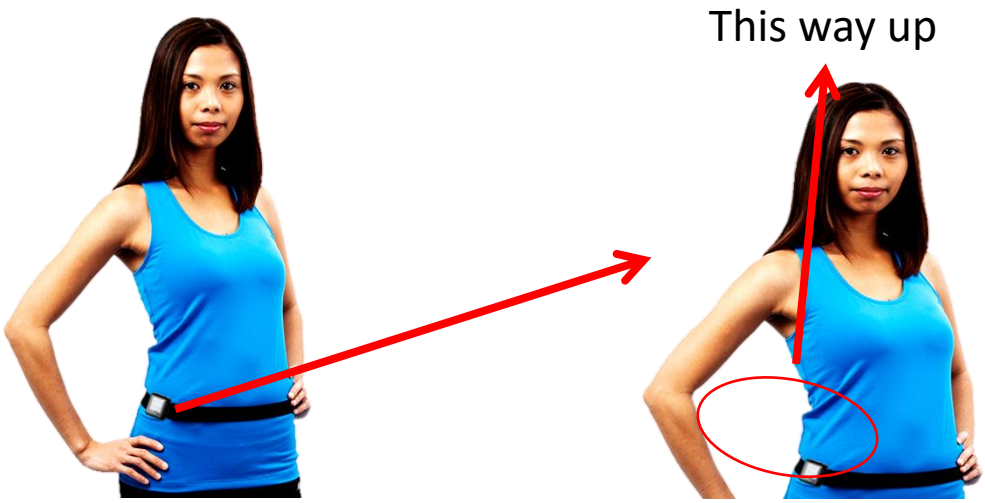
Wrist Monitors:

Your child can wear the monitors on their wrist just like a watch. You don't need to worry about charging it. Also, the screen won't display anything, but it doesn't mean that it's not working. The monitors are fully waterproof, so your child doesn't need to take them off, even for swimming or showering. The most important thing is to make sure that it's tight enough that it doesn't move around on their wrist, but not too tight that it's uncomfortable.

Hip Monitor:

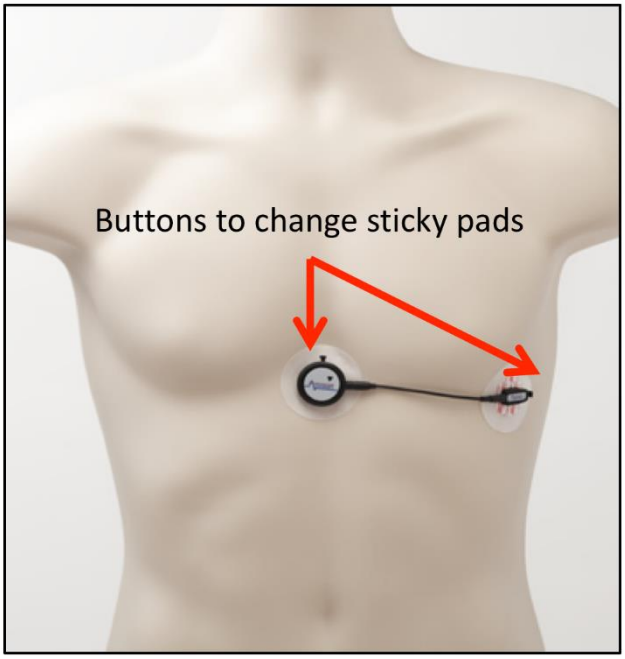
Your child should wear the monitor attached to the belt around their waist, just above their **right** hipbone. They can wear it either underneath or on top of their clothing. At first the belt may feel slightly awkward, but after a few hours they will probably get used to it and forget about it. Your child should wear the monitor so that the writing is facing the right way up (see figure below). The monitor should be snug against their body. If they need to adjust it, they can tighten it by pulling the end of the strap, or, to loosen it, push more of the strap through the loop. **Please check that the belt is tight enough that the monitor does not move when they are being active.**

Like the wrist monitors, you don't need to worry about charging it. The screen also won't display anything, but this doesn't mean that it is not working. The monitor is fully waterproof, but they may want to remove it if they are going swimming or showering/bathing so the belt doesn't get wet. Please make sure that they put it back on as soon as they can and record when they took it off and put it back on in the log we have provided them with.



