THE DEVELOPMENT, IMPLEMENTATION AND EVALUATION OF A PHYSICAL ACTIVITY INTERVENTION FOR ADULTS WITH CYSTIC FIBROSIS

Nicola Hurley, BSc.

Thesis submitted for the award of PhD

School of Health and Human Performance

Dublin City University

Under the supervision of

Prof. Niall Moyna

Prof. Karen Redmond (Mater Misericordiae University Hospital)

Dr. Bróna Kehoe (Waterford Institute of Technology)

September 2021

Declaration

I hereby certify that this material, which I now submit for assessment on the programme of study leading to the award of PhD is entirely my own work, that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge breach any law of copyright, and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work.

Signed: Nicola Hurley **ID No.:** 12402692

Nicola Hurley (PhD Candidate) **Date:** September 2021

Acknowledgements

This PhD is dedicated to Becky and the Jones Family.

~

There are a number of people that I would like to sincerely thank from the bottom of my heart, who have contributed immensely to my PhD experience over the past 4 years:

First and foremost, to my academic supervisors Prof. Niall Moyna and Dr. Bróna Kehoe. Thank you for the most incredible 4+ years. From taking me on as a 3rd year Sport Science and Health student for my INTRA placement, to the MedEx Summer Internship, FYP and beyond. Thank you for always believing in me and for pushing me to aim for the highest standards, always. Your unwavering support and guidance have provided me with an invaluable platform to develop as an independent researcher, and I am truly grateful.

To the postgraduate students past and present, thank you for your support and friendship along the way. Thank you to all of the staff in the School of Health and Human Performance, particularly Sarah Kelly, who was always a friendly face there to chat and provide words of wisdom and encouragement.

To Aisling Scally, you are one in a million. I am forever thankful for our giddy half-hours and am truly grateful to have had the opportunity to build a fantastic friendship with you over the past 4 years.

To my XB26 family, Clare, Eoin, Kevin, Aidan, Ciara, Cormac, Dessie and Paul, who provided endless hours of entertainment, laughter, and most importantly, support when it was needed the most. Thank you!

To Mickey, Mary, Maeve and George, thank you for making my PhD years full of endless laughter, wonderful stories and copious amounts of tea!

A sincere thank you to Dr. Noel McCaffrey for introducing me to the world of ExWell and for providing me with this incredible opportunity!

To Prof. Karen Redmond who was always in my corner. Thank you for everything!

To Dr. Sarah Hardcastle who joined the team when the going got tough with Covid-19. A sincere thank you for all of your time and support.

To my funding sources: Cystic Fibrosis Ireland, The Mater Foundation and the Jones Family. Thank you for not only funding this research and providing me with the opportunity to further my education, but for always believing in me and for being a wonderful support system throughout.

To all of my participants, from the healthcare professionals working in CF care across the country to my incredible intervention participants. Thank you for making the project possible!

To my friends who have been an incredible support system since day 1, thank you! A special thank you to Aoife and Sinead who have been truly incredible friends over the past number of years and even more so over the past few months when I have needed it the most. I am eternally grateful for the support you have shown me, you are the exception to the rule!

To my brother James, thank you for all of the times you'd drop into my room unannounced for the chats, giving me the breaks from working I never knew I needed. Your witty sense of humour and ability to make me laugh no matter what the circumstance has been a gift over the past 4+ years. Thank you!

To my sister Megan, thank you for *always* being there for me through thick and thin over the past 4+ years. I will be forever grateful for your surprise treats brought up while I was working and our late night drives to McDonalds. Thank you!

To my mum and dad, I cannot put into words how appreciative I am for all of the opportunities you have provided me with through life. Your unwavering support is something I feel eternally grateful for, *always*. Thank you for being so understanding throughout this PhD journey, and for always being there and giving me your undivided attention whenever I needed. Your endless love and belief in me have been the making of me, thank you!!

Finally, to Stephen; you may never fully understand how instrumental you have been over the past 4+ years. I am eternally grateful for your love, understanding and patience. You have been an incredible pillar of support throughout this journey, but even more so over the past number of months. Thank you for always believing in me! On to the next chapter!

Publications

Published Articles

- **Hurley, N**., Kehoe, B., McCaffrey, N., Redmond, K., Cullen, L., & Moyna, NM. (2020). Recommendations to improve physical activity prescription for the cystic fibrosis population: an Irish perspective. *BMC Health Services Research, 20:1052.* doi:10.1186/s12913-020-05910-2
- **Hurley, N**., Moyna, NM., Kehoe, B., McCaffrey, N., Redmond, K., & Hardcastle, SJ. (2021). Factors influencing physical activity in adults with cystic fibrosis. *BMC Pulmonary Medicine, 21:113.* doi:0.1186/s12890-021-01482-x

Communications

Conference Presentations

- **Hurley, N**., Kehoe, B., McCaffrey, N., Redmond, K., Cullen, L., & Moyna, NM. (2019). Recommendations to improve physical activity prescription for the cystic fibrosis population: an Irish perspective. *Oral Presentation at the Irish Thoracic Society Annual Scientific Meeting.* Galway, Ireland.
- **Hurley, N**., Kehoe, B., McCaffrey, N., Redmond, K., Cullen, L., & Moyna, NM. (2019). Recommendations to improve physical activity prescription for the cystic fibrosis population: an Irish perspective. *Poster Presentation at the Irish Thoracic Society Annual Scientific Meeting.* Galway, Ireland.

Invited Talks

- Cystic Fibrosis Ireland Annual Conference – April 2019
- Science Gallery Ireland & ICON – Living with…Cystic Fibrosis Series – November 2019
- Cystic Fibrosis and Exercise International Journal Club – September 2020

Public Dissemination

- Cystic Fibrosis Ireland Spectrum Patient Newsletter – 2018 & 2019
- ‘Fighting to Improve Care for People Living with Cystic Fibrosis’ – Medical Independent – 2019

Table of Contents

List of Figures

List of Tables

List of Appendices

List of Abbreviations

AIC = Akaike information criterion

ATP = Adenosine triphosphate

BCW = Behaviour change wheel

BIC = Bayesian information criterion

BL = Baseline

BMI = Body mass index

BP = Blood pressure

CF = Cystic Fibrosis

CFQ-R = CF questionnaire-revised

CFTR = Cystic fibrosis transmembrane conductance regulator

CG = Control group

CO_2 = Carbon dioxide

COPD = Chronic obstructive pulmonary disease

CPD = Continuing professional development

CPET = Cardiopulmonary exercise testing

DCU = Dublin city university

ECG = Electrocardiograph

EP = Exercise professional

FEV_1 = Forced expiratory volume in the 1st second

FITT = Frequency, intensity, time, type

FVC = Forced vital capacity

HAES = Habitual activity estimation scale

HCP = Healthcare professionals

HR = Heart rate

IG = Intervention group

LIPA = light intensity physical activity

MDT = Multidisciplinary tea

MRC = Medical research council

MVPA = Moderate-vigorous physical activity

NBS = Newborn screening

O_2 = Oxygen

PA = Physical activity

PEG = Percutaneous endoscopic gastrostomy

PEP = Positive expiratory pressure

Pwcf = People with cystic fibrosis

Q = Cardiac output

QoL = Quality of Life

RCT = Randomized-controlled trial

RPE = Rate of perceived exertion

SD = Standard deviation

SDT = Self-determination theory

SpO_2 = Oxygen saturation

SPSS = Statistical Package for the Social Sciences

TDF = Theoretical domains framework

TPB = Theory of planned behaviour

TTM = Transtheoretical model

UC = Usual Care

V_A/Q = Ventilation perfusion

$\dot{V}_E$ = Minute ventilation

$\dot{V}O_2max$ = Maximal Oxygen uptake

Abstract

Hurley, N. The Development, Implementation and Evaluation of a Physical Activity Intervention for Adults with Cystic Fibrosis.

Physical activity (PA) is an essential component in the management of cystic fibrosis (CF). However, optimal PA programmes for patients with CF (pwcf) are yet to be defined. The aim of this PhD was to develop, implement and evaluate a PA intervention for pwcf. Formative research, consisting of an online survey with CF healthcare professionals (HCP) and semi-structured interviews with pwcf, was first conducted to inform the intervention design. HCP reported lack of patient motivation and compliance as prominent barriers to PA prescription. Pwcf expressed a preference for home-based PA to ameliorate a myriad of disease-related barriers. A theoretically-informed intervention was developed to address both HCP and pwcf barriers to PA prescription and participation, respectively. To assess the potential for successful intervention implementation, and to reduce threats to validity, it is important that feasibility trials are conducted. A randomized-controlled trial assessed the feasibility of a theoretically-informed, home-based, self-regulated and technology-enabled PA intervention and compared its effectiveness in relation to PA and quality of life (QoL) to usual care (UC). Participants (n=11) completed self-reported PA and QoL questionnaires, and accelerometry at baseline, post-12- and 18-weeks. A maximal exercise test and basic spirometry were also performed at baseline. Participants in the IG were invited to complete semi-structured exit interviews. The intervention was deemed feasible in terms of acceptability, demand, implementation and practicality. There were no statistically significant changes in PA or QoL during the intervention.

The validity of the oxygen uptake efficiency slope (OUES) as a predictor for maximal oxygen consumption (VO_2max) was evaluated, as VO_2max has been shown to be a key indicator of longevity among pwcf. OUES at 50% of the test duration ($OUES_{50}$) was identified as a reliable submaximal parameter for predicting VO_2max in pwcf who are unable or unwilling to perform maximal-effort exercise due to excessive dyspnoea and/or lack of motivation.

Chapter I
Introduction

Introduction

Cystic Fibrosis (CF) is the most common life-limiting, autosomal recessive condition among Caucasian populations (Navarro, 2016). It is caused by a mutation in the CF transmembrane conductance regulator (CFTR) protein that disrupts chloride secretion, sodium reabsorption and water transport in the epithelial layer, leading to the development of dehydrated viscous mucus and decreased mucociliary clearance (Turcios, 2019). The dehydrated airways provide a platform for recurrent bacterial infections, inflammation, endobronchial obstructions, fibrosing of the lung tissue and the subsequent development of severe bronchiectasis, resulting in respiratory failure accounting for approximately 85% of deaths among CF populations (Lyczak, Cannon and Pier, 2002; Turcios, 2019).

Globally, there are approximately 70,000 people currently living with CF. The prevalence of CF in Europe ranges between 1/3,000 and 1/6,000 live births, equating to a carrier rate of 1/28 to 1/40. Ireland has the highest rate of CF per capita in the world (1/1353 live births), with approximately 1,400 children and adults living with the condition (Farrell, 2008). The median age of survival for people with CF (pwcf) in Ireland is between early to mid-thirties, and currently > 55% of the Irish CF population are ≥ 18 years of age.

There is currently no cure for CF. Emphasis remains on managing the condition and alleviating symptoms through the use of pharmacotherapies, nutrition, physiotherapy and PA, including structured exercise training. A major advancement has been the use of gene-therapy to target the underlying defect in the CFTR protein. Triple-therapy CFTR modulator drugs such as Trikafta® can now positively impact up to 90% of the CF population (those with at least 1 copy of the Δ F508 gene). Consequently, CF has slowly transitioned from a childhood disease to a more manageable long-term condition.

PA and exercise training play an increasingly important role in the management of CF, particularly for the ageing CF population, and as such the inclusion of physical activity (PA) and exercise training has been advocated as a cornerstone in CF care. PA is associated with a myriad of postulated benefits including increased aerobic capacity, muscle strength, quality of life (QoL), and a slower annual rate of decline in pulmonary function. It is now recommended that pwcf achieve between 150-300 min of habitual PA per week, including aerobic training for 30-60 min daily, and resistance training 2-3 times per week to achieve optimal health benefits (Swisher *et al.*, 2015). However, a large majority of pwcf do not meet the PA guidelines and tend to have lower PA levels than their healthy peers (Schneiderman, 2014). Lack of time, fatigue and not feeling well enough are among the most commonly reported barriers to PA adherence among CF populations (White, Stiller and Haensel, 2007).

Adherence to prescribed PA programmes among pwcf is typically varied, between 57-88% (O'Donohoe and Fullen, 2014). Research evaluating the effect of exercise training among pwcf have, for the most part, used prescribed exercise based on objectively measured thresholds of HRmax or $\dot{V}O_2$max. This method of exercise prescription may exceed an individual's desired threshold, or level of intensity, and may promote the development of negative attitudes towards long-term adherence to PA (Ekkekakis, 2009). Empowering individuals to use effort perception to self-regulate their desired exercise intensity may promote the establishment of autonomous motivation, enjoyment and sustained adherence to PA in the long-term (Johnson and Phipps, 2006). Underpinning interventions with theories of behaviour change provides potential to enhance intrinsic motivation and long-term PA engagement in chronic disease cohorts. To date, there is a dearth of research involving theoretically-driven PA interventions in CF populations.

While the positive impact of regular PA and physical fitness in pwcf is well documented, a lack of consensus remains in relation to identifying optimal PA programmes to support long-term PA adherence in this group. A recent systematic review (2017) concluded that more high-quality randomized-controlled trials (RCT) are required to identify the most effective PA programme components for pwcf, as the research evaluated to date is of poor methodological quality (Radtke *et al.*, 2017). The Medical Research Council (MRC) guidelines for the development, implementation and evaluation of complex interventions recommend conducting feasibility trials prior to assessing for full-scale efficacy, to assess intervention fidelity, participant experience and adherence prior to conducting a large trial to evaluate effectiveness (MRC, 2019).

The MRC guidelines also advocate for end-user and stakeholder involvement during the intervention development process to ensure that research is meaningful and relevant to the intended population (MRC, 2019). Limited research exists regarding HCP and pwcf perceptions of PA to guide the development of enjoyable and sustainable PA interventions for this patient group.

HCP have been identified as an important source for PA advice, information and motivation, and can play an integral role in optimizing PA behaviours in pwcf (Tomasone *et al.*, 2014; Speake *et al.*, 2016). Despite recommendations for PA to be embedded in usual care for all pwcf, the extent of PA promotion and prescription by CF HCP is not well understood.

There is a need to identify strategies that CF HCP can adopt to improve the provision of PA promotion and prescription to their patients. Exploration of the motivators and barriers to prescribing PA among CF HCP has received limited attention and warrants investigation.

Exercise intolerance is an established characteristic associated with CF populations and is dependent on disease progression (Rand, 2012). Cardiopulmonary exercise testing (CPET) is considered the most reliable method for assessing disease progression and the response to exercise in clinical populations (Akkerman *et al.*, 2010; Bongers *et al.*, 2012). Maximal oxygen uptake ($\dot{V}O_2max$), as determined by CPET, has been shown to be a key indicator of survival among CF populations (Gruet *et al.*, 2010). The attainment of $\dot{V}O_2max$ requires a maximal effort. However, some pwcf experience excessive dyspnoea and/or a lack of motivation, making maximal-effort exercise difficult to achieve. Exploration of submaximal parameters of aerobic capacity have been suggested as possible alternatives for the provision of such clinically important information (Tomlinson *et al.*, 2018).

Aim

The aim of this research was to explore PA from the HCP and pwcf perspective, and to develop, implement and evaluate a PA intervention for adults with CF.

Objectives

1. To conduct a systematic review of the literature to inform the intervention development process
2. To investigate the knowledge, barriers and practices surrounding PA promotion and prescription among CF HCP in Ireland (Chapter III – Study I)

3. To identify the factors that influence PA participation among adults with CF (Chapter IV – Study II)
4. To develop, implement and evaluate a PA intervention for adults with CF, compared to usual care (Chapter V – Study III)
5. To investigate the concurrent validity of submaximal oxygen uptake efficiency parameters (OUES and OUEP) as surrogates for VO_2max in adults with CF

Chapter II
Review of Literature

Review of Literature

A review of literature was conducted to identify the evidence base for PA and exercise in CF populations. The Cochrane Library of Controlled Trials (CENTRAL), EMBASE, MEDLINE (via PubMed) and Sport Discus were the search engines used to conduct the review. Search terms included, but were not limited to, cystic fibrosis, PA, exercise training, aerobic capacity, aerobic fitness, quality of life, muscle strength, lung function, behaviour change, motivators, barriers, exercise prescription, self-regulated exercise, adherence and compliance. The search terms were in line with the PICO format (patient, population, problem; intervention; comparison, control; outcome), and all study designs were included in the search.

Introduction

Cystic Fibrosis

CF is a progressive disease of autosomal recessive inheritance (Turcios, 2019). It is caused by a mutation in the CFTR protein, responsible for regulating the movement of chloride and sodium ions across epithelial cell membranes. When mutations occur in one or both copies of the gene, ion transport becomes defective, resulting in a build-up of viscous mucus that primarily affect the respiratory and gastrointestinal systems (Brown, White and Tobin, 2017). CF is the most common genetic condition among the Caucasian population, with a median age of survival between early to mid-thirties in Ireland (CFI, 2020). As there is currently no cure for CF, treatment strategies are focused on managing symptoms, using a combination of pharmacotherapies, nutrition, physiotherapy and exercise for those with mild to moderate symptoms, and ultimately lung transplantation for those with end-stage respiratory disease (Tomlinson *et al.*, 2018).

Prevalence and Incidence

Approximately 1,400 people in Ireland are currently living with CF, of which 55% of > 18 years of age (CFI, 2020). The CF population in Ireland has steadily increased as a direct result of advancements in the management of the condition, and is predicted to grow by 44% by 2025 (Burgel *et al.*, 2015). Ireland has the highest prevalence of CF in Europe, and indeed the world, at approximately 2.98 per 10,000 (Figure 2.1) (Farrell, 2008). The prevalence of CF in Europe is 0.74 per 10,000, with rates ranging from as low as 0.10 per 10,000 in Moldova, to 1.37 per 10,000 in the UK.

It is estimated that, worldwide, >70,000 people live with CF. The incidence of the disease varies greatly across the various regions of the world. Among populations of European descent, the incidence of CF is estimated to range from 1:3,000 and 1:6,000 live births, corresponding to a carrier rate of 1/28 and 1/40, respectively (Scotet, L'Hostis and Férec, 2020). The most recent estimated incidence of CF in Ireland is 1:1,353, with a carrier rate of 1/19, resulting in a 25% chance of two carriers giving birth to a child with CF (CFI, 2020).

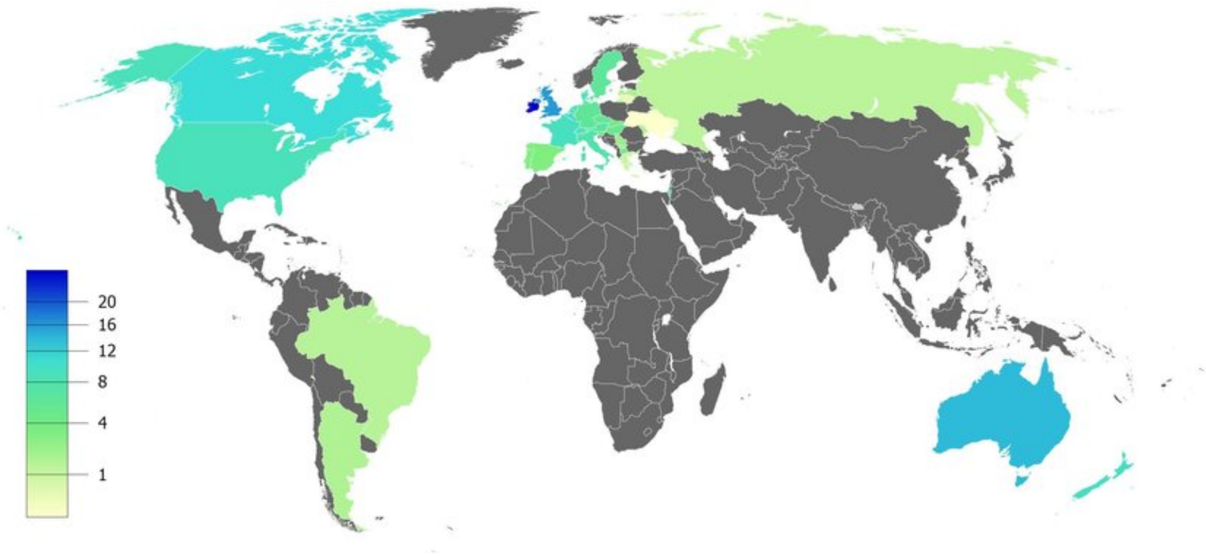


Figure 2.1: Prevalence of CF per 100,000 habitants, worldwide (grey areas indicate no published data).

Diagnosis

Newborn screening (NBS) for CF was first performed in New Zealand in 1981 and was introduced in Ireland in July, 2011 (Fitzgerald *et al.*, 2016). The most commonly performed NBS method involves measuring the level of immunoreactive trypsinogen, a pancreatic enzyme precursor, in blood spots typically taken via the heel-prick (Guthrie Test) method (Turcios, 2019). Newborns diagnosed with CF tend to have reduced mortality as a result of early intervention, compared to patients diagnosed following the onset of CF-related clinical manifestations, such as meconium ileus, failure to thrive and recurrent respiratory concerns.

First described in 1959, the sweat test remains the most reliable and widely available, gold standard diagnostic test for CF (De Boeck, Vermeulen and Dupont, 2017). The sweat test is conducted by quantitative pilocarpine iontophoresis. Pilocarpine nitrate is a cholinergic agent that binds to muscarinic receptors of eccrine sweat glands and induces sweat production. It is absorbed into the sweat glands in the forearm by iontophoresis (a small electrical current used to push the chemical agent through the skin) (Basu, Mitra and Ghosh, 2013). A sweat chloride concentration result > 60 mmol·L^{-1} indicates the presence of CF. A second confirmatory sweat test is recommended, unless mutation analysis identifies the presence of two CF-causing mutations.

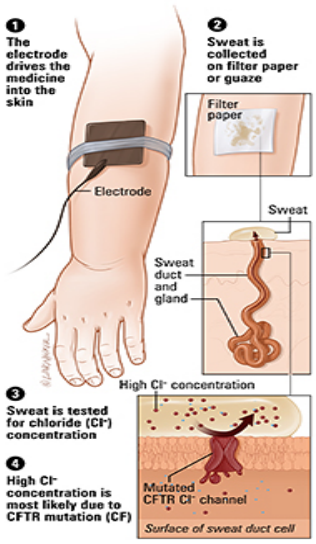


Figure 2.2: Sweat chloride test for the diagnosis of CF

Natural History

The clinical course of CF is progressive and multi-systemic in nature. Certain symptoms manifest early in life and can be detected in utero, such as fetal echogenic bowel ('bright' meconium accumulated within the lumen of the bowel from approximately 16 weeks' gestation) and visible by ultrasound imaging during the second trimester (De Oronzo, 2011). Although current evidence suggests that the CF lung is free of infection and inflammation at birth (Dakin *et al.*, 2002), over the course of subsequent months and years recurrent and chronic infections begin to appear with respiratory viruses such as Haemophilus influenzae and Staphylococcus aureus predominating in early life. Over time, more problematic and increasingly resistant pathogens such as Pseudomonas aeruginosa and other Gram-negative bacteria (Burkholderia Cepacia complex, Stenotrophomonas maltophilia, Achromobacter xylosoxidans) often become more dominant (Donaldson *et al.*, 2006).

The most fundamental manifestation of CF remains the dehydration of epithelial surface liquid and the accumulation of viscous mucus in the pulmonary and gastrointestinal systems. Poor airway surface hydration and defective mucociliary clearance in the respiratory system gives rise to mucus plugging, bacterial colonization and inflammatory responses, which can prompt a decline in pulmonary function, as a result of progressive fibrosing of lung parenchyma, and the onset of bronchiectasis (Eckles and Anderson, 2003). This repetitive cycle of obstruction and inflammation ultimately leads to respiratory failure and accounts for approximately 85% of deaths in this population (Flume *et al.*, 2005).

Secondary to respiratory failure, hypertrophy of the right heart (cor pulmonale) has been identified as a significant factor contributing to premature mortality in this population (Stern *et al.*, 1980). As a result of the ongoing developments in novel pharmacotherapies, people with CF are living longer albeit with severe lung disease, and are subsequently developing symptoms of pulmonary hypertension, right ventricular dysfunction and cor pulmonale. Ventilation-perfusion abnormalities arise due to alveolar air trapping, promoting local retention of carbon dioxide (hypercapnia) and decreased oxygen delivery. The resulting hypoxia causes a vasoconstrictive response in the pulmonary arteries. Initially, the right heart compensates for the elevated pulmonary pressures by increasing output. Chronic exposure to high pulmonary pressures results in right ventricular remodeling that initially involves hypertrophy followed by dilation leading to pulmonale and eventually right heart failure (Stern *et al.*, 1980).

Beyond the respiratory and subsequent cardiac manifestations of CF, gastrointestinal issues are also common in this group. Epithelial surface dehydration in the gastrointestinal tract contributes to stunted growth and failure to thrive among young children with CF (Moskowitz *et al.*, 2008). These symptoms are triggered by pancreatic insufficiency (insufficient secretion of pancreatic digestive enzymes), a hallmark of CF disease that occurs in approximately 85% of individuals with CF (Gibson-Corley, Meyerholz and Engelhardt, 2016; Ghodeif and Azer, 2020). Viscous mucus causes blockages in the pancreatic duct, preventing gastric enzymes from acting in sufficient volumes to appropriately aid in digestion. Blockages within the intestinal tract promote the malabsorption of fat and fat-soluble vitamins (A,D,E and K) which can often result in vitamin deficiencies, osteoporosis, gastro-intestinal reflux and small intestine bacterial overgrowth (Sabharwal, 2016). CF-related diabetes is triggered by insulin deficiencies that arise as a result of the chronic damage to the pancreas. CF-related diabetes is a distinct form of diabetes, as it shares features of both type I and type II diabetes such as, insufficient insulin production and insulin resistance, respectively (Marshall *et al.*, 2005). In addition, ionic imbalances within the biliary tract may lead to an increased risk of gallstones and hepatobiliary disease in this population (Eckles and Anderson, 2003). Further complications impacting the vas deferens arise as a consequence of CFTR dysfunction. Approximately 99% of adult males with CF have congenital bilateral absence of the vas deferens, affecting fertility (Eckles and Anderson, 2003).

Pathophysiology

The CFTR gene was first identified in 1989, and is located on the long arm of chromosome 7 (7q31.2) (Schmidt *et al.*, 2016). It is large, and spans approximately 250kb and contains 27 exons (Lubamba *et al.*, 2012). The CFTR protein is located in the apical membrane of cells lining the airways and also can be found in other bodily organs including the sweat glands, intestinal, reproductive, hepatic and renal epithelia (Saint-Criq and Gray, 2017). CFTR is a complex glycoprotein composed of 1,480 amino acids. It functions by allowing the passive diffusion of chloride ions down their electrochemical gradient. The CFTR protein is a member of the ATP-binding cassette protein super-family (Bergeron and Cantin, 2019). It is characterized by 2 membrane-spanning domains (MSD1 and MSD2), which anchor the protein in the plasma membrane. Each is conjoined to a nucleotide binding domain (NBD 1 and NBD2), which binds and hydrolyses ATP. Binding and hydrolysis of ATP are required for the opening and closing of the CFTR channel, a process also known as 'gating' (Fajac and Wainwright, 2017).

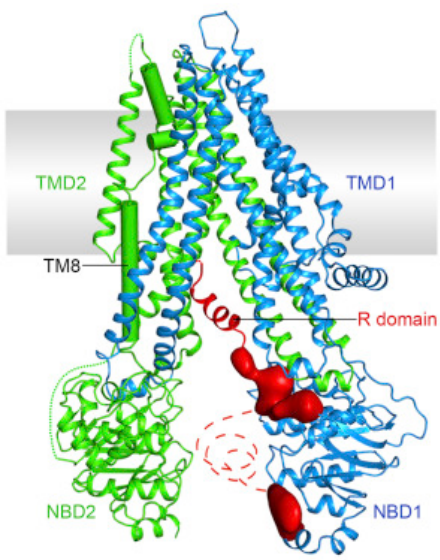
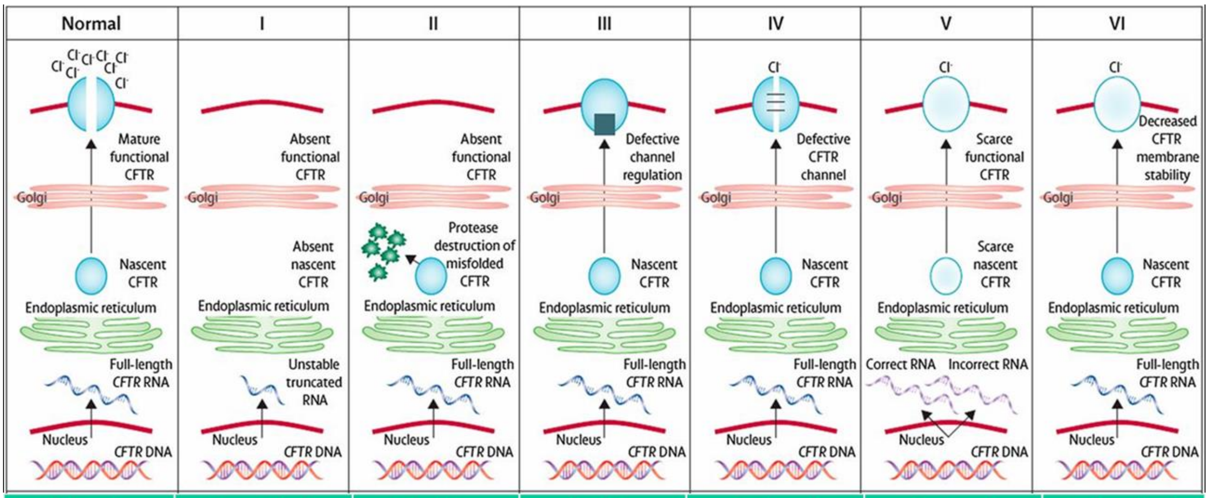


Figure 2.3: Molecular Structure of the Human CFTR Ion Channel

To date, approximately 2,000 mutations to the CFTR gene have been described (Fajac and Wainwright, 2017). Mutations in the CFTR gene can be classed into six categories depending on their severity (Figure 2.3). Individuals who are homozygous for class I, II and III mutations often have a severe CF phenotype. Whereas, class IV, V and VI mutations often have a less severe phenotype as a result of residual CFTR function (Fraser-Pitt and O'Neil, 2015). Class I mutations refer to variants whereby no protein is produced, and are comprised of stop codon mutations, frameshift mutations or significant deletions. Class I mutations (such as G542X) are representative of 10% of the CF population worldwide. The most common CFTR mutation that gives rise to CF is ΔF508, which is present on at least one allele in 70% of individuals with CF (Fernández Fernández *et al.*, 2018). This mutation belongs to class II, whereby a deletion of three nucleotides in the gene leads to the deletion of the phenylalanine residue at position 508 of the polypeptide chain giving rise to misfolding of the CFTR protein in the endoplasmic reticulum and subsequent protein degradation (Fraser-Pitt and O'Neil, 2015). Class III mutations are gating mutations that allow trafficking of CFTR to the apical membrane, but cause defective regulation of the chloride channel, resulting in a very poorly functioning CFTR protein. This class of mutations are present in 4-5% of individuals with CF worldwide, with the most common mutation G551D observed in approximately 3% of patients (Bompadre *et al.*, 2007). Class IV mutations lead to decreased conductance in CFTR protein at the apical membrane, with R117H common in this class. Class V mutations produce normal CFTR protein, but in a decreased quantity due to moderately reduced trafficking (A455E) or aberrant splicing (3849+10kbC>T). Class VI mutations lead to a high turnover of CFTR at the channel surface (120del23) (Fernández Fernández *et al.*, 2018).



Molecular defect	No synthesis	Block in processing	Block in regulation	Reduced conductance	Reduced synthesis	Reduced half-life
Functional abnormality	Protein is not synthesized	Folding defect	Channel opening defect	Ion transport defect	Decreased protein synthesis	Decreased half-life of the protein
Type of mutations	Nonsense; frameshift; canonical splice	Missense; Aminoacid deletion	Missense; Aminoacid change	Missense; Aminoacid change	Splicing defect; Missense	Missense; Aminoacid change
Main mutations	Gly542X Trp128X Arg553X 621+1G→T	Phe508del Asn1303Lys Ile507del Arg560Thr	Gly551Asp Gly178Arg Gly551Ser Ser549Asn	Arg117His Arg347Pro Arg117Cys Arg334Trp	3849+10kbC→ T 2789+5G→ A 3120+1G→ A 5T	4326delTC Gln1412X 4279insA

Figure 2.4: Overview of Class I-VI CF mutations

Treatment

As there is currently no cure for CF, it is typically considered a condition where the focus is on the management and alleviation of associated symptoms. In mild to moderate cases of the condition, management therapies consist of a combination of treatment strategies including pharmacological intervention, nutritional support, chest physiotherapy and exercise training.

Patients with severe and end-stage cases of CF require lung transplantation to optimize prognosis. Research suggests that lung transplantation confers a 51-80% (mean = 69%) reduction in the instantaneous risk of death among patients within this cohort. Survival after lung transplantation has been estimated at 96% at 3 months, 88% at 12 months and 67% at 3 years suggesting a significant survival benefit for adults with end-stage CF disease (Lynch *et al.*, 2015).

Pharmacological Intervention

Pharmacological interventions typically include a combination of antibiotics, mucolytics and CFTR modulators. Antibiotics can be delivered orally, intravenously or inhaled to eliminate or regulate bacterial and fungal species commonly found in the lung. Antibiotics can be administered to people with CF either as an in-patient in the hospital setting, an out-patient from their home environment, and either electively or to treat symptoms (Breen and Aswani, 2012).

Inhaled mucolytics work to decrease the viscoelasticity of secretions in the CF airways (Hurt and Bilton, 2014). Dornase alfa (Pulmozyme®) is a highly purified solution of recombinant human deoxyribonuclease (rhDNase), which reduces the viscosity of mucus in the lung, promoting enhanced airway clearance and expectoration (Yang and Montgomery, 2018). Hypertonic saline has been shown to increase mucociliary clearance and sputum expectoration among patients with CF, however when compared to Dornase alfa hypertonic saline did not appear as effective (Enderby and Doull, 2007).

Given the genetic nature of CF disease, gene therapy has become a promising approach to managing the condition. CFTR modulators are a class of drugs that act by improving the production and/or function of the defective CFTR protein. Their efficacy is dependent on the patient's individual CFTR mutation. Ivacaftor (Kalydeco®) was the first personalized or genomically-guided therapy for CF, targeted towards those with class III gating mutations (G551D), acting as a potentiator by improving chloride transport (Condren and Bradshaw, 2013). Ivacaftor has been shown to improve pulmonary function, quality of life and sweat chloride concentrations in ~3,400 patients with class III gating mutations (G551D), which is representative of 5% of the CF population (Fajac and Wainwright, 2017). Combining Ivacaftor with CFTR correctors (small molecules that target CF-causing mutations which act by improving the trafficking and processing of small-molecule therapies), Lumacaftor (Orkambi®) and Tezacaftor (Symkevi®), increases the volume of CFTR proteins at the cell surface, and have been shown to improve lung function and decrease the pulmonary exacerbations for patients who are homozygous for the ΔF508 mutation (Fajac and Wainwright, 2017; Maule, Arosio and Cereseto, 2020).

Recent developments have sought to target those with at least one ΔF508 mutation and one minimal function mutation or two ΔF508 mutations, which would represent up to 90% of the CF population. The novel triple-therapy Trikafta (Kaftrio®) is comprised of a combination of elexacaftor (CFTR corrector; ↑ amount of mature CFTR protein that reaches cell surface), tezacaftor (CFTR corrector; corrects CFTR positioning on cell surface) and ivacaftor (↑ CFTR protein activity) and has the potential to lead to transformative improvements in the lives of patients with CF (Mahase, 2019). Middleton et al., published the first study of the triple-therapy drug in 2019 (Middleton *et al.*, 2019). Four hundred and three patients (≥ 12 years of age) with one ΔF508 mutation were randomized to receive at least one dose of active treatment or placebo. Trikafta, when compared with the placebo, resulted in a 13.8 point increase in percent predicted forced expiratory volumes in the first second (FEV_1)

values at four weeks, and a 14.3 point increase at twenty-four weeks (Middleton *et al.*, 2019). The rate of pulmonary exacerbations was dramatically reduced (63%) in the Trikafta group, who also experienced a 20.2 point increase in quality of life scores and a 41.8 mmol/L decrease in sweat chloride concentrations. This study considered Trikafta safe with an acceptable side-effect profile. A second study conducted by Heijerman et al., in 2019 evaluated the effect of Trikafta in patients with two copies of the ΔF508 mutation (Heijerman *et al.*, 2019). Participants were given a dose of combined tezacaftor and ivacaftor alone for the first four weeks, following randomization 52 patients were assigned to further treatment with tezacaftor and ivacaftor and the remaining 55 patients to the elexacaftor-tezacaftor-ivacaftor triple therapy. The group receiving Trikafta had increases in FEV_1 of 10 points, quality of life of 17.4 points, and sweat chloride concentrations were decreased by 45.1mmol/L. Group comparisons for the outcome measures are presented in Figures 2.4-2.6. The authors concluded that the drug was well-tolerated by all participants (Heijerman *et al.*, 2019).

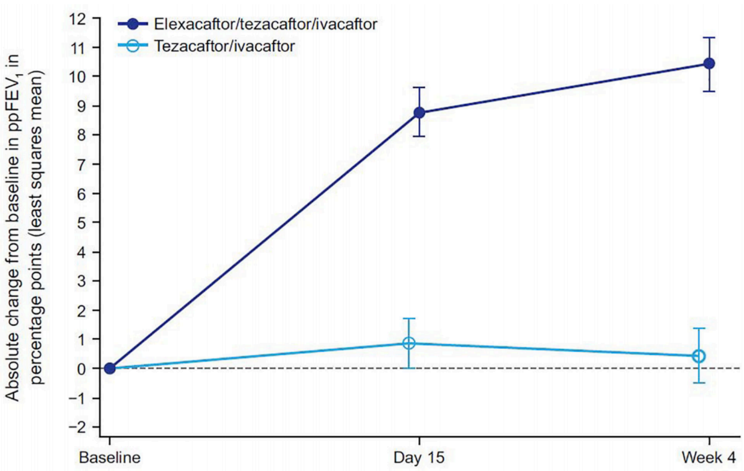


Figure 2.5: Absolute change from baseline for FEV_1 (Heijerman, 2019)

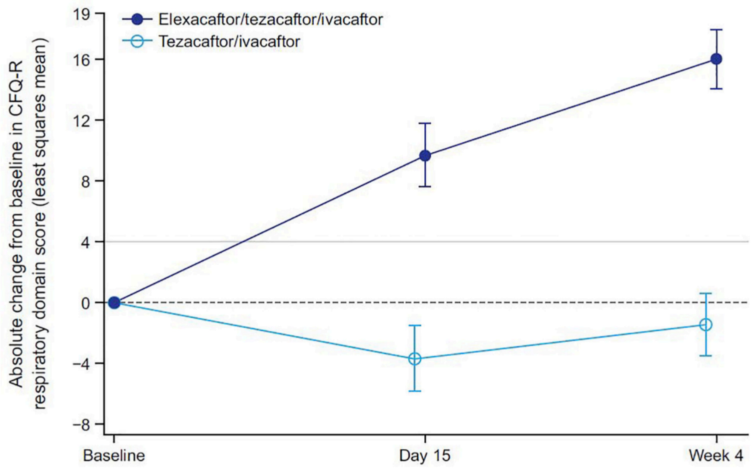


Figure 2.6: Absolute change from baseline in CFQ-R (QoL) (Heijerman, 2019)

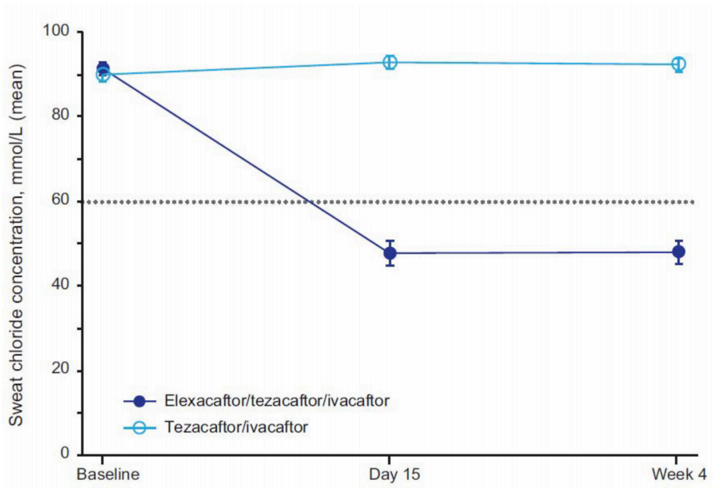


Figure 2.7: Changes in sweat chloride concentration (Heijerman, 2019)

CF Ireland announced the availability of Trikafta (Kaftrio®) to all patients with CF ≥ 12 years of age in Ireland in October 2020. Extensions to younger age groups will be introduced following approval by the European Medicines Agency (CFI, 2020).

The future of CF gene-therapy provides significant promise, as techniques such as CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats) tehnology gain momentum. CRISPR/Cas9 technology is a gene-editing technique that uses a protein-RNA complex that identifies the defective DNA sequence and removes it, replacing it with the correct sequence to restore effective CFTR function (Ensinck *et al.,* 2021). Proof of concept studies are currently being conducted to provide the evidence-base for translation to effective therapy for CF populations.

Nutrition

Nutritional management for CF includes the provision of evidence-based education and dietary advice (Williams *et al.*, 1999). It is recommended that the patient's nutritional needs be assessed and regularly reviewed, and treatment should be individually tailored to meet the changing clinical and psychosocial needs of the patient (MacDonald, 1996). Many people with CF (80-90%) require supplementing their diet with pancreatic enzymes, vitamins and minerals, while also increasing caloric intake, to prevent malnutrition and underweight, which is hallmark of CF disease (Somaraju and Solis-Moya, 2014).

Pancreatic enzyme replacement therapy contains three digestive enzymes; lipase for fat digestion, protease for protein digestion and amylase for carbohydrate digestion. In some patients with CF, pancreatic enzyme therapy is not sufficient to sustain a 'normal' body weight (BMI between 20-25 kg/m^2 for adults with CF) (Nutritional Management of Cystic Fibrosis; UK CF Trust, 2016). Therefore, more intensive nutritional support is necessary with patients often requiring percutaneous endoscopic gastrostomy (PEG), which involves the insertion of a feeding tube into the stomach through the abdominal wall and enables overnight feeding to occur. Utilization of PEG has been shown to be clinically effective in improving BMI and stabilizing pulmonary function in patients with CF (Williams *et al.*, 1999).

In addition, for patients with CF related diabetes, regular assessment of blood glucose levels is required, and subsequent administration of insulin may be needed. Supplementation of fat-soluble vitamins (A,D,E & K) may be required for those CF patients who are pancreatic insufficient, or if blood tests show suboptimal vitamin absorption (Rogers, 2013).

Physiotherapy

Chest physiotherapy plays an important role in assisting the clearance of airway secretions (Warnock and Gates, 2015). Airway clearance therapies are considered an integral component in the management of CF, and typically include manual techniques such as postural drainage and chest percussion, breathing techniques such as autogenic drainage and active cycle of breathing, oscillating devices such as the Acapella® and Flutter®, and the use of positive expiratory pressure (PEP) devices (Patterson *et al.*, 2019). A recent systematic review has suggested that there is little evidence to support the use of one airway clearance technique over another, instructing patients with CF to choose the technique that best meets their individual needs, considering comfort, convenience, practicality and cost (Wilson, Morrison and Robinson, 2019). The authors also highlight the need for more long-term, high-quality randomized-controlled trials to compare airway clearance techniques in this cohort. Incentive spirometry and inspiratory muscle training are two maneuvers that have been used to enhance lung expansion and inspiratory muscle strength in patients with CF. However, there is currently a lack of evidence to support or refute their use in CF care (Shei *et al.*, 2019).

It is well established that people with CF have lower adherence to traditional airway clearance techniques than other adjunct therapies, with daily adherence rates as low as 40%, compared with bronchodilators (60%) and antibiotics (76%) (Ward *et al.*, 2019). Poor adherence to airway clearance techniques in this population is typically linked to lack of time, perceived effort and energy required, and a sense of well-being without performing airway clearance techniques. A multi-center cross-sectional survey of 692 people with CF (≥18 years of age) reported that 43% of participants agreed or strongly agreed that exercise could be used as a substitute for traditional airway clearance techniques. Forty-four percent of participants reported having used exercise as a substitute for traditional airway clearance techniques over the previous three months.

Exercise Training

The concept of exercise as an adjunct therapy for CF populations was first described in the literature in the 1960's (Cox and Holland, 2019). However, in the years since 2010, contributions to the literature regarding exercise and CF are almost equal to the total publications on the topic in the previous 50 years. As a consequence of this increase in research over the past 10-20 years, exercise has been increasingly recommended as a cornerstone in the management of CF (Hebestreit, Kriemler and Radtke, 2015). The pleiotropic effects of exercise for CF populations are summarized in table 2.1, and include improvements in mucus clearance, aerobic capacity, muscle strength and QoL, while preserving or slowing the annual rate of decline in pulmonary function.

Table 2.1: Acute and chronic studies examining the effect of exercise on physical and psychological indices of health in people with CF

										Outcomes				
Author	**n**	**Age Range (yr)**	**Disease Severity**	**Duration (wk)**	**Frequency (·wk-1)**	**Time (min)**	**Mode**	**Location**	**Supervised**	**Mucus Clearance**	**Lung Function**	**Aerobic Capacity**	**Muscle Strength**	**Quality of Life**
Beaudoin et al., (2017)	14	22-57	MI-MO	12	3	20-40	AT + RT	Home	Partially				↑	
Corral et al., (2018)	39	5-16	MI-MO	6	5	30-60	AVGs	Home	Yes			↑	↑	↑
DeJong et al., (1994)	10	14-26		12	7	15	AT	Home	Partially			↑		
Dwyer et al., (2019)	14	≥ 17	MI-SE	SB		20		Lab	Yes	↑				
Gulmans et al., (1999)	14	12-16	MI-MO	52	5	20	AT	Home	Partially			↑	↑	↑
Gupta et al., (2019)	52	6-18	MI-MO	52	3		RT	Home	Partially			↑		↑
Hebestreit et al., (2010)	38	12-40	MI-MO	52	3	↑ 3hr/wk	Sport	Home	Partially		↑	↑		
Hommerding et al., (2015)	34	13-16	MI-MO	52	2	20	SS	Home	Partially			↑		
Klijn et al., (2004)	20	13-16	MI-MO	12	3	20	SS	Hospital	Yes	↑	↑	↑		
Kriemler et al., (2016)	12	16-29	MI-MO	12	3	30	AT + ACT	Gym	Yes	↑				
Kriemler et al., (2013)	39	16-27	MI-MO	24	3	30-45	AT + RT	Gym	Partially		↑			
Moorcroft et al., (2004)	48	23-29	MI-MO	52	3UB 3LB	20	RT	Home	No		↑	↑		
Orenstein et al., (1981)	31	10-30	MI-SE	12	3	60	AT	Gym	Yes			↑		
Paranjape et al., (2012)	78	6-16	MI	8	5	20-30	MVPA	Home	Partially	↑	↑			
Rovedder et al., (2014)	44	16-31	MO	12	7		AT + RT	Home	Partially		↑			
Salh et al., (1989)	19	16-32	MO-SE	8	5	10		Home	No	↑				

Table 2.1 Continued: Acute and chronic studies examining the effect of exercise on physical and psychological indices of health in people with CF

										Outcomes				
Author	**n**	**Age Range (yr)**	**Disease Severity**	**Duration (wk)**	**Frequency (·wk-1)**	**Time (min)**	**Mode**	**Location**	**Supervised**	**Mucus Clearance**	**Lung Function**	**Aerobic Capacity**	**Muscle Strength**	**Quality of Life**
Schneiderman-Walker et al., (2000)	72	7-19	MI-MO	156	3	20	AT	Home	Partially		↑			
Selvadurai et al., (2002)	66	8-16	MO	4	5	30	AT + RT	Hospital	Yes		↑	↑	↑	↑
Tucker et al., (2017)	33	9-43	MI-MO	SB			AT	Lab	Yes		↑			

MI, mild; MO, moderate; SE, severe; SB, single bout; UB, upper body; LB, lower body; AT, aerobic training; RT, resistance training; AVG: active video gaming; SS, self-selected; ACT, airway clearance techniques

*↑ = significant increase

Mucus Clearance

Exercise as a method for improving mucus clearance in CF is relatively under-studied. Current international guidelines recommend exercise as an adjunct to, but not a replacement for, traditional airway clearance techniques (Ward *et al.*, 2019). Indeed, some guidelines do not prescribe exercise as a therapeutic intervention for assisting with mucus clearance. Among an Australian cohort of adults with CF, almost half of the participants (43%) believed that exercise could be used as a substitute for traditional airway clearance, and 66% indicated that exercise undertaken before or during traditional airway clearance techniques could enhance its effectiveness (Ward *et al.*, 2019).

