IMPROVEMENTS IN PHYSICAL ACTIVITY AND PHYSIOLOGICAL ADAPTATION IN ADULTS WITH CYSTIC FIBROSIS

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Candidate declaration form

Name of candidate; James Shelley

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Degree for which thesis is submitted; Doctor of Philosophy (PhD)

1. **Statement of related studies undertaken in connection with the programme of research.**

I have undertaken a programme of related studies that aimed to develop my research skills and competence in understanding a research project.

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ABSTRACT

To undertake this research, a multi-methods approach was used to explore physical activity (PA) in adults with Cystic Fibrosis (CF). Study 1 was a systematic review of the literature and reported that adults with CF were insufficiently active to achieve PA recommendations, but their PA levels were largely comparable to their non-CF peers. The tools used to assess PA and outcomes reported in the literature were variable, many of which did not provide sufficient information to assess relevant components of PA, highlighting a requirement for high quality studies designed specifically to explore PA in adults with CF.

Study 2 included objective assessments of PA in 62 participants (31 with CF and 31 controls) using ActiGraph accelerometers. Quality of life (QoL) and self-reported PA were assessed using questionnaires. Vascular function (a marker of CVD risk) was assessed using flow-mediated dilatation (FMD) in sub-groups of adults with CF (n=12) and matched controls (n=12). Participants with CF engaged in significantly less moderate-to-vigorous PA (MVPA) than their non-CF peers, with significantly steeper intensity gradients, demonstrating a daily profile of PA with more time spent engaging in lower intensity PA and less time spent engaging in higher intensity PA. Higher levels of vigorous PA were positively correlated with lung function and QoL. There was no significant difference in FMD between groups or any association with objectively assessed PA.

Study 3 involved semi-structured interviews to explore patients' (n=11) perceptions of PA, devised using the PRECEDE component of the PRECEDE-PROCEED model. Phase 2 included focus groups to discuss the perceived barriers, facilitators and opportunities for PA participation and how this information could inform the promotion of PA in adults with CF. Separate focus groups were conducted with individuals with CF (n=9) and their families and CF clinicians (n=3).

The principle predisposing barriers identified related to participants physical and mental wellbeing, which manifested as both a barrier and a facilitator of PA behaviour. Participants perceived that PA had the potential to slow the rate of clinical deterioration and manage the symptoms associated with the condition. Despite recognition of the potential benefits of PA, it appears that enjoyment is an important correlate of PA. The presence of health care professionals with a special interest in

PA within CF MDTs and clinics was reported as a key reinforcing factor for PA behaviour. The family were also reported as reinforcing factors for PA behaviour. Finally, the transition process, during adolescence and early adulthood was reported as an important period in the life of an individual with CF, with both participants with CF and their clinicians suggesting that PA should be promoted as early as possible. The promotion of PA in adults with CF may not be best achieved through the delivery of a single intervention but through the role of an exercise professional as part of long-term routine CF care. PA promotion should begin during paediatric care and be reinforced throughout an individual's life with additional support during adolescence. The role of an exercise professional should be to identify the principle predisposing, enabling, reinforcing factors influencing PA behaviour at an individual level in order to remove barriers to PA, engage patients and improve 'wellbeing'.

This thesis contributes evidence to inform the use of accelerometry, including the use of raw data analysis and metrics such as average Euclidean Norm Minus One (ENMO) and the intensity gradient, which provide a comprehensive PA profile that may allow tailored PA advice for adults with CF, without requiring CF-specific PA cut-points. Additionally, this thesis provides an insight into the correlates of PA in this population, which may help to inform future PA activity promotion interventions. Future research should employ robust PA assessment methods and explore the role of exercise professional led PA promotion as part of routine CF care.

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1. INTRODUCTION

The following chapter will introduce the key topics discussed throughout this thesis. Although this will include a review of some relevant literature, to avoid repetition a full literature review is not included, as Chapter 2 includes a systematic review of literature relating to physical activity in adults with Cystic fibrosis.

1.1. Cystic Fibrosis

Cystic Fibrosis (CF) is an autosomal recessive disorder caused by mutation of the CF Transmembrane Conductance Regulator (*CFTR*) gene resulting in dysfunction or deficiency of CFTR protein [1]. The condition primarily affects those of European descent, though it affects ~70,000 people worldwide with cases reported in all races and ethnicities [2]. CF affects approximately 11,000 individuals in the United Kingdom (UK), with median predicted survival reported as 45 years of age [3]. Prevalence (per 10,000) in the UK is the second highest in Europe (1.37), second only to Ireland (2.98) [4].

The CFTR protein has an important role in co-ordinating transepithelial salt transport, which impacts on a number of important physiological functions [1]. The salt transport defect impairs mucociliary airway clearance by disrupting the airway surface liquid and predisposing the airway to a build-up of excess and viscous mucus. Subsequent chronic airway infection and inflammation leads to airway damage, recurrent respiratory infection and eventual respiratory failure as the primary cause of early death [3]. In addition, the CFTR defect impacts on other epithelial surfaces, such as the sweat glands, pancreas and liver [5]. Loss of pancreatic exocrine function results in malnutrition, poor growth and early mortality if untreated [2].

There are almost 2,000 reported CFTR variants, typically grouped into six classes based on their effect on CFTR protein function [6]. As depicted in Figure 1, class I mutations result in no functional CFTR protein [7]. Class II mutations are the most common and are characterised by minimal functional CFTR at the apical cell membrane, resulting from protein misfolding preventing trafficking of the CFTR to the cell [7]. The most common class II mutation is Phe508del with ~90% of individuals living with CF worldwide having this mutation on at least one CFTR gene

[7]. In Class III and IV mutations CFTR reaches the cell but chloride channel function is impaired [7]. Class V mutations are characterised by a reduced amount of CFTR at the cell, resulting in inadequate function [7]. Class VI mutations are rare and result in reduced functional CFTR due to decreased stability of mature CFTR at the cell membrane [7].

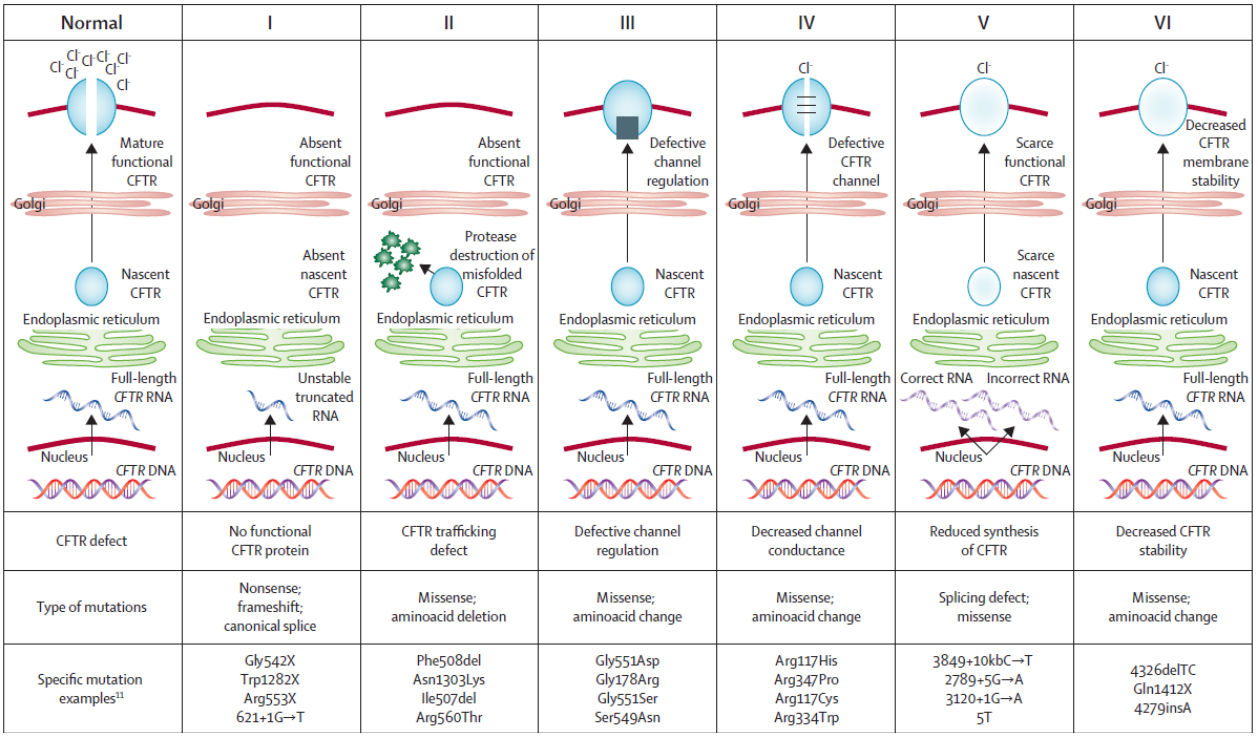


Figure 1 - Reprinted from Boyle and DeBoeck (2013) depicting the classes of CFTR [7].

As a result of the variety of mutations and the impact on a number of physiological systems CF is characterised by a variety of systemic complications including gastrointestinal, metabolic and muscoskeletal dysfunction [1], presenting patients with a significant symptom and treatment burden [8]. Patients report numerous physical and psychosocial symptoms with varied frequency and severity. Respiratory symptoms have highest prevalence, particularly coughing and shortness of breath, other symptoms related to chronic respiratory compromise include fatigue and sleep disturbances [8]. Psychosocial symptoms are also reported with high prevalence including worrying, irritability and sadness [9], with depressive symptoms reported in up to 30% of adults with CF which is also negatively associated with health related quality of life (HRQoL) [9].

There is currently no cure for CF, although an improved understanding of the molecular basis of CFTR mutations has been essential to developing pharmacological agents targeting specific mutations to repair CFTR function and reverse the basic defect [10]. Combined with improved therapeutic management of CF the CFTR modulator therapies offer promise for individuals with CF in future [10]. Advancements in treatments in recent decades has resulted in a steady increase in life expectancy whereby the proportion of adults living with CF now exceeds that of children [3]. The earliest data available from the UK CF registry is from 2002. Within the CF population in 2002 the proportion of adults (≥16 years) was 50.1% with a median age at death of 23 years old [11]. A decade later in 2012 the proportion of adults (≥16 years) with CF was 57.6% with a median age at death of 28 years old [12]. The most recent data from 2018 shows that within the CF population the proportion of adults (≥16 years) is 60.4% with a median age at death of 32 years old [3]. For an individual born with CF in 2018 the median predicted survival age is 47.3 years old [3]. In 2008 this figure was just 38.8 years old [13].

The therapies prescribed in the management of CF also present a significant burden, with patients reporting daily treatments taking approximately two hours to complete [14]. Treatments are usually prescribed in childhood, often before disease progression and the implementation of new treatments is usually in addition to existing treatments, therefore increasing the treatment burden over time [14].

1.2. Lung Function

Mucosal obstruction of distal airways and submucosal glands is a hallmark of CF lung pathophysiology. Pathogens such as Pseudomonas aeruginosa, Burkholderia cepacia and Staphylococcus aureus among others adhere to secretions and are not effectively eradicated resulting in infection [15]. Pulmonary inflammation is also a major cause of decline in pulmonary function and may precede the onset of infection [15].

Assessment of lung function is therefore recommended in CF care [16] and is now a cornerstone of CF management. Routine lung function, assessed using spirometry allows for monitoring of disease progression and identification of acute changes in

clinical condition associated with pulmonary exacerbations and response to therapy. Spirometry is also used to characterise the severity of the disease [17]. Respiratory failure remains the leading cause of mortality in CF [18]. Higher PA is independently associated with higher lung function and exercise capacity in patients with CF [19],[20]. Consequently, PA interventions should look to determine the impact on respiratory function.

1.3. Vascular function

Cardiovascular disease (CVD) in CF is typically associated with severe pulmonary disease and presents as pulmonary hypertension, right ventricular hypertension and cor pulmonale [21]. However, with increased life expectancy patients with CF have greater exposure to traditional risk factors for the development of CVD and atherosclerosis. Ageing, diabetes and metabolic disturbances are significant risk factors for CVD in the general population [22]. With increased life expectancy there is also increased incidence of CF related diabetes (CFRD) [23], [24]. This taken in combination with the high fat diets, altered fatty acid metabolism and abnormal lipid profiles [25] observed in patients with CF, there is a potentially increased risk of CVD within this population. Furthermore, CFTR dysfunction is associated with chronic bacterial infection and sustained inflammation, which contributes to oxidative stress through increased free radical production in addition to impaired antioxidant protection in CF [22], [26]. Oxidative stress is thought to contribute to endothelial dysfunction and atherosclerosis [27], [28], posing further risk of CVD. Atherosclerosis is characterised by the formation of a lipid and cholesterol laden mass in the intima or media of arteries and is a process that underlies many CVDs. Endothelial dysfunction plays a crucial role in the early phases, in which circulating low-density lipoproteins (LDL) infiltrate the intima, passing through the endothelial layer. LDLs become trapped within the vessel wall where they become oxidised by reactive oxygen species released from macrophages [29]. The oxidised LDLs are engulfed by macrophages which results in foam cell formation. Foam cells accumulate in the sub-intimal space forming fatty streaks, which in turn perpetuates the process of atherosclerotic plaque formation [29]. A lipid dense core develops consisting of foam cells and infiltrating smooth muscles cells which is covered by a

fibrous cap. This fibrous plaque calcifies and may haemorrhage, rupture or cause thrombosis resulting in cardiovascular complications [29]. Consequently, endothelial function is a strong predictor of future cardiovascular events [30]. Endothelial function, assessed by flow-mediated dilatation (FMD) has been shown to be reduced in young people with CF, despite preserved lung function and exercise capacity [31]. A potential mechanism for this reduction in FMD is the reduced bioavailability of nitric oxide (NO) observed in CF [31]. In a healthy artery, there is a high bioavailability of NO, which helps protect against the development of atherosclerosis [32] and this is lacking in individuals exhibiting risk factors for CVD [30]. It is also worth noting that the CFTR protein is present in the endothelium of patients with CF, which may impact on the development of atherosclerosis, although its function is not yet fully understood [33]. A better understanding of CVD and endothelial dysfunction is therefore required prevent the development of cardiovascular complications in an ageing CF population.

Exercise training is associated with reduced cardiovascular events in the general population, however modification of traditional risk factors does not account for the degree of risk reduction [34]. The extent of this risk reduction may also be explained by the direct effect of exercise or PA on the vasculature via repetitive increases in shear stress, which leads to functional and structural adaptations that decrease the atherosclerotic risk [35]. There is currently no research exploring the relationship between physical activity and vascular function in patients with CF.

1.4. Health related quality of Life

With improving lifespan in patients with CF, maintained lung function and nutritional status, additional markers of health and wellbeing are becoming equally important alongside lung function to describe the health and wellbeing of patients with CF. Health-related quality of life (HRQoL) is increasingly used as an outcome measure in clinical practice and in clinical trials [36]. This also demonstrates the increasing importance of psychosocial well-being alongside physiological function. The Cystic Fibrosis Questionnaire (CFQ) was the first disease specific questionnaire developed to assess HRQoL in patients with CF. The revised version (CFQ-R) is the most widely used assessment tool in CF and is available in developmentally appropriate

versions in 34 languages [37]. The CFQ-R is used as a self-reported outcome measure, containing generic and disease specific scales, the child, parent and teen/adult versions have 35, 40 and 50 items respectively [37]. The CFQ-R provides a valid and reliable assessment of HRQoL that is sensitive across age, gender, and disease severity and is responsive to the effects of treatments, interventions and exacerbations. It has been reported that the minimally clinically important difference is 4.0 points in stable patients and larger during exacerbation (8.5 points) [36]. In addition to physiological outcome measures, HRQoL should be considered as an important variable in assessing the impact of an intervention. Although HRQoL is routinely assessed in this population there is limited research exploring the relationship between HRQoL and PA.

1.5. Physical activity and sedentary behaviour

For the purpose of this thesis physical activity (PA) is defined as any bodily movement produced by contraction of skeletal muscle that substantially increases energy expenditure [38]. This definition encompasses leisure time PA (which may include sport, household activities or walking) and occupational activity [38]. Exercise is a sub-category of leisure time PA and refers to activity done in a planned, structured and repetitive manor to maintain or improve an aspect of fitness [38]. PA is a complex set of behaviours often described in terms of frequency (how often the activity occurs during a given period), intensity (rate of energy expenditure), time (spent engaging in PA over a given period) and type (of activity) [39].

1.5.1. Physical activity

Physical activity plays an important role in the management of CF, with higher PA being shown to have a positive effect on lung function [19], mucociliary clearance [40], bone health [41] and hospitalisation frequency [42]. Higher levels of PA are also associated with improved aerobic capacity [20], which is associated with reduced mortality in patients with CF, independent of body size, gender and lung function [43]. The promotion of PA and exercise is therefore recommended as part

of routine CF care [44][45]. The majority of research studies promoting PA in people with CF have only used exercise training interventions [46]. There is a lack of studies using other strategies such as health coaching or telemedicine to investigate the uptake and adherence to general PA participation [46]. Furthermore, determining the efficacy of exercise training interventions is limited by sample size, study duration and incomplete reporting in the available studies [47]. Although the benefits of exercise training remain unclear there is no evidence to suggest discouraging the routine clinical promotion of exercise [47]. There is also no standardisation for the assessment or reporting of PA and routine monitoring is not common [44]. Further research is required to understand PA levels and PA assessment methods in view of potentially standardising PA assessment for individuals with CF.

Patients with CF perceive PA to be more acceptable when compared to other therapies such as airway clearance techniques, though adherence to PA is still poor [48]. Assessment of adherence is challenging and often relies on indirect assessment methods such as self-report questionnaires or diaries. Self-reported adherence ('always adherent') to exercise was reported to be just 24.2% in adults with CF [48].

The majority of PA research in CF has focused on the implementation and efficacy of exercise training protocols, which has recently been reviewed elsewhere [47]. The studies included primarily employed aerobic, resistance or a combination of exercise protocols in both in-patient and out-patient settings over a period of time ranging from one month to three years. The findings suggest that exercise training interventions were safe in patients with CF, although high quality evidence to support improvements in key outcome measures was limited [47]. Improvements in exercise capacity, quality of life and lung function were not consistent across the studies reviewed, ranging from no effect to a clear beneficial effect [47]. The review was unable to determine the impact of exercise training interventions on other outcome measures such as body composition, exacerbation frequency, bone health, glucose control and PA due to a lack of available data [47]. An additional conclusion was that short-term interventions (less than one month) were unlikely to be of physiological benefit [47].

The disadvantage with exercise-training interventions is that strict segregation of patients is advised due to the risk of cross-contamination between patients with CF, which prevents group exercise sessions [49]. Group exercise sessions are widely used in patients with other conditions, for example in patients with cancer group exercise can facilitate a sense of group membership and solidarity, allowing participants to relate to each other through PA and temporarily relieve disease related concerns [50]. In addition to the physical benefits associated with exercise, individuals engaging in group exercise also perceived benefits to their mental health and quality of life overall [50].

There is also limited data to suggest that exercise training interventions have a positive impact on PA participation [46] and may in fact decrease habitual PA [51]. Training studies longer than six months in duration and interventions with self-directed behaviours appear to be more effective in increasing PA participation in individuals with CF than short-term and supervised exercise interventions respectively [46]. Self-regulation or autonomy is considered as fundamentally important to facilitating intrinsic motivation for PA, which is beneficial for long-term maintenance [52]. This may explain why interventions providing a form of exercise counselling to promote self-directed behaviours alongside exercise training were more effective in promoting long-term PA behaviour when compared to exercise training alone. An alternative explanation for the reduction of PA seen during or following and exercise intervention is the ‘activitystat’ hypothesis, first described by Rowland (1998). The activitystat hypothes suggests that individuals compensate for an increase in PA or energy expenditure in one domain by reducing PA or energy expenditure in another domain or increasing energy intake to maintain an overall level of PA or energy expenditure [53]. This hypothesis may help to provide an explanation for the high levels of drop out and loss to follow up typically associated with PA interventions [54] but evidence to support the hypothesis is inconsistent [55]. An example of this compensation can be seen in children who reduce PA on days following a day of increased PA across intensities [56]. This day-to-day compensation was not seen in healthy adults, although PA did return to baseline 3-6months post PA intervention [55]. Data is not available to test the activitystat hypothesis in adults with CF, but compensation of PA my warrant consideration when planning PA interventions in this cohort.

Activity counselling and advice to undertake exercise at home, over at least a six month period may result in improved PA participation [16], however there is limited research available exploring habitual PA and sedentary behaviour (SB) in individuals with CF. Interventions aiming to increase habitual PA may offer a more suitable opportunity to integrate PA into daily routines which may be more sustainable and improve adherence to exercise training interventions [57]. An additional benefit of increasing habitual activity as an alternative to exercise training is that it overcomes limitations of infection control measures. Future work may therefore benefit from interventions aimed at improving habitual PA, with the involvement of family members.

1.5.2. Sedentary behaviour

Sedentary behaviour (SB) is defined as any waking behaviour characterised by an energy expenditure ≤1.5METs while in a sitting or reclining posture [58]. This definition emphasises the distinction that SB is something other than the absence of PA. High levels of SB are negatively associated with health outcomes, even among individuals achieving global PA guidelines (150 minutes of moderate PA a week) and should be considered as an independent risk factor for cardiovascular disease and mortality [59], [60]. Approximately 60% of adults' waking time is spent engaging in SB, which is more than 8 hours a day [61]. Despite the recent research interest in SB and the data available from the general population, very little research reporting sedentary time or SB in patients with CF exists. In order to understand SB or to implement interventions targeting SB a valid and reliable assessment method is required. Assessment of SB using self-report methods may be limited by the difficulty of recalling SB due to its incidental nature [62], however objective assessment is possible using accelerometers and/or posture monitors such as the activPAL. The activPAL is thigh-worn device, which provides a valid and reliable assessment of posture, transitions and stepping, allowing the assessment of SB [63]. Given the growing body of evidence around the role of SB in other populations, it may warrant examination in patients with CF.

1.5.3. Physical activity measurement

There are multiple options available for both the objective and subjective assessment of PA in patients with CF including; motion sensors/accelerometers, questionnaires and diaries. The majority of literature uses self-report techniques as the primary measure of PA in CF. Self-report measures are appealing as they are able to provide a low-cost method for the assessment of PA which can capture qualitative and quantitative data in large samples with low participant burden [64]. Objective methods such as accelerometry are more expensive, require a level of expertise for time-consuming data analysis and require participant compliance [64]. Additionally, objective PA data is limited due to a lack in consensus for measurement tools used and outcome measures reported [44]. Accelerometers are small, non-invasive devices which provide an objective assessment of accelerations produced by human movement and are widely used in adult populations to assess PA in fee-living conditions [65]. Accelerometers were traditionally worn on the hip as this was thought to provide the most accurate estimation of activity intensity, however compliance to monitoring protocols is typically poor (i.e. people remove the devices) and it has since been argued that wrist-worn monitors can improve compliance to device wear [66]. Wrist and hip-worn estimates are strongly correlated, but owing to recognised association between duration of monitoring and reliability of PA estimates, the better compliance observed when using wrist-worn monitors can provide researchers with greater confidence in the data obtained [66].

Traditionally, accelerometers would filter and convert acceleration signals to a proprietary, dimensionless number (counts) over a specified time period (epoch) [67]. The count unit would then be the reported outcome measure, which represents the activity undertaken for a given epoch length [67]. Data are time stamped which enables researchers to examine patterns of activity using total counts, average counts for a given activity intensity and time spend in different intensities [64]. To determine activity intensity, cut-points are derived using device specific energy expenditure prediction equations and applied to epoch data [65]. There is considerable variability when using cut-point thresholds across different devices, activities and populations, which may influence the data reported [64]. There are currently no cut-points designed specifically for use in CF populations.

Recently accelerometer manufactures have made it possible to access raw acceleration data expressed in gravity (*g*) units from three axes [68]. Not only does this allow increased control over data processing, by removing proprietary counts, but potentially enables analysis across different devices [68]. Analysis of raw data has also resulted in the development of PA and SB cut-points derived from raw acceleration data [68], [69]. A method of raw data processing uses a data reduction method termed Euclidean Norm Minus One (ENMO), in which raw tri-axial signals are converted into one omnidirectional vector magnitude signal which is then corrected for the value of gravity [70]. These methods have not yet been used to assess PA in patients with CF and may provide an appropriate alternative to traditional count-based methods, providing more transparency and increasing the potential for comparisons across studies and accelerometer devices. Analysis of raw acceleration data can also be used to calculate alternative PA metrics that are independent of the cut-point approaches. For example, the PA intensity gradient (IG), is a novel metric used to describe the distribution of PA intensity [71]. The metric expresses the curvilinear relationship between time and time accumulated across different intensities as a straight line, using the R^2 value, gradient and constant to describe individuals' PA profiles [71]. A lower gradient (steeper slope) represents a poorer PA profile, reflecting more time spent in lower intensity activity, whereas a higher gradient (shallower slope) represent a better profile with more time across the range of intensities. Information about an individual's PA profile is not available using conventional PA analysis methods, but may be useful for providing individualised PA advice, including those with CF. Average ENMO has also been recently reported in PA literature and provides a measure of overall PA and when combined with the IG provides a detailed description of individual PA profiles. These emerging methods of accelerometer data analysis may provide insights into patients with CF's habitual PA and associations in health that remain undetected using traditional approaches.

1.5.4. Physical activity promotion

The promotion of physical activity (PA), which may include structured exercise is recommended as part of routine Cystic Fibrosis (CF) care [44][45]. Despite this there

are few examples of interventions designed to promote PA in this population [46]. A large proportion of research in the area has investigated the delivery of exercise training interventions, which gives little or no attention to behaviour change theory or long-term maintenance [47]. Additionally, evidence supporting a positive impact of exercise training interventions on clinical outcomes remains equivocal [47]. There is evidence to suggest that higher levels of PA are associated with positive effects on lung function [19] aerobic capacity [20], hospitalisation frequency [42] and mortality [43] in patients with CF. Translating this evidence into clinical practice has had limited success, though it has previously been proposed that increasing levels of habitual PA may be more feasible and result in greater compliance than conventional exercise training inventions [46]. Despite this, there is limited research exploring perceptions of PA among adults with CF.

The systematic development of interventions, based on the best evidence available and appropriate theory is recommended as best practice. The medical research council (MRC) also recommends a phased approach to intervention development with attention given to evaluation throughout [72], [73]. Interventions to promote behaviour change, such as increasing PA, should utilise an appropriate conceptual health promotion model and prioritise key factors of the target group [74]. One such model is the PRECEDE-PROCEED model [75], which is consistent with a socio-ecological model of health promotion and is designed to provide a framework to explain health behaviours and environments to inform the design and evaluation of interventions [76]. Involving participants and their families in a participatory formative process to explore attitudes, norms and perceptions and in the development process is central to a phased approach to complex intervention design [73]. Stakeholder (patients, practitioners and policy makers) involvement in the planning, development and implementation of interventions is termed ‘participatory research’ and can provide insights into the ‘real world’ applications of interventions [77]. A participatory approach has previously been used in adolescents with CF and led to the co-development of a functional and acceptable intervention to support transition in this population [78]. Despite the potential benefits of involving patients in the research process there are few examples of participatory research in the literature.

1.6. Philosophical positioning

Ontology is the study of being and is concerned, with the nature of existence, the structure of reality and 'what is' [79]. Epistemology is concerned with what knowledge is and what kinds of knowledge are possible [79]. Theoretical perspectives embody a certain way of understanding ‘what is’ (ontology) as well as a certain way of understanding what it means to ‘know’ (epistemology). Therefore, the following section identifies, explains and justifies the epistemological and theoretical perspectives underpinning the research methods utilised in the current research (Figure 2).

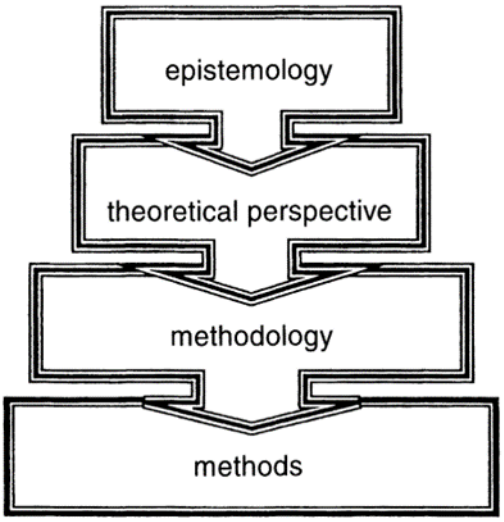


Figure 2 – Reprinted from Crotty (1998) illustrating the process by which epistemology informs theoretical perspectives, methodology and methods [79].

This thesis is constructed drawing on aspects of pragmatism. Pragmatism was first outlined by Charles Sanders Peirce in the early 1800’s and later extended and popularised by James, Dewey and more recently Rorty, among others [80]. The key assumptions of pragmatism are that at every stage of the research process from data collection to analysis and reporting researchers inject a host of assumptions [79]. To Crotty (1998) these assumptions about knowledge and reality shape the meaning of research, the purposiveness of the methodologies and the interpretability of the findings [79]. Unpacking these assumptions is necessary to understand the research process and what the findings mean [79].

Within fundamentals of epistemology a rationalist approach asserts that knowledge can be obtained through reason alone and not through empirical testing. The opposing empiricist position supposes that to obtain knowledge suitable scientific method should be applied. The major theoretical perspectives arrived at throughout this history of debate which are still present in modern philosophy and science are positivism, constructivism, and pragmatism.

Objectivism or empiricism as an epistemology gave rise to positivism as a theoretical perspective, which has been the prominent paradigm for scientific inquiry. The core assumption of a positivist paradigm is that reality exists external to the researcher and can be investigated through scientific enquiry to determine how causes (probably) determine effects or outcomes [81]. Therefore, research is concerned with identifying and assessing the causes influencing an outcome, through experiments [81]. This paradigm therefore lends itself to quantitative methods in which values and numbers and data are used to test hypothesis. This theoretical approach underlies Studies 1 & 2, in which objective methods were utilised to quantify PA and clinical outcome measures to determine the effects of PA behaviour on measures of health, using statistical analysis.

A constructivist paradigm would reject an objectivist approach and assert that truth and meaning do not exist in an external world but are constructed by the subject's interaction with the world [81]. Therefore, the purpose of research is to explore multiple participants' experiences within the context of their environments. It is therefore important for researchers to recognise how their own experiences and perceptions may influence their attempts to make sense of (or interpret) the meanings others have constructed about the world [81]. This approach takes a much more inductive approach to developing theory than the deductive hypothesis testing approach of positivism and is therefore typically viewed as a qualitative approach to research. It is important to note that this paradigm differs from subjectivism. A subjectivist perspectives suggests subjects do not construct meaning through interaction with the world, but rather impose meaning on objects through unconsciousness [81]. A constructivist perspective underlies Study 3, in that the research methodology adopted utilised qualitative interviews and focus groups to explore individual perspectives and identify themes through thematic analysis. Furthermore, there research was conducted by a researcher with prior

understanding and experience of CF, as such the analysis was constructed from the perspective of researcher and a practitioner.

The final paradigm discussed with relevance to the current thesis is pragmatism. There are many forms of pragmatism though a common characteristic is the emphasis on using the approaches best suited to understanding a particular problem. Pragmatism is not committed to any single epistemology, adopting a realist perspective of the physical world as well as a constructionist perspective of social interaction, it is therefore suited to mixed methods research [82]. Mixed methods research is an approach that includes collecting, analysing, and mixing both quantitative and qualitative data, using distinct designs that may involve multiple philosophical assumptions to provide a more complete understanding of a research problem than either approach alone [83]. Adopting a pragmatic approach throughout the current thesis has enabled quantitative and qualitative exploration of PA in adults with CF and provided a more comprehensive understanding of PA and the promotion of PA in this population.

1.7. Objectives

The focus of the thesis is to explore physical activity in adults with CF. It aims to explore the relationship between PA and markers of health and to understand the correlates of PA, to inform the promotion of PA and improve health outcomes in adults with CF.

Objectives:

- Study 1 (Chapter 3) To conduct a systematic review of peer-reviewed evidence to:
    - Establish the physical activity levels of adults with CF.
    - Compare reported PA levels between adults CF and their non-CF peers.
    - Examine the associations between PA and markers of health in adults with CF.
- Study 2 (Chapter 5) To conduct a study to:
    - To compare levels of physical activity in adults with CF to their non-CF peers and to determine the association between PA and vascular function.
- Study 3 (Chapter 7) To conduct a qualitative investigation to:
    - Understand the ecological correlates of physical activity in adults with Cystic Fibrosis. To inform the development of an ecological approach to physical activity promotion in this population.

2. THESIS STUDY MAP

A thesis study map is presented before each study chapter to highlight how each study contributes to achieving the overall aims of the thesis.

Study	Aims/objectives
One - Systematic review	Establish the physical activity levels of adults with CF. Compare reported PA levels between CF patients and their non-CF peers. Examine the associations between PA and markers of health in adults with CF.
Two - Assessment of physical activity and vascular function	To compare levels of physical activity in adults with CF to their non-CF peers and to determine the association between PA and vascular function
Three - Physical activity promotion in adults with CF	To understand the ecological correlates of physical activity in adults with Cystic Fibrosis. To inform the development of an ecological approach to physical activity promotion in this population

3. STUDY 1 - PHYSICAL ACTIVITY AND ASSOCIATIONS WITH CLINICAL OUTCOME MEASURES IN ADULTS WITH CYSTIC FIBROSIS: A SYSTEMATIC REVIEW.

3.1. INTRODUCTION

The main outcomes of this study have been published in the *Journal of Cystic Fibrosis:* Shelley, J., Boddy, L. M., Knowles, Z. R., Stewart, C. E., & Dawson, E. A. (2019). Physical activity and associations with clinical outcome measures in adults with cystic fibrosis; a systematic review. *Journal of Cystic Fibrosis*. https://doi.org/10.1016/j.jcf.2019.03.003. The published article can be found in Appendix A.

3.2. BACKGROUND

Life expectancy of patients with Cystic Fibrosis (CF) continues to increase with improvements in treatments over recent decades, resulting in a greater proportion of adults living with CF [3]. Physical activity (PA) is associated with a number of potential benefits in the management of CF including positive effects on lung function [19], mucociliary clearance [40], bone health [84] and hospitalisation frequency [42]. Higher levels of PA are also associated with improved exercise capacity [20], which is in turn associated with reduced mortality in patients with CF [43]. PA promotion is therefore recommended as part of the routine management of CF [44], [85]. Despite this PA assessment is not common or consistent [44]. However, CF presents patients with a number of potential barriers to PA including; physical symptoms (breathlessness, increased cough, fatigue), high treatment burden and low self-efficacy for PA [86].

PA can be defined as any bodily movement produced by contraction of skeletal muscle that substantially increases energy expenditure, this includes leisure-time PA, occupational PA and exercise [38]. Various self-reported and objective methods are reported in the literature for the assessment of PA in adults with CF, however inconsistencies in measurement tools, outcome measures reported and study design used limit our understanding of PA behaviour and its health associations in

this population. It is generally accepted that patients with CF engage in less PA than their non-CF peers, this is particularly evident for vigorous PA [87]**,** however this finding is inconsistent across the multiple assessment methods reported in the literature. Furthermore, little is known about sedentary behaviour (SB) in this population despite high levels of SB being negatively associated with health outcomes and cardiometabolic diseases in the general population, even among individuals achieving PA guidelines of 150 minutes of moderate-to-vigorous PA a week [59]. High levels of SB are considered as an independent risk factor for cardiovascular disease and mortality [59], yet remain relatively unexplored in an ageing CF population.

There are currently no PA guidelines specifically developed for individuals with CF, although guidelines for the general population appear to be applicable with some modifications depending on disease progression [88]. For the purpose of this review, the global physical activity guidelines outlined by the World Health Organisation (WHO) were used when interpreting reported PA levels. It is recommended that adults (18-64 years) should take part in at least 150 minutes of moderate-vigorous intensity aerobic PA (MVPA) or 75 minutes of vigorous intensity PA throughout the week [60]. The variation in outcome measures reported in the studies reviewed makes it difficult to compare reported levels of PA to recommended guidelines, comparison is therefore only possible in a small number of the studies reviewed. Achieving 10,000 steps daily also provides a reasonable estimate of daily activity and individuals achieving this typically meet the recommendations of 150 minutes MVPA per week [89]. Therefore assessing step count can help to quantify PA and through the use of the indices can provide information for screening, surveillance and intervention evaluation [89].

A large proportion of the PA research conducted in CF populations has been undertaken with children and adolescents [44] and may not be transferable to adult populations. It is well documented that PA declines with age in the general population [90] which may also be exacerbated by worsening disease severity in CF. Given the increasing life expectancy and number of adults living with CF, an understanding of PA levels in adult populations is required. It is important that healthcare professionals are familiar with PA guidelines, engage patients in

conversation around PA and are able provide advice and signpost patients to relevant resources.

3.3. AIMS

The purpose of this review therefore, was to: 1) Establish the physical activity levels of adults with CF. 2) Compare reported PA levels between CF patients and their non-CF peers. 3) Examine the associations between PA and markers of health in adults with CF.

3.4. METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were utilised to inform the review process [91]. Studies that assessed PA in adults with CF and were published from database inception to Feb 28th 2018 were identified. An *a priori* defined protocol was utilised to identify relevant articles that were then systematically screened against inclusion and exclusion criteria. The published protocol can be accessed via the PROSPERO database (CRD42018088434).

A narrative synthesis was performed to provide a summary of the assessment tools used, outcomes reported and overall quality of PA assessment [92]. An assessment of the quality of evidence was made to support the strength of the findings and conclusions made. It was not possible to conduct a meta-analysis due to the wide variation in the methods used to assess PA, the inconsistency of outcome measures reported and the low quality ratings of the available literature.

3.4.1. Search strategy and initial screening

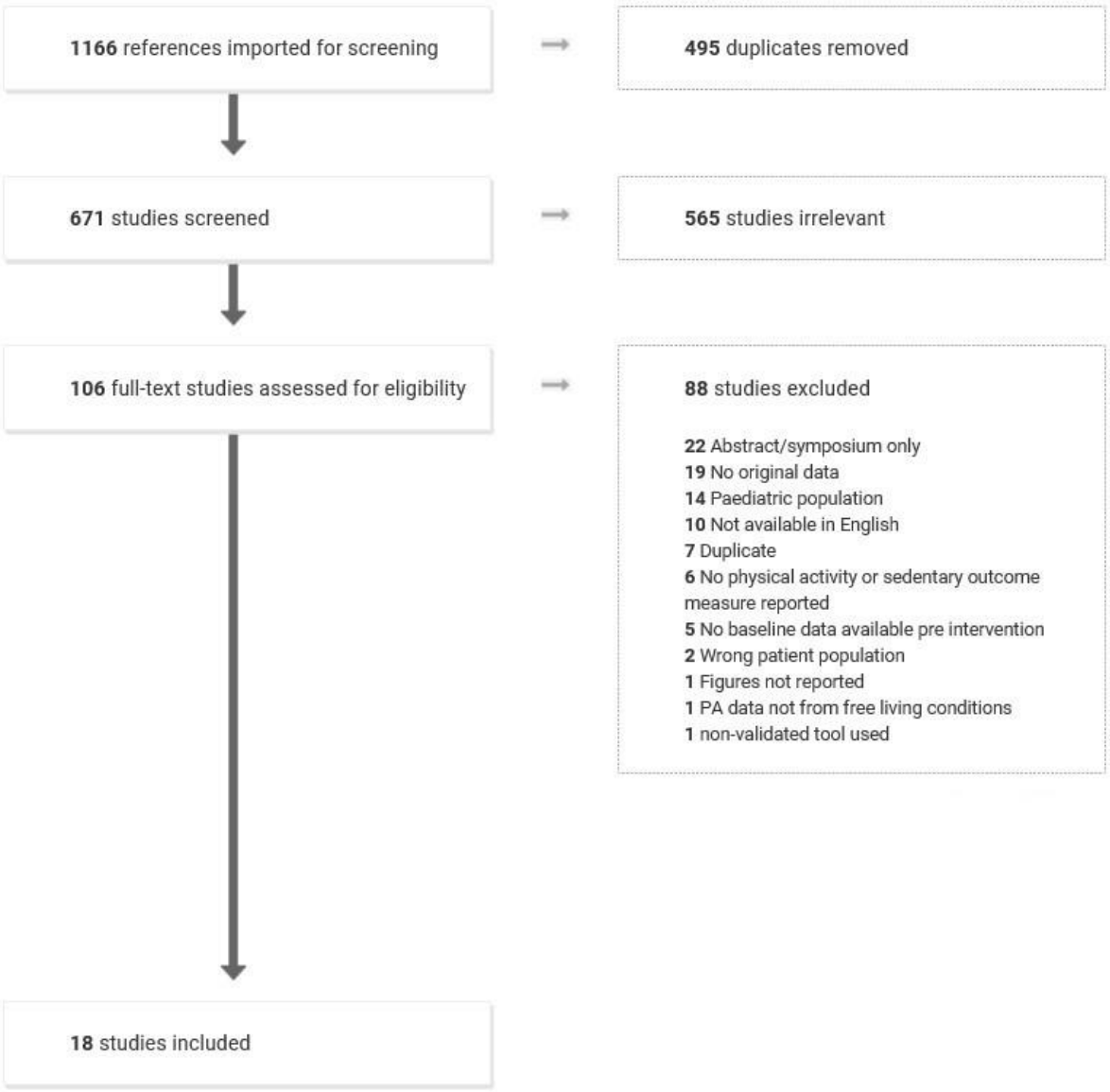
Electronic databases SCOPUS (Elsevier, EMBASE & ScienceDirect), Web of Science, Medical Literature Analysis and Retrieval System Online (MEDLINE) (Cumulative Index of Nursing and Allied Health Literature (CINAHL), SportDiscus & Psychinfo) and Oalster grey literature were searched using search terms individually

tailored for each database (Figure 3). Databases were selected to provide comprehensive coverage of indexed journals, which publish studies from relevant healthcare and PA fields. Title and abstract screening was employed to identify relevant articles and remove articles that were not eligible, this was preferred to applying search limits or 'NOT' terms. Reasons for removing articles at this stage included; non-CF population, paediatric population, no original data reported, not peer reviewed and written in languages other than English. No restrictions were applied to the date of publication, owing to the limited number of studies in a relatively novel field. The search terms yielded 1166 hits, representing 671 unique articles (Figure 2). A further 565 articles were removed during title and abstract screening, using the same criteria as above, resulting in screening of 106 full-text articles. Full-text articles were screened against inclusion and exclusion criteria, leaving 18 articles for data extraction (Figure 4). References of all included papers were screened, although this did not yield any additional articles.

Figure 3 – Boolean search terms

OR	**AND**
'physical activity' 'habitual activity', 'sedentary behaviour' 'accelerometers' 'motion sensors' 'actigraph' 'geneactiv' 'sensewear' 'activpal' 'HAES' 'caltrac' 'IPAQ' & variations on each term	'Cystic Fibrosis'.

Figure 4 - PRISMA flowchart



3.4.2. Application of eligibility criteria

Inclusion criteria included; measurement of physical activity and/or sedentary behaviour (SB) using a measurement tool validated for use in the general adult population and/or adults with CF. Baseline PA and/or SB reported prior to any interventions. Preferable but not essential criteria included; data reported for clinical outcome measures (lung function, exercise capacity, quality of life (QoL)).

Exclusion criteria included; paediatric (<18 years), non-CF or mixed populations where adult and paediatric data were not separated, use of non-validated methods for assessing PA and/or SB, no reporting of PA and/or SB or no baseline data available. Additionally, studies not written in English, providing no original data or that were not peer reviewed were also excluded. Studies that were written as abstracts only rather than full papers were also excluded. No restrictions were applied for study design. Randomised control trials, interventional and observational studies were considered based on satisfaction of the inclusion/exclusion criteria outlined above. Five articles were excluded as 'paediatric population' although they reported data for mixed adult and paediatric populations or defined adults by criteria other than ≥18 years [20] [100]–[103]. Whilst these articles may contain potentially relevant data the original authors were not able to provide the data on the request of the reviewers in the given time frame. Additionally, all studies that were excluded and used accelerometry are listed alongside the reason for exclusion.

3.4.3. Data extraction

A modified version of the 'Cochrane Data Extraction Form', from the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1) [98] was used. The form was modified to include relevant participant characteristics and outcome measures. Two authors (JS, ED) independently extracted the data, discrepancies were resolved through discussion, with a third reviewer (LB) where necessary. Extracted information included: Article characteristics; year of publication, journal, funding source, publication type. Study setting; study population and participant demographics and baseline characteristics. Study methodology; recruitment and study completion rates; outcomes and times of measurement. Information for assessment of the risk of bias.

3.4.4. Risk of bias assessment

Two reviewers (JS, ED) independently assessed the risk of bias for the included studies using the Cochrane risk of bias tool, agreement was reached between the reviewers although a third reviewer (LB) was available if required (Table 1).

Table 1 – Risk of bias assessment of studies included for review.

	Allocation concealment	Blinding of outcome assessors	Blinding of participants & personnel	Sequence Generation	Incomplete outcome data	Selective outcome reporting
Bhudhikanok 1998 [99]	high	high	high	high	low	low
Cox 2016 [42]	high	high	high	high	low	low
Currie 2017 [100]	high	high	high	high	low	low
Decorte 2017 [101]	low	high	high	high	low	low
Elkin 2001 [102]	high	high	high	unclear	low	low
Enright 2004 [103]	low	low	unclear	high	low	low
Enright 2007 [104]	high	low	high	high	low	low
Gruet 2016 [105]	unclear	high	high	high	low	low
Haworth 1999 [106]	high	high	high	high	low	low
Hollander 2005 [107]	high	high	high	high	low	low
Ionescu 2003 [108]	high	high	high	high	low	unclear
Rasekaba 2013 [109]	high	high	high	high	low	low
Savi 2013 [110]	high	high	high	high	low	low
Savi 2015 [111]	high	high	high	high	low	high
Savi 2015 [112]	high	high	high	high	high	high
Street 2006 [41]	high	high	high	high	low	low
Troosters 2009 [87]	high	high	high	high	low	low
Ziai 2016 [114]	high	high	high	high	low	low

3.4.5. Data synthesis

A narrative synthesis was used to describe the data in three sections; 1) PA levels of adults with CF in comparison to global PA recommendations, 2) PA levels of adults with CF in comparison to non-CF peers, 3) The relationship between PA and clinical outcome measures.