Chest Monitor:

The monitor on your child's chest is attached using two sticky patches (electrodes) as in the picture below. The most important thing is that the cable between the two ends is as horizontal as possible. Your child probably won't need to change the electrodes, but we will provide spare patches in case you do want to. This monitor is also waterproof so they can wear it for all their daily activities. Just like the other monitors, you don't need to worry about charging this monitor.



What should I do if I need to change the sticker on my child's chest?

First of all, your child will need to clean the skin where the sticky pad was. After cleaning the skin, they will need to make sure it's dry before they attempt to stick on a new pad. The sticky pad in the middle should be placed two palms from their belly button (in the middle of their chest), and the other one should be placed inline horizontally and as far round as it reaches comfortably. To attach, or release, the monitor to the metal electrode, you, or your child, will need to press in and hold each of the buttons as shown in the picture above.

If they have any trouble replacing the sticky pads, or any kind of problems with the monitors, feel free to contact us at any time!

And don’t forget that it is important to keep a track of every time they take off the monitors on the log sheet provided!

Please remind them to wear the monitors every day (including during the weekend and whilst sleeping) for the next week. If they do take them off for any reason, please remind them to put them back on as soon as possible. Do NOT let anyone else wear their monitors.

We kindly ask that your child takes care of the monitors. Each one broken or damaged will cost us the equivalent of a new iPad to replace.

If you have any questions or if something happens to your monitor please contact:

Mayara Silveira Bianchim

[redacted]

Alternatively, you can contact:

Dr Melitta McNarry

[redacted]

[redacted]

3. Chapters 5 to 8 – Accelerometry Instructions for under 12 years

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

School of Sport and Exercise Sciences, College of Engineering

Instructions on How to Use the Monitors (under 12 years)

(Version 1.2, Date 17/10/2017)

This is a Physical Activity Tracker! These monitors are like fancier '*FitBits',* and will record every movement you make! This way we will be able to tell exactly how active you really are.

All the monitors can be worn in water and when you are sleeping. You can wear them without taking them off, even if you go swimming. You can do everything you normally do.

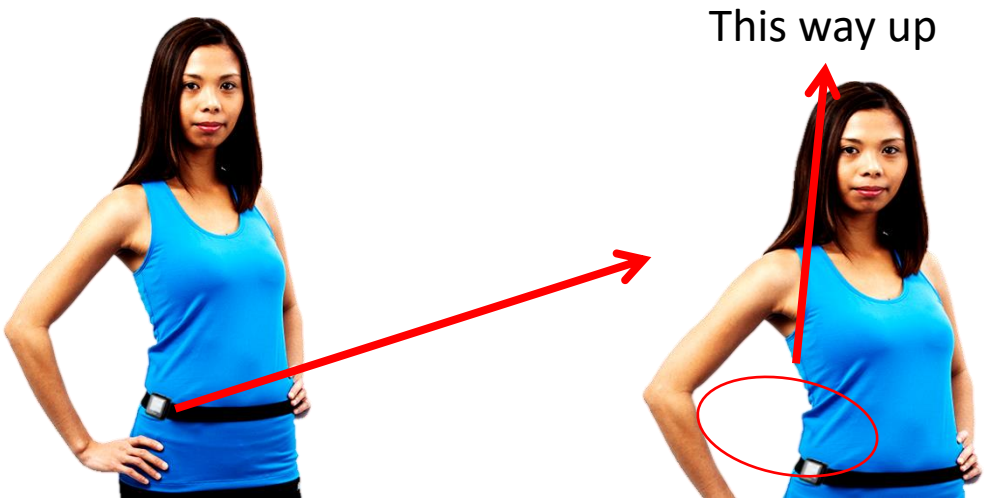
Wrist Monitors:

The monitors for your wrist can be worn like a watch. Some will tell you the time. Don't worry if there isn't anything on them, they will still be working. The monitors can be worn in water, so you don't need to take them off. You can even wear them when swimming or having a shower. Make sure it doesn't move around on your wrist when you're running or jumping around. You can make it looser if it's too tight.

Hip Monitor:

You should wear this monitor a bit like a belt. The monitor should be on your right hand side, like in the picture below. You can wear it under your clothes, or on top of them. It might feel a little bit funny at first, but you'll get used to it. Make sure the monitor is the right way up, like in the picture below. **The belt should be tight enough that it doesn't move when you're running or jumping around**. Make sure it's not too tight. You can make the belt bigger or smaller. To make the belt bigger, you can push more of the strap through the loop. To make it smaller, you can pull both ends of the strap.