Dwyer et al., recently compared treadmill exercise, resting breathing and positive expiratory pressure (PEP) therapy, on mucus clearance in adults with CF. Treadmill exercise improved whole lung mucus clearance compared to resting breathing. However, exercise alone was less effective than using PEP therapy. The authors concluded that to achieve optimal mucus clearance for adults with CF, huffing and coughing should be used with exercise training (Dwyer *et al.*, 2019).

Others have also concluded that a combination of exercise and physiotherapy, inclusive of airway clearance techniques, have the potential to significantly enhance sputum production in CF patients resulting in short-term improvements in oxygen saturation (Salh *et al.*, 1989; Kriemler *et al.*, 2016). The mechanism for enhanced mucus clearance is thought to be mediated by mechanical vibrations and trunk oscillations that occur in the presence of increased ventilation during exercise (Dwyer *et al.*, 2011; Kriemler *et al.*, 2016).

Lung Function

Several studies have investigated the relation between exercise training and lung function in CF populations. Tucker et al., (2017) found a substantial increase in forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1), and a decrease in lung clearance index following a single bout of exercise (Tucker *et al.*, 2017).

Short, medium and long-term bouts of exercise training have also been shown to improve lung function in CF. Significant improvements in lung function (FEV_1 increased by 10%) were found in children who participated in resistance training (Selvadurai *et al.*, 2002). Similar improvements in lung function were found following participation in a two-month, home-based exercise training program involving 20-30 min of exercise at a moderate-to-vigorous intensity on at least five days of the week (Paranjape *et al.*, 2012). Hebestreit et al., (2010) instructed children and adults with CF to increase their participation in sport by 3 hours per week for 6 months, with subsequent follow-up at 12, 18 and 24 months (Hebestreit *et al.*, 2010). There was a significant increase in FVC at 18 and 24 months, suggesting improved respiratory muscle function. Using a randomized-controlled design, Schneiderman-Walker et al., (2000) found that children and adolescents who participated in a home-based aerobic exercise training program had a significantly slower decline in lung function compared to a control group (Schneiderman-Walker *et al.*, 2000).

Aerobic Capacity

Nixon et al., (1992) were the first to describe the relation between aerobic capacity and survival in CF populations (Nixon *et al.*, 1992). After adjusting for age, gender, lung function, bacterial colonization and nutritional status, peak oxygen uptake ($\dot{V}O_2$peak) in children and adolescents with CF was directly associated with eight year survival (Stevens and Williams, 2007). Children and adolescents with a higher aerobic fitness (≥ 82% predicted $\dot{V}O_2$peak) had an 83% chance of survival at 8 years, compared to a 51% and 28% with moderate (59-81% predicted $\dot{V}O_2$peak) and low (≤ 58% predicted $\dot{V}O_2$peak) aerobic fitness levels, respectively (Nixon *et al.*, 1992).

The effect of exercise training on aerobic capacity has been widely studied in CF. Both short duration training ranging from four to twelve weeks (Selvadurai *et al.*, 2002; Klijn *et al.*, 2004; Paranjape *et al.*, 2012; Santana Sosa *et al.*, 2012; del Corral *et al.*, 2018) and longer-term studies ranging from 6 months to 1 year (Gulmans *et al.*, 1999; Moorcroft *et al.*, 2004; Hebestreit *et al.*, 2010; Hommerding *et al.*, 2015; Gupta *et al.*, 2019) have been shown to significantly improve aerobic capacity. These studies have shown that improvements in aerobic capacity can be achieved through supervised, in-patient, hospital-based training programs (Selvadurai *et al.*, 2002; Klijn *et al.*, 2004; Santana Sosa *et al.*, 2012) and partially- or non-supervised, home-based training programs (Gulmans *et al.*, 1999; Moorcroft *et al.*, 2004; Hebestreit *et al.*, 2010; Paranjape *et al.*, 2012; Gupta *et al.*, 2019).

The majority of CF studies investigating the relation between exercise training and aerobic capacity have involved children and adolescents. The exercise programs were typically prescriptive in nature. Some studies (Hommerding et al., 2015, Klijn et al., 2004) however, have allowed CF patients to select the mode of exercise training (Klijn *et al.*, 2004; Hommerding *et al.*, 2015). It seems that regardless of disease severity, individuals with CF will respond to exercise in a similar manner to their untrained healthy counterparts (Gruber, Orenstein and Braumann, 2011).

Muscle Strength

The first study to investigate the effects of exercise training on muscle strength was undertaken by Gulmans et al., (1999) (Gulmans *et al.*, 1999). Fourteen children with mild to moderate impairment of lung function undertook a 6-month home-based exercise program consisting of cycling for 20 min five times per week at an intensity corresponding to 140-160 beats per min. Knee extensor and ankle dorsiflexion strength significantly improved from baseline to repeat assessment (Gulmans *et al.*, 1999). A number of subsequent studies have examined the impact of combined aerobic and resistance training on muscle strength in CF. Supervised in-hospital programs, supervised remote programs and non-supervised home-based programs ranging from 4 to 12 weeks in duration, performed 3-5 d per week, for approximately 20-40 min, have reported encouraging results with respect to increasing muscle strength in CF populations (Gulmans *et al.*, 1999; Selvadurai *et al.*, 2002; Klijn *et al.*, 2004; Santana Sosa *et al.*, 2012; Rovedder *et al.*, 2014; Beaudoin *et al.*, 2017; del Corral *et al.*, 2018). However, longer-term studies are required to determine whether improvements in muscle strength can be sustained in the long-term.

Quality of Life

Few studies have objectively investigated QoL in response to exercise training in CF (Gulmans *et al.*, 1999; Selvadurai *et al.*, 2002; Klijn *et al.*, 2004; Corral *et al.*, 2018; Gupta *et al.*, 2019). Klijn et al., (2004) found a significant improvement in the physical functioning domain for QoL following 12-weeks of anaerobic training in children (Klijn *et al.*, 2004). No improvements were reported for other QoL domains. Corral et al., (2018) assessed the effects of a six-week, home-based exercise training program supported by the use of active video games on QoL in children and adolescents with CF. There were significant improvements reported for the intervention group for the respiratory symptoms domain of QoL and these scores were sustained at 1 year (Corral *et al.*, 2018). Gupta et al., (2019) also reported significant improvements in overall QoL at 1 year for children and adolescents who participated in a resistance training and plyometric jumping exercise program (Gupta *et al.*, 2019).

Summary

It is important to acknowledge that the majority of exercise training studies in CF populations have been conducted in children and adolescents. Although several studies have included adults among study participants, typically it is a combination of prepubescents, adolescents and adults ranging between 16-45 years. The majority of these studies fail to account for the influence of age, as well as the process and rate of aging, giving rise to misleading results that are difficult to interpret as it has long been established that prepubescents and adolescents are not simply "mini adults" (Shei *et al.*, 2019). To the authors' knowledge, there are only two studies that have exclusively included adult populations when investigate the effectiveness of exercise training in this cohort (≥ 18 years) (Moorcroft *et al.*, 2004; Beaudoin *et al.*, 2017).

Moorcroft et al., (2004) investigated the effectiveness of a year-long, individualized, unsupervised, home-based exercise program among adults with CF (Moorcroft *et al.*, 2004).

Participants undertook 3 resistance training sessions per week, targeting upper and lower limbs using bicycle and arm ergometry, and assessments were conducted at baseline and 12 months. Significant increases were recorded for both pulmonary function and resistance training. However, this study did not measure indices relating to QoL or strength among adult CF population. Beaudoin et al., (2017) conducted a randomized-controlled trial to evaluate the effectiveness of combined aerobic and resistance training on glycemic control in adults with CF over a 3 month period (Beaudoin *et al.*, 2017). Participants randomized to the intervention group participated in aerobic and resistance training, on the same day, three times per week, and received a supervised training session once per month. Significant improvements were recorded for muscle strength, as measured using the leg press and bench press for lower and upper limbs. However, this study also failed to record indices relating to QoL, aerobic capacity or pulmonary function, which are vital prognostic indicators for longevity in this cohort, and therefore warrant further investigation.

Although several studies have reported beneficial effects for exercise training in CF populations, the evidence tends to be of poor methodological quality (Radtke *et al.*, 2017). While many of the studies used a randomized-controlled design, sample sizes were generally small and study durations relatively short. The validity of some studies may have been negatively impacted by selection bias and confounding factors (Hebestreit *et al.*, 2010; Paranjape *et al.*, 2012; Santana Sosa *et al.*, 2012). Despite the lack of randomized-controlled exercise trials and long term follow-up, exercise training has become an accepted and valued component in the management of CF over the past 10-20 years (Radtke *et al.*, 2017).

Exercise (In)tolerance

The ability to perform exercise is an important determinant of both longevity and QoL for patients with CF. Exercise intolerance is a hallmark of CF disease and is multifactorial in nature (Troosters *et al.*, 2009; Hulzebos *et al.*, 2015). However, the causes of exercise intolerance in patients with CF are conflicting. Various organ systems including the pulmonary, cardiovascular and musculoskeletal systems, along with oxygen delivery/utilization, have been suggested contributors to exercise intolerance in this cohort (Pastré *et al.*, 2014; Hulzebos *et al.*, 2015).

Pulmonary Factors

The primary manifestation of CF is progressive obstructive lung disease, and as such, mechanical limitations are to be expected. Ventilatory dysfunction in CF may contribute to exercise intolerance through deleterious changes in lung function and dead space ventilation (Shei *et al.*, 2019). The presence of an increased dead space within the CF lung elicits greater ventilation challenges, prompting an increase in respiratory rate and/or tidal volume to maintain adequate alveolar ventilation (Urquhart, 2011; Almajed and Lands, 2012). As exercise ventilatory demands continue to increase, the combination of high respiratory rates and decreased expiratory flows may result in an insufficient expiratory time to completely exhale the inspired breath, giving rise to dynamic hyperinflation (Almajed and Lands, 2012). The subsequent shallow breaths and incomplete expiration lead to air trapping, whereby a significant proportion of each inhaled breath flows in and out of this dead space rather than participating in gas exchange; intrapulmonary shunting (Soni *et al.*, 2008; Urquhart, 2011). This air trapping increases the inspiratory elastic work of breathing, resulting in an increased sense of respiratory effort, commonly referred to as dyspnea (Almajed, 2012). Ventilation-perfusion (V_A/Q) inequality has also been proposed as a significant contributor to ventilatory dysfunction in this group. V_A/Q inequality occurs due to a mismatch between the ventilation and perfusion of individual lung units, and is a primary manifestation of progressive obstructive lung disease. This mismatch in V_A/Q gives rise to hypoxemia and subsequent respiratory failure (Soni *et al.*, 2008).

Cardiac Factors

An altered cardiac response has been postulated in CF populations, with limitations to stroke volume, as a result of airway obstruction, partly accounting for the observed exercise intolerance in this group (Marcotte *et al.*, 1986). Cardiac output (Q) at rest is similar between patients with CF and their healthy peers. During progressive exercise, Q is significantly reduced thereby negatively impacting exercise capacity. The reduction in Q occurs in response to a reduced stroke volume, prompting a compensatory increase in heart rate (HR). However, the higher HR fails to sufficiently increase Q resulting in a decreased oxygen delivery (Almajed and Lands, 2012; Shei *et al.*, 2019).

At more advanced stages of CF, patients have been shown to have an impaired ability to increase right ventricular ejection fraction during progressive exercise resulting in hypoxemia and subsequently increasing the risk of the development of pulmonary hypertension (Benson *et al.*, 1984). The incidence of pulmonary hypertension is approximately 60% in patients with severe CF lung disease (Tonelli *et al.*, 2010).

Musculoskeletal Factors

There is ongoing debate with respect to the musculoskeletal factors that may contribute to exercise intolerance in CF populations. The debate is focused on the 'qualitative' vs. 'quantitative' origin of musculoskeletal limitations to exercise (Hulzebos *et al.*, 2015; Rodriguez-Miguelez *et al.*, 2017).

Qualitative intrinsic skeletal muscle limitations can occur independent of muscle mass, lung function or PA status (de Meer *et al.*, 1995; Troosters *et al.*, 2009; Lamhonwah *et al.*, 2010). It is has been postulated that CFTR channel dysfunction contributes to disturbed ion transport, resulting in a decreased action-potential magnitude and impaired skeletal muscle function in CF populations. Alterations in mitochondrial morphology and the generation of ATP has been found to impair mitochondrial bioenergetics (Lamhonwah *et al.*, 2010; Wells *et al.*, 2011). A lower resting concentration of ATP among CF patients, secondary to dysfunctional CFTR, is an indication of altered skeletal muscle oxidative capacity in this population. Lower resting ATP levels along with significantly reduced ATP production during exercise may contribute to compromised muscle function and exercise intolerance in this group (de Meer *et al.*, 1995; Lamhonwah *et al.*, 2010; Rodriguez-Miguelez *et al.*, 2017).

In contrast, quantitative changes due to a reduced muscle mass have also been shown to impair muscle function in patients with CF. The reduced muscle mass in pwcf is precipitated by bouts of inflammation (van de Weert-van Leeuwen *et al.*, 2014), increased doses of corticosteroid medication (Barry and Gallagher, 2003), frequent exacerbations (Burtin *et al.*, 2013), altered nutritional status (Gea, Sancho-Muñoz and Chalela, 2018) and less engagement in activities of moderate-to-vigorous intensity (Troosters *et al.*, 2009;

Hulzebos *et al.*, 2015; Shei *et al.*, 2019). Hulzebos et al., (2015) suggest that in patients with reduced muscle performance, decreased muscle mass rather than metabolic dysfunction appears to be the underlying cause, arguing that small quantitative rather than qualitative abnormalities may give rise to exercise intolerance in this cohort (Hulzebos *et al.*, 2015).

Oxygen Uptake Efficiency Slope

Maximal oxygen uptake ($\dot{V}O_2max$) determined during a cardiopulmonary exercise test has proven to be one of the most significant markers of prognosis and longevity among CF populations (Gruet *et al.*, 2010). As the attainment of $\dot{V}O_2max$ is effort-dependent, some pwcf may find it difficult to achieve maximal exercise due to disease-specific limiting factors such as motivation, dyspnoea, pain and fatigue. As a result, several submaximal variables have been established to assess aerobic capacity, removing the necessity of performing maximal exercise. The ventilatory threshold and gas exchange threshold are submaximal parameters that have shown to be reliable and widely used in CF populations (Sexauer and Fiel, 2003). However, it is well established that it is often difficult to determine both submaximal parameters among patients with chronic airflow limitations (Belman, 1993).

Consequently, Baba et al., (1996) introduced the oxygen uptake efficiency slope (OUES), an objective submaximal measure of cardiopulmonary reserve, that does not require maximal exercise effort (Baba *et al.*, 1996). The OUES indicates how effectively oxygen is taken in by the lungs, transported and used in the periphery, and is represented by the rate of increase in maximal oxygen consumption ($\dot{V}O_2$) in response to a given minute ventilation (V_E) during incremental exercise, combining respiratory, cardiovascular and musculoskeletal function into a single index (Hollenberg and Tager, 2000). The OUES is not influenced by physiological parameters such as the onset of metabolic acidosis, which is triggered by several factors including muscle mass, distribution of blood flow to the working muscles, oxygen extraction and utilization, and physiologic pulmonary dead space (Hollenberg and Tager, 2000).

The OUES is calculated using the linear relation of $\dot{V}O_2$ (y-axis) versus the logarithm of V_E during incremental exercise and is highly reproducible and significantly correlated with other exercise parameters including $\dot{V}O_2max$ (Figure 2.4) (Akkerman *et al.*, 2010). The following equation is used to calculate OUES; $\dot{V}O_2 = a \log V_E + b$, where $\dot{V}O_2$ represents the oxygen uptake (ml·min^{-1}), the constant 'a' represents the increase in $\dot{V}O_2$ in response to the increasing $\dot{V}_E$ (OUES), $\log\dot{V}_E$ is the common logarithm of $\dot{V}_E$ and the constant 'b' represents the intercept (Baba *et al.*, 1996; Onofre *et al.*, 2017).

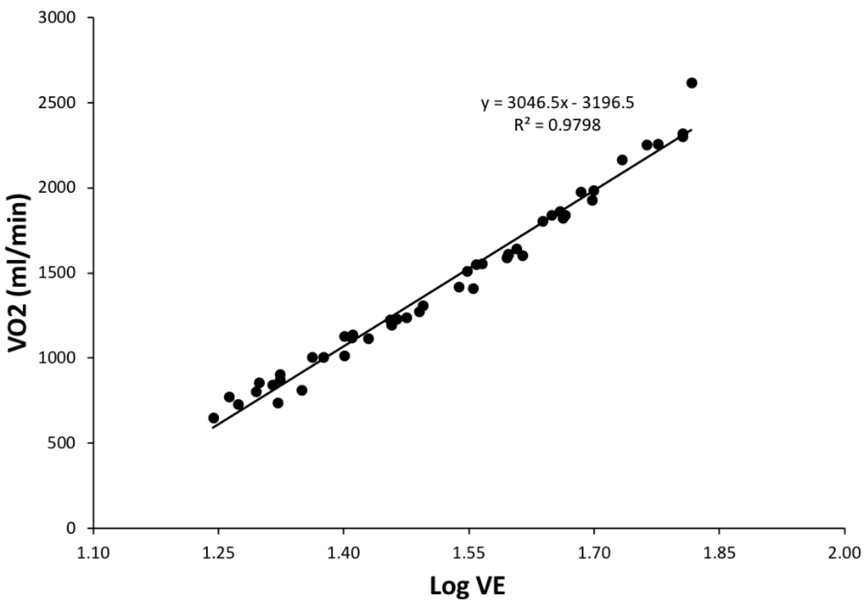


Figure 2.8: Calculation of the oxygen uptake efficiency slope (OUES)

Prognostic value of OUES

OUES has been found to have significant prognostic value in patients with coronary artery disease (Buys *et al.*, 2016) and heart failure (Davies *et al.*, 2006), with lower OUES values being predictive of 2-year cardiac related hospitalization (Ten Harkel and Takken, 2019). Few studies exist investigating the prognostic value of the OUES for patients with respiratory diseases. OUES has been found to provide important prognostic information for predicting clinical worsening and mortality in patients with idiopathic pulmonary artery hypertension (Tang *et al.*, 2017). Conversely, Barron et al., (2016) found that OUES had no prognostic value in COPD (Barron *et al.*, 2016).

Clinical Utility of OUES in CF

Despite the fact that only five published studies (four in children and one in adult) have examined the clinical utility of the OUES in CF, this submaximal measure of cardiopulmonary reserve has emerged as a prognostic indictor for survival in CF. In the only published study to investigate the clinical utility of the OUES in adults with CF, Gruet, et al., (2010) reported that the OUES, calculated using 80% of the exercise test duration, ($OUES_{80}$) was the most reliable and valid submaximal parameter for predicting $\dot{V}O_2max$ in this age profile of pwcf (Gruet *et al.*, 2010).

The first study to determine the validity of the OUES in children with mild to moderate CF, found that submaximal values of OUES had limited value due to its limited ability to distinguish between children with varying disease severities (Bongers *et al.*, 2012). Similarly, a subsequent study involving 36 children with CF and 36 age and gender matched controls found that OUES and oxygen uptake efficiency plateau [OUEP]) were not a suitable surrogate for $\dot{V}O_2$peak in children with CF and recommended the continued use of maximal exercise testing (Tomlinson *et al.*, 2018). These findings suggest that the OUES may be age-sensitive in CF populations.

Self-Regulated Exercise

Exercise prescription is as much an art as a science, and there is a need to balance physiological effectiveness with enjoyment and pleasure, while ensuring the attainment of optimal health benefits. The Hedonic Theory suggests that human behaviour is motivated by the pursuit of pleasure and the avoidance of pain, or displeasure (Murphy and Eaves, 2016). This theory indicates that individuals are likely to repeat an activity if they achieve a sense of pleasure, increased energy, or enjoyment following participation in the activity (Sheppard and Parfitt, 2008; Oliveira, Deslandes and Santos, 2015). In contrast, if feelings of displeasure, fatigue, pain, or discomfort are found following PA, the likelihood of the individual to repeat the activity would be significantly reduced (Ekkekakis, 2009).

Studies that have evaluated the effect of exercise training in CF populations have, for the most part, used prescribed exercise based on objectively measured thresholds of HRmax or $\dot{V}O_2$max. This form of exercise prescription may exceed an individual's preferred level of intensity and may promote the establishment of negative attitudes towards continued participation in PA (Ekkekakis, 2009).

Allowing individuals to use effort perception to self-regulate their preferred intensity may encourage the development of intrinsic motivation, enjoyment and subsequent long-term adherence to PA (Johnson and Phipps, 2006). This notion stems from the formative work by Cabanac and colleagues, who conducted a study whereby a conflict was created between muscular fatigue and ambient cold. Participants were allowed to choose either the slope of the treadmill, while ambient temperature was fixed or ambient temperatures between 5 to 25°C while the treadmill slope was fixed. Participants engineered their selections to maintain a steady core temperature and a heart rate that did not exceed 120 beats per minute, thus maximizing pleasure or minimizing displeasure (Cabanac and Leblanc, 1983; Ekkekakis, 2009). Cabanac also demonstrated that when the speed of the treadmill was fixed and the participants were allowed to choose the slope, or when the slope was fixed and the participants were allowed to choose the speed, the adjustments made by the participants were reciprocal, resulting in constant ratings of pleasure and power (Cabanac, 1986). Cabanac concluded that pleasure is the 'common currency' that individuals use when making behavioural choices in situations that involve conflicting concerns.

In a study conducted by Ekkekakis et al., (2006), a group of overweight women were allowed to self-select their preferred exercise intensity or were instructed to perform exercise at a prescribed intensity during two separate visits to the laboratory. The exercise intensity differed by only 10%, yet the level of enjoyment reported by the women was significantly higher when allowed to self-select their exercise intensity compared to undertaking a bout of exercise at a prescribed intensity (Ekkekakis and Lind, 2006). These findings may be due, in part, to the enhanced perceptions of autonomy and control that occur when individuals are allowed to self-regulate their exercise intensity.

Few studies have investigated the effectiveness of self-regulated exercise in CF populations. Studies conducted to date have focused solely on children (Bar-Or, 2000). Happ, et al., (2013) identified motivators and barriers among children and their parents to sustained participation in a self-regulated exercise programme (Happ *et al.*, 2013). Motivators included participation in a research trial, parent and family involvement, health benefits and personality traits whereas the main barriers were identified as competing activities, priorities and responsibilities (Happ *et al.*, 2013). Children appear to be capable of appropriately using an RPE scale (OMNI scale) to regulate exercise intensity (Higgins *et al.*, 2013). Britton, (2011) examined the physiological and perceptual responses during self-regulated exercise in children with CF (Britton, 2011). Although the mean $\%\dot{V}O_2$peak was within the recommended range for the improvement of health-related outcomes, there were large intra-individual variations in RPE and $\%\dot{V}O_2$peak during self-regulated exercise in this age group (Britton, 2011).

To date, no studies have investigated the feasibility or effectiveness of self-regulated exercise in adults with CF. Prescribing self-paced exercise may have considerable promise for increasing adherence to exercise programs (Ekkekakis and Lind, 2006).

Determinants of Physical Activity

Behaviour change is a complex process with multiple determinants. The World Health Organization (WHO) defines adherence to health-related behaviours as *"the extent to which a person's behaviour corresponds with agreed recommendations from healthcare providers*" (WHO, 2003). Adherence to such behaviours, including PA, is a complex behavioural process and is underpinned by a myriad of compounding factors (Middleton, Anton and Perri, 2013).

Understanding how these factors influence PA adherence is an important component to be considered when designing and implementing interventions aimed at enhancing engagement in PA. Tailoring an intervention to target factors that are known determinants for influencing PA behaviour for CF populations, such as physical, psychological and social factors, can contribute to the successful adoption, and long-term maintenance, of PA behaviours (Denford *et al.*, 2020).

Evidence suggests that both children and adults with CF are less physically active than their healthy peers (Swisher and Erickson, 2008; Schneiderman *et al.*, 2014). Although limited research exists investigating PA adherence rates among pwcf, a recent systematic review (2014) has concluded that adherence to exercise among pwcf is widely varied and ranges between 57-88% (Cox, Alison and Holland, 2013; O'Donohoe and Fullen, 2014). The most commonly reported barriers to PA adherence in this cohort include lack of time, lethargy and feeling unwell (White, Stiller and Haensel, 2007). In contrast, factors shown to facilitate adherence to exercise training among pwcf include participating in activities deemed enjoyable, and including methods of self-monitoring to foster the development of autonomous motivation and higher levels of self-competence (White, Stiller and Haensel, 2007; Shelley *et al.*, 2018; Denford *et al.*, 2019; Burnett, Barry and Mermis, 2020). Experts have advocated for the development of personalized PA programs that include activities enjoyed by the individual, and the incorporation of motivational interviewing and behavioural counseling to minimize barriers to, and maximize facilitators of, PA (Prasad and Cerny, 2002; Moran and Bradley, 2010).

Theories of Behaviour Change

Behaviour change theories are a set of pre-determined, inter-related concepts or predictions that outline relationships among variables in order to explain behaviour (Hagger and Weed, 2019). The application of behaviour change theory is advocated by the Medical Research Council (MRC) as an integral step for the development, implementation and evaluation of complex interventions (MRC, 2019). Behaviour change theories are typically used in three ways: i) to assist in the understanding of the determinants of behaviour, ii) to guide the development of interventions whose aim is to successfully change behaviours, and iii) to provide insights into the mechanisms underpinning successful behaviour change.

A recent systematic review has collated all of the existing theories of behaviour change (n=82), and reported that the most commonly used theories were the Transtheoretical Model of Change (TTM) and the Theory of Planned Behaviour (TPB), which accounted for 33% and 13% of the theories used, respectively (Davis *et al.*, 2015).

The Transtheoretical Model of Behaviour Change

The TTM incorporates elements of several theories of therapy, learning and behaviour change, lending to the term 'Transtheoretical'. The TTM posits that behaviour change occurs following a transition through the six stages of change: precontemplation, contemplation, preparation, action, maintenance and relapse (Prochaska and Velicer, 1997).

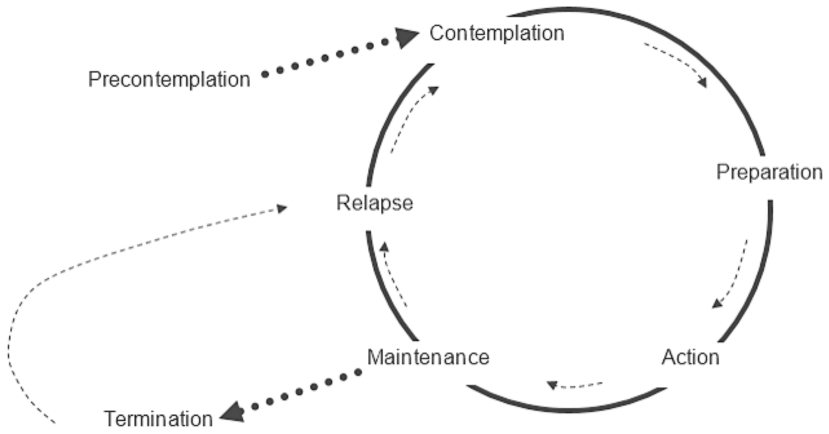


Figure 2.9: The Transtheoretical Model of Behaviour Change

Processes of change, including consciousness raising, self-reevaluation, environmental reevaluation, self-liberation, social liberation, counterconditioning, stimulus control, contingency management and helping relationships, have been linked with progress through the stages of change. Decisional balance and self-efficacy, and the acknowledgement that individuals can enter and exit the stages of change by relapsing, are the core concepts that underpin the TTM.

Although the TTM has received significant research attention and is arguably the most dominant model of health behaviour change, it has simultaneously attracted exceptional criticism (Armitage, 2009). Evidence suggests that flaws exist in the stages of change concept, and proposes that a model including an initial motivational phase followed by a volitional phase would more accurately reflect changes in PA behaviour. Further criticisms of the TTM recognize the arbitrary differentiation between stages, and West (2005) suggests that the definitions of stages represent a variety of different theoretical constructs which, for the most part, are predominantly incoherent (West, 2005).

The Theory of Planned Behaviour

The TPB was developed to predict an individual's intention to engage in a behaviour at a specific time and place, and sought to explain all of the behaviours that an individual can control (Ajzen, 1991). The core concept that underpins this theory is behavioural intent, such that behavioural intentions are influenced by the individual's attitude about the likelihood of the behaviour returning the expected outcome. The TPB posits that behavioural achievement depends upon both motivation (intention) and ability (behavioural control), and distinguishes between three types of beliefs: behavioural, normative and control (Figure 2.9). There are six constructs that make up the TPB: attitudes, behavioural intention, subjective norms, social norms, perceived power, and perceived behavioural control.

Despite the fact that the TPB has inspired a substantial amount of empirical health behaviour research, a significant debate persists within the literature. A systematic review conducted by Hardeman et al., (2002) identified 24 studies in which the TPB was used during the intervention development and evaluation processes, and concluded that the available evidence was insufficient to draw significant conclusions about the effectiveness of the theory (Hardeman *et al.*, 2002; Sniehotta, Presseau and Araújo-Soares, 2014). Sniehotta et al., (2014) have raised significant concerns regarding the validity of the TPB, and suggest that the theory has lost its utility as it has not been shown to positively support practitioners in the development of successful interventions, and indicates that the field has moved on as scientists have begun using 'extended' forms of the theory indicating disbelief in its accuracy (Sniehotta, Presseau and Araújo-Soares, 2014).

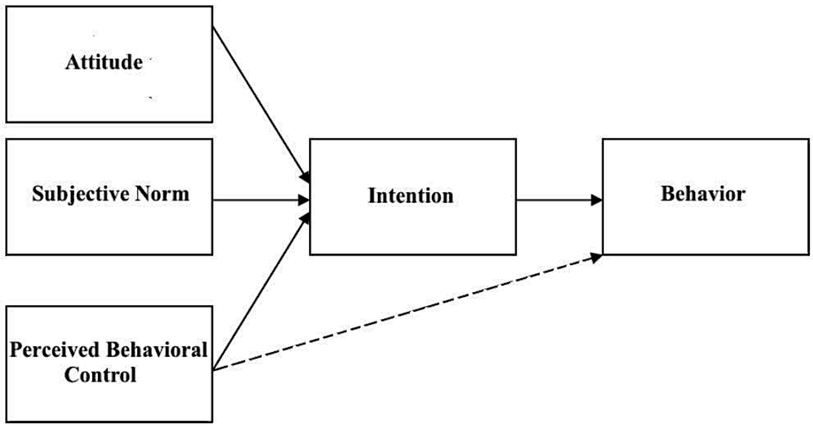


Figure 2.10: The Theory of Planned Behaviour

While it is recommended that researchers involved in the intervention development process draw on theory to inform intervention design, little guidance is offered in relation to the selection and application of appropriate theory (Michie, van Stralen and West, 2011). Michie et al., have questioned whether existing theories and frameworks are meeting intervention developers' needs, as few researchers have made use of the available frameworks during the intervention development process to systematically determine the cause for success or, indeed, failure (Michie, van Stralen and West, 2011).

Consequently, Michie and colleagues identified the need for the development of a comprehensive, stand-alone systematic approach that would focus on understanding the nature of the target behaviour and the importance of mapping intervention functions to appropriate behaviour change techniques, to form the starting point of the intervention design process (Michie, van Stralen and West, 2011). Thus, the novel behaviour change wheel (BCW) framework was developed. The BCW focuses on the interaction between an individual's capability, opportunity and motivation to successfully achieve a target behaviour (COM-B model). The BCW is the first framework that has been constructed from existing frameworks, explicitly to overcome their limitations. The Theoretical Domains Framework (TDF) is an adjunct framework that was subsequently developed to assist the BCW, whereby each domain of the TDF correlates to a specific BCW COM-B component. By using the BCW and TDF together it allows for an expansion of the COM-B components into very specific domains (Mangurian *et al.*, 2017).

The intervention development process in this thesis is primarily underpinned by the BCW, COM-B model and TDF, as they are heavily grounded in behaviour change theory and linked to evidence-based intervention functions that can facilitate the development of appropriate interventions for a targeted population (Michie, van Stralen and West, 2011; Cane, O'Connor and Michie, 2012).

The Behaviour Change Wheel

The Behaviour Change Wheel (BCW) was developed, by Michie et al., (2011), to address the limitations of existing theoretical frameworks, and to provide a systematic method for understanding behaviour change (Michie, van Stralen and West, 2011) (Figure 2.5). The BCW was created following a systematic review and analysis of 19 existing frameworks for classifying behaviour change, and provides a structured approach to designing behaviour change interventions and strategies (Michie, 2014).

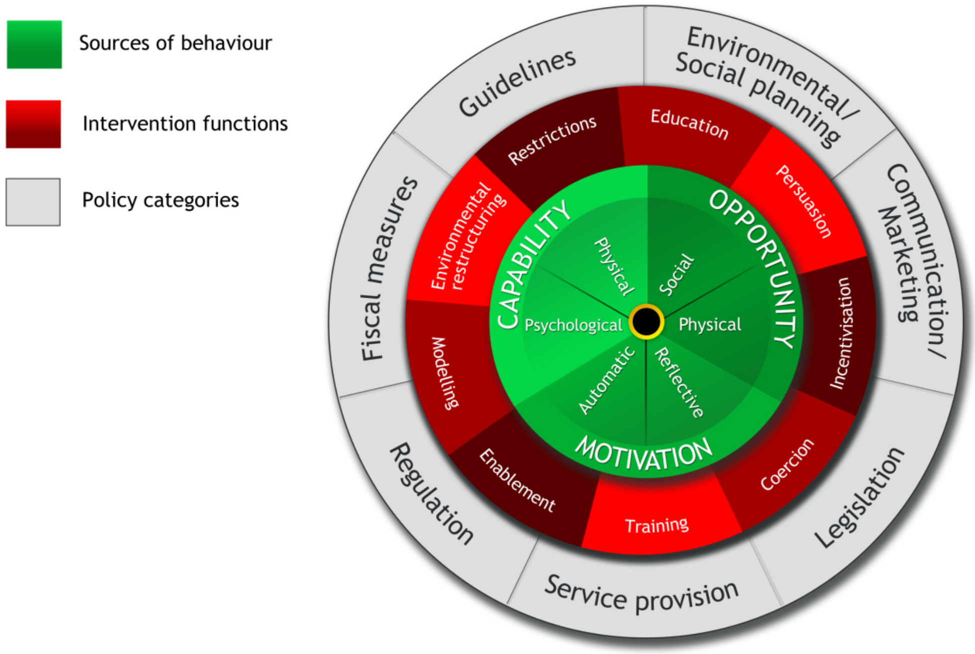


Figure 2.11: The Behaviour Change Wheel (Michie, Atkins & West, 2014)

At the core of the BCW is the COM-B model, which focuses on the interaction between an individual's capability, opportunity and motivation to participate in a given behaviour (See Figure 2.6). Capability refers to an individual's ability, both physical and psychological, to perform the target behaviour (i.e., PA). Opportunity refers to the external factors, both physical and social, that make a behaviour possible. Motivation, which includes automatic and reflective motivation, is defined as all those brain processes that energize and direct behaviour, not just goals and conscious decision-making (Michie, van Stralen and West, 2011).

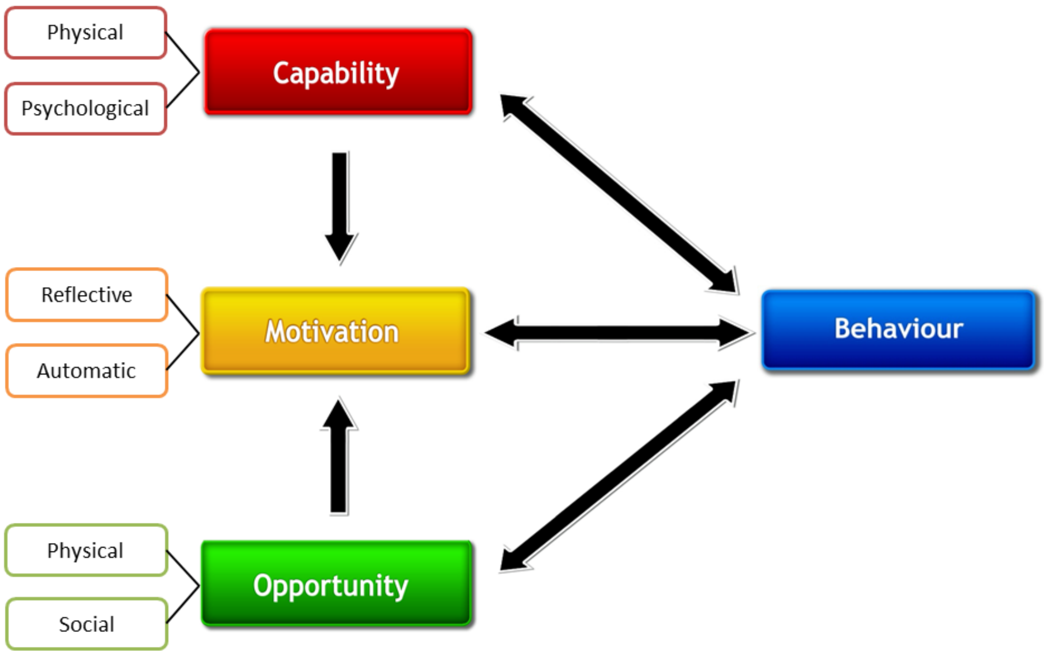


Figure 2.12: The COM-B Model (Michie, 2011)

The COM-B model is used to perform a behaviour diagnosis, and once identified, intervention functions (i.e., education, persuasion, incentivization, coercion, training, enablement, modelling, environmental restructuring and restrictions) are chosen from the BCW, to support the adoption of the target behaviour by the selected population. The most outer layer of the BCW consists of seven policy categories (environmental/social planning, communication/marketing, legislation, service provision, regulation, fiscal measures and guidelines) which each have the ability to support one or more of the intervention functions.

To the best of the authors knowledge, the BCW has yet to be used in the development, implementation or evaluation of PA interventions for CF populations. Very few studies exist regarding the use of the BCW in the development of PA interventions for chronic respiratory diseases. Of the studies that do exist in COPD cohorts, the majority are protocol publications, published in preparation for the determination of feasibility. Robinson et al., (2019) however, have recently published a protocol paper, and the results for a full-scale randomized-controlled efficacy trial, using the BCW to develop an intervention to promote PA upon completion of pulmonary rehabilitation in patients with COPD (Robinson *et al.*, 2019). The authors used the BCW to conduct a behavioural diagnosis and identified PA maintenance as the target behaviour for this intervention, and concluded that psychological capability, reflective motivation, automatic motivation, and physical and social opportunity needed to be changed in order to achieve the target behaviour. Four intervention functions that agreed with the APEASE criteria were selected for the intervention: education, environmental restructuring, enablement and persuasion. Thirteen BCTs were selected, based on the chosen intervention functions, and included three components of social support, instruction on how to perform a given behaviour, behavioural practice and rehearsal, self-monitoring of behaviour, written persuasion about capabilities, focus on past successes, prompts and cues, restructuring the social environment, social rewards, and feedback on behaviours. The resultant intervention components included i) the development of a peer support group, via WhatsApp messaging, ii) providing patients with a pedometer, and iii) a step diary for the 52-week intervention duration. The authors concluded that the use of the web-based, pedometer-mediated PA intervention can effectively increase PA levels by uncoupling the relationship that associates low exercise self-efficacy and low PA in patients with COPD (Robinson *et al.*, 2019).

Within the extended literature, the BCW has been employed in the development of interventions targeting physical inactivity in the workplace (Ojo *et al.*, 2019), smoking cessation (Gould, Lim and Mattes, 2017), and weight loss (Beleigoli *et al.*, 2018) and was found to be effective.

The Theoretical Domains Framework

Researchers are being encouraged, as part of the BCW method, to apply the Theoretical Domains Framework during the intervention development process (TDF) (Cane, O'Connor and Michie, 2012; Michie, 2014). The TDF was initially developed for implementation research and has been cited in almost 1,000 peer-reviewed publications (Atkins *et al.*, 2017). It provides a framework of theoretical domains to explain the barriers and facilitators of behaviour in any particular situation, and is informed by 128 explanatory constructs from 33 theories of behaviour, providing a theoretical lens through which to view cognitive, affective, social and environmental influences on behaviour (Davis *et al.*, 2015; Atkins *et al.*, 2017). The TDF assists in further unpacking the COM-B model behavioural diagnosis into the 14 domains specified within the TDF: 'knowledge', 'skills', 'social/professional role and identity', 'beliefs about capabilities', 'optimism', 'beliefs about consequences', 'reinforcement', 'intentions', 'goals', 'memory, attention and decision processes', 'environmental context and resources', 'social influences', 'emotions', and 'behavioural regulation'. Once the information gathered from the BCW and TDF has been collated, optimal behaviour change techniques can then be identified, selected and applied (Ojo *et al.*, 2019). Behaviour change techniques are defined as observable, replicable and irreducible components of an intervention that aim to change, or redirect causal processes that determine behaviour (Michie *et al.*, 2018).

Chapter III
Study I

Study I: Recommendations to Improve Physical Activity Prescription for the Cystic Fibrosis Population: An Irish Perspective

Abstract

Background: PA is a well-established therapeutic modality for the maintenance and improvement of long-term health in CF. HCP are considered credible and well-placed messengers for the delivery of PA advice. Limited research exists investigating the extent of PA prescription within CF care. This study aimed to identify Irish HCP i) knowledge and practice of, and ii) motivators and barriers to PA prescription, and iii) proposed strategies to optimize PA promotion and prescription in CF populations.

Methods: HCP from six designated CF centres in Ireland and members of the national physiotherapy CF clinical interest group were invited to participate. Following an expression of interest, each HCP (n=81) received an email containing the plain language statement and link to the online survey. A total of 48 HCP (physiotherapists n=24, other n=24) completed the 30-item investigator-developed survey, which included multiple choice single answer, matrix style and open-ended questions.

Results: Most HCP (81%) acknowledged that discussing PA with CF patients was part of their professional role. Almost all physiotherapists (95%) reported having sufficient knowledge regarding PA prescription, compared to 17% of other HCP. All physiotherapists reported discussing PA at every patient interaction, with 81% employing the current consensus guidelines, compared to 33% and 5% of other HCP, respectively. Among the most common barriers reported by HCP to recommending PA to their CF patients were; lack of motivation and compliance to adhere to PA advice, limited availability of PA programmes to refer patients, limited time with patients during clinic visits and a lack of knowledge regarding PA prescription for CF care. Three-quarters of HCP reported a need to improve PA services for CF patients in Ireland.

Conclusion: As people with CF are living longer, it is imperative that HCP expand their scope of practice to include discussions around PA at every patient visit. Formal educational opportunities in the form of continuing professional development programmes are warranted for CF HCP to optimize long-term patient management and outcomes. There is also a need to develop patient-centered and evidence-based PA programmes underpinned by theories of behaviour change to enhance motivation and compliance among CF patients.

Introduction

CF is an autosomal recessive disorder characterized by the abnormal functioning of the CFTR protein that is essential for the regulation of transmembrane chloride reabsorption (Brice, Jarrett and Mugford, 2007). It is a multisystem disorder involving abnormal function of chloride channels in secretory epithelial cells lining the airways, digestive system, reproductive system, and the skin and results in increased morbidity and mortality (Carbonera, Vendrusculo and Donadio, 2016). The prevalence of CF differs by ethnicity and geographical background. It is the most common inherited disease among the Caucasian population, with an annual incidence of approximately 1 in 2,500 live births (Farrell, 2008). Ireland has the highest incidence per capita in the world, with approximately 1 in every 19 people carrying the CF mutation and 7 in every 10,000 people living with the condition (CFI, 2021).

The life expectancy of CF patients has substantially lengthened in the past 25 years due to early diagnosis and improvements in symptomatic therapeutic regimens (Tejero García *et al.*, 2011). Optimal management of CF involves a multidisciplinary team (MDT) of HCP and is centered around slowing lung function deterioration, providing dietary interventions to compensate for pancreatic insufficiency and intestinal malabsorption and optimizing pharmacotherapy to eliminate infections (Rand and Prasad, 2012).

Exercise intolerance is a hallmark of CF disease. Evidence suggests that children with CF tend to have similar PA levels to their healthy peers until they reach adolescence when there is a notable decline. Cox et al., (2016) report that this decreased activity in adolescents with CF does not recover with increasing age (Cox *et al.*, 2016). Participation in regular PA has been shown to improve physical deconditioning in both adults and children with CF (de Meer *et al.*, 1995; Troosters *et al.*, 2009). Among CF patients, regular PA has the potential to decrease the annual rate of decline in pulmonary function, improve airway clearance, reduce hospitalization frequency and improve longevity, while also improving aerobic capacity, muscle strength, bone health and enhancing health-related quality of life(Williams and Stevens, 2013; Radtke *et al.*, 2017).