3.4.5.1. Moderate-Vigorous Physical Activity

Studies reporting a measure of PA described with a time unit, were compared to the 150 minutes of MVPA per week recommendation. In studies only measuring PA over 5 days the 150 minutes of MVPA recommendation was interpreted as 30 minutes per day on 5 days of the week.

3.4.5.2. Metabolic Equivalents (MET)

MET refers to metabolic equivalent, where 1 MET is the rate of energy expenditure while sitting at rest and is equivalent to an oxygen uptake of 3.5 millilitres per kilogram (kg) per minute, or a caloric consumption of 1kcal/kg/hour. METs are used to attempt to classify PA intensity in a number of studies reviewed, for example, a 3 MET activity expends 3 times the amount of energy used at rest. For the purposes of this review the following definitions are applied; moderate intensity (3-6 METs), vigorous activity (>6 METs) [115]. METs can also be expressed as MET-minutes, whereby the metabolic equivalence of an activity is multiplied by the number of minutes spent engaging in the activity. For example engaging in an activity of 3 METs for 30 minutes is equal to 90 MET-minutes. Consequently, 150 minutes MVPA per week equate to 450 MET-minutes per week, therefore recommendations for MET minutes per week are ≥450 MET-minutes per week.

3.4.5.3. Steps

Whilst it is not possible to make comparisons with the WHO guidelines, the following indices were applied to classify PA based on the number of daily steps reported; Sedentary (<5000), low active (5000-7499), somewhat active (7500-9999), active (≥10,000), highly active (>12,500) [89]. Total physical activity, described as time spent in weight bearing activity or walking was reported in two studies. It is not possible to compare levels of PA among adults with CF to recommended guidelines for MVPA using this data as there is no description of intensity.

3.4.5.4. Energy expenditure

Energy expenditure (EE) represents the sum of resting energy expenditure and the thermic effect of digestion in addition to physical activity [115]. Studies in the current review reported total energy expenditure (TTE) and not specifically the energy expenditure associated with PA. Whilst it has been proposed that adherence to recommended PA guidelines yields an energy expenditure of ~1000 kcal·wk-1, which is associated with improved health outcomes [116], TEE alone does not provide suitable information to assess if adults with CF achieved recommended guidelines for PA.

3.4.5.5. PA indices

The Baecke and Physical Activity Self-Administered Questionnaire (AQAP) questionnaires provide a PA index. The work domain classified occupations as; Low activity (1), Moderate activity (3), High activity (5). Sport and leisure domains were calculated by assigning a MET value for specified activities and assessing the time spent engaging in such activities again resulting in a PA score between 1-5. The sum of the three categories (work, sport, leisure) provides a total PA score between 3-15 [117]. These data do not provide information on minutes of PA therefore cannot be compared to PA guidelines.

3.5. RESULTS

3.5.1. Reporting of PA in adults with CF

In the 18 studies reviewed 33 separate outcome measures were reported using 11 assessment tools including 1 accelerometer (SenseWear Pro 3 armband) and 10 separate self-report questionnaires (Table 2). Questionnaire characteristics have been described elsewhere and are available as supplementary material (Appendix B).

Table 2 – Summary of assessment tools utilised and outcome measures reported.

Accelerometer	
SenseWear Pro 3 armband [42], [87], [110]–[112], [114]	Total energy expenditure (Kcal/day)
	Steps per day
	Total METs
	Total PA (mins/day)
	Light PA (mins/day)
	Moderate PA (mins/day)
	Vigorous PA (mins/day)
	Moderate to vigorous PA (mins/day)
Questionnaire	
Habitual Activity Estimation Scale (HAES) [110]	Total inactivity (min/day)
	Total activity (min/day)
Baecke [101], [106], [107]	Activity score
	Activity factor for sedentary lifestyle (1.5, 1.7, 2.1)
	Work index
	Sport index
	Leisure index
Physical Activity self-Administered Questionnaire (AQAP) [105]	Sport index
	Leisure index
	Global index
International Physical Activity Questionnaire (IPAQ) [109]	Work (min/week)
	Transport (min/week)
	Domestic (min/week)
	Leisure (min/week)
	Walking (min/week)
	Moderate (min/week)
	Vigorous (min/week)
Recall questionnaires [99], [100], [102]–[104], [108], [113]	METs (weekly)
	METs (daily)
	METs (1.5 Light) (hrs/week)
	METs (4 Moderate) (hrs/week)
	METS (6 Hard) (hrs/week)
	METs (10 Very hard) (hrs/week)
	Lying time (min/day)
	Energy expenditure (Kcal/day)

3.5.2. Levels of PA in adults with CF compared to recommended PA guidelines

Comparison between PA levels in adults with CF and global physical activity guidelines was only possible in 8 [42][87][112][114][111][109][100][104] of the 18 studies reviewed. Adults with CF only met PA guidelines in 3 [42][109][100] of the 8 studies, only one of which used objective methods to assess PA [42]. Table 3 displays the findings for the 13 studies which did not include a control group.

3.5.2.1. Studies reporting objectively assessed PA

Accelerometry was used in 3 of these studies [42], [112], [114] although only two reported MVPA [42], [112] with a third reporting step count and TEE [114]. Of the two studies reporting MVPA, participants achieved recommended PA guidelines in one [42]. In the study in which participants did not achieve recommended PA guidelines, step count was also reported, which would indicate that patients were 'somewhat active', despite not meeting guidelines for MVPA [112]. Despite using similar assessment methods in groups of comparable disease severity and participant characteristics the two studies reported different levels of MVPA. The final study [114] using objective assessment only reported step count, however these values appear to be similar to those previously reported [112], with both studies reporting 'somewhat active' cohorts achieving 8874 and 9508 steps respectively.

3.5.2.2. Studies reporting self-reported PA

One study [100] used a 7-day recall questionnaire to assess PA, and whilst this tool has previously been validated for use in CF [93], reported levels of PA are high in contrast to objectively assessed PA, with patients exceeding PA recommendations, reporting a mean of 282 minutes of moderate, hard or very hard PA per week. Three studies used the Baecke questionnaire [101], [106], [107], with a fourth using the AQAP [105], all of which report PA as an activity score and therefore results cannot be compared to PA guidelines. Furthermore one study did not provide group means,

which prevented interpretation [107]. Gruet *et al*. (2016) reported an overall PA score of 9 (of a possible 15) which may suggest that the population studied were moderately active [105]. Haworth *et al.* (1999) reported an activity score of 7.6 which likely represents low levels of activity in the study group [106]. Decorte *et al.* (2017) reported 2.6, 2.3 and 3.2 for work, sport and leisure time indices respectively, which suggests that occupational activity and engagement in sport were low in the population studied, whilst leisure time activity was higher [101].

Two studies reported mean daily METs [103], [108] assessed using recall questionnaires, which does not provide information for comparison to recommended PA guidelines. Both studies reported similar levels of PA (36.7 and 37.6 daily METs, respectively) which were reported to be comparable to non-CF young adults [103].

Energy expenditure was reported based on self-reported PA in one study [102]. Whilst it is not possible to make assumptions about PA levels from energy expenditure, the data reported indicates that TEE in the cohort studied (2071.39 Kcal) is comparable to what could be predicted for a typical sedentary/low active adult [115].

The final studies reported total PA (time spent walking or doing sport) and weight bearing PA using self-report techniques [99], [113]. The data reported did not include any information about intensity, which again prevents interpretation in the context of WHO recommended guidelines. The two studies reported considerably different values with Street *et al.* (2006) describing what could be considered as an active cohort (engaging in 11.3hrs per week of PA, including walking and sport) whilst data provided by Bhudikanok *et al.* (1998) would suggest that the cohort were inactive (engaging in 3hrs per week of weight bearing PA). It is possible that the two report different aspects of PA which is not clear from the methods described.

3.5.2.3. Sedentary behaviour (SB)

No studies assessed SB, although lying time was reported in one study, finding no significant difference between adults with CF (452.1 mins/day) and their non-CF peers (493.5 mins/day) (P =0.11) [110]. Inactivity, assessed using the HAES, was also reported and was not different between groups (367 vs. 376.6 mins/day for CF

and non-CF respectively (*P* =0.74)) [110], however inactivity describes insufficient levels of PA to meet guidelines and not necessarily SB [118].

3.5.3. Levels of PA in adults with CF compared to their non-CF peers

Whilst recommended PA guidelines provide a reference value to assess PA in adults with CF, it is also well recognised that a large proportion of the general adult population do not meet recommended PA guidelines [90]. It may therefore be more appropriate to compare adults with CF to comparable non-CF control groups rather than public health guidelines to determine if differences exist between the cohorts. Five studies [87], [104], [109]–[111] reported PA levels for a comparable non-CF control group, PA was therefore compared between these groups (Table 4).

3.5.3.1. Studies reporting objectively assessed PA

Three studies reported objectively assessed PA [87], [110], [111]. Time spent engaging in MVPA was significantly higher in the control group when compared to adults with CF in one study [87]. No significant differences were found between groups across any other outcome reported in the remaining studies, additionally, the significant difference found by Troosters *et al*. (2009) was found in activity above moderate intensity, with no difference at light intensity or in daily step count [87]. Step count was reported in two studies, neither found a significant difference between groups, however in both studies the control group would be considered as 'active' based on the daily number of steps (10281 and 10591 steps respectively), whereas each of the CF groups failed to meet this threshold (9398 and 9161 steps respectively) [87], [111]. Although there is evidence to suggest that there are beneficial effects associated with taking 10,000 steps, cut-points such as this should be interpreted with caution.

Table 3 – Comparison between reported PA in adults with CF and PA recommendations.

Study	Design	Assessment tool	Outcome measure reported		Achieving guidelines ✓/×	
Cox 2016 [42]	Cross-sectional study	SenseWear pro 3 armband accelerometer	**CF (n=61)**			150 minutes MVPA per week (30 minutes, 5 days per week)
			Moderate-Vigorous PA (mins/day) (median, IQR)	31 (15-53)	✓	
Savi 2015 [112]	Cross-sectional study	SenseWear pro 3 armband accelerometer	**CF (n=60)**			
			Duration of physical activity (min/day) (mean ± SD)	213 ±137		
			Mild intensity activities (min/day) (mean ± SD)	186 ±121	×	
			Moderate intensity activities (min/day) (median, IQR)	15 (9-29)		
			Vigorous intensity activities (min/day) (median, IQR)	1 0-3		
			Average METS (mean ± SD)	1.7 ±0.3		
			Steps per day (mean ± SD)	9508 ±3861	✓/×	10,000 steps daily
Ziai 2016 [114]	Cross-sectional study	SenseWear pro 3 armband accelerometer	**CF (n=36)**			
			Steps per day (mean ± SD)			
			Normal Glucose tolerance (n=10)	8874 ±2625	✓/×	
			Impaired Glucose tolerance (n=10)	9416 ±4172	✓/×	
			CFRD (n=16)	7033 ±3186	×	
			Daily TEE (mean ± SD)			

			Normal Glucose tolerance (n=10)	2300 ±412		
			Impaired Glucose tolerance (n=10)	2129 ±525		
			CFRD (n=16)	2152 ±461		
Currie 2017 [100]	Cross-sectional study	7 day recall questionnaire (7DPAR)	**CF (n=18)**			
			METs per week	14370 ±997	✓	500-1000 MET-minutes
			Light physical activity (1.5 METs), hrs/week (mean ± SD) (n=18)	103.3 ±9.4		
			Moderate physical activity (4 METs), hrs/week (mean ± SD) (n=15)	2.9 ±2.7	✓	150 minutes MVPA per week
			Hard physical activity (6 METs), hrs/week (mean ± SD) (n=8)	0.8 ±0.9		
			Very hard physical activity (10 METs), hrs/week (mean ± SD) (n=7)	1 ±1.9		
Enright 2004 [103]	Randomised control trial	Recall questionnaire	**CF (n=19)**		Unable to compare to global physical activity guidelines	
			METs over 24hrs (mean ± SD)	37.1 ±10.2		
			Inspiratory muscle training (80%) (n= 9),	40.1 ±8.9		
			Control group (n=10)	36.7 ±9.7		
Hollander 2005 [107]	Cross-sectional study	Baecke questionnaire	**CF (n=34)**			
			Activity factor for sedentary lifestyle 1.5 (%, n)	34%, 12		
			Activity factor for intensive work 1.7 (%, n)	60%, 21		
			Activity factor for sport 2.1 (%, n)	3%, 1		
Gruet 2016 [105]	Cross-sectional study	AQAP questionnaire	**CF (n=25)**			
			Daily physical activity index (median, IQR)	2.8 (2.0-3.1)		
			Sport index (median, IQR)	3.0 (2.3-3.3)		
			Leisure-time index (median, IQR)	3.3 (2.8-3.8)		
			Daily physical activity (Global score) (median, IQR)	9.0 (7.3-9.8)		

Elkin 2001 [102]	Cross-sectional study	7 day recall questionnaire (7DPAR)	**CF (n=87)** Mean daily energy expenditure (Kcal, (corrected for body weight))	2071.39 (613)	
Decorte 2017 [101]	Case-control study	Baecke questionnaire	**CF (n=15)** Baecke questionnaire work index (mean ± SD) Baecke questionnaire sport index (mean ± SD) Baecke questionnaire leisure time index (mean ± SD)	 2.6 ±0.5 2.3 ±0.4 3.2 ±0.6	
Ionescu 2003 [108]	Case-control study	Recall questionnaire	**CF (n=56)** METs (Daily) (mean, 95% CI) *Mild impairment (FEV_1>65% predicted) (n=22)* *Moderate impairment (FEV_1 >46% and < 65% predicted) (n=11)* *Severe impairment (FEV_1 <45% predicted) (n=23)*	 37.6 (33.6-41.5) 33.9 (31.3-36.6) 34.2 (30.2-38.2)	
Haworth 1999 [106]	Cross-sectional study	Baecke questionnaire	**CF (n=151)** Activity score (mean ± SD)	 7.6 ±1.4	
Street 2006 [41]	Cross-sectional study	Activity Questionnaire	**CF (n=17)** Physical activity (hrs/week) (mean ± SD) (Time spent walking or doing sport per week)	 11.3 ±1.1	
Bhudikanok 1998 [99]	Cross-sectional study	Interview & 3 day-diary	**CF (n=21),** Weight bearing physical activity (hrs/week) (mean ± SD) *Males (n=6)* *Females (n=15)*	 3 ±3 3 ±4	

3.5.3.2. Studies reporting self-reported PA

Three studies used self-report tools to assess PA [104], [109], [110]. PA was higher in the non-CF control group in 1 study [109], there were no significant differences in the remaining 2 studies [104], [110]. The significant difference observed between the CF and non-CF groups was found for total PA (MET min·week) (5309 and 7808 respectively, (P =0.011)) [109]. No significant differences were found between groups for MVPA, additionally, Rasekaba *et al.* (2013) described comparable levels of PA across domestic, leisure, moderate-vigorous domains, with reduced total activity being explained by reduced PA in work and transport domains [109]. The proportion of adults with CF and non-CF controls who met recommended guidelines for PA was also comparable with 93% in each group [109].

One study used both a validated questionnaire (HAES) and an accelerometer [110]. No significant correlation was observed between PA assessed using the objective or subjective methods (P >0.05), with self-reported PA being over-estimated in both groups, which may suggest an influence of measurement tool on PA [110].

3.5.4. Relationship between PA and clinical outcome measures

Thirteen studies explored the relationship between PA and other clinical outcome measures (lung function, body mass index (BMI), exercise capacity, exacerbation frequency) [42], [87], [111], [112], [114], [99], [100], [102], [104], [106], [108]–[110]. Whilst the remaining 5 studies [101], [103], [105], [107], [113] reported data on some of these outcome measures no correlations with PA were performed or reported.

Table 4 – Comparison between reported levels of PA in adults with CF and comparable non-CF control groups

Study	Design	Assessment tool	Outcome measure reported				Difference	*✓/✖ CF	CON
			CF (n=20)		**Control (n=20)**				
Troosters 2009 [87]	Case-control study	SenseWear pro 3 armband accelerometer	Moderate Physical activity (min/day) (mean, IQR)	14.8 (8.6-36.8)	Moderate Physical activity (min/day) (mean, IQR)	34.5 (20.6-53.8)	PA significantly higher in control group (p = 0.03)	✖	✓
			Steps per day (mean, IQR)	9398 (6317-12970)	Steps per day (mean, IQR)	10281 (7928-12360)	No significant difference in PA between groups (p = 0.37)	✖	✓
			CF (n=30)		**Control (n=15)**				
Savi 2015 [111]	Case-control study	SenseWear pro 3 armband accelerometer	Moderate & Vigorous activity (min/day) (mean, IQR)	16 (9-29)	Moderate & Vigorous activity (min/day) (mean, IQR)	12 (8-27)	No significant difference in PA between groups (p = 0.43)	✖	✖

			Mild intensity activity (min/day) (mean, IQR)	159 (100-246)	Mild intensity activity (min/day) (mean, IQR)	147 (77-205)	No significant difference in PA between groups (p = 0.22)		
			Moderate intensity activities (min/day) (mean, IQR)	13 (9-29)	Moderate intensity activities (min/day) (mean, IQR)	11 (7-16)	No significant difference in PA between groups (p = 0.34)		
			Vigorous intensity activities (min/day) (mean, IQR)	1 (0-3)	Vigorous intensity activities (min/day) (mean, IQR)	1 (0-5)	No significant difference in PA between groups (p = 0.94)		
			Steps per day (mean ± SD)	9160.5 ± 3825.6	Steps per day (mean ± SD)	10591 ± 4024.6	No significant difference in PA between groups (p = 0.25)	×	✓
Savi 2013 [110]	Case-control study	HAES Questionnaire & SenseWear pro 3 armband accelerometer	**CF (n=20)**		**Control (n=11)**				
			Lying Time (min/day) (mean ± SD)	452.1 ± 71.4	Lying Time (min/day) (mean ± SD)	493.5 ± 68.2	No significant difference in PA between groups (p = 0.11)		
			Duration Physical Activity (min/day) (mean ± SD)	230.4 ± 117.4	Duration Physical Activity (min/day) (mean ± SD)	212.7 ± 115.8	No significant difference in PA between groups (p = 0.74)		
			HAES Total Inactivity, (min/day) (mean ± SD)	367 ± 138.2	HAES Total Inactivity, (min/day) (mean ± SD)	376.6 ± 94.4	No significant difference in PA between groups (p = 0.74)		

			HAES Total Activity , (min/day (mean ± SD)	533.7 ± 147.7	HAES Total Activity , (min/day (mean ± SD)	506.7 ± 105.6	No significant difference in PA between groups (p = 0.48)		
Enright 2007 [104]	Case-control study	Recall questionnaire	**CF (n=40)**		**Control (n=30)**				
			METs (mean, 95% CI)	37.0 (35.0-39.0)	METs (mean, 95% CI)	41.5 (40.0-43.0)	No significant difference in PA between groups (p >0.01)	×	×
Rasekaba 2013 [109]	Case-control study	International physical activity questionnaire (IPAQ)	**CF (n=101)**		**Control (n=35)**				
			MET (min.week)(Total) (mean ± SD)	5309 ± 6277	MET (min.week)(Total) (mean ± SD)	7808 ± 5493	PA significantly higher in control group (p = 0.011)	✓	✓
			MET (min.week) Work (mean ± SD)	1887 ± 4285	MET (min.week) Work (mean ± SD)	3707 ± 5292	PA significantly higher in control group (p = 0.003)		
			MET (min.week) Transport (mean ± SD)	613 ± 1018	MET (min.week) Transport (mean ± SD)	1315 ± 1123	PA significantly higher in control group (p <0.001)		
			MET (min.week) Domestic (mean ± SD)	1513 ± 2496	MET (min.week) Domestic (mean ± SD)	1219 ± 2428	No significant difference in PA between groups (p = 0.801)		
			MET (min.week) Leisure (mean ± SD)	1269 ± 1607	MET (min.week) Leisure (mean ± SD)	1565 ± 2134	No significant difference in PA between groups (p = 0.376)		
			MET (min.week) Walking (mean ± SD)	1278 ± 1593	MET (min.week) Walking (mean ± SD)	2394 ± 2505	PA significantly higher in control group (p = 0.004)		
				1256 ± 1802		1645 ± 3223			

	MET (min.week) Moderate (mean ± SD)			MET (min.week) Moderate (mean ± SD)			No significant difference in PA between groups (p=0.648)
	MET (min.week) Vigorous (mean ± SD)		2170 ± 3560	MET (min.week) Vigorous (mean ± SD)		2787 ± 4242	No significant difference in PA between groups (p = 0.110)
* ✓✗ Indicates whether reported levels of PA meet recommended guidelines as describe in the methods section. ✓ indicates that guidelines were achieved, whilst ✗ indicates that guidelines were not met.							

3.5.4.1. Lung Function

Five studies reported on the relationship between lung function expressed as FEV_1 or FEV_1% predicted and objectively assessed PA [42], [87], [110]–[112]. Though MVPA was not different across categories of disease severity (FEV_1 <40, 40-60, 60-80 >80% predicted), participants engaging in 30 minutes or more MVPA per day had higher lung function than those engaging in less than 30 minutes MVPA [42]. Time spent engaging in MVPA was also positively associated with FEV_1% predicted (P = 0.04) [112]. Troosters *et al.* (2009) did not find a correlation between MVPA and FEV_1, although number of steps was positively correlated with near significance with FEV_1 (R = 0.39, P = 0.08) [87]. Savi *et al.* (2015) also found no correlation between MVPA and lung function [111]. MVPA was not reported by Savi *et al.* (2013), who reported on energy expenditure, finding a significant correlation between FEV_1 and activity energy expenditure during both week days (r = 0.436, P = 0.05) and weekends (r = 0.435, P = 0.05) [110].

Four studies reported the relationship between lung function and self-reported PA [100], [104], [108], [109]. No significant difference in FEV_1% was found between participants who achieved recommended PA guidelines compared to those who did not achieve guidelines [100]. No relationship was found between FEV_1 and self-reported PA, although low PA was associated with reduced vital capacity (VC) and total lung capacity (TLC) (P <0.01) [104]. Higher PA (MET·min·week) was associated with better lung function (FEV_1), although the relationship was weak (R = 0.26, P <0.05) and not statistically significant when analysing males alone, which may indicate gender differences in PA levels [109]. Patients with severe impairment (FEV_1 <45% predicted) were less active than those with mild impairment (FEV_1 >65% predicted) (P <0.01), with no difference between moderate and severe impairment [108].

3.5.4.2. Exercise capacity

Four studies explored the relationship between exercise capacity and PA, all of which assessed PA using objective methods [42], [87], [110], [111]. All found positive associations between PA (Total PA ((R = 0.51, P = 0.02)) [110] and MVPA

((ß = 0.59, *P* = 0.002, (R^2 = 0.32)), (R = 0.44 p = 0.01)) [42], [87], [111]) and exercise capacity ($VO2_{peak}$ [42], [87], [111] and 6-minute walk test distance [110]). This relationship was not evident when using the HAES questionnaire to assess PA [110].

3.5.4.3. Exacerbations

Two studies explored the relationship between exacerbation and hospitalisation frequency and objectively assessed PA [42], [112]. More frequent exacerbations were associated with lower PA, although this was not significant once corrected for other clinical covariates [112]. Time spent engaging in MVPA was moderately, yet significantly correlated with reduced need for hospitalisation (r_s = *-0.3, P* = 0.05) [42].

3.5.4.4. Body composition

Three studies explored the relationship between body composition and self-reported PA [104], [108], [109]. Lower PA was associated with lower fat free mass (FFM) [104], [108] but not BMI [109].

Four studies [99], [102], [106], [108] explored the relationship between self-reported PA and bone mineral density (BMD), all of which reported a positive association between higher PA and higher BMD ((*r* = 0.249, *P,0.05), (r = 0.3, P <0.01),(r = 0.53, P <0.01))* [102], [106], [108] with the exception of Bhudikanok *et al.* (1998) who reported no association [99].

3.5.4.5. Blood glucose control

Two studies reported on the association between blood glucose control and PA, using objective [114] and self-reported PA assessment [100]. No significant association between blood glucose control and PA was reported in either study [100], [114].

3.5.4.6. Quality of Life (QoL)

Only one study reported on quality of life, finding higher scores for QoL in patients achieving recommendations for MVPA when compared to those who did not (P <0.05) [42].

3.6. DISCUSSION

In the majority of studies reviewed adults with CF fail to meet recommended PA and step count guidelines. Non-CF peers also failed to meet guidelines, with comparable levels of PA between adults with CF and their non-CF peers. There was low quality evidence to support associations between lung function, exercise capacity and PA. Associations between PA and clinical variables were more evident in studies using objective PA assessments, when compared to those using self-reported PA.

3.6.1. Achievement of recommended PA guidelines

Adults with CF did not achieve recommended PA guidelines and daily step count targets in five out of the eight studies in which comparison to guidelines was possible. However, their non-CF peers also failed to achieve recommended guidelines in two out of five studies. Many of the assessment tools used did not provide sufficient information about frequency, intensity and time of PA to allow for comparison to guidelines. Whilst it is recommended that patients meet PA guidelines it is also worth noting that a small increase in PA levels is associated with beneficial effects on health outcomes and risk of all-cause mortality, even when recommended levels are not achieved. Such health benefits can be achieved by individuals moving from the category of ‘no activity’ to ‘some levels of’ of activity [60].

3.6.2. Physical activity in adults with CF compared to non-CF peers

No significant differences in PA were found between groups in 3 of the 5 studies with comparable control groups. The differences observed between groups were reported in work and transport domains, suggesting variation in lifestyle and

employment opportunities in adults with CF when compared to their non-CF peers in one of these studies [109]. Individuals with CF are more likely to work in jobs which are sedentary or involve light work, with two thirds of patients with CF reporting CF as an obstacle to their career, with over half reporting being limited in their work by CF [119]. Occupational PA in patients with CF may warrant further investigation. In the second study, the differences between groups were observed at moderate intensities and above [87]. Classifying PA intensity remains problematic in clinical populations. Activity intensity is classified using cut-points which are derived using device specific energy expenditure prediction equations [64], which may not be appropriate for CF populations as no CF specific cut-points exist. Raw data analysis is recommended as best practice in PA research [120] and cut-points derived from raw data are available [68], which increases research control of the data. Unfortunately, these methods were not employed in any of the studies reviewed and have not been examined in patients with CF to date. Future research should look to employ these methods when assessing PA in patients with CF.

3.6.3. The relationship between PA and secondary outcomes

The evidence for an association between PA and lung function was inconsistent with 5/9 finding a positive association. There appears to be stronger evidence for an association between PA and exercise capacity with all 4 studies reviewed reporting a positive association, albeit in a small number of low quality studies. Evidence of an association with PA was also inconsistent across all other outcome measures reviewed. Additionally only one study reviewed reported a measure of QoL.

The majority of studies which found an association between PA and lung function used an objective assessment of PA, with only one study finding an association using self-reported PA. Likewise, all of the studies finding an association between PA and exercise capacity used objective PA assessment, whereas the association was not evident when using a self-report questionnaire. Given the limited number of studies comparing objective and self-reported PA assessment, it is not possible to assess the influence of assessment tool on the ability to detect correlations between PA and clinical outcome measures. Though the available data would suggest that objective PA assessment may be more appropriate than self-reported methods

[110]. Future research should utilise objective PA assessment wherever possible, with additional self-report methods considered alongside, in order to provide evidence for future PA guidelines.

An additional consideration when exploring the relationship between PA and clinical outcome measures is that of variation in the population due to the nature of the disease. Patients will inevitably experience periods of stability and instability, and disease progression and severity is highly variable within cohorts, all of which presents challenges for monitoring PA. Exacerbations of CF symptoms and hospitalisation impact levels of PA [121]. This may result in data attrition if exacerbations occur during study monitoring periods. Additionally, PA assessed pre, during or post-exacerbation may not accurately reflect habitual PA. Routine monitoring throughout the year and not just during admissions is required to overcome this issue. Monitoring devices and cut-points need to be validated for use in CF populations, both in terms of criterion validity to gold standard measures of PA assessment and in terms of the ability to discriminate between disease severities. Additional work is required to develop disease specific cut-points. Alternatively, standardised cut-points should be agreed upon and adopted universally.

3.6.4. Variability in reported PA variables

There were a wide range of measurement tools used in the studies reviewed. Five studies used an objective method [42], [87], [110]–[112], [114] with the remaining 12 studies using self-report questionnaires, in addition to one study using both methods [110]. Comparisons between studies are difficult due to the large range of outcomes reported (Table 2). There is no consistent variable (e.g. steps, total PA time, METs) reported meaning analysis of pooled effects was not possible. There were no consistent findings for PA in comparison to guidelines or non-CF peers when assessed using different PA assessment methods, suggesting no difference between the assessment methods used. This may be due to variances in validity and reliability of these assessment methods as well as differences in populations' studied and study designs. There is therefore a need for an adoption of standardised, objective measures of PA, with consistent outcomes reported.

Standardisation may enable a better understanding of PA in this cohort and allow for comparisons to be made to global PA recommendations and non-CF peers.

3.6.5. Assessment tools utilised

Questionnaires may be useful for large scale epidemiological research, or as secondary outcome measures of PA, however objective PA assessment should be considered as the informed choice for PA assessment in clinical practice and research [44]. The IPAQ was the only self-report tool which allowed PA levels to be compared to guidelines in the current review. The Baecke questionnaire was the most frequently used questionnaire, used in 3 studies, all of which described low levels of PA in adults with CF. Understanding of PA levels in adults with CF has previously been based on such studies though it may be possible that the Baecke questionnaire underestimates PA in this population. The questionnaire is not disease specific and was developed in healthy, individuals and may not be appropriate for use in CF populations. Whilst the IPAQ is well validated across multiple populations [122], it is not valid or appropriate for use in clinical populations such as; breast cancer [123], HIV [124] or fibromyalgia [125], which highlights the importance of validating tools in the population in which they are intended to be used. The HAES questionnaire has previously been described as a valid, reliable and responsive PA assessment tool in adolescents with CF [126]. The current review only included one study using the HAES questionnaire, the findings of which suggest that the questionnaire overestimates PA in adults with CF when compared to accelerometry [110]. The studies in the current review span almost two decades, during which time the management of CF has changed considerably. Additionally, the assessment of physical activity has also changed with the increased accessibility and use of accelerometry in the previous decade. The data available in the current review does not allow for comparisons of clinical outcome measures and PA assessment throughout this period and caution should be taken when interpreting data across such a long period.

3.6.6. Limitations

The quality of data reported in the studies reviewed limits the strength of the conclusions which can be made from this review, this review therefore highlights the need for further research in this area. The majority of the studies were graded as low quality, based primarily on a lack of a control groups and/or randomisation. The majority of studies were not specifically designed to investigate PA levels, often reporting PA as a secondary outcome measure. The non-standardised reporting of outcome measures prevents any meta-analysis or collation of data to strengthen the evidence and improve understanding of PA behaviour. Additionally, assessing the risk of bias in the studies reviewed is problematic. The tools currently available to assess risk of bias are not designed to assess studies using a cross-sectional design. Consequently, the assessment of risk of bias and the ability to make recommendations based on this assessment may be limited when using the tools currently available.

3.7. CONCLUSIONS

The literature reviewed would suggest that PA in adults with CF is largely comparable to their non-CF peers, despite being insufficiently active to achieve global PA recommendations. The choice of PA assessment tool and reported outcomes are highly variable, many of which do not provide sufficient information about the frequency, intensity or time of PA in adults with CF. The associations between PA and clinical outcomes appear to be stronger when using objectively assessed PA when compared to self-reported PA, although there are few studies available for analysis. The previously reported associations between PA and lung function appear to be supported by the data reviewed, although a number of studies found no associations. The association between PA and exercise capacity is also supported by data reviewed, albeit from a limited number of studies.

3.8. FUTURE RECOMMENDATIONS

The current review has highlighted a requirement for high quality studies designed specifically to explore PA in adults with CF. The increased emphasis on adults with

CF is also reflected by the recently updated European Cystic Fibrosis society (ECFS) best practice guidelines, who also recognise a shift in focus to adult populations given the current trend in life expectancy. Whilst this is true for wider CF care it is particularly relevant with regards to PA assessment, given the lack of available evidence. Standardisation of PA monitoring and reporting is essential for future research, it has previously been recommended that time spent engaging in PA of different intensities, time spent sedentary, step count and energy expenditure should be the minimum standard for reporting PA [44]. A wrist-worn accelerometer (compliance has previously been shown to be higher when using wrist worn devices [68]), worn for seven consecutive days during waking hours, using at least 10 hours per day as a minimum wear time criteria should be used to assess habitual PA [127]. Where possible raw data analysis should be used to analyse data with outcomes reported as outlined above. Standardisation will allow for comparisons between cohorts as well as data pooling to improve statistical precision. Levels of PA and its impact on health and wellbeing in CF are still not clear in the literature. Which may be attributed to the lack of high-quality research, using appropriate PA assessment methods to examine PA behaviours and the relationship with clinical outcomes. Further work is therefore needed to fully elucidate the impact of PA in CF, with an ultimate aim of providing an evidence base to inform guidelines and clinical practice. The scope of the current review only extends to adults (≥18 years), additional reviews are required to understand any differences between paediatric and adult/mixed populations.

The quality of PA assessment would benefit from an approach similar to the European CF Exercise group's recommended guidelines for exercise testing [128]. This involved experts from a range of backgrounds from different organisations and geographical areas were involved in a process to inform the development of the guidelines [128]. The guidance recommends the standardised use of routine exercising testing in CF care, and whilst this provides an important assessment of exercise capacity, this is only one component of PA. Further assessment methods are required to assess habitual PA; a combination of exercise testing, objective and self-reported PA assessment methods should be considered in clinical practice to screen participants and inform and evaluate PA interventions.

4. THESIS STUDY MAP

Study	Aims/objectives	Key findings
One - Systematic review	Establish the physical activity levels of adults with CF. Compare reported PA levels between CF patients and their non-CF peers. Examine the associations between PA and markers of health in adults with CF.	• PA in adults with CF is largely comparable to their non-CF peers, despite being insufficiently active to achieve global PA recommendations • Highlighted a requirement for high quality studies designed specifically to assess PA in adults with CF
Two - Assessment of physical activity and vascular function	To compare levels of physical activity in adults with CF to their non-CF peers and to determine the association between PA and vascular function	
Three – Physical activity promotion in adults with CF	To understand the ecological correlates of physical activity in adults with Cystic Fibrosis. To inform the development of an ecological approach to physical activity promotion in this population	

5. STUDY 2 - PHYSICAL ACTIVITY AND VASCULAR FUNCTION IN ADULTS WITH CYSTIC FIBROSIS AND THEIR NON-CF PEERS.

5.1. BACKGROUND

Physical activity (PA) is of clear benefit for the general population [129], and a small increase in PA is positively associated with clinically relevant changes in health outcomes in a number of clinical and/or inactive populations [129]. The association between sedentary behaviour (SB) and increased risk for cardiometabolic disease and mortality is also well documented [59]. There is less evidence available regarding the health associations of PA in individuals with Cystic Fibrosis (CF) [47], though PA has been associated with beneficial effects on lung function [19], hospitalisation frequency [130] and quality of life (QoL) [47]. Despite these potential benefits of PA, beyond those in the general population, there are currently no recommended guidelines for PA devised specifically for individuals with CF [88], or evidence to demonstrate a requirement for such guidelines [3]. Additionally, there is no consensus regarding the monitoring or reporting of PA or SB in this population [44].

Understanding of PA-health associations in adults with CF remains limited due to the variety of PA assessment methods and outcome measures reported in the literature [131]. Accelerometry is the most widely used objective method for the assessment of PA in adults with CF [131]. Traditionally, using accelerometry to quantify PA relied on device specific proprietary algorithms to collect, process, filter, and scale raw signal data to produce device-specific counts [132]. Recent advancements in accelerometer technology have resulted in accelerometers capable of collecting and exporting raw acceleration data, which allows researchers greater control of data processing. It has therefore been proposed that standardised raw data analysis techniques should be utilised with meaningful, interpretable and comparable outputs reported [133]. Proposed outcomes include a measure of the volume of PA (average acceleration, corrected for gravity) and the intensity gradient, which provide an overall PA profile for individuals, rather than focussing on minutes of activity spent in discrete intensity categories alone [133]. These novel metrics have not yet been applied in a CF population and may offer the potential to improve the quality of PA assessment and increase understanding of PA in CF.

Whilst cardiovascular disease (CVD) is the leading cause of mortality in Europe (accounting for 45% of all deaths) [134], it is uncommon in individuals with CF and typically only associated with severe pulmonary disease [21]. However, with increased life expectancy individuals with CF have greater exposure to traditional CVD risk factors including ageing, diabetes and metabolic disturbances [22]. Furthermore, CF is also associated with chronic inflammation, altered fatty acid metabolism and abnormal lipid profiles which may pose even further risk of CVD [25] [28]. Endothelial (dys)function, assessed using flow-mediated dilatation (FMD), is a strong predictor of future cardiovascular events [30] and is evident in young people with CF despite preserved lung function and exercise capacity [31]. The relationship between PA and vascular function is yet to be explored in individuals with CF, however PA may be associated with reduced CV risk, not only through the modification of traditional risk factors but also via direct effects on vasculature [35].

5.2. AIMS

The primary aim of the current research was to compare levels of objectively assessed PA in adults with CF to their non-CF peers. The secondary aim was to determine the association between PA and vascular function in a sub-sample of participants. In addition to this, the relationships between objective PA and lung function, quality of life and self-reported PA were explored.

5.3. METHODS

5.3.1. Participants

Ethical approval was granted by the North West – Greater Manchester West Research Ethics Committee, National Health Service (NHS) Health Research Authority (17/NW/0360) and Liverpool John Moores University (LJMU) (18/SPS/034) (Appendix C-I). Adults with CF were recruited from outpatient CF clinics at the regional adult CF Centre (n=340) at Liverpool Heart and Chest Hospital NHS Foundation Trust (LHCH). Participants for the non-CF control group were recruited via advertisements within the University. All participants were screened for

eligibility (Figure 5) and invited to attend testing at LHCH (CF) or LJMU (non-CF), during which informed written consent was obtained and all procedures were carried out as outlined below. Vascular function was assessed in a sub-group of individuals with CF who were then matched on sex, age and ethnicity with a non-CF control participant. All participants were invited be take part in both the PA assessment and vascular assessment, however the vascular assessment required participants to arrive fasted and extended the length of their routine clinic appointment. A proportion of participants therefore opted out of the sub-group, participating in the main study group only. The reason given (if any) for opting out of the sub-group was primarily a lack of time owing to the additional burden of the test and in some case participants did not want to be fasted for their clinic visit.

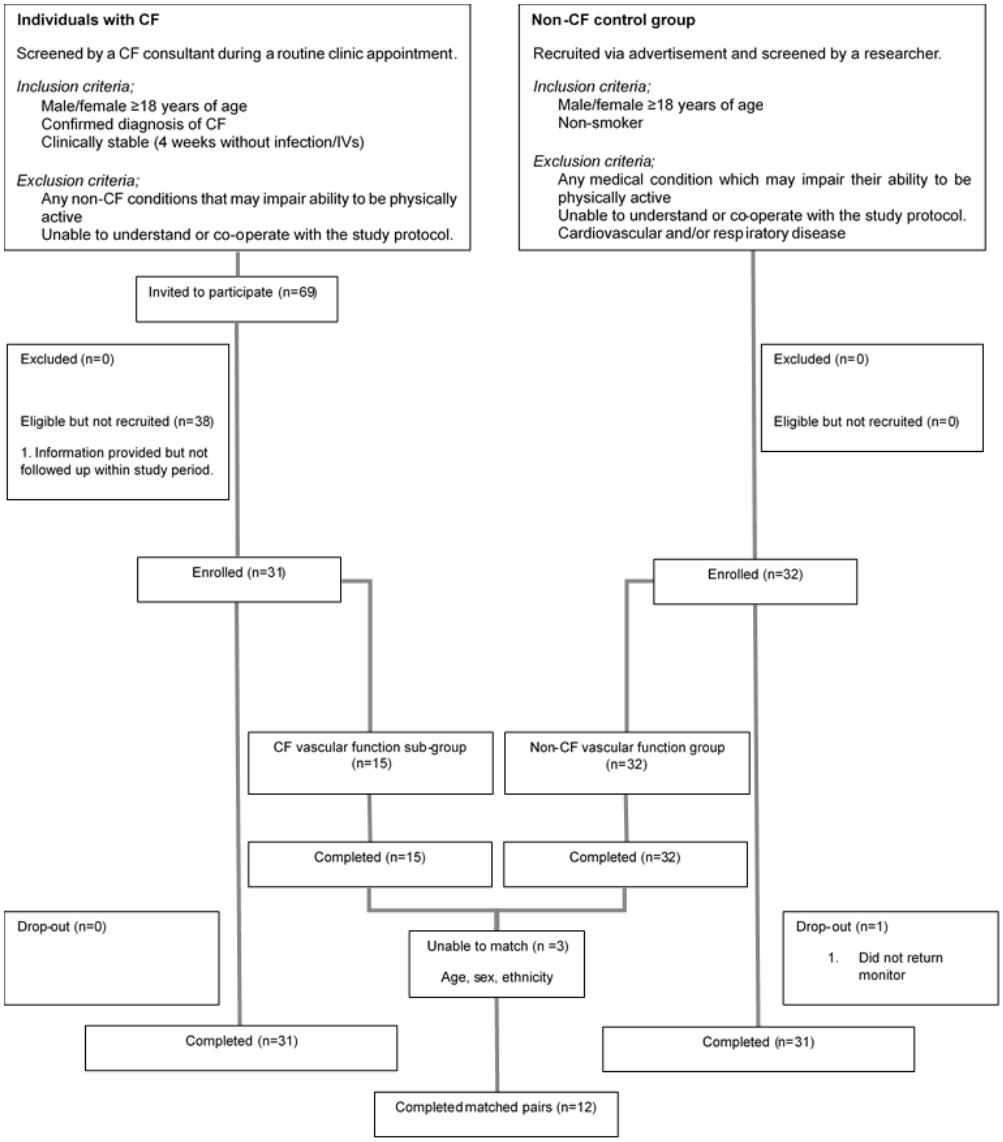


Figure 5 – CONSORT diagram displaying the recruitment, inclusion/exclusion and completion of participants.

5.3.2. Data collection

5.3.2.1. Clinical measures

Pulmonary function was assessed according to American Thoracic Society (ATS) /European Respiratory Society (ERS) standard operating procedures [135] using a standard laboratory based spirometer (Spirostik, Geratherm, Germany) or a portable handheld spirometer (Micro Medical Ltd, Rochester, UK) for the CF and non-CF groups respectively. Height and body weight were measured to the nearest 0.1 cm and 0.1 kg respectively using a digital scale and stadiometer (Seca, Birmingham, UK), with body-mass index (BMI) subsequently calculated (weight/height^2). Blood pressure was measured using an Omron M2 (Omron Healthcare, Hoofddorp, Netherlands) or Dinamap Pro 300V2 (Dinamap, GE Healthcare, Chicago, IL) automated sphygmomanometer, placed around the left upper arm, for the CF and non-CF groups respectively. Medical notes were reviewed to obtain microbiology status, current medications and genotype for participants with CF.

5.3.2.2. Quality of life

Health related quality of life was assessed using the Cystic Fibrosis Questionnaire-Revised (CFQ-R). The CFQ-R is a validated disease-specific patient-reported outcome tool providing assessment of QoL and health status, covering a range of physical, emotional and social factors [136]. To control for a confounding influence of QoL on PA, QoL was also assessed in the non-CF group using the EQ-5D-5L health questionnaire, which provides a simple descriptive profile and a single index value for health status [137].

5.3.2.3. Physical activity

All participants were asked to wear an ActiGraph Link GT9x tri-axial accelerometer (ActiGraph, Pensacola, FL) on their non-dominant wrist, during waking hours for

seven consecutive days. The device was initialised to record data from midnight on the date following their visit, at 30Hz. The device displayed a 24hr clock only.

The Global Physical Activity Questionnaire (GPA-Q) was already used as part of routine clinical care and was therefore used alongside the monitors to compare self-reported PA and SB with an objective measure. The GPA-Q was not used in any of the studies identified in Study 1, however, of the questionnaires reviewed only the HAES and IPAQ provided sufficient information to allow comparison with PA guidelines. The HAES was reported to over-estimate PA and there is evidence to suggest that the tool is not accurate in adolescents or adults with CF [93]. Whilst the IPAQ is well validated across multiple populations [122], it is not validated for use in CF and has previously been shown to be inappropriate for use in clinical populations such as; breast cancer [123], HIV [124] and fibromyalgia [125]. Additionally, the long-form IPAQ was utilised in the study reviewed [109], the shorter GPA-Q was therefore the preferred method for collecting self-reported PA data. The GPA-Q comprises of 16 questions collecting information on PA participation in three domains (at work, travel and recreational activities) as well as SB [60]. The GPA-Q was also used in the non-CF group to allow for comparison of self-reported PA between groups.

5.3.2.4. Vascular function

Vascular function was assessed in sub-groups of both CF and non-CF groups using Flow Mediated Dilatation (FMD). FMD is a non-invasive assessment of nitric-oxide dependent endothelial function [138] and has recently been shown to be reliable and repeatable in individuals with CF [139]. Participants were asked to arrive for testing having fasted for 8 hours and avoided vigorous activity for 24 hours, all participants were non-smokers. In accordance with guidelines, after 10 minutes rest in the supine position ultrasound images of the brachial artery were captured to measure artery diameter and blood flow velocity [138]. A Hokanson cuff (Hokanson, Bellevue, WA) placed around the participants forearm was inflated to suprasystolic pressure (>220 mmHg) to induce ischemia. Following the 5-minute period of downstream-occlusion, the cuff was released, resulting in increased blood flow

velocity through the brachial artery. Changes is artery diameter and blood flow were then recorded for a further 3 minutes.