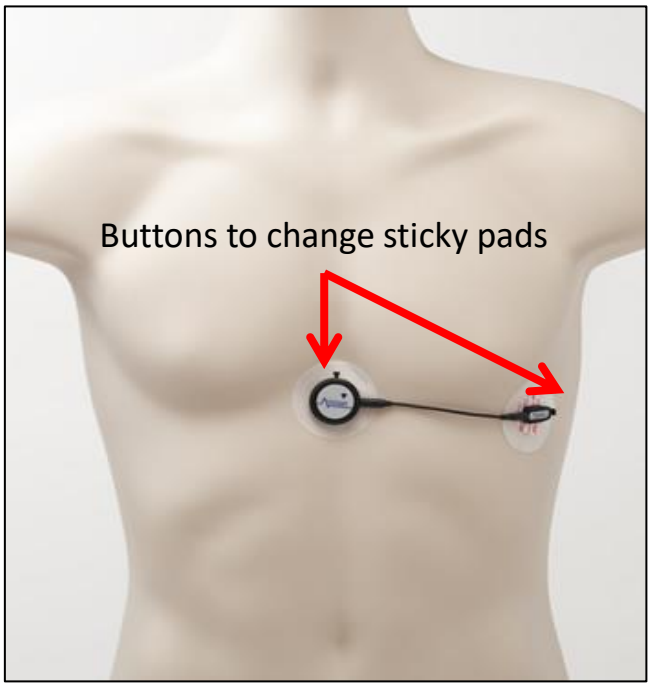
The monitor will have enough battery to last for the week. Don't worry if the screen is blank, the monitor will be working! The monitor can get wet, but you might not want the belt to get wet. Please take the monitor off for swimming or having a shower, but put it back on as soon as you can. Remember to fill in your log sheet with the times you took the monitor off.



Chest Monitor:

The monitor on your chest will be stuck to you using two stick pads. Make sure the two sticky pads are in a straight line with each other. It should look like the picture below. We will give you some spare pads if you want to put new ones on. The monitor can

get wet, so you can leave it on. It can even be worn when you are swimming or having a shower. We will make sure the battery is full for the week.



How do I change the sticky pads?

You will need to take off the old sticky pads from your chest and clean your skin it was stuck to. Make sure your chest is dry. Stick new pads where the others were before. Push the buttons (see picture above) in and place over the metal ‘popper’ and then let go. You can do this for the middle and side sticky pad separately.

If you cannot change the sticky pads, ask an adult to ask us! We will be happy to help you.

Please make sure you fill in the log sheet we have given you. You need to write down the time you take any monitors on and off.

Please wear the monitors every day for the next week. Even at the weekend and when you sleep! If you take any off, please put them back on as soon as you can. Do not let anyone else wear your monitors.

Please look after the monitors. Each one costs the same as a PS3 or Xbox.

If you have any questions or if something happens to your monitor, an adult can get in touch with:

Mayara Silveira Bianchim

[redacted]

Or, they can get in touch with:

Dr Melitta McNarry

[redacted]

[redacted]

4. Chapter 6 – Accelerometry Log Sheet

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

School of Sport and Exercise Sciences, College of Engineering

Log Sheet

(Version 1.2, Date: 17/10/2017)

NHS

Your name: _____

Day and Date	Time you woke up in the **morning**	Time periods when activity monitor was taken off	Reason activity monitor was taken off	Time you went to **bed**	Quality of sleep (1-10) 1 = poor ☹ 10 = very good ☺	What monitor(s) was/were taken off
Example: Monday, 01/08/17	7:15am	8:00am-8:15am 3:30pm-4:30pm	Showering Swimming	9:00pm		Hip All

Day:	Time you woke up in the **morning**	Time periods when activity monitor was taken off	Reason activity monitor was taken off	Time you went to **bed**	Quality of sleep (1-10) 1 = poor ☹ 10 = very good ☺	What monitor(s) was/were taken off

PLEASE RETURN THE ACTIVITY MONITOR AND LOG SHEET ON YOUR NEXT VISIT

Appendix J: Rate of Perceived Exertion Scale