HCP are considered desired, credible and well-placed messengers for the delivery of PA advice and have the capacity to play an integral role in the promotion of PA behaviours among their patients (Tomasone *et al.*, 2014; Speake *et al.*, 2016). There is a greater likelihood of patient engagement in PA behaviours following pro-active counseling by HCP (Lange and Mager, 2011; Joy *et al.*, 2013). According to the American College of Sports Medicine *Exercise is Medicine* initiative, all HCP should incorporate discussions about PA into *every* patient interaction (Lange and Mager, 2011). Therefore, it is imperative that HCP work collectively within the multidisciplinary team to ensure their PA recommendations are underpinned by both up-to-date and evidence-based theory. Expert consensus guidelines have been developed for use by CF HCP responsible for discussing and prescribing PA with their patients (Swisher *et al.*, 2015).

It is critical that every member of the MDT strives to maintain the same philosophy regarding the importance of PA, particularly for individuals with chronic disease. Although the primary responsibility for PA prescription currently lies with the physiotherapist, it is important that other members within the MDT positively reinforce PA prescription with evidence-based PA promotion.

PA prescription is considered to be synonymous with any other form of prescription, including a type, dose, frequency, duration and therapeutic goal (Seth, 2014). PA prescription should involve careful pre-participation screening including the patient's capacity for PA, as well as a needs analysis to identify the individual's goals and interests. Currently no data exist on Irish HCP practice of PA prescription within CF care.

The purpose of this study was to investigate the knowledge and practice surrounding PA promotion and prescription among CF HCP in Ireland. Specifically, the study evaluated i) the current level of knowledge regarding CF-specific PA guidelines and prescription, ii) the practice of discussing and appropriately prescribing PA, iii) the motivators and barriers to recommending PA, and iv) strategies to optimize HCP prescription of PA to patients with CF.

Methods

Participants

HCP working in hospitals and specialist CF centres were invited to participate in the study. The term healthcare professional, within the context of this study, refers to medical and allied HCP working in CF care. In Ireland, the CF MDT is typically comprised of consultants, registrars, clinical nurse specialists, dieticians, physiotherapists, psychologists, social workers and pharmacists. Historically, in Ireland, exercise-related programmes have been delivered by physiotherapists, as the role of the exercise scientist does not yet have professional recognition within the Health Service Executive.

Recruitment and Survey Dissemination

Participants were recruited via two routes: i) direct contact with clinical CF teams, and ii) through the national physiotherapy CF clinical interest group. The email address and/or telephone number for eleven of the designated CF centres in Ireland were obtained from the Cystic Fibrosis Ireland website. Each clinical centre was contacted by phone or email to explain the background of the study, and were requested to confirm their willingness to participate by email. Six of the eleven centres agreed to participate. In addition, a physiotherapist from one of the six CF centres distributed the survey to members of the national physiotherapy CF clinical interest group. The survey was disseminated to a total of 81 HCP.

An individual HCP from each of the six participating CF centres was identified as a source of contact between the researcher and the individual's MDT. This individual was responsible for circulating the plain language statement (Appendix A) and the link to the online survey among their colleagues within their MDT. Participants were asked to provide informed consent (Appendix B) at the beginning of the online survey. Data was collected using a web-based survey tool (SurveyMonkey®) between February and March 2019. Ethical approval was granted by Dublin City University Research Ethics Committee (DCUREC/2018/141). Participants were given an initial deadline of 2 weeks from receipt of the first email containing the link to the survey. The deadline was extended for a further two weeks and reminders were sent via email, once per week, to optimize response rate.

Survey

The 30-item survey (Appendix C) was developed by the research team and included questions that were adapted from previous research investigating HCP knowledge and practice of PA prescription in cancer care (O'Hanlon and Kennedy, 2014; Cantwell *et al.*, 2018), and the role of person-centered exercise provision within the CF MDT (full survey is included as Additional File 1) (Tomlinson *et al.*, 2018). The survey consisted of four sections, which aimed to identify i) the HCP demographic and professional backgrounds ii) their knowledge and practice, and motivators and barriers in relation to PA promotion and prescription and iii) strategies to enhance such prescription in CF care. The format included multiple choice single answer and matrix style questions. Three open ended questions were also included to identify, from the HCP perspective, motivators and strategies to optimize PA prescription to their CF patients.

Data Analysis

Data were analysed using IBM Statistical Package for the Social Sciences (SPSS) version 24. Descriptive statistics, including frequencies, were conducted. Open-ended, free text, data were analysed using thematic analysis (Braun and Clarke, 2006). Thematic analysis involved a 6-step process whereby codes were generated and emergent themes were identified, reviewed and defined, ensuring no incidence of overlap to offer a credible and trustworthy interpretation of the participants perceptions. The data were analyzed for all HCP combined and separately for physiotherapists (n=24) and other HCP (n=24).

Results

Eighty-one HCP received the invitation, and forty-eight HCP participated in the study (59.2% response rate). The respondents demographic and professional characteristics are outlined in Table 1.

Table 3.1: HCP demographic and professional characteristics

Gender	Female	85%
	Male	15%
Age	20-29y	11%
	30-39y	52%
	40-49y	27%
	50-59y	10%
Occupation	Physiotherapist	50%
	Clinical Nurse Specialist	23%
	Registrar	9%
	Dietician	6%
	Consultant	6%
	Surgeon	2%
	Psychologist	2%
	Physician	2%
Years Qualified	0-5y	10%
	6-9y	15%
	10-19y	50%
	>20y	25%
Years in CF care	0-5y	40%
	6-9y	8%
	10-19y	42%
	>20y	10%
Work Setting	Public Hospital	73%
	Specialist Centre	27%
Patient Group	Adult	50%
	Paediatric	27%
	Combined Adult + Paediatric	23%
Pre or Post Transplant	Pre	74%
	Post	26%

Education regarding PA prescription in CF care

Only 11.6% of HCP reported to have received education in relation to PA prescription for CF populations during their undergraduate studies. For the most part, there was no difference in the education received by physiotherapists and other HCP at undergraduate level. HCP who graduated during the past 5 years, were no more likely to have received education regarding PA promotion and prescription at undergraduate level than those who graduated >20 years ago.

Since graduating, three out of every four HCP sought to improve their knowledge of PA prescription for CF populations. Conference attendance, self-directed learning and informal discussion were the three most common sources of further education. Less commonly reported sources of further education included in-service training, workshop or study-day attendance, supervised clinical placement and graduate training by MSc or PhD.

Knowledge of PA prescription for CF populations

Likert responses indicating HCP level of agreement for having sufficient knowledge of, and familiarity with, the current consensus guidelines are outlined in table 2. A very high proportion (95%) of physiotherapists agreed or strongly agreed that they had sufficient knowledge about prescribing PA to people with CF, with 85% agreeing or strongly agreeing that they were familiar with the current PA consensus guidelines for people with CF. In contrast, among other HCP, 38.1% agreed or strongly agreed to having sufficient knowledge of and familiarity with the consensus guidelines.

Table 3.2: HCP level of agreement for sufficient knowledge of, and familiarity with, the current consensus PA guidelines for CF populations

	Occupation	Strongly Disagree (%)	Disagree (%)	NAND (%)	Agree (%)	Strongly Agree (%)
Sufficient Knowledge	Physiotherapist	0.0	5.0	0.0	60.0	35.0
	Other HCP	4.3	47.8	30.4	17.4	0.0
Familiarity with Guidelines	Physiotherapist	0	0	15	40	45
	Other HCP	13	47.8	17.4	17.4	4.3

**NAND: Neither agree nor disagre*

HCP were asked to describe the current consensus guidelines (14), with respect to the FITT principle criteria, where; F = frequency; the number of times PA should be carried out per week, I = intensity; how hard the individual should be working, T = time; the duration of the PA session and T = type; the mode of activity. Physiotherapists were typically very accurate in their description of the FITT principle criteria with accuracy ranging from 89.5-100%, compared to other HCP who largely reported incorrectly, particularly with respect to the frequency (15%) and intensity (10%) components. Table 3 outlines the proportion of participants that correctly described the FITT principle components with respect to the current consensus guidelines.

Table 3.3: HCP accuracy in reporting the current consensus guidelines (13), with respect to the FITT principle criteria

	Physiotherapist	Other HCP
Frequency (%)	94.4	15.0
Intensity (%)	100.0	10.5
Time (%)	94.7	73.7
Type (%)	89.5	47.4

Practice of PA prescription in CF care

There was almost unanimous consensus (94.3%) among the HCP that the physiotherapist, as the PA specialist within the MDT, should take the lead for PA prescription. Among HCP, 80.6% agreed or strongly agreed that recommending PA to their CF patients was part of their professional role. All physiotherapists reported routinely discussing PA at every patient interaction and the majority (81.3%) reported incorporating the current consensus guidelines into their prescription of PA during patient interactions, compared to only 5% of other HCP. Among other HCP, only 42.1% discussed PA at every patient interaction, with the remainder discussing PA at every second patient visit (25%), rarely (8.3%), only at annual review (8.3%) or only when the patient asks (4.2%). The majority of physiotherapists (75%) communicated their PA prescription through a combined method of verbal and written advice, compared to 100% of other HCP communicating this prescription through verbal advice alone.

Half of physiotherapists reported finding it ‘easy’ or ‘extremely easy’ to prescribe PA to their CF patients. The remaining 37.5% and 12.6% of physiotherapists reported finding PA prescription ‘neither easy not difficult’ and ‘difficult’ or ‘extremely difficult’, respectively. Of the other HCP, 30% reported PA prescription to be ‘easy’ or ‘extremely easy’, with 50% and 20% of the remaining HCP finding it ‘neither easy nor difficult’ and ‘difficult’ or ‘extremely difficult’, respectively.

Motivators

HCP were asked to identify, through an open-ended question, the most prominent motivators that facilitated their PA prescription. Among the most common motivators reported were; improving patient outcomes such as survival rates, pulmonary function, exercise tolerance, psychological well-being and quality of life. The motivators described by HCP are outlined in Table 4.

Table 3.4: HCP motivators for prescribing PA to their CF patients

1.	Improving survival rates
2.	Improving pulmonary function
3.	Improving exercise tolerance
4.	Improving psychological well-being
5.	Improving quality of life

Barriers

HCP were asked to rank the most prominent barriers to prescribing PA and the results are summarized in Figure 1. Lack of patient motivation to participate in PA, poor compliance to PA advice given by HCP and a lack of PA programmes to refer patients were the most common barriers reported by all HCP.

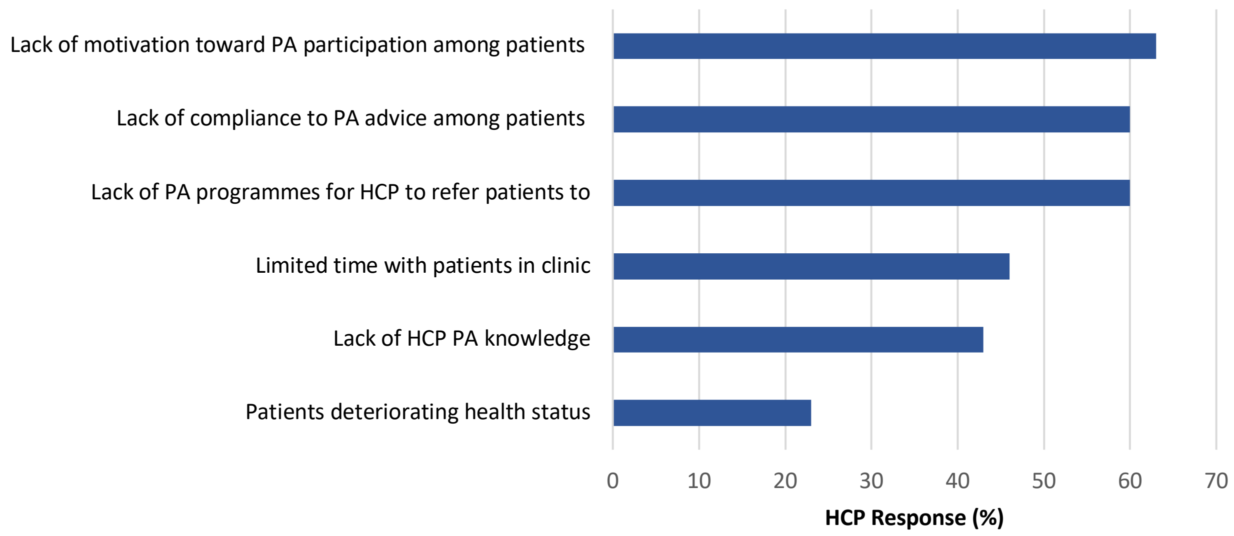


Figure 3.1: Barriers to HCP prescription of PA to their CF patients

Strategies to optimize PA prescription among HCP

HCP were asked to identify strategies that they believed would improve their ability to prescribe PA to their CF patients. The most common strategies reported by HCP were: i) to recognize one member of the MDT (physiotherapist) as the lead for PA prescription, ensuring that other MDT members are educated and skilled to reinforce this prescription with evidence-based PA promotion, ii) the development of formal, standardized and accredited continuing professional development programmes to improve HCP knowledge surrounding PA prescription and promotion for CF populations, and iii) to increase the development and availability of PA programmes for HCP to refer their CF patients. The strategies identified by HCP were collated and formed, by the investigator, into statements summarized in table 5.

Table 3.5: Strategies identified by HCP to optimize their prescription of PA to CF patients

1. Identify one member of the MDT (physiotherapist) as the lead for PA prescription, ensuring other MDT members are educated and skilled to reinforce PA promotion
2. Improve HCP knowledge surrounding PA prescription and promotion by developing formal, standardized and accredited continuing professional development (CPD) programmes
3. Increase the development and availability of PA programmes for HCP to refer their CF patients to

Discussion

The key findings that emerged from the current study include: i) the lack of education at undergraduate level with respect to PA promotion and prescription for CF populations, ii) sources of further education sought by the majority of HCP were typically mixed and non-accredited, iii) physiotherapists were more confident in their knowledge and prescription of PA, ensuring use of the guidelines at every patient interaction, compared to other HCP who lacked sufficient knowledge and confidence, and iv) the lack of patient motivation and compliance toward PA advice were among the most common barriers to PA prescription reported by HCP.

The number of HCP who received education with respect to PA prescription for CF populations during their undergraduate degree was very low. This appears not to be specific to CF, as education focusing on PA promotion and prescription for clinical populations in general has been identified as essentially missing from the physiotherapy curriculum in Ireland (O'Donoghue, Doody and Cusack, 2011). This is concerning, given the global movement to transition the healthcare service from primarily focusing on sickness, to a service that focusses on prevention and health promotion. The physiotherapy curriculum in Ireland is primarily focused on impairment, injury and disability, with little time devoted to PA prescription for CF and other chronic disease populations (O'Donoghue, Doody and Cusack, 2011). This is highlighted by the fact that HCP who have graduated during the past 5 years were no more likely to have received education in relation to PA prescription for CF populations during their undergraduate degree than those that graduated 10-19 years ago.

This study has found that HCPs lack confidence in their ability to promote PA. It is a topic that is largely missing from the undergraduate curriculum, and knowledge of certain elements of the guidelines could be improved. The design and implementation of a formal, standardized and structured continuing professional development programme for HCP seeking to improve their knowledge within the area of PA promotion and prescription for CF populations in warranted at this time. In similar survey studies conducted in the UK and Germany, 100% and 87% of HCP who responded, respectively, indicated that they would benefit from additional CF-specific education, training and resources in relation to PA in CF care (Barker *et al.*, 2004; Lobelo and de Quevedo, 2016).

There was unanimous consensus among the HCP that the physiotherapist should take the lead, when prescribing PA to patients with CF. This echoes the European CF Society Standards of Care Framework, which indicated that the specialist CF physiotherapist should take the lead role in delivering high quality treatment, involving physical exercise training (Conway *et al.*, 2014). Physiotherapists reported high levels of knowledge and familiarity with the current consensus guidelines, suggesting that they are confident and skilled to adopt this leadership role. Additionally, all physiotherapists reported discussing PA at every patient visit, using a combination of verbal and written PA prescription, largely based on the current consensus guidelines.

Although a significant number of other HCP reported discussing PA with CF patients as part of their professional role, there appeared to be a dearth of knowledge in relation to the appropriate PA prescription for CF populations. This is concerning, as over half of the other HCP actively sought further education to improve their knowledge regarding PA prescription in CF care. Interestingly, the other HCP were not familiar with the current consensus guidelines, and they tended to under-prescribe with respect to the *frequency* and *intensity* components of the FITT principle criteria. CF patients receiving this advice may not achieve an appropriate overload stimulus to maintain or improve functional capacity.

When discussing PA, other HCP used verbal advice alone, with only 5% basing their advice on the current consensus guidelines. To ensure optimal patient outcomes, it is important that all HCP within the MDT are working synchronously to effectively communicate the significance of PA to their CF patients (Brannan *et al.*, 2019). Identifying the physiotherapist as the lead for PA prescription, with other members of the MDT positively reinforcing the benefits of PA through scheduled discussions during clinic visits, will ensure that the patient receives more exposure to PA dialogue, than with the physiotherapist alone. Other HCP recognize the importance of PA prescription and deem it to be part of their professional role. However, the majority of other HCP currently lack the appropriate knowledge to efficiently reinforce PA promotion. There is an immediate need to develop standardized and structured CPD programmes, focusing on patient-centered, evidence-based PA promotion and prescription for CF populations, for all HCP working in CF care.

Although HCP are primarily motivated to prescribe PA to improve patient outcomes, they identified a number of barriers to achieving this goal. These included a lack of compliance and motivation among CF patients to adhere to PA advice. The scarcity of PA programmes for HCP to refer patients was another significant barrier to PA prescription. The development of patient-centered, evidence-based PA programmes, underpinned by theories of behaviour change, would greatly enhance PA prescription for CF HCP. Due to HCP reporting time constraints as a barrier to PA prescription, we suggest that the expert in behaviour change within the MDT, the psychologist, should work in close collaboration with the physiotherapist to implement the behaviour change component of future PA interventions.

Wearable technology has the potential to enhance patient motivation and compliance, allowing them to be more active, and to better understand how their PA behaviours can affect their health in real-time (Tomlinson *et al.*, 2020; Bove, 2019). The adoption of wearable technology, such as activity trackers, and mobile phone applications has the potential to promote patient engagement through personalized PA interventions. Incorporating components of e-health that are convenient and easily accessible for the patient has the potential to change how they engages with healthcare services, and reduce the burden of care and costs associated with healthcare delivery. Previous research suggests that the use of an internet-based program to monitor and encourage PA participation, is both feasible and acceptable among adults with CF (Cox *et al.*, 2012).

A multifaceted approach is required to address the barriers experienced by HCP regarding PA prescription for CF populations. Recommendations to overcome the aforementioned barriers, and to optimize HCP prescription of PA for CF populations, include i) recognising the physiotherapist as the lead for PA prescription, with other members of the MDT positively reinforcing with appropriate PA promotion, particularly as the patient may not always attend the physiotherapist at every clinic visit, it is critical that a multidisciplinary approach is adopted to ensure that there are regular and consistent discussions around PA, ii) the development of recognized, structured and standardized further education and training opportunities to enable HCP to upskill and develop confidence with respect to PA prescription for their CF patients, iii) the introduction of formal in-house educational sessions or workshops, provided by exercise specialists within CF care, to create more awareness around the importance and benefits of PA for CF populations, iv) the development of personalised and evidence-based PA programmes for HCP to refer patients and v) promote the use of components of telemedicine and interventions underpinned by behaviour change theories to employ a patient-centred approach for eliciting positive and sustainable change.

Limitations

There are number of limitations that must be considered when interpreting the present results. Firstly, it is important to acknowledge the possible presence of sampling bias. Opportunistic sampling may have resulted in a sample of HCP who recognise the therapeutic impact of PA, overlooking the opinions of those who are not interested in using PA as a therapeutic modality for CF populations. There was also an over-representation of physiotherapists within the current study as a result of the survey invitation being sent to the National Physiotherapy CF Clinical Interest Group and not to other professional clinical interest groups. The nurse cohort as a stand alone occupation, alongside clinical nurse specialists, should be included in future studies. Ensuring a blend of large hospital-based CF MDTs and smaller community-based MDTs in future research will provide a more cross-sectional insight. As the data is self-reported, there is a risk that social desirability bias may have occurred making the results more desirable and portraying a less realistic representation of current knowledge and practice [12,20]. Clinical exercise physiologists and exercise scientists were not included in this survey as they are not accredited by the Health Service Executive in Ireland.

Conclusion

Although HCP have the capacity to play an important role in influencing patient PA behaviours, a multi-disciplinary approach is required. It is recommended that a CPD programme is developed that focused on enhancing CF HCP knowledge and confidence in relation to PA prescription and promotion. Future success will depend on objectively recognising, evaluating and addressing the barriers that are preventing HCP from prescribing and promoting PA to their CF patients. The development of a HCP referral pathway to patient-centred, evidence-based PA programmes that are underpinned by behaviour change may improve CF patient compliance and motivation towards adherence to PA advice. Involving an exercise physiologist and/or exercise scientist as an adjunct, community-based, support for PA prescription and exercise testing may have the potential to enhance patient motivation and compliance to PA advice, if conducted outside of the clinical setting.

Chapter IV
Study II

Study II: Factors Influencing Physical Activity in Adults with Cystic Fibrosis

Abstract

Background: PA is a well-documented and accepted adjunct therapy for the maintenance and improvement of long-term health in CF. Although the benefits of PA for CF populations are well-established, adherence to PA programmes within this population remains low. This study aimed to investigate the factors that influence engagement in PA, and to explore exercise preferences, among adults with CF.

Methods: Semi-structured telephone interviews were conducted. Participants were twenty-one adults (mean age 35 years, SD ± 8) with an established diagnosis of CF, living in Ireland. Interview scripts were digitally recorded and transcribed verbatim. Thematic analysis was used to analyse the data.

Results: Four main themes emerged: *barriers, motives, value of exercise-related outcomes, and exercise preferences*. The main barriers included: low energy levels, time, the weather, and exercise-related confidence. Enjoyment and perceived competence underpinned autonomous motivation. Participants who self-identified as being regularly active valued personally identified exercise-related outcomes such as, accomplishment and affect regulation. Participants indicated a preference for home-based PA programs compared to gym-or facility-based programs.

Conclusion: Interventions aimed at promoting PA among adults with CF should involve programs that foster autonomous motivation, enjoyable activities, personally identified outcomes, competence and that can be conducted from the home environment.

Clinical Implications: To increase PA participation among adults with CF, interventions that can be conducted from the home environment, that pay attention to the patients' personally-valued exercise outcomes may be required.

Introduction

CF is a progressive, multi-system, inherited condition affecting approximately 1,400 people in Ireland, and more than 70,000 worldwide. Today, with advancements in early diagnosis and the development of highly effective CF transmembrane regulator modulator therapies, people with CF are living longer (Happ *et al.*, 2013; Shei *et al.*, 2019). As such, increased emphasis is being placed on improving lifestyle-related behaviours in order to enhance long-term health in adults with CF (Burnett, Barry and Mermis, 2020).

Aerobic fitness has been shown to be an important predictor of survival in individuals with CF (Williams and Stevens, 2013). Those who have a higher aerobic capacity ($\dot{V}O_2 \geq 82\%$ predicted $\dot{V}O_2max$) have an increased survival rate of 83% at 8-years, compared to 51% and 28% survival with moderate (59-81% predicted $\dot{V}O_2$ max) and low fitness (≤ 58%), respectively (Nixon *et al.*, 1992). In a recent systematic review and meta-analysis including six studies, Vendrusculo et al., (2019) have shown that lower $\dot{V}O_2max$ levels are associated with a 4.9 fold increase risk of mortality in pwcf (Vendrusculo *et al.*, 2019). Evidence suggests that there is a positive relation between increased PA at moderate intensity and improvements in aerobic capacity, independent of improvements in muscle strength and pulmonary function (Hebestreit, 2006; Savi *et al.*, 2015). Regular participation in PA; performing 150 $min \cdot wk^{-1}$, and preferably 300 $min \cdot wk^{-}$ of moderate-to-vigorous PA (Swisher *et al.*, 2015) improves a myriad of outcomes in CF, such as exercise tolerance (Cerny, 2013) , airway clearance (Dwyer *et al.*, 2011) energy levels (Schneiderman-Walker *et al.*, 2000) and QoL (Radtke *et al.*, 2017). Sustained PA also has the potential to slow the annual rate of decline in pulmonary function (Hebestreit, Kriemler and Radtke, 2015). Despite the established benefits of PA for individuals with CF, adherence to PA programs within this population can be poor (Swisher PT and Pt, 2008; Hebestreit, Kriemler and Radtke, 2015). In order to develop the optimal PA program for individuals with CF, a better understanding of patient attitudes towards PA (Burnett, Barry and Mermis, 2020).

Few studies have investigated the factors influencing exercise participation in adults with CF (White, Stiller and Haensel, 2007; Swisher PT and Pt, 2008; Myers, 2009; Burnett, Barry and Mermis, 2020; Dwyer *et al.*, 2020). The most commonly reported motivators for sustained PA participation included enjoyment (Dwyer *et al.*, 2020), motivation (Dwyer *et al.*, 2020), improving general and/or lung-health (Swisher and Erickson, 2008), and feeling healthy (Swisher PT and Pt, 2008). Feelings of breathlessness (Dwyer *et al.*, 2020), fatigue (White, Stiller and Haensel, 2007), lack of good health (Burnett, Barry and Mermis, 2020), reduced energy (Burnett, Barry and Mermis, 2020), and embarrassment when exercising in public (White, Stiller and Haensel, 2007) were among the most common barriers reported. Severity of CF lung disease and being female were found to be associated with a more significant and rapid decline in lung function and may contribute to poorer long-term adherence to PA (Myers, 2009). Lack of motivation and time were also reported as barriers to exercise (Burnett, Barry and Mermis, 2020; Dwyer *et al.*, 2020).

Several models have been developed to provide a more thorough understanding of the relation between PA and behaviour change. The theory of planned behaviour focuses on beliefs and attitudes and social norms (Ajzen, 1991), Bandura's social cognitive theory (Ayotte, Margrett and Hicks-Patrick, 2010) focuses primarily on self-efficacy and outcome expectancies, and the self-determination theory (Ryan and Deci, 2000) focuses on the quality of motivation and the importance of satisfying key psychological needs such as autonomy and competence-relatedness. There is currently no optimal model to explain PA and behaviour change. Qualitative research has therefore been helpful, by not taking a deductive approach and approaching the topic with a broad perspective to unravel which dimensions appear to be most important (Maxwell-Smith *et al.*, 2017). The current study is not aligned to any particular theoretical framework as it is inductive in nature. It will seek to understand the dimensions most important for PA behaviour change in a CF population, and therefore provide an insight into which models may be most suitable when designing PA interventions. Given previous research findings and the aforementioned theories, we expect that low self-competence and motivation may be theoretical components of emerging barriers to exercise in the CF cohort (Maxwell-Smith *et al.*, 2017).

The purpose of this study was to explore the attitudes towards, and dimensions influencing, PA participation among Irish adults with CF. Such knowledge concerning the dimensions influencing PA and attitudes towards PA would be beneficial in the development of appropriate intervention strategies to promote PA in practice.

Methods

The current study conformed to suggested guidelines by Clark in appropriateness of method, transparency of procedures, and soundness of approach (Clarke, 2003).

Participant recruitment

Convenience sampling was used to recruit adults with an established diagnosis of CF (confirmatory diagnostic sweat chloride test). An email including a patient information leaflet

(Appendix D) was circulated by CF Ireland, the national CF charity, to all adults with CF on the registry in Ireland (n=861). Following an expression of interest, participants were screened for eligibility. Participants were eligible for inclusion in the study if they were ≥ 18 years of age and living in Ireland. Written informed consent (Appendix E) was obtained in accordance with the Dublin City University (DCU) Research Ethics Committee (DCUREC/2018/141).

Data Collection

Semi-structured telephone interviews lasting up to 30 min were conducted. An interview guide (Appendix F) was developed based on previously published work (Teixeira *et al.*, 2012; Willem, De Rycke and Theeboom, 2017), regarding the factors that may influence PA in adults with CF. Interviews were digitally recorded and transcribed verbatim. Interviews were conducted in the Autumn of 2019 (September-October).

Data Analysis

Data were analyzed inductively using thematic analysis, which involved several steps (Braun and Clarke, 2006). The first step involved active and repeated reading of the transcripts to gain an insight into the data, and to explore initial codes. The second step involved systematically (i.e., line by line) coding features of interest within the dataset (data extracts) that are related to the research question. The third step involved exploring whether codes may be collated to form over-arching themes. This step, which re-focuses the analysis at the broader level of themes, rather than codes, involves sorting the different codes into potential themes, and collating all the relevant coded data extracts within the identified themes. A theme captures something important about the data in relation to the research question and represents some degree of patterned response within the data set. Confidence of the existence of a theme is established when a number of instances of the theme is identifed across the data set or across the sample (Braun and Clarke, 2006). The fourth step involved reviewing and refining the potential themes. This phase involved checking whether there was sufficient data to support the existence of a theme or whether there was overlap such that themes might collapse into each other (e.g., two apparently separate themes might form one theme). In step four, the researchers' checked that for coherence between the data and the themes and checked for clear and identifiable distinctions between themes. The final step involved the refining and defining of themes. Once a satisfactory thematic map of the data had been generated, the themes to be presented for analysis were defined and further refined and cross-checked with the data extracts, i.e., identifying the essence of each theme as well as the themes overall. During this step, checks were undertaken to insure that the theme and sub-themes matched the data and that each theme was coherent and internally consistent (i.e., not too much overlap between themes). As part of the refinement, decisions were also made concerning hierarchy and the presence of sub-themes that fit into a broader overarching theme. Sub-themes are used for giving structure to a particularly large and complex theme, and also for demonstrating the hierarchy of meaning within the data.

A second researcher experienced in qualitative data analysis served as a second reader of the transcripts and offered further insight with respect to emergent themes to broaden data interpretation and assist with coding, reviewing and refining of themes. Data saturation was determined following analysis and occurred at the point when no new information was gained to develop or broaden themes. The analysis provided represents the research teams evaluation of the data set, and it is acknowledge that other interpretations are possible. Nonetheless, a credible interpretation of participants' attitudes towards and dimensions influencing PA engagement are presented. Credibility and rigor of the analysis ar demonstrated in the following ways; (i) using data saturation to determine sample size, (ii) describing in detail the steps taken in conducting the analysis, (iii) involving two researchers in the process of analysis thereby broadening the number of interpretations and (iv) providing 'thick description' via the use of extensive and direct quotations so that the reader can evaluate the interpretation (i.e., the fit between data extracts and the theme labels) (Hardcastle and Hagger, 2016).

To identify potential differences between responses according to activity status during the thematic analysis process, each transcript was labelled according to self-reported activity status using 'low-active' defined as not meeting the current consensus CF PA guidelines, 'moderately active' defined as meeting, or likely to be meeting, the guidelines, or 'highly active' defined as exceeding the minimum PA guidelines for PWCF.

Results

Twenty-one adults (57% males) with an established diagnosis of CF participated in the study. The mean ± SD age of subjects was 35 ± 8 years, with 16% of participants having undergone lung transplantation. Participants' pseudonyms, characteristics and demographics are outlined in Tables 1 and 2. Table 3 displays participant characteristics compared to the Irish CF population.

Table 4.1: Participant pseudonyms and individual characteristics

ID Code	Pseudonym	Gender	Age	Self-Reported PA	Transplant Status
1	Paul	Male	30	High	No
2	Mary	Female	30	Moderate	No
3	Jenny	Female	44	Low	Yes
4	William	Female	34	Low	Yes
5	Richard	Male	49	Low	No
6	Matthew	Male	28	High	No
7	Shane	Male	33	High	No
8	Robert	Male	41	High	No
9	Emily	Female	50	High	No
10	Dorothy	Female	29	Moderate	No
11	Carol	Female	36	High	No
12	Kevin	Male	33	High	No
13	Amy	Female	32	Low	Yes
14	Eric	Male	50	Low	No
15	Brenda	Female	35	Moderate	No
16	Frank	Male	26	High	No
17	Peter	Male	19	Low	No
18	Keith	Male	38	High	No
19	Hannah	Female	36	Low	No
20	John	Male	31	High	No
21	Jason	Male	35	Low	No

Table 4.2: Participant demographics

FEV_1 (% predicted)	84.1 ± 19.7
BMI ($kg \cdot m^2$)	24.1 ± 2.4
Diabetes Status	CFRD (n=2)
Pancreatic Status	Pancreatic Insufficiency (n=5)
Co-existing Conditions	Neurocardiogenic syncope; Osteopenia; Asthma; Nasal Polyps; CF Liver Disease; Gastro-intestinal Reflux; CF-related Arthritis
Homozygous ΔF508	4
Heterozygous ΔF508	3
Other CF Alleles	G542x; R117H; E60x
Location of CF Centre	Dublin (n=15) Cork (n=3) Limerick (n=2) Galway (n=1)

Results are reported as mean ± SD; *Note: Results for FEV_1, BMI, CF Alleles, Diabetes and Pancreatic Status for 9/21 participant*

Table 4.3: Study participant characteristics compared to the Irish CF population

	Study CF Population	Irish CF Population
Age (yr)	Median: 34	Median: 21
Gender (male:female)	42% : 58%	42% : 58%
BMI ($kg \cdot m^2$)	Median: 23.4	Median: 22.3
FEV_1 (% predicted)	89	82.3
Genotype (at least 1 copy of Δf508)	87.5%	91.7%
Transplant Status	14%	5%

Note: data for BMI, FEV_1 and Genotype are only available for 8/21 participants. Data regarding the Irish CF population was obtained from the CF Registry in Ireland Annual Report for 2019

Data analysis identified four key themes relating to factors that influence PA engagement in adults with CF: (i) barriers underpinned by four subthemes including energy levels, time, weather and exercise-related confidence; (ii) motivation with sub-themes of enjoyment and perceived competence; (iii) valued outcomes, underpinned by sub-themes of accomplishment and affect regulation; and (iv) preferences (refer to thematic map in Figure 1). Each quote is followed by a pseudonym and the individual's age. To further contextualize the data, self-reported PA and additional quotes are provided in tables 3 and 4. In accordance with Sandelowski (2000), pronouns will represent indeterminate quantities where 'many' implies approximately 75%, 'several' implies approximately 50%, and 'few' implies approximately 20% of the sample (Sandelowski, 2000).

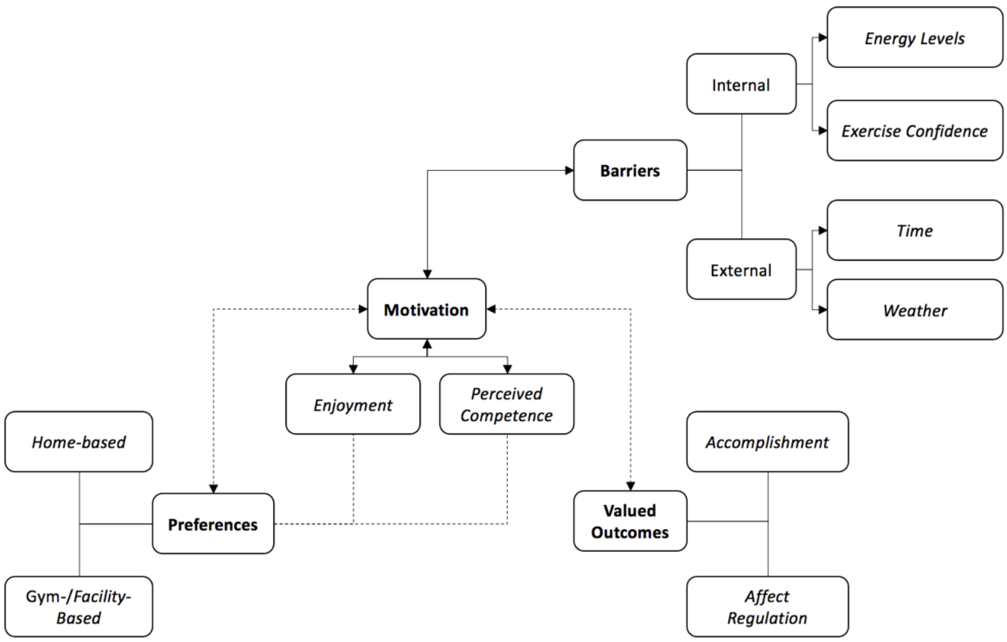


Figure 4.1. Thematic map displaying themes and relationship between themes. The thematic map displays the four primary themes (motivation, barriers, valued outcomes and preferences), and sub-themes. The arrows provided reflect the relationship between and within themes. For example, an individual who values exercise outcomes (through feelings of accomplishment or through affect regulation) is more motivated to exercise. Enjoyment of exercise and perceptions of competence affect motivation and preferences for PA.

Barriers

Participants reported both internal and external barriers to PA participation. The most common internal barrier was low energy: "There are some days where I'm just really mentally drained…So, the idea then of having to get up on a bike can be a huge barrier because I just feel so exhausted" (Amy, 32); "I'll just be generally really tired…so that might get in the way of being motivated, I don't want to push myself (Dorothy, 29); "Energy would be a big one. Sometimes I've just enough energy to get up and do my nebs, and I don't really have the energy to do other things" (Emily, 50). Participants also reported barriers pertaining to exercise-related confidence, such as self-consciousness: "In gyms and public when you're coughing, there's people looking at you to say what is wrong with you?" (Eric, 50), and concerns of capability; "The thing that turns me off PA is the fear of not being able to do [it], if that makes sense? Everyone in the class is jumping up and down on the step and I'm like oh my God, I can't keep up" (Hannah, 36).

External barriers to regular participation in PA included time: "I just generally don't think I get the time" (Mary, 30); "Essentially it's time. Time is the major one for me… prior to the kids…I was getting much more exercise, but time is the main thing" (Richard, 49); and the weather: "The weather here in Ireland is just…you could plan to go and have a round of golf, or play tennis at the weekend, and then it's raining all day so that stops that" (Matthew, 28); "If the weather is bad, my motivation is squat. I'm very much a fair-weather walker, you know?" (Jenny, 44).

Motivation

Motivation was a dominant theme identified throughout, with several participants displaying higher levels of motivation: "I'm always very self-motivated actually, I suppose from a young age I always kind of realised that…, it's me that's going to do it, nobody else can do it for me" (Amy, 32); "I'm very self-motivated, I don't need somebody shouting at me in a gym" (John, 31), compared to others who were primarily motivated by external drivers, such as guilt: "It's more guilt than anything I have to say. I go through stages of doing it but it's guilt more than anything else" (Eric, 50); and "It's hard to keep motivated because you know you have to do it" (Mary, 30). Enjoyment and perceptions of competence appeared to underpin PA motivation.

Enjoyment underpinning motivation

articipants who expressed positive attitudes towards and enjoyment of PA: "It's always been a positive, I have been really active most of my life now" (Kevin, 33); "Yeah, very positive. I feel the more exercise I do, the better I feel" (Richard, 49), seemed to engage in more regular PA: "I go to the gym five days a week; I do twenty-five minutes of cardio and then I do one particular muscle" (Kevin, 33), and "I'm very active, I'd get up at 7 o'clock I go for a 3 km run…then in the afternoon I go to the gym for an hour weight session. And I do that for 2 days and then I have the third day off…then I go through all that again" (Robert, 41). Exercise enjoyment appeared to be a motivating factor for adherence: "I think the main thing is to do something you enjoy. Anytime I've been successful at kind of maintaining sport, it's just doing something I enjoy" (William, 34); "I suppose …the main reason is, I enjoy it" (Matthew, 28).

In contrast, some participants reported a lack of enjoyment as a reason for their physical inactivity: “None of it. I’m going to be very honest with you, I do not enjoy PA at all” (Eric, 50); “To be honest, I don’t particularly enjoy it!” (Mary, 30); “Mainly, I just don’t like exercise” (Peter, 19), which was typically underpinned by poor engagement: “At the moment I would say my PA is pretty much zero… I haven’t been doing much exercise” (Peter, 19), and/or negative past experiences with PA: “Very negative. For me, PA was just hard” (Jenny, 44); “I suppose negative. I wouldn’t be going to the gym. I wouldn’t be interested in any of that” (Eric, 50).

Perceived competence underpinning motivation

Several participants reported high levels of perceived competence that appeared to underpin their exercise motivation: “You know, even though I have this illness, I never really felt like I did because it really didn’t keep me from setting records on the leader board when I was younger…I was very fast” (Carol, 36): “But it’s just the realization that I am as fit as most of them in the room and it’s at that… and keeping that level up, it’s keeping me on par with most of them in the room and for my own benefit as well” (Robert, 41); “I know I’m well able to do it” (Emily, 50).

Other participants did not identify as being the sporty or exercise type : “I’ve probably never been that person. I was never a sporty person” (Jenny, 44); “Exercise wouldn’t be in my remit. I wouldn’t be interested in any of that. I wouldn’t be a gym bunny; I’d be far from it. As far away from it as you can imagine” (Eric, 50), and expressed low perceived competence in their ability to perform PA: “I’ve been thinking a lot about this, and it’s not being able to do it. The thing that turns me off PA is the fear of not being able to do the activity if that makes sense" (Hannah, 36).

Valued Outcomes

Many participants who were regularly physically active reported exercise-related outcomes, such as accomplishment and affect regulation as drivers for continued engagement in PA. Many of the participants identified with the importance of keeping healthy: "I mean, just being healthy and not getting sick. Feeling good…and my lung functions being good, that motivates me" (Brenda, 35); "To try and stay as healthy as possible is a motivator" (Richard, 49); "I just realise that if I want to be healthy and if I want to live a kind of normal life, I have to do this…so that pushes me to keep myself as healthy as I can be" (Robert, 41).

Several participants were reportedly driven by a sense of accomplishment: "I do like it in the end…when you feel like you have accomplished something" (Mary, 30); "I like…the feeling after that you have accomplished being able to physically do an activity" (Emily, 50). Affect regulation emerged as a key influencing factor among participants who regularly engaged in PA: "I like how it makes me feel good and I'm always in a better mood, like it releases endorphins and I'm a happier person afterwards definitely" (Brenda, 35); "Just how you feel after doing them, you just feel well and it's good for everything, not just CF, but your mental health and everything…whether you are sick or not, you do feel great about yourself" (Paul, 30).

Preferences

Many participants reported a preference for exercising within their home environment, as opposed to the gym: "I love doing my treadmill and stuff at home…it reduces the risk of infection as well" (Mary, 30); "At home, just because it's less time consuming and less daunting… it's easier than going to the gym…if your treadmill is sitting there looking at you" (Dorothy, 29); "Home-based…like it can be stressful for me to go to the gym…it's germy and noisy and if you don't feel well you kind of just want to leave once you get there" (Carol, 36).

The concept of attending a gym was perceived negatively by a large number of participants, due to the risk of cross-infection: "They say the worst place to pick up germs that are bad bacteria is in the gym, because everyone is in there sweating. And people that feel sick still go to the gym and they are coughing all over the place and sweating and that kind of puts me off" (Robert, 41); "Going to anything like a gym I just have total war against…I think they're a hive of infection. I think they're the most unclean environments you could possibly get" (Richard, 49), and illness-related embarrassment: "I don't like when people listen to me coughing when I'm in the gym…and if I have any secretions, at least if I'm at home, I'll get rid of it there" (Mary, 30); "Going to the gym, especially on oxygen and things is quite intimidating for people…it's very easy to feel self-conscious so, I think home programmes for people… might help" (William, 34).

Many participants highlighted the Exercise Grant, made available biannually by CF Ireland, as a beneficial tool for enabling home-based exercise: "I have a treadmill at home that I was able to get through the CF Ireland Exercise Grant, which is fantastic, and that is what I would use at home. And, I have got a few little weights…it's easier for me than driving to the gym, which takes more time out of my day" (Emily, 50), and "From a CF Ireland point of view, the Exercise Grant is really good because it can kind of help with the financial burden of exercise" (William, 34).

Discussion

The present study is one of the first to explore factors influencing PA in adults with CF. The main barriers among participants were internal (*low energy*), external (*time* and *the weather*) and related to exercise confidence (*self-consciousness* and *capability*). The findings of the current study are consistent with previous research which found that the lack of energy and time, and bad weather contributed to poor PA compliance among adults with CF (Burnett, Barry and Mermis, 2020; Dwyer *et al.*, 2020) and COPD (Kosteli *et al.*, 2017). Exercise-related confidence as a barrier to sustained PA engagement among adults with CF is a novel finding.

Motivation was a dominant theme underpinned by enjoyment and perceived competence, and appeared to differentiate between those more and less physically active. Specifically, those who reported positive past experiences with PA, higher levels of perceived competence, and more autonomous forms of motivation appeared to engage in more frequent and sustained PA. In contrast, those who reported negative past experiences with PA and lower perceived competence appeared to be less physically active, linked to feelings of external or introjected regulation. Our findings are consistent with the self-determination theory (SDT) in relation to the innate psychological needs (specifically competence and autonomy) that must be satisfied in order to be autonomously and more intrinsically motivated (Ryan and Deci, 2000). According to SDT, controlled motivation is when individuals are motivated in order to satisfy some form of external pressure (e.g., physician) or internal pressure (e.g., sense of guilt). Some participants in the current study that were notably less motivated to exercise reported motives driven by extrinsic factors and reported participating in PA to avoid feelings of guilt (introjected regulation). More autonomous motivation is achieved when the individual values health or physical fitness, or when the behaviour (PA) is consistent with his or her ambitions in life or identity (identifying with valued outcomes). Indeed, the present study found that valued exercise-related outcomes were drivers for continued exercise participation amongst participants who appeared to be more regularly physically active. Consistent with SDT and previous research, more autonomous motivation rather than controlled or externally driven motivation are associated with regular exercise behaviour (Teixeira *et al.*, 2012; Willem, De Rycke and Theeboom, 2017). The strongest predictor of exercise maintenance is personally valued outcomes (Teixeira *et al.*, 2012). Participants in the present study who appeared to be more regularly active reported affect regulation as a motive for continued engagement in PA. The role of exercise for affect regulation is a novel finding.

A key finding was that most participants, particularly those who were more motivated, expressed a preference for home-based, rather than gym- or facility-based PA. This is notable, since home-based interventions have the capacity to potentially ameliorate feelings of low perceived competence, self-consciousness and remove barriers associated with time and changing weather (Hardcastle and Cohen, 2017). It is possible, however, that the wider CF population, likely to be less interested in exercise are unlikely to prefer the gym. Tailoring PA programmes according to patient preferences and psychographic profiling (Hardcastle and Hagger, 2016) may optimise uptake and adherence.

The study was limited by the relatively low uptake which is unlikely to be representative of the wider CF population in Ireland. The absence of exclusion criteria and discussion surrounding the presence of symptoms is also a limiting factor. The study did not explore whether other comorbidities influenced the results. There is a lack of demographic information to account for extraneous variables. A further limitation is the absence of objectively-derived PA data for the sample. The potential of sampling bias must also be acknowledged when interpreting the results of the present study. Opportunistic sampling may have resulted in a sample of people with CF who are more physically active and recognise the benefits of regular PA participation, overlooking the perceptions of those who are disinterested in PA. The findings in the current study are tentative, and it is unclear as to whether they are transferable to the wider CF population. Further research is required to comprehensively evaluate the factors influencing PA among adults with CF. It is also important to acknowledge the relevance of the findings in relation to the Covid-19, and post-Covid-19, environment, highlighting the value of home-based exercise for vulnerable populations, such as those with CF.