5.3.3. Data analysis

5.3.3.1. Physical activity data

ActiGraph data were downloaded using ActiLife (version 6.13.3), saved in raw format as .gt3x files and converted to .csv files for data processing. The raw ActiGraph data files were processed in R (http://cran.r-project.org) using the GGIR package (version 1.9-0) which autocalibrated the raw triaxial accelerometer signals [140]. Signals were then converted into gravity-corrected vector magnitude units, termed the Euclidean norm minus one (ENMO) [70], which were expressed as the average ENMO values per 1 second epoch. Accelerometer wear time inclusion criteria were a minimum of 10 $h \cdot day^{-1}$, with non-wear estimated on the basis of the standard deviation and value range of each accelerometer axis, calculated for moving windows of 60 min with 15 min increments [70]. For each 15 min period detected as non-wear time over the valid days, missing data were replaced by the mean value calculated from measurement on other days at the same time of day [141]. Sleep logs were used to determine the average waking period, which was used to standardise the analysis window at 08:52 – 23:45 to correct for sleep in all participants. Hildebrand *et al*.'s adult non-dominant wrist cut-points were used for classifying activity into sedentary time, light intensity PA (LPA), moderate intensity PA (MPA), moderate-vigorous intensity PA (MVPA) and vigorous intensity PA (VPA) [68]. The PA intensity gradient (IG) is a novel metric to describe the distribution of PA intensity, calculated from raw acceleration data [71]. To calculate the IG, intensity (*mg*), classified using 25*mg* categories and time (mins) accumulated at each intensity were log transformed and used to calculate a linear regression for each participant (Figure 6). The R^2 value, gradient and constant were used to describe individuals' PA profiles (IG) [71]. A lower gradient (steeper slope) represents a poorer PA profile, reflecting more time spent in lower intensity activity, whereas a higher gradient (shallower slope) represent a better profile with more time across the range of intensity.

5.3.3.2. Questionnaires

GPA-Q data was manually cleaned and analysed to provide estimates for moderate, vigorous and sedentary time, including travel, recreation and work domains as well as calculating a total weekly metabolic equivalence (MET) value [60].

EQ-5D-5L was analysed using the questionnaire specific scoring and analysis guidance to provide an overall index for QoL [137].

5.3.3.3. Flow-Mediated Dilation (FMD)

FMD was assessed in accordance with recent guidelines [138]. Assessment of brachial artery diameter was done using custom edge-detection and wall-tracking software [138]. Peak velocity was calculated from analysis of the Doppler signal. Duplex ultrasound-derived velocity and diameter were used to calculate shear rate area under the curve up to peak diameter. Analysis of covariance (ANCOVA) using an allometric approach was performed to analyse change in brachial artery diameter and estimate mean difference in endothelial function between groups, adjusted for baseline diameter to produce covariate-adjusted FMD% [142].

5.3.3.4. Statistical analysis

Descriptive statistics are displayed as mean ± SD unless otherwise stated. Independent t-tests were used to compare baseline characteristic between groups (Table 5). Analysis of covariance (ANCOVA) and multivariate analysis of covariance (MANCOVA) were used to compare variables between groups and to control for covariates (age and sex). Pearson's correlation analyses were performed to explore the relationship between variables and Spearman's correlation were performed where the assumptions of normal distribution were violated.

5.4. RESULTS

5.4.1. Baseline characteristics

The groups were well matched for age, height and BMI but lung function was significantly lower ($p < 0.001$) in individuals with CF when compared to their non-CF peers (Table 5).

Table 5. Participant characteristic for whole group.

	CF (n=31)	Non-CF (n=31)	P value
Clinical characteristic			
Male: Female	22:9	18:13	
Age, y	29 ± 6	28 ± 9	0.464
Body weight, kg	68.5 ± 15.7	74.5 ± 19.4	0.193
Height, cm	171.6 ± 10.5	172.2 ± 9.4	0.810
BMI, kg/m^2	23.1 ± 4.3	24.7 ± 4.7	0.153
CFRD (with:without)	18:13		
Lung Function			
FEV_1, L	2.56 ± 1.06	4.31 ± 1.08	**< 0.001**
FEV_1, % predicted	66 % ± 23	113% ± 18	**< 0.001**
FVC, L	3.74 ± 1.18	5.38 ± 1.39	**< 0.001**
FVC, % predicted	80% ± 20	121% ±17	**< 0.001**
Genotype			
Homozygous ΔF508 (n, %)	15, 48%		
Heterozygous ΔF508 (n, %)	29, 94%		
Other Alleles (n, %)	2, 6%		
Microbiology			
Pseudomonas Aeruginosa (n, %)	17 (55%)		
*Pseudomonas Aeruginosa (LES+)** (n, %)	3 (10%)		
Staphylococcus aureus (n, %)	5 (16%)		
Other (n, %)	6 (19%)		
Employment			
Working full or part time (n, %)	19 (61%)	21 (68%)	0.596
Attending school outside of the home	2 (6%)	10 (32%)	**0.010**
Not attending school or working due to health	7 (23%)	0 (0%)	**0.005**
Not working for other reasons	3 (10%)	0 (0%)	0.066

*Values are displayed as mean±SD or n(%). P-value refers Pearson Chi-square for categorical data and independent t-tests for all other variables. BMI indicates body mass index; CRFD, Cystic Fibrosis related diabetes; FEV_1, forced expiratory volume in 1 second; FVC, Forced vital capacity; *LES+, Liverpool Epidemic strain of Pseudomonas Aeruginosa.*

5.4.2. Physical activity & sedentary time

Objectively assessed PA was significantly different between groups when controlling for age and sex (p <0.001). Separate univariate analysis of variance indicated no significant difference between groups for wear time (p = 0.881), total PA (p = 0.741), sedentary time (p = 0.551), or light PA (p = 0.097), but all other variables (average ENMO, MVPA, MPA, VPA) were significantly lower in individuals with CF when compared to their non-CF peers (p <0.05) (Table 6).

PA intensity gradient was significantly different between groups when controlling for age and sex (p = <0.001). Differences between groups were significant (p <0.05) for each of the three variables used to describe the PA profile (Table 6). Adults with CF had a steeper gradient and lower constant representing a poorer PA profile, reflecting more time spent in lower intensity activity and less time across the range of intensities when compared to their non-CF peers (Figure 6).

When assessed using the GPA-Q questionnaire there was no significant difference in self-reported PA between groups when controlling for age and sex (p = 0.089). Univariate analysis of variance highlighted significantly less PA reported in the travel domain in individuals with CF when compared to their non-CF peers (p = 0.004) but no other significant differences were observed between groups using the GPA-Q (Table 7).

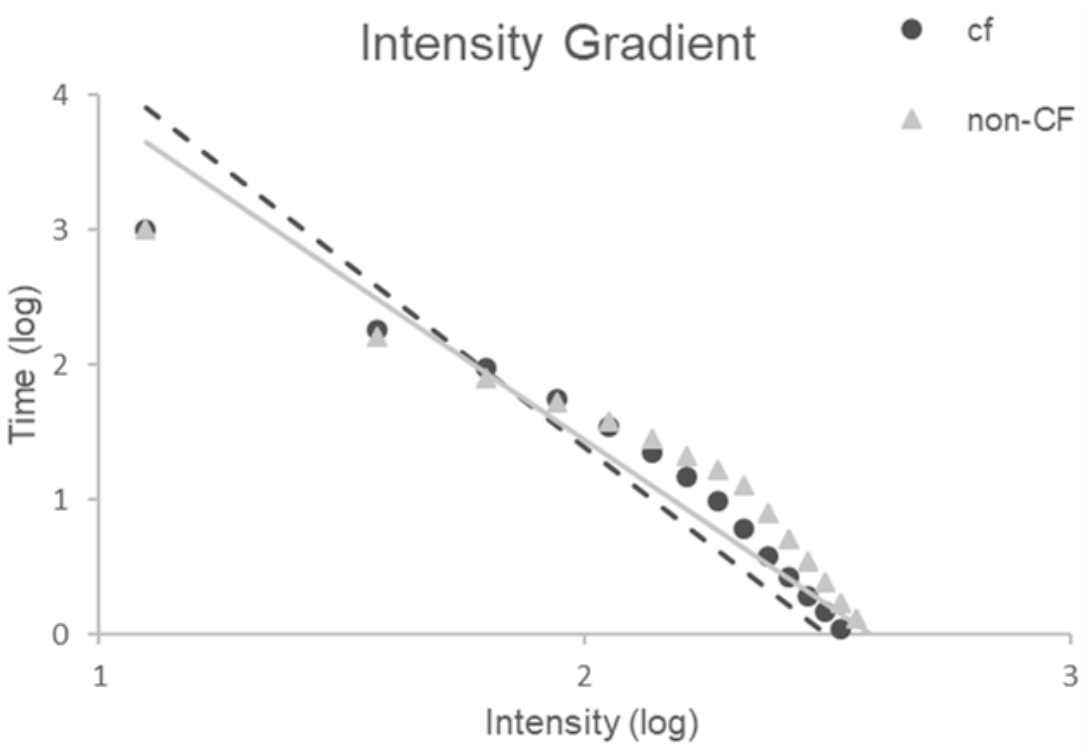


Figure 6 - Displaying the mean intensity gradient for individuals with CF (*y*=-2.62x + 14.93, R^2 = 0.92) *(circle markers and dashed line) compared to their non-CF peers* (*y*=-2.37x + 13.99, R^2 = 0.87) *(triangle markers and solid line). A steeper (less shallow) gradient represents a poorer PA profile, reflecting more time spent in lower intensity activity and less time across the range of intensities.*

Higher levels of objectively assessed VPA were positively correlated with lung function (Table 8). Higher objectively assessed MVPA and mean ENMO values were also positively correlated with FEV_1%, but no other measures of lung function (table 4). Objectively assessed sedentary time was not significantly correlated with any measures of lung function.

Pearson's and Spearman's correlation analyses were used to assess the relationship between objective and self-reported PA. Self-reported sedentary time and MPA were significantly correlated with objectively assessed sedentary time and MPA, r = 0.372 (p = 0.003), r = 0.272 (p = 0.034), respectively. There was no significant correlation between the remaining item assessed using the GPA-Q (VPA) and objectively assessed VPA, r_s 0.178 (p = 0.171). There were no significant correlations observed when analysing the CF group separately (all $p > 0.05$). Objective and self-reported sedentary time were correlated for the non-CF group when analysed separately (r = 0.498, p = 0.004), but objective and self-reported MPA and VPA were not significantly correlated (p > 0.05).

Table 6. Physical activity variables assessed using objective (accelerometry).

	CF (n=31)	Non-CF (n=31)	P value	95% CI for difference
Wear time (hrs·day)	13.71 ± 0.82	13.67 ± 0.73	0.881	-0.38 – 0.44
ENMO	35.09 ± 10.60	44.62 ± 13.78	**0.005**	-16.10 - -3.04
Intensity gradient	-2.62 ± 0.20	-2.37 ± 0.23	**< 0.001**	-0.38 - -0.12
Constant (y intercept)	14.93 ± 0.63	13.99 ± 1.13	**0.001**	-0.40 – 1.51
R^2	0.92 ± 0.02	0.87 ± 0.04	**< 0.001**	0.03 – 0.06
MVPA (mins·day)	86.02 ± 36.21	114.12 ± 39.34	**0.009**	-46.48 - -6.89
Total PA (mins·day)	323.40 ± 76.45	330.59 ± 76.98	0.741	-46.59 – 33.32
Sedentary time (mins·day)	557.92 ± 80.74	543.28 ± 89.57	0.551	-31.40 – 58.23
Light PA (mins·day)	237.38 ± 48.88	216.48 ± 48.98	0.097	-3.73 – 43.83
Moderate PA (mins·day)	82.53 ± 34.22	106.16 ± 36.93	**0.021**	-40.58 - -3.44
Vigorous PA (mins·day)	3.50 ± 3.57	7.96 ± 6.01	**0.001**	-7.29 - -2.07

Values are displayed as mean±SD. P-value refers univariate analysis of variance for all variables. ENMO indicates Euclidean norm minus one; MVPA, moderate-vigorous physical activity; PA, physical activity.

Table 7. Physical activity variables assessed using self-report (GPA-Q) methods.

	CF (n=31)	Non-CF (n=31)	P value	95% CI for difference
Vigorous activity at work (hr·week)	1.55 ± 3.68	0.16 ± 11.20	0.071	-0.12 – 2.67
Moderate activity at work (hr·week)	6.58 ± 11.20	4.78 ± 10.85	0.364	-3.05 – 8.19
Activity travelling (hr·week)	1.86 ± 3.43	4.66 ± 3.76	**0.004**	-4.68 - - 0.93
Vigorous recreational activity (hr·week)	3.15 ± 3.97	3.99 ± 6.10	0.436	-3.71 – 1.62
Moderate recreational activity (hr·week)	2.76 ± 4.18	3.48 ± 3.19	0.330	-2.84 – 0.97
Sedentary time (hr·week)	38.27 ± 21.78	46.85 ± 20.22	0.079	-19.63 – 1.09
Total vigorous activity (hr·week)	4.70 ± 6.18	4.15 ± 6.22	0.885	-2.97 – 3.43
Total moderate activity (hr·week)	11.20 ± 12.99	12.92 ± 11.79	0.714	-7.54 – 5.20
Total weekly METs (hr·week)	82.41 ± 87.71	84.92 ± 73.89	0.894	-45.30 – 39.65

Values are displayed as mean±SD. P refers to univariate analysis of variance for all variables. MET indicates, Metabolic equivalence.

Table 8 – Correlations between objectively assessed physical activity and lung function.

	FEV_1 (L)			FEV_1 (% predicted)			FVC (L)			FVC (% predicted)		
	r	***Sig***	**95% CI**	***r***	***Sig***	**95% CI**	***r***	***Sig***	**95% CI**	***r***	***Sig***	**95% CI**
MEAN ENMO	r = 0.204	p = 0.119	[-0.038, 0.436]	r = 0.308	p = 0.**017***	[0.078, 0.527]	r = 0.145	p = 0.269	[-0.087, 0.369]	r = 0.278	p = 0.031	[0.051, 0.489]
MVPA	r_s 0.170	p = 0.195	[-0.087, -0.415]	r_s 0.267	p = **0.039***	[0.050, 0.474]	r_s 0.107	p = 0.415	[-0.150, 0.358]	r_s 0.214	p = 0.100	[-0.019, 0.426]
SED	r = -0.008	p = 0.952	[-0.296, 0.275]	r = -0.130	p = 0.320	[-0.394, 0.158]	r = 0.026	p = 0.843	[-0.259, 0.310]	r = -0.111	p = 0.399	[-0.375, 0.179]
LIGHT	r = -0.242	p = 0.063	[-0.482, 0.010]	r = -0.111	p = 0.397	[-0.378, 0.151]	r = -0.255	p = 0.**049***	[-0.467, -0.027]	r = -0.104	p = 0.429	[-0.378, 0.160]
MOD	r = 0.185	p = 0.156	[-0.035, 0.397]	r = 0.270	p = 0.**037***	[0.059, 0.462]	r = 0.143	p = 0.277	[-0.081, 0.369]	r = 0.261	p = 0.**044***	[0.040, 0.442]
VIG	r_s 0.359	p = 0.**005***	[0.101, 0.598]	r_s 0.494	p < **0.001***	[0.258, 0.684]	r_s 0.296	p = 0.**022***	[0.045, 0.549]	r_s 0.475	p < 0.**001***	[0.236, 0.677]

**Indicates statistical significance (<0.05). Pearson's and Spearman's correlation analysis are displayed with [Bias corrected and accelerated Confidence Intervals].*

5.4.3. Vascular function

Vascular function was assessed in a sub-group of adults with CF who were then matched for sex, age and ethnicity with a non-CF control participant, of the fifteen participants tested twelve were successfully matched a with non-CF control. There was no significant difference in FMD% between groups, (p = 0.114). Separate univariate analysis of variance revealed that baseline diameter (p = 0.008) and peak diameter (p = 0.012) were significantly lower in individuals with CF when compared to their non-CF peers. Diastolic blood pressure was also significantly higher in individuals with CF when compared to their non-CF peers, although there was no significant difference in FMD% change (p = 0.313), (Table 9).

FMD% was positively associated with age for the groups combined (r_s 0.460, p = 0.027) and the CF group alone (r_s 0.618, p = 0.043) but not in the non-CF group when analysed separately. FMD% was significantly positively correlated with BMI in the CF group when analysed separately (r_s -0.645, p = 0.032) but not for the whole group or the non-CF group. FMD% was not significantly correlated with any other variable assessed in either group (all p >0.05).

Higher baseline artery diameter was positively associated with lung function FEV_1 L (r = 0.445, p = 0.033), FVC L (r = 0.423, p = 0.044) and MVPA (r_s 0.502, p = 0.015) for the groups combined but not when analysed separately. Peak artery diameter was also positively associated with MVPA (r_s 0.548, p = 0.007) but not lung function (p > 0.05).

Table 9. Subject characteristics of sub-group with vascular function assessment.

	CF (n=12)	Non-CF (n=12)	Mean difference	95% CI for difference	P value
Participant characteristic					
Male: Female	10:2	10:2			
Age, y	28.5 ± 4.6	28.3 ± 4.1	0.25	-3.46 – 3.96	0.890
Body weight, kg	68.4 ± 17.4	79.6 ± 21.4	-11.17	-27.73	0.176
Height, cm	174.4 ± 9.1	175.8 ± 8.7	-1.37	-9.10	0.716
BMI, kg/m^2	22.0 ± 3.9	25.4 ± 5.7	-3.4	-7.6 – 0.9	0.111
FEV_1 (L)	2.91 ± 1.3	4.84 ± 0.99	-1.92	-2.90 – -0.94	**<0.001**
FEV_1 (% predicted)	70 ± 27	117 ± 22	-47	-68 - -26	**<0.001**
Pseudomonas Aeruginosa (n, %)	7 (58%)				
Staphylococcus aureus (n, %)	3 (25 %)				
Other (n, %)	2 (17%)				
CFRD (with:without)	7:5				
Objectively assessed Physical activity					
Wear time (hrs·day)	13.80 ± 0.86	19.95 ± 0.61	-0.15	-0.78 – 0.48	0.626
ENMO	34.21 ± 13.09	48.21 ± 17.85	-14.00	-27.5 - -0.75	**0.039**
MVPA (mins·day)	83.19 ± 41.91	115.77 ± 43.76	-32.58	-68.86 – 3.70	0.076
Total PA (mins·day)	302.90 ± 97.19	340.45 ± 77.88	-37.54	-112.31 - -37.22	0.308
Sedentary time (mins·day)	576.31 ± 108.25	534.60 ± 95.38	41.71	-44.74 - 128.17	0.327
Light PA (mins·day)	219.71 ± 59.46	224.67 ± 51.65	-4.97	-52.17 – 42.24	0.829
Moderate PA (mins·day)	79.44 ± 39.60	105.28 ± 37.58	-25.84	-58.53 – 6.85	0.115
Vigorous PA (mins·day)	3.75 ± 3.08	10.49 ± 7.75	-6.74	-11.90 - -1.59	**0.010**
Vascular function					
SBP (mm Hg)	125 ± 12	118 ± 12	8	-3 – 18	0.137
DBP (mm Hg)	77 ± 8	66 ± 9	11	4 - 19	**0.003**
Baseline diameter (mm)	3.54 ± 0.41	4.13 ± 0.56	-0.59	-1.01 - -0.17	**0.008**
Peak diameter (mm)	3.73 ± 0.43	4.31 ± 0.60	-0.58	-1.03 - -0.14	**0.012**
Diameter difference (mm)	0.19 ± 0.10	0.18 ± 0.07	0.01	-0.07 -0.08	0.873
FMD%	5.29 ± 2.76	4.34 ± 1.58	0.95	-0.98 – 2.88	0.313
Time to peak (sec)	44.12 ± 12.75	52.57 ± 10.14	-8.45	-18.23 – 1.33	0.087
SRAUC	14902.89 ± 8694.52	15660.86 ± 3356.24	-757.971	-6520.430 - -5004.487	0.782
Corrected FMD%	5.23	4.39	1.01	0.99-1.03	0.457

Values are displayed as mean±SD. P-value refers to univariate analysis of variance. 'corrected FMD' refers to an ANCOVA with baseline diameter as a covariate. BMI indicates body mass index; CRFD, Cystic Fibrosis related diabetes; FEV_1, forced expiratory volume in 1 second; ENMO, Euclidean norm minus one; MVPA, moderate-vigorous physical activity; PA, physical activity. FMD, flow-mediated dilation (uncorrected); SRAUC, shear rate area under the curve.

5.4.4. Quality of life

The quality of life index, assessed using the EQ-5D-5L was 0.95 (±0.09) for the non-CF group where a score of 1 represents no problems at all across 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a score of 0 indicating extreme problems.

Quality of life scores for the CF group are displayed in table 5. Objectively assessed VPA was positively associated with scores for the 'physical' and 'role' domains (r = 0.412, p = 0.024), (r = 0.395, p = 0.038) respectively. Additionally, sedentary time was negatively associated with the 'role' domain (r = -0.382, p = 0.045). There were no other significant associations between PA and QoL (Table 10).

Table 10. Quality of life data for individuals with CF.

	Physical	***Vitality***	***Emotion***	***Eating***	***Treatment Burden***	***Health Perception***	***Social***	***Body image***	***Role***	***Weight***	***Respiratory***	***Digest***
Mean	60.0	52.7	74.2	80.8	53.9	51.1	62.2	64.8	67.1	63.3	57.0	83.1
SD	24.8	16.9	21.3	21.1	24.6	22.7	20.3	31.4	28.3	37.5	22.7	17.8

Values are displayed as mean±SD. Scoring across each domain ranges from 0-100, with higher scores indicating better health.

5.5. DISCUSSION

The aim of the current research was to compare levels of objectively assessed PA in adults with CF to their non-CF peers and to determine the association between PA and vascular function. Adults with CF engaged in significantly less MVPA than their non-CF peers. VPA in particular was positively associated with lung function and QoL. Lower levels of sedentary time was also positively associated with QoL. Average ENMO (a measure of total PA) was significantly lower in adults with CF, who also had a poorer PA profile (intensity gradient) when compared to non-CF peers. There were no significant differences in FMD between adults with CF and their non-CF peers and no association between FMD and PA.

5.5.1. Physical activity

The average ENMO metric and the IG provide a comprehensive PA profile that may allow tailored PA advice for individuals with CF without requiring CF specific PA cut-points to classify intensity, which are not yet available. The IG metric is relatively independent of overall activity in comparison to traditional intensity categories and is independently associated with health outcomes, highlighting the potential relevance of the distribution of PA for individualised PA interventions [71]. Normative values are not yet available and the metric is not compatible with current PA guidelines. However, it can be calculated retrospectively using variables commonly reported, which could allow for age- and sex-specific population-referenced percentiles to be generated [71]. This would enable comparison to normative values and longitudinal tracking of PA [71] which could be advantageous in CF populations.

Use of these methods may improve the quality of objective PA assessment in this population and supports earlier research suggesting that individuals with CF engage in less MVPA than their non-CF peers [87], despite engaging in similar amounts of LPA. These differences were only evident when using objective assessment methods and were not present when using the self-report tool (GPA-Q). The GPA-Q provided useful information relating to PA domains, highlighting that individuals with CF report spending less time engaging in active transport than their non-CF peers. Interventions promoting active travel have the potential to generate substantial health benefits [143] and may therefore be of interest for future research.

The correlations between accelerometer assessed PA components and the GPA-Q were weak, particularly for VPA which is positively associated with lung function and QoL. The GPA-Q correlated better with accelerometry for estimating sedentary time, as such utilisation of this tool may be limited to assessment of sedentary time and facilitating discussion around PA behaviour rather than accurately quantifying PA levels. There are no studies that validate the use of the GPA-Q in individuals with CF, consequently the GPA-Q should only be considered as a supplementary assessment tool to use alongside accelerometry to provide context. The habitual estimation scale is currently recommend for self-reported assessment of PA in individuals with CF [44], though this tool was validated for use in adolescents [126]

and it has subsequently been suggested that the tool is not accurate enough to be used for individualised activity counselling in adolescents or adults [93].

5.5.2. Flow-mediated dilation

Given that previous research has demonstrated impaired FMD response in young people with CF [31] it was somewhat surprising that no difference was observed between groups in the current study. Paradoxically, the older participants with CF had higher FMD% response than younger participants, which possibly results from a selection bias where only relatively 'well' individuals with CF survive to later life. It is also important to note that the confounding effect of pharmaceutical treatments was not controlled for in the current research, the effects of which on FMD are not known. Whilst there was no difference in FMD% change, baseline and peak artery diameter were significantly lower in individuals with CF when compared to their matched non-CF peers. In addition, diastolic blood pressure was also higher in individuals with CF, although BP is within normal range for both groups. These findings may be indicative of inward vascular remodelling [144]. FMD was not correlated with PA but was positively correlated with BMI. Low BMI is a marker of poorer outcome in CF, so it follows that individuals with higher BMI may have less severe disease along with higher FMD. The sub-group was also not sufficiently powered to explore difference between genotype or CFRD status.

5.5.3. Associations between PA and other variables

Increased total acceleration (average ENMO), VPA and MVPA were positively associated with lung function, suggesting that to maximise the beneficial effects of PA on lung function, individuals with CF should engage in PA of moderate intensity or greater. Additionally, only VPA was associated with improved QoL. This is in contrast to previous research which was unable to find an association between objectively assessed MVPA and QoL, although change in PA was positively associated with QoL [96]. The authors acknowledged that the accelerometer data analysis and cut-offs for MVPA may have obscured the relationship between PA

and QoL [96]. In the current study, high levels of sedentary time were negatively associated with QoL and interventions which aim to reduce sedentary time, regardless of PA may also be of benefit for individuals with CF.

5.5.4. Limitations

Sedentary behaviour is categorised by posture (sitting or reclining) and low energy expenditure [118]. The assessment methods employed in the current study measured acceleration (movement), therefore sedentary time was determined by low or no movement and not by determining posture. A new method, termed the Sedentary Sphere makes it possible to identify, analyse and visualise posture from wrist-worn accelerometry data [145], which may improve the assessment of sedentary behaviour in future research. Additionally, sleep duration was determined using a self-report diary. Given the good wear time and compliance evident in the current study it may be feasible to employ 24 hour wear protocols in future studies, which would allow for sleep analysis and the determination of a full 24 hour movement profile.

The novel PA assessment methods used in the current research may have limited clinical application owing to the cost of accelerometers and the level of expertise and time required for data analysis [64], as such these methods may be more appropriate as research tool at present. It is also important to note that the control group for this study was primarily recruited from an academic institution with a large cohort of sports and exercise science students and staff, the PA levels of these individuals may not be reflective of the wider population, however PA was largely comparable between this group and individuals with CF.

Exercise capacity was not assessed as part of this study. Exercise capacity is known to be an independent predictor of mortality [146] and is also associated with lung function [19] in individuals with CF and could therefore be of significance in relation to both PA and FMD. Exploring the relationship between PA and exercise capacity may be beneficial in view of understanding the nature of exercise intolerance seen in CF, which is likely a consequence of inactivity, pulmonary limitation and impaired skeletal muscle function [147].

Vascular function was only assessed using FMD, future research would benefit from including additional risk factors for CVD including analysis of cholesterol (high and low -density lipoproteins), triglycerides, glucose, and high- sensitivity C-reactive protein to provide a more comprehensive profile of cardiovascular health. Given the indications of adapted vascular structure it may also be of interest to assess intima-media thickness (IMT) in addition to FMD to quantify and track the atherosclerotic process. Finally, the researcher performing all FMDs also conducted the analysis and was therefore not blinded for the analysis.

5.6. CONCLUSION

Adults with CF engaged in less moderate to vigorous PA and demonstrated a poorer PA profile than their non-CF peers. Analysis of raw acceleration data, reporting the average ENMO and IG metrics can provide meaningful, interpretable and comparable analysis of PA in adults with CF. Higher levels of PA, particularly VPA were associated with positive health outcomes in CF, including lung function and QoL. Further research is required to explore vascular function in individuals with CF and provide a more comprehensive understanding of cardiometabolic risk in this population.

5.7. FUTURE RECOMMENDATIONS

Raw acceleration data can be used for the analysis of PA in adults with CF, with average ENMO and the IG reported, although additional research utilising these methods is warranted in this population. Clinicians should continue to support adults with CF to engage in PA above moderate intensity and to reduce their sedentary time, in order to benefit lung function and QoL.

6. THESIS STUDY MAP

Study	Aims/objectives	Key findings
One - Systematic review	Establish the physical activity levels of adults with CF. Compare reported PA levels between CF patients and their non-CF peers. Examine the associations between PA and markers of health in adults with CF.	• PA in adults with CF is largely comparable to their non-CF peers, despite being insufficiently active to achieve global PA recommendations • Highlighted a requirement for high quality studies designed specifically to explore PA in adults with CF.
Two - Assessment of physical activity and vascular function	To compare levels of physical activity in adults with CF to their non-CF peers and to determine the association between PA and vascular function	• Adults with CF are significantly less active than there non-CF peers. • Higher PA is associated with higher lung function and quality of life but not vascular function.
Three – Physical activity promotion in adults with CF	To understand the ecological correlates of physical activity in adults with Cystic Fibrosis. To inform the development of an ecological approach to physical activity promotion in this population	

7. STUDY 3 - DEVELOPING AN ECOLOGICAL APPROACH TO PHYSICAL ACTIVITY PROMOTION IN ADULTS WITH CYSTIC FIBROSIS.

7.1. BACKGROUND

The promotion of physical activity (PA), which may include structured exercise is recommended as part of routine Cystic Fibrosis (CF) care [44][45]. Despite this there are few examples of interventions designed to promote PA in this population [46]. A large proportion of research in the area has investigated the delivery of exercise training interventions, which give little or no attention to behaviour change theory or long-term maintenance [47]. Additionally, evidence supporting a positive impact of exercise training interventions on clinical outcomes remains equivocal [47]. There is evidence to suggest that higher levels of PA are associated with positive effects on lung function [19] aerobic capacity [20], hospitalisation frequency [42] and mortality [146] in patients with CF. Translating this evidence into clinical practice has had limited success, though it has previously been proposed that increasing levels of habitual PA may be more feasible and result in greater compliance than conventional exercise training inventions [46]. Despite this, there is limited research exploring perceptions of PA among adults with CF.

Interventions to promote behaviour change, such as increasing PA, should utilise an appropriate conceptual health promotion model and prioritise key factors of the target group [74]. The systematic development of interventions, based on the best evidence available and appropriate theory is recommended as best practice. The Medical Research Council (MRC) recommends a phased approach to intervention development with attention given to evaluation throughout [72],[73]. Whilst the MRC guidance for the development and evaluation of complex interventions identifies the stages of intervention development as; developing theory, modelling processes and outcomes and assessing feasibility, the guidance does not does not specify how to select and apply theory and is primarily concerned with evaluation [148]**.** An alternative framework used in health promotion is intervention mapping, which provides a framework to enable effective decision making at each step in the intervention development process [149]. Intervention mapping involves a systematic process off mapping behaviour on to its 'theoretical determinants' in order to identify potential levers for change, however this may be less effective for complex

multifactorial behaviours [150]. As with intervention mapping, the PRECEDE-PROCEED (P-P) model [151] provides a systematic process for intervention development and allows for the integration of appropriate behaviour change theory. The P-P model, which is consistent with a socio-ecological model of health promotion is designed to provide a framework to explain health behaviours and environments to inform the design and evaluation of interventions [151]. Within the P-P model it is recognised that behaviours are complex and multifaceted [152] the model has therefore previously been used to explore predisposing, enabling and reinforcing correlates of PA participation to inform the development of PA interventions [153]. Involving participants and their families in a formative process to explore attitudes, norms and perceptions and in the development process is central to a phased approach to complex intervention design [73]. The P-P model provides a framework to engage the target population in a structured and comprehensive assessment of their own needs and barriers to a healthy lifestyle in order to develop a sound ecologically based approach to addressing the health issues identified [153].

The current paper describes a formative process to explore the perceptions of PA among adults with CF, their families and clinicians. The research adopts a constructivist approach in interpreting the qualitative interview/focus group data and employs reflexive thematic analysis utilising deductive and inductive coding [154] to construct themes centred around the P-P model [151]. Stakeholder (patients, practitioners and policy makers) involvement in the planning, development and implementation of interventions is termed ‘participatory research’ and can provide insights into the ‘real world’ applications of interventions [77]. Therefore to translate the evidence supporting the beneficial effects of PA in adults with CF into clinical practice it is necessary to involve patients, their families and clinicians in a process to understand the correlates of PA behaviour and to inform the promotion of PA in adults with CF.

7.2. AIM

The aim of the current research was to understand the ecological correlates of physical activity in adults with Cystic Fibrosis. Specifically the objectives were: 1) to

utilise a formative approach to inform the development of an ecological approach to physical activity promotion in this population. 2) Involve individuals with CF, their families (where applicable) and clinicians throughout all aspects of the process.

7.3. METHODS

7.3.1. Participants

Ethical approval was granted by the London – Queen Square Research Ethics Committee and NHS Health Research Authority (19/LO/0305) (Appendix J-S). Participants with CF were recruited from outpatient CF clinics at the regional adult CF Centre (n=340) at Liverpool Heart and Chest NHS Foundation Trust (LHCH). There were no specific inclusion/exclusion criteria applied, beyond being an adult with a confirmed diagnosis of CF (sweat chloride > 60 mmol·L-1 > 100 mg sweat, where possible, diagnostic genotyping). During phase 2 participants' nominated family members were also invited to take part in the focus groups. Focus group membership was determined by the participant and the term family was used to describe the individuals that participants deemed significant to invite and in some cases referred to friends as well as immediate relatives. Family members below the age of 14 were excluded as it was been deemed that an appropriate level of maturity was required to comprehend and participate in the process [155]. Additionally, members of the CF multi-disciplinary team (MDT) responsible for participants care at LHCH were recruited to participate in phase 2. Recruitment aimed to include representatives from each discipline within the MDT (i.e. Consultant, Physiotherapist, Physiologist, Dietitian and Nurse) and informed written consent was obtained prior to data collection.

7.3.2. Data collection

An iterative approach was utilised, whereby findings from earlier phases of the research informed subsequent phases (Figure 7). The data collection and analysis were conducted by a researcher outside of the usual clinical care team but with prior knowledge and experience working with this population in a clinical setting. The semi-structured interview guides and focus group schedules included open-ended

questions structured to facilitate open discussion centred on the P-P model. The interview guides were refined through discussion with a second researcher, the final versions and are available as appendices (Q-S).

7.3.3. Phase 1

Individualised semi-structured interviews were conducted to explore patients' perceptions of PA, devised using the PRECEDE component of the PRECEDE-PROCEED model (Figure 8) [151]. Interviews were scheduled for a time and place convenient for participants and were conducted via telephone or face-to-face. Interviews were audio recorded using a Dictaphone (Sony-ICD-PX370, Sony Corporation, Japan) and transcribed verbatim for further data analysis.

7.3.4. Phase 2

Phase 1 and 2 ran consecutively as findings from phase 1 informed the structure of phase 2. Phase two comprised of separate focus groups, the first included individuals with CF and their families, the second included CF MDT members. The aim of the focus groups was to discuss the perceived barriers, facilitators and opportunities for PA participation and how this information could inform the development of a PA intervention. Individuals with CF attended separate focus groups in order to adhere to segregation procedures. Focus group membership was proposed to be between 3-8 individuals including a researcher, an individual with CF and their family. Where family members did not wish to participate a second semi-structured interview was conducted between the researcher and individual with CF, covering the same topics discussed during the focus groups. Members of the CF MDT participated in a separate focus group made up of MDT members and researchers, aiming for 3-8 members. All focus groups were audio recorded using a Dictaphone (Sony-ICD-PX370, Sony Corporation, Japan) and transcribed verbatim for further data analysis.

7.3.5. Clinical measures

Medical notes were reviewed to obtained demographic data, anthropometric data, lung function, microbiology status and genotype for patients with CF. This data was used to describe the study sample in terms of demographics and disease severity.

7.3.6. Data analysis

Thematic analysis of the transcripts was consistent with the robust process outlined by Braun & Clarke (2006) [156]. Transcripts were re-read to enable the researcher to become familiarised with the data and become immersed in the content. NVivo Pro 12 software package (QSR International Pty Ltd.,Doncaster, Victoria, Australia, 2019) was used to store and organise the transcripts. Data were coded in NVivo using deductive then inductive analyses to capture latent meaning, adopting a constructivist approach to examine realities, meanings, and experiences of PA within a socio-economic framework. Initial themes were generated, reviewed and defined through discussion with a Health and Care Professions Council (HCPC) Registered Psychologist, with expertise using thematic analysis acting as a critical friend. The constructed themes were clustered around the existing P-P model [151] and displayed using pen profiles centred around the key predisposing, enabling and reinforcing factors of the P-P model. Verbatim quotes are also used to illustrate findings where appropriate. Pen profiles provide a visual representation of data-sets via a diagram of key themes, a method previously used in similar research [157] and in line with the deductive framework provide by the P-P model [151]. Pen profiles were manually constructed from the transcribed data, with frequency count (square brackets) and verbatim quotes added to provide context. Trustworthiness and credibility were achieved through the following of robust guidelines and procedures for conducting thematic analysis. Consistent with the method and epistemological positioning this does not include traditional methods for assessing rigor such as member checking, inter-rater reliability or universal criteria but is achieved through appropriate transparency in reporting of epistemological stance, methodological approach, analytic procedures and presentation of themes and data [156].

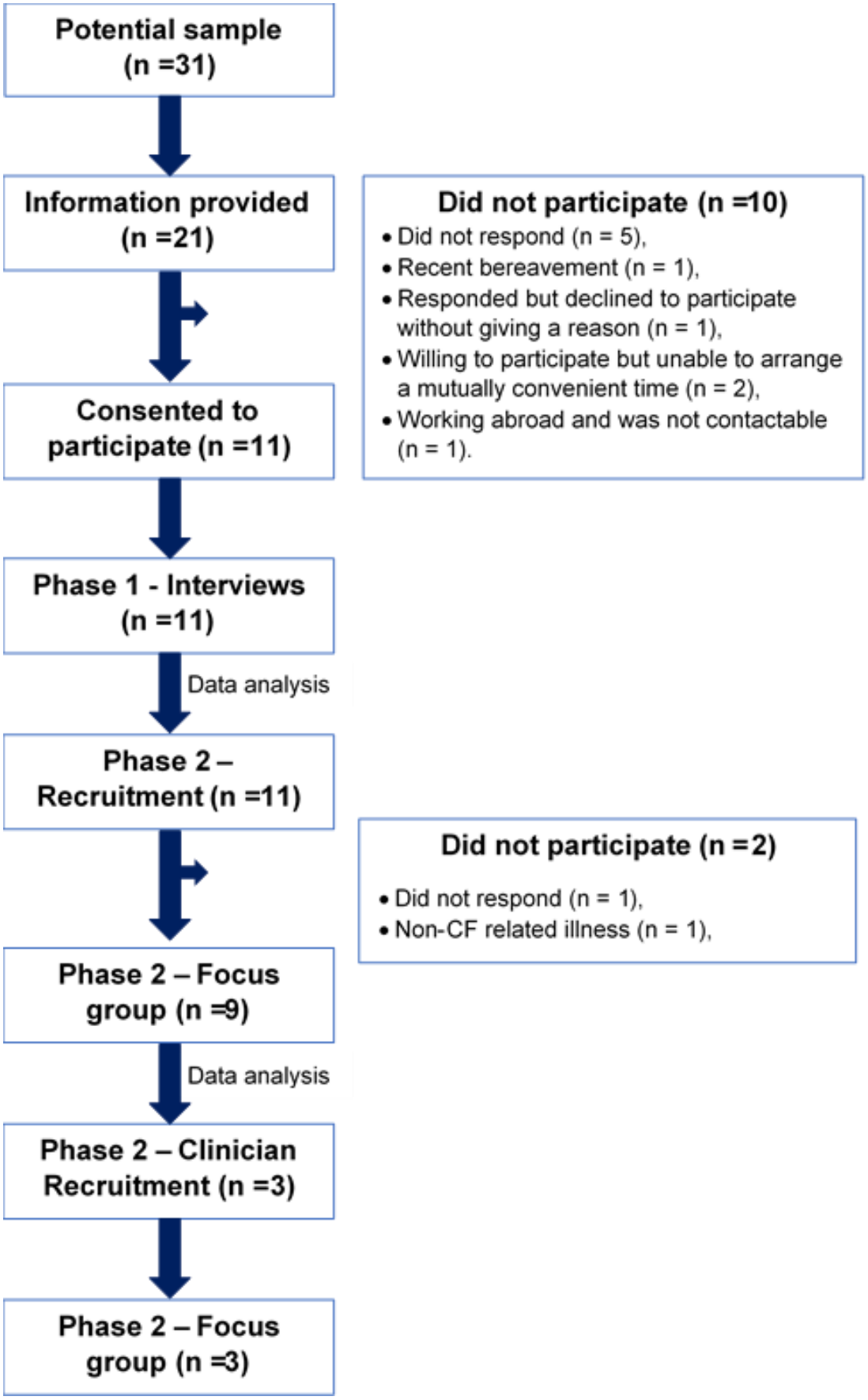


Figure 7 – Illustrating the iterative process from participant screening and recruitment to data collection and analysis.

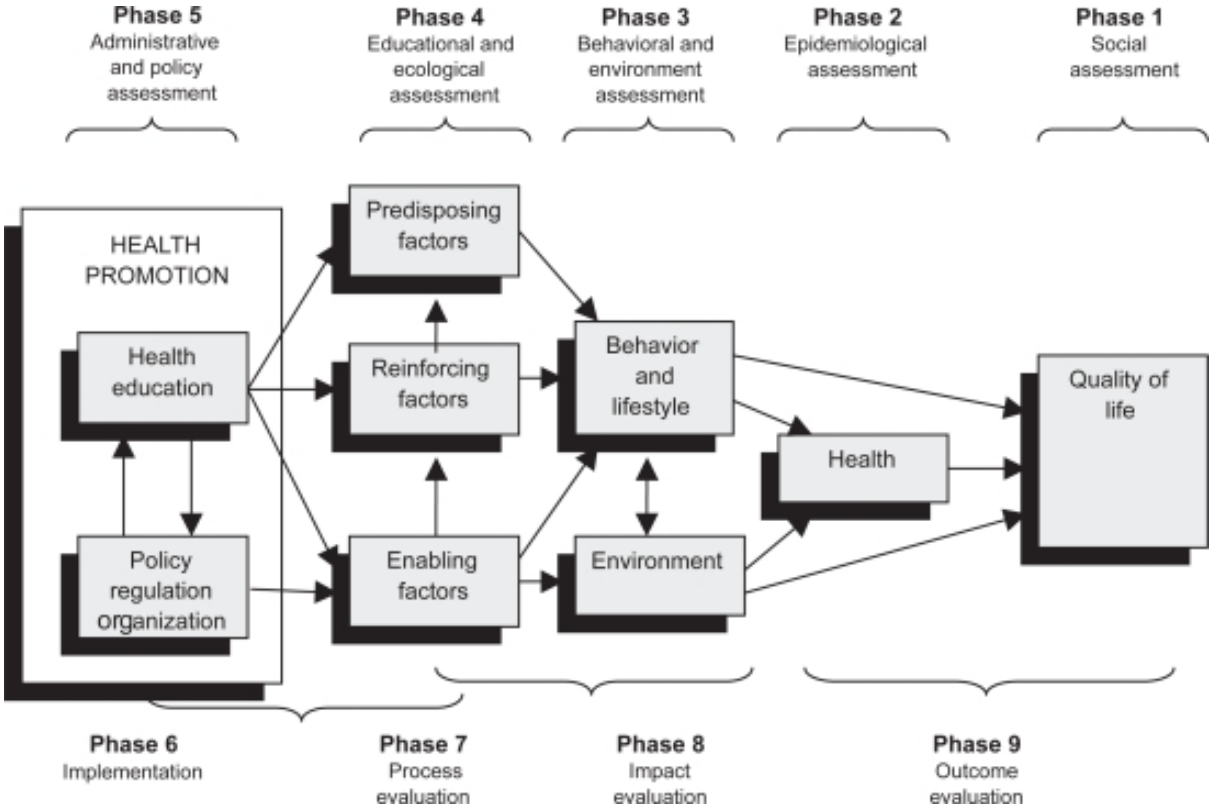


Figure 8 - The PRECEDE-PROCEED model for health promotion, planning and evaluation [151].

7.4. PHASE 1 RESULTS

7.4.1. Participant characteristics

Eleven participants (6 male) completed phase 1 of the study. Average age was 33.2 ± 7.1 years, Forced Expiratory Volume in one second (FEV_1) was 2.06 ± 1.03 litres (54 ± 17%predicted) and Body Mass Index (BMI) was 22.5 ± 4.5.

7.4.2. Phase 1 – Individual interviews

Eleven semi-structured interviews were conducted. Interviews were audio recorded and transcribed verbatim (generating 8 hours 30 minutes of audio and 5,425 lines, 78,039 words of text). Average interview length, 42 minutes 22 seconds of audio, 493 lines, 7,094 words of text (Size 11 Calibri font with 1.15 line spacing).

Constructed themes are displayed using the principle predisposing, reinforcing, and enabling factors outlined in the PRECEDE component of the P-P model [151]. The analysis is represented using pen profiles.

7.4.2.1. Predisposing factors

Predisposing factors include knowledge, attitudes, beliefs and perceived abilities. These factors may predispose a given health-related behaviour, in this case increase the likelihood of an individual engaging in PA [151].

The principle predisposing factors discussed during the phase 1 interviews are organised into constructed themes and displayed as a pen profile (Figure 9). Themes are divided into two higher order themes *'Is it worth it?*' and *'Am I able?'*, and further divided into five and four sub-groups respectively.

7.4.2.1.1. Is it worth it?

The 'Is it worth it?' higher order theme is related to the benefits and costs associated with PA, this includes attitudes, beliefs and enjoyment of PA.

7.4.2.1.1.1. Enjoyment

Enjoyment was reported as a key predisposing factor, with participants reporting that engaging in PA was easier as a result of enjoying activity. For example;

"Luckily I like sport, I enjoy sport, so obviously that helps [to engage in PA]. I'm not being forced into keeping fit and active... I genuinely always enjoyed sport anyway, so I think that helped" (P-02, lines 94-97).

With participants expressing a preference for activities that they perceive to be more enjoyable;

"I think everyone hates the gym... Just running on a treadmill, it's just boring. Do something like fun like a class or something, that makes you forget you're working out" (P-26, lines 280-282).

However, in some cases participants reported that regardless of whether or not they enjoyed activity it was necessary to engage in PA;

"…just generally activity for the sake of activity is what I'd call it [using a gym] rather than particularly enjoyment" (P-09, lines 136-137).