Practice Implications

The reported barriers to PA may be modifiable. For example, self-consciousness and low perceived competence could be mitigated through the provision of mastery experiences to provide a sense of accomplishment and competence. Clinicians could be trained in assisting patients with effective goal-setting, action planning and problem solving for PA to provide a sense of accomplishment and alleviate barriers. Home-based interventions that focus on PA rather than facility-based exercise or sport may help alleviate feelings of self-consciousness and low energy. Clinicians could also be trained to help foster autonomous motivation by asking patients to describe some personally valuable outcomes of exercise participation, in addition to providing a rationale for the health benefits of exercise to CF patients.

Several systematic and meta-analyses have highlighted motivational interviewing (MI) as an effective approach to changing health behaviours (Hardcastle *et al.*, 2017). Providing healthcare professionals with additional training in the use of activity counselling, brief motivational interviewing and techniques to foster the increased importance of PA and confidence to exercise (for example, the use of importance and confidence rulers in brief MI), may have the potential to increase autonomous motivation, and decrease external regulation, toward long-term engagement in PA among patients with CF (Denford *et al.*, 2020). Indeed it has been recommended in other patient cohorts. Motivational interviewing is advantageous in the clinical setting because it is an individualized intervention appropriate to all patients along the continuum of motivation. For those CF patients that are less motivated to change, strategies can focus on raising the importance of PA and exploring confidence to change. For those patients more 'ready' to change, more action-oriented strategies such as goal-setting and action planning can be implemented (Teixeira *et al.*, 2012). Individual barriers and exercise preferences can also be explored to devise a patient-centred intervention. Including the individuals' family unit as a support system when designing future interventions may enhance patient motivation and compliance. MyAction, an evidence-based programme that aims to reduce the risk of developing cardiovascular diseases, utilises familial support to increase long-term adherence among patients, and has proved effective in Ireland.

Given the findings in relation to participants' motives and exercise preferences, home-based interventions may hold promise, as they have the potential to ameliorate the barriers associated with facility-based exercise programmes, such as the fear of exercising in public and the risk of cross-infection. Interventions aimed at developing feelings of competence and a sense of accomplishment (via goal setting) may facilitate increased adherence as they have been found to underpin autonomous motivation. Prior to the development of exercise interventions for adults with CF, there needs to be confirmation or expansion of the exploratory findings of the present study. Future research that ascertains exercise perspectives of those CF patients less interested in PA would be worthwhile. In addition, it would be worthwhile to canvass attitudes towards PA engagement amongst CF patients experiencing symptom exacerbations and/or more severe disease progression.

Conclusion

Barriers to PA engagement in the current study were low energy levels, time, the weather, and exercise-related confidence. A tentative but important finding was the preference for home-based rather than gym-or facility-based PA. Effective interventions will likely require the promotion of autonomous motivation, enjoyable activities, personally identified outcomes and competence among adults with CF.

Chapter V
Study III

Study III: The Development, Implementation and Evaluation of a Theoretically-Informed, Home-Based, Self-Regulated and Technology-Enabled Physical Activity Intervention for Adults with Cystic Fibrosis

Introduction

Regular participation in PA can lead to a myriad of health benefits in people with pwcf, including increased airway clearance and improved muscle strength, body image and QoL (Prasad and Cerny, 2002; Selvadurai *et al.*, 2002; Klijn *et al.*, 2004; Cox and Holland, 2019). Sustained engagement in PA has been shown to improve or slow the rate of decline of important prognostic indicators in CF such as lung function and aerobic fitness (Williams and Stevens, 2013). In fact, aerobic fitness is a key independent predictor of prognosis and mortality in this population (Nixon *et al.*, 1992). It is currently considered part of routine CF care to encourage a physically active lifestyle and a recent consensus statement by the Exercise Working Group of the European CF Society recommends PA as an adjunct therapy for individuals with CF (Williams and Stevens, 2013; Swisher *et al.*, 2015).

Despite the benefits associated with regular participation in PA for this population, adults with CF have been shown to accumulate low levels of PA and less PA than healthy counterparts (Schneiderman *et al.*, 2014). Adherence to exercise programmes developed to support people with CF to become more physically active vary, with average adherence rates of 57-88% reported in a recent systematic review (O'Donohoe and Fullen, 2014; Cox and Holland, 2019). Considering that theoretically informed interventions have the potential to enhance the effectiveness of long-term behaviour change (Michie *et al.*, 2018), it is possible that the diverse adherence rates to exercise programmes may be due in part to the omission of behaviour change theory in their design. To the authors' knowledge, no interventions underpinned by theories of behaviour change exist for promoting habitual exercise in adults with CF. The most common barriers to adherence to exercise regimens reported by pwcf include lack of time, tiredness, not being bothered and not feeling well enough to exercise (White, Stiller and Haensel, 2007). Factors shown to enhance adherence to exercise training among this group include participating in activities deemed enjoyable by the individual, feeling good about oneself, having high perceptions of self-competence, and a sense of autonomy (White, Stiller and Haensel, 2007; Denford *et al.*, 2019).

It is well-established that exercise prescription, by nature, is often considered relatively controlling and aversive (Sheppard and Parfitt, 2008). Prescribing exercise that exceeds an individual's preferred level of intensity may promote negative attitudes towards PA and contribute to lower adherence rates (Perri *et al.*, 2002). There is a greater likelihood of long-term adherence among all chronic disease populations (Burnett, Barry and Mermis, 2020) when enjoyment is prioritized as a key component in the prescription of exercise. Allowing individuals to use effort perception to self-regulate their exercise intensity may increase enjoyment, improve perceptions of autonomy and the development of intrinsic motivation; central components to enhancing adherence to exercise training. Research in other clinical populations has shown that when allowed to self-regulate their exercise intensity, patients select an intensity that corresponds to the training zones required to achieve optimal health-related benefits (Johnson and Phipps, 2006).

The methodological quality of trials assessing the efficacy of physical exercise training in CF populations is poor (Radtke *et al.*, 2017). There is an acknowledged need for the development of high-quality randomized-controlled trials to define the optimal exercise training program for this patient group (Radtke *et al.*, 2017). The MRC guidelines for the development and evaluation of complex interventions recommends conducting feasibility trials in order to address the issues associated with poor methodological quality and assess the potential for successful intervention implementation prior to evaluations of full-scale efficacy (MRC, 2019). The aim of this study is to develop, implement and evaluate a PA intervention for adults with CF. In addition, the study will determine the preliminary effectiveness of the intervention on PA levels and QoL in adults with CF, compared to UC.

Methods

Intervention Development

In accordance with the MRC guidelines for the development and evaluation of complex interventions, the development of the intervention involved three stages: i) identifying the evidence base, ii) identifying/developing theory, and iii) modelling processes and outcomes. The first stage in the process involved i) conducting a review of the literature to identify the evidence-base for PA and exercise for pwcf, ii) undertaking a survey of HCPs to identify the barriers that challenge, and strategies that optimize, HCP prescription of PA; and iii) semi-structured interviews to evaluate the factors influencing PA participation among pwcf. The second stage involved the selection and application of appropriate behaviour change theories, techniques and theoretical frameworks, and the third stage involved engagement with relevant stakeholders throughout the decision-making process.

Review of Literature

A review of literature was undertaken to identify the evidence base for PA and exercise in CF. Specifically, the literature review aimed to identify effective PA program components, and strategies to enhance compliance. The review focused on previous PA and exercise training interventions that have shown positive outcomes, including increases in physical, physiological, perceptual and psychological indices in children, adolescents and adults with CF. The following databases were searched when conducting the review of literature: The Cochrane Library of Controlled Trials (CENTRAL), EMBASE, MEDLINE (via PubMed) and SportDiscus. Search terms included, but not limited to, cystic fibrosis, PA, exercise training, aerobic capacity, aerobic fitness, quality of life, muscle strength, lung function, motivators, barriers, exercise prescription, self-regulated exercise, adherence and compliance. The search terms were in line with the PICO format (patient, population, problem; intervention; comparison, control; outcome), and all study designs were included in the search.

A total of twenty six original research papers and two systematic reviews, were identified to inform the intervention development process (Cox *et al.*, 2012; Radtke *et al.*, 2017). Home-based exercise emerged as the most prominent intervention component considered to be safe and effective for increasing PA levels in CF populations. Home-based interventions reduced the risk of a myriad of CF-related exercise concerns, such as cross-infection, disease-related exercise self-consciousness, and the travel or membership costs associated with facility-based exercise training (Schneiderman-Walker *et al.*, 2000; Moorcroft *et al.*, 2004; Rovedder *et al.*, 2014). Self-regulated exercise was identified as an important programme component to increase compliance. In contrast, compliance was poor among pwcf undertaking regimented exercise programs (Bar-Or, 2000). The inclusion of an exercise consultation and methods for self-monitoring were highlighted to support the interventions in optimizing perceived motivators and minimizing perceived barriers to promote the adoption of long-term adherence to PA (Shelley *et al.*, 2018; Cox and Holland, 2019; Denford *et al.*, 2019).

Reviews by Prasad et al., (2002) and Moran et al., (2010) suggested the following strategies for enhancing long-term PA adherence in CF: i) individually tailoring exercise training programs to incorporate activities that are enjoyed by the participants, as prescribed exercise has been associated with poor long-term adherence, ii) minimizing the perceived barriers to PA and exercise, and optimizing motivators through motivational interviewing and behaviour counseling, iii) ensuring regular contact between the exercise therapist and the patient, not to supervise exercise training, but to express an interest and enquire as to the patient's well-being, allowing an open forum for barriers to be addressed, iv) to promote social inclusion and familial support, and v) to encourage a change in behaviour among participants by underpinning exercise training programmes with theories of behaviour change (Prasad and Cerny, 2002; Moran and Bradley, 2010).

The conclusions drawn from the two systematic reviews highlight the limited evidence regarding strategies to promote the uptake and continued participation in PA for this group, and the need for high-quality randomized-controlled trials to comprehensively assess the benefits of exercise training programmes in pwcf (Radtke *et al.*, 2017; Cox and Holland, 2019).

Survey of CF Healthcare Professionals

Forty-eight HCP working in six designated CF centres in Ireland participated in an investigator-developed 30-item online survey with the aim to identify the barriers that challenge HCP when prescribing PA to their CF patients, and strategies to optimize PA prescription by HCP for this group. The methodology and results from this study have been reported in detail elsewhere (Chapter 3). Briefly, the most common barriers to PA prescription reported by CF HCP included lack of motivation and compliance among patients to adhere to PA advice, and the limited availability of PA programmes to refer patients. One of the key strategies identified by the HCP to optimize PA prescription was to increase the availability of CF specific PA programmes and associated referral pathways.

Semi-structured Interviews with CF Patients

A semi-structured interview was undertaken with twenty-one adults with an established diagnosis of CF participated to gain an insight into the factors influencing PA engagement from the patient's perspective. Interview scripts were developed using the COM-B model and questions focused on exploring individuals' capability, opportunity and motivation to be regularly physically active. Data were analyzed using thematic analysis (Braun and Clarke, 2006). Details regarding the methodology and results from this study have been reportedin chapter 4. Briefly, fatigue, exercise-related confidence, time and the weather were the most common reported barriers challenging PA participation among this group, while enjoyment and perceived competence were linked to long-term engagement in PA. Patients who were regularly active valued personally identified exercise-related outcomes such as, accomplishment and affect regulation, and the majority of participants expressed a preference for home-based PA programs compared to facility-based programs.

Theoretical framework selection and application

The BCW and the TDF were chosen to guide the intervention development process as they are heavily grounded in behaviour change theory, and linked to evidence-based intervention functions that can direct an intervention to a targeted setting and population (Michie, 2014; Truelove *et al.*, 2020). In order to conduct a behavioural diagnosis to identify the appropriate strategies for successful adoption of the target behaviour, the findings from the literature review, along with the HCP survey and patient semi-structured interviews, were compiled in accordance with the BCW method. The behavioural diagnosis was then used to identify suitable intervention functions (e.g., education, training and enablement) that were likely to increase pwcf PA levels. The APEASE criteria, which lists important factors to be considered when designing an intervention, such as acceptability, practicability, effectiveness/cost-effectiveness, affordability, safety/side-effects and equity, was applied in the selection of intervention functions. The Behaviour Change Taxonomy and TDF were used to identify the most appropriate behaviour change techniques to deliver the selected intervention functions (Michie *et al.*, 2013; Atkins *et al.*, 2017). The final step involved identifying the optimal mode of delivery.

A mapping exercise was conducted to outline the links between the intervention components, COM-B and TDF constructs, and BCW intervention functions, to ensure that the behaviour change techniques were embedded appropriately throughout the intervention (Table 5.1).

Operationalizing findings into intervention components

The intervention content was developed based on the information collated from the review of literature, survey of HCPs, semi-structured interviews with pwcf, and the identification of appropriate theory. The BCW and TDF provided the theoretical framework for the intervention design, while the strategies and perceptions from the HCP and pwcf formed the foundation for the development of the intervention content.

Table 5.1: Mapping of Intervention Components to COM-B constructs, TDF domains and BCW intervention functions

Intervention Component	COM-B Constructs		TDF Domains	BCW Intervention Functions
1:1 Exercise consultation	C	Physical and Psychological	Knowledge; Skills; Memory, Attention and Decision Processes; Behaviour Regulation	Education; Training; Enablement; Persuasion; Environmental Restructuring
	O	Physical	Environment	
	M	Automatic	Beliefs about capabilities; Goals	
Home-based exercise	C	Physical and Psychological	Knowledge; Skills; Memory, Attention and Decision Processes; Behaviour Regulation	Education; Training; Enablement; Environmental Restructuring
	O	Physical	Environment	
	M	Automatic and Reflective	Beliefs about capabilities; Goals	
PA guide	C	Physical and Psychological	Knowledge; Skills; Memory, Attention and Decision Processes; Behaviour Regulation	Education; Training; Enablement; Environmental Restructuring
	O	Physical	Environment	
	M	Reflective	Goals	
Online PA diary	C	Psychological	Knowledge; Skills; Memory, Attention and Decision Processes; Behaviour Regulation	Education; Training; Enablement; Environmental Restructuring
	O	Physical	Environment	
	M	Reflective	Goals	
Weekly support phone call	C	Psychical	Behaviour Regulation	Enablement; Environmental Restructuring
	M	Reflective	Beliefs about capabilities; Goals	
Fitbit	C	Psychological	Knowledge; Skills; Memory, Attention and Decision Processes; Behaviour Regulation	Education; Training; Enablement; Environmental Restructuring
	M	Automatic and Reflective	Beliefs about capabilities; Goals	

Assessments of PA and quality of life	C	Physical and Psychological	Knowledge; Skills; Memory, Attention and Decision Processes; Behaviour Regulation	Education; Training; Enablement; Environmental Restructuring
	M	Automatic and Reflective	Beliefs about capabilities; Goals; Beliefs about consequences	

C: Capability; O: Opportunity; M: Motivation

Note: *Ineligibility to participate in the current study was due to environmental and condition-specific factors, such as; the presence of multi-drug resistant bacteria or bugs, an FEV_1 value less than ≤ 40% predicted, individuals having undergone lung transplantation, and residing outside of the Republic of Ireland.*

Stakeholder Engagement

Relevant stakeholders were involved at key decision-making stages of the intervention development process. Stakeholders included: a pwcf, a parent of a pwcf, a senior CF physiotherapist, a cardiothoracic surgeon, a respiratory consultant, the medical director of an exercise rehabilitation program for individuals with chronic disease and two academics with expertise in clinical exercise physiology. All stakeholders attended the initial research design meeting, and consultation was then undertaken with stakeholders on an individual basis regarding the final content, format and delivery of the intervention.

Trial Methodology

Study Design

This study used a randomized-controlled design. An overview of the trial procedures is illustrated in Figure 5.1. Prior to randomization, participants completed baseline assessment. Participants were then randomized into either the intervention (IG) or control group (CG). The IG completed 12 weeks of the remotely supervised exercise program, followed by a further 6 weeks of an unsupervised maintenance phase. Repeat assessments were conducted at week 12 and 18. The feasibility of the intervention was monitored throughout, and via participants interviews upon completion of the trial.

Participants

Adults with an established diagnosis of CF were invited to participate. An email was circulated to individuals with CF (≥ 18 years) on the CF registry held by CF Ireland, the national

CF charity. The email contained a plain language statement (Appendix G) detailing the purpose, benefits, risks, commitments and requirements for the study and a call for expressions of interest. Following an expression of interest via email, participants were screened for eligibility. Potential participants were excluded if they had a bacterial colonization of multi-drug resistant or highly infectious bugs, an $FEV_1 \leq 40$ % predicted or if they had received a previous lung transplantation. Participants provided written informed consent (Appendix H; Appendix H(a)) prior to participation. This study was approved by the Dublin City University (DCU) Research Ethics Committee (DCUREC/2019/186).

Randomization

Participants were randomized to either IG or CG. Simple randomization was performed in a 1:1 ratio. Randomization schedules were generated using a computerized random number generator. This ensured concealed allocation to the experimental condition and helped to minimize selection bias. Participants received an individual identification code that was used on all subsequent documents to ensure anonymity of the data.

Intervention

Participants completed an 18-week home-based exercise intervention, that was technology-enabled for self-monitoring purposes, and underpinned by theories of behaviour change to enhance long-term adherence. The first 12-weeks of the programme was remotely supervised, and was followed by an unsupervised 6-week maintenance phase to assess whether the intervention facilitated the adoption of independent exercise once the support component was removed.

Participants were instructed to self-regulate their exercise mode and intensity, to foster the development of autonomous and intrinsic motivation. Participants were allowed to self-select activities and intensities that they deemed enjoyable and that could be easily incorporated into their daily lives, with the aim of achieving the current consensus guidelines of 150-300 min·week^{-1} of habitual PA; 30-60 min daily of aerobic training; and 2-3 sessions per week involving resistance training of the major limbs. Examples of PA modes for each of the three components (habitual PA, aerobic, and resistance training) were provided via a drop-down list in the online PA diary. During a weekly phone call, participants were given the opportunity to discuss the barriers and challenges associated with the self-regulation of PA, and guidance on appropriate activities was provided where necessary.

Exercise consultation

A face-to-face exercise consultation took place following baseline assessment, and lasted approximately 30 min. The purpose of the consultation was to initiate the intervention process by introducing intervention components such as the PA guide, Fitbit and online PA diary, and behaviour change techniques to enhance the likelihood of sustained adherence to exercise training. The consultation was standardized, underpinned by the COM-B model, and conducted in a private room adjacent to the assessment laboratory at DCU. Short, medium and long-term goals were discussed in depth and agreed with each participant. In addition, potential barriers to continued PA participation were considered and possible solutions were offered to maximize opportunities for adherence.

PA Guide

Participants were provided with a hard copy, purposely designed PA guide at the beginning of the exercise consultation (Appendix I). The researcher provided a thorough explanation of the guide's contents and ensured that all queries relating to the guide and its use were answered at the beginning of the consultation. Participants were encouraged to consult the guide as needed throughout the intervention period. The PA guide served as a comprehensive and patient-friendly resource detailing i) the importance of and benefits associated with PA for CF populations, ii) a detailed overview of the current consensus PA guidelines, iii) a section for goal setting, followed by details of several coping mechanisms for overcoming challenges and setbacks during the intervention period, iv) tips for exercising safely in the home environment, v) how to format an exercise session; emphasizing the importance of warm-up, cool down, and fluid intake (of particular importance for CF populations), vi) how to self-select an appropriate exercise intensity and vii) guided home exercises with detailed visual and written cues for adaptations and progressions. Contact details for the researcher were also included for any queries or concerns relating to the intervention program.

Self-monitoring

Participants were provided with a Fitbit Charge 3 device to monitor daily activities, exercise training sessions and step count during the remotely supervised phase. During the exercise consultation, participants were instructed to install the Fitbit app onto their smart phone or tablet, and were subsequently sent a video on how to set-up and navigate the app and device. The information logged to the Fitbit app (steps and active minutes) was used when discussing weekly progress with participants.

Participants were also provided with a link to access an online PA diary and instructions to download the Google Sheets app on their smart phone or tablet for ease of use. The online PA diary was used to log daily activities, and was divided into the three components of PA as per the current consensus guidelines: habitual PA, aerobic exercise, and resistance training. Daily time spent at each activity was self-reported, and subjective responses were recorded at the end of each session for RPE and affect using the 16-point Borg Scale and Feeling Scale, respectively. Participants were instructed to log their PA at the end of each day, or preferably upon completion of the activity.

Weekly Support

At the end of the exercise consultation, a time and day was agreed for the participant to receive a weekly support phone call. The weekly phone call was incorporated into the intervention to discuss any barriers or challenges that had prevented participants from achieving their goals in the previous 7 days. Data from the Fitbit Dashboard and the online PA diary were used to guide conversations. The weekly support phone calls were standardized, and a checklist was developed to ensure consistency. The checklist covered topics relating to the functioning of the technological components (Fitbit and online PA diary), achievement of weekly goals and meeting the current consensus PA recommendations, and addressing any issues pertaining to perceived barriers and levels of motivation (Appendix J). Topics relating to ratings of enjoyment were also covered during the weekly phone call.

Maintenance Phase

Upon completion of the 12-week remotely-supervised phase, participants entered a 6-week maintenance phase. The purpose of the maintenance phase was to facilitate the transition to long-term adoption of the PA behaviours learned during the 12-week remotely-supervised phase. During the maintenance phase, the use and syncing of the Fitbit device and logging PA to the online diary were no longer compulsory. However, participants could continue using the aforementioned intervention functions, if desired. The weekly phone-call was no longer scheduled.

Control

The CG received routine medical care but no formal intervention, and received the PA guide upon completion of the trial.

Procedures

Baseline assessment involved two visits to DCU, separated by 7 days. Visit one included anthropometric measurements and completion of the CFQ-R and habitual activity estimation scale [HAES] quesionnaires. Participants were then provided with an accelerometer (ActivPAL^3 Micro) to wear continuously for 7 days. During the second visit, lung function was assessed using spirometry, after which participants were randomly assigned to IG and CG. Participants randomized to the IG participated in an exercise consultation at the end of visit two.

Repeat assessments were conducted remotely. Participants received and returned the ActivPAL™ device via registered post and the questionnaires were sent and returned in electronic format via email. Upon completion of week 18, semi-structured interviews were conducted over the telephone with IG by an independent researcher.

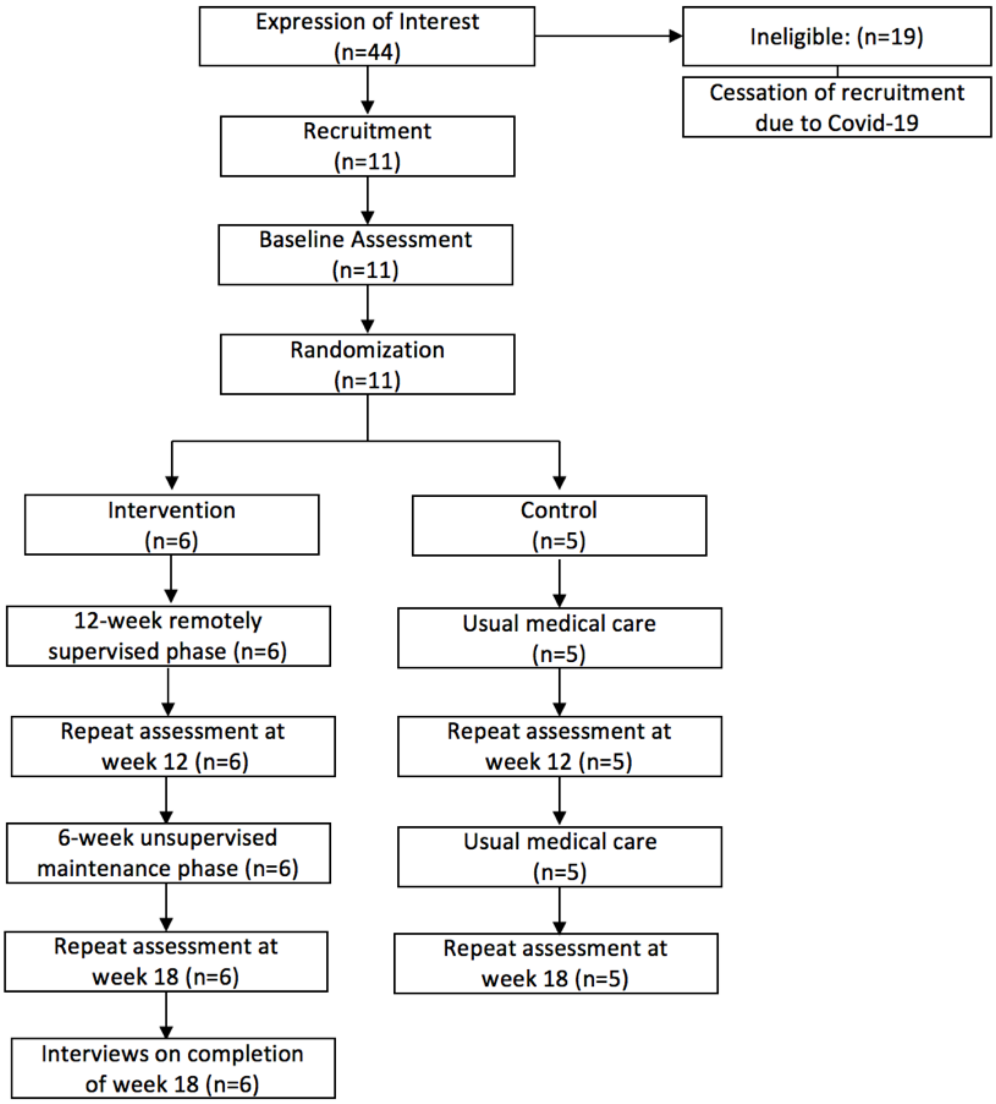


Figure 5.1: Schematic representation of the intervention design and assessment timepoints

Outcome Measures

Assessment of Feasibility

To determine feasibility, guidelines by Bowen et al., (2009) were used. Primary areas of evaluation for this intervention included i) implementation: *the extent, likelihood and manner in which an intervention can be fully implemented as planned and proposed*, ii) demand: *the estimated or measured use of selected intervention activities*, iii) acceptability: *how the intended individual recipients reacted to the intervention*, and iv) practicality: *the extent to which an intervention can be delivered when resources, time, commitment or some combination thereof are constrained* (Bowen *et al.*, 2009). The researcher took detailed field notes throughout the intervention period to describe the implementation process, the fidelity of the intervention and the dose-delivered and received to assess implementation. Monitoring of engagement and usability of the Fitbit device and online PA diary were used to assess demand, and the number and duration of sessions completed over the 12-week remotely supervised phase were recorded and compared against the current consensus guidelines.

Feedback interviews were used to assess the acceptability and practicality of the intervention from participants perspective. Upon completion of week 18, an independent researcher conducted a 20-30 min semi-structured telephone interview with each of the IG participants (n=6). A semi-structured script, including prompts, was developed using Bowen's areas of focus for determining feasibility. The script covered topics relating to participant perceptions of the intervention, usability of the intervention functions, and support received during the remotely-supervised and maintenance phases (Appendix K). Interviews were audio-recorded and transcribed verbatim.

Secondary Outcome Measures

Physical Activity

Accelerometry

The ActivPAL^3 Micro triaxial accelerometer (PAL Technologies Ltd. Glasgow, Scotland) was used to objectively measure PA. The ActivPAL^3 Micro samples at 10 Hz for 15 sec epochs and has an in-built inclinometer, to detect posture. Participants were given verbal and written instructions regarding the application of the device and contact details for the research team in the event of any issues or queries relating to the device. The device was worn continuously day and night for 7 days. Each device was placed in a nitrile sleeve, water-resistant barrier, and secured to the midpoint of the anterior aspect of the right thigh using 3M Tegaderm™ adhesive dressing (Kooperationspartner Wundversorgung, Germany). Participants were instructed to perform their usual daily activity and to remove the device only during activities involving water immersion in depths > 1 metre (i.e., swimming, bathing).

For data to be included in the analysis, participants were required to meet wear-time criteria; ≥4 valid days, including 1 weekend day. A valid day was defined as ≥ 600 min of recording during the daytime hours of 7 am-11 pm (Trost, McIver and Pate, 2005). Non-wear time was defined as ≥60 min of consecutive zero accelerometer counts (Dowd, Harrington and Donnelly, 2012). The ActivPAL™ software (PALconnect, PALanalysis, PALbatch) was used for analysis, where algorithms classify activities of daily living into time spent upright, standing, stepping, non-upright, lying, in car travel, cycling, and also includes number of sit-to-stand transitions, sitting bouts (> 30 minutes, > 60 minutes), step count and non-wear time.

Habitual Activity Estimation Scale

The HAES is a self-reported PA questionnaire and a reliable and valid instrument for the assessment of activities of varying intensities in patients with CF (Wells *et al.*, 2008). Participants completed the HAES questionnaire for a typical weekday (Tuesday, Wednesday or Thursday) and Saturday. The percentage time spent in each of the following four activity categories was documented; inactive, somewhat inactive, somewhat active and very active. To calculate the total number of hours per day spent in each of the four aforementioned categories, wake-up, bed and mealtimes were used. Total activity was calculated each day from the values reported for 'somewhat active' plus 'very active'.

Quality of Life

QoL was assessed using the revised, self-administered and disease-specific CFQ-R questionnaire. The CFQ-R questionnaire is comprised of fifty items that make up nine QoL domains (physical functioning, vitality, emotion, social, body image, eating, treatment burden, role limitations and health perceptions), and three symptom scales (weight, respiratory and digestion). Each domain is scored separately, and scores range from 0 to 100 for each scale, with higher scores denoting higher QoL, i.e., better physical functioning and less symptoms (Hebestreit *et al.*, 2014). The CFQ-R questionnaire is a reliable and valid measure of QoL for adolescents and adults with CF, with high test-retest reproducibility and internal consistency reported. Significant correlations have been reported between the CFQ-

R and the Nottingham Health Profile and St. George's Respiratory Questionnaire for validity (Henry, 2003; Wenninger, 2003).

Anthropometry

Body Mass Index

Participants height and body mass were measured using a wall stadiometer and electronic balance (Seca 797, USA), respectively. Footwear and heavy outer clothing were removed prior to the measurement. Height was measured to the nearest 0.1 cm and body mass was measured to the nearest 0.1 kg. Body mass index (BMI) was calculated by dividing body weight in kilograms by height in meters squared ($kg \cdot m^2$).

Body Fat

Body fat measurements were recorded using a bioelectrical impedance scale (Tanita BF300, Tokyo, Japan). The device measures the resistance and reactance of the participant's body tissues in reference to a small electrical current produced by the device. Participants stood barefoot on the scale for this measurement. Body fat was recorded in kg, and as a percentage of total body mass. Participants were measured twice to obtain an average value.

Waist-to-hip Ratio

Waist and hip circumferences were measured in duplicate using a non-elastic flexible standard measuring tape (RollFix, Hoechstmass, Germany). Measurements were recorded to the nearest 0.1 cm. A third measurement was performed if the difference between measurements was >1.5 cm. Waist circumference was measured at the iliac crest. When the iliac crest could not be palpated, the measurement was taken at the navel. Hip circumference was measured at the greater trochanter. When the greater trochanter could not be palpated, the measurement was taken at the maximal circumference over the buttocks. Waist-to-hip ratio was calculated by dividing the mean waist measurement by the mean hip measurement.

Lung Function

Lung function was assessed using flow-volume loop spirometry. Participants were instructed to sit upright in a chair with arms and legs uncrossed and feet flat on the ground. The participant was then prompted to place the plastic mouthpiece between their teeth and maintain a tight seal with their lips. Careful attention was paid to ensure that the tongue did not occlude the mouthpiece. Participants were instructed to tidal-breathe for a few breaths. From the end of tidal breathing, the participants were coached to inhale maximally and rapidly, and while maintaining an upright posture, to exhale forcefully and maximally until the end of test criteria was met. In order for an attempt to be deemed valid, at least 3 acceptable maneuvers with consistent repeatability (largest and second largest values for both FEV_1 and FVC within 150 mL were achieved. Maximal values from three acceptable maneuvers for FEV_1 and FVC were expressed relative to normative reference values from the Global Lung Index (Quanjer *et al.*, 2012).

Data Analysis

Qualitative data were inductively analyzed using thematic analysis, which involved several steps (Braun and Clarke, 2006). The first step involved immersion and careful repeated reading of the transcripts to identify initial codes and themes. The second step involved systematically coding salient text segments. The third step involved the exploration of themes at a broader level, and investigated whether codes may be combined to create an overarching theme. The final step involved refining themes by cross-checking for overlap and differences, and finally defining emergent themes. A second independent researcher served as a second reader of the transcripts to offer further insight and to broaden data interpretation.

Quantitative data were entered into and analyzed using SPSS v27 (IBM, New York, United States). A linear mixed model analysis was used to assess longitudinal changes in PA and QoL. The mixed model was analysed using first-order autoregressive, compound symmetry and diagonal structures. The Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) were used as metrics to determine which covariance and model structures were of best fit. The main effects for treatment (intervention vs. control) and time (baseline, week 12 and week 18), and the interaction effect for treatment*time were investigated for dependent variables; PA (light intensity PA [LIPA], moderate-to-vigorous PA [MVPA], step count, stepping time, standing time, sedentary behaviour and the self-reported HAES scale) and the 12 CRF-Q domains of QoL. To determine the time points at which significant treatment effects occurred, Bonferroni post-hoc stratified analysis comparing estimated marginal means at each time point were performed.

Results

Participants

Eleven adults with CF were recruited and no dropouts were recorded during the study period. Participant characteristics are outlined in Table 5.2.

Table 5.2: Participants baseline characteristics

	Baseline *n = 11*
Gender (Male:Female)	5:6
Age (years)	31.2 ± 9.5
Height (m)	170.5 ± 8.2
Weight (kg)	70.3 ± 9.4
BMI ($kg.m^2$)	24.1 ± 1.9
Resting HR	72.3 ± 6.7
Resting systolic blood pressure	122.7 ± 7.8
Resting diastolic blood pressure	78.7 ± 4.3
Resting SpO_2	94 ± 3
FEV_1 (L)	3.0 ± 1.1
FEV_1 (% predicted)	77.6 ± 20.4
FVC (L)	4.2 ± 1.1
FVC (% predicted)	89.3 ± 15.1
Homozygous ΔF508	4
Heterozygous ΔF508	4
Other alleles	7

Continuous variables are presented as mean ± standard deviation. BMI: body mass index; FEV_1: forced expiratory volume in first second; FVC: forced vital capacity; SpO_2: Oxygen saturation; *Note: FEV_1 and FVC are only available for 9/11 participants due to facility closures in response to Covid-19.* Other alleles: ΔI507; R117H; c.489+1g>T; p.Arg560Thr; E60x; c1585; IG>A

Assessment of Feasibility

Implementation

Of the 44 participants who expressed an interest in participating, 43% (n=19) were deemed ineligible. Ineligibility was due to bacterial colonization of multi-drug resistant and highly contagious bugs (n=8), severe CF lung disease (FEV_1 ≥ 40% predicted), prior lung transplantation (n=3), and residing outside of the Republic of Ireland (n=1). Cessation of recruitment occurred as a consequence of factors relating to Covid-19, which capped the final number of study participants at 11.

Regarding the fidelity of the intervention, several adaptations were required in response to Covid-19. Weekly phone-calls were adapted to an online Google form, whereby participants provided information in response to a set of standardized questions relating to the functioning of the technology components (Fitbit and online PA diary), and factors relating to their activities completed during the previous week (Swisher *et al.*, 2015). This adaptation was implemented to overcome the difficulties associated with scheduling weekly phone-calls due to an increase in various personal responsibilities associated with the lockdown restrictions such as, childcare, home-schooling and working from home. Participants were instructed to complete the tailor-made Google form on the same day each week. Repeat assessments at DCU were not feasible as a result of the government restrictions. To overcome this challenge, face-to-face repeat assessments were transformed to remote, home-based assessments for the measurement of PA (accelerometry and HAES) and QoL (CFQ-R) at weeks 12 and 18. Each participant received and returned a pre-programmed ActivPAL Micro[3] accelerometer via registered post. Questionnaires were sent and returned via email. No adverse events related to exercise training were reported during the intervention period.

Demand

Demand was assessed by monitoring daily syncing of the Fitbit device and adherence to recording PA in the online diary during the 12-week remotely-supervised phase. Fitbit usage was monitored by the researcher via the Fitbit wellness dashboard. Participants were instructed to sync their devices daily to ensure accurate reporting of weekly statistics. Adherence to appropriately syncing the Fitbit device was 96% during the intervention period. Participants were requested to log their activities in the online PA diary daily. Compliance with reporting PA was 100% during the intervention period. Based on Fitbit and PA diary reports all study participants successfully achieved PA levels during the intervention phase. that agreed with the current consensus guidelines (Table 5.3) (Swisher *et al.*, 2015).

Participants used the online diary to record the form of PA completed (habitual PA, aerobic exercise training or resistance training), the location of the activity (home, gym, outdoors), the type of activity (participants selected an activity from a drop-down menu, and were given the option to over-ride the menu to input their desired activity), and the total duration spent at the activity during the day. An example of weekly PA diary is shown Figure 5.2. Table 5.4 presents the mean RPE and affect scores recorded for each form of PA during the intervention period.

Day	WEEK 8					
	What form of PA?	Where?	Type?	Duration	RPE (6-20)	Affect Score
Monday	Habitual Physical Activity	Home	Housework	30 min	6 (No Exertion)	Good
	Aerobic Exercise Training	Home	HiTT	33 min	16	Good
	Resistance (Strength) Training	Home	Full Body	30 min	16	Good
Tuesday	Habitual Physical Activity	Outdoors	Walking	30 min	6 (No Exertion)	Good
	Aerobic Exercise Training	Home	Spinning	1hr 5 mins	15 (Hard)	Good
	Resistance (Strength) Training	--	--	--	--	--
Wednesday	Habitual Physical Activity	Home	Housework	50 min	Select (6-20)	Good
	Aerobic Exercise Training	Home	Spinning	1hr 10	16	Very good
	Resistance (Strength) Training	Where?	Squats	13mins	15 (Hard)	Very good
Thursday	Habitual Physical Activity	Home	Housework	60 min	6 (No Exertion)	Neither good nor bad
	Aerobic Exercise Training	Outdoors	Walking	74mins	11 (Light)	Neither good nor bad
	Resistance (Strength) Training	--	--	--	--	--
Friday	Habitual Physical Activity	Home	Housework	50 min	6 (No Exertion)	Good
	Aerobic Exercise Training	--	--	--	--	--
	Resistance (Strength) Training	Home	Full Body	40 min	13 (Somewhat Hard)	Good
Saturday	Habitual Physical Activity	Home	Housework	40 min	6 (No Exertion)	Good
	Aerobic Exercise Training	--	--	--	--	--
	Resistance (Strength) Training	Home	Upper Body	26mins	14	Good
Sunday	Habitual Physical Activity	Home	Housework	30 min	6 (No Exertion)	Good
	Aerobic Exercise Training	Outdoors	Walking	2hrs	12	Good
	Resistance (Strength) Training	--	--	--	--	--

Figure 5.2: Example of the online PA diary

Table 5.3: Frequency and duration of PA during the intervention compared to the current guidelines

	Intervention Group (n=6)		Consensus Guidelines	
	Frequency (days)	Duration (min)	Frequency (days)	Duration (min)
Habitual PA	5.0 ± 2.4	38.6 ± 11.5	5	30-60
Aerobic training	4.0 ± 1.6	33.5 ± 10.4	5	30-60
Resistance training	2.0 ± 0.9	25.1 ± 6.0	2-3	Not specified

Table 5.4: Perceptual and effective responses during the intervention

	RPE	Affect
Habitual PA	Fairly light (9)	Good (4)
Aerobic training	Fairly light to somewhat hard (11-13)	Good (4)
Resistance training	Fairly light (9)	Good (4)

Acceptability

Enjoyment of the intervention was initially evaluated once per week during the weekly phone-call, and then via Google forms. Participants were asked to rate their level of enjoyment of the intervention for the previous week on a scale of 1 to 10 (1 = not enjoyable at all and 10 = very enjoyable). The mean ± SD score for enjoyment was 8.1 ± 1.7 for the remotely-supervised phase. Semi-structured interviews conducted by an independent researcher with participants in the intervention group (n=6), indicated intervention acceptability. Responses were grouped in relation to perceptions of enjoyment, support and self-monitoring throughout the intervention.

Feelings of positivity and enjoyment towards participation in the intervention were expressed by all participants:

"Really it was so positive…I enjoyed it all, so it was great. It will definitely make me more active." (Participant 1)

"I'm in a better place now, health and well-being, everything since I participated in the intervention. Especially being stuck at home the last four months, if I didn't have the intervention…that motivation and something to keep me going like exercise, I don’t know…things could’ve been a lot different. So, I really enjoyed it.” (Participant 2)

All participants reported feeling satisfied with the support received during the remotely-supervised phase:

“ [The support] was great. So, with the online diary I was trying to get into a routine of doing it when I was going to bed every night or else it depends on the day, I would fill it in as I did something. It was interesting because I had never done that before to see what you are doing, and it can make you want to do more as well. Then the chats each week, they were good. Just if I needed anything but also interesting for me to evaluate how I was feeling every week.” (Participant 1)

“There was always support there if you had any questions, I think that was great, it really helped me” (Participant 5)

Regarding the removal of support during the unsupervised maintenance phase, the majority of participants expressed a satisfactory transition:

“It was fine because it was all so gradual. It was fine.” (Participant 1)

“I was a bit anxious at first. I was like am I going to be able to do this? Am I going to be able to keep going? Because I’ll be honest with you, I’m a quitter…But no, for the first few days I kind of maybe was lost a little bit, but only for a day or two. That was just me taking rest…but no, kept going… and I have developed little things that motivate me now, that keep me going.” (Participant 2)

Two participants reported decreased motivation following the transition to the maintenance phase:

“When the support was removed, not that I slipped a lot but I kind of felt maybe there’s not someone looking over me as much, if I didn’t do this run or didn’t go for a walk, that maybe I wouldn’t get caught out as such…so, I did find when the support left, maybe my motivation dropped a little.” (Participant 3)

“I think I was probably slacking a little bit in the maintenance phase, because I didn’t have that, I suppose, filling in the diary every week…so I think I probably did slack a little bit. And I think it was probably that support, I think it does make a difference, like I didn’t think it would. But I think it did, I probably don’t have as much push in myself than when I had someone.” (Participant 5)

The use of the Fitbit device as a self-monitoring tool was deemed acceptable and was reported as a key factor for motivation by the majority of participants:

“I definitely found the Fitbit to be the best throughout the entire programme, it definitely served as one of the best ways to record what I’m doing and to see my achievements.” (Participant 4)

“I will definitely continue with the Fitbit…monitoring what exercise I do…because I like to be able to look back on my Fitbit for the month as it showed all my active days and I was like yes, that’s brilliant…it was lovely to be able to look back and see how active I was. It kind of gave me a boost.” (Participant 2)

One participant expressed less interest towards the use of the Fitbit device:

"If you are goal orientated, like you have an event that you are training for, I can see the benefit of a Fitbit, but if you are just doing general exercise I think a Fitbit causes more obsession than is healthy because you are obsessed with the data and you are obsessed with your heart rate and so on…whereas I could happily do the intervention programme without a Fitbit." (Participant 6)

Three participants suggested that the intervention would benefit others with CF:

"Yeah, I think the trial is something that should be implemented in hospitals. I think physiotherapists should have some sort of online database that they are monitoring every week…to see everything that you have filled in…something similar to the trial I think would benefit a lot of people with CF. If everyone had access to the trial, I think it would be great" (Participant 5)

"Definitely. I think adherence is something that's very hard when you have something like CF. There's a lot going on with medications, there's so much to fit in and exercise is so important. So, yeah, I think it is 110% beneficial for anyone in a similar situation." (Participant 3)

The majority of participants suggested that they would continue to use the program in the future:

"I'll definitely use elements of it. Definitely keep monitoring. I realise the importance of it now." (Participant 3)

Four participants stated that they would participate in similar interventions in the future.

Practicality

Several participants reported positive responses towards the intervention for usability:

"It was just really straight forward, nothing tricky. It was to go at my own pace and to do what I wanted to meet the guidelines… so yes, it was just very straight forward…I wasn't puzzled or like oh gosh, what do I do here, because it was so clear." (Participant 1)

"It was very easy to follow and it made a lot of sense. I think it was definitely helpful that it was broken up into time and different areas of training, that was really helpful." (Participant 4)

Two participants suggested strategies for improving the practicality of the intervention:

"I think I definitely would have worked better with a more structured approach or a more heavily information based approach." (Participant 4)

"I think you need to tailor the intervention based on broad age categories, to be more age appropriate…possibly for a 60-year old, versus a 40-year old, versus a 20-year old." (Participant 6)

The remaining participants identified no requirement for improvement in any of the intervention components.

Participant Feedback

The self-regulation of exercise was perceived both positively:

"I think it was good to realise that there's all different types of exercise as well…that was helpful so you could kind of…instead of just pushing yourself in the gym or something, you realise there are things you can do that you enjoy too, but by pushing yourself." (Participant 5)

And negatively:

"The programme was so, I suppose, person-led and that's the way it was explained to me, which I completely understood, and it sounded very exciting. But I think for me that looseness just didn't work for me. I think it kind of gave me, not that it gave me too much choice, it just left me in a space where I was very unsure. And when I became too unsure for too long, I tended to just put it off and go, oh well I don't need to do it now, I'll do it tomorrow." (Participant 4)

Several participants reported developing an increased awareness surrounding the importance and the benefits of PA for CF populations:

"I'm definitely more cognitively aware of what a person with CF, in terms of PA, needs to do…because I was probably like every Irish person and I felt that there's so much emphasis on aerobic fitness and I probably ignored resistance training a little bit…and I actually didn't appreciate the importance of habitual PA." (Participant 3)

Covid-19 reached Ireland in late February 2020, and the national government restrictions were imposed on the 12th of March. The lockdown took effect between, on average, between weeks 1 and 4 of the remotely-supervised phase, depending on individual start-dates, and its impact served as both a motivator:

"I think going into quarantine helped, or going into self-isolation helped, as well to find a better routine and that kept motivation up. I found myself a lot more, I found a routine, but I think I've learned from that to make a plan and to plan ahead and to have a routine. It's something that I've learned from all this as well.

And a barrier to PA participation:

"I think a huge factor for me was the Covid-19 restrictions and then the lockdown, and the fear of leaving your house and that was a huge factor because I certainly did very little running because I didn't want to…because with running you are breathing in so deeply and if you're passing anyone…I was just reluctant to take that risk, because I live in a busy estate. Whereas, if Covid-19 wasn't an issue, I would probably have gotten into a pattern of doing two or three runs a week." (Participant 6)

Secondary Outcome Measures

Results for the linear mixed model analyses on indices of PA and QoL are presented in table 5.5. Statistically significant main effects for treatment were found for LIPA (p=0.042), MVPA (p=0.013) and the QoL domain Vitality (p=0.009). Post-hoc analysis revealed that the difference for LIPA was due to differences between the groups at baseline, and not in response to treatment, and the differences in MVPA and QoL domain Vitality were accounted for by increases in the control group. There was a statistically significant main effect for time for QoL domain Social, and post-hoc analysis identified that the decrease occurred in the control group across all 3 time points. There was no significant interaction effect for treatment*time for any of the outcome variables. PA parameters (LIPA, MVPA, step count and sedentary behaviour) at baseline (BL), 12 and 18 weeks are presented in figures 5.3-5.5.