7.4.2.1.1.2. Health and Fitness

Other factors reported related to the perceived improvements to health and fitness, frequently described as feeling better or living longer, with participants also aware of the negative consequences of inactivity for health, collectively these factors were coded as 'health and fitness' (Figure 3). For example;

"Because you feel better [following exercise]… not just CF-wise, but in general" (P-30, line 91).

"To stay alive, simply. I know it sounds morbid, but as simple as that" (P-02, line 241).

"Yes, because I think my health could be a lot worse, really, if I don't do all those things [PA]" (P-28, line 19).

7.4.2.1.1.3. Psychological factors

Participants also reported a number of psychological factors, with some describing a 'mental aspect' to engaging in PA or a perceived 'mental benefit' from engaging in PA.

"When you're not in a good place mentally, you can't drive yourself to do things like go to the gym, because you've still got to drive yourself to just do things like take your meds, so it's like one extra thing that you've got to do when you're in a poor mental state" (P-04, lines 164-166).

"Just general health and wellbeing, specifically CF, and just generally as well, because I think it's good to be active, and it makes you feel better mentally" (P-23, lines 92-93).

Some factors relating to the participants' beliefs about the benefits of PA were also considered to have an influence psychologically and formed a cluster (Figure 3). The factors forming sub-themes included a perceived 'social' benefit from engaging in PA, a desire to improve 'aesthetically', whether that be increased muscle mass and size or an improvement in shape and weight loss and finally engaging in PA to gain a 'sense of accomplishment' or achievement.

"it's [group based resistance training] a social thing as well for me, exercise, so I would have felt like I was missing out on that if I didn't go [to a session]" (P-23, lines 64-66).

"When you're talking about why I've probably done that [weightlifting], I've probably done that for self-image, looking back" (P-04, lines 227-228).

"I love seeing an improvement in getting stronger as well. I like being able to look at the weights I couldn't lift a month ago" (P-15, lines 163-164).

Participants in the current study also reported a lack of motivation as a barrier to PA:

"I did have problems with being motivated to do it [PA], especially when you're ill and you can't be bothered. You're just tired and you're run down, so you like motivate yourself to get up and do something, and I think that's a big struggle" (P-26, lines 110-112).

One participant described how their motivation to lead a full and healthy life was also their motivation to engage in PA.

"You don't want to leave them all behind [family], and you don't want to put yourself in such a position that they can't enjoy their life because you're in a [poor] state. They're the things that drive me" (P-04, lines 357-359).

A separate but related sub-theme was coded as 'frustration'. Participants reported becoming demoralised when trying to achieve a desired level fitness, particularly following a period of exacerbation or admission. Other sources of frustration and disappointment included injuries, lack of exercise capacity or perceived poor performance. For example;

“I know I'm not the worst [runner], but also I get a bit frustrated that I should be able to get to the top of that hill, and I can't get there, or I'm slowing down, so I have to come to a stop, as opposed to a slower pace” (P-03, lines 87-89).

This participant also expressed how they would like to know what their performance could be like if they were not limited by their CF. Highlighting an awareness that CF could limit PA but not to an extent that meant participating was not possible.

I'd love to know how good a runner I could be if I didn't have CF (P-03, line 146).

7.4.2.1.2. Am I able?

The ‘Am I able?’ higher order theme is concerned with perceived competence and self-efficacy for PA.

7.4.2.1.2.1. Attitude towards physical activity

PA was valued as important with participants demonstrating a positive attitude towards PA.

“It's the most important thing. I understand sometimes it hurts. I know it hurts. Your body doesn't want you to do it, 100%... it'll keep you alive that little bit longer, and that's how you've got to look at it” (P-02, lines 194-198).

It was also evident that a negative attitude towards PA could be detrimental to PA behaviour, even when individuals perceive PA to be important. For example;

“I guess that kind of says everything about my attitude towards physical activity, like something that I just don't want to do, that I could otherwise use my time doing things that I prefer to be doing. So I guess that is my attitude towards it. Attitude is part of the problem, I guess” (P-09, lines 110-113).

Participants suggested that CF provided an opportunity to use the condition as an excuse to not engage in PA. It was also evident that ambiguity exists between when CF presents real barriers to PA and when it serves as a convenient excuse. For example;

“And I've seen it for myself, a lot of CF patients use it as an excuse or something, and I don't like that. It's not an excuse, it's just a different way of living” (P-02, lines 180-181).

“I don't know how much that's just me in my head, saying, "Oh yes, just blame CF for it and move on"” (P-09, lines 306-307).

7.4.2.1.2.2. Progression with age

The ability to engage in PA changes across the life course of an individual with CF, with participants describing how they have adjusted their activities and their expectations of what they could engage in as their disease has progressed.

“I was more or less a normal teenager, and you can see the progression as you get older, and the deterioration in your lungs, and so you know that that's not normal because everybody's still doing the same stuff…” (P-01, lines 132-134).

7.4.2.1.2.3. Physical symptoms

Many of the barriers to PA described were real physical symptoms rather than perceived factors. Despite a willingness to engage in PA, the physical symptoms described could make this challenging. For example;

“Even if I haven't got the line in, if I'm having a bad day, like chest-wise, and I've got like a tight chest, and I just can't loosen it up or it's too loose and I'm feeling wheezy, I don't want to exercise, so I will stay in bed” (P-15, lines 110-112).

“You just can't expel what you want to, because I can feel my airways kind of closing up, and it's a bit of a pain, and I get quite wheezy” (P-01, lines 205-206).

“It's a struggle sometimes when you're walking round. So you get out of breath quite easily, and you'll get tight-chested quite often. It's a bit horrid, yes” (P-28, lines 7-8).

7.4.2.1.2.4. Uncontrolled set-backs

Participants accepted that managing the symptoms of CF was inherent to the condition, though the difficultly of managing the unpredictable and uncontrollable nature of the set-backs was a source of frustration. Set-backs were often described as part of a cycle of improvements in health and fitness followed by a set-back undoing those improvements.

"I wish I could do more, but it's just every time I get somewhere, I get sick, so it kind of goes back to square one…" (P-21, lines 114-115).

"The difference, the switch from being fit and unfit with CF, it literally is just like a light switch" (P-02, lines 248-24

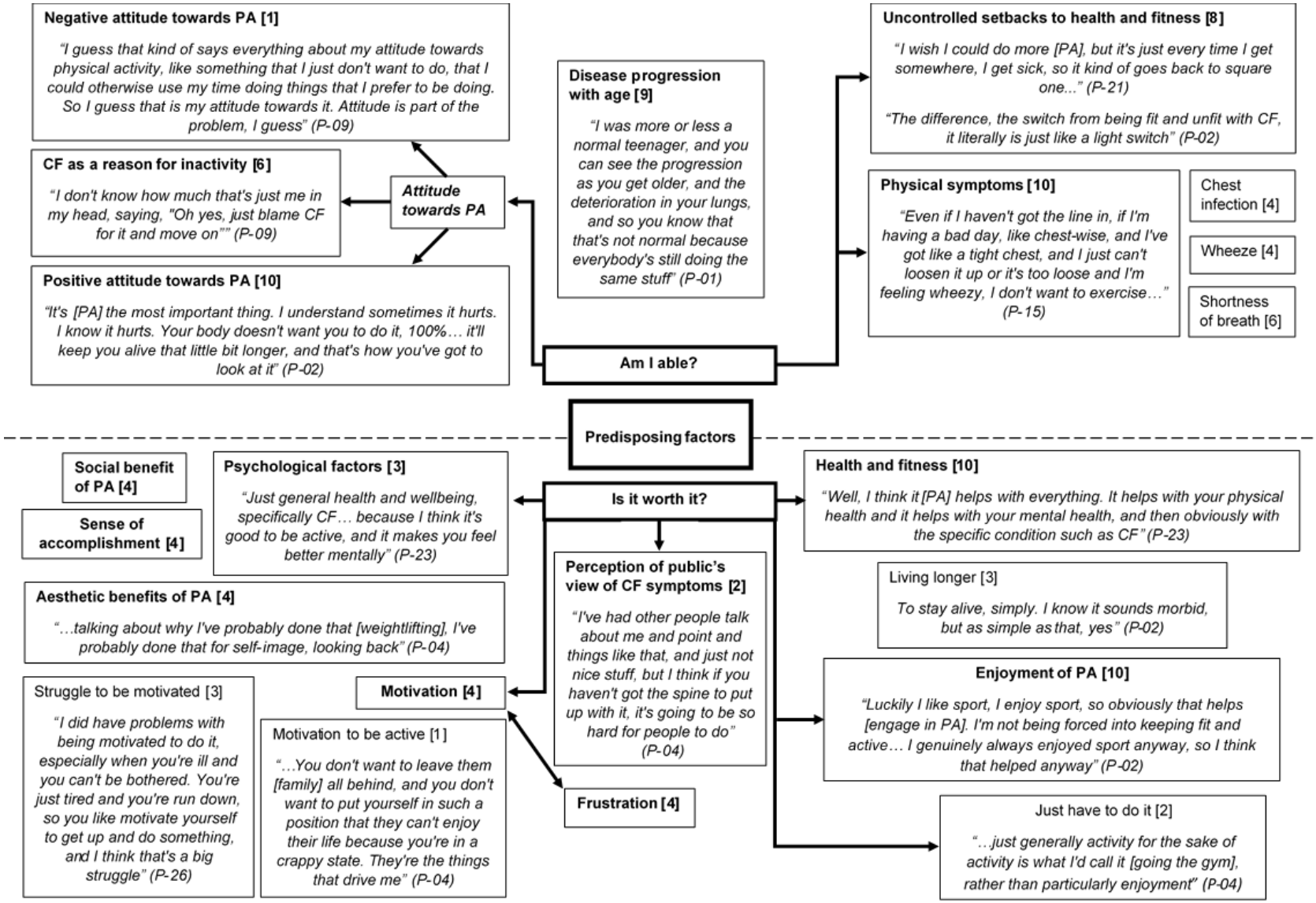


Figure 9 - Pen profile displaying predisposing factors (n=11).

7.4.2.2. Enabling factors

Enabling factors represent the immediate targets for interventions as they represent the new skills and/or organisational changes required to allow engagement in PA [151]. Enabling factors can include environmental conditions such as the availability and accessibility of resources, conditions of living such as childcare arrangements or transport, weather and safety [151]. Enabling factors also relate to the necessary skills required to complete a behaviour. Enabling factors are presented in Figure 10.

7.4.2.2.1. Environmental opportunity for physical activity

The participants in the current study were recruited from a CF centre providing care for a large geographical area, with some patients living ~150 miles from clinic. Despite this, participants across different geographical areas reported having access to resources and facilities to allow them to engage in PA.

"I don't lay any blame for my lack of activity on the local area" (P-09, line 297-298).

The physical environment and terrain were reported as barriers to PA. Although this is not a factor that could be modified as part of an intervention, it may require consideration.

"…I would probably take up running as well, but the difficulty with taking up running is, if you're outside, you've obviously got different gradients wherever you go, so I can't really do hills and stuff, but I do try…" (P-01, lines 198-200).

7.4.2.2.2. Safety

Factors relating to safety were also constructed as a theme. Whilst one participant felt that the local area was a safe place to engage in PA they also expressed concerns about exercising whilst alone and potentially in isolation which led them to only engage in PA in controlled environments such as a gym. This concern was echoed by participants describing a level of fear of exercise. For example;

"You don't feel at risk at all here" (P-01, line 411).

"…I think it's too dangerous to be far away from home or anything. At least in the gym you're in a controlled environment" (P-01, lines 214-215).

"…I was a bit worried at first, and I was getting really out of breath, and I didn't know if my lungs could handle…I didn't know how much they could handle…" (P-21, lines 183-185).

Not all participants deemed their local environment as safe and stated this as a barrier to their activity, although it was a barrier that they could negotiate by finding alternative activities.

"Yes, it's not the best area. It's quite rough. That's why I'm a bit reluctant to go to the gym nearby as well…" (P26, lines 228-229).

"… I don't like to actually see people running alongside traffic, and there's a motorway by me as well, so there can be an awful lot of pollution and stuff, and I know we can't see it, but it's always in the back of my mind as well" (P-04, lines 537 -540).

7.4.2.2.3. Weather

Weather conditions were also reported as factor affecting PA and general well-being of participants and were coded as a sub-theme containing both positive and detrimental aspects.

"…because I was abroad, you know, the temperature and the weather was different, and I barely ever got sick, and I was only admitted like once every couple of years" (P-26, lines 218-220).

"…if it's too cold, it takes your breath away as soon as you step out of the front door. You can feel it. If it's too warm, you get very wheezy very quickly…" (P-01, lines 217-219).

7.4.2.2.4. Perceived ability

Having the skills required to participate in PA is considered as a necessary determinant of PA. Participants acknowledge that their ability to take part in certain activities may be limited, however there was an awareness of such limitations, with participants perceiving themselves as able to engage in PA. For example;

"I'm sort of happy that I can take part in most activity, really, and I feel like I know my sort of limits, if there are any, and I feel quite capable of doing most things" (P-23, lines 223-224).

For some these limitations were perceived to negatively affect their ability to engage in PA.

"There's obviously the fitness, and then there's the CF side. They're linked, but they're not quite the same. My fitness is not good for most activities, but I'm not particularly the type of person who would care about the fact that I was less fit than everyone else" (P-9, lines 300-302).

Having the skills necessary to engage in PA was not always related to physical ability but rather to having a knowledge of PA. Participants reported a lack of information about PA for individuals with CF, stating that specific guidance would help to facilitate their PA. For example;

"…I wouldn't say that there's an awful lot of CF-specific activity stuff out there, at least not that I've found, but perhaps I've not looked hard enough" (P-09, lines 326-328).

"I can never find CF-specific information…" (P-15, line 427).

"I've not really had much information really…" (P-28, line 206).

"I know that I should do exercise, but it's like it would be easier if I knew exactly what to do…" (P-30, lines 239-240).

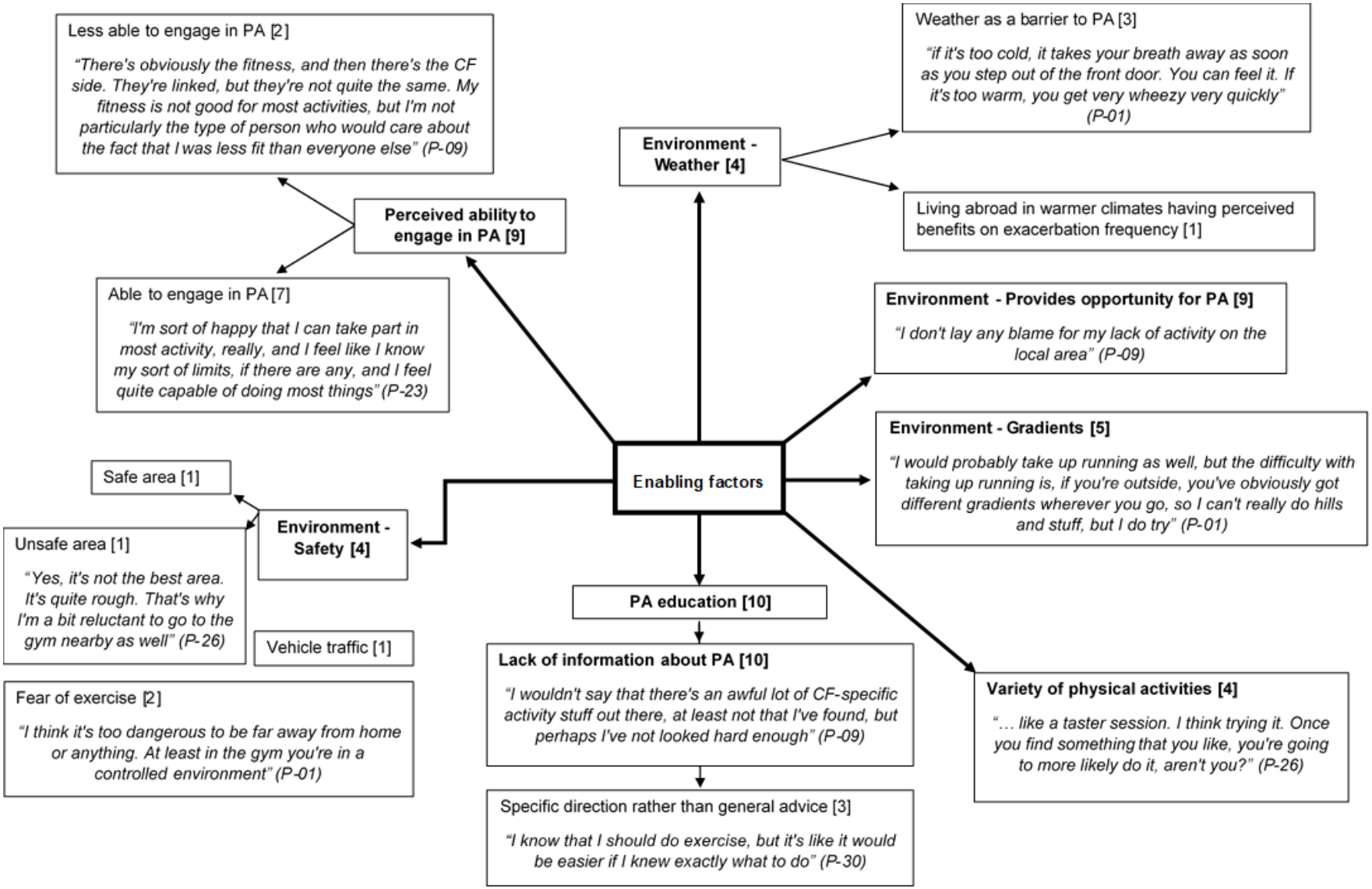


Figure 10 - Pen profile displaying enabling factors (n=11).

7.4.2.3. Reinforcing factors

Reinforcing factors relate to the consequences of a behaviour and whether individuals receive positive or negative feedback or social support for the behaviour [151]. In the current study these are factors that reinforce PA behaviour and could include the influence of peers and family either directly or indirectly.

7.4.2.3.1. Clinician promotion of physical activity

Within reinforcing factors the influence of clinical teams was constructed as a higher order theme with a number of sub-themes (Figure 11). The first of which was the presence of an exercise professional at routine CF clinics as part of the CF multi-disciplinary team. The benefit of having access to an exercise team was recognised, although participants were also aware that the service could be limited.

"I do think the exercise team or someone exercise background should be part of the team on every visit" (P-15, lines 461-462).

"I think it's hard to...exercise physiology aren't present in clinics, and I believe that's just because they don't have the numbers" (P-04, lines 468-469).

Some participants also reflected on their experience within paediatric centres and the influence this had on their subsequent PA behaviour throughout their life. These experiences were mixed, with some participants grateful for receiving *'good'* paediatric care and being encouraged to be physically active, whilst others felt that there was a lack of promotion of PA during their paediatric care.

"I was very lucky. I had a really good paediatric doctor who, when it came to me growing up, he was probably the most influential person apart from obviously, my parents…" (P-02, lines 198-200).

"When I was in [paediatric centre] it [PA] was never a big thing back then, though. You know, exercise, and it was there, but it was never promoted, do you know what I mean? and encouraged" (P-21, lines 222-223).

Participants reported seeking out support in their local community from gyms or leisure centres, however participants felt that exercise professionals outside of CF

care such as personal trainers would need an understanding of CF to be able to provide effective exercise programmes and work with individuals with CF.

“I didn't know whether to get a personal trainer…I went, "To increase my lung function". They'd probably look at me and go, "OK", because they wouldn't know what to do...it'd be someone that had to specialise in it” (P-01, lines 549-554).

7.4.2.3.2. Family physical activity

Through the course of the research the participants self-defined the term family. Participants varied in age (25-42 years), marital status (n=6 single/never married) and living arrangements (parental home, rented accommodation, home owner), with some participants having children of their own (n=3). Therefore, the term family relates to the individuals that participants perceived to be significant within their lives, either at present or during their childhood, this may include a spouse/partner, child, sibling and/or parent/carer. Separate themes were constructed for activity as a child, and the influence of children on activity. The family were perceived to have significant influence on PA behaviour, with participants describing positive experiences engaging in PA as a child. Having their own children was also described as a positive influence on participants’ own PA.

“…that's back to how I was brought up, really, with Mum and Dad. We'd go off on a Sunday afternoon and go out for a good walk and enjoy it. So I think that's why I do it, and my sister does it as well, in the family” (P-03, lines 131-133).

“I mean, as a kid, cardio-wise, I was brilliant at it [cardiovascular activity], because my Mum was constantly on me” (P-15, line 368).

“My son wanted to go trampolining, and I go with them…Just to make sure I do something. I'm not going to stand in a field and watch him play football, but I'll go trampolining with him” (P-01, lines 178-190).

7.4.2.3.3. Peer support

Peer support and solo PA were constructed as separate themes and given equal attention. Whilst participants described engaging in PA with others at various stages in their lives and perceiving motivational benefits of this, they also described engaging in a large proportion of their PA alone and having a preference for this.

"…they [friends] make me want to go [to the gym] more, if I'm participating with someone, rather than just by myself" (P-26, lines 162-163).

"I sometimes train with two friends, but I prefer to do it on my own, purely because over the years, I've found what works for me…" (P-15, lines 181-182).

Aside from actually engaging in PA with each other participants perceived that being able to communicate with individuals deemed *'like them'* would serve as support and reinforce positive PA behaviours. Participants also stated that the support would be best coming from someone in a similar position to them in terms of fitness, disease severity and lung function.

"…but it's all very well having medical professionals telling you what to do, but for somebody who is going through the same thing as you tell you physical therapy, physical activity helps, it works, would probably have even more prominence, simply because they know they're not [deceiving] you, they're telling you the truth, because they've gone through exactly what you're going through" (P-02 lines, 513-518).

7.4.2.3.4. Employment

Of the participants in the current study 8 (73%) were employed in full- or part-time work. Work commitments presented challenges for managing CF, with participants reporting a requirement to have flexible arrangements in order to manage their CF, in some cases this included reducing hours from full- to part-time or leaving work all together.

"…I try and get the shifts that are more in the afternoon so I've got time to get a decent sleep and then time in the morning to still do all my treatments and eat as well" (P-15, lines 49-51).

Whilst for some employment offered the opportunity to be physically active throughout working hours for others employment facilitated large periods of inactivity. For example;

"Well, I was on my feet all day at work...we're on our feet quite a lot. I don't sit down at a computer, I don't sit down at a desk. I'm standing and walking up and down…all day, lifting, carrying heavy boxes, putting away stock" (P-03, lines 51-54).

"…in an office environment, it's very much you're just sat on a chair with very little in the way of movement for the day, and I think that makes it harder to manage from that sort of point of view because yes, if it's just doing something that's part of the rest of your life, it's always easier to manage that rather than having to specifically think, "Right, ok, I'm going to do some physical exercise now because I have to"…" (P-09, lines 49-54).

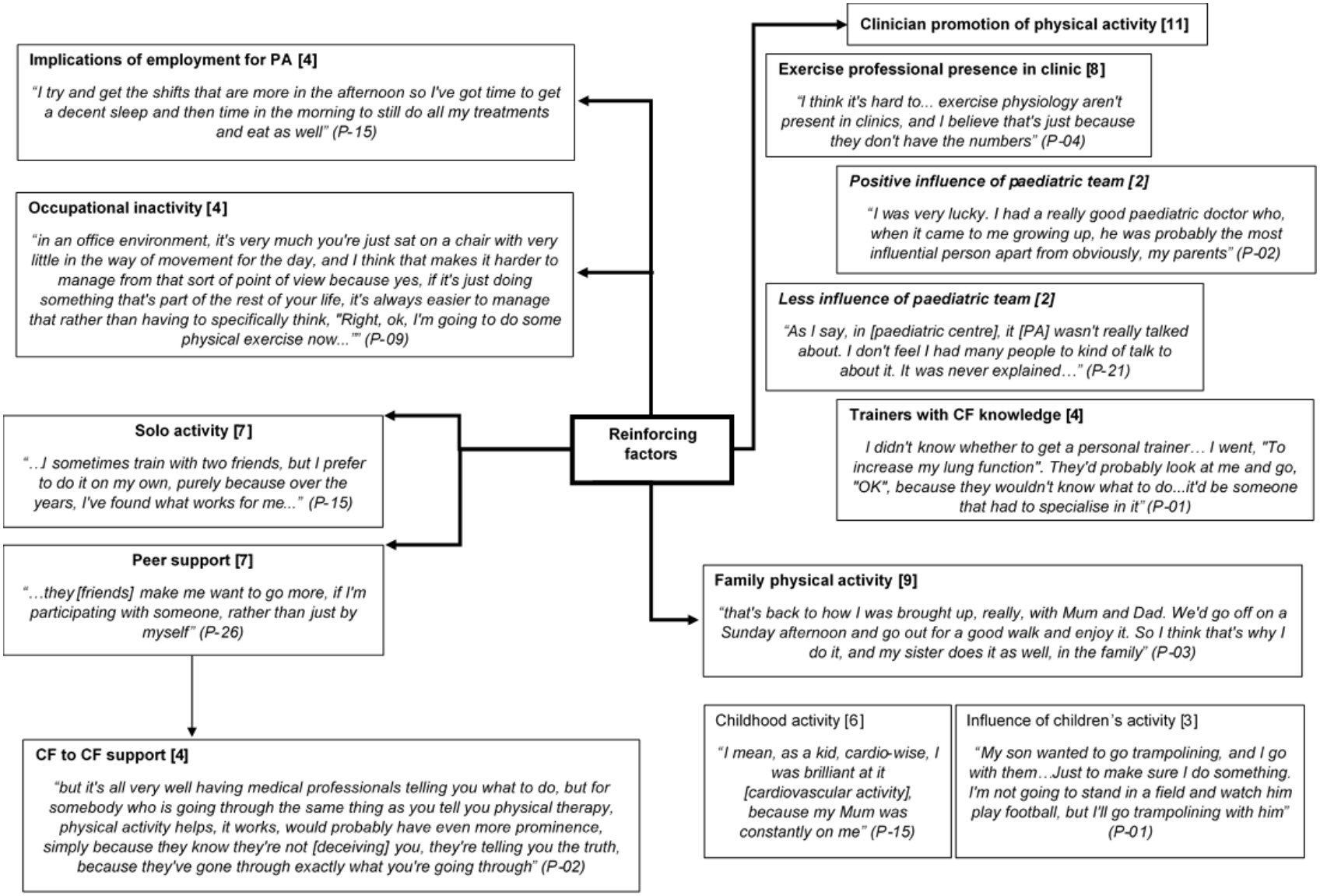


Figure 11 - Pen profile displaying reinforcing factors (n=11).

7.4.2.4. Nuanced

The P-P model provides a framework to explore health behaviours and whilst many of the themes discussed fit within this framework not all of the constructed themes did and are denoted as ‘other factors’. This inductive content analysis approach to thematic analysis is also consistent with theoretically-flexible reflexive thematic analysis [154]. These factors relate to transitioning from paediatric to adult care (transition), living with CF (normal for CF), the management of CF (treatment) and the role of social media and technology in the management of CF (Figure 12).

7.4.2.4.1. Transition

The majority of CF centres in the UK typically care for either adult or paediatric patients with a small number of combined centres. The transition process differs between centres but typically involves patients moving from receiving care within a paediatric centre to an adult centre and occurs around the age of 16-18 years of age [158]. A number of participants recognised this as an important period in their lives, during which they felt they would have benefitted from support around their PA. For example;

“…I don't know what they do in paediatrics these days, but leaving it [discussing PA] until someone goes into adult CF units, it's too late” (P-01, lines 304-306).

The burden of CF during childhood was reported to be much lower, with participants describing that they were relatively well as a child but at a certain period (often as a teenager into early adulthood) CF began to have a greater impact on their life. Some also described that they came to a stark realisation that CF was serious and that it was going to have a significant impact on their life and require significant effort to manage. For example;

“It's [CF] very much changed over the period of my life, but I expect that's normal for most people. When I was younger, and I'm talking quite a lot younger, up until the age of fifteen, sixteen, it was something that I had. I had to go to doctors' appointments, I had to take all these medicines and things like that, but in terms of my actual impact on my life, it was, I would say, fairly minor” (P-9, lines 10-14).

"…I would do it [treatment], but not like very rigorously, but nowadays when I do it properly, that's the biggest impact, in just doing the treatments regularly…" (P-30, lines 35-37).

Participants also described the impact CF can have on their lives as an adult.

"I mean, I get sick a lot, but I think it more annoys me when I have plans and I'm trying to get on with my life, and then I get sick and then I have to come in…" (P-26, lines 18-19).

"It [CF] impinges on my work, because sometimes I'll stay in work until my lung function's around forty [%predicted]. I'm dragging myself round, but I still do it, because I don't go off work unless I'm on IV antibiotics" (P-01, lines 195-197).

7.4.2.4.2. Treatment

Previous research demonstrates that the management of CF requires a complex and burdensome routine [8] and PA is often recommended in routine clinical care as part of the management of the condition. For study participants, PA was therefore perceived as a 'treatment' and likened to taking medication, with some describing how they 'have to do it *[PA]*'.

"It should be like taking your medicine. In fact, I'd rather exercise than take medicine" (P-01, lines 499-500).

Others felt that PA should not be perceived this way, instead it should be less structured and done for the purposes of fun and enjoyment rather than as treatment.

"Everything's so regimented with CF as it is, with the treatment and stuff, so I don't think exercise should be regimented as well. Because I think it just puts people off, and I think it should be a bit more relaxed…" (P-26, lines 314-316).

Ultimately though the management of CF includes many factors, with participants describing how each aspect of their treatment required their efforts and that shortcomings in any one aspect could have consequences for the other aspects of their management and their health overall. For example;

"I've found it's very hard work to keep up with everything. You've got to kind of keep up with everything, like all the meds and never missing medication or never miss physio or the gym, because I said if I miss one thing, it just falls apart. I never used to be like that. I could go without one set of meds, but I have to be consistent for things to work now" (P-21, lines 37-40).

An example of the multi-faceted treatment of CF is that of nutritional management. Participants reported symptoms relating to digestion such as bloating and frequently needing to use the toilet as barriers to PA as well as stating that PA could improve some of these symptoms. It's not surprising then that participants perceived PA and nutrition to be complementary to each other. For example;

"I think the dieticians and the exercise team should be definitely coming up with some sort of conjoined plan to make exercise easy, accessible, and I say easy in terms of if your body's fed, you can clearly have a bit more energy to do things like exercise" (P-04, lines 680-683).

7.4.2.4.3. Social media and technology

There is an increasing interest in the use of technology to support PA in health care [159] not only reported in the academic literature but also amongst participants. For example;

"…there's a couple of other fit CF people who do YouTube blogs and things, but…I don't think there's enough promoting it, because it just has such a massive impact on people" (P-23, line 258-260).

"I think it'd be the right kind of thing for patients to see our own exercise physiologists or physiotherapists, to do presentations or something on YouTube. Social media is a big influence…" (P-04, lines 619-621).

7.4.2.4.4. Normal for CF

Finally, when discussing CF, participants stated that they didn't know any different often using the phrase "it's just normal for CF". Participants accepted that their lives may be impacted by CF but that's what is normal for them so they 'just get on with it' with an expectation to be treated like everyone else. For example;

"…I don't know how it's impacted me really…I've always grown up with it, so I've always known that that is the norm for me. I've just got on with it…" (P-02, lines 64-67).

"…it's just part of life and part of who I am, really" (P-02, lines 222-223).

"…certainly wouldn't wrap me up in cotton wool. I'd do things just as much as anyone else…" (P-03, lines 23-24).

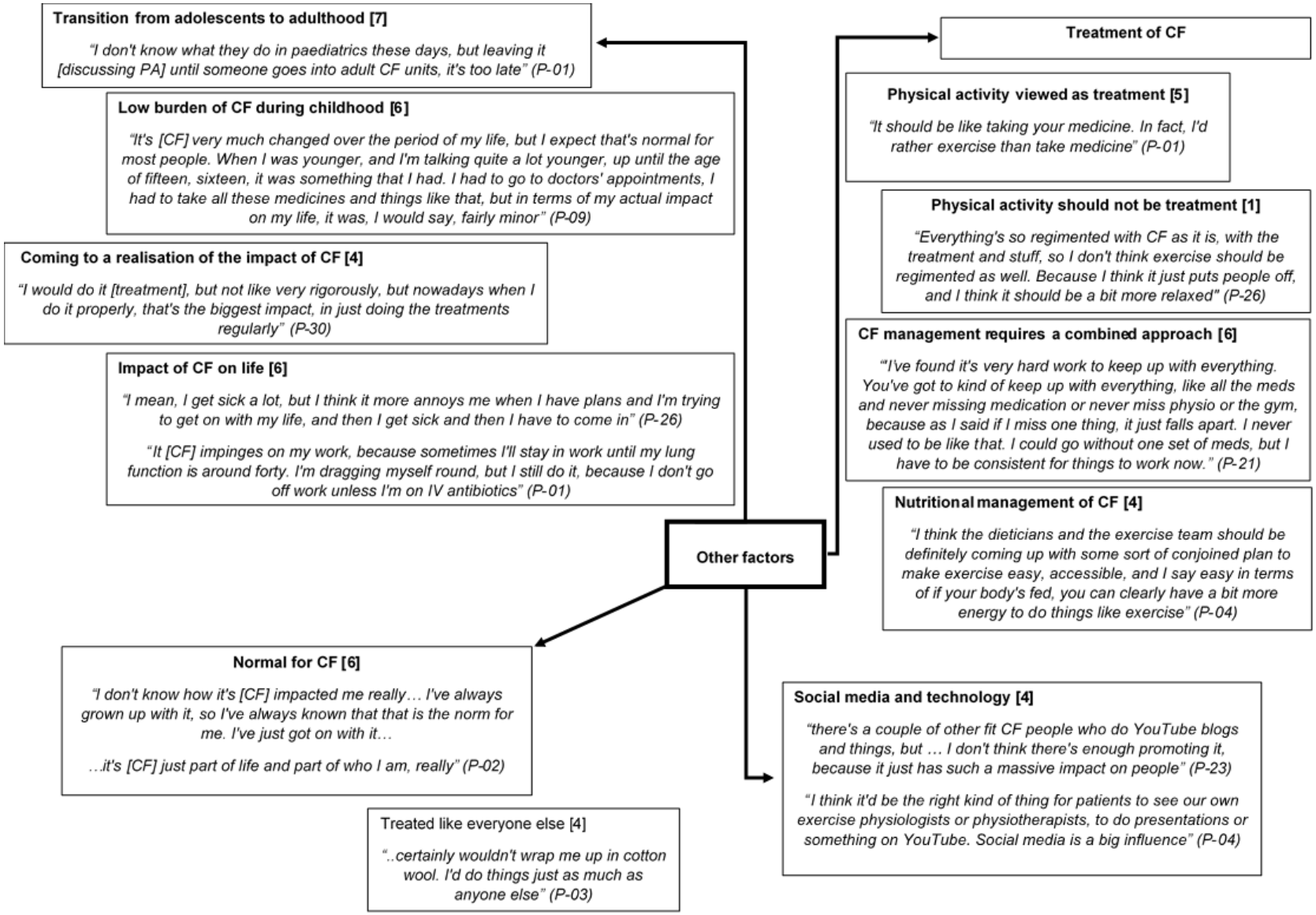


Figure 12 - Pen profile displaying 'other' factors (n=11).

7.5. PHASE 1 DISCUSSION

The aim of phase 1 was explore patients' perceptions of PA and understand the ecological correlates of PA in adults with Cystic Fibrosis. The data obtained during this phase contributes to the social and epidemiological diagnosis as outlined in phase 1 and 2 of the P-P model [151].

The principle predisposing barriers related to participants physical and mental wellbeing, which manifested as both a barrier and a facilitator of PA behaviour. CF is characterised by a progressive decline in physical function, which for the participants presented as a number of challenging symptoms and set-backs for an individual with CF. The findings of the current study are consistent with existing literature in that the range of symptoms reported includes numerous physical and psychosocial symptoms, reported with varied frequency and severity [8]. Participants perceived that PA had the potential to slow the rate of this decline and manage the symptoms associated with the condition. There is limited data available to assess the association between PA and symptom burden or HRQoL [131], although there is evidence to support an association between higher level of PA and reduced rate of decline in lung function [131][19]. Despite recognition of the potential benefits of PA, it appears that enjoyment is an important correlate of PA. This finding is consistent with findings from similar qualitative research exploring the perceptions of PA among children with CF, which also reported enjoyment as a facilitating factor for PA [160]. Lewis *et al*. suggests that interventions to promote PA in low-active adults should target increasing enjoyment first, which may in turn improve self-efficacy and motivation for PA [161]. Based on these findings it was recommended that practitioners should encourage individuals to engage in a variety of activities and promote enjoyment [161]. Motivation for PA was also reported as barrier to PA in the current study. It is well reported in the literature that motivation is an important determinant of PA behaviour [162], with a recent review of PA literature finding motivation, self-efficacy and self-regulation were consistently reported as correlates of PA [129]. Understanding of motivation is therefore important for informing the development of interventions to promote PA. The phased approach of the current research allowed for factors to be explored further in phase 2. Since disease progression and physical symptoms were not modifiable behaviours the focus of

phase two was to understand the impact of these factors and to further explore the enjoyment of and motivation for PA.

The principle enabling factors related to participants having the skills necessary to engage in PA. Higher self-efficacy for PA and the perceived ease of activity has previously been shown to be associated with increased levels of PA [163]. Participants reported having the skills necessary to engage in PA but felt that additional support and further direction would be beneficial to enhance PA participation. Whilst the environment offered opportunity to engage in PA, safety (of the environment) and fear of limitations to exercise were reported as factors that may require consideration. Whilst the fear of exercise induced complications was not universal in participants in the currently study it is well recognised in other populations such as patients attending cardiac rehabilitation and individuals with Type I diabetes [164], [165]. Following a programme of exercise-based cardiac rehabilitation the fear of exercise reduced in participants, likewise a programme of support and education is recommended to reduce the fear of hypoglycaemic events during exercise in individuals with Type I diabetes [164], [165]. The safety concerns in the current study also related to environmental factors such as traffic and pollution.

The presence of health care professionals with a special interest in PA and exercise within CF MDTs and clinics was reported as a key reinforcing factor for PA behaviour. The family also play a role in reinforcing PA behaviour in both childhood and adulthood. Similar research with families of children with and without CF also recommend involving the family in PA promotion, providing education for parents and incorporating PA into familial daily lifestyle [86], [166]. Understanding the roles of the clinical team and families in delivering a PA intervention was therefore integrated into the phase 2 focus groups schedules.

The transition process, during adolescence and early adulthood was reported as an important period in the life of an individual with CF. This period is also associated with a reduction in PA in the general population [167], highlighting the need for additional support during this period, particularly for individuals with CF for whom the transition period can present a number of additional challenges [78]. This period was therefore explored further during the phase 2 focus groups, with the aim of

determining when the most appropriate time to implement a PA intervention would be. Additionally, social media and technology were perceived to be influential for PA and were also explore further during phase 2.

The focus groups were designed to identify the modifiable behavioural characteristics associated with each of the factors identified in phase 1 in order to set achievable objectives for an intervention to promote PA in adults with CF. The constructed themes were interpreted based on; 1) Who an intervention should target 2) What action or change is required 3) To what extent an improvement in health outcomes can be expected 4) When the behaviour should be targeted. In keeping with an action research design, factors that could be modified were prioritised over factors in which modifiable action could not be taken.

7.6. PHASE 2 RESULTS

Nine semi-structured focus groups were conducted with an individual with CF, nominated members of their family and a researcher. Focus groups were audio recorded and transcribed verbatim (generating 8 hours 30 minutes of audio and 6,221 lines, 87,558 words of text). Average focus group length, 56 minutes 38 seconds of audio, 691 lines, 9,729 words of text (Size 11 Calibri font with 1.15 line spacing).

An additional semi-structured focus group was conducted with three members of the CF care team (2 consultants and 1 exercise physiologist) and a researcher. Generating 48 minutes of audio and 652 lines, 9372 words of text (Size 11 Calibri font with 1.15 line spacing).

During each focus group the principle predisposing, reinforcing, enabling and nuanced themes identified during phase 1 were discussed to inform the development of the objectives of an intervention to promote PA in adults with CF. The collective results from both the clinician and patient focus groups are discussed below, with areas of agreement/disagreement highlighted.

7.6.1. Participant characteristics

Nine participants with CF (5 male) completed phase two of the study. Average age was 32.8 ± 7.0 years, FEV_1 was 2.07 ± 1.08 litres (52 ± 18%predicted) and BMI was 22.9. ± 5.0.

7.6.2. Overall aim of an intervention to increase PA in individuals with CF

The primary aim of an intervention was reported as improving the overall 'wellbeing' of individuals with CF. For some participants this meant improvements in key outcome measures (Lung function, exacerbation frequency, fitness or expectoration), for others this meant an ability to perform activities of daily living without limitation. A second aim was simply to increase PA, likely in view of this being associated with positive health outcomes. A final aim was to be able to engage individuals with CF a programme and to keep them motivated to engage in PA.

"Well, obviously, increased physical activity, but yes…It has to be working with the patient to find something that they're going to do, basically, and that sounds really stupid and obvious, but...You've got to ease yourself into it…" (P-09, lines 465-471).

7.6.3. Outcomes

Consistent with phases 3 and 4 of the P-P model [151] the focus group data was used to help create themes to create measurable behavioural and environmental objectives which could ultimately be used to determine the success of an intervention (Figure 13).

Participants reported that an improvement in how they felt would be an important outcome to determine the success of an intervention. For example:

"Yes, I think the way I feel, maybe I probably lose weight, I'd probably be healthier, I think. My attitude would be that I'd probably be happier doing it. I think just having a conversation with me" (P-26, lines 397-399).

Whilst participants perceived that the way they felt and general wellbeing were important they also acknowledged that this may not be a measurable outcome:

"…I know myself [how I feel], but I don't know how you would capture it" (P-23, lines 424-425).

A proposed measure to reflect general wellbeing was the use of a questionnaire to assess self-reported quality of life:

"…you're sort of relying on their [patients] view, so maybe measure it with some online questionnaire" (P-30, lines 332-333).

"Well, I mean, there must be some quality of life questionnaires" (C-1, line 382).

There were a number of outcome measures reported as themes which related to improved physical function such as lung function, reduced exacerbations, reduced breathlessness and improved sputum clearance that corresponded to the predisposing factors identified during phase 1. This physical function can be reflected in a measure of 'functional capacity' or fitness. Participants recognised that a functional measure could reflect their ability to complete activities of daily living and meet the demands of their environment. Clinicians also recognised that a measure of functional capacity could reflect 'overall robustness' of patients. For example:

"So I think a functional measure of some kind of fitness test, like maybe they use in the police or the army or whatever, some kind of functional test" (P-23, F, lines 363-364).

"it's just being able to do everything that you want to in life without feeling ill and tired" (P-23, lines 549-550).

"I mean, a CPET (cardiopulmonary exercise test) is the way forward, isn't it?" (C-1, line 374).

The final outcomes reported related to the overall satisfaction with an intervention and willingness to engage with PA. Attendance was suggested as a measure of engagement;

"I think me attending. If I didn't enjoy it, I wouldn't do it. I wouldn't even bother turning up" (P-26, line 393).

As was contact time between individuals with CF and a member of the clinical team responsible for the promotion of PA;

"So that is obviously something that you can measure by the staff attendance, and then the patients, communication with them, the time spent with the patients" (P-04, line 551-512).

"I think initially, more contact time with patients would show that there's more activity" (C-2, line 633).

7.6.4. Intervention design

In order to further explore how these objectives could be achieved the design of the intervention was discussed, with focus on who would be responsible for managing the intervention, where the intervention could take place and what the intervention would look like.

7.6.4.1. Intervention design – Who is responsible for managing a PA intervention?

Individuals reported as reinforcing PA during phase 1 were also reported as individuals important to the development of an intervention. This included the presence of an exercise professional within the CF MDT, engaging the family and the patients themselves. Patients and their families perceived that the success of an intervention would require the whole CF care team to view PA with the same importance as other treatments, going on to state that this would have to start with the consultant. For example:

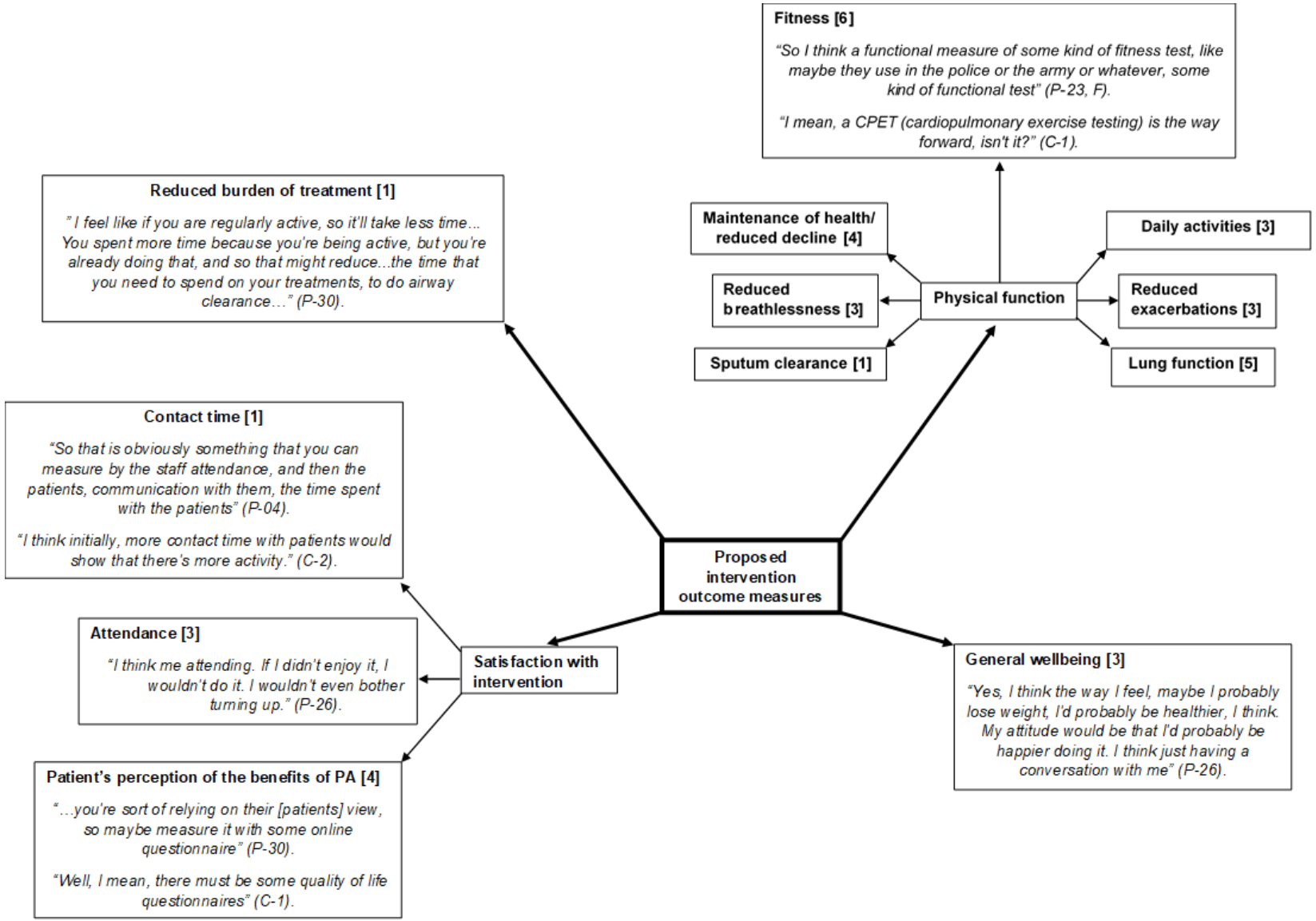


Figure 13 - Pen profile displaying participant (patients (n=9) & clinicians (n=3) selected intervention outcome measures.