Table 5.5: Type III analysis of treatment, timepoint and treatment*timepoint for secondary outcome variables

Outcome Variable	BL		12 Weeks		18 Weeks		Treatment			Time			Treatment* Time		
	INT	CON	INT	CON	INT	CON	**df**	**F**	**sig**	**df**	**F**	**sig**	**df**	**F**	**sig**
LIPA (hr)	11.3 ± 2.0	7.9 ± 2.2	14.7 ± 2.6	7.1 ± 2.8	10.6 ± 1.7	9.4 ± 1.9	(1,24)	4.6	**.042**	(2,19)	0.1	.866	(2,20)	0.9	.414
MVPA (hr)	2.2 ± 0.9	3.6 ± 1.0	1.8 ± 0.8	3.7 ± 0.8	1.7 ± 0.9	4.4 ± 0.9	(1,26)	7.0	**.013**	(2,17)	0.1	.936	(2,17)	0.2	.756
Step Count	9647 ± 1758	8819 ± 1926	8827 ± 1758	7079 ± 1926	9598 ± 1758	10742 ± 1962	(1,9)	0.4	.838	(2,18)	2.0	.163	(2,18)	0.8	.430
Stepping Time (hours)	2.0 ± 0.3	1.7 ± 0.3	1.9 ± 0.3	1.4 ± 0.3	2.0 ± 0.3	2.1 ± 0.3	(1,9)	0.3	.591	(2,18)	1.8	.184	(2,18)	1.5	.249
Standing Time (hours)	4.3 ± 0.5	3.3 ± 0.5	3.8 ± 0.5	2.8 ± 0.5	3.8 ± 0.5	4.4 ± 0.5	(1,9)	0.4	.510	(2,18)	3.2	.062	(2,18)	4.3	**.028**
Sed Time (hours)	7.8 ± 0.7	8.4 ± 0.8	7.3 ± 0.7	9.1 ± 0.8	7.7 ± 0.7	7.6 ± 0.7	(1,9)	0.6	.439	(2,18)	0.5	.562	(2,18)	2.0	.158
HAES Inactivity	70.8 ± 3.9	78.2 ± 4.2	67.8 ± 3.9	76.1 ± 4.2	67.2 ± 3.9	75.0 ± 4.2	(1,9)	2.4	.150	(2,18)	0.9	.392	(2,18)	0.0	.987
HAES Activity	29.9 ± 3.8	21.7 ± 4.2	32.2 ± 3.8	23.9 ± 4.2	32.7 ± 3.8	24.9 ± 4.2	(1,9)	2.6	.139	(2,18)	0.7	.480	(2,18)	0.0	.996
QoL Physical	87.5 ± 8.7	86.6 ± 9.6	94.4 ± 1.6	99.1 ± 1.7	93.1 ± 2.0	100.0 ± 2.2	(1,9)	0.4	.535	(2 9)	1.3	.296	(2,9)	1.9	.197
QoL Vitality	63.8 ± 4.8	76.6 ± 5.2	59.7 ± 7.3	90.0 ± 8.0	62.5 ± 5.1	90.0 ± 5.5	(1,9)	10.9	**.009**	(2,9)	1.2	.333	(2,9)	1.4	.290
QoL Emotion	85.4 ± 3.3	94.6 ± 3.6	84.4 ± 6.6	89.3 ± 7.3	85.5 ± 4.0	97.3 ± 4.4	(1,9)	2.0	.190	(2,10)	1.5	.267	(2,10)	0.9	.436
QoL Eating	85.6 ± 6.2	91.1 ± 6.7	92.6 ± 4.3	97.7 ± 4.7	92.6 ± 4.0	100.0 ± 4.4	(1,9)	1.4	.252	(2,9)	1.6	.252	(2,9)	0.6	.553
QoL Treatment Burden	57.0 ± 9.2	75.5 ± 10.1	55.5 ± 6.8	80.0 ± 7.5	53.7 ± 9.1	77.8 ± 10.0	(1,9)	3.4	.094	(2,14)	0.2	.755	(2,11)	0.5	.585
QoL Health Perceptions	78.7 ± 6.9	82.2 ± 7.6	74.0 ± 7.7	91.1 ± 8.4	75.9 ± 5.5	91.1 ± 6.1	(1,9)	2.1	.173	(2,9)	0.4	.674	(2,9)	0.4	.622
QoL Social	62.0 ± 8.8	93.3 ± 9.6	50.0 ± 9.2	79.9 ± 10.1	58.3 ± 11.2	76.6 ± 12.3	(1,9)	4.3	.067	(2,15)	3.7	**.046**	(2,11)	0.4	.625
QoL Body Image	75.9 ± 8.2	97.7 ± 9.0	75.9 ± 8.2	95.5 ± 9.0	74.0 ± 8.8	97.7 ± 9.6	(1,9)	3.1	.112	(2,12)	0.1	.835	(2,16)	1.2	.323
QoL Role	81.9 ± 3.8	98.3 ± 4.2	77.7 ± 7.2	92.2 ± 8.3	81.9 ± 5.8	94.2 ± 6.7	(1,9)	3.1	.110	(2,8)	1.4	.290	(2,9)	0.4	.653
QoL Weight	88.8 ± 11.6	86.6 ± 12.7	94.4 ± 10.7	73.3 ± 11.7	100.0 ± 4.9	86.6 ± 5.4	(1,9)	0.9	.344	(2,9)	1.9	.199	(2,9)	1.0	.386
QoL Respiratory	75.9 ± 7.0	74.4 ± 7.6	75.0 ± 3.4	85.5 ± 3.7	68.5 ± 7.2	85.5 ± 7.9	(1,10)	1.9	.195	(2,12)	0.7	.472	(2,15)	0.8	.452
QoL Digestion	83.3 ± 6.3	88.9 ± 6.9	77.8 ± 6.1	86.6 ± 6.7	77.8 ± 5.8	91.1 ± 6.3	(1,9)	1.3	.277	(2,14)	1.0	.379	(2,10)	0.4	.678

Values at Baseline, 12 and 18 weeks are Mean ± Standard Error: BL = Baseline; Sed Time = Sedentary Time

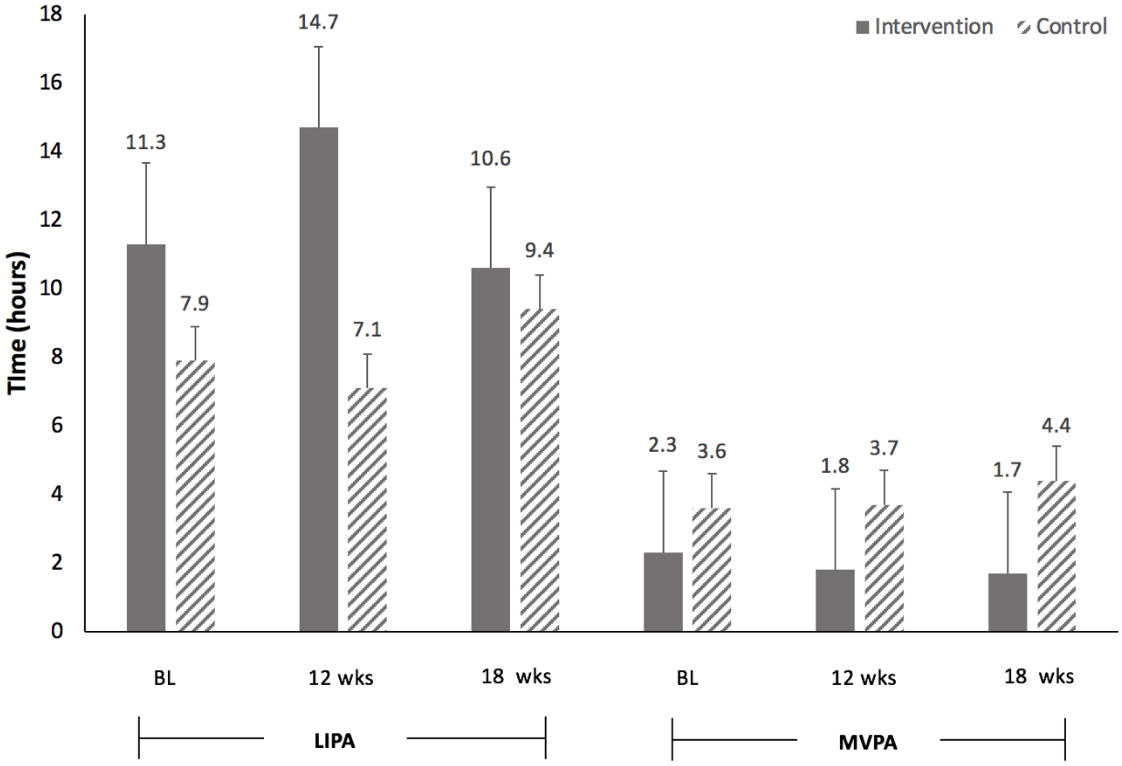


Figure 5.3: Light-intensity PA and moderate-to-vigorous PA (hours) for intervention and control groups at baseline, week 12 and week 18

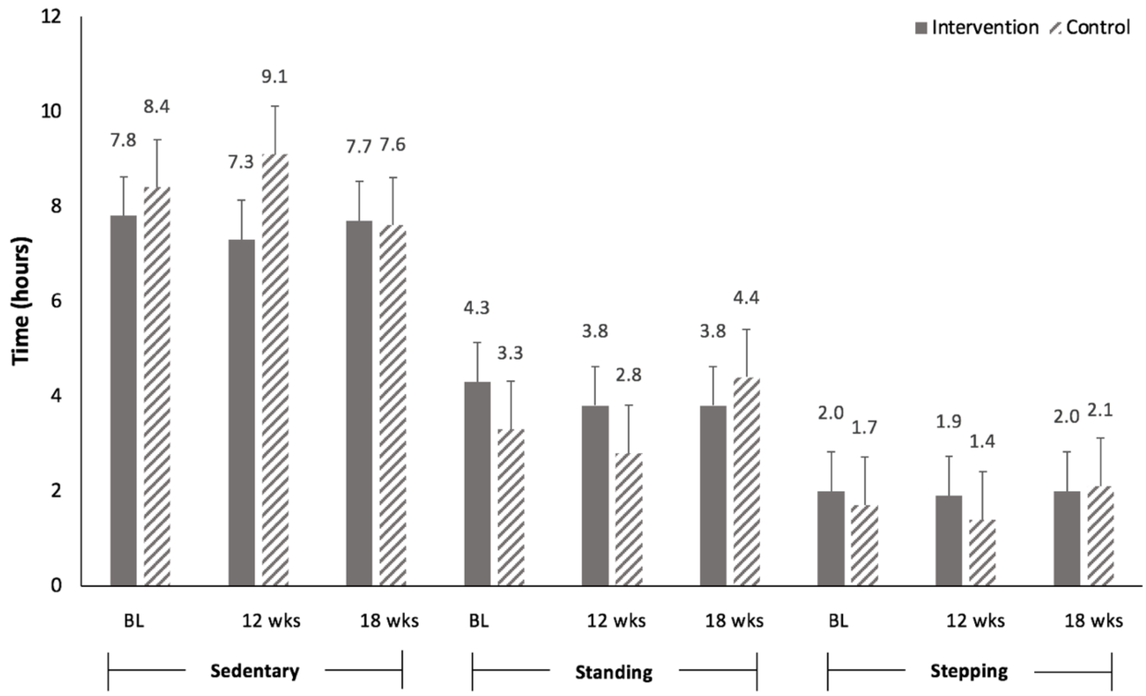


Figure 5.4: Sedentary, standing and stepping time (hours) for intervention and control groups at baseline, week 12 and week 18

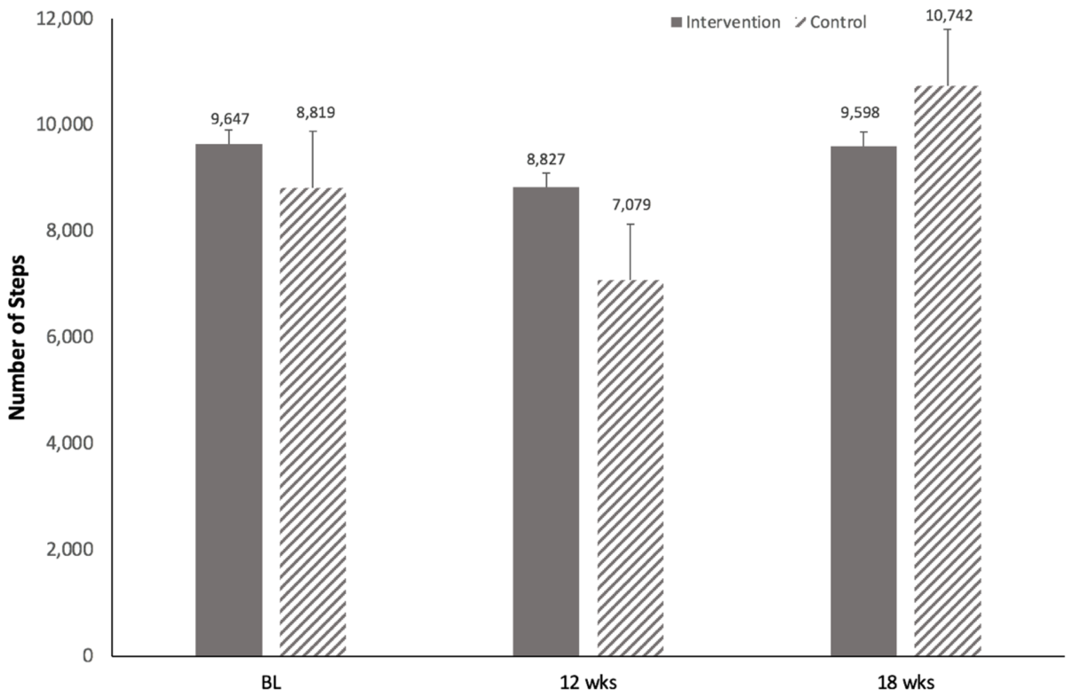


Figure 5.5: Step count (number of steps) for intervention and control groups at baseline, week 12 and week 18

Discussion

The purpose of this study was to develop, implement and evaluate the feasibility of a home-based, self-regulated and technology-enabled PA intervention among adults with CF. The present study is the first to systematically describe the development of a multifaceted PA intervention, underpinned by theories of behaviour change, for adults with CF. This intervention added value to behavioural science methodology as it is, to the authors' knowledge, the first PA intervention for adults with CF that has been developed using the MRC (MRC, 2019) framework for the development, implementation and evaluation of complex interventions, alongside the BCW and TDF.

Interventions that are underpinned by theories of behaviour change have the potential to increase the efficacy of PA programs for CF populations, as they provide valuable insight into the relation between targeted constructs and their influence on the chosen behaviour (Bluethmann *et al.*, 2017). Limited research exists investigating the effect of PA interventions underpinned by theories of behaviour change among CF populations. There is a need for additional studies to further our understanding of the role of theory-based PA interventions in improving intervention effectiveness, and to promote intervention replicability.

This study is also the first to explore the feasibility of home-based, self-regulated and technology-enabled exercise among adults with CF. Although many areas of focus can be used to determine feasibility (Bowen *et al.*, 2009), this study focused on implementation, demand, acceptability and practicality. The results indicate that the PA intervention was feasible as it was i) easily implemented despite the changing environment due to COVID-19, ii) well accepted in terms of enjoyment, and iii) sustained a high level of engagement throughout both phases of the intervention. Importantly, the intervention was also deemed safe, as no adverse events were reported.

To date, the majority of exercise related research has focused on individuals with mild-moderate classifications of CF lung disease. It is important to acknowledge that almost half of those who expressed an interest were ineligible for participation in the intervention. This finding may have significant implications for practice, as these subgroups represent a significant proportion of the CF population that are typically excluded from similar studies, raising the question of whether exercise training may also be of benefit for these cohorts? Future research should aim to conduct PA interventions on a case-by-case basis with individuals who have multi-drug resistant and contagious bugs, severe CF lung disease and those who are post lung transplant, in order to extend the evidence-base for the benefits of exercise training to the wider CF population.

Although not statistically significant (small sample size) there was a positive trend for increases in LIPA among participants in the intervention group during the supported remotely-supervised phase. This finding is of particular significance as there is accumulating evidence highlighting the importance of increasing LIPA for maintaining and enhancing health among individuals with chronic disease (Amagasa *et al.*, 2018). Although there has yet to be evidence published among pwcf, increases of approximatrly 1,000 steps per day (LIPA) reduced the risk of hospitalisation by 20% among individuals with COPD (Donaire-Gonzalez *et al.*, 2015). Increasing daily LIPA may be a more achievable goal for pwcf who are unable to meet the recommended guidelines for MVPA as a consequence of symptom-limitations and disease-related physical deconditioning. This study sought to increase pwcf PA levels, QoL, and long-term maintenance of PA behaviours through home-based, self-regulated and technology-enabled exercise. Further trials are required to investigate whether the potential positive trend in LIPA is evident among the wider CF population. Improvements in PA have been shown to positively impact QoL and longevity in this cohort (Lannefors, 2012).

There was however, a marked decrease in LIPA during the unsupported maintenance phase. Some participants in the present study perceived the removal of support during the maintenance phase as an opportunity to disengage, despite reporting an increased awareness of the benefits and importance of regular PA participation. This, coupled with participant feedback, highlights the need for an increase in individually-tailored PA advice and behavioural counselling to identify those individuals in need of further encouragement, guidance and support to achieve optimal health-related benefits.

The quality of motivation expressed by participants during the intervention was also mixed. Some participants reported elements of introjected regulation, feeling obligated to participate in PA, rather than having an internal drive to improve health outcomes. Others, however, expressed components of autonomous motivation, reporting that exercise has now become a priority in their lives and they have found a way to incorporate PA into their daily routine. The mixture of motivational qualities among participants suggests the need for the development of a PA prescription continuum, whereby the HCP and/or supporting exercise professional (EP) works in close contact with pwcf on an individual basis. The HCP/EP should employ methods of motivational interviewing and behavioural counseling to identify where on the continuum the individual lies, and prescribe PA appropriately. Individuals who are primarily motivated by external factors and rely on support from the HCP/EP will require a more structured, supervised and prescriptive approach to PA advice, where adherence to PA is closely monitored and the individual is reassured regularly with encouragement. However, for those who exhibit higher levels of intrinsic motivation and an increased value for exercise-related outcomes, the instruction to self-regulate PA could be introduced, albeit continually monitored by the HCP/EP, but to a lesser extent. This will foster an increase in autonomous motivation, enhancing self-competence and improving long-term PA adherence.

Participants in the present study achieved the recommended dose of PA, as per the current consensus guidelines, while performing self-regulated exercise. The use of self-regulation for the selection of individual intensities and modes of PA was well accepted by many of the study participants and we believe that future research is worth pursuing to evaluate the full-scale effectiveness of PA interventions that are self-regulated and underpinned by theories of behaviour change to confirm the results of the current feasibility study.

Strengths and Limitations

A clear strength of this study was the iterative systematic approach taken to develop the intervention, as it was underpinned by behaviour change theory and sought input and feedback from HCP, pwcf and relevant stakeholders, providing a co-design approach to informing the intervention development process.

The small sample size, given the feasibility-driven nature of this investigation, will limit the utility of findings to the wider CF population. However, findings from the present study can be used to inform and statistically power future efficacy trials. The impact of COVID-19 is another noteworthy limitation to consider when interpreting the findings of the current study. Other than the impact on recruitment, it is important to raise the question as to whether engagement in the intervention would have been as high if the individuals were not in self-isolation; would they have been as happy to have had it as an outlet, or would they have enjoyed it as much? However, it is relevant to note that participating in bouts of self-isolation is not uncommon for pwcf, as it is often routinely required following bouts of pulmonary exacerbations. Therefore, it could be proposed that the COVID-19 environment was not as significant a limitation as once perceived.

Conclusions

A tailor-made, home-based, self-regulated and technology enabled PA intervention is feasible and acceptable among adults with CF. The integration of a systematic review of the literature combined with input from HCP, pwcf and relevant stakeholders and evidence-based theory provides a platform for the development of potentially effective PA interventions for adults with CF. The absence of this complex approach and the determination of feasibility prior to full-scale evaluation may be responsible for the lack of high-quality PA interventions in this cohort to date. Future research should aim to refine the current study, with further stakeholder engagement, by conducting a follow-on feasibility trial in a larger sample size. Subsequent research should aim to determine the efficacy of a full-scale randomized-controlled trial employing the refined PA intervention, to optimise long-term health-related outcomes for pwcf.

Chapter VI
Study IV

Study IV: Maximal Oxygen Consumption and Oxygen Uptake Efficiency in Adults with Cystic Fibrosis

Introduction

The importance of aerobic fitness for CF populations has been well documented. Aerobic fitness is a strong prognostic indicator(Gruet *et al.*, 2010) and is associated with eight-year survival in this cohort, regardless of confounding factors such as age, gender or lung function (Nixon *et al.*, 1992). Furthermore, higher levels of aerobic fitness are associated with an increased QoL (Hebestreit, 2006). Maximal oxygen uptake ($\dot{V}O_2max$) determined during CPET is the gold standard measurement of cardiorespiratory fitness. Some CF patients may have difficulties achieving a true maximal effort during a CPET due to effort-dependent influencing factors such as motivation, pain and shortness of breath (Gruet *et al.*, 2010; Tomlinson *et al.*, 2018). Submaximal parameters of aerobic capacity can be used as potential alternatives for the provision of such clinically useful information (Tomlinson *et al.*, 2018).

The OUES was developed to provide an objective submaximal measure of aerobic fitness (Baba *et al.*, 1996). It is derived from the linear relation between oxygen uptake and the logarithm of minute ventilation ($\dot{V}_E$) during incremental exercise, using the formula, $\dot{V}O_2 = a \log \dot{V}_E + b$; where $\dot{V}O_2$ represents oxygen uptake (mL·min^{-1}), the constant 'a' represents the rate of increase in $\dot{V}O_2$ in response to an increasing $\dot{V}_E$ (OUES), log $\dot{V}_E$ is the common logarithm of $\dot{V}_E$ and the constant 'b' represents the intercept,(Baba, 2000). The logarithmic transformation of $\dot{V}_E$ results in the linearization of the relation between $\dot{V}O_2$ and $\dot{V}_E$ during incremental exercise.

The clinical utility of the OUES as a potential surrogate for $\dot{V}O_2max$ has been demonstrated in heart failure (Davies *et al.*, 2006), obesity (Onofre *et al.*, 2017), lung cancer (Yakal *et al.*, 2018), pulmonary embolism (Liu *et al.*, 2014) and in patients scheduled for lung surgery (Broek *et al.*, 2019). Among adults with CF, OUES at 80% of the entire maximal duration was found to be the most valid and reliable predictor of $\dot{V}O_2max$ (Gruet *et al.*, 2010).

The oxygen uptake efficiency plateau (OUEP) is the highest 90-sec oxygen uptake efficiency value recorded during an incremental exercise test. It typically occurs at an exercise intensity prior to, or at the ventilatory threshold and was found to be a predictor of mortality among patients with heart failure (Sun, Hansen and Stringer, 2012). In contrast, OUEP was found to be a weak surrogate for maximal aerobic capacity in children and adolescents with CF (Tomlinson *et al.*, 2018). The clinical utility of the OUEP has not been investigated in adults with CF.

Study Aim:

To determine the concurrent validity of the $OUES_{50-80}$ and the $OUEP_{50-80}$ as predictors of $\dot{V}O_2max$ in an adult CF population

Study Hypothesis:

1. Among adults with CF, OUES at 80% of the test duration ($OUES_{80}$) will be a better predictor of $\dot{V}O_2max$ than OUES at 50,60 and 70% ($OUES_{50}$, $OUES_{60}$, $OUES_{70}$) of the test duration
2. There will be no significant relation between OUEP and $\dot{V}O_2max$ in adults with CF

Methods

Study Design

This study used a cross-sectional study design. Participants made a single visit to the clinical exercise physiology laboratory at DCU, during which body composition, blood pressure (BP), heart rate (HR), and maximal aerobic capacity ($\dot{V}O_2max$) were measured.

Participants

Eleven adults (20-49 years) with an established diagnosis of CF participated in the study. The participants in the present study are the same as those in Chapter V.

Participant Recruitment

As previously described in the methods section of Chapter V.

Outcome Measures

Body Mass Index

As previously described in the methods section of Chapter V.

Body Fat

As previously described in the methods section of Chapter V.

Waist-to-hip Ratio

As previously described in the methods section of Chapter V.

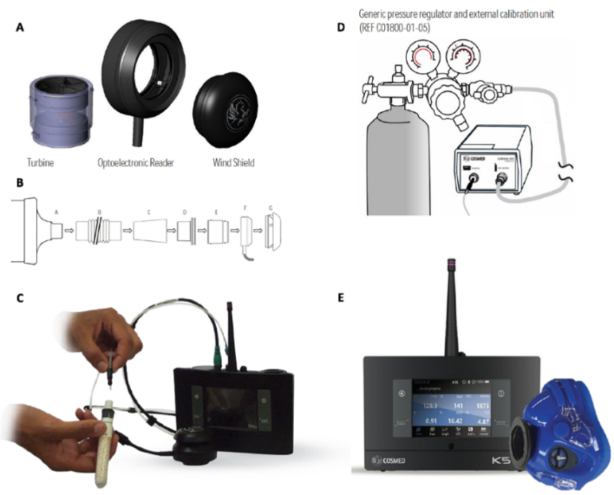
Maximal Aerobic Capacity ($\dot{V}O_2max$)

Maximal aerobic capacity ($\dot{V}O_2max$) was measured during a continuous, Godfrey protocol (Godfrey and Mearns, 1971) , incremental protocol on an electronically-braked cycle ergometer (Ergoselect 100, Ergoline GmbH, Germany). The protocol was designed to ensure that participants reached volitional fatigue between 8-12 min (Hebestreit, Kriemler and Radtke, 2015). Depending on the participant's height, the initial work rate was 10 (<120 cm), 15 (120-150 cm) or 20 watts (>150 cm) and the workrate was increased by 10, 15 or 20 W per min, respectively. aseline measurements for heart rate, ECG, BP and ventilatory gases were made for 3 min prior to test commencement, and participants warmed up with a further 3 min of unloaded pedaling.

Ventilatory and metabolic measures were continuously monitored throughout the test, and $\dot{V}O_2max$ was determined by averaging the three highest consecutive 20 sec values. The electrical activity of the heart was continuously monitored using a 12-lead electrocardiograph (GE Case 8000 12 Lead ECG). Overall and differentiated ratings of perceived exertion for the chest and legs were measured using the 16-point Borg scale and 10-point modified ratio scale, respectively. Oxygen saturation (SpO_2) was recorded during the final 15s of each stage using a pulse oximeter (NONIN, Plymouth, England). A test was considered maximal if at least two of the following four criteria were met; peak $\dot{V}O_2$ >85% predicted; peak HR >85% predicted; respiratory exchange ratio ≥1.10; overall RPE ≥ 18 (Gruet *et al.*, 2010).

Cardiorespiratory Measures

The Cosmed K5 open-circuit spirometry system (Rome, Italy) was used to measure respiratory and metabolic responses. The K5 system uses a galvanic fuel cell and a non-dispersive infrared sensor for the analysis of oxygen (O_2) and carbon dioxide (CO_2) in the inhaled and exhaled air, and an opto-electric reader with a high performance turbine flowmeter to measure flow rate. Following a 20 min warm-up, the flowmeter, gas, scrubber and delay time calibrations were performed following the manufacturer's recommendations. The two-point gas calibration involved sampling the ambient air and gas from a certified tank containing 16% O_2, 5% CO_2 and standard atmospheric nitrogen. A 0% CO_2 sampling was performed using a CO_2 scrubber to obtain an accurate 0% CO_2 reading and for the CO_2 and O_2 values in the atmospheric air. Flowmeter calibration was performed by connecting the turbine to a Hans-Rudolph 3L syringe and completing six full strokes. A delay time calibration was performed with the flowmeter and sample line connected to the face mask, by executing six breaths at a standard rhythm while breathing into the facemask.



A: Turbine set-up; B: Connection of turbine to 3L syringe for flowmeter calibration; C: Scrubber calibration; D: Gas analyzer calibration; E: K5 unit and face mask

Figure 6.1: Calibration steps for the K5 open-circuit spirometry unit

Resting Blood Pressure

Prior to the measurement of resting BP, participants rested in an upright seated position for 5 min in a temperature controlled room. BP was measured at the left upper arm using a mercury sphygmomanometer (Dekamet Model Accoson Sphygmomanometers, Harlow, Essex) and stethoscope (Classic II 3M Littman, St. Paul, MN).

Electrocardiographic Monitoring

The signal to noise ratio at the skin electrode interface was reduced by cleansing the area with an alcohol saturated gauze pad. The superficial layer of skin was then removed using light abrasion with fine grain emery paper. Electrodes were placed on the 10 standard anatomical landmarks.

Oxygen Uptake Efficiency

Ventilatory gas data during the maximal exercise test was exported in breath-by-breath format and averaged over 20 sec intervals for the calculation of the oxygen uptake efficiency slope (OUES). The OUES was calculated using the equation recommended by Baba et al., (1996); $\dot{V}O_2 = a \log\dot{V}_E + b$, on spreadsheet software (Microsoft Excel v16). $\dot{V}_E$ was logarithmically transformed and the slope, $\dot{V}O_2$ (y-axis) and $\dot{V}_E$ (x-axis), was determined.

The first minute of exercise was excluded from the calculation of OUES to eliminate the confounding influence of hyperventilation that often occurs at the beginning of exercise. Exercise data up to 50, 60, 70, and 80% of $\dot{V}O_2$max were included in the analysis for determination of submaximal OUES. The OUEP was determined as the 90 sec average of the highest consecutive values for oxygen uptake efficiency. Relative values for $\dot{V}O_2$max, OUES and OUEP were calculated by dividing the absolute values by body mass.

Statistical Analysis

Statistical analysis was performed using SPSS v27. Continuous variables are expressed as mean ± SD. Estimates of $\dot{V}O_2$max were calculated from the regression equation of the relation between $\dot{V}O_2$max and submaximal OUES and OUEP at varying intensities (50, 60, 70 and 80% $\dot{V}O_2$max). The Bland-Altman technique (2010) was used to examine the level of agreement between measured and predicted $\dot{V}O_2$max values using $OUES_{50\text{-}80}$ and $OUEP_{50\text{-}80}$ (Bland and Altman, 2010). The sum of the two measurement methods ($\dot{V}O_2$measured + $\dot{V}O_2$predicted using $OUES_X$) and ($\dot{V}O_2$measured + $\dot{V}O_2$predicted using $OUEP_X$) were divided by 2 and plotted against the difference between the two measurement methods ($\dot{V}O_2$measured – $\dot{V}O_2$predicted using $OUES_X$) and ($\dot{V}O_2$measured – $\dot{V}O_2$predicted using $OUEP_X$). The limits of agreement were defined by adding and subtracting 1.96 x SD of the differences from the mean value (Gruet *et al.*, 2010).

Results

Participant characteristics and CPET results

Participant characteristics and CPET results are summarized in Table 6.1. All exercise tests were completed without any adverse events. At least one of three predetermined criteria used to verify the attainment of $\dot{V}O_2$max was achieved by all (100%) of the participants, with almost half (45%) achieving two out of three criteria. All of the study participants reached a HR > 85% max and 45% achieved an RER > 1.05. OUES was obtained for all of the study participants. Absolute and relative values for $\dot{V}O_2max$, OUES and OUEP are summarized in Table 6.1 and expressed as mean (SD).

Table 6.1: Baseline characteristics, physiological and perceptual response during the CPET results

Variables	**Participants (n=11)**
Gender (M:F)	5:6
Age (yr)	32.9 (8.92)
Height (cm)	172.2 (7.9)
Weight (kg)	70.7 (8.3)
BMI ($kg{\cdot}m^2$)	23.8 (1.6)
$\dot{V}O_2$peak ($mL{\cdot}min^{-1}$)	2645.1 (674.07)
$\dot{V}O_2$peak ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$)	36.6 (7.4)
Peak workload, watts	189.5 (44.7)
Peak RER	1.0 (0.1)
Peak VE ($L{\cdot}min^{-1}$)	96.1 (30.3)
Peak HR (bpm)	176.7 (10.7)
End exercise SpO_2	93.1 (2.3)
OUES ($mL{\cdot}min^{-1}$)	1323.6 (311.4)
OUES ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$)	18.6 (3.1)
OUEP ($ml{\cdot}min^{-1}$)	36.8 (5.8)
OUEP ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$)	0.5 (0.1)
Peak RPE-O	16.3 (1.7)
Peak RPE-C	7.3 (2.2)
Peak RPE-L	7.7 (1.74)

Validity of submaximal OUE parameters as predictors of $\dot{V}O_2max$

Measured $\dot{V}O_2max$ ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$) was significantly correlated with $OUES_{50}$ ($r = 0.925$, $r^2 = 0.863$, $p < 0.001$), $OUES_{60}$ ($r =0.925$, $r^2 = 0.861$, $p < 0.001$), $OUES_{70}$ ($r = 0.928$, $r^2 = 0.855$, $p < 0.001$) and $OUES_{80}$ ($r = 0.929$, $r^2 = 0.856$, $p < 0.001$) (Figures 2-5). There was no significant relation between measured $\dot{V}O_2max$ and $OUEP_{60}$ ($r = 0.84$, $r^2 = 0.007$, $p = 0.806$) or $OUEP_{80}$ ($r = 0.84$, $r^2 = 0.007$ $p = 0.806$). Regression analysis was not possible for $OUEP_{50}$ and $OUEP_{70}$, as the relative values for OUEP at 50 and 70% were the same for all participants, and therefore could not be determined.

There was no significant difference between measured $\dot{V}O_2max$ (36.69 ± 7.48) and $\dot{V}O_2max$ predicted by $OUES_{50}$ (36.69 ± 6.93), $OUES_{60}$ (36.69 ± 6.92), $OUES_{70}$ (36.69 ± 6.94) or $OUES_{80}$ (36.69 ± 6.95). There was a significant difference between measured $\dot{V}O_2max$ and $\dot{V}O_2max$ predicted by $OUEP_{60}$ (25.68 ± 2.90), and $OUEP_{80}$ (32.75 ± 3.72). Values for $OUEP_{50}$ and $OUEP_{70}$ could not be determined, as stated previously.

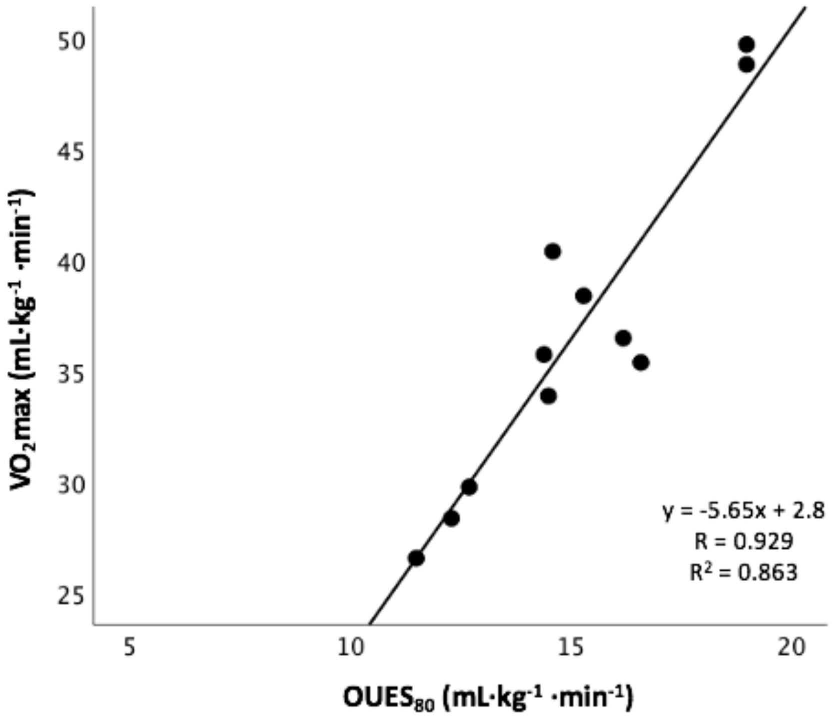


Figure 6.2: Regression analysis for $\dot{V}O_2$max and $OUES_{80}$

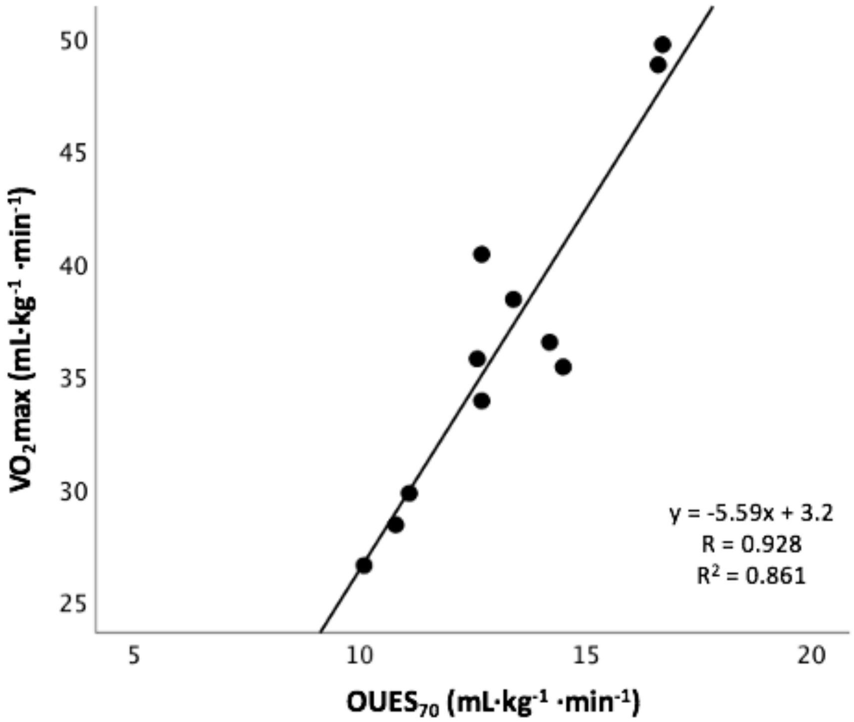


Figure 6.3: Regression analysis for $\dot{V}O_2$max and $OUES_{70}$

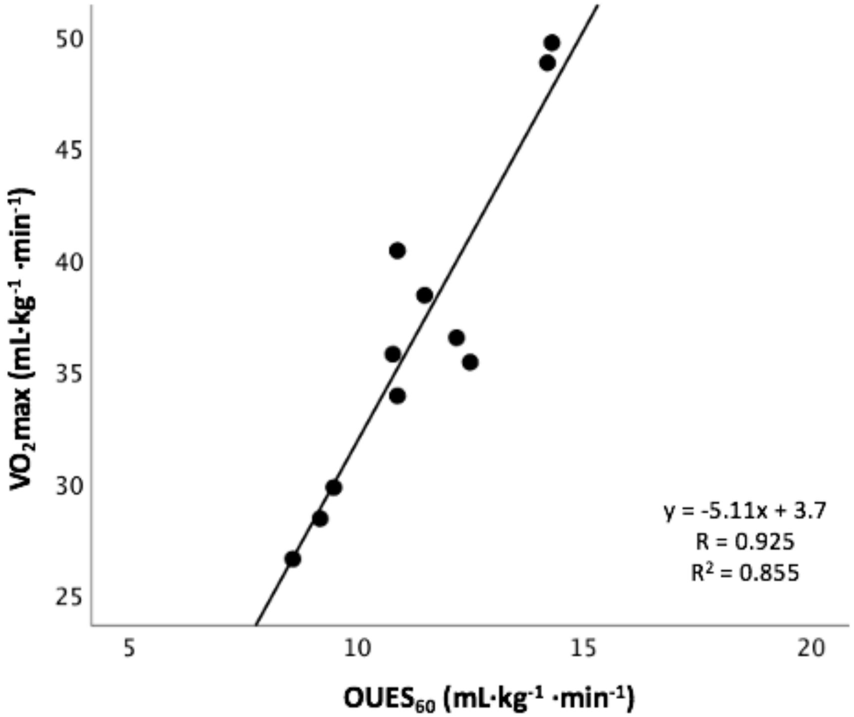


Figure 6.4: Regression analysis for $\dot{V}O_2max$ and $OUES_{60}$

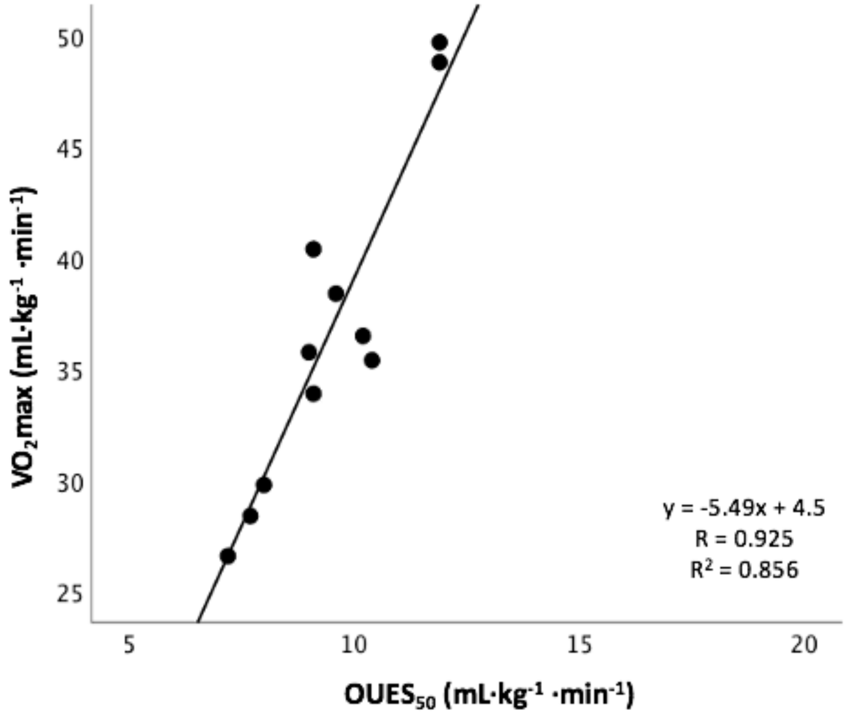


Figure 6.5: Regression analysis for $\dot{V}O_2max$ and $OUES_{50}$

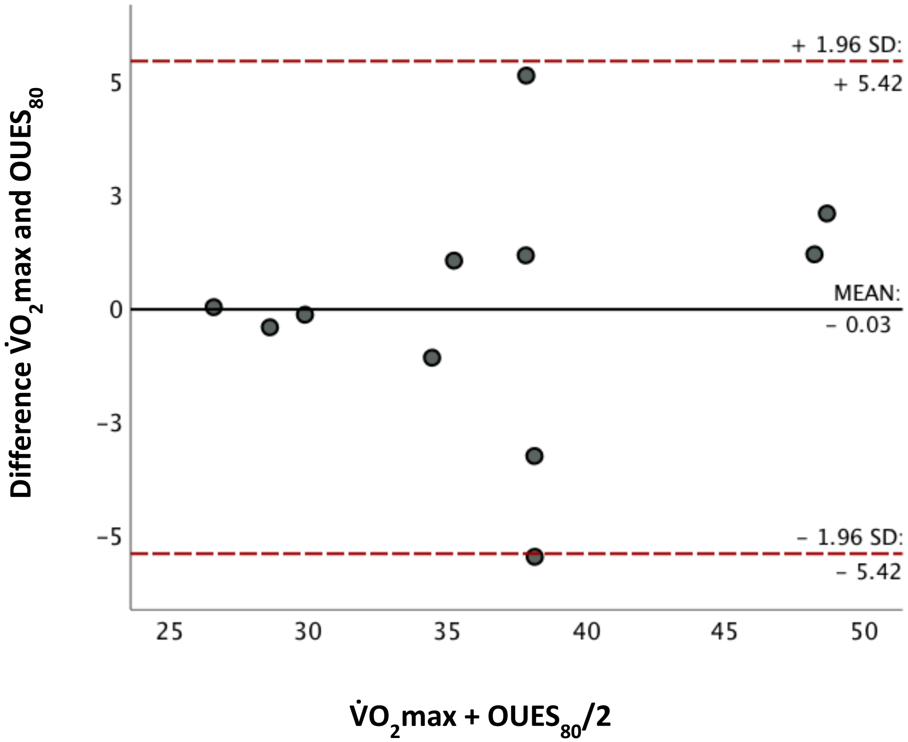


Figure 6.6: Bland Altman plot of two methods ($OUES_{80}$)

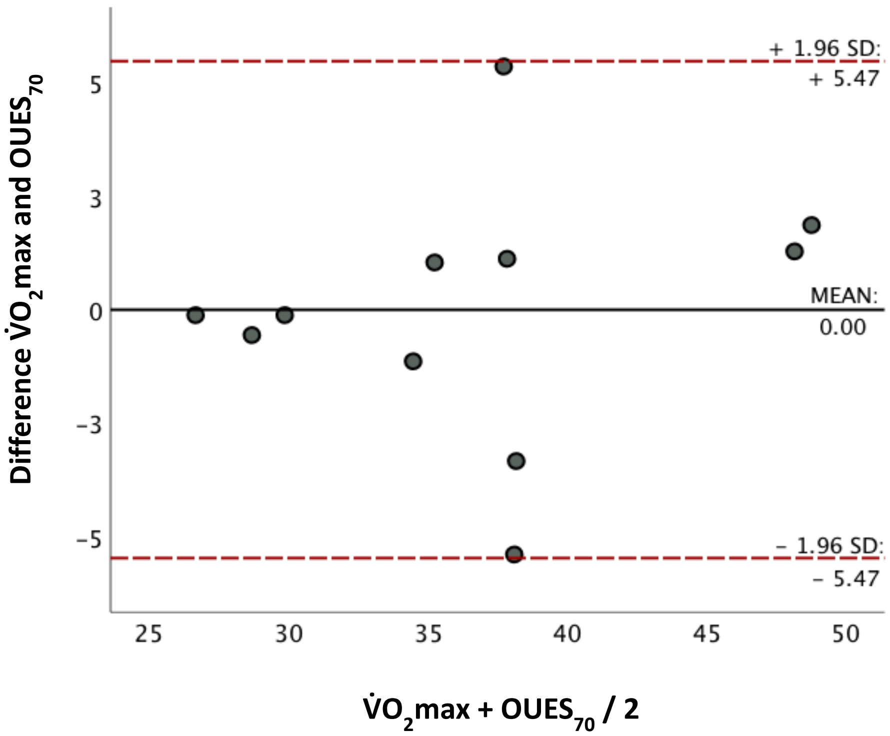


Figure 6.7: Bland Altman plot of two methods ($OUES_{70}$)

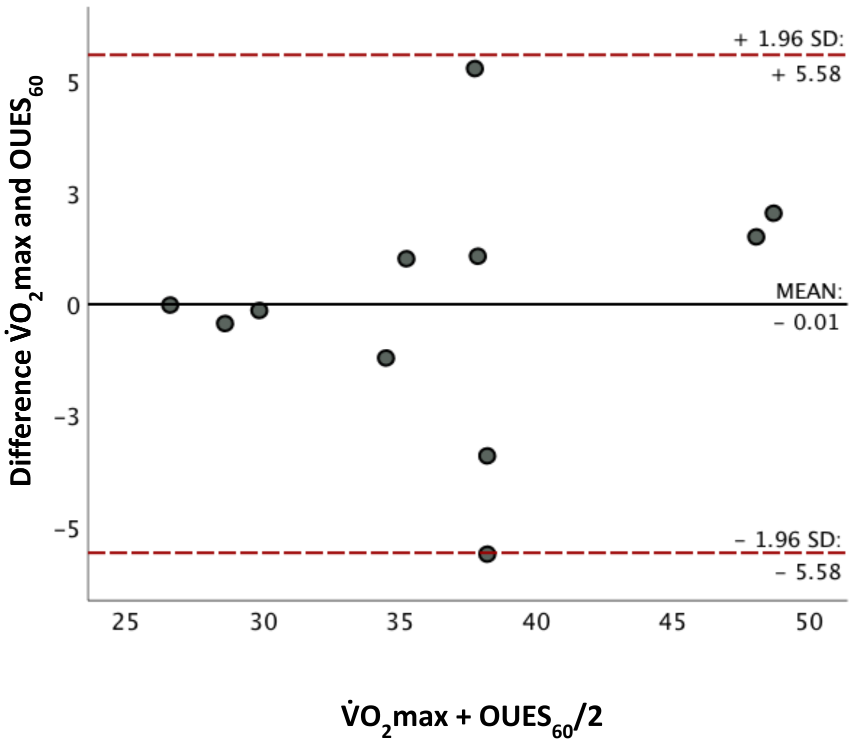


Figure 6.8: Bland Altman plot of two methods ($OUES_{60}$)

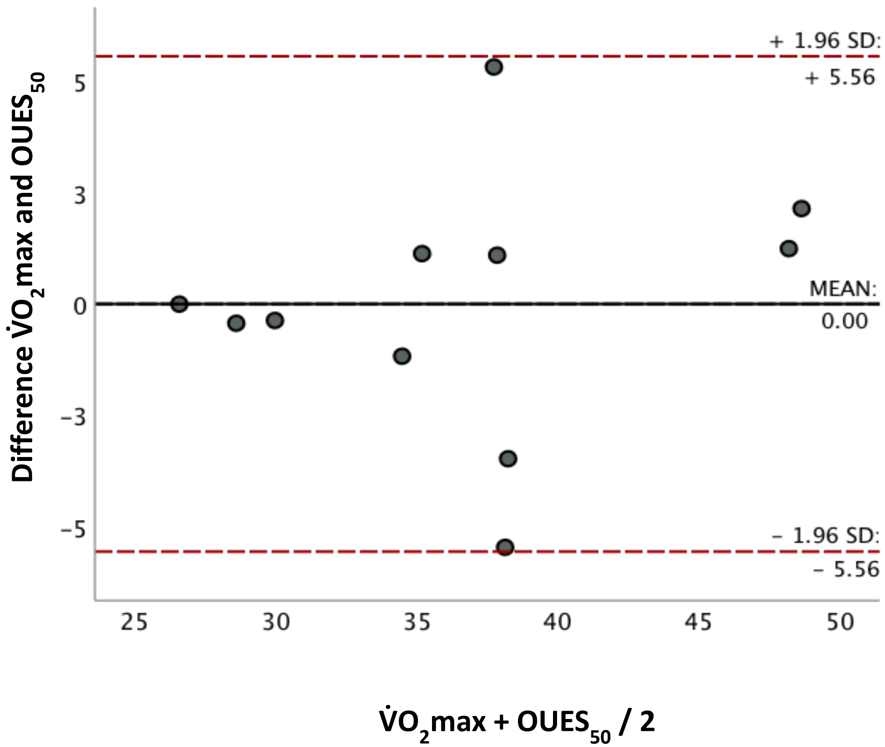


Figure 6.9: Bland Altman plot of two methods ($OUES_{50}$)

Discussion

The present study assessed the concurrent validity of the $OUES_{50-80}$ and the $OUEP_{50-80}$ as predictors of $\dot{V}O_2max$ in an adult CF population. The findings indicate that the OUEP is not a valid submaximal predictor of $\dot{V}O_2max$ in this adult CF cohort. In contrast, OUES is a valid and reliable submaximal predictor of $\dot{V}O_2max$, and can be easily determined in CF patients.

$\dot{V}O_2max$ is the gold standard measurement for determining cardiorespiratory fitness among CF populations. Achieving the effort dependent predetermined criteria for the determination of $\dot{V}O_2max$ during a CPET can be difficult for individuals with excessive dyspnoea and/or a lack of motivation (Sheridan *et al.*, 2021). Importantly, OUES is a submaximal indice of cardiorespiratory function and does not require maximal exertion during exercise (Baba *et al.*, 1996; Sun, Hansen and Stringer, 2012). A higher OUES value is indicative of a higher $\dot{V}O_2$ for a given $\dot{V}_E$ (more efficient).

Previous research investigating the validity of the $OUES_{50-80}$ in adults with CF found $OUES_{80}$ to be a reliable and valid submaximal surrogate for $\dot{V}O_2max$ (Gruet *et al.*, 2010). In the present study, there was no significant difference in the association between $\dot{V}O_2max$ predicted using $OUES_{50}$, $OUES_{60}$, $OUES_{70}$, $OUES_{80}$ and measured $\dot{V}O_2max$. This finding may provide significant clinical utility as it would no longer require pwcf to provide a maximal, or near-maximal, physical effort during CPET. Utilizing the $OUES_{50}$ shows promise for predicting $\dot{V}O_2max$ among patients who experience excessive dyspnoea and/or lack the motivation to reach volitional exhaustion (Tomlinson *et al.*, 2018). Previous research investigating the clinical utility of the OUEP in CF populations involved children and adolescents. Similar to the present study in adults, they found that OUEP was not a valid surrogate for $\dot{V}O_2max$ in children and youth.

Strengths and Limitations

This is the first study to investigate the validity of the OUEP as a submaximal surrogate for $\dot{V}O_2max$ in adults with CF. The results should, however, be interpreted with caution as the small sample size may limit the utility of findings to the wider CF population..

Conclusions

OUES ranging from 50-80% $\dot{V}O_2max$ was found to be a good predictor of $\dot{V}O_2max$ in adults with CF. In contrast, despite promising findings in other clinical populations, the OUEP was a poor predictor of $\dot{V}O_2max$ in adults with CF

Chapter VIII
Discussion

Discussion

Overview of the Research

Discussions for each individual study have been included in the preceding chapters. The aim of this chapter is to contextualise the overall research findings within the existing scientific literature. The purpose of this research was to explore PA from the HCP and pwcf perspective to inform the development of a PA intervention for adults with CF, and to subsequently implement and evaluate its effectiveness.

The onset of Covid-19 significantly impacted the intervention, and the laboratory-based testing. Laboratory-based testing ceased with less than half of the intended participants having completed baseline testing. As the intervention was home-based in nature, and our participants were self-isolating, we were able to continue albeit with a smaller sample size, to assess feasibility rather than effectiveness. The baseline physiological testing data served as an opportunity to explore the CPET data in greater depth, specifically to investigate the utility of the OUES and OUEP as submaximal predictors of maximal aerobic capacity, a relatively understudied physiological parameter in this patient group.

In summary, the findings emphasize the limited practice of PA prescription by Irish HCP for their CF patients, despite deeming PA prescription an integral component of their professional role. One of the most common barriers challenging HCP prescription of PA is the poor availability of PA programmes to refer their patients to. Lack of patient motivation and compliance were among the other most commonly reported barriers. Low energy, exercise-related self-consciousness, time and the weather were the most frequently reported barriers preventing sustained participation in PA among pwcf. Motivational quality, enjoyment, perceived competence and valued outcomes were identified as important facilitators of long-term PA compliance in this patient group. The findings from this formative research informed the development of the PA intervention underpinned by theories of behaviour change, which included a 1:1 exercise consultation, a remotely-supervised, home-based, self-regulated PA programme, use of technology for self-monitoring and real-time feedback, and a follow-on maintenance phase to evaluate the long-term adoption of learned PA behaviours. The intervention was evaluated using a randomized-controlled design. Results from the intervention provide preliminary evidence to support the feasibility of theoretically-informed, home-based, self-regulated and technology-enabled exercise in adult CF populations. Future research that investigates the effectiveness of the intervention in a larger adult CF population group is warranted.

Cystic Fibrosis and Exercise Intolerance

CF is the most prevalent genetic disease among Caucasian populations and is caused by mutations in the CFTR gene which primarily affect the pulmonary, gastrointestinal and reproductive systems (Shei, 2019). Defects in the CFTR gene promote airway dehydration and the production of viscous mucus, resulting in chronic inflammation and recurrent infection that causes irreversible lung damage and progressive airway obstruction. Exercise intolerance is an established characteristic associated with CF populations, and is dependent on disease progression (Rand, 2012).

Maximal aerobic capacity ($\dot{V}O_2max$) assessed during a CPET is an excellent integrative measure of the cardiovascular, pulmonary and metabolic systems and is considered the gold standard for assessing aerobic fitness. It is routinely assessed to follow the evolution of CF disease and for the prescription of physical exercise (Vendrusculo, 2019). Some pwcf may, however, experience difficulty achieving a true maximal effort during CPET due to aforementioned effort-dependent influencing factors such as motivation, pain and shortness of breath (Tomlinson, 2018; Gruet, 2010). A number of submaximal parameters, such as the OUES and OUEP, have been proposed as potential alternatives to predict maximal aerobic capacity in patients with chronic disease (Baba, 1996; Sun, 2012).

The clinical utility of the OUES and OUEP as potential surrogates for maximal aerobic capacity has been demonstrated in individuals with cardiovascular disease (Davies 2006), obesity (Onofre, 2017), lung cancer (Yakal, 2018), pulmonary embolism (Liu, 2014) and patients scheduled for lung surgery (Van Den Broek, 2019). Previous research has found that the OUES at 80% of the maximal CPET test duration to be the most valid and reliable predictor of maximal aerobic capacity in CF populations (Gruet, 2010). In contrast, there was no significant difference between $\dot{V}O_2max$ predicted using $OUES_{50}$, $OUES_{60}$, $OUES_{70}$, $OUES_{80}$ and measured $\dot{V}O_2max$ in the present study. This finding may provide novel clinical utility as it would no longer require pwcf to provide a maximal, or near maximal, physical effort during CPET, removing barriers related to motivational quality and exercise-induced and/or excessive dyspnoea. Previous research investigating the clinical utility of the OUEP in CF populations involved children and adolescents, and similar to the findings in Study V in adults with CF, they found that OUEP was not a valid surrogate at any stage during the test duration for $\dot{V}O_2max$ (Tomlinson, 2018).

Clinical parameters such as, poor FEV_1 values, low BMI, chronic airway inflammation and infection, and CF-related diabetes were once the primary predictors of premature mortality in pwcf (Hayllar, 1997). However, parameters such as VO_2peak, and change in VO_2peak over time, Work Rate peak, the respiratory equivalent for Oxygen (VE/VO_2), and the breathing reserve index at the ventilatory threshold (VE/MVV), extrapolated from CPET data have been validated as more precise prognostic indicators for longevity in CF populations and warrant further investigation (Nixon, 1992; Moorcroft, 1997; Hebestreit, 2019).

Cystic Fibrosis and Exercise Prescription

Given the high prognostic value of aerobic fitness for mortality and QoL in this patient group (Nixon, 1992; Vendrusculo, 2018) regular participation in PA and/or exercise training is highly recommended. It has been shown that pwcf can increase their aerobic fitness with regular exercise training, regardless of disease severity (Rand, 2012). Regular and sustained participation in PA can provide a non-invasive means for delaying or preventing the onset of secondary co-morbidities, which is of particular importance for the ageing CF population (Andersen, 2019). The European CF Society Exercise Working Group have published a set of consensus guidelines for use when prescribing exercise to pwcf (Swisher, 2015). However, Study I found that although HCP viewed exercise prescription as an integral component of their professional role, few were familiar with the current consensus guidelines or were confident in their ability to accurately prescribe PA to CF populations. Study I is the first to report on the PA prescription practices of HCP in the delivery of CF care in Ireland.

A recent cross-sectional study evaluated the perceptions of PA among CF HCP across 12 countries and found that despite HCP rating the importance of PA in the management of

CF highly, recommendations regarding PA prescription and promotion remained variable with little consistency within locations or age groups (Denford, 2020). HCP reported the need for greater access to training to maximize their ability to prescribe and promote PA to their CF patients (Denford, 2020). Similar studies conducted among CF HCP in the UK and Germany found that 100% and 87% of respondents, respectively, suggested that they would benefit from additional CF-specific education, training and resources for prescribing PA (Lobelo, 2016; Barker, 2004). These findings agree with those in the current thesis, as many HCP suggested the development of a formal and standardized education and training programme as a strategy to optimize their ability to prescribe PA to their CF patients.

It is important to acknowledge that HCP play an integral role in the delivery and promotion of PA advice to their CF patients, and that there is a greater likelihood of patient in engagement in PA behaviours following pro-active counselling by HCP (Speake, 2016; Tomasone, 2014). Recent research evaluating PA perceptions among pwcf has highlighted that although many pwcf rate the importance of PA highly, substantial variability remains in relation to the quality of the clinical support available (Denford, 2020). Condition-specific barriers to PA such as excessive dyspnoea, lack of energy and embarrassment exercising in public due to symptom-limitations, are commonly reported by pwcf (Dwyer, 2020; Burnett, 2020; White, 2007). However, it appears this patient group are not adequately educated or reassured on how to overcome such disease-related barriers by HCP. These findings further emphasize the need to develop a formal, standardized and internationally recognised education and training programme for CF HCP, regarding PA promotion and prescription for this patient group.

Cystic Fibrosis and Physical Activity/Exercise Adherence

Lack of patient motivation and compliance to PA advice were among the most commonly reported barriers to PA prescription by HCP. This finding is noteworthy as adherence to targeted therapies in this patient group is challenging, often sub-optimal and typically varies according to treatment type, mode of treatment administration, age, season, time and method of adherence measurement (Narayanan, 2017; Moran & Bradley, 2010). Adherence to prescribed PA and/or exercise training in CF populations is generally lower compared with other treatments, and is reportedly between 57% and 88%, which highlights significant variability (O'Donohoe, 2014; Moran & Bradley, 2010). To gain a greater insight into the aforementioned barriers reported by HCP, we sought to understand the factors challenging motivation and compliance from the pwcf perspective in Study II.

To our knowledge, Study II is the first to document the factors that influence PA participation among adults with CF in the Republic of Ireland. Participants reported a combination of internal and external barriers to sustained PA participation, including low energy, exercise-related self-consciousness, time and the weather. In contrast, this patient group reported enjoyment and perceived competence, coupled with feelings of accomplishment and affect regulation as motivating factors for long-term adherence to PA.

Many participants, particularly those who were more intrinsically motivated, reported a preference for exercising in their home environment as opposed to participating in gym-based PA programmes due to the perceived heightened risk of cross-infection and illness-related embarrassment. This finding is noteworthy, as home-based interventions have the potential to reduce feelings of low perceived competence, exercise-related self-consciousness and remove barriers related to time and the changing weather, while providing pwcf with the opportunity to participate in a mode of PA that they enjoy and feel confident doing (Ryan, 2000). When viewed concurrently, the findings from studies I and II indicate that pwcf experience an unmet need for personalized PA prescription, that takes account of individual barriers, motivators and preferences for sustained PA participation, shifting from the almost one-size-fits-all approach to PA prescription currently adopted by CF HCP in Ireland.

To the best of the authors' knowledge, no previous research has involved both HCP and patients in the intervention development process for CF populations. The Medical Research Council recommend the involvement of relevant end-users during the intervention development process to ensure that the research is meaningful and relevant to the intended population (MRC, 2019). In the context of this research, the involvement of CF HCP and pwcf was important to further develop our understanding of the barriers that challenge PA prescription from the HCP perspective, and compliance to PA advice from the patient perspective.

Pwcf expressed a preference for home-based PA. Incorporating technology-enabled intervention components that provide real-time feedback as tools for self-monitoring has the potential to change how pwcf engage with exercise services. Including telehealth technologies in the intervention development process can also aid in ameliorating factors associated with facility-based PA that may negatively affect participation, such as the risk of cross-infection and exercise-related self-consciousness (Tomlinson, 2020; Cox, 2015). Telehealth technologies and remotely-delivered PA can also assist patients in overcoming external barriers such as time and the weather. Previous research suggests that pwcf are willing to adopt and adhere to such telehealth technologies, and that the use of an online platform to engage patients in PA is feasible and acceptable (Tomlinson, 2020; Cox, 2015). For example, using the internet as a means to deliver a PA intervention allows participants the convenience of accessing the programme at a time and place of their choosing, and does not place a geographical limitation on participation (Cox, 2015). Studies evaluating patient preferences relating to internet-based PA programmes suggests incorporating the use of behavioural strategies such as feedback, goal-setting and self-monitoring tools coupled with easy programme accessibility incorporating simple interactive features such as; the ability to document, track and monitor personal progress and the ability to access expert advice via e-mail (Cox, 2015). A silver lining from the Covid-19 pandemic has seen an acceleration in the development and availability of home-based technologies. This rapid advancement is facilitating the adoption of home-based, technology-enabled PA programmes for all.

Participants in Study II reported low energy and lack of enjoyment as barriers challenging their participation in sustained PA. According to the hedonic theory of motivation, people are likely to repeat an activity if they derive pleasure, a sense of energy, or enjoyment from participation in the activity (Ekkekakis, 2009). Conversely, if people derive displeasure, a sense of exhaustion or a lack of enjoyment, the likelihood of repeating the activity would be reduced. Exercise prescription procedures typically involve the titration of exercise intensity, to elicit a predetermined HR, VO_2, RPE or blood lactate level (Hughes, 2011). However, the culture of exercise prescription is often deemed highly controlling and aversive, and contributes to the establishment of negative attitudes towards PA participation

(Ekkekakis, 2009). Longitudinal studies report that participants tend to deviate from prescribed exercise intensities in favour of their apparently preferred levels (Ekkekakis, 2003). In contrast, empowering individuals to self-regulate their exercise intensity may encourage the development of intrinsic motivation, a central element in promoting adherence to exercise and an increase in enjoyment and participation levels (Cox, 2003).

Intervention Development

To the best of the authors' knowledge, the intervention developed in the current thesis is the first to combine home-based, self-regulated and technology-enabled exercise with evidence-based theories of behaviour change to enhance adherence to PA among adults with CF. The intervention development process used a combination of the formative research conducted in Studies I and II along with a review of the current literature to inform the design. Interventions that are underpinned by theories of behaviour change have the potential to increase the efficacy of PA interventions for CF populations, as they provide valuable insight into the relation between targeted constructs and their influence on the chosen behaviour (Bluethmann, 2017). Incorporating theories of behaviour change during the intervention development process is a unique method employed to address the concerns regarding barriers and compliance in Studies I and II, as previous PA interventions for CF populations have failed to do so. Empowering individuals to self-regulate their PA to meet the current consensus PA guidelines is also a novel, and relatively understudied, approach to improving health outcomes in CF populations.

To the best of the authors' knowledge, this study is the first to explore the feasibility of theoretically-informed, home-based, self-regulated and technology-enabled PA among adults with CF. Four areas of focus were included in the assessment of feasibility; implementation, demand, acceptability and practicality, as outlined by Bowen (2009). The PA intervention was feasible as it i) was easily implemented despite the changing environment due to Covid-19, ii) sustained high levels of engagement throughout, iii) was well accepted in terms of enjoyment, and iv) received positive responses regarding usability and practicality. Importantly, the intervention was safe, as no adverse events were reported. High-quality feasibility trials have the potential to advance the future success of clinical trials in PA (El-kotob, 2018). Feasibility trials are of substantial significance to assess intervention fidelity, participant experience and adherence prior to conducting a large trial to evaluate effectiveness. In the context of the current research, this study demonstrated that theoretically-informed, home-based, self-regulated and technology-enabled PA programmes can be successfully used to engage pwcf in regular PA. The majority of the participants responded positively to the PA programme, suggesting that this approach may be feasible in practice to deliver future PA interventions.

Findings from the remotely-supervised phase of the intervention indicate a potential positive trend in LIPA over the 12-week period. Encouraging an increase in daily LIPA may be a more achievable goal for pwcf unable to meet the recommended guidelines for MVPA as a consequence of symptom-limitations and deconditioning. Indeed, emerging evidence is demonstrating that independent of MVPA, LIPA is associated with various cardiometabolic and mental health outcomes in individuals with chronic disease (Amagasa, 2018; Loprinzi, 2016). Recent research has outlined the association between objectively measured LIPA and health outcomes after adjusting for MVPA in adults and found that regular participation in

LIPA promotes favourable outcomes for longevity, mortality, waist circumference, fat mass, triglycerides, diabetes, metabolic syndrome, systemic inflammation, mental health, well-being, medical multimorbidity and risk of hospitalization (Amagasa, 2018; Chastin, 2019; Donaire-Gonzalez et al., 2015; Fuezeki et al., 2017). These findings have significant implications for the ageing CF population, as it is well established that the prevalence of CF-related diabetes increases with age, and its presence often leads to poorer outcomes such as increased risk of pulmonary exacerbations, sharper decline in pulmonary function and premature mortality (Prentice, 2021; Andersen, 2006). Empowering pwcf to incorporate LIPA into their daily routines has the potential to dramatically improve health outcomes over time, particularly as CF begins its transition from a once life-limiting childhood disease to a long-term adulthood condition.

Conversely, during the 6-week maintenance phase there was a marked decrease in LIPA, following the removal of supervision and weekly communication. This finding is interesting when viewed concurrently with the feedback interview responses. Some of the participants who reported feeling as though they had participated in less PA during the maintenance phase also reported elements of introjected regulation, such as feeling obligated or driven by guilt to participate in PA once the supervision had been removed, rather than having an internal drive to improve health outcomes. Incorporating behavioural counselling techniques such as motivational interviewing, when designing interventions, may have the potential to increase autonomous motivation, and decrease external regulation, toward long-term PA participation among pwcf, and has been recommended in other patient cohorts (Denford, 2020). Motivational interviewing can be defined as a person-centred directive counselling style used to address hesitancy about behaviour change by placing emphasis on patients producing their own argument for change (O'Halloran, 2014). Interventions that incorporate elements of motivational interviewing can significantly improve weight loss, PA and cardiovascular disease risk factors, and these positive health outcomes can be sustained at 1-year post-intervention (Hardcastle, 2013). It is acknowledged that motivational interviewing can lead to modest improvements in PA in people with chronic diseases, and there may be benefit in incorporating it into routine clinical practice (O'Halloran, 2014).

The findings from the current research provide meaningful evidence that is specific to the Irish context and advocates for a patient-centred, individualised and theory-driven approach to developing PA interventions for CF populations. Findings from the current research suggest that there is scope to develop a continuing professional development programme for CF HCP, to enhance the knowledge around prescribing and promoting PA to this patient group. Additional training for HCP in the use of activity counselling, brief motivational interviewing and techniques to foster the increased importance of PA and confidence to exercise may have the potential to enhance autonomous motivation and long-term PA engagement in CF populations, and is warranted for HCP working in CF care. Further, as HCP reported limited availability of PA programmes to refer their patients to as a prominent barrier challenging PA prescription, there is scope to create a referral pathway between hospital-based HCP and community-based exercise professionals (EP). The establishment of this referral pathway could ameliorate the barrier reported by HCP for limited time with patients, and also remove the negative connotations associated with PA prescription in the clinical setting from the pwcf perspective. This novel pathway also has the potential to increase accessibility to routine CPET assessments by EPs for pwcf to monitor both disease and PA progression, as this is currently not routinely conducted in hospital settings in Ireland.

Despite the intervention being underpinned by theories of behaviour change and driven by the MRC framework for the development, implementation and evaluation of complex interventions, varying motivational qualities existed among participants, evident during the feedback interviews (MRC, 2019). This highlights the importance of individually-tailoring PA interventions for patients with chronic diseases, as CF lung disease is multifactorial in nature. For instance, a pwcf who has had a recent period of ill-health, or is overcoming a hospital-stay for a pulmonary exacerbation may require a more sensitive, supervised approach, requiring more detailed exercise prescription and increased encouragement, guidance and support to overcome internal barriers to PA participation. However, for those individuals who are more 'ready' to change their PA behaviours, action-orientated, strategies such as goal-setting and action-planning may be implemented, along with the encouragement to self-regulate their exercise mode and intensity, with advice on how to incorporate PA into their daily lives autonomously. The current research suggests that due to the complexity of CF lung disease, a one-size-fits-all approach is not feasible, and that the development of an individually-tailored, PA prescription continuum which enables individuals to move freely from one end of the continuum to the other dependent on their personal circumstance, may hold promise in clinical practice, to cater for patients at every stage of the CF journey.

It is important to acknowledge that the shift to a more patient-centric PA prescription continuum may place a strain on the time commitments of the HCP. EP are well-positioned to adopt this role as they are educated in PA promotion and prescription for chronic disease cohorts, and have extensive training in conducting CPET and analysing the associated results. Many EP are also trained in behavioural counselling techniques such as motivational interviewing. The development of a referral pathway between HCP and EP may remove the patient-perceived pressures associated with hospital-based clinic appointments, and empower pwcf to incorporate PA into their daily lives through lifestyle management in the community.

Summary

Physical activity and exercise training have been acknowledged as a cornerstone in the management of CF. To date, PA interventions for this patient group have adopted a one-size-fits-all approach, which represents an important missed opportunity to maximise patient engagement. The current research provides meaningful evidence that is specific to the Irish context, which can be used to advocate for increased education and training support for CF HCP to enhance PA prescription-related knowledge and confidence, and the inclusion of theoretically-informed, home-based, self-regulated and technology-enabled exercise to ameliorate barriers associated with poor PA compliance in this patient group. The novel approach to intervention development enabled the development of a PA intervention, underpinned by behaviour change theories that was patient-orientated and evidence-based. Preliminary findings from the randomized-controlled feasibility intervention offer promise and warrant further investigation.

Immediate Recommendations

- The development of a formal, standardized and recognized CPD training course for CF HCP to enhance their knowledge of PA promotion and prescription for this patient group.
- The establishment of a referral pathway between hospital-based CF HCP and community-based EP, to increase the availability of and accessibility to routine CPET assessments and personalised PA prescription.
- Encourage the utilization of submaximal CPET parameters, such as the OUES, in patients who are unable to complete maximal effort exercise. Incorporating submaximal parameters to routine CPET testing will ameliorate barriers such as lack of motivation, fear, and excessive dyspnoea for a large cohort of pwcf.

Future Recommendations

- Future research should aim to evaluate the effects of a formal and standardized PA promotion and prescription education and training programme on HCP prescription practices
- Future PA interventions should aim to incorporate a PA prescription continuum, whereby the HCP/EP can assess the pwcf readiness to change and motivational quality before assigning the appropriate PA prescription:
    i. For pwcf who are experiencing introjected or external regulation, the HCP/EP can prescribe a more detailed PA intervention; focusing on educating the individual on the benefits of PA for pwcf, individually-tailoring their PA programme to incorporate activities that are enjoyed by the individual,

increasing the frequency of communication and providing a more person-centred support structure

ii. For pwcf who are deemed 'ready to change', who exhibit autonomous or intrinsic motivation, the HCP/EP can adopt a less prescriptive approach, empowering the individual to self-regulate their mode and intensity of PA to enhance enjoyment and long-term maintenance

- Future research should aim to conduct a further feasibility trial, taking the findings from the present thesis and engaging with relevant stakeholders (including; patients with CF, their families, HCP, exercise physiologists/exercise scientists, and the national charity CF Ireland), to revise and refine the programme prior to full-scale evaluation
- Following this, subsequent research should involve randomized-controlled trials, that incorporate the proposed PA prescription continuum, to investigate the effectiveness of home-based, self-regulated and technology-enabled PA interventions in a larger cohort of adult CF populations, and include:

  i. Individually-tailored education and motivational interviewing techniques to adequately support and foster the adoption of PA behaviours that can be sustained post-intervention

  ii. CPET assessment at baseline, post 12-week remotely-supervised phase and upon completion of the maintenance phase

- Future research should seek to focus on individual patients' unique CFTR mutations, and in particular, individual performance enhancing polymorphisms, when prescribing PA to enhance personalised prescription.

Conclusion

Despite the established beneficial effects of PA for CF populations, compliance and prescription to PA programmes in this patient group remains varied. HCP require further education and training to provide adequate PA promotion, prescription and behavioural counselling to this patient group. The current thesis used the MRC guidelines for the development and evaluation of complex interventions, by incorporating end-user and stakeholder perspectives, a review of the current literature, and appropriate behaviour change theories to develop a novel theoretically-informed, home-based, self-regulated and technology-enabled PA intervention. This intervention was deemed feasible, and identified a potential positive trend in LIPA during the remotely-supervised phase, which warrants further investigation in a larger adult CF cohort. As CF shifts from being a once life-limiting childhood disease to a long-term adulthood condition, there is an urgent need to identify effective approaches to implementing individually-tailored, evidence-based and behaviour change theory-driven PA services to optimize adherence and subsequent health outcomes in the long-term for this patient group. Future trials are required to refine the current intervention, with relevant stakeholder engagement, to be assessed for feasibility in a larger sample size, prior to full-scale evaluation.

References

References

Ajzen, I. (1991) 'The Theory of Planned Behavior', *Organizational Behavior and Human Decision Processes*, 50, pp. 179–211. doi: 10.1016/0749-5978(91)90020-T.

Akkerman, M. *et al.* (2010) 'The oxygen uptake efficiency slope: what do we know?', *Journal of Cardiopulmonary Rehabilitation and Prevention*, 30(6), pp. 357–373. doi: 10.1097/HCR.0b013e3181ebf316.

Almajed, A. and Lands, L. C. (2012) 'The evolution of exercise capacity and its limiting factors in Cystic Fibrosis', *Paediatric Respiratory Reviews*, 13(4), pp. 195–199. doi: 10.1016/j.prrv.2012.01.001.

Amagasa, S. *et al.* (2018) 'Is objectively measured light-intensity physical activity associated with health outcomes after adjustment for moderate-to-vigorous physical activity in adults? A systematic review', *The International Journal of Behavioral Nutrition and Physical Activity*, 15. doi: 10.1186/s12966-018-0695-z.

Andersen, H. U. *et al.* (2006) 'Cystic Fibrosis–Related Diabetes: The presence of microvascular diabetes complications', *Diabetes Care*, 29(12), pp. 2660–2663. doi: 10.2337/dc06-0654.

Anderson, E. and Durstine, J. L. (2019) 'Physical activity, exercise, and chronic diseases: A brief review', *Sports Medicine and Health Science*, 1(1), pp. 3–10. doi: 10.1016/j.smhs.2019.08.006.

Armitage, C. J. (2009) 'Is there utility in the transtheoretical model?', *British Journal of Health Psychology*, 14(2), pp. 195–210. doi: 10.1348/135910708X368991.

Atkins, L. *et al.* (2017) 'A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems', *Implementation Science*, 12(1), p. 77. doi: 10.1186/s13012-017-0605-9.

Ayotte, B. J., Margrett, J. A. and Hicks-Patrick, J. (2010) 'Physical Activity in Middle-aged and Young-old Adults: The Roles of Self-efficacy, Barriers, Outcome Expectancies, Self-regulatory Behaviors and Social Support', *Journal of Health Psychology*, 15(2), pp. 173–185. doi: 10.1177/1359105309342283.

Baba, R. *et al.* (1996) 'Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise', *Journal of the American College of Cardiology*, 28(6), pp. 1567–1572. doi: 10.1016/s0735-1097(96)00412-3.

Baba, R. (2000) 'The Oxygen Uptake Efficiency Slope and Its Value in the Assessment of Cardiorespiratory Functional Reserve', *Congestive Heart Failure*, 6(5), pp. 256–258. doi: https://doi.org/10.1111/j.1527-5299.2000.80164.x.

Barker, M. *et al.* (2004) 'Exercise testing and training in German CF centers', *Pediatric Pulmonology*, 37(4), pp. 351–355. doi: 10.1002/ppul.10430.

Bar-Or, O. (2000) 'Home-based exercise programs in cystic fibrosis: Are they worth it?', *The Journal of Pediatrics*, 136(3), pp. 279–280. doi: 10.1067/mpd.2000.104388.

Barron, A. *et al.* (2016) 'Oxygen Uptake Efficiency Slope and Breathing Reserve, Not Anaerobic Threshold, Discriminate Between Patients With Cardiovascular Disease Over Chronic Obstructive Pulmonary Disease', *Jacc. Heart Failure*, 4(4), pp. 252–261. doi: 10.1016/j.jchf.2015.11.003.

Barry, S. C. and Gallagher, C. G. (2003) 'Corticosteroids and skeletal muscle function in cystic fibrosis', *Journal of Applied Physiology (Bethesda, Md.: 1985)*, 95(4), pp. 1379–1384. doi: 10.1152/japplphysiol.00506.2002.

Basu, S., Mitra, M. and Ghosh, A. (2013) 'Evaluation of Sweat Production by Pilocarpine Iontophoresis: A Noninvasive Screening Tool for Hypohidrosis in Ectodermal Dysplasia', *Indian Journal of Clinical Biochemistry*, 28(4), pp. 433–435. doi: 10.1007/s12291-013-0334-z.

Beaudoin, N. *et al.* (2017) 'Combined Exercise Training Improves Glycemic Control in Adult with Cystic Fibrosis', *Medicine & Science in Sports & Exercise*, 49(2), pp. 231–237. doi: 10.1249/MSS.0000000000001104.

Beleigoli, A. M. *et al.* (2018) 'Using the Behaviour Change Wheel for Designing an Online Platform for Healthy Weight Loss - "POEmaS"', *Studies in Health Technology and Informatics*, 254, pp. 1–10.

Belman, M. J. (1993) 'Exercise in patients with chronic obstructive pulmonary disease.', *Thorax*, 48(9), pp. 936–946. doi: 10.1136/thx.48.9.936.

Benson, L. N. *et al.* (1984) 'Radionuclide assessment of right and left ventricular function during bicycle exercise in young patients with cystic fibrosis', *The American Review of Respiratory Disease*, 130(6), pp. 987–992. doi: 10.1164/arrd.1984.130.6.987.

Bergeron, C. and Cantin, A. M. (2019) 'Cystic Fibrosis: Pathophysiology of Lung Disease', *Seminars in Respiratory and Critical Care Medicine*, 40(6), pp. 715–726. doi: 10.1055/s-0039-1694021.

Bland, J. M. and Altman, D. G. (2010) 'Statistical methods for assessing agreement between two methods of clinical measurement', *International Journal of Nursing Studies*, 47(8), pp. 931–936. doi: 10.1016/j.ijnurstu.2009.10.001.

Bluethmann, S. M. *et al.* (2017) 'Use of Theory in Behavior Change Interventions', *Health Education & Behavior: The Official Publication of the Society for Public Health Education*, 44(2), pp. 245–253. doi: 10.1177/1090198116647712.

Bompadre, S. G. *et al.* (2007) 'G551D and G1349D, two CF-associated mutations in the signature sequences of CFTR, exhibit distinct gating defects', *The Journal of General Physiology*, 129(4), pp. 285–298. doi: 10.1085/jgp.200609667.

Bongers, B. C. *et al.* (2012) 'Validity of the Oxygen Uptake Efficiency Slope in Children With Cystic Fibrosis and Mild-To-Moderate Airflow Obstruction', *Pediatric Exercise Science*, 24(1), pp. 129–141. doi: 10.1123/pes.24.1.129.

Bove LA. Increasing Patient Engagement Through the Use of Wearable Technology. The Journal for Nurse Practitioners. 2019; 15(8): 535-539

Bowen, D. J. *et al.* (2009) 'How We Design Feasibility Studies', *American journal of preventive medicine*, 36(5), pp. 452–457. doi: 10.1016/j.amepre.2009.02.002.

Brannan, M. *et al.* (2019) 'Moving healthcare professionals - a whole system approach to embed physical activity in clinical practice', *BMC medical education*, 19(1), p. 84. doi: 10.1186/s12909-019-1517-y.

Braun, V. and Clarke, V. (2006) 'Using thematic analysis in psychology', *Qualitative Research in Psychology*, 3(2), pp. 77–101. doi: 10.1191/1478088706qp063oa.

Breen, L. and Aswani, N. (2012) 'Elective versus symptomatic intravenous antibiotic therapy for cystic fibrosis', *Cochrane Database of Systematic Reviews*, (7). doi: 10.1002/14651858.CD002767.pub2.

Brice, P., Jarrett, J. and Mugford, M. (2007) 'Genetic screening for cystic fibrosis: An overview of the science and the economics', *Journal of Cystic Fibrosis*, 6(4), pp. 255–261. doi: 10.1016/j.jcf.2007.02.002.

Britton, F. (2011) *Physiological and perceptual responses during self-regulated exercise in children with cystic fibrosis*. masters. Dublin City University. Available at: http://doras.dcu.ie/16633/ (Accessed: 27 May 2021).

Broek, L. V. D. *et al.* (2019) 'A new submaximal prediction model of VO2max in lung surgery patients using the Oxygen Uptake Efficiency Slope (OUES)', *European Respiratory Journal*, 54(suppl 63). doi: 10.1183/13993003.congress-2019.PA1638.

Brown, S. D., White, R. and Tobin, P. (2017) 'Keep them breathing: Cystic fibrosis pathophysiology, diagnosis, and treatment', *Journal of the American Academy of Physician Assistants*, 30(5), pp. 23–27. doi: 10.1097/01.JAA.0000515540.36581.92.

Burgel, P.-R. *et al.* (2015) 'Future trends in cystic fibrosis demography in 34 European countries', *The European Respiratory Journal*, 46(1), pp. 133–141. doi: 10.1183/09031936.00196314.

Burnett, D. M., Barry, A. N. and Mermis, J. D. (2020) 'Physical Activity Level and Perception of Exercise in Cystic Fibrosis', *Respiratory Care*, 65(4), pp. 500–506. doi: 10.4187/respcare.07193.

Burtin, C. *et al.* (2013) 'Impact of exacerbations of cystic fibrosis on muscle strength', *Respiratory Research*, 14(1), p. 46. doi: 10.1186/1465-9921-14-46.

Buys, R. *et al.* (2016) 'Prognostic value of the post-training oxygen uptake efficiency slope in patients with coronary artery disease', *European Journal of Preventive Cardiology*, 23(13), pp. 1363–1371. doi: 10.1177/2047487316643446.

Cabanac, M. (1986) 'Performance and perception at various combinations of treadmill speed and slope', *Physiology & Behavior*, 38(6), pp. 839–843. doi: 10.1016/0031-9384(86)90051-x.

Cabanac, M. and Leblanc, J. (1983) 'Physiological conflict in humans: fatigue vs. cold discomfort', *The American Journal of Physiology*, 244(5), pp. R621-628. doi: 10.1152/ajpregu.1983.244.5.R621.

Cane, J., O'Connor, D. and Michie, S. (2012) 'Validation of the theoretical domains framework for use in behaviour change and implementation research', *Implementation Science*, 7(1), p. 37. doi: 10.1186/1748-5908-7-37.

Cantwell, M. *et al.* (2018) 'Healthcare professionals' knowledge and practice of physical activity promotion in cancer care: Challenges and solutions', *European Journal of Cancer Care*, 27(2), p. e12795. doi: 10.1111/ecc.12795.

Cantwell, M. *et al.* (2020) 'Physical Activity Across the Cancer Journey: Experiences and Recommendations From People Living With and Beyond Cancer', *Physical Therapy*, 100(3), pp. 575–585. doi: 10.1093/ptj/pzz136.

Carbonera, R. P., Vendrusculo, F. M. and Donadio, M. V. F. (2016) 'Physiological responses during exercise with video games in patients with cystic fibrosis: A systematic review', *Respiratory Medicine*, 119, pp. 63–69. doi: 10.1016/j.rmed.2016.08.011.

Cerny, F. (2013) 'Exercise and Cystic Fibrosis (CF) 2.0', *Pediatric Exercise Science*, 25(4), pp. 616–623. doi: 10.1123/pes.25.4.616.

Cfireland.ie. 2021. *Cystic Fibrosis*. [online] Available at: <https://www.cfireland.ie/> [Accessed 25 May 2021].

Chastin, S. F. M. *et al.* (2019) 'How does light-intensity physical activity associate with adult cardiometabolic health and mortality? Systematic review with meta-analysis of experimental and observational studies', *British Journal of Sports Medicine*, 53(6), pp. 370–376. doi: 10.1136/bjsports-2017-097563.

Clark JP: (2003) How to peer review a qualitative manuscript. In Peer Review in Health Sciences.2ndedition. Edited by Godlee F, Jefferson T. London: BMJ Books: 219-235.

Condren, M. E. and Bradshaw, M. D. (2013) 'Ivacaftor: A Novel Gene-Based Therapeutic Approach for Cystic Fibrosis', *The Journal of Pediatric Pharmacology and Therapeutics : JPPT*, 18(1), pp. 8–13. doi: 10.5863/1551-6776-18.1.8.

Conway, S. *et al.* (2014) 'European Cystic Fibrosis Society Standards of Care: Framework for the Cystic Fibrosis Centre', *Journal of Cystic Fibrosis: Official Journal of the European Cystic Fibrosis Society*, 13 Suppl 1, pp. S3-22. doi: 10.1016/j.jcf.2014.03.009.

del Corral, T. *et al.* (2018) 'Effectiveness of a Home-Based Active Video Game Programme in Young Cystic Fibrosis Patients', *Respiration*, 95(2), pp. 87–97. doi: 10.1159/000481264.

Corral, T. del *et al.* (2018) 'Effectiveness of a Home-Based Active Video Game Programme in Young Cystic Fibrosis Patients', *Respiration*, 95(2), pp. 87–97. doi: 10.1159/000481264.

Cox, K. L. *et al.* (2003) 'Controlled comparison of retention and adherence in home- vs center-initiated exercise interventions in women ages 40-65 years: The S.W.E.A.T. Study (Sedentary Women Exercise Adherence Trial)', *Preventive Medicine*, 36(1), pp. 17–29. doi: 10.1006/pmed.2002.1134.

Cox, N. S. *et al.* (2012) 'Telehealth in cystic fibrosis: a systematic review', *Journal of Telemedicine and Telecare*, 18(2), pp. 72–78. doi: 10.1258/jtt.2011.110705.

Cox, N. S. *et al.* (2015) 'Feasibility and acceptability of an internet-based program to promote physical activity in adults with cystic fibrosis', *Respiratory Care*, 60(3), pp. 422–429. doi: 10.4187/respcare.03165.

Cox, N. S. *et al.* (2016) 'Physical activity participation by adults with cystic fibrosis: An observational study', *Respirology (Carlton, Vic.)*, 21(3), pp. 511–518. doi: 10.1111/resp.12719.

Cox, N. S., Alison, J. A. and Holland, A. E. (2013) 'Interventions for promoting physical activity in people with cystic fibrosis', *Cochrane Database of Systematic Reviews*. Edited by Cochrane Cystic Fibrosis and Genetic Disorders Group. doi: 10.1002/14651858.CD009448.pub2.

Cox, N. S. and Holland, A. E. (2019) 'Current perspectives of physical activity in cystic fibrosis', *Expert Review of Respiratory Medicine*, 13(1), pp. 13–22. doi: 10.1080/17476348.2019.1552833.

Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I., Petticrew, M. (2019). Developing and evaluating complex interventions: new guidance.

Dakin, C. J. *et al.* (2002) ‘Inflammation, infection, and pulmonary function in infants and young children with cystic fibrosis’, *American Journal of Respiratory and Critical Care Medicine*, 165(7), pp. 904–910. doi: 10.1164/ajrccm.165.7.2010139.

Davies, L. C. *et al.* (2006) ‘Enhanced prognostic value from cardiopulmonary exercise testing in chronic heart failure by non-linear analysis: oxygen uptake efficiency slope’, *European Heart Journal*, 27(6), pp. 684–690. doi: 10.1093/eurheartj/ehi672.

Davis, R. *et al.* (2015) ‘Theories of behaviour and behaviour change across the social and behavioural sciences: a scoping review’, *Health Psychology Review*, 9(3), pp. 323–344. doi: 10.1080/17437199.2014.941722.

De Boeck, K., Vermeulen, F. and Dupont, L. (2017) ‘The diagnosis of cystic fibrosis’, *Presse Medicale (Paris, France: 1983)*, 46(6 Pt 2), pp. e97–e108. doi: 10.1016/j.lpm.2017.04.010.

De Oronzo, M. A. (2011) ‘Hyperechogenic fetal bowel: an ultrasonographic marker for adverse fetal and neonatal outcome?’, *Journal of Prenatal Medicine*, 5(1), pp. 9–13.

Denford, S. *et al.* (2019) ‘Enhancing intrinsic motivation for physical activity among adolescents with cystic fibrosis: a qualitative study of the views of healthcare professionals’, *BMJ Open*, 9(6), p. e028996. doi: 10.1136/bmjopen-2019-028996.

Denford, S. *et al.* (2020) ‘Barriers and facilitators to physical activity among children, adolescents, and young adults with cystic fibrosis: a systematic review and thematic synthesis of qualitative research’, *BMJ Open*, 10(2). doi: 10.1136/bmjopen-2019-035261.

Donaire-Gonzalez, D. *et al.* (2015) ‘Benefits of physical activity on COPD hospitalisation depend on intensity’, *European Respiratory Journal*, 46(5), pp. 1281–1289. doi: 10.1183/13993003.01699-2014.

Donaldson, S. H. *et al.* (2006) ‘Mucus clearance and lung function in cystic fibrosis with hypertonic saline’, *The New England Journal of Medicine*, 354(3), pp. 241–250. doi: 10.1056/NEJMoa043891.

Dowd, K. P., Harrington, D. M. and Donnelly, A. E. (2012) ‘Criterion and concurrent validity of the activPAL^{TM} professional physical activity monitor in adolescent females’, *PloS One*, 7(10), p. e47633. doi: 10.1371/journal.pone.0047633.

Dwyer, T. J. *et al.* (2011) ‘Effects of Exercise on Respiratory Flow and Sputum Properties in Patients With Cystic Fibrosis’, *Chest*, 139(4), pp. 870–877. doi: 10.1378/chest.10-1158.

Dwyer, T. J. *et al.* (2019) ‘Effects of exercise and airway clearance (PEP) on mucus clearance in cystic fibrosis: a randomised cross-over trial’, *European Respiratory Journal*. doi: 10.1183/13993003.01793-2018.

Dwyer, T. J. *et al.* (2020) ‘Elicitation interview study to identify salient beliefs about exercise participation in adults with cystic fibrosis’, *Physiotherapy*, 107, pp. 286–291. doi: 10.1016/j.physio.2019.10.004.