"This is lots of little nudges to change the course of their behaviour, and that's just every clinician, nurse, physio, one of us when we [clinical team] see them [patients]" (C-2, lines 549-550).

"So I think it [PA promotion] has to stem from the consultant or doctor, that firstly they see physiotherapy and physical activity as high up as medicine" (P-01, lines 566-567).

Within the wider team an exercise physiologist was identified as the key individual who would be responsible for the day-to-day patient contact and reinforcing the promotion of PA. As demonstrated below:

"Yes, from day one…you've got to have a team of physiotherapists, physiologists that fully understand" (P-01, lines 571-572).

This quote also highlights the requirement for the intervention to be delivered by individuals with a knowledge and understanding of CF, an opinion shared by both patients and clinicians. Despite this there is not a defined qualification, training pathway or accreditation for exercise professionals to specialise in CF.

"…they know CF and they're sympathetic to your needs and the demands of the condition. That's what I feel. It needs to come from a CF-based background" (P-03, lines 584-585).

"somebody with some experience and a real interest in it [CF]" (C-2, line 595).

Involvement of a psychologist as part of an intervention was also perceived as important, owing to the psychological barriers to PA discussed during phase 1;

"Because it is a huge amount of that [barriers to PA], it is all in your head, so perhaps someone who deals in your head will help" (P-09, lines 400-401).

There was a belief that the care team could, in effect, become 'family by proxy' in the absence of family support but patients with family support felt that they should be involved in any interventions to promote PA and in their CF care more broadly. For example:

"What we should be doing is having the parents gradually support you, and if you haven't got parents, you need peers around you. Maybe it's guardians, maybe it's friends, or the CF team" (P-04, lines 154-156).

“I think it has to be family, doesn't it, really? Getting you more involved, and...motivate you more…” (P-28, lines 392-394).

7.6.4.2. Intervention design – Where should an intervention take place?

Findings from phase 1 indicated that participants did not perceive environmental factors to be a barrier to PA *per se.* The hospital/clinic, home, wider community and internet were identified as potential locations for a PA based intervention to take place. The hospital represented a familiar and convenient location, as well as providing access to health care professionals.

“I think practically, it would probably be in clinic” (P-30, line 237).

The home was also perceived as suitable location for a PA intervention, particularly for individuals who may have limited functional capacity and/or feel less able to participate in PA. Although PA would be carried out away from the hospital, a level of support in the form of communication or an occasional home visit was deemed as an important component of the intervention. For example:

“ They could include just household-type stuff, like perhaps ten flights of stairs per week, or walk for thirty minutes daily, or some kind of programme that somebody can just take away home from the hospital and think, "Right, I'm beginning this, I've got to do week one, week two, week three, week four", and then even if they were just a call at the end of each week, just from somebody at the hospital, just to sort of hold them to account” (P-23, F, lines 84-89).

For others the hospital and home environments contributed to the isolation often associated with CF and therefore stated a preference for engaging in PA within the wider community. The wider community may also offer a greater range of activities than those available with the confines of a hospital or home based programme.

“I think CF can be quite isolating, where you're kind of forced to stay indoors more than you'd like to, so I think having somewhere that's not a hospital and then not your home, but somewhere else that you can go to [to engage in PA]” (P-26, lines 371-373).

The use of technology, in particular online video calling was suggested as a potential method to overcome the isolation resulting from segregation in CF. This may allow participants to benefits from the social aspects of engaging in PA as a group as well as provide the opportunity for peer support. Participants and clinicians acknowledged the potential benefits of such an intervention:

"online sounds quite a good idea, so everyone could train, everyone with the same condition can do activity, and then I reckon in the hospital would be good as well" (P-03, lines 272-273).

"Could you do this as in tele-medicine? You know, a group of ten patients, it could be in North Wales or wherever, and if they all have exercise bikes set up" (C-3, lines 472-473).

7.6.4.3. Intervention design – When should PA be promoted?

(You've got giraffes on the wall. (P-02, line 626))

As identified during phase 1 the transition from paediatric to adult care is an important period in the life of an individual with CF and often coincides with a worsening of disease severity, increased independence and responsibility for treatment as well other significant events such as moving away from home, employment or further study. The 'giraffes on the wall' are symbolic of the nurturing and friendly environment of a paediatric clinic, following transition to adult care there are no more giraffes on the wall. Participants (clinicians and patients) reported that PA should be encouraged from an early age;

"Early. As early as possible" (P-04, line 167).

"Oh, from day one" (C-2, lines 438).

With an increase in PA promotion and support throughout the transition period;

"I think maybe to definitely start, always try and start as early as possible, definitely, but take particular care and attention when they're teenage" (P-21, lines 88-89).

"Teenage, yes, because you kind of go off a little bit. Well, I did a little bit then…So that probably would be a really good time, because then you could do quite a lot of damage in those years if you're not doing anything…" (P-23, lines 210-217).

"…when they're active as children and have got active families, when they drop off as a teenager, because all teenagers are naughty, they're easier to regain it later on, but if they've never been active and they don't have an active family, it's never been something they do, it's very hard for them to start with [lung function] of 40 to 50% as mid-twenties" (C-2, lines 273-277).

7.6.4.4. Intervention design – What action is required?

(It's more of a long game, isn't it?" (P-21, lines 473-478))

Exploration of how such support may be offered and how an intervention could be structured to meet the previously discussed objectives provided valuable information for the intervention design. A number of factors were previously discussed in phase 1, these included providing a variety of activities and opportunities for PA, the use of self-monitoring as a motivational tool and education for patients and parents. Engaging families in PA promotion was also constructed as an additional factor to consider when designing an intervention. It was reported that the family could have a role in holding individuals with CF to account with regards to adhering to a PA programme as well as making PA more enjoyable. For example:

"…if you just say, "Oh, there's an intervention", they won't be motivated, but then if you say there'll be support and the family will be involved, I think they're more likely to do it" (P-03, F, lines 566-567).

Physical symptoms and uncontrolled setbacks were identified as barriers to PA during phase 1. Participants conceded that there was little that they could do to control for or plan for these. It was perceived that as part of an intervention it would be important to acknowledge that there may be set-backs and to be prepared to adapt to this to limit their impact, particularly in terms of the psychological impact such as causing frustration and becoming demoralising. For example:

"…in terms of when uncontrolled setbacks and things were really really hard for me to deal with, not even necessarily from like a physical point of view, but just it's so defeating when you get, especially if you... Because you used to set yourself milestones, "I want to be able to do this, this week", and invariably I would set things that were a little bit unreasonable, and it would take me longer than I thought, but it felt really good when I got there, and then if that gets taken away from you by a chest infection, it's really, really tough to then go back" (P-09, lines 184-188).

From a clinician perspective, the approach to PA promotion among adults with CF is the same as for that of the non-CF population. The challenge faced in a CF population is that the consequences of inactivity are greater than in non-CF peers. For example:

"I don't think there's anything clever about CF exercise compared to exercise in the general public. It's exactly the same…the consequences are greater, but the mechanisms and the strategies to get them to do exercise should be exactly the same…" (C-1, lines 449-453).

From the outset of the research, the term 'intervention to promote physical activity among adults with CF' has been used to describe the end point of the formative action research process. There has been no definition of what an intervention is or any parameters to work within when designing the intervention. It was anticipated that the resulting intervention may mirror examples of exercise interventions within the literature, with the addition of specific objectives to target behaviours identified in earlier phases. These exercise interventions are typically structured programmes with or without supervision delivered in home-, community- or hospital-based settings. Typically, such interventions are delivered over a discrete period ranging from ~8 weeks to ~3 months. However, the key message resulting from the current research is that the promotion of PA in this population would be most effective as part of routine CF care rather than as a bespoke intervention. Participants suggested that PA promotion should form an integral part of their care and be given the same emphasis as other treatments. This would include regular contact with professionals reinforcing PA. For example:

"So for me, I think it'd be better if it [PA] was a bigger topic in clinic in general, so yes, I would move away from this intervention whatever, more to just make it a more rigorous part of the treatment regime in the first place" (P-30, lines 245-248).

"I don't think there's going to be any one kind of thing. I think it's got to be all of it linking together. I've got no doubts about that… I think you've got to address all the barriers at once" (P-04, lines 467-470).

Participants emphasised the importance of the relationship between healthcare professional and patient, suggesting than an individualised approach, developed through building a rapport and understanding individual needs is essential to increasing PA. For example:

"…you need to find out what matters to them…what does matter to you? Does it matter to you that you're physically capable to climb the stairs in your house? Does it matter to you that you're physically capable to keep up with your peers? If it matters to you, shall we do something about it? And it's that approach, rather than, "Are you booking us in today?" (P-04, lines 308-315).

One participant highlighted the unique nature of the relationship between individuals with CF and the CF team, describing it as follows:

"It's different with CF. You're with the team, aren't you, for a long time?...Even when you're a kid, you're with them for a long time, then you move to adult, and then you've got to, hopefully, be with them for a long time…but you are going to build up a relationship, aren't you, with these people? It's more of a long game, isn't it?" (P-21, lines 473-478).

This quote encapsulates one of the unique aspects of PA promotion in this population, in that there is not a pre-determined end date or discharge representing the natural conclusion of an intervention.

7.6.5. Resources an policy

Phase 5 of the P-P model outlines the assessment of the budgetary, staffing and resources available to support an intervention as well as identification potential barriers and facilitators of an intervention at an administrative and policy level [151]. This phase was primarily conducted during the clinician focus group meeting.

7.6.6. Assessment of resources

The promotion of PA is currently recommended as part of routine CF care, with specific recommendations for best practice outlined for physiotherapists [85]. In addition to this, numerous sources of information and resources useful in the promotion of PA were identified, including written information, mobile applications and online video content from existing organisations. Although there is no requirement to employ staff with a background in exercise science or an existing pathway for such individuals to work in CF the service participating in the current research employed two full-time members of staff to deliver exercise services. There was also access to a small facility to conduct exercise testing and prescription.

"it's [exercise provision] just this is an unmet need, and to a certain extent, it's unrecognised" (C-1, lines 610-611).

7.6.7. Barriers to implementation

Reported barriers to implementation included additional staffing requirements, a lack of space, an underrepresentation in clinic and an inability to perform CPETs. For example:

"We don't have the staff and we don't have the place to bring them" (C-2, lines 604-605).

"Years ago, for about two years, we came down to clinic…and to be honest, never had a room, never had space, and nowhere to talk to people, and that was hard enough, and then on top, I just felt that was a waste of their time, that I could do more on the wards" (C-2, lines 252-256).

"The only thing we're missing is the gold standard cardio-pulmonary exercise testing on all the patients… but you're talking money there" (C-2, lines 618-620).

"*there's no doubt now that if we didn't have an exercise physiology team, we wouldn't be getting one. Now that's not because they're not valuable, it's just because this organisation's really strapped for cash…and so what we've got is what we have, and we're very grateful and it's good" (C-1, lines 634-638).*

7.6.8. Facilitators for implementation

There are specialist CF centres established throughout the UK with specialised teams already in place to support individuals with CF, adding to current services could provide the opportunity to promote PA whilst maintaining familiarity. Although employing an appropriately trained and experienced member of staff has financial implications. For example:

"You'd need another Band 6 [exercise professional], somebody with some experience and a real interest in it [CF and exercise], so that salary straight away per year's a lot…"(C-2, lines 595-596).

The primary objective of CF care is often to slow the rate of decline and so the aim of an intervention may not be to produce drastic short-term improvements but rather to have improved outcome long-term. As illustrated here:

"It's maintaining the levels. Reaching an optimum level for that patient and then maintaining it, because it's a slippery slope with CF" (C-1, lines 503-504).

As referred to as part of the assessment of resources there are a range of resources available to support the promotion of PA in individuals with CF. The role of the clinical team is to be aware of these resources and to be able to signpost patients to relevant resources and services at an individual level.

7.7. PHASE 2 DISCUSSION

The aim of the current study was to understand the ecological correlates of physical activity in adults with Cystic Fibrosis and to use these findings to inform the development of an ecological approach to physical activity promotion in this population. In doing so a formative approach was employed, involving patients with CF, their families (where applicable) and clinicians.

Principle predisposing factors which represent suitable targets for increasing PA in adults with CF relate to removing the barriers associated with disease progression, increased symptom burden and uncontrolled set-backs. A key facilitator of PA for the participants with CF was improved wellbeing, which is typically associated with improvements in clinical measures including lung function and fitness. Both participants with CF and their clinicians reported enjoyment as a significant facilitator of PA, although this represents a challenge for PA promotion as participants describe PA being enjoyable as a child when the impact of CF is less pronounced and enjoyment turning to necessity and treatment with disease progression. With participants describing their PA as 'normal' during childhood. Participants with CF reported that the impact of CF becomes more pronounced during adolescence, which contributes to the shift from enjoying PA to PA being viewed as a treatment. This period is also associated with transition from paediatric to adult care. A systematic review of qualitative studies exploring correlates of PA reported enjoyment of PA as a motivation for PA across all age groups [168]. In older adults participation in prescribed PA was also maintained through enjoyment [168]. Enjoyment is clearly important, however enjoyment of PA is highly variable between individuals, as such PA promotion should adopt an individualised approach, encourage individuals to engage in a variety of activities to promote enjoyment, which may improve self-efficacy and motivation for PA [161].

Enabling factors which represent targets of PA promotion include providing a range of activities to encourage enjoyment of PA. Additionally, education and specific direction to help to overcome some of the challenges of being active with CF, particularly managing symptoms and set-backs. Participants reported that the environment did not present barriers to PA. In terms of intervention delivery there appears to be scope to promote PA in a number of settings including at hospital,

home, community and online, although this requires an awareness of local resources and individual needs.

From the perspective of participants with CF and their families the clinical team and in particular the presence of an exercise professional appears to be central to reinforcing PA behaviour. Regular contact at each clinic visit with such an individual and the development of a rapport appears to be key facilitator of PA. Whilst neither the participants with CF nor their clinicians alluded to how this rapport may be established this finding is consistent with previous research in this population. Participants with CF participating in a counselling intervention reported that they perceived consistent contact with a healthcare professional beneficial for their psychological health and valued informal long-term enduring relationships with healthcare professionals [169]. In addition to this, the role of the family in supporting individuals with CF was reported as a reinforcing factor, important to the promotion of PA. Participants reported that their family played a role in holding them accountable for the PA levels as well as making engaging in PA more enjoyable.

Participants with CF and their clinicians suggested that the overall aim of an intervention to promote PA should be to improve the overall 'wellbeing' of individuals with CF. This encompassed improvements in key outcome measures, increased PA and an ability to engage individuals with CF in PA. There was a belief among participants with CF that PA should have the same emphasis as other aspects of the management of CF. Both participants with CF and their clinicians highlighted promoting PA as early as possible as an important factor in increasing PA in individuals with CF, with additional support given during the transition from adolescent to adulthood.

The key message resulting from the current research is that the promotion of PA in this population would be most effective as part of routine CF care rather than as a bespoke intervention. To achieve the aims of improving wellbeing and physical function in individuals with CF, as well as engaging them in a programme of PA there appears to be a requirement to have a dedicated healthcare professional within the CF team. An individual with expertise in PA who understand CF and has the capacity to provide individually tailored advice through frequent contact and support. Although PA is recommended as part of routine CF care there no

requirement for CF services to include an exercise professional and no standardised role for an exercise professional within CF MDTs. A number of UK centres are now employing individuals to oversee exercise provision but these roles remain largely undefined [173]. The model of PA promotion suggested in the current study is considerably different to the conventional exercise-training model that has constituted the majority of research in this area. Existing exercise training interventions do not consider local environments and interests at an individual level, are resource intensive and often lack long-term sustainability [177]. The integration of exercise professional led PA promotion into CF care may represent a more sustainable and effective model to increase PA in individuals with CF. In addition to the role of an exercise professional participants with CF also alluded to the inclusion of a psychologist in supporting the promotion of PA. Clinical psychologist are already present within CF MDTs and play an active role in supporting patients, however the nature of the role described here may be more akin to the role of a Health Psychologist. Health psychology is concerned with the psychological, behaviour and social factors contributing to health and typically takes a person centred approach to behaviour change and health promotion [170], whereas clinical psychology primarily focuses on treating psychological disorders. Whilst the CF clinic was identified as the primary location for the promotion of PA to take place participants also expressed a desire to have multiple options including access to community resources, home-based programmes and thorough the use of online technology and media. The use of technology in promoting PA in individuals with CF is an emerging area of research and represents a feasible and acceptable method of intervention delivery [168]. Clinicians suggested that the promotion of PA in adults with CF is similar to in the general population, indeed a number of the correlates of PA discussed in Phase 1 were comparable to non-CF populations. Aspects unique to individuals with CF related to the additional consequences of inactivity for health, the physical and psychological barriers associated with the condition and the long-term nature of the relationship between patients and clinicians. It is therefore important for clinicians working with individuals with CF to acknowledge that there may be set-backs and to be prepared to adapt to this to limit their impact, particularly in terms of the psychological impact. Supporting patients with setting goals, managing setbacks and overcoming such psychological barriers could form part of the role of exercise physiologists and psychologists who were reported as key

individuals in delivering an intervention. The long-term enduring relationships between healthcare professionals and individuals with CF provides a unique opportunity to support patients, more broadly and in terms of PA promotion. Previous research has demonstrated that individuals with CF value this long-term presence of a healthcare professional [169]. However, self-regulation is consistently reported as a correlate of PA, as such healthcare professionals face the challenge of providing support whilst also promoting self-regulation and avoiding participants reliance on their support [129].

There are numerous resources available to support clinicians and patients to increase PA, although clinic space, equipment and staffing represent barriers to implementation. Access to resources is commonly reported as a limitation to adherence with PA recommendations across UK CF services, despite PA being valued among clinicians [171].

7.8. Strengths and Limitations

There are a number of strengths apparent in the present study. Firstly, the formative research design allowed detailed exploration of factors influencing PA and discussion with individuals with CF, their families and clinicians providing novel insight into the correlates of PA. Furthermore, the research advances the use of qualitative methodologies including participatory research and the use of pen profiles in this population. The findings from this study also have important implications for the design of future interventions promoting PA in adults with CF. The formative data presented in the current study provides information to inform the development of a PA intervention for individuals with CF but does not outline a deliverable invention. Whilst the P-P model provides a framework to explain health behaviours and environments to inform the design and evaluation of interventions it does not provide a framework to develop the content of an intervention and requires the integration of other theoretical models and behaviour change techniques.

Participation was voluntary, as such, the self-selecting nature may have resulted in a sample of patients already motivated to be physically active.

Finally, there was a relatively small sample of participants from a single centre. The addition of wider MDT members, namely the CF Physiotherapist, may have provided an additional perspective and additional information relating to the promotion of PA. Physiotherapists are typically responsible for the promotion of PA within CF services, however the current research was conducted in a centre that employed exercise physiologists who were responsible for the provision of exercise and PA, as such, it was deemed that focus group membership was appropriate. Additionally, the study design and analysis methods allowed for the collection of in depth qualitative data from patients, families and clinicians perspectives. Given the constructivist approach underpinning the qualitative methods the generalisability of the results was not based on conventional statistical probability (which would rely on a larger sample size) but was based on the detailed exploration of multiple perspectives from a diverse sample of individuals with CF of varied age, disease severity and experiences [172].

7.9. CONCLUSION

The promotion of PA in adults with CF may not be best achieved through the delivery of a single intervention but through the role of an exercise professional as part of routine CF care long-term. PA promotion should begin during paediatric care and be reinforced throughout an individual's life with additional support during adolescence. The role of an exercise professional should be to identify the principle predisposing, enabling, reinforcing factors influencing PA behaviour at an individual level in order to remove barriers to PA, engage patients and improve 'wellbeing'.

7.10. RECOMMENDATIONS

PA promotion should form part of routine clinical care, with designated exercise professionals available to identify barrier and facilitators to PA, reinforce PA behaviour and support patients at an individual level. PA promotion should involve family members from an early age and throughout the course of an individuals' life, although support should be intensified during adolescence. The role of an exercise professional as part of the CF MDT is not currently a requirement of CF services, with PA promotion typically a responsibility of the CF physiotherapist. In order to

establish the role of an exercise professional as part of the CF MDT an accreditation pathway and standardised role are required.

7.11. APPLICATION TO PRACTICE

The current research utilises the social-ecological approach of the P-P model [151] to understand the predisposing, reinforcing and enabling correlates of PA among adults with CF. Whilst the P-P model provides a framework to help to understand the broad range of correlates of PA it does not provide a framework to inform the choice of intervention techniques. Therefore, complementary frameworks are required to detail the behaviour change techniques underpinning an intervention.

The COM-B system identifies three key mechanisms of behaviour change termed; capability, motivation and opportunity [150]. Drawing upon this system for understanding behaviour, the behaviour change wheel (BCW) provides a framework to identify which aspects of the behavioural system need to be influenced and in what ways in order to achieve a behavioural target [150]. The BCW facilitates the identification of the intervention functions most likely to be effective in changing a particular target behaviour, these can then be linked to specific behaviour change techniques (BCTs) [173]. The intervention functions form the second layer of the BCW and are mapped to the COM-B components, represented in the centre of the model. The outer layer comprises of policy categories that could be used to deliver interventions (Figure 14).

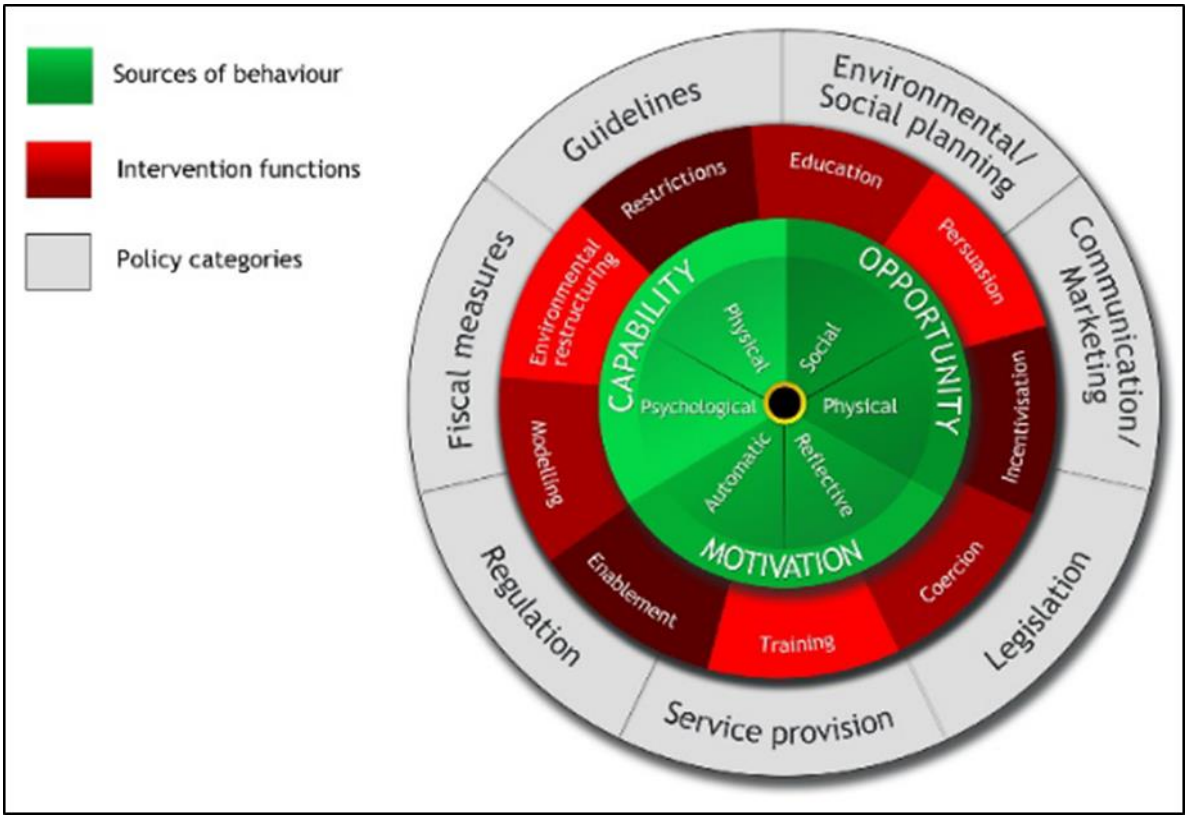


Figure 14 – The behaviour change wheel, reprinted from Michie, et al. (2011) [150]**.**

Within the COM-B model, capability refers the individual's psychological and physical capacity to engage in PA and includes having the necessary knowledge and skills. Motivation includes the cognitive processes that direct behaviour [150]. This includes goals, conscious decision-making, habitual processes, emotional responding, and analytical decision-making. Opportunity referrers to external factors that enable or prompt PA [150]**.** The COM-B can add to the understanding of the mechanisms of behaviour change in social ecological models [150] and has recently been used alongside socioecological models to identify the underpinning mechanisms of behaviour change (opportunity, capability and motivation) for PA interventions [174], [175].

The data collected within the current study provides information relating to the population specific correlates of PA that can inform intervention development. The BCW is an example of a framework that may be used to inform the choice of intervention functions and appropriate BCTs. By way of example, the 'is it worth it?' theme within predisposing factors relates to motivation for and enjoyment of PA,

which within the context of the COM-B model could be categorised as ‘motivation’. Therefore, when using the BCW, ‘enablement’ (increasing means/reducing barriers to increase capability or opportunity) and ‘training’ (imparting skills) would be identified as appropriate intervention functions to target behaviour change, this would be best achieved through service provision.

8. THESIS STUDY MAP

Study	Aims/objectives	Key findings
One - Systematic review	Establish the physical activity levels of adults with CF. Compare reported PA levels between CF patients and their non-CF peers. Examine the associations between PA and markers of health in adults with CF.	• PA in adults with CF is largely comparable to their non-CF peers, despite being insufficiently active to achieve global PA recommendations • Highlighted a requirement for high quality studies designed specifically to explore PA in adults with CF
Two - Assessment of physical activity and vascular function	To compare levels of physical activity in adults with CF to their non-CF peers and to determine the association between PA and vascular function	• Adults with CF are significantly less active than there non-CF peers. • Higher PA is associated with higher lung function and quality of life but not vascular function.
Three – Physical activity promotion in adults with CF	To understand the ecological correlates of physical activity in adults with Cystic Fibrosis. To inform the development of an ecological approach to physical activity promotion in this population	• PA promotion should form an integral part of CF care, led by a designated exercise professional. • PA promotion should start in paediatrics with additional support during adolescents.

9. SYNTHESIS OF FINDINGS

The focus of this thesis was to determine and to discuss PA and physiological adaptations in adults with CF. Specifically aiming to: 1) Establish the physical activity levels of adults with CF. 2) Compare PA levels between individuals with CF and their non-CF peers. 3) Examine the associations between PA and markers of health in adults with CF. 4) Objectively compare levels of physical activity in adults with CF to their non-CF peers and determine the association between PA and vascular function. 5) Understand the ecological correlates of physical activity in adults with CF to inform the development of an ecological approach to physical activity promotion in this population.

Objectives relating to the assessment of PA and associations with physiological outcomes were addressed in Chapters 3 and 5. The formative research process, involving patients, their families and clinicians to inform the development of a PA intervention was outlined in Chapter 7. The contributions to existing literature are outlined below for each of the stated objectives. Additionally, the strengths and limitations of the work are discussed along with recommendations for clinical practice and further research.

9.1. PHYSICAL ACTIVITY LEVELS IN ADULTS WITH CF

Chapter 3 provides an overview of the available literature relating to the analysis of PA in adults with CF. In combining the available literature the findings suggest that adults with CF fail to meet recommended PA and step count guidelines, although levels of PA were comparable to their non-CF peers. Only eight studies provided sufficient information to allow comparison to PA guidelines, and adults with CF did not meet global PA guidelines in five of those studies. Only three studies were identified that used objective PA assessment methods to assess PA in adults with CF and a non-CF control group. Only one of these studies found any significant differences between groups, finding that adults with CF engaged in less vigorous PA than their non-CF peers [87]. Determining levels of PA among adults with CF using the available literature is therefore challenging.

The aim of Study 2 (Chapter 5) was therefore to objectively compare levels of PA in adults with CF to their non-CF peers. Accelerometers were used and raw data analysis was employed to improve the quality of PA assessment in this population. This study represents a significant contribution to existing literature by providing a PA assessment method capable of describing the frequency, intensity and time of PA without the requirement for CF specific cut points. Use of raw data analysis allows for consistent, comparable and interpretable PA reporting in adults with CF that may improve understanding of PA in this population and its association with clinical measures. Use of the objective methods in Study 2 (Chapter 5) provided evidence to suggest that PA (average ENMO, MVPA, MPA, VPA) was significantly lower in individuals with CF when compared to their non-CF peers when controlling for age and sex.

The average ENMO and IG metrics allow for additional information regarding the distribution of PA and PA profiles, which are not captured by conventional methods. These results indicated that adults with CF demonstrated a poorer PA profile than their non-CF peers. IG was significantly different between groups when controlling for age and sex. Adults with CF had a steeper gradient and lower constant representing a poorer PA profile, reflecting more time spent in lower intensity activity and less time across the range of intensities when compared to their non-CF peers. These findings support those of the systematic review (Chapter 3) and prior research in that individuals with CF engaged in less vigorous PA than their non-CF peers [87]. These findings also demonstrate that individuals with CF have lower average ENMO and a poorer PA profile (IG), providing novel information about PA in this population.

9.2. PHYSICAL ACTIVITY ASSESSMENT METHODS

The process of conducting the review (outlined in Chapter 3) emphasised a lack of consistency in assessment and reporting of PA-related outcome measures. However, the review highlighted an interest amongst clinicians and researchers in assessing PA in adults with CF, with studies identified spanning two decades. A number of recommendations were made based on the findings of the review including the recommendation to utilise objective PA assessment with raw data

analysis wherever possible. Study 2 provides evidence to support that the analysis of raw acceleration data and use of the average ENMO and IG metrics can provide meaningful, interpretable and comparable analysis of PA in adults with CF and warrants further investigation.

Study 2 (Chapter 5) also investigated associations between self-reported and objective PA assessment. Weak correlations between objective and self-report PA assessment methods were observed. Additionally, when assessed using the GPA-Q there was no significant difference in self-reported PA between groups, despite a difference being observed when using objective methods, therefore supporting the recommendation for the use of objective PA assessment. Self-reported measures may be influenced by biases such as subjective recall of PA, the misinterpretation of questions and participants' desire to please researchers [176]. Additionally questionnaires are less effective for assessing incidental PA such as low intensity ambulatory activity [176].

9.2. PHYSICAL ACTIVITY AND ASSOCIATION WITH CLINICAL OUTCOME MEASURES

Study 2 highlighted the potential for CVD with increased life expectancy in adults with CF. There are few studies investigating vascular function in CF, with Study 2 being the first to explore PA and vascular function in adults with CF. The results were surprising in that no significant differences in FMD% were observed between adults (19-35y) with CF and their non-CF peers, although there were some differences in vascular structure. Vascular function was not associated with PA, though this may warrant further investigation in a larger sample across multiple time points.

As alluded to earlier in the thesis the assessment of lung function is a cornerstone of CF care [16] providing an indicator of disease progression and severity [17]. Improvements in lung function therefore represent a key therapeutic target for interventions in individuals with CF. Higher levels of objectively assessed PA (average ENMO, VPA and MVPA) were associated with higher lung function, therefore supporting findings from earlier research using counts based data and

step counts [87]. Whilst it is accepted that higher levels of PA are positively associated with higher lung function [19], the findings outlined in Chapter 3 provide inconsistent support for such an association. The systematic review conveyed that studies using self-reported measures of PA were unable to detect an association between PA and lung function, though one of the four studies did report that PA was lower in participants with severe impairment (FEV_1 <45% predicted) when compared to those with mild impairment (FEV_1 >65% predicted) [108]. Studies using objective PA assessments reported multiple outcome measures for both PA and lung function with four of five studies demonstrating a positive association between a measure of PA and a measure of lung function.

Despite the apparent benefits of assessing HRQoL only one study reviewed in Chapter 3 reported a measure of HRQoL. Cox et al. (2016) reported higher QoL scores in participants achieving ≥30mins of MVPA per day than those engaging in <30 mins MVPA per day [177]. This finding supports an association between engaging in daily MVPA and improved QoL, although it is also possible that individuals with higher function would report higher QoL and engage in more MVPA. Associations between objectively assessed PA and HRQoL were also observed in Study 2. VPA was positively associated with scores for the 'physical' and 'role' domains. Additionally, sedentary time was negatively associated with the 'role' domain. Thus providing additional support to the review findings (Chapter 3) for an association between PA and HRQoL in adults with CF. Additional research is warranted to fully understand any potential association between PA and HRQoL

Higher levels of PA are positively associated with higher exercise capacity [20], which is an independent predictor of mortality in CF [43]. The study by Hebestreit (2006) and colleagues was not included in the systematic review (Chapter 3) as it included a mix of both paediatric and adult participants [20]. Objective PA assessment methods were used in the study, with data reported as counts per day and time spent engaging in MVPA. MVPA was arbitrarily defined as >1,000 counts·min^{-1}, despite a value of >1952 counts·min^{-1} being validated and widely used as a threshold for MVPA using counts based accelerometry in adult populations [178]. Regardless of the cut-points used the association between PA and exercise capacity evident in this study was supported by the review findings (Chapter 3), with

all four studies reviewed finding a positive association between objectively assessed PA and VO_2 [177][87][111][110].

This thesis provides evidence to support that PA is potentially associated with improved lung function, exercise capacity and HRQoL in adults with CF, highlighting the value of having an accurate and valid assessment of PA to determine PA levels and to aid clinical decision making in this population. These finding also support recommendations for the promotion of PA within routine clinical practice [88].

9.3. PHYSICAL ACTIVITY PROMOTION IN ADULTS WITH CF

Collectively the systematic review and objective assessments of PA indicate that adults with CF do not meet guidelines for PA and are less active than their non-CF peers despite evidence to support positive associations between PA and health outcomes. Study 3 therefore employed qualitative methods to explore the perceptions of PA among adults with CF and inform the development of an intervention to increase PA utilising a participatory action research process involving patients, their families and clinicians.

Although the promotion of PA has been recommended as part of routine clinical practice for a number of years there are few examples of successful PA interventions [46]. The purpose of Study 3 (Chapter 7) was to understand the ecological correlates of PA and inform the promotion PA in adults with CF. Individuals with CF, their families (where applicable) and clinicians were involved throughout all aspects of the process. The main finding of study three was that the promotion of PA in adults with CF may not be best achieved through the delivery of a single intervention but through the role of a dedicated healthcare professional within the CF team. An individual with expertise in PA who understands CF and has the capacity to provide individually tailored advice addressing key predisposing, reinforcing and enabling factors through frequent contact and support. Additionally, it was perceived that PA should be assigned the same value as other treatments in the management of CF and should be promoted from an early age with additional emphasis during adolescence.

The principle predisposing factors presenting barriers to PA related to the progression of disease severity with age, increased symptom burden and uncontrolled set-backs. The negative impact of CF symptoms on PA have previously been documented in children with CF [160], though it is likely that this problem is only confounded with the added complications associated with advanced disease in adulthood. A key facilitator of PA was improved wellbeing, a factor which may be captured through the use of a measure of functional capacity and quality of life. Enjoyment was also a significant facilitator of PA. Environmental factors were not reported as barriers to PA, additionally participants did not feel that they lacked the skills required to engage in PA. A variety of PA options reported as enabling factors were associated with increased enjoyment of PA. The clinical team and family were reported as reinforcing factors for PA, additionally peer support through online-based exercise sessions were also described as a potential reinforcing factor. There are numerous resources available to support clinicians and patients to increase PA, although clinic space, equipment and staffing represent barriers to implementation. Additionally there is currently no requirement for CF services to include an exercise professional. This model of PA promotion is considerably different to the conventional exercise-training model that has constituted the majority of research in this area. Existing exercise training interventions do not consider local environments and interests at an individual level, are resource intensive and often lack long-term sustainability [179]. The integration of exercise professional led PA promotion into CF care may represent a more sustainable and effective model to increase PA in individuals with CF.

9.4. METHODOLOGICAL LIMITATIONS

Limitations are briefly discussed within each of the previous chapters but are discussed in greater detail here. The primary limitations of the current thesis relate to the limitations inherent for each outcome measure, selection bias, the impact of confounding variables and the use of correlations, sampling and the limitations of each individual outcome measure.

9.4.1. Systematic review

The systematic review was conducted utilising guidelines to ensure that the process was systematic, transparent and repeatable. Despite this there were a number of limitations (as acknowledged in Chapter 3), namely the risk of bias assessment tool used. The PRISMA framework provides a suitable framework for conducting systematic reviews to answer specific questions. Typically this follows the PICO format, meaning; population, intervention, control, outcome. This framework works well for randomised control study designs in which there is a clear intervention and outcome of interest. There were few examples of studies assessing PA in adults with CF that utilised a randomised controlled trial design, and in those that did PA was not a primary outcome measure. Given that most studies were cross-sectional designs the tools designed to assess the risk of bias were not ideal and resulted in most studies being graded as low quality due to a lack of control group and randomisation. At the time of conducting the review a more suitable tool was not available, however Cochrane have since recommended a risk of bias tool in non-randomised studies - of interventions (ROBINS-I) and a risk of bias tool in non-randomised studies - of exposures (ROBINS-E) is currently under development. These tools could be more appropriate for assessing risk of bias, but it is unlikely to alter the findings as studies were not excluded for high risk of bias based on assessment using the old tool.

It was also not possible to conduct a meta-analysis of the available data due to the variety of methods used. PA was often reported as a secondary outcome measure, was not reported in sufficient detail or as part of a study graded as low quality. Although this was initially viewed as a limitation it became an important finding and provided the rationale for including a robust PA assessment in Study 2 and for making a number of recommendations for improving the quality of PA assessment in CF.

9.4.2. Physical activity assessment

The GPA-Q provides a self-reported estimate of PA, providing estimates of time spent engaging in moderate and vigorous PA and time spent inactive [180]. The tool

is not validated for use in individuals with CF and correlations with accelerometry were weak (Chapter 5). Additionally, as with all self-reported PA assessment methods, issues with recall, misinterpretation and social desirability are a major limitation, as discussed in earlier sections [181].

Accelerometry is widely used to assess PA in individuals with CF despite the lack of disease specific intensity cut-points. A strength of this thesis is the use of raw accelerometer data analysis [182] and novel PA metrics (average ENMO and IG). The use of raw acceleration data removes the reliance on device-specific algorithms to convert counts based data into PA metrics and goes some way towards having a standardised measure. An additional strength of this thesis is the observed compliance to wearing the wrist-worn monitors, with no participants excluded for failing to achieve wear time criteria (>10 hours per day).

The lack of standardisation in accelerometry-based research is major limitation. There are a number of different devices available each with different signal processing and algorithms, there are numerous wear sites each producing different results, finally there is a lack of consensus for which metric to report [132]. PA is a complex multidimensional behaviour, condensing this into a single metric is therefore challenging. Accelerometers are unable to capture information about subjective or perceived aspects of PA such as location or context [132]. Therefore future research should consider the use of self-report methods alongside accelerometry to obtain a more comprehensive assessment of PA behaviours.

9.4.3. Sedentary behaviour assessment

Sedentary behaviour has previously been assessed using accelerometry, based on minimal or no movement and therefore presumably low energy expenditure [17]. This method of calculating SB therefore does not account for posture [145]. The sedentary sphere method can be used to determine the most likely posture using data from wrist-worn triaxial accelerometers and offers an alternative to the thigh worn activPAL inclinometer [145]. The sedentary sphere method provides valid assessment of posture in adults during activities of free living and does not require the use of an additional device [183]. Future studies may choose to integrate a

postural assessment of sedentary behaviour using metrics such as the sedentary sphere to more accurately assess sedentary behaviour levels within the CF population.

9.4.4. Assessment of vascular function

In the current thesis vascular function was only assessed in a sub-group as a secondary outcome measure. There are few studies investigating vascular function in individuals with CF, though there is an increased awareness of the risk of CVD with increasing life expectancy within the CF population. No differences in FMD were observed between individuals with CF and their non-CF peers and there was no association between PA and FMD in the current study. Further research in a larger sample with additional measures of cardiovascular structure and function are necessary to elucidate the impact of CF on cardiovascular health in an ageing CF population. Additionally, longitudinal studies are required to monitor changes in cardiovascular function over time.

9.4.5. Qualitative methods

The philosophical perspectives underlying the qualitative methods are outlined in Chapters 1 and 7 along with the steps taken to ensure that the methods were robust. Regardless of this the nature of qualitative research allows for interpretation and there may be scope to debate about the perspectives, methods and theories utilised when conducting Study 3. Every attempt has been made to make the process as transparent as possible and the methods and results have been reported in sufficient detail to justify the interpretability of the findings and the extent to which this research contributes to existing knowledge.

The research has utilised both qualitative and quantitative methods from a pragmatic perspective. The extent to which the quantitative data from Study 2 and qualitative date from Study 3 can be integrated to answer a single research question may be limited. It may be the case that the research is not truly mixed-methods, but

rather each chapter answerers a different research question related to one area of interest and is in that sense multi-method.

9.4.6. Selection Bias

Participants for Studies 2 and 3 were recruited from a single regional CF centre. Although this centre serves a large geographical area the findings may not be representative of the UK collectively. Additionally, during recruitment participants were informed that the primary focus of the research was PA. This could have resulted in a bias towards participants with a pre-existing interest in PA being more likely to volunteer to participate. The participants were also recruited from routine CF clinics, consequentially participants who attended clinic less frequently were less likely to be recruited. Statistical tests were used to control for such biases where possible, with baseline characteristics measured in all participants to assess if differences existed between groups. Further research employing similar methodologies in wider CF populations is required to support the findings outlined in this thesis and to investigate any differences between demographic groups.

The sample size achieved was satisfactory but did not allow for drop out or loss to follow up. Given the qualitative nature of Study 3 fewer participants were required, however there was a higher dropout rate than expected due to the multiple phases of data collection. Whilst there were a number of factors beyond the control of the research team, the loss to follow up could have been reduced if the period of time in which follow was possible was longer. The Study 3 sample also consisted of participants who had previously participated in Study 2, which included objective assessment of PA. Whilst this enabled the researcher to develop a rapport with participants and fostered a relaxed and comfortable environment for the interviews and focus groups, it may have had negative consequences for recruitment and retention of participants by increasing participant burden and the likelihood of research fatigue.

9.4.7. Confounding

Throughout the research careful consideration has been given to the influence of potential confounding variables. Due to the variation in phenotype in CF, impact of multiple physiological systems and the complexity in treatment regimens this is a challenging aspect of research with this population. Where possible confounding variables were controlled for using multivariate statistical models. Where it was not possible to control for variables this was acknowledged as a limitation in the relevant study.

9.4.8. Establishing causality

The association between PA and health in adults with CF was explored using correlations during both chapter 3 and 5. Correlations are used to assess the strength and direction of an association between variables and are not appropriate for determining causal relationships between variables [184]. The purpose of this research was not to establish a causal relationship between PA and health in individuals with CF but to explore whether any relationships exist. Correlation data can provide preliminary data to inform further experimental research to address questions relating to causation [185]. The evidence presented within this thesis supports that PA is associated with positive health outcomes and therefore justifies the promotion of PA clinically and provides the rationale for further research using robust study designs. Additionally, Study 3 was not concerned with establishing causality, nor generalisability through statistical methods, but instead sought to explore perceptions of PA using a constructivist approach [172]. The epistemological positioning and reflexive version of thematic analysis used are not consistent with forms of qualitative enquiry which look to obtain rigour though prioritising reliability and objectivity, consistent with positivist quantitative paradigms [186]. Within the approach described in the current thesis, quality comes from detailed exploration of multiple perspectives within the data and reflexive interpretation [186].

9.5. REFLECTION

Throughout the process of conducting the research and constructing this thesis I have developed as a researcher and extended my knowledge immensely. I have gained experience utilising a quantitative and qualitative methodologies, gaining the skills I will require to continue to research in this field. Furthermore, I have engaged in a process to acknowledge my philosophical positioning as researcher utilising multiple research methods. These include PA assessment using accelerometry and raw data analysis, vascular assessment using flow-mediated dilatation, conducting systematic reviews, conducting interviews and focus groups and performing thematic analysis of qualitative data. In doing so I have questioned my own ontological perspective and with that the theoretical perspective underlying my research. Each of those methods bringing multiple and varied challenges which have and will continue to shape me as a researcher.