Eckles, M. and Anderson, P. (2003) ‘Cor Pulmonale in Cystic Fibrosis’, *Seminars in Respiratory and Critical Care Medicine*, 24(3), pp. 323–330. doi: 10.1055/s-2003-41093.

Ekkekakis, P. (2003) ‘Pleasure and displeasure from the body: Perspectives from exercise’, *Cognition & Emotion*, 17(2), pp. 213–239. doi: 10.1080/02699930302292.

Ekkekakis, P. (2009) ‘Let Them Roam Free?’, *Sports Medicine*, 39(10), pp. 857–888. doi: 10.2165/11315210-000000000-00000.

Ekkekakis, P. and Lind, E. (2006) ‘Exercise does not feel the same when you are overweight: The impact of self-selected and imposed intensity on affect and exertion’, *International journal of obesity (2005)*, 30, pp. 652–60. doi: 10.1038/sj.ijo.0803052.

El-Kotob, R. and Giangregorio, L. M. (2018) ‘Pilot and feasibility studies in exercise, physical activity, or rehabilitation research’, *Pilot and Feasibility Studies*, 4(1), p. 137. doi: 10.1186/s40814-018-0326-0.

Enderby, B. and Doull, I. (2007) ‘Hypertonic saline inhalation in cystic fibrosis—salt in the wound, or sweet success?’, *Archives of Disease in Childhood*, 92(3), pp. 195–197. doi: 10.1136/adc.2006.094979.

Ensinck, M. *et al.* (2021) 'On the Corner of Models and Cure: Gene Editing in Cystic Fibrosis', *Frontiers in Pharmacology,* doi.org/10.3389/fphar.2021.662110

Fajac, I. and Wainwright, C. E. (2017) ‘New treatments targeting the basic defects in cystic fibrosis’, *Presse Medicale (Paris, France: 1983)*, 46(6 Pt 2), pp. e165–e175. doi: 10.1016/j.lpm.2017.01.024.

Farrell, P. M. (2008) ‘The prevalence of cystic fibrosis in the European Union’, *Journal of Cystic Fibrosis: Official Journal of the European Cystic Fibrosis Society*, 7(5), pp. 450–453. doi: 10.1016/j.jcf.2008.03.007.

Fernández Fernández, E. *et al.* (2018) ‘Biopolymer-Based Nanoparticles for Cystic Fibrosis Lung Gene Therapy Studies’, *Materials (Basel, Switzerland)*, 11(1). doi: 10.3390/ma11010122.

Fitzgerald, C. *et al.* (2016) ‘Newborn bloodspot screening for cystic fibrosis: What do antenatal and postnatal women know about cystic fibrosis?’, *Journal of Cystic Fibrosis*, 15(4), pp. 436–442. doi: 10.1016/j.jcf.2015.11.014.

Flume, P. A. *et al.* (2005) ‘Massive hemoptysis in cystic fibrosis’, *Chest*, 128(2), pp. 729–738. doi: 10.1378/chest.128.2.729.

Fraser-Pitt, D. and O’Neil, D. (2015) ‘Cystic fibrosis – a multiorgan protein misfolding disease’, *Future Science OA*, 1(2). doi: 10.4155/fso.15.57.

Gea, J., Sancho-Muñoz, A. and Chalela, R. (2018) ‘Nutritional status and muscle dysfunction in chronic respiratory diseases: stable phase versus acute exacerbations’, *Journal of Thoracic Disease*, 10(Suppl 12), pp. S1332–S1354. doi: 10.21037/jtd.2018.02.66.

Ghodeif, A. O. and Azer, S. A. (2020) ‘Pancreatic Insufficiency’, in *StatPearls*. Treasure Island (FL): StatPearls Publishing. Available at: http://www.ncbi.nlm.nih.gov/books/NBK555926/ (Accessed: 5 January 2021).

Gibson-Corley, K. N., Meyerholz, D. K. and Engelhardt, J. F. (2016) ‘Pancreatic Pathophysiology in Cystic Fibrosis’, *The Journal of pathology*, 238(2), pp. 311–320. doi: 10.1002/path.4634.

Godfrey, S. and Mearns, M. (1971) ‘Pulmonary Function and Response to Exercise in Cystic Fibrosis’, *Archives of Disease in Childhood*, 46(246), pp. 144–151. doi: 10.1136/adc.46.246.144.

Gould, G. S., Lim, L. L. and Mattes, J. (2017) ‘Prevention and Treatment of Smoking and Tobacco Use During Pregnancy in Selected Indigenous Communities in High-Income

Countries of the United States, Canada, Australia, and New Zealand: An Evidence-Based Review', *Chest*, 152(4), pp. 853–866. doi: 10.1016/j.chest.2017.06.033.

Gruber, W., Orenstein, D. M. and Braumann, K. M. (2011) 'Do Responses to Exercise Training in CF Depend on Initial Fitness Level?', *European Respiratory Journal*. doi: 10.1183/09031936.00192510.

Gruet, M. *et al.* (2010) 'Clinical utility of the oxygen uptake efficiency slope in cystic fibrosis patients', *Journal of Cystic Fibrosis: Official Journal of the European Cystic Fibrosis Society*, 9(5), pp. 307–313. doi: 10.1016/j.jcf.2010.03.003.

Gulmans, V. a. M. *et al.* (1999) 'Outpatient exercise training in children with cystic fibrosis: Physiological effects, perceived competence, and acceptability', *Pediatric Pulmonology*, 28(1), pp. 39–46. doi: https://doi.org/10.1002/(SICI)1099-0496(199907)28:1<39::AID-PPUL7>3.0.CO;2-8.

Gupta, S. *et al.* (2019) 'Effects of Exercise Intervention Program on Bone Mineral Accretion in Children and Adolescents with Cystic Fibrosis: A Randomized Controlled Trial', *Indian Journal of Pediatrics*, 86(11), pp. 987–994. doi: 10.1007/s12098-019-03019-x.

Hagger, M. S. and Weed, M. (2019) 'DEBATE: Do interventions based on behavioral theory work in the real world?', *International Journal of Behavioral Nutrition and Physical Activity*, 16(1), p. 36. doi: 10.1186/s12966-019-0795-4.

Happ, M. B. *et al.* (2013) 'Parent and Child Perceptions of a Self-Regulated, Home-Based Exercise Program for Children With Cystic Fibrosis':, *Nursing Research*, 62(5), pp. 305–314. doi: 10.1097/NNR.0b013e3182a03503.

Hardcastle, S. J. *et al.* (2013) 'Effectiveness of a motivational interviewing intervention on weight loss, physical activity and cardiovascular disease risk factors: a randomised controlled trial with a 12-month post-intervention follow-up', *International Journal of Behavioral Nutrition and Physical Activity*, 10(1), p. 40. doi: 10.1186/1479-5868-10-40.

Hardcastle, S. J. *et al.* (2017) 'Identifying content-based and relational techniques to change behaviour in motivational interviewing', *Health Psychology Review*, 11(1), pp. 1–16. doi: 10.1080/17437199.2016.1190659.

Hardcastle, S. J. and Cohen, P. A. (2017) 'Effective Physical Activity Promotion to Survivors of Cancer Is Likely to Be Home Based and to Require Oncologist Participation', *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, 35(32), pp. 3635–3637. doi: 10.1200/JCO.2017.74.6032.

Hardcastle, S. J. and Hagger, M. S. (2016) 'Psychographic Profiling for Effective Health Behavior Change Interventions', *Frontiers in Psychology*, 6. doi: 10.3389/fpsyg.2015.01988.

Hardeman, W. *et al.* (2002) 'Application of the Theory of Planned Behaviour in Behaviour Change Interventions: A Systematic Review', *Psychology & Health*, 17(2), pp. 123–158. doi: 10.1080/08870440290013644a.

Hayllar, K. M. *et al.* (1997) 'A prognostic model for the prediction of survival in cystic fibrosis', *Thorax*, 52(4), pp. 313–317. doi: 10.1136/thx.52.4.313.

Hebestreit, H. (2006) 'Physical activity is independently related to aerobic capacity in cystic fibrosis', *European Respiratory Journal*, 28(4), pp. 734–739. doi: 10.1183/09031936.06.00128605.

Hebestreit, H. *et al.* (2010) 'Long-term effects of a partially supervised conditioning programme in cystic fibrosis', *The European Respiratory Journal*, 35(3), pp. 578–583. doi: 10.1183/09031936.00062409.

Hebestreit, H. *et al.* (2014) 'Quality of life is associated with physical activity and fitness in cystic fibrosis', *BMC Pulmonary Medicine*, 14(1), p. 26. doi: 10.1186/1471-2466-14-26.

Hebestreit, H. *et al.* (2019) 'Cardiopulmonary Exercise Testing Provides Additional Prognostic Information in Cystic Fibrosis', *American Journal of Respiratory and Critical Care Medicine*, 199(8), pp. 987–995. doi: 10.1164/rccm.201806-1110OC.

Hebestreit, H., Kriemler, S. and Radtke, T. (2015) 'Exercise for all cystic fibrosis patients: is the evidence strengthening?', *Current Opinion in Pulmonary Medicine*, 21(6), pp. 591–595. doi: 10.1097/MCP.0000000000000214.

Heijerman, H. G. M. *et al.* (2019) 'Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial', *Lancet (London, England)*, 394(10212), pp. 1940–1948. doi: 10.1016/S0140-6736(19)32597-8.

Henry, B., Aussage, P., Grosskopf, C., Goehrs, JM. (2003). Development of the Cystic Fibrosis Questionnaire (CFQ) for assessing quality of life in pediatric and adult patients. Qual Life Res. 2003; 26:81-94

Higgins, L. W. *et al.* (2013) 'Exercise intensity self-regulation using the OMNI scale in children with cystic fibrosis', *Pediatric Pulmonology*, 48(5), pp. 497–505. doi: https://doi.org/10.1002/ppul.22639.

Hollenberg, M. and Tager, I. B. (2000) 'Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise', *Journal of the American College of Cardiology*, 36(1), pp. 194–201. doi: 10.1016/s0735-1097(00)00691-4.

Hommerding, P. X. *et al.* (2015) 'Effects of an Educational Intervention of Physical Activity for Children and Adolescents With Cystic Fibrosis: A Randomized Controlled Trial', *Respiratory Care*, 60(1), pp. 81–87. doi: 10.4187/respcare.02578.

Hughes, S. Physiological and vascular responses to acute and chronic exercise in men and women with cardiovascular disease. (2011). DORAS DCU. p50

Hulzebos, H. J. *et al.* (2015) 'Mechanisms of Exercise Limitation in Cystic Fibrosis', in *Diet and Exercise in Cystic Fibrosis*, pp. 291–297. doi: 10.1016/B978-0-12-800051-9.00033-X.

Hurt, K. and Bilton, D. (2014) 'Inhaled Interventions in Cystic Fibrosis: Mucoactive and Antibiotic Therapies', *Respiration*, 88(6), pp. 441–448. doi: 10.1159/000369533.

Johnson, J. H. and Phipps, L. K. (2006) 'PREFERRED METHOD OF SELECTING EXERCISE INTENSITY IN ADULT WOMEN', *The Journal of Strength & Conditioning Research*, 20(2), pp. 446–449.

Joy, E. L. *et al.* (2013) 'Physical activity counselling in sports medicine: a call to action', *British Journal of Sports Medicine*, 47(1), pp. 49–53. doi: 10.1136/bjsports-2012-091620.

Klijn, P. H. C. *et al.* (2004) 'Effects of anaerobic training in children with cystic fibrosis: a randomized controlled study', *Chest*, 125(4), pp. 1299–1305. doi: 10.1378/chest.125.4.1299.

Kosteli, M.-C. *et al.* (2017) 'Barriers and enablers of physical activity engagement for patients with COPD in primary care', *International Journal of Chronic Obstructive Pulmonary Disease*, 12, pp. 1019–1031. doi: 10.2147/COPD.S119806.

Kriemler, S. *et al.* (2016) 'Short-Term Effect of Different Physical Exercises and Physiotherapy Combinations on Sputum Expectoration, Oxygen Saturation, and Lung Function in Young Patients with Cystic Fibrosis', *Lung*, 194(4), pp. 659–664. doi: 10.1007/s00408-016-9888-x.

Lamhonwah, A.-M. *et al.* (2010) 'Cystic fibrosis transmembrane conductance regulator in human muscle: Dysfunction causes abnormal metabolic recovery in exercise', *Annals of Neurology*, 67(6), pp. 802–808. doi: https://doi.org/10.1002/ana.21982.

Lange, J. and Mager, D. (2011) 'The Nurse's Role in Promoting Optimal Health of Older Adults: Thriving in the Wisdom Years', *Nursing and Health Studies Faculty Book Gallery*. Available at: https://digitalcommons.fairfield.edu/nursing-books/35.

Lannefors, L. (2012) 'Physical training: vital for survival and quality of life in cystic fibrosis', *Breathe*, 8(4), pp. 308–313. doi: 10.1183/20734735.022111.

Liu, J. *et al.* (2014) 'Clinical usefulness of the oxygen uptake efficiency in pulmonary embolism', *European Respiratory Journal*, 44(Suppl 58). Available at: https://erj.ersjournals.com/content/44/Suppl_58/P2168 (Accessed: 26 December 2020).

Lobelo, F. and de Quevedo, I. G. (2016) 'The Evidence in Support of Physicians and Health Care Providers as Physical Activity Role Models', *American Journal of Lifestyle Medicine*, 10(1), pp. 36–52. doi: 10.1177/1559827613520120.

Loprinzi, P. D. (2016) 'Implications of light-intensity physical activity in improving health-related quality of life among congestive heart failure patients', *International Journal of Cardiology*, 212, pp. 16–17. doi: 10.1016/j.ijcard.2016.03.015.

Lubamba, B. *et al.* (2012) 'Cystic fibrosis: insight into CFTR pathophysiology and pharmacotherapy', *Clinical Biochemistry*, 45(15), pp. 1132–1144. doi: 10.1016/j.clinbiochem.2012.05.034.

Lyczak, J. B., Cannon, C. L. and Pier, G. B. (2002) 'Lung Infections Associated with Cystic Fibrosis', *Clinical Microbiology Reviews*, 15(2), pp. 194–222. doi: 10.1128/CMR.15.2.194-222.2002.

Lynch, J. P. *et al.* (2015) 'Lung Transplantation for Cystic Fibrosis: Results, Indications, Complications, and Controversies', *Seminars in respiratory and critical care medicine*, 36(2), pp. 299–320. doi: 10.1055/s-0035-1547347.

MacDonald, A. (1996) 'Nutritional management of cystic fibrosis.', *Archives of Disease in Childhood*, 74(1), pp. 81–87.

Mahase, E. (2019) 'Cystic fibrosis: triple therapy shows promising results', *BMJ (Clinical research ed.)*, 367, p. l6347. doi: 10.1136/bmj.l6347.

Mangurian, C. *et al.* (2017) 'Utilization of the Behavior Change Wheel framework to develop a model to improve cardiometabolic screening for people with severe mental illness', *Implementation Science*, 12(1), p. 134. doi: 10.1186/s13012-017-0663-z.

Marcotte, J. E. *et al.* (1986) 'Multiple factors limit exercise capacity in cystic fibrosis', *Pediatric Pulmonology*, 2(5), pp. 274–281. doi: https://doi.org/10.1002/ppul.1950020505.

Marshall, B. C. *et al.* (2005) 'Epidemiology of cystic fibrosis-related diabetes', *The Journal of Pediatrics*, 146(5), pp. 681–687. doi: 10.1016/j.jpeds.2004.12.039.

Maule, G., Arosio, D. and Cereseto, A. (2020) 'Gene Therapy for Cystic Fibrosis: Progress and Challenges of Genome Editing', *International Journal of Molecular Sciences*, 21(11). doi: 10.3390/ijms21113903.

Maxwell-Smith, C. *et al.* (2017) 'Barriers to physical activity participation in colorectal cancer survivors at high risk of cardiovascular disease', *Psycho-Oncology*, 26(6), pp. 808–814. doi: 10.1002/pon.4234.

de Meer, K. *et al.* (1995) 'Efficiency of oxidative work performance of skeletal muscle in patients with cystic fibrosis', *Thorax*, 50(9), pp. 980–983. doi: 10.1136/thx.50.9.980.

Michie, S. *et al.* (2013) 'The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions', *Annals of Behavioral Medicine: A Publication of the Society of Behavioral Medicine*, 46(1), pp. 81–95. doi: 10.1007/s12160-013-9486-6.

Michie, S. (2014) 'Implementation science: understanding behaviour change and maintenance', *BMC Health Services Research*, 14(Suppl 2), p. O9. doi: 10.1186/1472-6963-14-S2-O9.

Michie, S. *et al.* (2018) 'Evaluating the effectiveness of behavior change techniques in health-related behavior: a scoping review of methods used', *Translational Behavioral Medicine*, 8(2), pp. 212–224. doi: 10.1093/tbm/ibx019.

Michie, S., van Stralen, M. M. and West, R. (2011) 'The behaviour change wheel: A new method for characterising and designing behaviour change interventions', *Implementation Science*, 6(1), p. 42. doi: 10.1186/1748-5908-6-42.

Middleton, K. R., Anton, S. D. and Perri, M. G. (2013) 'Long-Term Adherence to Health Behavior Change', *American Journal of Lifestyle Medicine*, 7(6), pp. 395–404. doi: 10.1177/1559827613488867.

Middleton, P. G. *et al.* (2019) 'Elexacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele', *The New England Journal of Medicine*, 381(19), pp. 1809–1819. doi: 10.1056/NEJMoa1908639.

Moorcroft, A. *et al.* (2004) 'Individualised unsupervised exercise training in adults with cystic fibrosis: a 1 year randomised controlled trial', *Thorax*, 59(12), pp. 1074–1080. doi: 10.1136/thx.2003.015313.

Moorcroft, A. J., Dodd, M. E. and Webb, A. K. (1997) 'Exercise testing and prognosis in adult cystic fibrosis', *Thorax*, 52(3), pp. 291–293. doi: 10.1136/thx.52.3.291.

Moran, F. and Bradley, J. (2010) 'Incorporating exercise into the routine care of individuals with cystic fibrosis: is the time right?', *Expert Review of Respiratory Medicine*, 4(2), pp. 139–142. doi: 10.1586/ers.10.18.

Moskowitz, S. M. *et al.* (2008) 'Clinical practice and genetic counseling for cystic fibrosis and CFTR-related disorders', *Genetics in medicine : official journal of the American College of Medical Genetics*, 10(12), pp. 851–868. doi: 10.1097/GIM.0b013e31818e55a2.

Murphy, S. L. and Eaves, D. L. (2016) 'Exercising for the Pleasure and for the Pain of It: The Implications of Different Forms of Hedonistic Thinking in Theories of Physical Activity Behavior', *Frontiers in Psychology*, 7. doi: 10.3389/fpsyg.2016.00843.

Myers, L. B. (2009) 'An exploratory study investigating factors associated with adherence to chest physiotherapy and exercise in adults with cystic fibrosis', *Journal of Cystic Fibrosis*, 8(6), pp. 425–427. doi: 10.1016/j.jcf.2009.08.005.

Narayanan, S. *et al.* (2017) 'Adherence to therapies in cystic fibrosis: a targeted literature review', *Expert Review of Respiratory Medicine*, 11(2), pp. 129–145. doi: 10.1080/17476348.2017.1280399.

Navarro, S. (2016) '[Historical compilation of cystic fibrosis]', *Gastroenterologia Y Hepatologia*, 39(1), pp. 36–42. doi: 10.1016/j.gastrohep.2015.04.012.

Nixon, P. A. *et al.* (1992) 'The prognostic value of exercise testing in patients with cystic fibrosis', *The New England Journal of Medicine*, 327(25), pp. 1785–1788. doi: 10.1056/NEJM199212173272504.

O'Donoghue, G., Doody, C. and Cusack, T. (2011) 'Physical activity and exercise promotion and prescription in undergraduate physiotherapy education: content analysis of Irish curricula', *Physiotherapy*, 97(2), pp. 145–153. doi: 10.1016/j.physio.2010.06.006.

O'Donohoe, R. and Fullen, B. M. (2014) 'Adherence of Subjects With Cystic Fibrosis to Their Home Program: A Systematic Review', *Respiratory Care*, 59(11), pp. 1731–1746. doi: 10.4187/respcare.02990.

O'Halloran, P. D. *et al.* (2014) 'Motivational interviewing to increase physical activity in people with chronic health conditions: a systematic review and meta-analysis', *Clinical Rehabilitation*, 28(12), pp. 1159–1171. doi: 10.1177/0269215514536210.

O'Hanlon, E. and Kennedy, N. (2014) 'Exercise in cancer care in Ireland: a survey of oncology nurses and physiotherapists', *European Journal of Cancer Care*, 23(5), pp. 630–639. doi: 10.1111/ecc.12206.

Ojo, S. O. *et al.* (2019) 'Breaking barriers: using the behavior change wheel to develop a tailored intervention to overcome workplace inhibitors to breaking up sitting time', *BMC Public Health*, 19(1), p. 1126. doi: 10.1186/s12889-019-7468-8.

Oliveira, B., Deslandes, A. and Santos, T. (2015) 'Differences in exercise intensity seems to influence the affective responses in self-selected and imposed exercise: a meta-analysis', *Frontiers in Psychology*, 6. doi: 10.3389/fpsyg.2015.01105.

Onofre, T. *et al.* (2017) 'Oxygen uptake efficiency slope as a useful measure of cardiorespiratory fitness in morbidly obese women', *PLOS ONE*, 12(4), p. e0172894. doi: 10.1371/journal.pone.0172894.

Paranjape, S. M. *et al.* (2012) 'Exercise improves lung function and habitual activity in children with cystic fibrosis', *Journal of Cystic Fibrosis*, 11(1), pp. 18–23. doi: 10.1016/j.jcf.2011.08.003.

Pastré, J. *et al.* (2014) 'Determinants of exercise capacity in cystic fibrosis patients with mild-to-moderate lung disease', *BMC Pulmonary Medicine*, 14(1), p. 74. doi: 10.1186/1471-2466-14-74.

Patterson, K. D. *et al.* (2019) 'Exercise versus airway clearance techniques for people with cystic fibrosis', *The Cochrane Database of Systematic Reviews*, 2019(3). doi: 10.1002/14651858.CD013285.

Perri, M. G. *et al.* (2002) 'Adherence to exercise prescriptions: effects of prescribing moderate versus higher levels of intensity and frequency', *Health Psychology: Official*

Journal of the Division of Health Psychology, American Psychological Association, 21(5), pp. 452–458.

Prasad, S. A. and Cerny, F. J. (2002) ‘Factors that influence adherence to exercise and their effectiveness: Application to cystic fibrosis’, *Pediatric Pulmonology*, 34(1), pp. 66–72. doi: 10.1002/ppul.10126.

Prentice, B. J. *et al.* (2021) ‘Cystic fibrosis-related diabetes and lung disease: an update’, *European Respiratory Review*, 30(159). doi: 10.1183/16000617.0293-2020.

Prochaska, J. O. and Velicer, W. F. (1997) ‘The transtheoretical model of health behavior change’, *American journal of health promotion: AJHP*, 12(1), pp. 38–48. doi: 10.4278/0890-1171-12.1.38.

Quanjer, P. H. *et al.* (2012) ‘Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations’, *The European Respiratory Journal*, 40(6), pp. 1324–1343. doi: 10.1183/09031936.00080312.

Radtke, T. *et al.* (2017) ‘Physical exercise training for cystic fibrosis’, *Cochrane Database of Systematic Reviews*, (11). doi: 10.1002/14651858.CD002768.pub4.

Rand, S. and Prasad, S. A. (2012) ‘Exercise as part of a cystic fibrosis therapeutic routine’, *Expert Review of Respiratory Medicine*, 6(3), pp. 341–351; quiz 352. doi: 10.1586/ers.12.19.

Robinson, S. A. *et al.* (2019) ‘A web-based physical activity intervention benefits persons with low self-efficacy in COPD: results from a randomized controlled trial’, *Journal of Behavioral Medicine*, 42(6), pp. 1082–1090. doi: 10.1007/s10865-019-00042-3.

Rodriguez-Miguelez, P. *et al.* (2017) ‘CrossTalk proposal: Skeletal muscle oxidative capacity is altered in patients with cystic fibrosis’, *The Journal of Physiology*, 595(5), pp. 1423–1425. doi: https://doi.org/10.1113/JP272486.

Rogers, C. L. (2013) ‘Nutritional Management of the Adult with Cystic Fibrosis – Part I’, *PRACTICAL GASTROENTEROLOGY*, p. 10.

Rovedder, P. M. E. *et al.* (2014) ‘Exercise programme in patients with cystic fibrosis: a randomized controlled trial’, *Respiratory Medicine*, 108(8), pp. 1134–1140. doi: 10.1016/j.rmed.2014.04.022.

Ryan, R. M. and Deci, E. L. (2000) ‘Self-Determination Theory and the Facilitation of Intrinsic Motivation, Social Development, and Well-Being’, *American Psychologist*, p. 11.

Sabharwal, S. (2016) ‘Gastrointestinal Manifestations of Cystic Fibrosis’, *Gastroenterology & Hepatology*, 12(1), pp. 43–47.

Saint-Criq, V. and Gray, M. A. (2017) ‘Role of CFTR in epithelial physiology’, *Cellular and Molecular Life Sciences*, 74(1), pp. 93–115. doi: 10.1007/s00018-016-2391-y.

Salh, W. *et al.* (1989) ‘Effect of exercise and physiotherapy in aiding sputum expectoration in adults with cystic fibrosis.’, *Thorax*, 44(12), pp. 1006–1008. doi: 10.1136/thx.44.12.1006.

Sandelowski, M. (2000) ‘Whatever happened to qualitative description?’, *Research in Nursing & Health*, 23(4), pp. 334–340. doi: https://doi.org/10.1002/1098-240X(200008)23:4<334::AID-NUR9>3.0.CO;2-G.

Santana Sosa, E. *et al.* (2012) ‘Intrahospital weight and aerobic training in children with cystic fibrosis: a randomized controlled trial’, *Medicine and Science in Sports and Exercise*, 44(1), pp. 2–11. doi: 10.1249/MSS.0b013e318228c302.

Savi, D. *et al.* (2015) ‘Relationship between daily physical activity and aerobic fitness in adults with cystic fibrosis’, *BMC Pulmonary Medicine*, 15(1), p. 59. doi: 10.1186/s12890-015-0036-9.

Schmidt, B. Z. *et al.* (2016) ‘Cystic fibrosis transmembrane conductance regulator modulators in cystic fibrosis: current perspectives’, *Clinical Pharmacology : Advances and Applications*, 8, pp. 127–140. doi: 10.2147/CPAA.S100759.

Schneiderman, J. E. *et al.* (2014) ‘Longitudinal relationship between physical activity and lung health in patients with cystic fibrosis’, *European Respiratory Journal*, 43(3), pp. 817–823. doi: 10.1183/09031936.00055513.

Schneiderman-Walker, J. *et al.* (2000) ‘A randomized controlled trial of a 3-year home exercise program in cystic fibrosis’, *The Journal of Pediatrics*, 136(3), pp. 304–310. doi: 10.1067/mpd.2000.103408.

Scotet, V., L’Hostis, C. and Férec, C. (2020) ‘The Changing Epidemiology of Cystic Fibrosis: Incidence, Survival and Impact of the CFTR Gene Discovery’, *Genes*, 11(6). doi: 10.3390/genes11060589.

Selvadurai, H. C. *et al.* (2002) ‘Randomized controlled study of in-hospital exercise training programs in children with cystic fibrosis’, *Pediatric Pulmonology*, 33(3), pp. 194–200. doi: 10.1002/ppul.10015.

Seth, A. (2014) ‘Exercise prescription: what does it mean for primary care?’, *The British Journal of General Practice*, 64(618), pp. 12–13. doi: 10.3399/bjgp14X676294.

Sexauer, W. P. and Fiel, S. B. (2003) ‘Aerosolized antibiotics in cystic fibrosis’, *Seminars in Respiratory and Critical Care Medicine*, 24(6), pp. 717–726. doi: 10.1055/s-2004-815667.

Shei, R.-J. *et al.* (2019) ‘Exercise Physiology Across the Lifespan in Cystic Fibrosis’, *Frontiers in Physiology*, 10. doi: 10.3389/fphys.2019.01382.

Shelley, J. *et al.* (2018) ‘A formative study exploring perceptions of physical activity and physical activity monitoring among children and young people with cystic fibrosis and health care professionals’, *BMC Pediatrics*, 18. doi: 10.1186/s12887-018-1301-x.

Sheppard, K. E. and Parfitt, G. (2008) ‘Acute Affective Responses to Prescribed and Self-Selected Exercise Intensities in Young Adolescent Boys and Girls’, *Pediatric Exercise Science*, 20(2), pp. 129–141. doi: 10.1123/pes.20.2.129.

Sheridan, S. *et al.* (2021) ‘Maximal oxygen consumption and oxygen uptake efficiency in adolescent males’, *Journal of Exercise Science & Fitness*, 19(2), pp. 75–80. doi: 10.1016/j.jesf.2020.11.001.

Shoemaker, M. J., Hurt, H. and Arndt, L. (2008) ‘The Evidence Regarding Exercise Training in the Management of Cystic Fibrosis: A Systematic Review’, *Cardiopulmonary Physical Therapy Journal*, 19(3), pp. 75–83.

Sniehotta, F. F., Presseau, J. and Araújo-Soares, V. (2014) ‘Time to retire the theory of planned behaviour’, *Health Psychology Review*, 8(1), pp. 1–7. doi: 10.1080/17437199.2013.869710.

Somaraju, U. R. and Solis-Moya, A. (2014) ‘Pancreatic enzyme replacement therapy for people with cystic fibrosis’, *The Cochrane Database of Systematic Reviews*, (10), p. CD008227. doi: 10.1002/14651858.CD008227.pub2.

Soni, R. *et al.* (2008) ‘Gas exchange in stable patients with moderate-to-severe lung disease from cystic fibrosis’, *Journal of Cystic Fibrosis*, 7(4), pp. 285–291. doi: 10.1016/j.jcf.2007.11.003.

Speake, H. *et al.* (2016) ‘Embedding Physical Activity in the Heart of the NHS: The Need for a Whole-System Approach’, *Sports Medicine (Auckland, N.Z.)*, 46(7), pp. 939–946. doi: 10.1007/s40279-016-0488-y.

Stern, R. C. *et al.* (1980) ‘Heart failure in cystic fibrosis. Treatment and prognosis of cor pulmonale with failure of the right side of the heart’, *American Journal of Diseases of Children (1960)*, 134(3), pp. 267–272. doi: 10.1001/archpedi.1980.02130150025007.

Stevens, D. and Williams, C. A. (2007) ‘Exercise Testing and Training with the Young Cystic Fibrosis Patient’, *Journal of Sports Science & Medicine*, 6(3), pp. 286–291.

Sun, X.-G., Hansen, J. E. and Stringer, W. W. (2012) ‘Oxygen uptake efficiency plateau best predicts early death in heart failure’, *Chest*, 141(5), pp. 1284–1294. doi: 10.1378/chest.11-1270.

Swisher, A. K. *et al.* (2015) ‘Exercise and Habitual Physical Activity for People With Cystic Fibrosis: Expert Consensus, Evidence-Based Guide for Advising Patients’, *Cardiopulmonary Physical Therapy Journal*, 26(4), pp. 85–98. doi: 10.1097/CPT.0000000000000016.

Swisher, A. K. and Erickson, M. (2008) ‘Perceptions of Physical Activity in a Group of Adolescents with Cystic Fibrosis’, *Cardiopulmonary Physical Therapy Journal*, 19(4), pp. 107–113.

Swisher PT, A. K. and Pt, M. E. (2008) ‘Perceptions of Physical Activity in a Group of Adolescents with Cystic Fibrosis’:, *Cardiopulmonary Physical Therapy Journal*, 19(4), pp. 107–114. doi: 10.1097/01823246-200819040-00002.

Tang, Y. *et al.* (2017) ‘Oxygen Uptake Efficiency Slope Predicts Poor Outcome in Patients With Idiopathic Pulmonary Arterial Hypertension’, *Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease*, 6(7). doi: 10.1161/JAHA.116.005037.

Teixeira, P. J. *et al.* (2012) ‘Exercise, physical activity, and self-determination theory: A systematic review’, *The International Journal of Behavioral Nutrition and Physical Activity*, 9, p. 78. doi: 10.1186/1479-5868-9-78.

Tejero García, S. *et al.* (2011) ‘Bone health, daily physical activity, and exercise tolerance in patients with cystic fibrosis’, *Chest*, 140(2), pp. 475–481. doi: 10.1378/chest.10-1508.

Ten Harkel, A. D. and Takken, T. (2019) ‘Oxygen uptake efficiency slope in children: Its role in exercise testing’, *European Journal of Preventive Cardiology*, 26(2), pp. 171–173. doi: 10.1177/2047487318810872.

Tomasone, J. R. *et al.* (2014) ‘“Changing Minds”: determining the effectiveness and key ingredients of an educational intervention to enhance healthcare professionals’ intentions to prescribe physical activity to patients with physical disabilities’, *Implementation Science*, 9(1), p. 30. doi: 10.1186/1748-5908-9-30.

Tomlinson, O. W. *et al.* (2018) ‘Analysis of oxygen uptake efficiency parameters in young people with cystic fibrosis’, *European Journal of Applied Physiology*, 118(10), pp. 2055–2063. doi: 10.1007/s00421-018-3926-8.

Tomlinson, O. W. *et al.* (2020) ‘The feasibility of online video calling to engage patients with cystic fibrosis in exercise training’, *Journal of Telemedicine and Telecare*, 26(6), pp. 356–364. doi: 10.1177/1357633X19828630.

Tonelli, A. R. *et al.* (2010) ‘Prevalence of pulmonary hypertension in end-stage cystic fibrosis and correlation with survival’, *The Journal of Heart and Lung Transplantation*, 29(8), pp. 865–872. doi: 10.1016/j.healun.2010.04.006.

Troosters, T. *et al.* (2009) ‘Skeletal muscle weakness, exercise tolerance and physical activity in adults with cystic fibrosis’, *European Respiratory Journal*, 33(1), pp. 99–106. doi: 10.1183/09031936.00091607.

Trost, S. G., McIver, K. L. and Pate, R. R. (2005) ‘Conducting accelerometer-based activity assessments in field-based research’, *Medicine and Science in Sports and Exercise*, 37(11 Suppl), pp. S531-543. doi: 10.1249/01.mss.0000185657.86065.98.

Truelove, S. *et al.* (2020) ‘The use of the behaviour change wheel in the development of ParticipACTION’s physical activity app’, *Preventive Medicine Reports*, 20, p. 101224. doi: 10.1016/j.pmedr.2020.101224.

Tucker, M. A. *et al.* (2017) ‘A single bout of maximal exercise improves lung function in patients with cystic fibrosis’, *Journal of Cystic Fibrosis*, 16(6), pp. 752–758. doi: 10.1016/j.jcf.2017.05.011.

Turcios, N. L. (2019) ‘Cystic Fibrosis Lung Disease: An Overview’, *Respiratory Care*. doi: 10.4187/respcare.06697.

Urquhart, D. (2011) ‘Exercise testing in cystic fibrosis: why (and how)?’, *Journal of the Royal Society of Medicine*, 104(Suppl 1), pp. S6–S14. doi: 10.1258/jrsm.2011.s11102.

Vendrusculo, F. M. *et al.* (2019) ‘Peak Oxygen Uptake and Mortality in Cystic Fibrosis: Systematic Review and Meta-Analysis’, *Respiratory Care*, 64(1), pp. 91–98. doi: 10.4187/respcare.06185.

Ward, N. *et al.* (2019) ‘Exercise is commonly used as a substitute for traditional airway clearance techniques by adults with cystic fibrosis in Australia: a survey’, *Journal of Physiotherapy*, 65(1), pp. 43–50. doi: 10.1016/j.jphys.2018.11.006.

Warnock, L. and Gates, A. (2015) ‘Chest physiotherapy compared to no chest physiotherapy for cystic fibrosis’, *The Cochrane Database of Systematic Reviews*, 2015(12). doi: 10.1002/14651858.CD001401.pub3.

van de Weert-van Leeuwen, P. B. *et al.* (2014) ‘Chronic inflammation and infection associate with a lower exercise training response in cystic fibrosis adolescents’, *Respiratory Medicine*, 108(3), pp. 445–452. doi: 10.1016/j.rmed.2013.08.012.

Wells, G. D. *et al.* (2008) ‘Reliability and validity of the habitual activity estimation scale (HAES) in patients with cystic fibrosis’, *Pediatric Pulmonology*, 43(4), pp. 345–353. doi: 10.1002/ppul.20737.

Wells, G. D. *et al.* (2011) ‘Skeletal muscle metabolism in cystic fibrosis and primary ciliary dyskinesia’, *Pediatric Research*, 69(1), pp. 40–45. doi: 10.1203/PDR.0b013e3181fff35f.

Wenniger, K., Weiss, C., Wahn, U., Stabb, D. (2003). Body image in cystic fibrosis - development of a brief diagnostic scale. J Behav Med; 26:81-94.

West, R. (2005) 'Time for a change: putting the Transtheoretical (Stages of Change) Model to rest', *Addiction*, 100(8), pp. 1036–1039. doi: https://doi.org/10.1111/j.1360-0443.2005.01139.x.

White, D., Stiller, K. and Haensel, N. (2007) 'Adherence of adult cystic fibrosis patients with airway clearance and exercise regimens', *Journal of Cystic Fibrosis: Official Journal of the European Cystic Fibrosis Society*, 6(3), pp. 163–170. doi: 10.1016/j.jcf.2006.06.006.

Who.int.2021.[online] Available at: <https://www.who.int/chp/knowledge/publications/adherence/full_report.pdf> [Accessed 25 May 2021].

Willem, A., De Rycke, J. and Theeboom, M. (2017) 'The Role of Autonomous and Controlled Motivation in Exercise Intentions of Participants in a Mass Cycling Event', *Frontiers in Psychology*, 8. doi: 10.3389/fpsyg.2017.00354.

Williams, C. A. and Stevens, D. (2013) 'Physical activity and exercise training in young people with cystic fibrosis: Current recommendations and evidence', *Journal of Sport and Health Science*, 2(1), pp. 39–46. doi: 10.1016/j.jshs.2012.11.002.

Williams, S. *et al.* (1999) 'Percutaneous endoscopic gastrostomy feeding in patients with cystic fibrosis', *Gut*, 44(1), pp. 87–90.

Wilson, L. M., Morrison, L. and Robinson, K. A. (2019) 'Airway clearance techniques for cystic fibrosis: an overview of Cochrane systematic reviews', *The Cochrane Database of Systematic Reviews*, 1, p. CD011231. doi: 10.1002/14651858.CD011231.pub2.

Yakal, S. *et al.* (2018) 'Oxygen Uptake Efficiency Slope and Prediction of Post-operative Morbidity and Mortality in Patients with Lung Cancer', *Lung*, 196(2), pp. 255–262. doi: 10.1007/s00408-018-0085-y.

Yang, C. and Montgomery, M. (2018) 'Dornase alfa for cystic fibrosis', *The Cochrane Database of Systematic Reviews*, 2018(9). doi: 10.1002/14651858.CD001127.pub4.

Appendices

Appendix A: Plain Language Statement (Chapter III, Study I)

Plain Language Statement

Dublin City University

Knowledge and Practice of Exercise Prescription in CF Healthcare Professionals

Principle Investigator: Prof. Niall Moyna, School of Health and Human Performance, DCU

Contact details: 01 7008802,

Other investigators: Dr. Noel McCaffrey, Miss. Nicola Hurley (School of Health & Human Performance, DCU), Dr. Bróna Furlong (Waterford IT) and Prof. Karen Redmond (Mater Misericordiae University Hospital)

Details of involvement in the Research Study
Participation in this study will involve taking part in an online survey that will require 10-15 minutes of your time. You may complete the survey online via the SurveyMonkey link provided in your email invitation. The aim of this study is to determine Healthcare Professionals' knowledge and practice in relation to exercise prescription in CF care. This information will be used to inform the development of an exercise intervention, specific to patients with CF.

Potential risks to participants from involvement in the Research Study
There are no risks with this project above those of normal living.

Benefits (direct or indirect) to participants from involvement in the Research Study
The research will contribute to the development of the CF-specific exercise intervention.
Feedback regarding the study's outcomes will also be shared with participants.

Advice as to arrangements to be made to protect confidentiality of data, including that confidentiality of information provided is subject to legal limitations
Dublin City University will protect your confidentiality with regard to your part in this study.
Questionnaires are anonymous. Your information will be assigned a unique code, which will protect your identity. All information will be stored securely and saved in a password-protected file in a computer at DCU. Hardcopy files will be stored in a secure, locked filing cabinet in DCU.

Your identity or personal information will not be revealed or published. The study findings may be presented at scientific meetings and published in a scientific journal but your identity will not be divulged and only presented as part of a group.

Confidentiality of information provided can only be protected within the limitations of the law. It is possible for data to be subject to subpoena, freedom of information claim or mandated reporting by some professions.

After a 5-year period all data will be destroyed in accordance with DCU policy.

Statement that involvement in the Research Study is voluntary
Involvement in this study is completely voluntary. You may withdraw from the study at any point. You are under no obligation to stay involved if you do not wish to.

This research is funded by Cystic Fibrosis Ireland and the Mater Foundation.

If participants have concerns about this study and wish to contact an independent person, please contact:
The Secretary, Dublin City University Research Ethics Committee, c/o Research and Innovation Support, Dublin City University, Dublin 9. Tel 01-7008000

Appendix B: Informed Consent via online SurveyMonkey tool (Chapter III, Study I)

Dear Health Care Professional,

Thank you for taking the time to complete this questionnaire on exercise prescription in cystic fibrosis.

It should take less than 15 minutes and all of your responses will be anonymous.

Many thanks,
The MedEx Research Team at Dublin City University

Please see the Plain Language Statement (attached to your e-mail invitation to this questionnaire) for all of the details in relation to this study.

Please answer the below questions if happy to do so.

Participation is optional and you can exit the questionnaire at any time by closing this window on your computer.

1. Informed Consent:

- ☐ I have read the Plain Language Statement
- ☐ I understand the information provided
- ☐ I have had the opportunity to ask questions and discuss this study
- ☐ I have received satisfactory answers to all of my questions

Appendix C: Healthcare Professional Survey (Chapter III, Study I)

Section 1: Your Profile

2. Gender:

- ◯ Male
- ◯ Female

3. Age range:

- ◯ 20 - 29 years
- ◯ 30 - 39 years
- ◯ 40 - 49 years
- ◯ 50 - 59 years
- ◯ 60+ years

4. Your occupation:

- ◯ Consultant
- ◯ General Practitioner
- ◯ Surgeon
- ◯ Registrar
- ◯ Physiotherapist
- ◯ Exercise Physiologist
- ◯ Research Nurse
- ◯ Clinical Nurse Specialist
- ◯ Dietician
- ◯ Psychologist
- ◯ Occupational Therpaist
- ◯ Other (please specify)

5. How many years have you been qualified?

- ◯ 0 - 5 years
- ◯ 6 - 9 years
- ◯ 10 - 19 years
- ◯ 20+ years

6. How many years of clinical experience do you have working within CF care?

- ◯ 0 - 5 years
- ◯ 6 - 9 years
- ◯ 10 - 19 years
- ◯ 20+ years

7. Please indicate your work setting:

- ◯ Public Hospital
- ◯ Private Hospital
- ◯ Specialist CF Centre
- ◯ Primary Care Centre
- ◯ Community
- ◯ Other (please specify)

[ ]

8. Is your centre:

- ◯ Adult
- ◯ Paediatric
- ◯ Combined

9. Do you specialise in treating patients who are:

- ◯ Pre-lung transplant
- ◯ Post-lung transplant

10. Please indicate how many CF patients you see in a week (Individual patients, not number of contacts with same patient):

Inpatients: [ ]

Outpatients: [ ]

[Knowledge]
Education Regarding Exercise in CF Care

The remaining questions relate to physical activity and exercise, which are defined as follows:

Physical Activity:
Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure. Physical activity includes all forms of activity, such as everyday walking or cycling to get from A to B, active play, work-related activity, active recreation (such as working out in a gym), dancing, gardening or playing active games, as well as organised and competitive sport (World Health Organisation, 2018).

Exercise:
Exercise is a subcategory of physical activity that is planned, structured, repetitive, and purposeful in the sense that the improvement or maintenance of one or more components of physical fitness is the objective (World Health Organisation, 2018)

11. During your undergraduate degree, did you receive educational training in relation to physical activity / exercise prescription specific to people with CF?

○ Yes

○ No

12. Since qualifying, have you received any information regarding prescribing physical activity / exercise to people with CF?

○ Yes

○ No

13. If yes, how was this information provided? (Please tick all that apply)

☐ Workshop
☐ Conference
☐ Study day
☐ Graduate training (MSc, PhD)
☐ Other (please specify)
☐ In-service training
☐ Informal discussion
☐ Supervised clinical placement
☐ Self-directed learning

14. Please indicate your level of agreement with the following statement:
I have sufficient knowledge about prescribing exercise to people with CF

Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
○	○	○	○	○

15. Please indicate your level of agreement with the following statement:
I am familiar with the current consensus exercise guidelines for people with CF

Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
○	○	○	○	○

16. Can you describe the current consensus exercise guidelines for adults with CF:

Frequency
(how many times per week)

Intensity
(how hard should the individual work)

Time
(how long should the session last)

Type
(what mode of physical activity / exercise)

17. Please indicate your level of agreement with the following statement:
There is a need to improve exercise services available to people with CF

Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
○	○	○	○	○

[Practice]
Exercise Provision within the CF Healthcare Setting

18. Who in your MDT is primarily responsible for discussing exercise training and/or exercise prescription with CF patients?

- ◯ Consultant
- ◯ Registrar / SHO
- ◯ Nurse
- ◯ Physiologist
- ◯ Physiotherapist
- ◯ Dietician
- ◯ Psychologist
- ◯ Social Worker
- ◯ Pharmacist
- ◯ Occupational Therapist
- ◯ Other (please specify)

19. Please indicate your agreement with the following statement:
"Recommending physical activity / exercise to people with CF is part of my role"

Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
◯	◯	◯	◯	◯

20. Please indicate your level of agreement with the following statement:
"I would be confident in appropriately prescribing physical activity / exercise programmes to my CF patients"

Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
◯	◯	◯	◯	◯

21. Do you routinely discuss physical activity / exercise with your CF patients?

- ◯ Yes, at every visit
- ◯ Yes, regularly (1 in every 2 visits)
- ◯ Rarely
- ◯ Only at annual review
- ◯ Only when the patient asks
- ◯ Never

22. If yes, is this advice:

- ◯ Written
- ◯ Verbal
- ◯ Both

23. Please specify what advice is given to patients?

24. Is this advice based on the guidelines?

- ◯ No, not based on guidelines
- ◯ Yes, based on guidelines: (Please provide guidelines used)

25. Please estimate what % of your CF patients you recommended physical activity/exercise to in the past 6 months?

- ☐ <10%
- ☐ 10 - 25%
- ☐ 25 - 50%
- ☐ 50 - 75%
- ☐ 75 - 100%

26. How difficult, in your opinion, is it to include prescription of physical activity / exercise into appointments with your CF patients?

Extremely Difficult	Difficult	Neither Difficult nor Easy	Easy	Extremely Easy
◯	◯	◯	◯	◯

27. What are the most prominent barriers that you face in relation to prescribing exercise to your CF patients? *(Please rank your top 3 in order from the list below: 1 = most significant barrier)*

☐ Limited time with patients

☐ Poor physical activity compliance among CF patients

☐ Patients' health status deems physical activity/exercise promotion inappropriate

☐ Lack of motivation/interest from CF patients in relation to physical activity/exercise

☐ Lack of knowledge regarding physical activity/exercise prescription for people with CF

☐ Lack of exercise rehabilitation programmes to refer to

Please note, for the final 3 questions in this section, responses in the form of bullet points, short sentences and paragraphs are all welcome

28. What motivates you/would motivate you to prescribe exercise to CF patients? (Please provide as much detail as possible)

29. What strategies do you think would optimise healthcare professionals' **prescription of exercise** to CF patients? (Please provide as much detail as possible)

30. What strategies do you think would optimise **adherence** of CF patients to prescribed exercise programmes? (Please provide as much detail as possible)

Appendix D: Plain Language Statement (Chapter IV, Study II)

Plain Language Statement

DUBLIN CITY UNIVERSITY

Physical Activity for Cystic Fibrosis: Patient Perspectives

Principal Investigator:
Prof. Niall Moyna,
School of Health and Human Performance – Dublin City University

[tel] 01 700 8802 [email] niall.moyna@dcu.ie

Other Investigators:
Dr. Noel McCaffrey – *ExWell Chronic Illness Rehabilitation*
Dr. Bróna Kehoe – *Waterford Institute of Technology*
Ms. Nicola Hurley – *School of Health and Human Performance, Dublin City University*
Ms Karen Redmond – *Mater Misericordiae University Hospital*

Details of involvement in the research study
Involvement in this study will require you to participate in a telephone interview in relation to physical activity and exercise. The telephone interview will be audio-recorded and will last approximately 20-30 minutes. As part of the session, you will be asked for your opinions and views on physical activity and exercise, and about what motivates and prevents you from participating in physical activity and/or exercise.

Potential risks
There are no risks with this project above those of normal everyday living.

Benefits
This study will explore participant's physical activity levels, motivators and barriers to exercise participation, in order to develop a CF-specific exercise program that can be easily integrated into everyday life.

Confidentiality
DCU will protect your confidentiality with regard to your part in this study. Your information will be assigned a unique code, under which your information will be collected and stored. The audio recordings will be de-identified through the use of coding. The audio data will be transcribed and transformed into electronic data (i.e. interview scripts). In accordance with DCU policy all data will be kept on-site in DCU in a locked secure area. All raw data will only be available to the research team. The study findings may be presented at scientific meetings and published in a scientific journal but your identity will not be divulged and only presented as part of a group. The confidentiality of information provided can only be protected within the limitations of the law. It is possible for data to be subject to subpoena, freedom of information claim or mandated reporting by some professions.

The data will be stored for 5 years following the completion of the study and then deleted irretrievably on-site at DCU by the principal investigator.

Voluntary
If at any point during your participation in the study you feel as if you wish to withdraw, this is not a problem. You are under no obligation to stay involved if you do not wish to. Please contact the investigators if you are unable or unwilling to continue in the project so as we can address any issues within the project.

Funding
This research is funded by Cystic Fibrosis Ireland and the Mater Foundation.

If participants have concerns about this study and wish to contact an independent person, please contact:
The Secretary, Dublin City University Research Ethics Committee, c/o Research and Innovation Support, Dublin City University, Dublin 9. Tel 01-7008000

Appendix E: Informed Consent (Chapter IV, Study II)

Informed Consent Form

DUBLIN CITY UNIVERSITY

Physical Activity for Cystic Fibrosis: Patient Perspectives

Principal Investigator:
Prof. Niall Moyna,
School of Health and Human Performance – Dublin City University
[tel] 01 700 8802 [email] niall.moyna@dcu.ie

Other Investigators:
Dr. Noel McCaffrey – *ExWell Chronic Illness Rehabilitation*
Dr. Bróna Kehoe – *Waterford Institute of Technology*
Ms. Nicola Hurley – *School of Health and Human Performance, Dublin City University*
Ms Karen Redmond – *Mater Misericordiae University Hospital*

The purpose of this study is to obtain the views of people with cystic fibrosis on factors that influence their level of physical activity. This information will be used to inform the development of an exercise programme specific for cystic fibrosis.

I will be asked to participate in a telephone interview about my physical activity levels. The interview will last approximately 20-30 minutes. I will be asked for my opinions and views on physical activity and the motivators that facilitate and the barriers that prevent me from participating in exercise. The session will be audio-recorded and will be conducted over the phone.

Participant – please complete the following (Circle Yes or No for each question)

I have read the Plain Language Statement (or had it read to me)	Yes/No
I understand the information provided	Yes/No
I have had an opportunity to ask questions and discuss this study	Yes/No
I have received satisfactory answers to all my questions	Yes/No
I am aware that my interview will be audiotaped	Yes/No

Involvement in this study is completely voluntary. I may withdraw from the study at any point.

Dublin City University will protect my confidentiality. My information will be assigned a unique ID number, which will protect my identity. The audio recordings will be de-identified through the use of coding. All information will be stored securely and saved in a password-protected file in a computer at DCU. All hard copy data will be securely filled and recorded in a locked cabinet in DCU. Any personal information I provide will not be disclosed or published in the findings of this study. The study findings may be presented at scientific meetings and published in a scientific journal, but my identity will not be revealed and only presented as part of a group. I am aware that the confidentiality of information provided is subject to legal limitations. It is possible for data to be subject to subpoena, freedom of information claim or mandated reporting by some professions.

If I have questions about the research project, I am free to call Ms. Nicola Hurley at 01-7008470.
This research is funded by Cystic Fibrosis Ireland and the Mater Foundation.

Signature:
I have read and understood the information in this form. The researchers have answered my questions and concerns, and I have a copy of this consent form. Therefore, I consent to take part in this research project

Participants Signature: ________________________ Name in Block Capitals: _____________________

Date: ____/____/________

Appendix F: Interview Guide (Chapter IV, Study II)

INTRODUCTION
Hi, my name is Nicola Thank you very much for agreeing to participate in this telephone interview. Today, we are going to talk about the topic of physical activity with respect to cystic fibrosis – more specifically we will touch on aspects such as your current physical activity levels, what motivates you to participate in physical activity, the challenges that you face that may prevent you from participating in physical activity and finally, we will discuss strategies that you think may improve enjoyment levels, in turn, enhancing participation in physical activity and physical activity programs. So, we would like you to be as honest as possible during this interview, there is absolutely no right or wrong answers! Also, if it is ok with you, we will audio-tape our discussion so that we can go back and listen to it at a later date for analysis. No one else will hear this tape and we will keep your personal information absolutely confidential and anonymous. You may end the interview at any point, should you not want to continue. Do you have any questions before I start the audio-recording? ~ ~ ~ Start tape. Say the date, ID code for the interviewee, recorder/interviewer name *(e.g. Monday 23rd September, Interview 1 with participant [ID code] and Nicola recording)* Ok, let's get started… First, I am going to give you a brief definition of physical activity, so that we are clear on terms before we begin: Physical activity is defined as any bodily movement, produced by skeletal muscles that requires energy expenditure. Physical activity encompasses all activities, at any intensity, performed during any time of the day or night. It includes exercise and incidental activity integrated into daily activity – this might include activities such as walking, running, cycling, swimming, or might even be activity within your day such as taking the stairs, walking to/from work etc…..
PATIENT INFORMATION
Could you please confirm your consent to participate in the following telephone interview Have you been given the opportunity to ask questions prior to your participation? Have your questions been answered satisfactorily?

Could you also please confirm your age and date of birth? Have you had a lung transplant?	
CURRENT PHYSICAL ACTIVITY LEVELS	
Let's start with what you are doing currently, would you say that you are physically active?	(**prompt:** do you participate in PA often during a typical week? If yes, how often, what intensity, for how long?)
Can you tell me about your past experiences with physical activity?	(**prompt:** positive/negative experiences?)
Are you aware of the current physical activity guidelines for PWCF?	(**prompt:** how often, for how long, at what intensity, what type)
MOTIVATORS	
What motivates you to participate in physical activity?	(**prompt:** **[a – social]** routine, your health status, support from family and friends… **[b – personal]** goal-setting, self-motivation, feeling better in yourself… **[c – access]** access to gym facilities, healthcare professionals…)
What do you like or enjoy about physical activity?	
BARRIERS	
In general, what prevents you from participating in physical activity?	(**prompt:** what challenges you, why don't you like to participate in physical activity, what would stop you) (**prompt:** time, lack of energy, lack of willpower, fear of injury/exacerbation, lack of ability, lack of access to facilities…) (**prompt:** lack of support – HCP/family/friends, lack of HCP prescription/follow-up, transport, financial burden, perceptions of self – "I am too ill")
STRATEGIES TO IMPROVE ENJOYMENT / ADHERENCE	
If you were to give other PWCF advice on how to be more physical active, what would you say?	(**prompt:** if you were to tell them something that would empower them to be physically active and to more importantly **maintain** that behaviour…)
Now, in your opinion, what would make participating in physical activity more appealing to you?	(**prompt:** what would make physical activity easier for you to participate in; what would make physical activity more enjoyable for

	you; what would make you adhere to a physical activity program more?**)**
Do your healthcare providers discuss physical activity with you?	**(prompt:** Regularly? In great detail? Prescribe?**)**
How supportive were your HCPs in relation to physical activity?	**(prompt:** spoke about it at every visit, spoke about it often, rarely spoke about it, only spoke about it when I brought it up**)**
What could your HCP do to help you to increase your physical activity levels?	**(prompt:** would your HCP monitor your physical activity?**)**
What would you like to see in a physical activity program, that would make you more inclined to incorporate it into your daily life and maintain it in the long term?	**(prompt:** physical activity broken up into smaller bouts throughout the day, rather than one long strenuous session/ technology/ hardcopy manual/ home-based/ community-based**)**

Appendix G: Plain Language Statement (Chapter V, Study III)

Plain Language Statement

DUBLIN CITY UNIVERSITY

Evaluation of a 12-week CF-Specific Exercise Intervention

Principal Investigator: Prof. Niall Moyna,
School of Health and Human Performance – Dublin City University
tel: 01 700 8802
email: niall.moyna@dcu.ie

Other Investigators: Ms Karen Redmond – Mater Misericordiae University Hospital
Ms. Nicola Hurley – School of Health and Human Performance, DCU

Purpose of the study

Although physical activity is a well-established mode of therapy for people with CF, there is a large gap in our understanding of what constitutes the optimal exercise program for improving functional capacity and optimizing health related quality of life. Ideally, exercise programs should be enjoyable, easily incorporated into day-to-day life, undertaken with friends and family and improve quality of life.

The purpose of this study is to evaluate how participating in an individually designed exercise programme affects your physical fitness and health related quality of life and to seek feedback from you regarding your thoughts about the training programme.

Details of involvement in the research study

Involvement in this study will require that you visit the Clinical Exercise Physiology Unit at DCU on two occasions at baseline and twice again upon completion of the study (week 14). During the visits to DCU you will undergo a series of physiological tests to measure your fitness and complete a questionnaire. During visit 1, you will have your height, weight, waist and hip circumference measured, your upper and lower body strength assessed and undergo a maximal exercise test on a bike. During your second visit you will complete a questionnaire, have your lung function assessed, and undertake a submaximal exercise test on a bike. You will be asked to wear a small device for 7 days to measure your levels of physical activity. At the end of your second visit, you will have an exercise consultation with a member of the research team to identify whether you will be in the control group, receiving usual care, or the exercise group. The exercise training will last 12 weeks in total. Regardless of which group you are assigned, you will return to DCU for two final visits, separated by 7 days, for your post-intervention testing. In addition, if you are assigned to the intervention group, you will be invited to participate in a feedback interview to express your opinions about the experience.

If you are assigned to the control group, you will be given the exercise guide upon completion of the study for your personal use.

Potential risks

Exercise carries with it a very small risk of abnormal heart rhythms, heart attack, or death in less than one in 30,000 patients. In patients with established chronic illness the risk is higher. The yearly incidence of cardiac arrhythmias during exercise testing and physical conditioning in people with CF was 0-0.1% and matches that of the healthy population. An emergency room and automated external defibrillator (AED) are available onsite. The research team are appropriately qualified and experienced working with clinical populations in a safe and professional manner.

Benefits

You will receive a copy of your results, summarizing information such as body composition, pulmonary function score, muscular strength and cardiovascular fitness.

Confidentiality

DCU will protect your confidentiality with regard to your part in this study. In accordance with DCU policy all data will be kept on-site in DCU in a locked secure area. All raw data will only be available to the research team. Your information during the feedback interview, should you participate, will be assigned a unique code, under which your information will be collected and stored. The audio recordings will be de-identified through the use of coding. The audio data will be transcribed and transformed into electronic data (i.e. interview scripts). The study findings may be presented at scientific meetings and published in a scientific journal but your identity will not be divulged and only presented as part of a group. The confidentiality of information provided can only be protected within the limitations of the law. It is possible for data to be subject to subpoena, freedom of information claim or mandated reporting by some professions.

The data will be stored for 5 years following the completion of the study and then deleted irretrievably on-site at DCU by the principal investigator.

Voluntary

If at any point during your participation in the study you feel as if you wish to withdraw, this is not a problem. You are under no obligation to stay involved if you do not wish to. Please contact the investigators if you are unable or unwilling to continue in the project so as we can address any issues within the project.

Funding

This research is funded by Cystic Fibrosis Ireland and the Mater Foundation.

If participants have concerns about this study and wish to contact an independent person, please contact:

The Secretary, Dublin City University Research Ethics Committee, c/o Research and Innovation Support, Dublin City University, Dublin 9. Tel 01-700800

Appendix H: Informed Consent (Chapter V, Study III)

<u>Informed Consent Form</u>

Evaluation of a 12-week CF-Specific Exercise Intervention

Principal Investigator: Prof. Niall Moyna,
School of Health and Human Performance – Dublin City University
tel: 01 700 8802
email: niall.moyna@dcu.ie

Other Investigators: Ms Karen Redmond – Mater Misericordiae University Hospital
Ms. Nicola Hurley – School of Health and Human Performance, DCU

Purpose of the study

Although, physical activity is a well-established mode of therapy for people with CF, there is a large gap in our understanding of what constitutes the optimal exercise program for improving functional capacity and optimizing health related quality of life. Ideally, exercise programs should be enjoyable, easily incorporated into day-to-day life, undertaken with friends and family and improve quality of life.

The purpose of this study is to evaluate how participating in an individually designed exercise programme effects your physical fitness and health related quality of life and to seek feedback from you regarding your thoughts about the training programme

Participant requirements

Involvement in this study will require me to visit the Clinical Exercise Physiology Unit at DCU on two occasions at baseline and twice again during the week after I complete the study. During the visits to DCU I will undergo a series of physiological tests to measure my fitness and complete a questionnaire. During visit 1, I will have my height, weight, waist and hip circumference measured, my upper and lower body strength assessed and undergo a maximal exercise test on a bike. During the second visit I will complete a questionnaire, have my lung function assessed, and undertake a submaximal exercise test on a bike. I will also be asked to wear a small device, called an accelerometer, for 24h a day for a week to measure how physically active I am. At the end of the second visit, I will have an exercise consultation with a member of the research team to identify whether I will be assigned to the control group, receiving usual care, or the exercise group. The exercise training will last 12 weeks in total. Regardless of which group I am assigned to, I will return to DCU for two final visits for my post-intervention testing. In addition, if I am assigned to the intervention group, I will be given the opportunity to participate in a feedback interview to express my opinions about the experience. The interview will last approximately 20-30 minutes. The session will be audio-recorded and will be conducted at DCU after my last day of testing.

Participant – please complete the following (Circle Yes or No for each question)

I have read the Plain Language Statement (or had it read to me)	Yes/No
I understand the information provided	Yes/No
I have had an opportunity to ask questions and discuss this study	Yes/No
I have received satisfactory answers to all my questions	Yes/No
I am aware that my interview will be audiotaped	Yes/No

Involvement in this study is completely voluntary. I may withdraw from the study at any point.

Dublin City University will protect my confidentiality. My information will be assigned a unique ID number, which will protect my identity. The audio recordings, should I participate, will be de-identified through the use of coding. All information will be stored securely and saved in a password-protected file in a computer at DCU. All hard copy data will be securely filled and recorded in a locked cabinet in DCU. Any personal information I provide will not be disclosed or published in the findings of this study. The study findings may be presented at scientific meetings and published in a scientific journal, but my identity will not be revealed and only presented as part of a group. I am aware that the confidentiality of information provided is subject to legal limitations. It is possible for data to be subject to subpoena, freedom of information claim or mandated reporting by some professions.

If I have questions about the research project, I am free to call Ms. Nicola Hurley at 01-7008470.

This research is funded by Cystic Fibrosis Ireland and the Mater Foundation.

Signature:
I have read and understood the information in this form. The researchers have answered my questions and concerns, and I have a copy of this consent form. Therefore, I consent to take part in this research project

Participants Signature: ______________________ Name in Block Capitals: ____________________

Date: ____/____/________

Appendix H(a): Informed Consent for Maintenance Phase (Chapter V, Study III)

Informed Consent Form

Evaluation of a 6-week unsupported physical activity maintenance phase, following completion of a 12-week partially supervised intervention

Principal Investigator: Prof. Niall Moyna,
School of Health and Human Performance – Dublin City University
tel: 01 700 8802
email: niall.moyna@dcu.ie

Other Investigators: Prof. Karen Redmond – Mater Misericordiae University Hospital
Dr. Bróna Kehoe – Waterford Institute of Technology
Ms. Nicola Hurley – School of Health and Human Performance, DCU

Purpose of the study

There is extensive evidence that physical activity reduces the decline in pulmonary function and improves exercise tolerance and quality of life in people living with cystic fibrosis. Long-term health benefits are most often the result of regular and sustained activity, that can be carried out efficiently and effortlessly.

The purpose of this study is to evaluate the effects of a 6-week unsupported maintenance phase, following the completion of the 12-week partially supervised physical activity intervention, on physical activity levels and quality of life.

Participant requirements

Involvement in this study will require me to participate in a 6-week maintenance phase, upon completion of the 12-week partially-supervised intervention. During the 6-week phase, I will endeavor to sustain the physical activity habits that I have put in place over the past 12-weeks.

I understand that during the maintenance phase, I will not receive weekly support and I will not be required to fill out the daily online diary. However, I will continue to wear my Fitbit device.

I will complete a questionnaire, regarding my motivation for physical activity, at week 1 and week 6 of the maintenance phase. I will also complete a health related quality of life questionnaire and habitual activity estimation scale at the end of week 6 (as per baseline and week 12 assessments).

I agree to participate in a feedback interview upon completion of the 6-week period to discuss the intervention, in its entirety, from my perspective.

Participant – please complete the following (Circle Yes or No for each question)

I have read the Plain Language Statement (or had it read to me)	Yes/No
I understand the information provided	Yes/No

I have had an opportunity to ask questions and discuss this study	Yes/No
I have received satisfactory answers to all my questions	Yes/No
I am aware that my interview will be audiotaped	Yes/No

Involvement in this study is completely voluntary. I may withdraw from the study at any point.

Dublin City University will protect my confidentiality. My information will be assigned a unique ID number, which will protect my identity. The audio recordings, should I participate, will be de-identified through the use of coding. All information will be stored securely and saved in a password-protected file in a computer at DCU. All hard copy data will be securely filled and recorded in a locked cabinet in DCU. Any personal information I provide will not be disclosed or published in the findings of this study. The study findings may be presented at scientific meetings and published in a scientific journal, but my identity will not be revealed and only presented as part of a group. I am aware that the confidentiality of information provided is subject to legal limitations. It is possible for data to be subject to subpoena, freedom of information claim or mandated reporting by some professions.

If I have questions about the research project, I am free to call or email Ms. Nicola Hurley at:
Tel: 0872360663
Email: nicola.hurley.cf@gmail.com

This research is funded by Cystic Fibrosis Ireland and the Mater Foundation.

Signature:
I have read and understood the information in this form. The researchers have answered my questions and concerns, and I have a copy of this consent form. Therefore, I consent to take part in this research project

Participants Signature: ________________________ Name in Block Capitals: _____________________

Date: ____/____/________

Appendix I: Physical Activity Guide (Chapter V, Study III)

CF-Ex
2020

CF-Ex

Physical Activity & Exercise Booklet

Funded by Cystic Fibrosis Ireland
& The Mater Foundation

DCU

Cystic Fibrosis Ireland

the Mater Foundation
Advancing care for every patient, every day

CONTENTS

ACKNOWLEDGEMENTS

Content development and authorship:

Nicola Hurley

Supervised by:

Prof. Niall Moyna

Prof. Karen Redmond

Adapted from the MedEx Wellness Home Programme, with permission from Dr. Noel McCaffrey, Eóin Durkan and Mairéad Cooney.

This research is funded by Cystic Fibrosis Ireland and the Mater Foundation

For more information, please email nicola.hurley5@mail.dcu.ie

THE IMPORTANCE OF PHYSICAL ACTIVITY

Let's consider physical activity as medicine that can be used to improve our health and well-being. Many people living with a chronic condition can easily become physically inactive, with the burden of treatment taking precedence and physical activity becoming an afterthought, that is soon forgotten. This can lead to progressive deconditioning, which refers to a decrease in muscle strength and a reduction in physical fitness. By enhancing your habitual physical activity and participation in exercise you can improve your ability to perform many physical tasks and activities that enrich your daily life. No matter how unfit or deconditioned you may feel, you CAN get better!

THE BENEFITS OF PHYSICAL ACTIVITY?

There is extensive evidence to support the role of physical activity in the management of Cystic Fibrosis. There are many benefits of physical activity and exercise for Cystic Fibrosis:

- Improved fitness
- Improved mood
- Improved self-esteem
- Improved confidence
- Improved energy and concentration
- Decreased annual rate of decline in lung function
- Decreased anxiety and depression
- Decreased fatigue
- Decreased risk of developing an additional chronic disease

THE BENEFITS OF PHYSICAL ACTIVITY FOR ME

Take a moment to think about how being more physically active will benefit YOU? Think about your day to day life at present. Is there anything you would like to do but can't, at the moment? Would you like to get back to doing activities that you have done in the past? Is there anything that you would like to improve?

Write down what you think the benefits of physical activity and exercise could be for you. Some examples are listed below:

- Having more energy to play with my children or friends
- Increasing my confidence
- Sleeping better
- Walking or jogging 5km

The benefits of physical activity for me are:
1. 2. 3. 4. 5.

HOW MUCH EXERCISE IS ENOUGH?

In order to improve or maintain health and well-being, the EXERCISE WORKING GROUP of the EUROPEAN CYSTIC FIBROSIS SOCIETY have developed physical activity guidelines that recommend:

	Habitual Physical Activity	**Aerobic Exercise**	**Resistance/Strength Training**
Adolescent (13-19years)	60 min daily in a variety of activities enjoyed, especially with family or friends	30-60 min daily of moderate-to-vigorous exercise (at least 70% of maximal heart rate)	Formal resistance training 2-3 times per week per muscle group, incorporate limb and trunk muscles, 1-3 sets of 8-12 repetitions at 70-85% of maximal load (1 repetition maximum)
Adult (>19 years)	150 min per week or more (preferably 300 min) in a variety of activities of choice	30-60 min daily of moderate-to-vigorous exercise (at least 70% of maximal heart rate)	Formal resistance training 2-3 times per week per muscle group, incorporate limb and trunk muscles, 1-3 sets of 8-12 repetitions at 70-85% of maximal load (1 repetition maximum)

GOAL SETTING

Goals have the potential to provide motivation for physical activity and feedback on what you have achieved. Those who actively write down their goals are more likely to achieve them, than those who don't. There is space at the back of this booklet to log, monitor and review your goals for physical activity.

TIP: Ask yourself is your goal S M A R T:

S – Specific
M – Measurable
A – Achievable
R – Realistic
T – Timely

The F I T T principle helps us to think of our weekly physical activity in more detail, and allows us to see if we are achieving the recommended guidelines set out by the Exercise Working Group of the European CF Society.

F – Frequency – How many days will I be active?
I – Intensity – What intensity will I exercise at?
T – Time – How long will I exercise for?
T – Type – What type of activity will I do?

Example of the FITT Principle:

Frequency: How many days will I be active? **5**

Intensity: What intensity will I exercise at? **Moderate intensity**

Time – How long will I exercise for? **30 minutes x 5 evenings**

Type: What type of activity will I do? **Brisk walk**

OVERCOMING CHALLENGES & COPING WITH SETBACKS

From time to time, we may not be as active as we had intended. We may not meet our goals for various reasons. It is important to mention that you may experience some challenges to being more physically active. Many factors including other treatment commitments, work commitments, a prolonged period of ill health or decreased motivation can affect the amount of activity you do.

Let's try to anticipate difficult situations that you may cross in your day-to-day life and write down a plan as to how you can manage these situations to include time for activity.

In the table on the next page we have included some challenges that you may experience and some prompted plans that can be put in place to overcome these setbacks.

This time, we hope overcoming your setbacks is different! The team at DCU are here to support and guide you along your journey to living a more physically active life.

'IT ALWAYS SEEMS IMPOSSIBLE UNTIL IT IS DONE!'
NELSON MANDELA

CHALLENGES	SOLUTIONS
'I don't have time to exercise'	Think about ways that you can incorporate activity into everyday life. Walk or cycle to and from work, college, school. If you get the bus, get off a few stops earlier and walk the rest of the way. If you have to drive, park the car further away. Take the stairs instead of the lift. Include some exercise during your lunch break. Remember, EVERY step counts!
'Exercise isn't for me'	All types of movement benefit our health and there are many different types of activity. Find an activity that you

	ENJOY (e.g. walking, dance classes, football, golf) and ask a family member or friend to exercise with you. Try to incorporate some activity into your daily routine and write down how you feel afterwards. Focus on the benefits of exercise for YOU. Contact Nicola if you want to discuss your exercise regime.
'My family think I should rest'	It is important to make our family and friends aware of the importance of physical activity for our health. Share the information included at the start of this guide with family members and friends. Ask them to support your decision to be more active and ask them to be active with you.
'I'm bored of exercise'	Think about alternative types of exercise that you've tried in the past, or possibly have never tried before. Write down a plan of the exercise you intend to do for the coming week. Try to include a different type of exercise each day – go for a walk, swim, cycle to work, play golf or maybe take part in an exercise class with a friend. At the end of the week, look back on your plan and how you felt. What did you enjoy? What would you like to change for next week?
'I've had a bad exacerbation and have not exercised for a while. I'm not sure where to start?'	What type of exercise do you see yourself doing? Set a short term goal and write down a physical activity plan for the week ahead. Depending on where you feel you are now, try to go for a 10 minute walk and gradually increase that to 10 minutes, 3 times a day. When you've achieved your short term goal, set a medium term goal and aim to increase the amount and intensity of activity that you do each week. The hardest part is getting started, so take the first step and get going!

SAFETY TIPS FOR EXERCISE

Physical activity and exercise are very beneficial for your health, regardless of disease severity. If you participate in regular physical activity and exercise, you have a greatly reduced risk of having a sudden severe medical event that could damage your health or cause sudden death. There may be a slightly increased risk of suffering an adverse medical event while exercising, but the overall benefit to your health from participating in physical activity and exercise is far greater than the risk. By being sensible and taking appropriate precautions where necessary, any risk is minimized.

On some occasions it may not be appropriate to exercise. If you notice any of the following (or if you are worried about any symptoms) you should consult your own doctor:

- Chest pain at rest or on mild exercise
- An abnormally high temperature
- Dizziness
- Feeling ill (nausea, vomiting, diarrhoea)
- Sever or unusual headaches
- Any unexplained pain

IF YOU HAVE ANY CONCERNS ABOUT BEING ACTIVE THAT ARE NOT ADDRESSED IN THIS BOOKLET, PLEASE CONTACT A MEMBER OF THE RESEARCH TEAM!

STAY HYDRATED!

Dehydration, due to increased salt loss, during physical activity and exercise is a major concern for people living with CF. This is of particular concern when exercising in hot or humid environments. Preventing dehydration is key!

Start by drinking more fluids before, during and immediately after exercising to help you to maintain or replace the electrolytes lost during activity. You should also try to **avoid** caffeinated drinks, which can negatively impact the re-hydration process as they promote fluid loss.

FORMAT OF AN EXERCISE SESSION

Regular exercise may take many forms. There is no one-size-fits-all solution. Becoming more physically active for you may mean sitting less, watching less television or walking to the shops. For others, it may mean increasing the intensity and duration of existing exercise sessions. However it is important to realise that in order to get fitter and stronger you NEED to stress your body's systems, even if this is only very slightly at the beginning. This stress or exertion is what encourages your body to adapt and become fitter and stronger.

An exercise session involves a set of structured and varied activities. It is designed to make you fitter and stronger and more able to be physically active.

In each exercise session it is important to include a mixture of aerobic and resistance exercise (please refer to the guidelines). Aerobic exercise is the term used to describe exercise that raises your heart rate, increases your rate and depth of breathing and makes you sweat a little. An example would be a brisk walk or a jog.

Resistance exercise involves using your muscles and making them stronger. An example would be lifting weights or simply standing up from a chair. As we age our muscles can weaken. In addition, certain illnesses can increase the rate at which our muscles weaken.

Skeletal muscle is a remarkable organ in that it can be strengthened throughout your entire lifetime. Bone is just the same. Stronger muscles create stronger bones! An exercise session might typically involve the following types of exercise:

- Aerobic exercise, e.g. walking, cycling, swimming
- Resistance or strength exercise, e.g. exercises with weights
- Flexibility exercises, e.g. stretching
- Stability or balance exercise, e.g. yoga, pilates

All of these types of exercises target different aspects of your physical health and well-being. By training them all in a structured exercise session you will improve your overall health.

THE IMPORTANCE OF A WARM-UP

It is important to gradually warm up prior to exercising. This prepares your body for exercise. It can slowly increase your heart rate, raise your body temperature and increase the flow of blood to your muscles. It can also increase flexibility, improve balance and reduce the chance of injury.

It might be the case that your exercise session will be a brisk walk. In this instance, your warm up will involve starting your walk at a slower pace. You would then gradually increase your walking pace over a couple of minutes until you reach the intensity that you want to walk at for the main part of your exercise session.

Your warm up should last a minimum of 15 minutes.

THE IMPORTANCE OF A COOL-DOWN:

As important as it is to warm up, it is equally vital to cool down. This means not stopping your exercise too suddenly. You should reduce the intensity at the end of your exercise session and try to incorporate some stretching and balance exercises. There are plenty of examples of exercises you can try in this manual.

Your cool down should last a minimum of 10 minutes.

HOW HARD SHOULD I EXERCISE?

In order to get fitter and stronger, you need to train your body. Training involves putting your whole body or isolated parts of your body under stress. This means doing a task that is challenging but still achievable. After your exercise session, your body repairs itself and adapts to the stress that it was put under - this makes you stronger and fitter. The next time you train you will have to make the session slightly more difficult again in order to continue this process. When you are doing aerobic exercise (e.g. walking, cycling) you can judge whether you are working hard enough by asking yourself the following questions:

- Do I have a red face?
- Am I starting to sweat a little?
- Am I slightly out of breath?

These are the normal responses of your body to exercise. If the answer to these questions is mostly yes, then you should be exercising at a sufficient intensity.

THE TALK TEST:

We can also judge how hard we are exercising by using the talk test. Ask yourself, can you easily hold a conversation while exercising? If yes, there is room to increase your exercise intensity a little more! You'll know you are exercising at the right intensity when you can talk in bursts between catching your breath.

WHEN YOU ARE INVESTING YOUR TIME IN PHYSICAL ACTIVITY AND EXERCISE, GET THE MOST BENEFIT FOR YOUR HEALTH – GET THE INTENSITY RIGHT

RATE OF PERCEIVED EXERTION SCALE

Perceived exertion can be defined as a method to determine the intensity of effort, stress, or discomfort that is felt during exercise

RATING	PERCEIVED EXERTION	
6	No Exertion	How you feel when lying in bed or sitting in a chair relaxed Little or no effort
7	Extremely Light	
8		
9	Very Light	
10		
11	Fairly Light	
12		TARGET RANGE How you should feel with exercise or activity
13	Somewhat Hard	
14		
15	Hard	
16		
17	Very Hard	How you felt with the hardest work you have ever done Do not work this hard!!
18		
19	Extremely Hard	
20	Maximal Effort	

WARM-UP AT HOME

1. Marching on the spot

a. Stand tall, with shoulders back
b. Begin marching bringing knees high and swinging arms

2. Heel digs

a. Place hands on hips
b. Tap one heel out in front
c. Alternate between left and right

3. Side steps

a. Place your hands on your hips
b. Step the right and stand with your feet together
c. Step to the left and stand with your feet together
d. Repeat

4. High knees

a. March on the spot ensuring to bring knees up high
b. Keep arms at chest height and push forwards and backwards with arms in an upright position

5. Marching on the spot with boxing arms

a. Continue marching on the spot
b. Punch out the arms in front as if boxing

6. Shoulder rolls

a. While marching on the spot, roll shoulders forwards
b. Change direction and roll shoulders backwards
c. Repeat

7. Arm circles

a. While marching on the spot, extend the arms making circles in a forward direction
b. Change direction

8. Upper back stretch

a. Lock the fingers of the hands together
b. Push the hands away from you as far as you can
c. You will feel the stretch across the top of your back
d. While marching, hold this stretch for 10-15 seconds

9. Chest stretch

a. Lock the fingers of the hands together behind your back
b. Push the hands away from you as far as you can
c. You will feel the stretch across the top of your chest
d. While marching, hold this stretch for 10-15 seconds

FUNDAMENTAL EXERCISES AND INSTRUCTIONS

REMEMBER, BEFORE YOU START EXERCISING, CHECK THE SPACE AROUND YOU AND ENSURE THAT YOU HAVE ENOUGH ROOM TO EXERCISE. ENSURE THAT THE SPACE IS FREE FROM OBJECTS THAT COULD CAUSE A FALL AND THAT YOU ARE EXERCISING ON A FLAT AND EVEN SURFACE.

LUNGE

A foundation bodyweight exercise for developing the leg muscles. The lunge is suitable for beginners and can be adapted with additional weight to increase intensity.

Primary Muscle: Quadriceps
Secondary Muscles: Calves, Hamstrings

How to do the Lunge:

1. Stand tall, keep your abdominal muscles tight
2. Take a long step forward with your right leg and lower your body until your right leg is at 90 degrees and your back knee almost touches the floor (your right knee should not extend over your toes)
3. Start to lift your body back to starting position, bringing your right foot back in line with your left at shoulder width apart
4. Repeat with the left leg

Aim to use a 3 second tempo on the way down and 1 second on the way up

Regression:

1. Start with shorter steps forward, lower yourself to your threshold
2. Aim to go further as you improve

Progression:

1. Lunge jumps – begin in the lunge position, jump up and quickly swap leg positions while in the air, keeping torso straight, land in lunge position bending your knees to absorb the impact and launch straight into the next jump, switching leg positions again and landing in the original lunge position

SQUAT

The bodyweight squat is a lower body strengthening exercise that can be performed virtually anywhere with no equipment and limited space. It is a highly functioning movement working all of the major muscles in the legs.

Primary Muscle: Quadriceps
Secondary Muscles: Calves, Hamstrings

How to do the Squat:

1. Begin with your feet shoulder-width apart, turning your toes slightly outward. Pull in your lower abs and keep your head up
2. Slowly bend at the knees and drop your hips, as if to sit down, to lower your body, keeping your heels flat on the floor
3. At the bottom of the exercise, in the seated position, pause for 1 second and push yourself back to the starting position, pushing your hips forward at the top
4. Repeat for desired number of reps

Aim to use a 3 second tempo on the way down and 1 second on the way up

Regression:

1. Start with a sit-to-stand – use a chair with arms, sit into the chair, cross your arms in and X across your chest with right hand on left shoulder, left hand on right shoulder and use your legs to stand from a seated position
2. Aim to progress to a stand-alone squat

Progression:

1. Begin to use weight
    a. Gym – barbell or dumbbells
    b. Home – hold a bottle of water or can of beans in each hand and aim to progress

SIT–UP

A classic abdominal strengthening exercise.

Primary Muscle: Abdominals
Secondary Muscles: None

How to do the Sit-Up:

1. Lie with your back on the floor, knees bent and feet flat on the ground
2. Place your hands behind your head, keeping the thumbs straight and aligned with your neck for support
3. Lift your body from the floor towards the knees, exhale !
4. Contract your abdominal muscles
5. Lower the body back down to the floor and repeat

Aim to use a 3 second tempo on the way down and 1 second on the way up

Modified Sit-Up:

1. Reverse sit-up: lie with your back on the floor, bend the knees into your chest and lift your knees towards your chin, tightening your abdominal muscles. Use your hands for support on the ground

Progression:

1. Begin to use weight
    c. Gym – medicine ball, weighted plate
    d. Home – hold a bottle of water or a sports ball

PUSH–UP

The push-up is a fundamental upper-body strength exercise that has many variations for developing strength and definition in the chest, shoulders and arms

Primary Muscle: Chest
Secondary Muscles: Shoulders, Triceps

How to do the Push-Up:

1. Lie face-down, flat on the ground. Place your hands slightly wider than shoulder-width apart
2. Push down on the ground with your hands and raise the body up by extending the arms
3. Lower the body back to the ground by bending the arms
4. Repeat for desired reps

Aim to use a 3 second tempo on the way down and 1 second on the way up

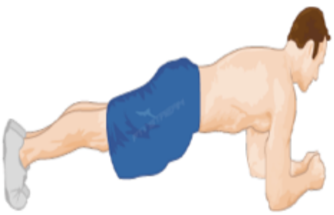
Modified Push-Up:

1. Wall-Press: stand in front of the wall with your feet shoulder width apart, squeezing your stomach muscles tight
2. Place your two hands on the wall at shoulder height and shoulder width apart
3. Bend the elbows, bringing your body closer to the wall
4. Keeping your hands on the wall, push off the wall to return to the starting position
5. Remember to keep your back straight
6. Repeat for desired reps

Progression:

1. Begin to use weight
    a. Gym – place a weighted plate on your back, begin light
    b. Home – place a box of cereal on your back, begin light

PLANK



A fundamental core conditioning exercise.

Primary Muscle: Abdominals
Secondary Muscles: Back

How to do the Plank:

1. Begin lying on the ground, face down, resting your weight on your fore-arms and toes, pull your abdominal muscles in tight
2. Maintain a hold, keeping your body in a straight line from your shoulders to your heels for your required rep time

Aim to start with 10 seconds and progress.

Modified Plank:

1. Instead of holding the weight through your toes, bend your knees on the ground, feet in the air and arms straight – hold for desired time and aim to progress

Progression:

1. Increase hold time

BICEP CURL

A fundamental strength training exercise.

Primary Muscle: Biceps
Secondary Muscles: Forearms

How to do the Bicep Curl:

1. Start with arms shoulder width apart, underhand grip with palms of hands facing up.
2. Contract the biceps and raise the arms up through an arc motion, so that the forearms progress to a vertical position, with hands in line with your shoulders
3. Lower the arms back down to the starting position

Aim to use a 1 second tempo up and 3 second tempo down.

Modified Bicep Curl:

1. Use small bottles of water or cans of beans and aim to progress

Progression:

1. Gym: Progressivelyncrease the weights with dumbbells or a barbell
2. Home: Increase the weights with heavier objects such as larger water bottles or milk cartons

TRICEP EXTENSION

A fundamental strength training exercise.

Primary Muscle: Triceps
Secondary Muscles: None

How to do the Tricep Extension:

1. Lie on your back, either on a bench or on the floor
2. Position your weights (barbell or home-weights) over your forehead, arms extended
3. Bend the arms at the elbow, lowering the weight over your head
4. Press the weight back up to the starting position by extending the arms back up to starting position
5. Repeat for desired reps

Aim to use a 1 second tempo up and 3 second tempo down.

Modified Tricep Extension:

1. Use small bottles of water or cans of beans and aim to progress

Progression:

5. Gym: Increase the weights with dumbbells or a barbell
6. Home: Increase the weights with heavier objects such as larger water bottles or milk cartons

COOL-DOWN AT HOME

1. Slow march on the spot

a. Stand tall, with shoulders back
b. Begin marching slow, bringing knees high and swinging arms

2. Hip circles

a. Stand with feet shoulder width apart and hands on hips
b. Make circles with the hips – change direction

3. Adductor Stretch

a. Stand with hands on hips
b. Step to the left
c. Bend the left knee and feel the stretch on the inside of the right leg – repeat by stepping to the right

4. Calf Raise

a. Use a chair or stand beside a wall for balance if needed
b. Begin by standing with feet shoulder width apart
c. Have a slight bend in knees
d. Squeeze stomach muscles tight
e. Lift and lower the heels off the ground

5. Hamstring Stretch

a. Stand with hands on hips
b. Place right heel out in front
c. Keeping back straight, bend left knee and sit back into the stretch – keep head and chest up

6. Calf Stretch

a. Stand with hands on hips
b. Step out in front with the left leg
c. Keeping both heels on the ground and both feet facing forward, push forward with the left knee
d. You should feel the stretch on the back of your right leg
e. Change to the opposite leg

7. Quad Stretch

a. Use a chair of the wall for balance if needed
b. Stand tall with shoulders back
c. Squeeze stomach muscles tight
d. Raise right leg up behind you to meet your hand
e. Keep your knees together and hips pushed forward
f. Pull foot towards bum until you feel a stretch down the front of your leg – repeat on opposite leg

NOTE: if you can't hold your foot, try to hold your trouser leg or shoe

8. Shoulder Rolls

a. While marching on the spot, roll shoulders forwards
b. Change direction and roll the shoulders backwards

9. Chest stretch

a. Lock the fingers of the hands together behind your back
b. Push the hands away from you as far as you can
c. While marching, hold this stretch for 10-15 seconds
d. Repeat with hands in front of body

GOALS AND PROGRESS

GOALS AND PROGRESS

GOALS AND PROGRESS

GOALS AND PROGRESS

GOALS AND PROGRESS

Appendix J: Weekly Support Checklist (Chapter V, Study III)

CF-Ex Weekly Telephone Call Script

Participant ID Code:

Hi…

Firstly, thank you for taking the time to have this very quick chat.

So, before we get started, I will give you a quick run-through of what we will chat about each week. We will try to keep it as standardized as possible so that we tick each box each week, to make sure that you get the best out of the programme.

During this phone call each week, we will run through a number of things, relative to the intervention, just to make sure that things are both working, from the technology side, and that you are enjoying the programme as best you can! So, please be as honest as possible with your responses and I will do what I can to ensure that we make this process as enjoyable and easy as possible!

We will go through the technology first, followed by a quick run-through of your online diary data.

We will then discuss any challenges or set-backs that you may have encountered over the past week and we will work to try to resolve them going forward.

Following this, we will discuss enjoyment and give you a space to feedback on what could be better, or be put in place to enhance your enjoyment levels, from our side.

CF-Ex Weekly Telephone Call Script

ID Code:	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Everything Working? (Tech)												
Fitbit												
Online Diary												
Meeting Recommended Guidelines												
Habitual PA												
Aerobic Training												
Resistance Training												
Barriers												
Difficulty to Adhere	/10	/10	/10	/10	/10	/10	/10	/10	/10	/10	/10	/10
Challenges / Setbacks	/10	/10	/10	/10	/10	/10	/10	/10	/10	/10	/10	/10
Motivation												
Enjoyment	/10	/10	/10	/10	/10	/10	/10	/10	/10	/10	/10	/10

CF-Ex Weekly Telephone Call Script (Week 1)

- How has the past week been?
- How has everything been with the technology-based components?
    - Fitbit
    - Online Diary
- If we have a quick run though, in terms of what you have achieved over the past week
    - Habitual PA:
    - Aerobic Training:
    - Resistance Training:
    - Steps:
- Guidelines met: Yes / No
- Barriers over the past week
    - Challenges?
    - Setbacks?
- Enjoyment over the past week
    - Have you enjoyed the past week?
    - What could be done differently to improve your enjoyment levels?
    - Any comment on how we could improve, to help you to enjoy the programme more?

Appendix K: Feedback Interview Script (Chapter V, Study III)

<table>
<tr><th colspan="2">INTRODUCTION</th></tr>
<tr><td colspan="2">Hi,

My name is Ciara, I'm a colleague of Nicola's from DCU. The reason I am conducting this interview, instead of Nicola, is to ensure that you have the space to speak very honestly about your perceptions of the intervention.

Firstly, thank you very much for agreeing to participate in this feedback interview.

Today, we are going to talk about your experience in relation to the exercise intervention. We will hope to identify the components that you found positive, and beneficial, and those that you believe could be improved.

We would like you to be as honest as possible during this interview, there is absolutely no right or wrong answers!

Also, if it is ok with you, we will audio-tape our discussion so that we can go back and listen to it at a later date for analysis. No one else will hear this tape and we will keep your personal information absolutely confidential and anonymous.

You may end the interview at any point, should you not want to continue.

Do you have any questions before I start the audio-recording?

~ ~ ~

Start tape. Say the date, ID code for the interviewee, recorder/interviewer name
(e.g. Monday 1st July, Interview 1 with participant [ID code] and Ciara recording)

Ok, let's get started…</td></tr>
<tr><th colspan="2">PROCESS QUESTIONS (How is the program operating?)</th></tr>
<tr><td>Could you chat to me about your experience, participating in the exercise intervention?</td><td>(prompt: was it a positive/negative experience?)

(prompt: was the program explained satisfactorily to you?) – If no, what could have been done better?

(prompt: was the program easy to follow/use?) – If not, what could have been done better?)</td></tr>
</table>

	(**prompt:** usability – technology functionality – weekly update / Fitbit / online diary) (**prompt:** did you receive adequate support during the intervention?) – If not, what would you have liked to see? (**prompt:** did you encounter problems with the intervention?) – If yes, were they resolved to your satisfaction? – If not, what could have been done to solve this problem? (**prompt:** could you chat to me about the maintenance phase – how did you find that – the removal of weekly contact and support)
RESULT-FOCUSED QUESTIONS (Is the program accomplishing intended results?)	
Could you chat to me about how you feel now that the intervention is over?	(**prompt:** did you like or enjoy participating in the exercise intervention?) – If yes, why? If no, why? (**prompt:** do you feel like you have achieved something beneficial from participating in this intervention?) (**prompt:** did you find the self-monitoring aspect beneficial? – if yes, why? – if no, why?) (**prompt:** how did you find the program in terms of adherence, did you find it easy to adhere to / more difficult to adhere to – why?) (**prompt:** practicality – is this program something you would continue to use in the long-term?) – If yes, why? – If not, why? (**prompt:** was the intervention well-managed, in your opinion? – what could have been done better?) (**prompt:** what do you see as the benefits of having been involved in this trial?)

	(**prompt:** what were the key challenges that you experienced during this trial?) (**prompt:** what do you think we could do to improve the program?) (**prompt:** is there anything else you would like to add or that you think is important?)