9.5.1. Positionality

Prior to this PhD I worked in a CF centre as a therapy practitioner in CF. My role was to provide exercise testing and prescription for both paediatric and adult patients with CF. This role meant that I had an interest and enthusiasm to work in CF and an understanding of the population and clinical services prior to my PhD studies. I feel that this experience was important in enabling me to establish myself within the clinic environment and being accepted by the MDT. I feel I adopted a position of a colleague conducting a piece of research rather than a student shadowing clinic. I also feel it was important for recruitment and retention as it allowed me to create a rapport with patients and potential participants. It is possible that patients could have be less receptive to an individual they deemed to be less knowledgeable in the condition. I felt that patients were more receptive to me once they judged that I understood CF. Utilising a pragmatic approached allowed for quantitative investigation to determine PA levels and associations with clinical outcome measures of health, whilst also enabling qualitative exploration of perceptions of PA among adults with CF, helping to provide a more detailed understanding of PA behaviour in this population. I adopted a constructivist

approach throughout the qualitative analysis process, acknowledging that I had prior knowledge of CF and that the analysis was constructed from my perspective as a researcher and a practitioner. A critical friends approach to data collection and interpretation was adopted to explore this perspective and minimise biases through discussion with the research team.

9.5.2. Challenges conducting research in clinical populations

There are numerous approvals required before conducting research within the NHS. In the case of the current programme of research it was necessary to establish communication with clinical team within the host NHS Trust and gain their approval to support the application process and research. It was then necessary to obtain local site-specific approvals from the research and innovation department, which included writing and presenting a proposal to the hospital research committee. Site-specific approval was also contingent on obtaining approval from the patient advisory group which was a separate committee made up of lay members and patients. Following approval from the site-specific committees it was then possible to apply to an NHS research ethics committee and for Health Research Authority Approval. Once the appropriate reviews were complete and the appropriate revisions were made it was then possible to start the research. This process was completed on two separate occasions to gain approval for Study 2 and Study 3. Prior to collecting data within the host site it was also necessary to obtain an honorary contract and complete a local induction. Additionally, university ethical approval was required to recruit the healthy control participants who were not covered under the NHS application. Whilst this process is necessary to ensure the safety of patients and researchers and is an intrinsic part of clinical research it is also time-consuming and labour intensive. Establishing external collaborations and receiving correct approvals should be an immediate priority when conducting clinical research and appropriately accounted for in the overall timeline of the project. I have developed a greater interest in the processes surrounding research ethics and as a result of this experience volunteered to sit on the university research ethics committee. I had prior experience of obtaining NHS ethics so this process was not

unbeknown to me, however I now have a greater understanding of the process required to establish external collaborators.

In order to avoid the research team having access to patients' personal data prior to obtaining consent all patients were screened for eligibility during routine clinic appointments. A researcher was present in two clinics per week to discuss the study with any potential participants and to provide invitation letters and information sheets. This was a time consuming method of recruitment. Whilst this process was time consuming it allowed me to be embedded within the service, I spent significant periods of time in clinic over a period of two years. During which time I built up rapport with clinical staff and patients as well as gaining a greater understanding of the organisation and service. This insight could be viewed as a strength of the research, in that I was able to gain a greater understanding of the environment in which the research was being conducted. This could also be viewed as a limitation as this level of immersion could have unknowingly reinforced my biases and/or altered my perspective of the research.

This method of recruitment also presented a number of barriers including competing clinical trials, participants' clinical instability, time/treatment burden and geographical barriers. Whilst the research in the current study could have been conducted with participants from on-going clinical studies this was unlikely due to the time commitments and regular attendance required to participate in a clinical trial. It was also unknown how the trials may influence typical PA behaviours and clinical markers. The current research required participants to be clinically stable during the data collection period as the primary interest was habitual PA. This resulted in the inability to include patients who expressed an interest to participate but were subsequently treated for an exacerbation. Finally, as referred to earlier, the regional centre covered a large geographical area, which made it less likely for participants to travel upwards of two hours to attend an appointment outside of their routine clinic. All data collection completed face-to-face was done after routine clinic appointments to minimise participant burden, this often meant eight weeks would pass between providing study information packs and the patient's next routine appointment. This again highlights the inefficiency of the recruitment and testing. The primary researcher was external to the clinical team, but if they were embedded within the clinical team this may have improved the efficiency of the recruitment and

testing. However, this would have been at the expense of the impartiality offered by being external to the clinical team. Conducting the recruitment in the manner it was conducted allowed the researcher to remain independent, reduced the burden placed on participants and complied with ethical principles of clinical research and General Data Protection Regulation (GDPR).

9.6. CONCLUSION

The evidence presented within this thesis suggests that adults with CF engage in insufficient amounts of PA to achieve global PA recommendations. When assessed using accelerometry and applying cut-points derived from raw acceleration data, MVPA in adults with CF was significantly lower than their non-CF peers. Additionally, when using the average ENMO and intensity gradient metrics to describe a comprehensive profile of PA, adults with CF engage in significantly less PA and have a poorer PA profile (intensity gradient) than their non-CF peers.

Data to support an association between PA and lung function is inconsistent within the literature. Although, when using objective PA assessment methods increased total acceleration (average ENMO), VPA and MVPA were positively associated with lung function. Although limited, the data presented throughout the thesis supports an association between PA and exercise capacity.

There are limited data available to assess the relationship between PA and quality of life. Vigorous activity was positively associated with HRQoL and sedentary time was negatively associated with HRQoL when assessed using accelerometry and the CFQ-R.

There was no evidence of endothelial dysfunction in adults with CF in the current thesis. No significant difference in FMD% was found between adults with CF and their non-CF peers, which is in contrast to previous paediatric research [31] and may warrant further investigation using longitudinal studies and larger sample sizes.

The integration of exercise professional led PA promotion into CF care may represent a model to increase PA in individuals with CF. The role of such an individual would be to provide individually tailored advice addressing key predisposing, reinforcing and enabling factors through frequent contact and support.

The promotion of PA should begin as early as possible and be assigned importance thought the life of an individual with CF.

The role of an exercise professional as part of routine CF care warrants further investigation, particularly relating to the impact of regular long-term contact on motivation for PA, engagement in PA and the subsequent effect on the health and wellbeing of adults with CF. Additionally, further research should explore the role of families in supporting adults with CF to be physically active. Finally, strategies to promote enjoyment of PA require further research, although there appears to be evidence to support the provision of a variety of PA activities, in a number of settings including, hospital, home, community and via online technology.

9.7. RECOMMENDATIONS FOR FUTURE WORK

Based on the findings presented in this thesis there are a number of recommendations to further understanding of physical activity in adults with CF. Recommendations are made for both future research and clinical practice.

9.7.1. RECOMMENDATIONS FOR RESEARCH

- Standardise PA assessment using wrist-worn accelerometry and raw data analysis, with average ENMO and the IG reported. Standardised use of raw acceleration data would overcome issues associated with the variety of cut-points and algorithms currently in use. Standardisation across studies would also allow comparison to be made based on the same wear location. Using of standardise metrics may also facilitate the development of population based reference data and age- and gender-specific PA percentiles.
- More high quality studies designed specifically to explore PA in individuals with CF are required, including randomised control trails and longitudinal designs. This will help to determine the associations between PA and clinical outcome measures and inform the advice given to patients around PA.
- Explore additional co-morbidities associated with aging in CF such as cardiovascular health to provide a better understanding of CVD risk in this population and the potential impact of PA.
- There is a requirement for evaluation of a long-term PA promotion programme utilising a socio-ecological approach to PA promotion at an individual level within a CF service.

9.7.2. RECOMMENDATIONS FOR CLINICAL PRACTICE

- A combination of exercise testing, objective and self-reported PA assessment methods should be considered in clinical practice to screen participants, inform and evaluate PA interventions.
- Collaboration with researchers with an expertise in PA assessment is recommended to provide a more comprehensive evaluation of PA using objective assessment methods and robust analysis.
- Clinicians should continue to support adults with CF to engage in PA at a moderate intensity or greater and to reduce their sedentary time to maximise pulmonary function and maintain quality of life.
- Physical activity promotion should form part of routine clinical care, with designated exercise processionals available to identify barrier and facilitators to PA, reinforce PA behaviour and support patients at an individual level.
- An accreditation pathway and standardised role are required to establish the role of an exercise professional working in CF.
- Physical activity promotion should involve family members and support networks from an early age and throughout the course of an individuals' life, although support should be intensified during adolescence.

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11. LIST OF APPENDICES

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Physical activity and associations with clinical outcome measures in adults with cystic fibrosis; a systematic review

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ABSTRACT

Background: Physical activity (PA) is important in the management of Cystic Fibrosis (CF) and is associated with a number of beneficial effects. PA assessment is not commonplace or consistent in clinical practice, therefore understanding of PA in adults with CF remains limited. The purpose of this review was to evaluate PA levels in this population and compare PA to global recommendations and non-CF peers.
Methods: The Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines were utilised to inform the review process. Original research was identified and screened against inclusion/exclusion criteria. Quality was assessed, data extracted and a narrative synthesis undertaken to describe the findings.
Results: Adults with CF did not achieve recommended PA guidelines and step count targets in 5/8 studies where assessment was possible. No significant differences in PA were found between CF and non-CF peers in 3/5 studies. Associations between PA and improved lung function were inconsistent with 4/9 studies finding a positive association. Evidence for an association between PA and higher exercise capacity was stronger with all 4 studies reviewed reporting a positive association. Quality ratings were low across all studies.
Conclusions: PA in adults with CF is largely comparable to their non-CF peers, despite being insufficiently active to achieve PA recommendations. Assessment tools used and outcomes reported are variable, many of which do not provide sufficient information to assess relevant components of PA. There is a requirement for high quality studies designed specifically to explore PA in adults with CF, ideally employing standardised PA assessment methods.
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Contents

Abbreviations: PA, Physical activity; SB, Sedentary behaviour; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; MVPA, Moderate-Vigorous Physical Activity; METs, Metabolic Equivalents.

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1. Introduction

Life expectancy of patients with Cystic Fibrosis (CF) continues to increase with improvements in treatments over recent decades, resulting in a greater proportion of adults living with CF [1]. Physical activity (PA) is associated with a number of potential benefits in the management of CF including positive effects on lung function [2], mucociliary clearance [3], bone health [4] and hospitalisation frequency [5]. Higher levels of PA are also associated with improved exercise capacity [6], which is in turn associated with reduced mortality in patients with CF [7]. PA promotion is therefore recommended as part of the routine management of CF [8,9]. Despite this PA assessment is not common or consistent [8]. However, CF presents patients with a number of potential barriers to PA including; physical symptoms (breathlessness, increased cough, fatigue), high treatment burden and low self-efficacy for PA [10].

PA can be defined as any bodily movement produced by contraction of skeletal muscle that substantially increases energy expenditure, this includes leisure-time PA, occupational PA and exercise [11]. Various self-reported and objective methods are reported in the literature for the assessment of PA in adults with CF, however inconsistencies in measurement tools, outcome measures reported and study design used limit our understanding of PA behaviour and its health associations in this population. It is generally accepted that patients with CF engage in less PA than their non-CF peers, this is particularly evident for vigorous PA [12], however this finding is inconsistent across the multiple assessment methods reported in the literature. Furthermore, little is known about sedentary behaviour (SB) in this population despite high levels of SB being negatively associated with health outcomes and cardiometabolic diseases in the general population, even among individuals achieving PA guidelines of 150 min of moderate-to-vigorous PA a week [13]. High levels of SB are considered as an independent risk factor for cardiovascular disease and mortality [13], yet remain relatively unexplored in an ageing CF population.

There are currently no PA guidelines specifically developed for individuals with CF, although guidelines for the general population appear to be applicable with some modifications depending on disease progression [14]. For the purpose of this review, the global physical activity guidelines outlined by the World Health Organisation (WHO) were used when interpreting reported PA levels. It is recommended that adults (18–64 years) should take part in at least 150 min of moderate-vigorous intensity aerobic PA (MVPA) or 75 min of vigorous intensity PA throughout the week [15]. The variation in outcome measures reported in the studies reviewed makes it difficult to compare reported levels of PA to recommended guidelines, comparison is therefore only possible in a small number of the studies reviewed. Achieving 10,000 steps daily also provides a reasonable estimate of daily activity and individuals achieving this typically meet the recommendations of 150 min MVPA per week [16]. Therefore assessing step count can help to quantify PA and through the use of the indices can provide information for screening, surveillance and intervention evaluation [16].

A large proportion of the PA research conducted in CF populations has been undertaken with children and adolescents [8] and may not be transferable to adult populations. It is well documented that PA declines with age in the general population [17] which may also be exacerbated by worsening disease severity in CF. Given the increasing life expectancy and number of adults living with CF, an understanding of PA levels in adult populations is required. It is important that healthcare professionals are familiar with PA guidelines, engage patients in conversation around PA and are able provide advice and signpost patients to relevant resources.

1.1. Aims

The purpose of this review therefore, is to: 1) Establish the physical activity levels of adults with CF. 2) Compare reported PA levels between CF patients and their non-CF peers. 3) Examine the associations between PA and markers of health in adults with CF.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were utilised to inform the review process [18]. Studies that assessed PA in adults with CF and were published from database inception to Feb 28th 2018 were identified. An a priori defined protocol was utilised to identify relevant articles that were then systematically screened against inclusion and exclusion criteria.

The published protocol can be accessed via the PROSPERO database (CRD42018088434).

A narrative synthesis was performed to provide a summary of the assessment tools used, outcomes reported and overall quality of PA assessment [19]. An assessment of the quality of evidence was made to support the strength of the findings and conclusions made. It was not possible to conduct a meta-analysis due to the wide variation in the methods used to assess PA, the inconsistency of outcome measures reported and the low quality ratings of the available literature.

2.1. Search strategy and initial screening

Electronic databases SCOPUS (Elsevier, EMBASE & ScienceDirect), Web of Science, Medical Literature Analysis and Retrieval System Online (MEDLINE) (Cumulative Index of Nursing and Allied Health Literature (CINAHL), SportDiscus & Psychinfo) and Oalster grey literature were searched using search terms individually tailored for each database (Fig. 1). Databases were selected to provide comprehensive coverage of indexed journals, which publish studies from relevant healthcare and PA fields. Title and abstract screening was employed to identify relevant articles and remove articles that were not eligible, this was preferred to applying search limits or 'NOT' terms. Reasons for removing articles at this stage included; non-CF population, paediatric population, no original data reported, not peer reviewed and written in languages other than English. No restrictions were applied to the date of publication, owing to the limited number of studies in a relatively novel field. The search terms yielded 1166 hits, representing 671 unique articles (Fig. 2). A further 565 articles were removed during title and abstract screening, using the same criteria as above, resulting in screening of 106 full-text articles. Full-text articles were screened against inclusion and exclusion criteria, leaving 18 articles for data extraction (Fig. 2). Study characteristics are presented as supplementary material (additional file 1). References of all included papers were screened, although this did not yield any additional articles.

2.2. Application of eligibility criteria

Inclusion criteria included; measurement of physical activity and/or sedentary behaviour (SB) using a measurement tool validated for use in the general adult population and/or adults with CF. Baseline PA and/or SB reported prior to any interventions. Preferable but not essential criteria included; data reported for clinical outcome measures (lung function, exercise capacity, quality of life (QoL)).

Exclusion criteria included; paediatric (<18 years), non-CF or mixed populations where adult and paediatric data were not separated, use of non-validated methods for assessing PA and/or SB, no reporting of PA and/or SB or no baseline data available. Additionally, studies not written in English, providing no original data or that were not peer reviewed were also excluded. Studies that were written as abstracts only rather than full papers were also excluded. No restrictions were applied for study design. Randomised control trials, interventional and observational studies were considered based on satisfaction of the inclusion/exclusion criteria outlined above. Five articles were excluded as 'paediatric population' although they reported data for mixed adult and paediatric populations or defined adults by criteria other than ≥18 years [6,20–23]. Whilst these articles may contain potentially relevant data the original authors were not able to provide the data on the request of the reviewers in the given time frame. Additionally, all studies that were excluded and used accelerometry are listed alongside the reason for exclusion (additional file 2).

OR	AND
'physical activity'	'Cystic Fibrosis'.
'habitual activity',	
'sedentary behaviour'	
'accelerometers'	
'motion sensors'	
'actigraph'	
'geneactiv'	
'sensewear'	
'activpal'	
'HAES'	
'caltrac'	
'IPAQ'	
& variations on each term	

Fig. 1. Boolean search terms.

2.3. Data extraction

A modified version of the 'Cochrane Data Extraction Form', from the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1) [24] was used. The form was modified to include relevant participant characteristics and outcome measures. Two authors (JS, ED) independently extracted the data, discrepancies were resolved through discussion, with a third reviewer (LB) where necessary. Extracted information included: Article characteristics; year of publication, journal, funding source, publication type. Study setting; study population and participant demographics and baseline characteristics. Study methodology; recruitment and study completion rates; outcomes and times of measurement. Information for assessment of the risk of bias.

2.4. Risk of bias assessment

Two reviewers (JS, ED) independently assessed the risk of bias for the included studies using the Cochrane risk of bias tool, agreement was reached between the reviewers although a third reviewer (LB) was available if required (Table 1).

2.5. Data synthesis

A narrative synthesis was used to describe the data in three sections; 1) PA levels of adults with CF in comparison to global PA recommendations, 2) PA levels of adults with CF in comparison to non-CF peers, 3) The relationship between PA and clinical outcome measures.

2.5.1. Moderate-vigorous physical activity

Studies reporting a measure of PA described with a time unit, were compared to the 150 min of MVPA per week recommendation. In studies only measuring PA over 5 days the 150 min of MVPA recommendation was interpreted as 30 min per day on 5 days of the week.

2.5.2. Metabolic equivalents (MET)

MET refers to metabolic equivalent, where 1 MET is the rate of energy expenditure while sitting at rest and is equivalent to an oxygen uptake of 3.5 ml per kilogram (kg) per minute, or a caloric consumption of 1 kcal/kg/h. METs are used to attempt to classify PA intensity in a number of studies reviewed, for example, a 3 MET activity expends 3 times the amount of energy used at rest. For the purposes of this review the following definitions are applied; moderate intensity (3–6 METs), vigorous activity (>6 METs) [25]. METs can also be expressed as MET-minutes, whereby the metabolic equivalence of an activity is multiplied by the number of minutes spent engaging in the activity. For example engaging in an activity of 3 METs for 30 min is equal to 90 MET-minutes. Consequently, 150 min MVPA per week equate to 450 MET-minutes per week, therefore recommendations for MET minutes per week are ≥450 MET-minutes per week.

2.5.3. Steps

Whilst it is not possible to make comparisons with the WHO guidelines, the following indices were applied to classify PA based on the number of daily steps reported; Sedentary (<5000), low active (5000–

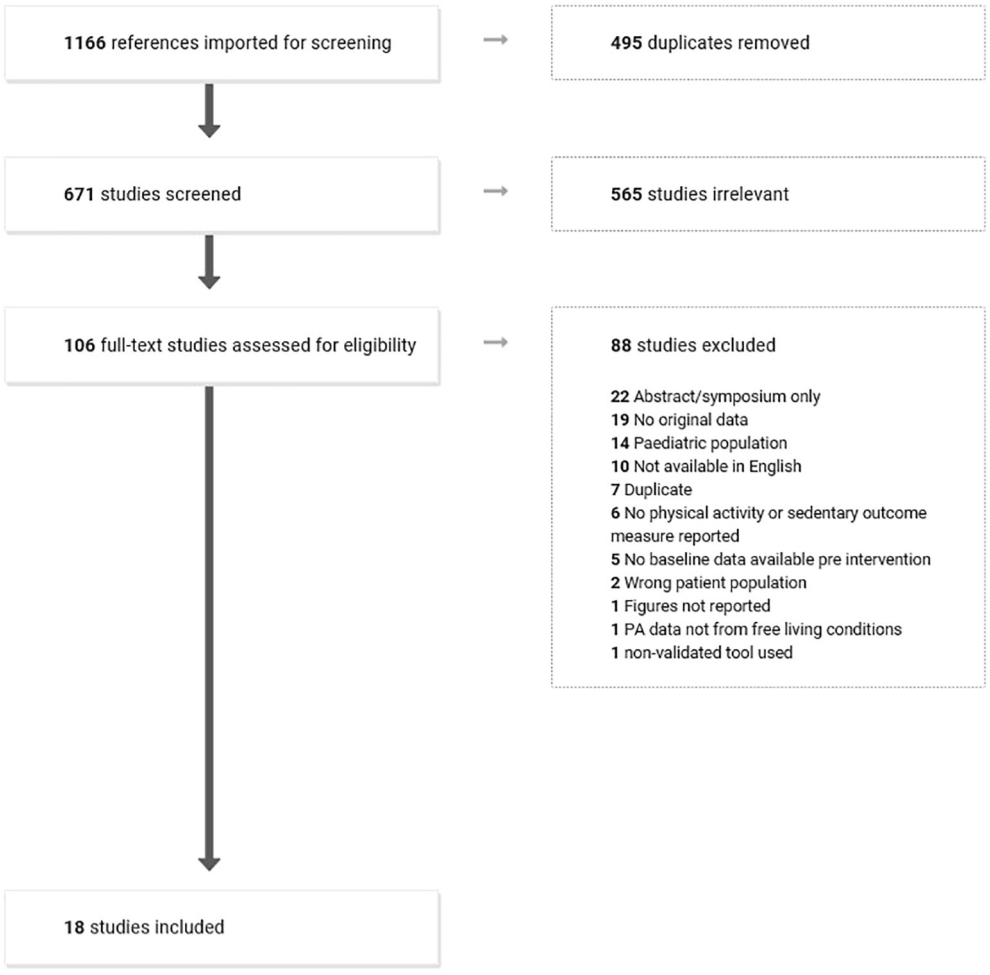

Fig. 2. PRISMA flowchart.

7499), somewhat active (7500–9999), active (≥10,000), highly active (>12,500) [16]. Total physical activity described as time spent in weight bearing activity or walking was reported in two studies. It is not possible to compare levels of PA among adults with CF to recommended guidelines for MVPA using this data as there is no description of intensity.

2.5.4. Energy expenditure

Energy expenditure (EE) represents the sum of resting energy expenditure and the thermic effect of digestion in addition to physical activity [25]. Studies in the current review reported total energy expenditure (TTE) and not specifically the energy expenditure associated with

Table 1
Risk of bias assessment of studies included for review.

	Allocation concealment	Blinding of outcome assessors	Blinding of participants & personnel	Sequence Generation	Incomplete outcome data	Selective outcome reporting
Bhudhikanok 1998 [42]	high	high	high	high	low	low
Cox 2016 [5]	high	high	high	high	low	low
Currie 2017 [37]	high	high	high	high	low	low
Decorte 2017 [33]	low	high	high	high	low	low
Elkin 2001 [39]	high	high	high	unclear	low	low
Enright 2004 [38]	low	low	unclear	high	low	low
Enright 2007 [43]	high	low	high	high	low	low
Gruet 2016 [35]	unclear	high	high	high	low	low
Haworth 1999 [34]	high	high	high	high	low	low
Hollander 2005 [32]	high	high	high	high	low	low
Ionescu 2003 [40]	high	high	high	high	low	unclear
Rasekaba 2013 [36]	high	high	high	high	low	low
Savi 2013 [31]	high	high	high	high	low	low
Savi 2015 [30]	high	high	high	high	low	high
Savi 2015 [28]	high	high	high	high	high	high
Street 2006 [41]	high	high	high	high	low	low
Troosters 2009 [12]	high	high	high	high	low	low
Ziai 2016 [29]	high	high	high	high	low	low

PA. Whilst it has been proposed that adherence to recommended PA guidelines yields an energy expenditure of ~1000 kcal·wk-1, which is associated with improved health outcomes [26], TEE alone does not provide suitable information to assess if adults with CF achieved recommended guidelines for PA.

2.5.5. PA indices

The Baecke and Physical Activity Self-Administered Questionnaire (AQAP) questionnaires provide a PA index. The work domain classified occupations as; Low activity (1), Moderate activity (3), High activity (5). Sport and leisure domains were calculated by assigning a MET value for specified activities and assessing the time spent engaging in such activities again resulting in a PA score between 1 and 5. The sum of the three categories (work, sport, leisure) provides a total PA score between 3 and 15 [27]. These data do not provide information on minutes of PA therefore cannot be compared to PA guidelines.

3. Results

3.1. Reporting of PA in adults with CF

In the 18 studies reviewed 33 separate outcome measures were reported using 11 assessment tools including 1 accelerometer (SenseWear Pro 3 armband) and 10 separate self-report questionnaires (Table 2).

3.2. Levels of PA in adults with CF compared to recommended PA guidelines

Comparison between PA levels in adults with CF and global physical activity guidelines was only possible in 8 [5,12,28–30,36,37,43] of the 18 studies reviewed. Adults with CF only met PA guidelines in 3 [5,36,37] of the 8 studies, only one of which used objective methods to assess PA [5]. Table 3 displays the findings for the 13 studies which did not include a control group.

Table 2
Summary of assessment tools utilised and outcome measures reported.

Accelerometer	
SenseWear Pro 3 armband [5,12,28–31]	Total energy expenditure (Kcal/day) Steps per day Total METs Total PA (mins/day) Light PA (mins/day) Moderate PA (mins/day) Vigorous PA (mins/day) Moderate to vigorous PA (mins/day)
Questionnaire	
Habitual Activity Estimation Scale (HAES) [31]	Total inactivity (min/day) Total activity (min/day)
Baecke [32–34]	Activity score Activity factor for sedentary lifestyle (1.5, 1.7, 2.1) Work index Sport index Leisure index
Physical Activity self-Administered Questionnaire (AQAP) [35]	Sport index Leisure index Global index
International Physical Activity Questionnaire (IPAQ) [36]	Work (min/week) Transport (min/week) Domestic (min/week) Leisure (min/week) Walking (min/week) Moderate (min/week) Vigorous (min/week)
Recall questionnaires [37–43]	METs (weekly) METs (daily) METs (1.5 Light) (hrs/week) METs (4 Moderate) (hrs/week) METS (6 Hard) (hrs/week) METs (10 Very hard) (hrs/week) Lying time (min/day) Energy expenditure (Kcal/day)

3.2.1. Studies reporting objectively assessed PA

Accelerometry was used in 3 of these studies [5,28,29] although only two reported MVPA [5,28] with a third reporting step count and TEE [29]. Of the two studies reporting MVPA, participants achieved recommended PA guidelines in one [5]. In the study in which participants did not achieve recommended PA guidelines, step count was also reported, which would indicate that patients were 'somewhat active', despite not meeting guidelines for MVPA [28]. Despite using similar assessment methods in groups of comparable disease severity and participant characteristics the two studies reported different levels of MVPA. The final study [29] using objective assessment only reported step count, however these values appear to be similar to those previously reported [28], with both studies reporting 'somewhat active' cohorts achieving 8874 and 9508 steps respectively.

3.2.2. Studies reporting self-reported PA

One study [37] used a 7-day recall questionnaire to assess PA, and whilst this tool has previously been validated for use in CF [20], reported levels of PA are high in contrast to objectively assessed PA, with patients exceeding PA recommendations, reporting a mean of 282 min of moderate, hard or very hard PA per week. Three studies used the Baecke questionnaire [32–34], with a fourth using the AQAP [35], all of which report PA as an activity score and therefore results cannot be compared to PA guidelines. Furthermore one study did not provide group means, which prevented interpretation [32]. Gruet et al. (2016) reported an overall PA score of 9 (of a possible 15) which may suggest that the population studied were moderately active [35]. Haworth et al. (1999) reported an activity score of 7.6 which likely represents low levels of activity in the study group [34]. Decorte et al. (2017) reported 2.6, 2.3 and 3.2 for work, sport and leisure time indices respectively, which suggests that occupational activity and engagement in sport were low in the population studied, whilst leisure time activity was higher [33].

Two studies reported mean daily METs [38,40] assessed using recall questionnaires, which does not provide information for comparison to recommended PA guidelines. Both studies reported similar levels of PA (36.7 and 37.6 daily METs, respectively) which were reported to be comparable to non-CF young adults [38].

Energy expenditure was reported based on self-reported PA in one study [39]. Whilst it is not possible to make assumptions about PA levels from energy expenditure, the data reported indicates that TEE in the cohort studied (2071.39 Kcal) is comparable to what could be predicted for a typical sedentary/low active adult [25].

The final studies reported total PA (time spent walking or doing sport) and weight bearing PA using self-report techniques [41,42]. The data reported did not include any information about intensity, which again prevents interpretation in the context of WHO recommended guidelines. The two studies reported considerably different values with Street et al. (2006) describing what could be considered as an active cohort (engaging in 11.3 h per week of PA, including walking and sport) whilst data provided by Bhudikanok et al. (1998) would suggest that the cohort were inactive (engaging in 3 h per week of weight bearing PA). It is possible that the two report different aspects of PA which is not clear from the methods described.

3.2.3. Sedentary behaviour (SB)

No studies assessed SB, although lying time was reported in one study, finding no significant difference between adults with CF (452.1 min/day) and their non-CF peers (493.5 mins/day) ($P = 0.11$) [31]. Inactivity, assessed using the HAES, was also reported and was not different between groups (367 vs. 376.6 mins/day for CF and

Table 3
Comparison between reported PA in adults with CF and PA recommendations.

Study	Design	Participants age (years) (Mean, SD)	Disease severity	Assessment tool	Outcome measure reported		Achieving guidelines ✓/×	
Cox 2016 [5]	Cross-sectional study	28 ± 8	All	SenseWear pro 3 armband accelerometer	**CF (n = 61) - Male = 35, Female = 26**			
					Moderate-Vigorous PA (mins/day) (median, IQR)	31 (15–53)	✓	
Savi 2015 [28]	Cross-sectional study	33.5 ± 10.5	All	SenseWear pro 3 armband accelerometer	**CF (n = 60) - Male = 35, Female = 25**			
					Duration of physical activity (min/day) (mean ± SD)	213 ± 137		
					Mild intensity activities (min/day) (mean ± SD)	186 ± 121	×	150 min MVPA per week (30 min, 5 days per week)
					Moderate intensity activities (min/day) (median, IQR)	15 (9–29)		
					Vigorous intensity activities (min/day) (median, IQR)	1 0–3		
					Average METS (mean ± SD)	1.7 ± 0.3		
					Steps per day (mean ± SD)	9508 ± 3861	✓/×	
Ziai 2016 [29]	Cross-sectional study	23.2 ± 2.65 (Control), 21.0 ± 2.3 (IGT), 21.7 ± 2.29 (CFRD)	All	SenseWear pro 3 armband accelerometer	**CF (n = 36) - Male = 18, Female = 18**			
					Steps per day (mean ± SD)			
					Normal Glucose tolerance (n = 10)	8874 ± 2625	✓/×	
					Impaired Glucose tolerance (n = 10)	9416 ± 4172	✓/×	10,000 steps daily
					CFRD (n = 16)	7033 ± 3186	×	
					Daily TEE (mean ± SD)			
					Normal Glucose tolerance (n = 10)	2300 ± 412		
					Impaired Glucose tolerance (n = 10)	2129 ± 525		
					CFRD (n = 16)	2152 ± 461		
Currie 2017 [37]	Cross-sectional study	41 ± 9	All	7 day recall questionnaire (7DPAR)	**CF (n = 18) - Male = 10, Female = 8**			
					METs per week	14,370 ± 997	✓	
					Light physical activity (1.5 METs), hrs/week (mean ± SD) (n = 18)	103.3 ± 9.4		
					Moderate physical activity (4 METs), hrs/week (mean ± SD) (n = 15)	2.9 ± 2.7	✓	500–1000 MET-minutes 150 min MVPA per week
					Hard physical activity (6 METs), hrs/week (mean ± SD) (n = 8)	0.8 ± 0.9		
					Very hard physical activity (10 METs), hrs/week (mean ± SD) (n = 7)	1 ± 1.9		
Enright 2004 [38]	Randomised control trial	24.8 ± 5.5 (80%), 20.0 ± 4.7 (20%)	All	Recall questionnaire	**CF (n = 19) - Male = 10, Female = 9**			
					METs over 24 h (mean ± SD)	37.1 ± 10.2		Unable to compare to global physical activity guidelines
					Inspiratory muscle training (80%) (n = 9),	40.1 ± 8.9		
					Control group (n = 10)	36.7 ± 9.7		
Hollander 2005 [32]	Cross-sectional study	21.3 ± 2.7 (control)	All	Baecke questionnaire	**CF (n = 34) - Male = 22, Female = 12**			
					Activity factor for sedentary lifestyle 1.5 (%, n)	34%, 12		
					Activity factor for intensive work 1.7 (%, n)	60%, 21		
					Activity factor for sport 2.1 (%, n)	3%, 1		
Gruet 2016 [35]	Cross-sectional study	27.4 ± 7.8 (males), 22.8 ± 5.0 (females)	All	AQAP questionnaire	**CF (n = 25) - Male = 17, Female = 8**			
					Daily physical activity index (median, IQR)	2.8 (2.0–3.1)		
					Sport index (median, IQR)	3.0 (2.3–3.3)		

(continued on next page)

Table 3 (*continued*)

Study	Design	Participants age (years) (Mean, SD)	Disease severity	Assessment tool	Outcome measure reported		Achieving guidelines ✓/×
					Leisure-time index (median, IQR)	3.3 (2.8–3.8)	
					Daily physical activity (Global score) (median, IQR)	9.0 (7.3–9.8)	
Elkin 2001 [39]	Cross-sectional study	30 ± 9	All	7 day recall questionnaire (7DPAR)	**CF (n = 87)** Mean daily energy expenditure (Kcal, (corrected for body weight))	2071.39 (613)	
Decorte 2017 [33]	Case-control study	28 ± 8	Mild-Mod	Baecke questionnaire	**CF (n = 15) - Male = 12, Female = 3**		
					Baecke questionnaire work index (mean ± SD)	2.6 ± 0.5	
					Baecke questionnaire sport index (mean ± SD)	2.3 ± 0.4	
					Baecke questionnaire leisure time index (mean ± SD)	3.2 ± 0.6	
Ionescu 2003 [40]	Case-control study	28.1 ± 6.2 (CF), 26.5 ± 4.6 (control)	Mild-Mod	Recall questionnaire	**CF (n = 56) - Male = 27, Female = 29**		
					METs (Daily) (mean, 95% CI)		
					Mild impairment (FEV1 > 65% predicted) (n = 22)	37.6 (33.6–41.5)	
					Moderate impairment (FEV1 > 46% and < 65% predicted) (n = 11)	33.9 (31.3–36.6)	
					Severe impairment (FEV1 < 45% predicted) (n = 23)	34.2 (30.2–38.2)	
Haworth 1999 [34]	Cross-sectional study	23.0 (CF)	All	Baecke questionnaire	**CF (n = 151) - Male = 83, Female = 68** Activity score (mean ± SD)	7.6 ± 1.4	
Street 2006 [41]	Cross-sectional study	23.6 (control)	All	Activity Questionnaire	**CF (n = 17) - Male = 4, Female = 13** Physical activity (hrs/week) (mean ± SD) (Time spent	11.3 ± 1.1	

non-CF respectively (P = 0.74)) [31], however inactivity describes insufficient levels of PA to meet guidelines and not necessarily SB [45].

3.3. Levels of PA in adults with CF compared to their non-CF peers

Whilst recommended PA guidelines provide a reference value to assess PA in adults with CF, it is also well recognised that a large proportion of the general adult population do not meet recommended PA guidelines [17]. It may therefore be more appropriate to compare adults with CF to comparable non-CF control groups rather than public health guidelines to determine if differences exist between the cohorts. Five studies [12,30,31,36,43] reported PA levels for a comparable non-CF control group, PA was therefore compared between these groups (Table 4).

3.3.1. Studies reporting objectively assessed PA

Three studies reported objectively assessed PA [12,30,31]. Time spent engaging in MVPA was significantly higher in the control group when compared to adults with CF in one study [12]. No significant differences were found between groups across any other outcome reported in the remaining studies, additionally, the significant difference found by Troosters et al. (2009) was found in activity above moderate intensity, with no difference at light intensity or in daily step count [12]. Step count was reported in two studies, neither found a significant difference between groups, however in both studies the control group would be considered as 'active' based on the daily number of steps (10,281 and 10,591 steps respectively), whereas each of the CF groups failed to meet this threshold (9398 and 9161 steps respectively) [12,30]. Although there is evidence to suggest that there are beneficial effects associated with taking 10,000 steps, cut-points such as this should be interpreted with caution.

3.3.2. Studies reporting self-reported PA

Three studies used self-report tools to assess PA [31,36,43]. PA was higher in the non-CF control group in 1 study [36], there were no significant differences in the remaining 2 studies [31,43]. The significant difference observed between the CF and non-CF groups was found for total PA (MET min·week) (5309 and 7808 respectively, (P = 0.011)) [36]. No significant differences were found between groups for MVPA, additionally, Rasekaba et al. (2013) described comparable levels of PA across domestic, leisure, moderate-vigorous domains, with reduced total activity being explained by reduced PA in work and transport domains [36]. The proportion of adults with CF and non-CF controls who met recommended guidelines for PA was also comparable with 93% in each group [36].

One study used both a validated questionnaire (HAES) and an accelerometer [31]. No significant correlation was observed between PA assessed using the objective or subjective methods (P > 0.05), with self-reported PA being over-estimated in both groups, which may suggest an influence of measurement tool on PA [31].

3.4. Relationship between PA and clinical outcome measures

Thirteen studies explored the relationship between PA and other clinical outcome measures (lung function, body mass index (BMI), exercise capacity, exacerbation frequency) [5,12,28–31,34,36,37,39,40,42,43]. Whilst the remaining 5 studies [32,33,35,38,41] reported data on some of these outcome measures no correlations with PA were performed or reported.

3.4.1. Lung function

Five studies reported on the relationship between lung function expressed as FEV_1 or FEV_1% predicted and objectively assessed PA [5,12,28,30,31]. Though MVPA was not different across categories of disease severity (FEV_1 < 40, 40–60, 60–80 > 80% predicted), participants engaging in 30 min or more MVPA per day had higher lung function

Table 4
Comparison between reported levels of PA in adults with CF and comparable non-CF control groups.

Study	Design	Participants age (years) (Mean, SD)	Disease severity	Assessment tool	Outcome measure reported				Difference	*✓/× CF	CON
					CF (n = 20)		**Control (n = 20)**				
Troosters 2009 [12]	Case-control study	25 ± 6 (CF, Male), 27 ± 9 (CF, Female), 24 ± 3 (Control, Male), 26 ± 6 (Control, Female)	All	SenseWear pro 3 armband accelerometer	Moderate Physical activity (min/day) (mean, IQR)	14.8 (8.6–36.8)	Moderate Physical activity (min/day) (mean, IQR)	34.5 (20.6–53.8)	PA significantly higher in control group (p = 0.03)	×	✓
					Steps per day (mean, IQR)	9398 (6317–12,970)	Steps per day (mean, IQR)	10,281 (7928–12,360)	No significant difference in PA between groups (p = 0.37)	×	✓
Savi 2015 [30]	Case-control study	33 ± 9 (CF), 29 ± 5 (control)	All	SenseWear pro 3 armband accelerometer	**CF (n = 30) - Male = 20, Female = 10**		**Control (n = 15) - Male = 10, Female = 5**				
					Moderate & Vigorous activity (min/day) (mean, IQR)	16 (9–29)	Moderate & Vigorous activity (min/day) (mean, IQR)	12 (8–27)	No significant difference in PA between groups (p = 0.43)	×	×
					Mild intensity activity (min/day) (mean, IQR)	159 (100–246)	Mild intensity activity (min/day) (mean, IQR)	147 (77–205)	No significant difference in PA between groups (p = 0.22)		
					Moderate intensity activities (min/day) (mean, IQR)	13 (9–29)	Moderate intensity activities (min/day) (mean, IQR)	11 (7–16)	No significant difference in PA between groups (p = 0.34)		
					Vigorous intensity activities (min/day) (mean, IQR)	1 (0–3)	Vigorous intensity activities (min/day) (mean, IQR)	1 (0–5)	No significant difference in PA between groups (p = 0.94)		
					Steps per day (mean ± SD)	9160.5 ± 3825.6	Steps per day (mean ± SD)	10,591 ± 4024.6	No significant difference in PA between groups (p = 0.25)	×	✓
Savi 2013 [31]	Case-control study	33 ± 8 (CF), 30 ± 4 (control)	Mild-Mod	HAES Questionnaire & SenseWear pro 3 armband accelerometer	**CF (n = 20) - Male = 15, Female = 5**		**Control (n = 11) - Male = 7, Female = 4**				
					Lying Time (min/day) (mean ± SD)	452.1 ± 71.4	Lying Time (min/day) (mean ± SD)	493.5 ± 68.2	No significant difference in PA between groups (p = 0.11)		
					Duration Physical Activity (min/day) (mean ± SD)	230.4 ± 117.4	Duration Physical Activity (min/day) (mean ± SD)	212.7 ± 115.8	No significant difference in PA between groups (p = 0.74)		
					HAES Total Inactivity, (min/day) (mean ± SD)	367 ± 138.2	HAES Total Inactivity, (min/day) (mean ± SD)	376.6 ± 94.4	No significant difference in PA between groups (p = 0.74)		
					HAES Total Activity, (min/day (mean ± SD)	533.7 ± 147.7	HAES Total Activity, (min/day (mean ± SD)	506.7 ± 105.6	No significant difference in PA between groups (p = 0.48)		
Enright 2007 [43]	Case-control study	22.4 (CF), 21.7 (control)	All	Recall questionnaire	**CF (n = 40) - Male = 22, Female = 18**		**Control (n = 30) - Male = 15, Female = 15**				
					METs (mean, 95% CI)	37.0 (35.0–39.0)	METs (mean, 95% CI)	41.5 (40.0–43.0)	No significant difference in PA between groups (p > 0.01)	×	×
Rasekaba 2013 [36]	Case-control study	29 ± 9 (CF), 32 ± 10 (control)	Mild-Mod	International physical activity questionnaire (IPAQ)	**CF (n = 101)- Male% = 55, Female% = 45**		**Control (n = 35) - Male% = 31, Female% = 69**				
					MET (min.week)(Total) (mean ± SD)	5309 ± 6277	MET (min.week)(Total) (mean ± SD)	7808 ± 5493	PA significantly higher in control group (p = 0.011)	✓	✓
					MET (min.week) Work (mean ± SD)	1887 ± 4285	MET (min.week) Work (mean ± SD)	3707 ± 5292	PA significantly higher in control group (p = 0.003)		
					MET (min.week) Transport (mean ± SD)	613 ± 1018	MET (min.week) Transport (mean ± SD)	1315 ± 1123	PA significantly higher in control group (p < 0.001)		
					MET (min.week) Domestic (mean ± SD)	1513 ± 2496	MET (min.week) Domestic (mean ± SD)	1219 ± 2428	No significant difference in PA between groups (p = 0.801)		
					MET (min.week) Leisure (mean ± SD)	1269 ± 1607	MET (min.week) Leisure (mean ± SD)	1565 ± 2134	No significant difference in PA between groups (p = 0.376)		
					MET (min.week) Walking (mean ± SD)	1278 ± 1593	MET (min.week) Walking (mean ± SD)	2394 ± 2505	PA significantly higher in control group (p = 0.004)		
					MET (min.week) Moderate (mean ± SD)	1256 ± 1802	MET (min.week) Moderate (mean ± SD)	1645 ± 3223	No significant difference in PA between groups (p = 0.648)		
					MET (min.week) Vigorous (mean ± SD)	2170 ± 3560	MET (min.week) Vigorous (mean ± SD)	2787 ± 4242	No significant difference in PA between groups (p = 0.110)		

* ✓× Indicates whether reported levels of PA meet recommended guidelines as describe in the methods section. ✓ indicates that guidelines were achieved, whilst × indicates that guidelines were not met.

than those engaging in <30 min MVPA [5]. Time spent engaging in MVPA was also positively associated with FEV_1% predicted (P = 0.04) [28]. Troosters et al. (2009) did not find a correlation between MVPA and FEV_1, although number of steps was positively correlated with near significance with FEV_1 (R = 0.39, P = 0.08) [12]. Savi et al. (2015) also found no correlation between MVPA and lung function [30]. MVPA was not reported by Savi et al. (2013), who reported on energy expenditure, finding a significant correlation between FEV_1 and activity energy expenditure during both week days (r=0.436, P=0.05) and weekends (r=0.435, P=0.05) [31].

Four studies reported the relationship between lung function and self-reportedPA [36,37,40,43]. No significant difference in FEV_1% was found between participants who achieved recommended PA guidelines compared to those who did not achieve guidelines [37]. No relationship was found between FEV_1 and self-reported PA, although low PA was associated with reduced vital capacity (VC) and total lung capacity (TLC) (P<0.01) [43]. Higher PA (MET·min·week) was associated with better lung function (FEV_1), although the relationship was weak (R = 0.26, P < 0.05) and not statistically significant when analysing males alone, which may indicate gender differences in PA levels [36]. Patients with severe impairment (FEV_1 < 45% predicted) were less active than those with mild impairment (FEV_1 > 65% predicted) (P < 0.01), with no difference between moderate and severe impairment [40].

3.4.2. Exercise capacity

Four studies explored the relationship between exercise capacity and PA, all of which assessed PA using objective methods [5,12,30,31]. All found positive associations between PA (Total PA ((R = 0.51, P = 0.02)) [31] and MVPA ((β = 0.59, P = 0.002, (R^2 = 0.32)), (R = 0.44 p = 0r.01)) [5,12,30]) and exercise capacity ($VO2_{peak}$ [5,12,30] and 6-min walk test distance [31]). This relationship was not evident when using the HAES questionnaire to assess PA [31].

3.4.3. Exacerbations

Two studies explored the relationship between exacerbation and hospitalisation frequency and objectively assessed PA [5,28]. More frequent exacerbations were associated with lower PA, although this was not significant once corrected for other clinical covariates [28]. Time spent engaging in MVPA was moderately, yet significantly correlated with reduced need for hospitalisation ($r_s = -0.3$, $P = 0.05$) [5].

3.4.4. Body composition

Three studies explored the relationship between body composition and self-reported PA [36,40,43]. Lower PA was associated with lower fat free mass (FFM) [40,43] but not BMI [36].

Four studies [34,39,40,42] explored the relationship between self-reported PA and bone mineral density (BMD), all of which reported a positive association between higher PA and higher BMD (($r = 0.249$, $P,0.05$), ($r = 0.3$, $P < 0.01$),($r = 0.53$, $P < 0.01$)) [34,39,40] with the exception of Bhudikanok et al. (1998) who reported no association [42].

3.4.5. Blood glucose control

Two studies reported on the association between blood glucose control and PA, using objective [29] and self-reported PA assessment [37]. No significant association between blood glucose control and PA was reported in either study [29,37].

3.4.6. Quality of life (QoL)

Only one study reported on quality of life, finding higher scores for QoL in patients achieving recommendations for MVPA when compared to those who did not (P < 0.05) [5].

4. Discussion

In the majority of studies reviewed adults with CF fail to meet recommended PA and step count guidelines. Non-CF peers also failed to meet guidelines, with comparable levels of PA between adults with CF and their non-CF peers. There was low quality evidence to support associations between lung function, exercise capacity and PA. Associations between PA and clinical variables were more evident in studies using objective PA assessments, when compared to those using self-reported PA.

4.1. Achievement of recommended PA guidelines

Adults with CF did not achieve recommended PA guidelines and daily step count targets in five out of the eight studies in which comparison to guidelines was possible. However, their non-CF peers also failed to achieve recommended guidelines in two out of five studies. Many of the assessment tools used did not provide sufficient information about frequency, intensity and time of PA to allow for comparison to guidelines. Whilst it is recommended that patients meet PA guidelines it is also worth noting that a small increase in PA levels is associated with beneficial effects on health outcomes and risk of all-cause mortality, even when recommended levels are not achieved. Such health benefits can be achieved by individuals moving from the category of 'no activity' to 'some levels of' of activity [15].

4.2. Physical activity in adults with CF compared to non-CF peers

No significant differences in PA were found between groups in 3 of the 5 studies with comparable control groups. The differences observed between groups were reported in work and transport domains, suggesting variation in lifestyle and employment opportunities in adults with CF when compared to their non-CF peers in one of these studies [36]. Individuals with CF are more likely to work in jobs which are sedentary or involve light work, with two thirds of patients with CF reporting CF as an obstacle to their career, with over half reporting being limited in their work by CF [46]. Occupational PA in patients with CF may warrant further investigation. In the second study, the differences between groups were observed at moderate intensities and above [12]. Classifying PA intensity remains problematic in clinical populations. Activity intensity is classified using cut-points which are derived using device specific energy expenditure prediction equations [47], which may not be appropriate for CF populations as no CF specific cut-points exist. Raw data analysis is recommended as best practice in PA research [48] and cut-points derived from raw data are available [49], which increases research control of the data. Unfortunately, these methods were not employed in any of the studies reviewed and have not been examined in patients with CF to date. Future research should look to employ these methods when assessing PA in patients with CF.

4.3. The relationship between PA and secondary outcomes

The evidence for an association between PA and lung function was inconsistent with 5/9 finding a positive association. There appears to be stronger evidence for an association between PA and exercise capacity with all 4 studies reviewed reporting a positive association, albeit in a small number of low quality studies. Evidence of an association with PA was also inconsistent across all other outcome measures reviewed. Additionally only one study reviewed reported a measure of QoL.

The majority of studies which found an association between PA and lung function used an objective assessment of PA, with only one study finding an association using self-reported PA. Likewise, all of the studies finding an association between PA and exercise capacity used objective PA assessment, whereas the association was not evident when using a self-report questionnaire. Given the limited number of studies

comparing objective and self-reported PA assessment, it is not possible to assess the influence of assessment tool on the ability to detect correlations between PA and clinical outcome measures. Though the available data would suggest that objective PA assessment may be more appropriate than self-reported methods [31]. Future research should utilise objective PA assessment wherever possible, with additional self-report methods considered alongside, in order to provide evidence for future PA guidelines.

An additional consideration when exploring the relationship between PA and clinical outcome measures is that of variation in the population due to the nature of the disease. Patients will inevitably experience periods of stability and instability, and disease progression and severity is highly variable within cohorts, all of which presents challenges for monitoring PA. Exacerbations of CF symptoms and hospitalisation impact levels of PA [50]. This may result in data attrition if exacerbations occur during study monitoring periods. Additionally, PA assessed pre, during or post-exacerbation may not accurately reflect habitual PA. Routine monitoring throughout the year and not just during admissions is required to overcome this issue. Monitoring devices and cut-points need to be validated for use in CF populations, both in terms of criterion validity to gold standard measures of PA assessment and in terms of the ability to discriminate between disease severities. Additional work is required to develop disease specific cut-points. Alternatively, standardised cut-points should be agreed upon and adopted universally.

4.4. Variability in reported PA variables

There were a wide range of measurement tools used in the studies reviewed. Five studies used an objective method [6,11,22–25] with the remaining 12 studies using self-report questionnaires, in addition to one study using both methods [31]. Comparisons between studies are difficult due to the large range of outcomes reported (Table 2). There is no consistent variable (e.g. steps, total PA time, METs) reported meaning analysis of pooled effects was not possible. There were no consistent findings for PA in comparison to guidelines or non-CF peers when assessed using different PA assessment methods, suggesting no difference between the assessment methods used. This may be due to variances in validity and reliability of these assessment methods as well as differences in populations' studied and study designs. There is therefore a need for an adoption of standardised, objective measures of PA, with consistent outcomes reported. Standardisation may enable a better understanding of PA in this cohort and allow for comparisons to be made to global PA recommendations and non-CF peers.

4.5. Assessment tools utilised

Questionnaires may be useful for large scale epidemiological research, or as secondary outcome measures of PA, however objective PA assessment should be considered as the informed choice for PA assessment in clinical practice and research [8]. The IPAQ was the only self-report tool which allowed PA levels to be compared to guidelines in the current review. The Baecke questionnaire was the most frequently used questionnaire, used in 3 studies, all of which described low levels of PA in adults with CF. Understanding of PA levels in adults with CF has previously been based on such studies though it may be possible that the Baecke questionnaire underestimates PA in this population. The questionnaire is not disease specific and was developed in healthy, individuals and may not be appropriate for use in CF populations. Whilst the IPAQ is well validated across multiple populations [51], it is not valid or appropriate for use in clinical populations such as; breast cancer [52], HIV [53] or fibromyalgia [54], which highlights the importance of validating tools in the population in which they are intended to be used. The HAES questionnaire has previously been described as a valid, reliable and responsive PA assessment tool in adolescents with CF [55]. The current review only included one study using the HAES questionnaire, the findings of which suggest that the questionnaire overestimates PA in adults with CF when compared to accelerometry [31]. The studies in the current review span almost two decades, during which time the management of CF has changed considerably. Additionally, the assessment of physical activity has also changed with the increased accessibility and use of accelerometry in the previous decade. The data available in the current review does not allow for comparisons of clinical outcome measures and PA assessment throughout this period and caution should be taken when interpreting data across such a long period.

4.6. Limitations

The quality of data reported in the studies reviewed limits the strength of the conclusions which can be made from this review, this review therefore highlights the need for further research in this area. The majority of the studies were graded as low quality, based primarily on a lack of a control groups and/or randomisation. The majority of studies were not specifically designed to investigate PA levels, often reporting PA as a secondary outcome measure. The non-standardised reporting of outcome measures prevents any meta-analysis or collation of data to strengthen the evidence and improve understanding of PA behaviour. Additionally, assessing the risk of bias in the studies reviewed is problematic. The tools currently available to assess risk of bias are not designed to assess studies using a cross-sectional design. Consequently, the assessment of risk of bias and the ability to make recommendations based on this assessment may be limited when using the tools currently available.

5. Conclusions

The literature reviewed would suggest that PA in adults with CF is largely comparable to their non-CF peers, despite being insufficiently active to achieve global PA recommendations. The choice of PA assessment tool and reported outcomes are highly variable, many of which do not provide sufficient information about the frequency, intensity or time of PA in adults with CF. The associations between PA and clinical outcomes appear to be stronger when using objectively assessed PA when compared to self-reported PA, although there are few studies available for analysis. The previously reported associations between PA and lung function appear to be supported by the data reviewed, although a number of studies found no associations. The association between PA and exercise capacity is also supported by data reviewed, albeit from a limited number of studies.

6. Future recommendations

The current review has highlighted a requirement for high quality studies designed specifically to explore PA in adults with CF. The increased emphasis on adults with CF is also reflected by the recently updated European Cystic Fibrosis society (ECFS) best practice guidelines, who also recognise a shift in focus to adult populations given the current trend in life expectancy. Whilst this is true for wider CF care it is particularly relevant with regards to PA assessment, given the lack of available evidence. Standardisation of PA monitoring and reporting is essential for future research, it has previously been recommended that time spent engaging in PA of different intensities, time spent sedentary, step count and energy expenditure should be the minimum standard for reporting PA [8]. A wrist-worn accelerometer (compliance has previously been shown to be higher when using wrist worn devices [49]), worn for seven consecutive days during waking hours, using at least 10 h per day as a minimum wear time criteria should be used to assess habitual PA [56]. Where possible raw data analysis should be used to analyse data with outcomes reported as outlined above. Standardisation will allow for comparisons between cohorts as well as data pooling to improve statistical precision. Levels of PA and its impact on health and

wellbeing in CF are still not clear in the literature. Which may be attributed to the lack of high-quality research, using appropriate PA assessment methods to examine PA behaviours and the relationship with clinical outcomes. Further work is therefore needed to fully elucidate the impact of PA in CF, with an ultimate aim of providing an evidence base to inform guidelines and clinical practice. The scope of the current review only extends to adults (≥18 years), additional reviews are required to understand any differences between paediatric and adult/mixed populations.

The quality of PA assessment would benefit from an approach similar to the European CF Exercise group's recommended guidelines for exercise testing [57]. This involved experts from a range of backgrounds from different organisations and geographical areas were involved in a process to inform the development of the guidelines [57]. The guidance recommends the standardised use of routine exercising testing in CF care, and whilst this provides an important assessment of exercise capacity, this is only one component of PA. Further assessment methods are required to assess habitual PA; a combination of exercise testing, objective and self-reported PA assessment methods should be considered in clinical practice to screen participants and inform and evaluate PA interventions.

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Conflict of interest

The authors declare that there are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcf.2019.03.003.

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Appendix B - Characteristics of physical activity questionnaires

Questionnaire (Study using questionnaire)	**Description and properties**
Habitual Activity Estimation Scale (HAES) (Savi et al., 2013)	**Description of questionnaire:** Physical activity in one typical weekday and one typical Saturday in the past 2 weeks. % time spent in each of 4 time periods: bed – breakfast, breakfast – lunch, lunch – supper, supper-bedtime 4 domains: Inactive, Somewhat inactive, Somewhat active, Very active **Output/units:** energy expenditure – no step counts – no time spent in different intensities – yes sedentary – yes other – no **Method of administration:** Child: Two days in the life of my child - interviewer administered**;** Adolescent: Two days in my life- interviewer administered or supervised**;** Adult: Two days in my life - interviewer administered or supervised NB: A Standard Operating Procedure has been developed and available by JE Schneiderman. **Scoring method:** Excel score sheet **Scoring range:** 0-100% **Instructions available:** Available from author **Length of time to administer:** 15-20 minutes
Baecke Questionnaire (Decorte et al., 2017; Haworth et al., 1999; Hollander et al., 2005)	**Description of questionnaire:** 16-item questionnaire with 3 dimensions to assess physical activity in the previous 12 months: at work (work index), sport (sport index) and leisure (leisure index). **Output/units:** energy expenditure – no step counts – no time spent in different intensities – yes (total score for physical activity is represented in a work index, sport index and leisure index) sedentary – somewhat other – no **Method of administration:** Self-administered **Scoring method:** The total score for habitual physical activity is obtained by summating the work index, sport index and leisure index [Work index = ((6 – (points for sitting)) + SUM(points for the other 7 parameters)) / 8; Sport index = (SUM(points for all 4 parameters)) / 4; Leisure index = ((6 – (points for television watching)) + SUM(points for remaining 3 items)) / 4 **Scoring range:** n/a **Instructions available:** n/a **Length of time to administer:** n/a
Physical Activity Status Questionnaire (Enright et al., 2004) (Enright et al., 2007) (Ionescu et al., 2003)	**Description of questionnaire:** A recall questionnaire relating to physical activity in a preceding timeframe **Output/units:** energy expenditure – yes step counts – no time spent in different intensities – no sedentary – no other – no **Method of administration:** n/a **Scoring method:** The activity score is expressed in metabolic equivalents (METs) [1 MET = the energy expended by a person at rest]. **Scoring range:** n/a **Instructions available:** n/a **Length of time to administer:** n/a

7-day Physical Activity Recall (Interview) (7-Day PAR) (Elkin et al., 2001) (Currie et al., 2017)	**Description of questionnaire:** Estimates an individual's time spent in physical activity, strength, and flexibility activities for the 7 days prior to the interview. The participant to recall time spent sleeping and doing physical activities for the past 7 days. Duration and intensity of the physical activities are determined. **Output/units:** energy expenditure – yes step counts – no time spent in different intensities – yes sedentary – no other – sleep **Method of administration:** Semi structured interview face to face. Can be administered by telephone or self-administered. **Scoring method:** The number of hours spent in sleep and different activity levels (moderate, hard, and very hard intensity) are obtained and an estimate of total kilocalories/day is calculated. Time spent in sleep (1 MET), light (1.5 METs), moderate (4 METs), hard (6 METs), and very hard (10 METs) activities for the past 7 d are multiplied by their respective MET values and then summed. **Scoring range:** n/a **Instructions available:** Yes **Length of time to administer:** n/a
International Physical Activity Questionnaire (IPAQ) (Rasekaba et al., 2013)	**Description of questionnaire:** 7 day recall of work, transport, domestic and leisure related habitual physical activities, activities included if performed for at least 10 minutes, time and number of days are then converted to weighted MET minutes per week **Output/units:** energy expenditure – yes step counts – no time spent in different intensities – yes sedentary – no other – no **Method of administration:** self-administered **Scoring method:** work, transport, domestic and leisure activity and then a total physical activity score are calculated in MET/min/week; MET/min/week for walking, moderate and vigorous activities, and then a total physical activity score used to categorise patients as: Low, moderate or high physical activity category; Sitting score in time spent sitting **Scoring range:** Scored as per IPAQ protocol. **Instructions available:** IPAQ protocol available for scoring **Length of time to administer:** n/a
AQAP Questionnaire (Gruet et al., 2016)	**Description of questionnaire:** 22-item questionnaire with 4 domains to assess physical activity in the previous 12 months: usual activity PA index, sport PA index, leisure PA index and global PA index. **Output/units:** energy expenditure – no step counts – no time spent in different intensities – yes (total score for physical activity is represented in a work index, sport index, leisure index and global index.) sedentary – somewhat (including leisure time screen viewing) other – no **Method of administration:** Self-administered **Scoring method:** The total score for global physical activity is obtained by summating the usual PA index, sport index and leisure. **Scoring range**: 0-5 (usual activity, sport, leisure) 0-15 (Global PA) **Instructions available:** Original article cited **Length of time to administer:** n/a

Activity recall questionnaire (Street et al., 2006)	**Description of Questionnaire:** Questions regarding physical education classes (frequency, time, and intensity), questions regarding time spent each week in 11 specific activities, and one regarding participation in 12 team sports. **Output/units:** **energy expenditure – no** **step counts – no** **time spent in different intensities – yes** **sedentary – no** **other – sleep** **Method of administration: Self-administered** **Scoring method: Mean time (weekly) spent in activities.** **Scoring range: n/a** **Instructions available: n/a** **Length of time to administer: n/a**
3 Day Physical Activity Diary (Bhudhikanok et al., 1998)	**Description of diary:** 3 day activity record for estimation of energy expenditure. **Output/units:** energy expenditure – yes step counts – no time spent in different intensities – yes sedentary – no other – sleep **Method of administration:** Self-administered **Scoring method:** Mean time (Minutes per day) spent in activities. Activities are converted to METs to compute daily energy expenditure **Scoring range:** n/a **Instructions available:** n/a **Length of time to administer:** n/a

Abbreviation: $h \cdot wk^{-1}$=hours per week; METS=metabolic equivalents; n/a=information is not available

Table adapted from Bradley, J., O'Neill, B., Kent, L., Hulzebos, E. H., Arets, B., & Hebestreit, H. (2015). Physical activity assessment in cystic fibrosis: A position statement. *J Cyst Fibros*, *14*(6), e25-32. https://doi.org/10.1016/j.jcf.2015.05.011.

Health Research Authority

Mr James Shelley
PhD research student
Liverpool John Moores University
62 Great Crosshall Street
Liverpool
L3 2AT

Email: hra.approval@nhs.net

28 June 2017

Dear Mr Shelley

Letter of HRA Approval

Study title:	**Association between physical activity, sedentary behaviour and physiological outcome measures of cardiovascular and respiratory function in patients with Cystic Fibrosis**
IRAS project ID:	**219672**
Protocol number:	**N/A**
REC reference:	**17/NW/0360**
Sponsor	**Liverpool Heart and Chest Hospital NHS Foundation Trust**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators",* issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

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

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

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

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

HRA Training

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

Your IRAS project ID is **219672**. Please quote this on all correspondence.

Yours sincerely

Kevin Ahmed

Assessor

Telephone: 0207 104 8171

Email: hra.approval@nhs.net

Copy to: *Gillian Hamblin, Sponsor Contact, Liverpool Heart and Chest Hospital NHS Foundation Trust*

Appendix A - List of Documents

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

Document	*Version*	*Date*
Copies of advertisement materials for research participants [LHCH recruitment poster (V1 - 04.04.2017)]	1	04 April 2017
GP/consultant information sheets or letters [GP Letter (V1 12.01.2017)]	1	12 January 2017
IRAS Application Form [IRAS_Form_19052017]		19 May 2017
Letter from sponsor [10. 1146- CF Cross-sectional Physical Activity Res Com approval letter]		25 April 2017
Letters of invitation to participant [Participant invitation letter (V2 04.04.2017)]	2	04 April 2017
Other [NW.0360 219672 SL07 (PRS) Provisional opinion letter response (V1 - 13.06.2017)]	1	13 June 2017
Participant consent form [Participant consent form (18+) (V3 - 13.06.2017)]	3	13 June 2017
Participant information sheet (PIS) [Participant information (18+) (V2 04.04.2017)]	2	04 April 2017
Referee's report or other scientific critique report [Shelley James (447798) RD9R Feedback FRDSGC 14.12.16]		14 December 2016
Research protocol or project proposal [James Shelley RD9R - PhD Research proposal (V1 04.04.2017)]	1	04 April 2017
Summary CV for Chief Investigator (CI) [J Shelley CV (V1-18.05.17)]	1	18 May 2017
Summary CV for supervisor (student research) [Ellen Adele Dawson cut down CV May 2017]		
Summary CV for supervisor (student research) [Claire Stewart 2 page cv 0517]	1	
Summary CV for supervisor (student research) [Dr Lynne Boddy summary CV May 2017]	1	
Summary CV for supervisor (student research) [Dr Zoe Knowles CV may 2017]	1	
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Protocol for Hospital (V2 04.04.2017)]	2	04 April 2017
Summary, synopsis or diagram (flowchart) of protocol in non technical language [LCCG RCF application form CF 091015]	1	09 October 2015
Validated questionnaire [All Versions English-UK CFQ-R FINAL]		
Validated questionnaire [GPAQ_EN]		
17.NW.0360 219672 FIFO letter 15.06.2017		15 June 2017

Appendix B - Summary of HRA Assessment

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

For information on how the sponsor should be working with participating NHS organisations in England, please refer to the, *participating NHS organisations*, *capacity and capability* and *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sections in this appendix.

The following person is the sponsor contact for the purpose of addressing participating organisation questions relating to the study:

Name: Gillian Hamblin

Tel: 0151 600 1467

Email: Gillian.hamblin@lhch.nhs.uk

HRA assessment criteria

Section	HRA Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	No comments
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	This is a non-commercial single site study taking place in the NHS where that single NHS organisation is also the study sponsor. Therefore no study agreements are required.
4.2	Insurance/indemnity arrangements assessed	Yes	Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical defence organisation covers the activities expected of them for this

Section	HRA Assessment Criteria	Compliant with Standards	Comments
			research study
4.3	Financial arrangements assessed	Yes	No application for external funding has been made.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
This is a non-commercial single site study taking place in the NHS where that single NHS organisation is also the study sponsor. Therefore there is only one site type involved in the research. If this study is subsequently extended to other NHS organisation(s) in England, an amendment should be submitted to the HRA, with a Statement of Activities and Schedule of Events for the newly participating NHS organisation(s) in England. The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. For NIHR CRN Portfolio studies, the Local LCRN contact should also be copied into this correspondence. For further guidance on working with participating NHS organisations please see the HRA website. If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England which are not provided in IRAS or on the HRA website, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net. The HRA will work with these organisations to achieve a consistent approach to information provision.

Confirmation of Capacity and Capability

This describes whether formal confirmation of capacity and capability is expected from participating NHS organisations in England.
This is a single site study sponsored by the site. The R&D office will confirm to the CI when the study can start.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).
A Principal Investigator should be appointed at study sites GCP training is not a generic training expectation, in line with the HRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
As a non-commercial undertaken by local staff, it is unlikely that letters of access or honorary research contracts will be applicable, except where local network staff employed by another Trust (or University) are involved (and then it is likely that arrangements are already in place). Where arrangements are not already in place, network staff (or similar) undertaking any of the research activities listed in A18 or A19 of the IRAS form (except for administration of questionnaires or surveys), would be expected to obtain an honorary research contract from one NHS organisation (if university employed), followed by Letters of Access for subsequent organisations. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm enhanced DBS checks, including appropriate barred list checks, and occupational health clearance. For research team members only administering questionnaires or surveys, a Letter of Access based on standard DBS checks and occupational health clearance would be appropriate.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.
The applicant has indicated that they do intend to apply for inclusion on the NIHR CRN Portfolio.

Shelley, James

From: Williams, Mandy
Sent: 24 July 2018 11:06
To: Research Ethics Proportionate Review; Shelley, James
Cc: Dawson, Ellen
Subject: Ethics PR - Approved with Provisos - - REF: 18/SPS/034
Attachments: Shelley - SPS - Approved with Provisos.pdf

Follow Up Flag: Follow up
Flag Status: Flagged

Dear James

With reference to your application for Ethical Approval

REF: 18/SPS/034 - James Shelley – PGR - Physical activity and vascular function in healthy adults (Ellen Dawson)

UREC decision: Approved with provisos

The University Research Ethics Committee (UREC) has considered the above application by proportionate review. I am pleased to inform you that ethical approval has been granted subject to the provisos listed below. Once the final version of the ethics application with the provisos addressed has been emailed to ethicsPR@ljmu.ac.uk, the study can commence.

Provisos:

Page 5, Highlight (Yellow):
Content: "Please confirm whether the Principle Investigator (PI) has successfully completed the LJMU Research Ethics Training and a copy of the certificate of completion emailed to the PI has been appended to this ethics application"
Comment: Thank you for appending the certificate pertaining to the older version of the ethics training. However I do not seem to have a record of your completion of the updated training. Please can you complete the updated online training as it is a valuable part of your ongoing research ethics education. Please append your confirmation of completion as part of the final version of your form along with any other provisos addressed.

Page 9, Highlight (Yellow):
Content: "out a 'drop out' card to record reasons for not participating which may help to improve future research."
Comment: This drop out card essentially constitutes research data which would be used to inform study designs going forward - please include a statement of implied consent on this card with a brief description of how the drop out feedback will be used. Please make it clear that it is voluntary and that participants are not obliged to provide a reason for their drop out.

Page 22, Highlight (Yellow):
Content: "F1a. Please provide details of any personal, identifiable or sensitive information will be collected and stored (e.g. names, postal/email addresses, telephone numbers, date of birth, full postcode, medical"
Comment: Please also include consent forms in this section.

Page 32, Note (Orange):
Please note that UREC does not advise you include personal telephone numbers on PI sheets / recruitment emails and posters etc. Please remove.

Page 35, Highlight (Orange):
Content: "PARTICIPANT (18+) INFORMATION SHEET"
Comment: Please update the PI sheet to include the data protection notice in order to ensure you are compliant with GDPR. You can access more information here:

https://www2.ljmu.ac.uk/RGSO/93044.htm
https://www2.ljmu.ac.uk/RGSO/93131.htm

Page 36, Highlight (Yellow):

Content: "You will be given the opportunity to discuss any queries you may have, give your informed consent and be familiarised with the equipment we will use to measure physical activity."
Comment: Please inform participants that you will use a screening questionnaire to determine their eligibility to take part.

Page 36, Highlight (Yellow):
Content: "Questionnaires:"
Comment: Please specify approximately how long each questionnaire will take to complete

Page 36, Strike-Out (Red):
Content: "ed"

Page 37, Highlight (Yellow):
Content: "What are the possible risks of me taking part?"
Comment: Participants may also suffer a reaction to the adhesives used to secure the actiPAL or irritation from wearing the watch as specified in section E1. Please include this information and advise participants what they should do under these circumstances eg. remove and seek advice from GP

Page 38, Highlight (Yellow):
Content: "11. What if something goes wrong? "
Comment: Please refer to template for standard text

Page 38, Highlight (Yellow):
Content: "locked filing cabinet."
Comment: ..on LJMU premises

Page 41, Highlight (Orange):
Content: "understand that photographs may be taken during the study and I am happy to proceed."
Comment: This isn't mentioned in the PI sheet - please remove or inform participants in the PI sheet why this is being done, what it will be used for and how the data will be handled and stored.

Page 42, Highlight (Orange):
Content: "What is your gender?"
Comment: Please provide additional options for those who do not identify as male or female

Approval will be given on the understanding that:

- any adverse reactions/events which take place during the course of the project are reported to the Committee immediately by emailing ethicspr@ljmu.ac.uk;
- any unforeseen ethical issues arising during the course of the project will be reported to the Committee immediately emailing ethicspr@ljmu.ac.uk;
- the LJMU logo is used for all documentation relating to participant recruitment and participation eg poster, information sheets, consent forms, questionnaires. The LJMU logo can be accessed at http://www2.ljmu.ac.uk/corporatecommunications/60486.htm

Where any substantive amendments are proposed to the protocol or study procedures further ethical approval must be sought (https://www2.ljmu.ac.uk/RGSO/93205.htm)

Applicants should note that where relevant appropriate gatekeeper / management permission must be obtained prior to the study commencing at the study site concerned.

Please note that ethical approval is given for a period of five years from the date granted. An application for extension of approval must be submitted if the project continues after this date.

LIVERPOOL JOHN MOORES UNIVERSITY
Charlotte Mclean, BA (Hons), MSc
PR REC Manager
(Research Ethics and Governance)
Research and Innovation Services
Exchange Station, Tithebarn Street,
L2 2QP

PATIENT (18+) INFORMATION SHEET

1. Study Title

"Association between physical activity, sedentary behaviour and physiological outcome measures of cardiovascular and respiratory function in patients with Cystic Fibrosis."

2. Invitation paragraph

You are being invited to take part in a research study. Before you decide whether or not to be involved, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and/or your clinician/GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this information sheet.

3. What is the purpose of the study?

It is understood that the management of Cystic Fibrosis (CF) places a large treatment burden on individuals, including daily physiotherapy, nebulised and oral medication and increased nutritional requirements. In addition to this is it is also recommended that individuals with CF take part in regular physical activity and exercise to stay fit and healthy. We know that people with chronic chest diseases often have reduced fitness. Physical activity not only helps improve fitness and enhances quality of life, but it may also help CF patients to cope better with aspects of their disease. Despite this it has been reported that patients with CF are less active than their non-CF peers and little is known about sedentary behaviour (time spent sitting or lying down) in patients with CF.

This study will look at how physically active patients with CF are and how much time they spend being sedentary. We are interested in finding out if this is associated with quality of life and measures of respiratory and cardiovascular health.

4. Why have I been chosen?

We are interested in people with CF, aged 18+ years old, who are clinically stable.

5. Do I have to take part?

Taking part is entirely voluntary and it is up to you to decide whether or not you want to take part. If you do want to be involved, you will be given this information sheet to keep, and be asked to sign a consent form giving your permission. You are still free to withdraw from the study at any time and there is no need to give a reason. Any decision to withdraw at any time or a decision not to take part in the first place will not affect the standard clinical care you receive.

6. What will happen to me if I do want to take part?

The study will aim to minimise additional visits and it is expected that the study can be completed during your next routine clinic appointments. All participants will be asked to complete a number of tests, where possible a small group will also be asked to complete additional tests as outlined below.

Routine clinic

All participants

You will be given the opportunity to discuss any queries you may have, give your informed consent and be familiarised with the equipment we will use to measure physical activity.

*Baseline assessments: R*outine clinic measures will be taken including, height, weight, BMI and lung function.

Questionnaires: You will be given two questionnaires which can be completed during the clinic or taken home to complete and returned at a later date. The first will ask questions relating to quality of life, the second relating to your physical activity.

Physical activity: We are also interested in getting an idea of how active you usually are. To measure this you will be asked to wear two activity monitors for 7 days, whilst also completing a simple diary about what physical activities you have been doing between waking up and going to bed. The first is small device (like a watch) which you

will wear on your wrist. The second is a small device which will be secured to your thigh using an adhesive plaster, it would therefore be appreciated if you could dress appropriately for this (i.e. bring some shorts where possible). You will also be asked to keep a record of when you are wearing the monitors. You will be provided with a pre-paid, recorded delivery envelope to return the devices to us.

All testing will be completed during the routine clinic appointment. However, this appointment will be approximately 30 minutes longer than usual so please consider this.

Selected participants

Blood Vessel assessment

You may also be asked to complete an additional measure which is not required to participate in the research, however will be offered to as many participants as possible. If you wish to complete the additional measure, we will arrange to do this at a future clinic appointment. The additional measure includes an assessment of artery function.

You will be asked to arrive to clinic having fasted for 6 hours. You are encouraged to bring a small snack for eating straight after the testing. If you have any questions regarding this please do not hesitate to contact a member of the research team before your clinic appointment.

Artery Function: This non-invasive technique is widely used and validated within research to assess cardiovascular risk. This technique uses ultrasound, the same technology used to scan pregnant women. There are no known side effects associated with ultrasound. Using the ultrasound, we will take some more pictures of your brachial artery (in your upper arm) before and after a blood pressure cuff is inflated (blown up) around your forearm. We will use ultrasound to scan your artery for 1 minute before the blood pressure cuffs are inflated. The cuff can feel quite tight and reduces the amount of blood going through your artery. You may feel slightly uncomfortable with pins and needles. We will keep the cuff inflated for 5 minutes and continue scanning your artery. Once the cuff is deflated (let down) we will continue scanning your artery for a further 3 minutes. This part of the test will take 15 minutes. You can stop the test at any point and the pins and needles or slight numbness will quickly go away.

You can ask any questions to the research staff at any time during the session.

Participants who complete the artery assessment will be asked to move to a separate clinic room for the test, it is anticipated that your clinic appointment will be approximately 90 minutes longer than usual.

7. What else will I have to do?

If you do choose to take part, we would like you to attend your next clinic appointment and complete the measures as outlined above. Any specific questions regarding any physical activity you may be doing can be discussed with the research team on an individual basis. We ask that you bring appropriate clothing (e.g. shorts) which will make fitting the activity monitor to your thigh more convenient.

8. What are the possible risks of me taking part?

There are no known side effects to the tests we will use.

An assessment of your health will be made by the consultant running the clinic to ensure you are eligible to take part.

Measures will be taken to minimise the possible risk of cross-infection, all clinic appointments will operate in the same way including strict segregation. In addition, all equipment used for the study will be cleaned between patients and where applicable be for single patient use.

9. What are the potential benefits of me taking part?

This research is intended to further our understanding of physical activity and sedentary behaviour and the association with measures of respiratory and cardiovascular health in patients with CF. We hope that this information will help us to develop strategies to help patients with CF to benefit from physical activity.

Hopefully, you will also find involvement to be a positive and enjoyable experience. This will hopefully prove an interesting and constructive experience, particularly if you are interested and/or involved in physical activity.

10. What happens if I do not want to continue in the study?

You are free to withdraw from the study at any point without giving a reason. Dropping out of the study will not affect your clinical care in any way or your relationship with the clinical staff.

If you decide not to continue with the study then you will not be required to complete any additional tests, or attend any additional visits to the centre that are associated with the research. Results from any tests that you have previously completed will still be available to you.

11. What if something goes wrong?

In the unlikely event that something goes wrong and you are harmed during the study there are no special compensation arrangements above what you would usually be entitled to. If you are harmed and this is due to someone's negligence then you may have grounds for legal action for compensation against Liverpool Heart and Chest NHS Foundation Trust, but you may have to pay your own legal costs.

Should you need it, the normal NHS complaints procedure will still be available to you. Under the NHS constitution it is your right to complain, have your complaint investigated, and be given a full and prompt reply. Details can be obtained from the Liverpool Heart and Chest Patient Advice and Liaison Service (PALS), telephone: 0151 600 1257 or email: Lisa.Gurrell@lhch.nhs.uk. Alternatively, you can contact Dr Dave Harris, Research Governance Manager at Liverpool John Moores University, Tel: 0151 904 6236, Email: D.Harris@ljmu.ac.uk.

12. Will my involvement in this study be kept confidential?

We have a responsibility to inform you of how we will collect, store and use any of the information gathered about you during this study. The primary concern is that any information that we collect about you will be confidential. All information, such as your name, date of birth, contact details, details of health and test results will be transferred to a paper study file, which will be kept in a secure room in a locked filing cabinet. Members of the research team will be outside your direct standard care team and will have access to your medical data. However, your information will be kept anonymous by assigning you a unique study code and participant number. Personal information

stored electronically will be password protected. All the paper and computer files will be stored and archived, after this period paper files will be destroyed and computer files erased. Only researchers directly involved in the study will have access to your medical records.

13. What will happen to the results of the study?

Once the study is completed, which is targeted to be August 2019, the results will be analysed and interpreted and you will subsequently be sent a summary of our research findings. It is the intention to submit the results of the research to relevant journals for publication, and to inform our colleagues of the findings at scientific meetings. In publishing and talking about the study you will not be identifiable.

You will be given the opportunity to comment on the research protocol and testing procedure. This information will be collated and may inform future studies. You will also receive the results and conclusions from the research and are free to request information regarding your individual data.

14. Who is organising and funding the research?

This study is being conducted by members of staff at the Liverpool Heart and Chest Hospital in collaboration with Liverpool John Moores University. Funding for the study has been granted by Liverpool John Moores University.

15. Who has reviewed the study?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion.

16. What should I do if I would like to take part?

If you would like to take part in the study you must give your permission by completing a consent form. You should then return the forms to a member of the research team. This can be done at your next clinic appointment. You will complete the required tests at this appointment. One of the physical activity monitors will be fitted to your thigh, it would therefore be appreciated if you could dress appropriately for this (i.e. bring some shorts where possible).

17. What if I have a question?

If you have any questions please do not hesitate to get in touch with a member of the research team using the details provided below.

18. Contact for further information

If you need further information please contact the research team using the details provided. For more information regarding participation in research you can access the public information pack published by INVOLVE (a non-profit organization promoting public involvement in the NHS, public health and social care research). Visit their website www.involve.org.uk/ or obtain a paper copy by writing to: Involve, Royal London House, 22-25 Finsbury Square, London, EC2A 1DX. More specialised information regarding participation in clinical research is published by the UK Clinical Research Collaboration (UKCRC). For further information visit www.ukcrc.org or request a printed copy from: UKCRC, 20 Park Crescent, London, W1B 1AL.

The Research Team

Primary contact: Mr James Shelley

(Liverpool John Moores University)
Tel: 07870505039
E-mail: j.shelley@2016.ljmu.ac.uk

Dr Ellen Dawson
(Liverpool John Moores University)
Tel: 0151 904 6264
Email: E.Dawson@ljmu.ac.uk

Comments or complaints:

Dr Dave Harris
Research Governance Manager
Liverpool John Moores University
Tel: 0151 904 6236
Email: D.Harris@ljmu.ac.uk

Liverpool Heart and Chest Hospital NHS
NHS Foundation Trust

LIVERPOOL JOHN MOORES UNIVERSITY

Participant Consent Form (18+ years)

Title of study:	**Association between physical activity, sedentary behaviour and physiological outcome measures of cardiovascular and respiratory function in patients with Cystic Fibrosis.**
Name of Principal Investigator:	Mr James Shelley
Centre/Site number:	Liverpool John Moores University/ Liverpool Heart and Chest Hospital
Study number:	
Participant ID:	
REC approval number:	

Please **INITIAL** the boxes if you agree with each section:

1. I have read the information provided for the above study and have been given a copy to keep. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the research team, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. I understand that the information will be kept confidential. ☐
4. I understand that any personal information collected during the study will be anonymised and remain confidential ☐
5. I understand that my Doctor will be informed of my participation and also if any of the results of tests done as part of the research are important for my health. ☐
6. I know how to contact the research team if I need to. ☐

Please select one of the two options below to indicate which aspects of the study you wish to participate in.

7. I agree to participate in this study (Including vascular assessment and exercise test) ☐

Or

8. I agree to participate in this study (Excluding vascular assessment and exercise test) ☐

Name of Participant	Date	Signature

Name of Person taking consent	Date	Signature taking consent

When complete 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.

PARTICIPANT (18+) INFORMATION SHEET

1. Study Title

"Physical activity and vascular function in healthy adults."

2. Invitation paragraph

You are being invited to take part in a research study. Before you decide whether or not to be involved, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and/or your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this information sheet.

3. What is the purpose of the study?

Exercise is associated with reduce cardiovascular events and it is thought this may result from functional and structural changes in blood vessels in response to exercise. Despite this it is well recognised that a large number of the general population do not meet recommended guidelines for physical activity. High levels of sedentary behaviour (SB) (time spent lying/sitting down) is also an independent risk factor for cardiovascular disease, even among individuals achieving physical activity guidelines. Approximately 60% of adults' waking time is spent being sedentary, which is more than 8 hours a day. In order to assess physical activity and sedentary behaviour accurate assessment tools are required, which will allow us to explore the relationship between physical activity, sedentary behaviour and cardiovascular function.

This study will look at how physically active healthy adults are and how much time they spend being sedentary. We are interested in finding out if this is associated with measures of respiratory and cardiovascular health.

4. Why have I been chosen?

We are interested in healthy individuals aged 18+ years old.

5. Do I have to take part?

Taking part is entirely voluntary and it is up to you to decide whether or not you want to take part. If you do want to be involved, you will be given this information sheet to keep, and be asked to sign a consent form giving your permission. You are still free to withdraw from the study at any time and there is no need to give a reason.

6. What will happen to me if I do want to take part?

The study can be completed during a single visit to Liverpool John Moores University. You will be asked to complete a number of tests as outlined below;

You will be given the opportunity to discuss any queries you may have, give your informed consent and be familiarised with the equipment we will use to measure physical activity. Your eligibility to take part will be assessed using a health-screening questionnaire.

Baseline assessments: Routine anthropometric measures will be taken including, height, weight and BMI.

Questionnaires: You will be given three questionnaires which can be completed during the visit or taken home to complete and returned at a later date. The first will ask questions relating to your medical history, the second relating to quality of life, and the third relating to your physical activity. The questionnaires will take approximately 25-40 minutes to complete, in total.

Physical activity: We are also interested in getting an idea of how active you usually are. To measure this you will be asked to wear two activity monitors for 7 days, whilst also completing a simple diary about what physical activities you have been doing between waking up and going to bed. The first is small device (like a watch) which you will wear on your wrist. The second is a small device which will be secured to your thigh using an adhesive plaster, it would therefore be appreciated if you could dress appropriately for this (i.e. bring some shorts where possible). You will also be asked to keep a record of when you are wearing the monitors. You will be provided with a pre-paid, recorded delivery envelope to return the devices to us.

Artery Function; You will be asked to arrive to university having fasted for 6 hours and avoid vigorous activity for 12 hours. You are encouraged to bring a small snack for eating straight after the testing. If you have any questions regarding this please do not hesitate to contact a member of the research team before your appointment.

This non-invasive technique is widely used and validated within research to assess cardiovascular risk. This technique uses ultrasound, the same technology used to scan pregnant women. There are no known side effects associated with ultrasound. Using the ultrasound, we will take some more pictures of your brachial artery (in your upper arm) before and after a blood pressure cuff is inflated (blown up) around your forearm. We will use ultrasound to scan your artery for 1 minute before the blood pressure cuffs are inflated. The cuff can feel quite tight and reduces the amount of blood going through your artery. You may feel slightly uncomfortable with pins and needles. We will keep the cuff inflated for 5 minutes and continue scanning your artery. Once the cuff is deflated (let down) we will continue scanning your artery for a further 3 minutes. This part of the test will take 15 minutes. You can stop the test at any point and the pins and needles or slight numbness will quickly go away.

Lung function: This will be assess using spirometry. This technique requires you to blow into a mouthpiece, which then records the amount of air exhaled in a single breath during a maximal effort.

You can ask any questions to the research staff at any time during the session.

It is anticipated that the visit will last approximately 90 minutes.

7. What else will I have to do?

If you do choose to take part, we would like you to visit Liverpool John Moores University labs on Byrom Street and complete the measures as outlined above. Any specific questions regarding any physical activity you may be doing can be discussed with the research team on an individual basis. We ask that you bring appropriate clothing (e.g. shorts) which will make fitting the activity monitor to your thigh more convenient.

8. What are the possible risks of me taking part?

In rare cases, individuals may experience some symptoms associated with the tests. During the vascular assessment you may feel a loss of feeling, tightness, pins and needles and mild discomfort in your arm whilst the cuff is inflated. This is temporary and will ease when the cuff is released. Additionally, you may feel dizzy or faint when performing the assessment of lung function, though this is uncommon and you will be monitored by a researcher throughout. In some cases, it may be possible that the adhesive plasters used to secure the monitoring devices cause a reaction or irritation to the skin. If this does occur, you should remove the device and adhesive plater and seek advice from your GP.

An assessment of your health will be made to ensure you are eligible to take part.

9. What are the potential benefits of me taking part?

This research is intended to further our understanding of physical activity and sedentary behaviour and the association with measures of respiratory and cardiovascular health. This will hopefully prove an interesting and constructive experience, particularly if you are interested and/or involved in physical activity.

10. What happens if I do not want to continue in the study?

You are free to withdraw from the study at any point without giving a reason.

If you decide not to continue with the study then you will not be required to complete any additional tests, or attend any additional visits that are associated with the research. Results from any tests that you have previously completed will still be available to you.

11. What if something goes wrong?

If you have a concern about any aspect of this study, please contact the relevant investigator who will do their best to answer your query. The researcher should acknowledge your concern within 10 working days and give you an indication of how they intend to deal with it. If you wish to make a complaint, please contact the chair of the Liverpool John Moores University Research Ethics Committee (researchethics@ljmu.ac.uk) and your communication will be re-directed to an

independent person as appropriate. If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action.

12. What will happen to the data provided and how will my taking part in this project be kept confidential?

We have a responsibility to inform you of how we will collect, store and use any of the information gathered about you during this study. The primary concern is that any information that we collect about you will be confidential. All information, such as your name, date of birth, contact details, details of health and test results will be transferred to a paper study file, which will be kept in a secure room in a locked filing cabinet on LJMU premises.

If necessary, personal data will be stored confidentially for 5 years after the study has finished. Personal data will be accessible to the research team. Your information will be kept anonymous by assigning you a unique study code and participant number. The link from the code to your identity will be stored securely and separately from the coded data. Personal information stored electronically will be password protected. All the paper and computer files will be stored and archived, after this period paper files will be destroyed and computer files erased. You will not be identifiable in any ensuing reports or publications.

13. What will happen to the results of the study?

Once the study is completed, which is targeted to be August 2019, the results will be analysed and interpreted and you will subsequently be sent a summary of our research findings. It is the intention to submit the results of the research to relevant journals for publication, and to inform our colleagues of the findings at scientific meetings. In publishing and talking about the study you will not be identifiable. The data will also be used as part of a separate research project within the NHS (17/NW/0360).

You will be given the opportunity to comment on the research protocol and testing procedure. This information will be collated and may inform future studies. You will also receive the results and conclusions from the research and are free to request information regarding your individual data.

14. Who is organising and funding the research?

This study is being conducted by members of staff at Liverpool John Moores University. Funding for the study has been granted by Liverpool John Moores University.

15. Who has reviewed the study?

All research is looked at by an independent group of people called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by LJMU's research ethics committee.

16. What should I do if I would like to take part?

If you would like to take part in the study, have any questions or would like further information please contact the research team using the details provided. For more information regarding participation in research you can access the public information pack published by INVOLVE (a non-profit organization promoting public involvement in the NHS, public health and social care research). Visit their website www.involve.org.uk/ or obtain a paper copy by writing to: Involve, Royal London House, 22-25 Finsbury Square, London, EC2A 1DX.

17. Data Protection Notice

The data controller for this study will be Liverpool John Moores University (LJMU). The LJMU Data Protection Office provides oversight of LJMU activities involving the processing of personal data, and can be contacted at secretariat@ljmu.ac.uk. This means that we are responsible for looking after your information and using it properly. LJMU's Data Protection Officer can also be contacted at secretariat@ljmu.ac.uk. The University will process your personal data for the purpose of research. Research is a task that we perform in the public interest.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained.

You can find out more about how we use your information by contacting secretariat@ljmu.ac.uk.

If you are concerned about how your personal data is being processed, please contact LJMU in the first instance at secretariat@ljmu.ac.uk. If you remain unsatisfied, you may wish to contact the Information Commissioner's Office (ICO). Contact details, and details of data subject rights, are available on the ICO website at: https://ico.org.uk/for-organisations/data-protection-reform/overview-of-the-gdpr/individuals-rights/

The Research Team

Primary contact: Mr James Shelley

(Liverpool John Moores University)

Tel: 07870505039

E-mail: j.shelley@2016.ljmu.ac.uk

Dr Ellen Dawson

(Liverpool John Moores University)

Tel: 0151 904 6264

Email: E.Dawson@ljmu.ac.uk

Comments or complaints:

Dr Dave Harris

Research Governance Manager

Liverpool John Moores University

Tel: 0151 904 6236

Email: D.Harris@ljmu.ac.uk

Participant Consent Form (18+ years)

Title of study:	**Physical activity and vascular function in healthy adults**
Name of Principal Investigator:	Mr James Shelley
Centre/Site number:	Liverpool John Moores University/ Liverpool Heart and Chest Hospital
Study number:	
Participant ID:	HCCS_ _
REC approval number:	18-SPS-034

Please **INITIAL** the boxes if you agree with each section:

1. I have read the information provided for the above study and have been given a copy to keep. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that any personal information collected during the study will be anonymised and remain confidential ☐

4. I know how to contact the research team if I need to. ☐

5. I agree to participate in this study ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature taking consent

When complete 1 for participant; 1 for researcher site file.

Global Physical Activity Questionnaire (GPAQ)

WHO STEPwise approach to NCD risk factor surveillance

Surveillance and Population-Based Prevention
Prevention of Noncommunicable Diseases Department
World Health Organization
20 Avenue Appia, 1211 Geneva 27, Switzerland
For further information: www.who.int/chp/steps

GPAQ

Physical Activity

Next I am going to ask you about the time you spend doing different types of physical activity in a typical week. Please answer these questions even if you do not consider yourself to be a physically active person.

Think first about the time you spend doing work. Think of work as the things that you have to do such as paid or unpaid work, study/training, household chores, harvesting food/crops, fishing or hunting for food, seeking employment. *[Insert other examples if needed].* In answering the following questions 'vigorous-intensity activities' are activities that require hard physical effort and cause large increases in breathing or heart rate, 'moderate-intensity activities' are activities that require moderate physical effort and cause small increases in breathing or heart rate.

	Questions	Response	Code
Activity at work			
1	Does your work involve vigorous-intensity activity that causes large increases in breathing or heart rate like *[carrying or lifting heavy loads, digging or construction work*] for at least 10 minutes continuously? *[INSERT EXAMPLES] (USE SHOWCARD)*	Yes 1 No 2 *If No, go to P 4*	P1
2	In a typical week, on how many days do you do vigorous-intensity activities as part of your work?	Number of days ⌊__⌋	P2
3	How much time do you spend doing vigorous-intensity activities at work on a typical day?	Hours : minutes ⌊__⌋⌊__⌋ : ⌊__⌋⌊__⌋ hrs mins	P3 (a-b)
4	Does your work involve moderate-intensity activity that causes small increases in breathing or heart rate such as brisk walking *[or carrying light loads*] for at least 10 minutes continuously? *[INSERT EXAMPLES] (USE SHOWCARD)*	Yes 1 No 2 *If No, go to P 7*	P4
5	In a typical week, on how many days do you do moderate-intensity activities as part of your work?	Number of days ⌊__⌋	P5
6	How much time do you spend doing moderate-intensity activities at work on a typical day?	Hours : minutes ⌊__⌋⌊__⌋ : ⌊__⌋⌊__⌋ hrs mins	P6 (a-b)
Travel to and from places			
The next questions exclude the physical activities at work that you have already mentioned. Now I would like to ask you about the usual way you travel to and from places. For example to work, for shopping, to market, to place of worship. [insert other examples if needed]			
7	Do you walk or use a bicycle (*pedal cycle*) for at least 10 minutes continuously to get to and from places?	Yes 1 No 2 *If No, go to P 10*	P7
8	In a typical week, on how many days do you walk or bicycle for at least 10 minutes continuously to get to and from places?	Number of days ⌊__⌋	P8
9	How much time do you spend walking or bicycling for travel on a typical day?	Hours : minutes ⌊__⌋⌊__⌋ : ⌊__⌋⌊__⌋ hrs mins	P9 (a-b)
Recreational activities			
The next questions exclude the work and transport activities that you have already mentioned. Now I would like to ask you about sports, fitness and recreational activities (leisure), [insert relevant terms].			
10	Do you do any vigorous-intensity sports, fitness or recreational (*leisure*) activities that cause large increases in breathing or heart rate like [*running or football,]* for at least 10 minutes continuously? *[INSERT EXAMPLES] (USE SHOWCARD)*	Yes 1 No 2 *If No, go to P 13*	P10
11	In a typical week, on how many days do you do vigorous-intensity sports, fitness or recreational (*leisure*) activities?	Number of days ⌊__⌋	P11
12	How much time do you spend doing vigorous-intensity sports, fitness or recreational activities on a typical day?	Hours : minutes ⌊__⌋⌊__⌋ : ⌊__⌋⌊__⌋ hrs mins	P12 (a-b)

Continued on next page

Physical Activity (recreational activities) contd.			
Questions		**Response**	**Code**
13	Do you do any moderate-intensity sports, fitness or recreational *(leisure*) activities that causes a small increase in breathing or heart rate such as brisk walking,(*cycling, swimming, volleyball*)for at least 10 minutes continuously? *[INSERT EXAMPLES] (USE SHOWCARD)*	Yes 1 No 2 *If No, go to P16*	P13
14	In a typical week, on how many days do you do moderate-intensity sports, fitness or recreational (*leisure*) activities?	Number of days ⌊__⌋	P14
15	How much time do you spend doing moderate-intensity sports, fitness or recreational (*leisure*) activities on a typical day?	Hours : minutes ⌊__⌋⌊__⌋ : ⌊__⌋⌊__⌋ hrs mins	P15 (a-b)
Sedentary behaviour			
The following question is about sitting or reclining at work, at home, getting to and from places, or with friends including time spent [sitting at a desk, sitting with friends, travelling in car, bus, train, reading, playing cards or watching television], but do not include time spent sleeping. *[INSERT EXAMPLES] (USE SHOWCARD)*			
16	How much time do you usually spend sitting or reclining on a typical day?	Hours : minutes ⌊__⌋⌊__⌋ : ⌊__⌋⌊__⌋ hrs min s	P16 (a-b)

Mr James Shelley
PhD research student
Liverpool John Moores University
5 Primrose Hill
Liverpool
L3 2EX

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

05 March 2019

Dear Mr Shelley

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

Study title:	**Using formative research with patients with Cystic Fibrosis, their families and clinicians to develop an ecological approach to physical activity promotion.**
IRAS project ID:	**252398**
Protocol number:	**N/A**
REC reference:	**19/LO/0305**
Sponsor	**Liverpool Heart and Chest Hospital NHS Foundation Trust**

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

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

This is a single site study sponsored by the site. The sponsor R&D office will confirm to you when the study can start following issue of HRA and HCRW Approval.

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

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

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

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

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

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

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

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

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

The sponsor contact for this application is as follows:

Name: Dr Bashir Matata
Tel: 0151 600 1380
Email: DrBashir.Matata@lhch.nhs.uk

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

Your IRAS project ID is **252398**. Please quote this on all correspondence.

Yours sincerely

Kevin Ahmed
Assessor

Telephone: 0207 104 8171
Email: hra.approval@nhs.net

Copy to: *Dr Bashir Matata, Sponsor Contact, Liverpool Heart and Chest Hospital*

List of Documents

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

Document	*Version*	*Date*
Interview schedules or topic guides for participants [Clinician focus group schedule]	4	11 February 2019
Interview schedules or topic guides for participants [Individual patient interview schedule]	4	11 February 2019
Interview schedules or topic guides for participants [Patient focus group schedule]	4	11 February 2019
IRAS Application Form [IRAS_Form_29012019]		29 January 2019
Letter from sponsor [LHCH Approval Letter]		07 January 2019
Letters of invitation to participant [Invitation letter]	1	05 October 2018
Other [Risk Assessment]	1	14 January 2019
Other [Lone Working Policy]		
Participant consent form [Participant Consent Form (18+ years)]	1	05 October 2018
Participant consent form [Participant Consent Form (Family member 18+ years)]	1	05 October 2018
Participant consent form [Participant Assent Form (Family member 14-18 years)]	1	05 October 2018
Participant consent form [Participant Consent Form (Clinician 18+ years)]	1	05 October 2018
Participant information sheet (PIS) [PARTICIPANT (18+) INFORMATION SHEET]	3	14 January 2019
Participant information sheet (PIS) [PARTICIPANT (Family member 18+) INFORMATION SHEET]	3	14 January 2019
Participant information sheet (PIS) [PARTICIPANT (Family member 14-18) INFORMATION SHEET]	3	14 January 2019
Participant information sheet (PIS) [PARTICIPANT (Clinician 18+) INFORMATION SHEET]	3	14 January 2019
Referee's report or other scientific critique report [Feedback from scientific review]		14 December 2016
Research protocol or project proposal [Protocol]	2	05 October 2018
Response to Request for Further Information [Application clarification]		11 February 2019
Summary CV for Chief Investigator (CI) [CI CV]		14 January 2019
Summary CV for supervisor (student research) [Ellen Dawson CV]		
Summary CV for supervisor (student research) [Dr Zoe Knowles CV]		
Summary CV for supervisor (student research) [CV Dr Lynne Boddy]		
Summary CV for supervisor (student research) [Prof. Claire Hamilton Stewart CV]		
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Summary]	2	14 January 2019

Summary of assessment

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

Assessment criteria

Section	Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	No comments
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	This is a non-commercial single site study taking place in the NHS where that single NHS organisation is also the study sponsor. Therefore no study agreements are required.
4.2	Insurance/indemnity arrangements assessed	Yes	No comments
4.3	Financial arrangements assessed	Yes	No application for external funding has been made.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments

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

Participating NHS Organisations in England and Wales

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
If this study is subsequently extended to other NHS organisation(s) in England or Wales, an amendment should be submitted, with a Statement of Activities and Schedule of Events for the newly participating NHS organisation(s) in England or Wales. The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England and Wales in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England and Wales which are not provided in IRAS, the HRA or HCRW websites, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net or HCRW at Research-permissions@wales.nhs.uk. We will work with these organisations to achieve a consistent approach to information provision.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).
A Principal Investigator should be appointed at study sites GCP training is not a generic training expectation, in line with the HRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
As a non-commercial undertaken by local staff, it is unlikely that letters of access or honorary research contracts will be applicable, except where local network staff employed by another Trust (or University) are involved (and then it is likely that arrangements are already in place). Where arrangements are not already in place, network staff (or similar) undertaking any of the research activities listed in A18 or A19 of the IRAS form, would be expected to obtain a Letter of Access based on standard DBS checks and occupational health clearance would be appropriate.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

James Shelley
Physical Activity Exchange
Liverpool John Moores University
5 Primrose
Liverpool
L3 2EX

Tel: 07870505039
Date:

Dear_____

The Cystic Fibrosis team at the Liverpool Heart and Chest Hospital are currently undertaking some exciting research in collaboration with Liverpool John Moores University. We are currently looking for adults (18+ years) with Cystic Fibrosis who would be interested in taking part.

An information sheet has been included for you to read, to help you to decide whether you would like to take part.

If you would like to take part, or discuss things in more detail before deciding, one of our researchers will be present on the day of your next clinic appointment. We can then answer any questions you may have and fill out the necessary paperwork if you choose to help us with the study. Participation in the study will require two separate sessions, which will each last approximately 1 hour each.

Your participation in this research project would be much appreciated. However, you are by no means obliged to take part in this study if you do not wish to. Furthermore, your medical care and individual rights are not affected by a decision to not participate, or subsequently withdraw from the study.

Kind regards,

Mr James Shelley
Chief investigator
(Liverpool John Moores University)

PARTICIPANT (18+) INFORMATION SHEET

1. Study Title

Using formative research with patients with Cystic Fibrosis, their families and clinicians to develop an ecological approach to physical activity promotion.

2. Invitation paragraph

You are being invited to take part in a research study. Before you decide whether or not to be involved, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and/or your clinician/GP if you wish. Ask a member of the research team if there is anything that is not clear or if you would like more information. Contact details are provided at the end of this document. Take time to decide whether or not you wish to take part.

Thank you for reading this information sheet.

3. What is the purpose of the study?

Physical activity (PA) is recommended as part of routine Cystic Fibrosis (CF) care, despite this there are few examples of interventions designed to promote PA in this population. To date, research has investigated the delivery of exercise training interventions, which give little or no attention to the role of behaviour change theory or what factors influence long-term maintenance of PA. Evidence which supports a positive impact of exercise training interventions on clinical outcomes currently remains unclear. It has previously been proposed that increasing levels of habitual PA may be more feasible and result in greater compliance for patients than 'typical' exercise training inventions. There is limited research exploring perceptions of PA, or thoughts, opinions and beliefs, among adults with CF. Involving participants and their families is important to intervention design, such as PA promotion

The aim of the research is to develop an intervention to promote physical activity among adults with CF. In doing so we wish to involve patients with CF, their families and clinicians throughout all aspects of this process.

4. Why have I been chosen?

We are interested in people with CF, aged 18+ years old**.**

5. Do I have to take part?

Taking part is entirely voluntary and it is up to you to decide whether or not you want to take part. If you do want to be involved, you will be given this information sheet to keep, and be asked to sign a consent form giving your permission. You are still free to withdraw from the study at any time and there is no need to give a reason. Any decision to withdraw at any time, even after you have taken part or a decision not to take part in the first place will not affect the standard clinical care you receive.

6. What will happen to me if I do want to take part?

The study will be completed in two phases, the first will involve a one-to-one interview with a member of the research team. For the second phase, we would also like to invite members of your family to join a meeting with a member of the research team as outlined below;

Phase 1

If you wish to take part you will be contacted via telephone, given the opportunity to discuss any queries you may have and be asked to return a signed consent form (using a the prepaid envelope provided).

You will then be invited to take part in a one-to-one interview with a member of the research team. The purpose of this will be to discuss your perceptions (thoughts, opinions, beliefs) of physical activity. The interview will be scheduled for a time and place convenient for you and can be done via telephone. If you prefer for the interview to take place face-to-face, this can be arranged and will take place at LHCH, or at LJMU. Interviews will be audio recorded using a Dictaphone or by recording a telephone call so that data can be analysed at a later date.

It is anticipated that the interview will last approximately 45-60 minutes.

Phase 2

Findings from phase 1 will inform what is discussed in phase 2. Phase 2 will therefore take place up to 3 months after the phase 1 interview. Phase 2 will include a focus group meeting which will involve you and a member of the research team, additionally, we would like to invite members of your family to be involved. To do so we have prepared a separate information sheet for them to read and will ask them to provide consent to participate. At the end of phase 1 we will ask you to indicate if members of your family would like to participate in phase 2, if so we will provide you with the relevant information. If they do not wish to participate you will still be able to take part in phase 2 and will be asked to take part in a follow up interview instead. Family members may include members of you household or relatives such as partners, parents/carers, siblings or children (+14 years). Where children are included parental consent and child assent will be required.

In order to provide a convenient and comfortable setting for the focus group meeting it can take place in your home, if desired. Alternatively a quiet, private space at LHCH or LJMU can be used. The purpose of the meeting will be to discuss the design and implementation of an intervention to promote physical activity among individuals with CF.

The meeting will be audio recorded using a Dictaphone and transcribed for further data analysis. We may also maintain contact following the focus group to provide information or to clarify discussion points, this will be done via email.

It is anticipated that the focus group meeting will last up to 1 hour.

7. What else will I have to do?

If you do choose to take part, you will not be asked to do anything else, other than attending the interview and focus group as outlined above. Any specific questions regarding any physical activity you may be doing can be discussed with the research team on an individual basis.

8. What are the possible risks of me taking part?

There are no anticipated risks associated with participating in the research. It is not anticipated that any of the topics discussed during the interview or focus group will be of a sensitive nature or cause any distress. Measures will be taken to minimise the possible risk of cross-infection, all clinic appointments will operate in the same way including strict segregation.

9. What are the potential benefits of me taking part?

This research is intended to further understanding of physical activity and sedentary behaviour in patients with CF. Additionally, we hope that by involving patients and their families in the development process we can develop an intervention to help patients with CF to benefit from physical activity.

Hopefully, you will also find involvement to be a positive and enjoyable experience.

10. What happens if I do not want to continue in the study?

You are free to withdraw from the study at any point without giving a reason. Dropping out of the study will not affect your clinical care in any way or your relationship with the clinical staff.

11. What if something goes wrong?

In the unlikely event that something goes wrong and you are harmed during the study there are no special compensation arrangements above what you would usually be entitled to. If you are harmed and this is due to someone's negligence then you may have grounds for legal action for compensation against Liverpool Heart and Chest NHS Foundation Trust, but you may have to pay your own legal costs.

If you have a concern about any aspect of this study, please contact the relevant investigator who will do their best to answer your query. The researcher should acknowledge your concern within 10 working days and give you an indication of how they intend to deal with it. Should you need it, the normal NHS complaints procedure will still be available to you. Under the NHS constitution it is your right to complain, have your complaint investigated, and be given a full and prompt reply. Details can be

obtained from the Liverpool Heart and Chest Patient & Family Support Team, telephone: 0151 600 1517. Alternatively, you can contact the chair of the Liverpool John Moores University Research Ethics Committee, Email: researchethics@ljmu.ac.uk.

12. What will happen to the data provided and how will my taking part in this project be kept confidential?

We have a responsibility to inform you of how we will collect, store and use any of the information gathered about you during this study. To reassure you any information that we collect about you will be confidential. All information, such as your name, date of birth, contact details, details of health and test results will be transferred to a paper study file, which will be kept in a secure room in a locked filing cabinet on LJMU premises.

If necessary, personal data will be stored confidentially for 5 years after the study has finished. Personal data will be accessible to the research team. Your information will be kept anonymous by assigning you a unique study code and participant number. The link from the code to your identity will be stored securely and separately from the coded data. Personal information stored electronically will be password protected. Audio recordings will be transferred to a secure drive on an LJMU computer and will then be permanently deleted from the recording device. All the paper and computer files will be stored and archived, after this period paper files will be destroyed and computer files erased. You will not be identifiable in any ensuing reports or publications. Only researchers directly involved in the study will have access to your medical records.

13. What will happen to the results of the study?

Once the study is completed, which is targeted to be October 2019, the results will be analysed and interpreted and you will be sent a summary of our research findings. In publishing and talking about the study you will not be identifiable, the findings will be presented for the group as a whole. It is the intention to submit the results of the research to relevant journals for publication, and to inform our colleagues of the findings at scientific meetings.

You will be given the opportunity to comment on the research protocol and procedures. This information will be collated and may inform future studies. You will also receive the results and conclusions from the research and are free to request information regarding your individual data.

14. Who is organising and funding the research?

This study is being conducted by members of staff at the Liverpool Heart and Chest Hospital in collaboration with Liverpool John Moores University. The research is being conducted as part of a PhD research project, funded by Liverpool John Moores University.

15. Who has reviewed the study?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion. This study has also been reviewed and given favourable opinion by LJMU's research ethics committee.

16. What should I do if I would like to take part?

If you would like to take part in the study you must give your permission by completing a consent form. You should then return the forms to a member of the research team. This can be done by returning a signed consent form using the prepaid envelope provided. If you have any questions or would like further information please contact the research team using the details provided. For more information regarding participation in research you can access the public information pack published by INVOLVE (a non-profit organization promoting public involvement in the NHS, public health and social care research). Visit their website www.involve.org.uk/ or obtain a paper copy by writing to: Involve, Royal London House, 22-25 Finsbury Square, London, EC2A 1DX.

17. Data Protection Notice

The data controller for this study will be Liverpool John Moores University (LJMU). The LJMU Data Protection Office provides oversight of LJMU activities involving the processing of personal data, and can be contacted at secretariat@ljmu.ac.uk. This

means that we are responsible for looking after your information and using it properly. LJMU's Data Protection Officer can also be contacted at secretariat@ljmu.ac.uk. The University will process your personal data for the purpose of research. Research is a task that we perform in the public interest.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained.

You can find out more about how we use your information by contacting secretariat@ljmu.ac.uk.

If you are concerned about how your personal data is being processed, please contact LJMU in the first instance at secretariat@ljmu.ac.uk. If you remain unsatisfied, you may wish to contact the Information Commissioner's Office (ICO). Contact details, and details of data subject rights, are available on the ICO website at: https://ico.org.uk/for-organisations/data-protection-reform/overview-of-the-gdpr/individuals-rights/

The Research Team

Primary contact: Mr James Shelley

(Liverpool John Moores University)
Tel: 07870505039
E-mail: j.shelley@2016.ljmu.ac.uk

Research supervisor: Dr Ellen Dawson

(Liverpool John Moores University)
Tel: 0151 904 6264
Email: E.Dawson@ljmu.ac.uk

Comments or complaints:

Dr Dave Harris

Research Governance Manager
Liverpool John Moores University
Tel: 0151 904 6236
Email: researchethics@ljmu.ac.uk

PARTICIPANT (Family member 14-18) INFORMATION SHEET

1. Study Title

Using formative research with patients with Cystic Fibrosis, their families and clinicians to develop an ecological approach to physical activity promotion.

2. Invitation paragraph

You are being invited to take part in a research study. Before you decide whether or not to be involved, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask a member of the research team if there is anything that is not clear or if you would like more information. Contact details are provided at the end of this document. Take time to decide whether or not you wish to take part.

Thank you for reading this information sheet.

3. What is the purpose of the study?

Being physically active is good for people with Cystic Fibrosis (CF), but the best way to encourage people to be active is unclear. We would like to speak to people with CF and members of their family, to understand what people with CF think about physical activity (PA) and try to help them be physically active.

4. Why have I been chosen?

A person with CF is already taking part and has told us that you are a member of their household/family, so we would also like to ask you to take part.

5. Do I have to take part?

Taking part is voluntary and it is up to you to decide whether or not you want to take part. If you do want to be involved, you will be given this information sheet to keep, and be asked to sign a consent form giving your permission. Your parents/guardians will also be asked to sign a consent form on your behalf. You are still free to withdraw from the study at any time, even after you have agreed to take part, and there is no need to give a reason.

6. What will happen to me if I do want to take part?

You will be invited to a focus group, which is a meeting to discuss how to create a programme to increase physical activity for individuals with CF. The focus group meeting can take place in your home or in a quiet, private space at Liverpool Heart and Chest Hospital (LHCH) or Liverpool John Moores University (LJMU). The meeting will include you, members of your family if they too have given consent and members of the research team (3-8 people).

You will be given the chance to ask any questions you may have before signing the consent form and also ahead of the focus group itself.

The meeting will be audio recorded using a Dictaphone and transcribed (written word for word) for data analysis.

It is anticipated that the focus group meeting will last up to 1 hour.

7. What else will I have to do?

If you do choose to take part, you will not be asked to do anything else, other than attending the focus group as outlined above.

8. What are the possible risks of me taking part?

There are no anticipated risks associated with participating the research.

9. What are the potential benefits of me taking part?

Taking part will help researchers to understand more about physical activity. We hope you enjoy taking part and find the process interesting but there will be no direct benefits to you.

10. What happens if I do not want to continue in the study?

You are free to withdraw from the study at any point even after you have taken part in a focus group without giving a reason.

11. What if something goes wrong?

If you have concerns or wish to make a complaint then your parent/guardian will be able to help you do this or do this on your behalf. We have supplied them with the relevant information to do so.

12. What will happen to the data provided and how will my taking part in this project be kept confidential?

All information, such as your name, date of birth and contact details will be kept in a paper study file, which will be kept in a secure room in a locked filing cabinet at LJMU.

You will be given a unique study code and participant number so that you cannot be identified. The link from the code to your identity will be stored securely and separately from the coded data. You will not be identifiable when the study is reported.

13. What will happen to the results of the study?

Once the study is completed, which is targeted to be October 2019, your parents/guardians will be sent a summary of the research findings. Your personal details will not be used in this report and you will not be identifiable, the summary will be based on the group data.

14. Who is organising and funding the research?

This study is being conducted by members of staff at the Liverpool Heart and Chest Hospital in collaboration with Liverpool John Moores University. The research is being conducted as part of a PhD research project, funded by Liverpool John Moores University.

15. Who has reviewed the study?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee to protect patient safety, rights, wellbeing and dignity. This study has been reviewed and approved.

16. What should I do if I would like to take part?

If you would like to take part in the study you must complete an assent form, your parents/careers will also complete a consent form on your behalf.

17. Data Protection Notice

Information has been provided to your parents/carer outlining that the data controller for this study will be Liverpool John Moores University (LJMU). The LJMU Data Protection Office provides oversight of LJMU activities involving the processing of personal data, and can be contacted at secretariat@ljmu.ac.uk. This means that we are responsible for looking after your information and using it properly. LJMU's Data

Protection Officer can also be contacted at secretariat@ljmu.ac.uk. The University will process your personal data for the purpose of research. Research is a task that we perform in the public interest.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. You can find out more about how we use your information by contacting secretariat@ljmu.ac.uk.

If you are concerned about how your personal data is being processed, please contact LJMU in the first instance at secretariat@ljmu.ac.uk. If you remain unsatisfied, you may wish to contact the Information Commissioner's Office (ICO). Contact details, and details of data subject rights, are available on the ICO website at: https://ico.org.uk/for-organisations/data-protection-reform/overview-of-the-gdpr/individuals-rights/

The Research Team

Primary contact: Mr James Shelley
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Tel: 07870505039
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Research supervisor: Dr Ellen Dawson
(Liverpool John Moores University)
Tel: 0151 904 6264
Email: E.Dawson@ljmu.ac.uk

Comments or complaints:

Dr Dave Harris
Research Governance Manager
(Liverpool John Moores University)
Tel: 0151 904 6236
Email: researchethics@ljmu.ac.uk

PARTICIPANT (Clinician 18+) INFORMATION SHEET

1. Study Title

Using formative research with patients with Cystic Fibrosis, their families and clinicians to develop an ecological approach to physical activity promotion.

2. Invitation paragraph

You are being invited to take part in a research study. Before you decide whether or not to be involved, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask a member of the research team if there is anything that is not clear or if you would like more information. Contact details are provided at the end of this document. Take time to decide whether or not you wish to take part.

Thank you for reading this information sheet.

3. What is the purpose of the study?

Physical activity (PA) is recommended as part of routine Cystic Fibrosis (CF) care, despite this there are few examples of interventions designed to promote PA in this population. To date, research has investigated the delivery of exercise training interventions, which give little or no attention to the role of behaviour change theory or what factors influence long-term maintenance of PA. Evidence which supports a positive impact of exercise training interventions on clinical outcomes currently remains unclear. It has previously been proposed that increasing levels of habitual PA may be more feasible and result in greater compliance for patients than 'typical' exercise training inventions. There is limited research exploring perceptions of PA, or thoughts, opinions and beliefs, among adults with CF. Involving participants and their families is important to intervention design, such as PA promotion

The aim of the research is to develop an intervention to promote physical activity among adults with CF. In doing so we wish to involve patients with CF, their families and clinicians throughout all aspects of this process.

4. Why have I been chosen?

We are interested in individuals proving specialist care for patients with Cystic Fibrosis.

5. Do I have to take part?

Taking part is entirely voluntary and it is up to you to decide whether or not you want to take part. If you do want to be involved, you will be given this information sheet to keep, and be asked to sign a consent form giving your permission. You are still free to withdraw from the study at any time, even after you have taken part and there is no need to give a reason.

6. What will happen to me if I do want to take part?

The study will be completed in two phases, the first phase will involve one-to-one interviews between patients and a member of the research team. This will inform the second phase which you will be asked to participate in.

If you wish to participate you will be given the opportunity to discuss any queries you may have and asked to give your informed consent.

The focus group meeting will then be arranged for a time and place convenient to you and members of the CF multi-disciplinary team (MDT). This will be a quiet, private space at LHCH or LJMU. The meeting will include members of the research team and members of the CF MDT (3-8 individuals). Ideally each discipline within the CF MDT will be represented at the meeting including; physiotherapist, physiologist, dietitian, doctor, nurse, psychologist. The aim of the meeting will be to discuss the development and implementation of an intervention to promote physical activity in patients with CF and will be informed by findings from study 1.

The meeting will be audio recorded using a Dictaphone and transcribed for further data analysis. We may also maintain contact following the focus group to provide information or to clarify discussion points, this will be facilitated via email.

It is anticipated that the focus group meeting will last up to 1 hour.

7. What else will I have to do?

If you do choose to take part, you will not be asked to do anything else, other than attending the focus group as outlined above.

8. What are the possible risks of me taking part?

There are no anticipated risks associated with participating in the research. It is not anticipated that any of the topics discussed during the focus group will be of a sensitive nature or cause any distress.

9. What are the potential benefits of me taking part?

This research is intended to further understanding of physical activity and sedentary behaviour in patients with CF. Additionally, we hope that by involving patients, their families and clinicians in the development process we can develop an intervention to help patients with CF to benefit from physical activity.

Hopefully, you will also find involvement to be a positive and enjoyable experience.

10. What happens if I do not want to continue in the study?

You are free to withdraw from the study at any point without giving a reason.

If you decide not to continue with the study then you will not be required to complete any additional tests, or attend any additional visits that are associated with the research. Any data from your involvement to that point will still be available to you.

11. What if something goes wrong?

In the unlikely event that something goes wrong and you are harmed during the study there are no special compensation arrangements above what you would usually be entitled to. If you are harmed and this is due to someone's negligence then you may have grounds for legal action for compensation against Liverpool Heart and Chest NHS Foundation Trust, but you may have to pay your own legal costs.

If you have a concern about any aspect of this study, please contact the relevant investigator who will do their best to answer your query. The researcher should acknowledge your concern within 10 working days and give you an indication of how

they intend to deal with it. Should you need it, the normal NHS complaints procedure will still be available to you. Under the NHS constitution it is your right to complain, have your complaint investigated, and be given a full and prompt reply. Details can be obtained from the Liverpool Heart and Chest Patient & Family Support Team, telephone: 0151 600 1517. Alternatively, you can contact the chair of the Liverpool John Moores University Research Ethics Committee, Email: researchethics@ljmu.ac.uk.

12. What will happen to the data provided and how will my taking part in this project be kept confidential?

We have a responsibility to inform you of how we will collect, store and use any of the information gathered about you during this study. To reassure you any information that we collect about you will be confidential. All information, such as your name, date of birth, contact details, details of health and test results will be transferred to a paper study file, which will be kept in a secure room in a locked filing cabinet on LJMU premises.

If necessary, personal data will be stored confidentially for 5 years after the study has finished. Personal data will be accessible to the research team. Your information will be kept anonymous by assigning you a unique study code and participant number. The link from the code to your identity will be stored securely and separately from the coded data. Personal information stored electronically will be password protected. Audio recordings will be transferred to a secure drive on an LJMU computer and will then be permanently deleted from the recording device. All the paper and computer files will be stored and archived, after this period paper files will be destroyed and computer files erased. You will not be identifiable in any ensuing reports or publications.

13. What will happen to the results of the study?

Once the study is completed, which is targeted to be October 2019, the results will be analysed and interpreted and you will subsequently be sent a summary of our research findings. It is the intention to submit the results of the research to relevant journals for

publication, and to inform our colleagues of the findings at scientific meetings. In publishing and talking about the study you will not be identifiable.

You will be given the opportunity to comment on the research protocol and testing procedure. This information will be collated and may inform future studies. You will also receive the results and conclusions from the research and are free to request information regarding your individual data.

14. Who is organising and funding the research?

This study is being conducted by members of staff at the Liverpool Heart and Chest Hospital in collaboration with Liverpool John Moores University. The research is being conducted as part of a PhD research project, funded by Liverpool John Moores University.

15. Who has reviewed the study?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion. This study has also been reviewed and given favourable opinion by LJMU's research ethics committee.

16. What should I do if I would like to take part?

If you would like to take part in the study you must give your permission by completing a consent form. You should then return the forms to a member of the research team. This can be done prior to the focus group meeting. If you have any questions or would like further information please contact the research team using the details provided. For more information regarding participation in research you can access the public information pack published by INVOLVE (a non-profit organization promoting public involvement in the NHS, public health and social care research). Visit their website www.involve.org.uk/ or obtain a paper copy by writing to: Involve, Royal London House, 22-25 Finsbury Square, London, EC2A 1DX.

17. Data Protection Notice

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Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. You can find out more about how we use your information by contacting secretariat@ljmu.ac.uk.

If you are concerned about how your personal data is being processed, please contact LJMU in the first instance at secretariat@ljmu.ac.uk. If you remain unsatisfied, you may wish to contact the Information Commissioner's Office (ICO). Contact details, and details of data subject rights, are available on the ICO website at: https://ico.org.uk/for-organisations/data-protection-reform/overview-of-the-gdpr/individuals-rights/

The Research Team

Primary contact: Mr James Shelley

(Liverpool John Moores University)
Tel: 07870505039
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Research supervisor: Dr Ellen Dawson

(Liverpool John Moores University)
Tel: 0151 904 6264
Email: E.Dawson@ljmu.ac.uk

Comments or complaints:

Dr Dave Harris

Research Governance Manager
Liverpool John Moores University
Tel: 0151 904 6236
Email: researchethics@ljmu.ac.uk

Liverpool Heart and Chest Hospital NHS
NHS Foundation Trust

LIVERPOOL JOHN MOORES UNIVERSITY

Participant Consent Form (18+ years)

Title of study:	Using formative research with patients with Cystic Fibrosis, their families and clinicians to develop an ecological approach to physical activity promotion.
Name of Principal Investigator:	Mr James Shelley
Centre/Site number:	Liverpool John Moores University/ Liverpool Heart and Chest Hospital
Study number:	252398
Participant ID:	CFCS_ _
REC approval number:	19/LO/0305

Please **INITIAL** the boxes if you agree with each section:

1. I have read the information provided for the above study and have been given a copy to keep. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the research team, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. I understand that the information will be kept confidential. ☐
4. I understand that any personal information collected during the study will be anonymised and remain confidential. ☐
5. I know how to contact the research team if I need to. ☐
6. I understand that interviews and focus groups will be audio recorded and I am happy to proceed. ☐
7. I agree to participate in this study (Both phase 1 & 2 as outlined in the information sheet provided) ☐
8. I agree to pass information on to my family regarding their potential involvement in phase 2. ☐

Name of Participant	Date	Signature

Name of Person taking consent	Date	Signature taking consent

When complete 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.

Liverpool Heart and Chest Hospital NHS
NHS Foundation Trust

LIVERPOOL JOHN MOORES UNIVERSITY

Participant Consent Form (Family member 18+ years)

Title of study:	Using formative research with patients with Cystic Fibrosis, their families and clinicians to develop an ecological approach to physical activity promotion.
Name of Principal Investigator:	Mr James Shelley
Centre/Site number:	Liverpool John Moores University/ Liverpool Heart and Chest Hospital
Study number:	252398
Participant ID:	
REC approval number:	19/LO/0305

Please **INITIAL** the boxes if you agree with each section:

1. I have read the information provided for the above study and have been given a copy to keep. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason. ☐
3. I understand that data collected during the study may be looked at by individuals from the research team, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I understand that the information will be kept confidential. ☐
4. I understand that any personal information collected during the study will be anonymised and remain confidential. ☐
5. I know how to contact the research team if I need to. ☐
6. I understand that focus groups will be audio recorded and I am happy to proceed. ☐
7. I agree to participate in this study ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature taking consent

When complete 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.

Liverpool Heart and Chest Hospital NHS
NHS Foundation Trust

LIVERPOOL JOHN MOORES UNIVERSITY

Participant Consent Form (Clinician 18+ years)

Title of study:	Using formative research with patients with Cystic Fibrosis, their families and clinicians to develop an ecological approach to physical activity promotion.
Name of Principal Investigator:	Mr James Shelley
Centre/Site number:	Liverpool John Moores University/ Liverpool Heart and Chest Hospital
Study number:	252398
Participant ID:	
REC approval number:	19/LO/0305

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5. I know how to contact the research team if I need to. ☐
6. I understand that focus groups will be audio recorded and I am happy to proceed. ☐
7. I agree to participate in this study ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature taking consent

When complete 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.

Individual participant interview schedule

Date: DD/MMM/YYYY **Location:** **Participant ID: CFCS ….**

Introduction

Hi, my name is [*researchers' name*]. I'm a researcher at Liverpool John Moores University and I am currently working with the Cystic Fibrosis (CF) team at Liverpool Heart and Chest Hospital to try and understand more about your experiences of living with CF and your thoughts and opinions about physical activity more generally. I'm here to get **your** perspective on these things as an individual with CF. There's no right or wrong answers.

Please try and give as much information as possible, using your own words and give examples where you would like to offer these. The interview will take around 45-60 minutes, which will include 13 questions relating to your general health and physical activity, please let me know if you would like to take a break at any point. I'd also like you to know that this interview will be audio recorded and transcribed – which means writing out our conversation like a script, so I can refer back to it. Additionally, I may make some notes as we are talking so that I can refer back to some of the points discussed. The things you say will remain confidential and your name or other details which may be used to identify you will not be reported. This research has been reviewed and given approval by an independent group of people known as a research ethics committee *[IRAS ID 252398]*.

Do you have any questions before we start?

Theme	Main Question	Sub-question(s)	Prompts/probes
[Transition statement] I'd like to start by finding out a little bit more about you.			
General health	1. To begin with could you tell me a bit about yourself?		
General health	2. Can you tell me about your experiences of living with CF?	How do you think you can best manage your health?	Thoughts/feelings Impact on self/ family
[Transition statement] It's really interesting to learn more about you and your health. I'd now like to find out a little bit more about your thoughts about physical activity.			
Physical activity			
General	3. What does the term physical activity mean to you?		What does the term physical mean to you? What does the term activity mean to you?
[Provide definition] - Physical activity is defined as any activity that increases energy expenditure and may include sport, work, household activities and transport such as walking or cycling.			
	4. Can you describe what your current physical activity behaviour is like?		Types of PA
	5. Can you describe any challenges to being as active as you'd like?		Thoughts/feelings
[Transition statement] Thank you, I'd now like to focus on factors that may lead you to be more or less active.			
Predisposing	6. What are your personal attitudes towards having a physically active lifestyle? Is it or why is it important to be physically active?	Do you enjoy being physically active?	Thoughts /feelings

	7. What would you like to do to be more physically active?		Motivations to engage with PA Goals relating to PA Daily lifestyle activity
Reinforcing	8. Who, if anyone, do you engage in physical activity with?	Can you describe any physical activities you do as a family? How do they influence you?	Types of PA Positively/negatively
	9. How, if at all, do you feel that the CF team influence your physical activity? In what ways do they influence your physical activity?		Positively/negatively
Enabling	10. How would you describe your past experiences with physical activity to someone else?	How has PA changed for you over the years?	
	11. How if at all, does your neighbourhood (the area you live and your local community) influence your physical activity? Does it make being active easy? Does it make being active hard?	Does it make being active easy? Does it make being active hard?	
	12. Please could you tell me how you feel about your ability to take part in physical activity?		*[reference to activities discussed in Q4]* Provision of information about CF and physical activity Satisfaction with information
	13. Finally, one of the reasons for my research is to understand how to increase physical activity amongst individuals with CF. So, do you have any ideas about what would be helpful to support physical activity engagement in individuals with CF?		Types of support Anything that would/wouldn't work Why? How could it work? What would it look like

**Prompts/Probes are there to be used as a guide for the interviewer. They are key words/phases to help the researcher ask questions and elicit responses from the participant. Prompting questions will be used in a conversational manner and only when deemed appropriate.*

Transition – It has been really useful finding out more about you. Let me briefly summarise the information we have discussed.

Closing

[Provide a summary of discussion]. I appreciate the time you took for this interview. Is there anything else you think would be helpful for me to know?

I should have all the information I need, thanks again. If you have any further questions or concerns you can contact me on; 07870505039 or the LJMU research governance officer at researchethics@ljmu.ac.uk.

Patient focus group schedule

Date: DD/MM/YYYY

Location:

Participants:

Hi, my name is [*researchers' name*]. I'm a researcher at Liverpool John Moores University and I am currently working with the Cystic Fibrosis (CF) team at Liverpool Heart and Chest Hospital to involve patients with CF, their families and clinicians in a process to develop an intervention to promote physical activity in adults with CF. The reason we're here today is to discuss the perceived barriers, facilitators and opportunities for physical activity participation and how this information can inform the development and delivery of a PA intervention for individuals with Cystic Fibrosis.

This research has been reviewed and given approval by an independent group of people known as a research ethics committee *[REC and reference number]*. I'd also like you to know that this meeting will be audio recorded and transcribed – which means writing out our conversation like a script. The recording and transcript will allow me to revisit our discussion for further analysis. Additionally, I may make some notes as we are talking so that I can refer back to some of the points discussed. The identities of all participants will not be included in this transcript or any other reports.

The goal of a focus group is to stimulate discussion to find out opinions and attitudes about a topic of interest, in this case physical activity in patients with CF. To allow the focus group to cover the pre-determined topics and flow smoothly, I'd like to go over some principles of focus groups.

1. This is a confidential discussion in that I will not report your name or what you have said. I would also like to request that this discussion remains in this room and is not discussed outside of the focus group.
2. Names of participants in any of the interviews will not even be included in the final report about this meeting.
3. I would like to stress confidentiality as I would like an open discussion. I want you to feel free to comment without concern that your comments will be repeated later and possibly taken out of context.
4. There are no "wrong answers", just different opinions and views.
5. Let me know if you need a break.

The focus group will take around 45-60 minutes, which will include questions in four separate phases.

Does anyone have any questions before we start?

Diagnostic phase	Objective	Themes	Questions
[Transition statement] I'd like to start by asking some questions to try and understand more about individuals with CF and present some of the themes (determinants of PA) identified during the phase 1 interviews.			
Stage 1: Social diagnosis	Ask and answer key questions related to the health issue	*Stage 1 will be informed by responses given during individual patient interviews and the themes subsequently identified.*	
		What is the health problem? (Associated with inactivity in CF?) Who is the priority population? (How is this defined, what characteristics do they share?) What are the important behaviours for inactivity? How do these differ between groups? Describing the context of an intervention (population, setting and community).	How if at all, does CF impact quality of life in patients with CF? How if at all, does CF impact physical activity in patients with CF? Who is the priority population? How is this population defined and what characteristics do the share? Who do you think would be responsible for delivering an intervention designed to increase physical activity in patients with CF?

<table>
<tr><td colspan="4">[Transition statement] Thank you for sharing your thoughts with me. I'd now like to move on to some questions relating to creating measurable behavioural outcomes for a potential intervention.
[Present logic model devised based on findings from phase 1 – displaying what change is needed to prevent, manage, or reduce identified health problems associated with inactivity. Outlining the proposed mechanisms of change, the determinants expected to influence and the behavioural and environmental outcomes that will address the health problem]</td></tr>
<tr><td rowspan="2">Stage 2:
Epidemiological diagnosis</td><td rowspan="2">Create measurable, time-limited, health-related objectives. The success of the program will ultimately be judged by these objectives</td><td colspan="2">Clinical data and cross-sectional PA data may also be used to inform this stage.</td></tr>
<tr><td>State expected outcomes for behaviour and environment

Specify performance objectives for behavioural and environmental outcomes.

Select determinants for behavioural and environmental outcomes.

Determine the aims of an intervention designed to increase physical activity in patients with CF?</td><td>What is the priority health problem associated with inactivity?

Which factors are associated with these behaviours?

Which methods do you believe may be effective in changing these behaviours? (as highlighted in logic model)

What needs to happen to enable these changes to take place? Prompts/probes (E.g. training, resources, communication).

Is it possible to measure this? If so, how could this be measured?</td></tr>
<tr><td colspan="4">[Transition statement] Thank you for sharing your ideas and developing these objectives. I would now like to discuss some of the smaller sub-objects which may be used to ensure that the main objectives are met, in doing so I would like you to consider which are related to behavioural factors and which are related to environmental factors.</td></tr>
<tr><td rowspan="2">Stage 3:
Behavioural and environmental diagnosis</td><td rowspan="2">Identify key environmental and behavioural factors; these will become sub-objectives that direct planning for intervention activities</td><td colspan="2">This phase will be informed by findings in stage 2 and any accompanying behaviour change theories/techniques adopted.</td></tr>
<tr><td>[Define] Environment - Interpersonal environment (family, friends, clinicians etc.), Organisation environment (Clinic, hospital, CF trust), Community environment (geographic, social environment, CF community)

Behaviour (beliefs, self-efficacy, perceived norms)</td><td>What are the priority behavioural and environmental contributors to inactivity in CF?

Who if anyone, can influence environmental conditions?

Which determinants of PA are important in achieving the [objectives outlined] and how might these be modified? (consider for each separate objective)</td></tr>
<tr><td colspan="4">[Transition statement] I'd now like to consider how it may be best to meet these objectives and how they may relate to the principle predisposing, reinforcing and enabling factors we discussed at the start.</td></tr>
<tr><td>Stage 4:
Educational</td><td></td><td colspan="2">Identify, sort, and categorise the predisposing, reinforcing, and enabling factors that influence health behaviours identified in phase 1.</td></tr>
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and ecological diagnosis	Develop a unique plan to achieve each sub-objective from step 3; Consider predisposing, reinforcing, and enabling factors, and use theory	Predisposing (motivation, opportunities, lifestyle) Reinforcing (Peers, family, health, enjoyment) Enabling (Cost, location, facilities, transport)	The key predisposing factors identified during phase 1 were […]. How might the objective outlined above be met considering these factors? The key predisposing factors identified during phase 1 were […] How might the objective outlined above be met considering these factors? The key predisposing factors identified during phase 1 were […] How might the objective outlined above be met considering these factors?
[Transition statement] Finally, I would like to discuss the feasibility of delivering such a plan.			
Stage 5: Administrative and policy assessment	Assess capacity and resources available to implement programs and change policies such that step 4 sub-objectives can be met	Budgetary and staff requirements and availability, barriers/limitations to overcome, and available policies to change or support. Health education Policy, regulation, and organizational structures	What are the existing policies and practices that could be leveraged to support the intervention? What are the existing organisation/groups that could help to support the intervention? What aspects of the natural or built environment could be harnessed to support the intervention?
Close *[Provide a summary of discussion].* I appreciate the time you took for this focus group. Is there anything else you think would be helpful for me to know? I should have all the information I need, thank you.			

Findings will inform the PROCEED component of the PRECEDE-PROCEED

Clinician focus group schedule

Date: DD/MM/YYYY

Location:

Participants:

Hi, my name is [*researchers' name*]. I'm a researcher at Liverpool John Moores University and I am currently working with the Cystic Fibrosis (CF) team at Liverpool Heart and Chest Hospital to involve patients with CF, their families and clinicians in a process to develop an intervention to promote physical activity in adults with CF. The reason we're here today is to discuss the perceived barriers, facilitators and opportunities for physical activity participation and how this information can inform the development and delivery of a PA intervention for individuals with Cystic Fibrosis.

This research has been reviewed and given approval by an independent group of people known as a research ethics committee *[REC and reference number]*. I'd also like you to know that this meeting will be audio recorded and transcribed – which means writing out our conversation like a script. The recording and transcript will allow me to revisit our discussion for further analysis. Additionally, I may make some notes as we are talking so that I can refer back to some of the points discussed. The identities of all participants will not be included in this transcript or any other reports.

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3. I would like to stress confidentiality as I would like an open discussion. I want you to feel free to comment without concern that your comments will be repeated later and possibly taken out of context.
4. There are no "wrong answers", just different opinions and views.
5. Let me know if you need a break. The bathrooms are *[location]*. Feel free to enjoy a beverage and a snack.

The focus group will take around 45-60 minutes, which will include questions in four separate phases.

Does anyone have any questions before we start?

Diagnostic phase	Objective	Themes	Questions
[Transition statement] I'd like to start by asking some questions to try and understand more about individuals with CF and present some of the themes (determinants of PA) identified during the phase 1 interviews.			
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