View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by LJMU Research Online

LJMU Research Online

Boddy, LM, Shelley, J, Knowles, ZR, Stewart, CE and Dawson, EA

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

http://researchonline.ljmu.ac.uk/id/eprint/10369/

Article

Citation (please note it is advisable to refer to the publisher's version if you intend to cite from this work)

Boddy, LM, Shelley, J, Knowles, ZR, Stewart, CE and Dawson, EA (2019) Physical activity and associations with clinical outcome measures in adults with cystic fibrosis; A systematic review. Journal of Cystic Fibrosis. ISSN 1873-5010

LJMU has developed **LJMU Research Online** for users to access the research output of the University more effectively. Copyright © and Moral Rights for the papers on this site are retained by the individual authors and/or other copyright owners. Users may download and/or print one copy of any article(s) in LJMU Research Online to facilitate their private study or for non-commercial research. You may not engage in further distribution of the material or use it for any profit-making activities or any commercial gain.

The version presented here may differ from the published version or from the version of the record. Please see the repository URL above for details on accessing the published version and note that access may require a subscription.

For more information please contact researchonline@ljmu.ac.uk

http://researchonline.ljmu.ac.uk/

PHYSICAL ACTIVITY AND ASSOCIATIONS WITH CLINICAL OUTCOME MEASURES IN ADULTS WITH CYSTIC FIBROSIS; A SYSTEMATIC REVIEW.

James Shelley[1*], Lynne M Boddy[1], Zoe R Knowles[1], Claire E Stewart[1], & Ellen A Dawson[1].

1. Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, L3 3AF, United Kingdom.

RUNNING TITLE: PHYSICAL ACTIVITY IN ADULTS WITH CYSTIC FIBROSIS.

***Corresponding Author**
Mr James Shelley
Physical Activity Exchange
School of Sports and Exercise Sciences
Liverpool John Moores University
5 Primrose Hill, Liverpool, L3 2EX
United Kingdom
j.shelley@2016.ljmu.ac.uk

Conflict of Interest
The authors declare that there are no conflicts of interest.

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 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.

KEYWORDS

PRISMA; respiratory disease; exercise; quality of life.

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.

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 minutes 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 minutes of moderate-vigorous intensity aerobic PA (MVPA) or 75 minutes 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 minutes 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.

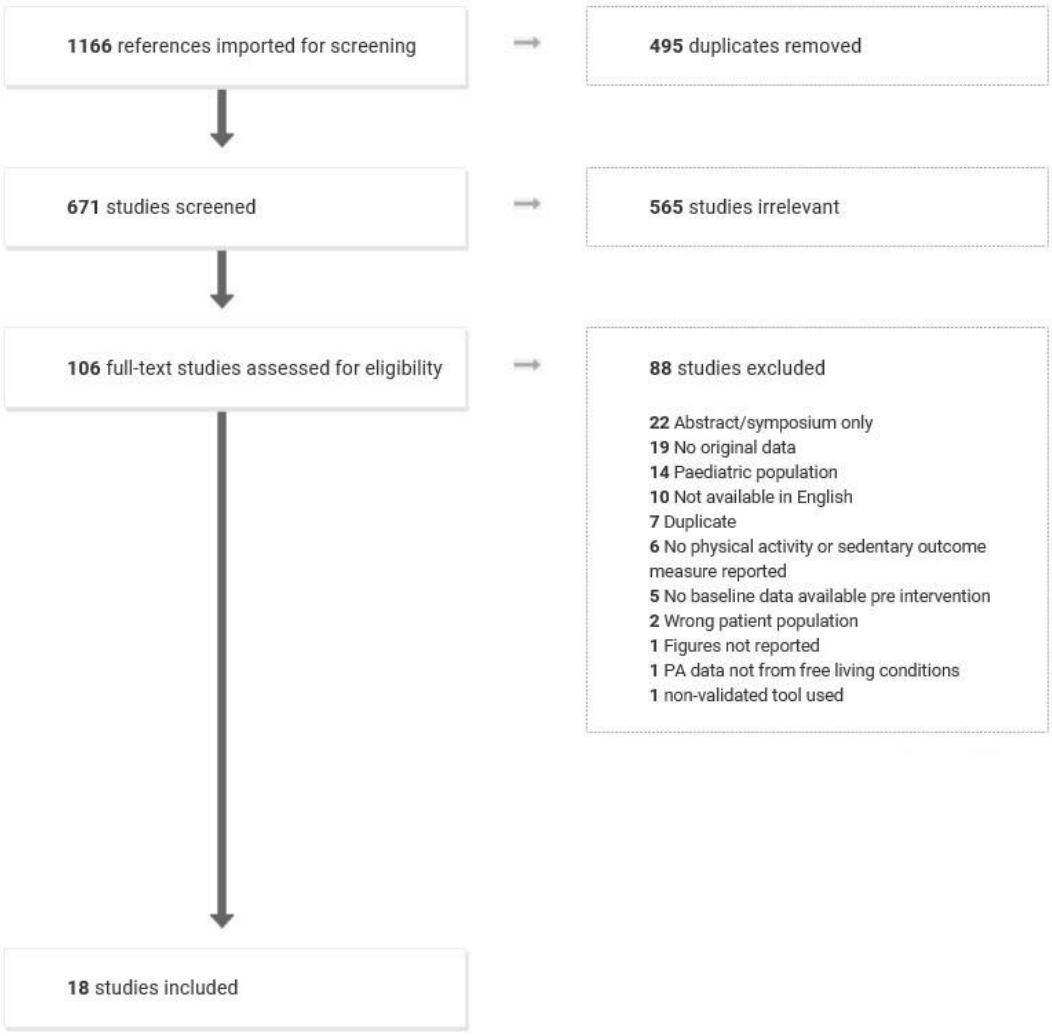
2.1 Search strategy and initial screening

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 (Figure 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 (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 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.

Figure 1 – 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 2 - PRISMA flowchart



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).

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).

180 **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

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 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.

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 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) [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 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.

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 (5000-7499), 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

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 1-5. The sum of the three categories (work, sport, leisure) provides a total PA score between 3-15 [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).

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 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.

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 minutes 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 11.3hrs 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.

3.2.3 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) [31]. 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)) [31], however inactivity describes insufficient levels of PA to meet guidelines and not necessarily SB [45].

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

[Insert Table 3 here – attached as additional file]

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 (10281 and 10591 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].

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

[Insert Table 4 here – attached as additional file]

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) [5,12,40,42,43,28–31,34,36,37,39]. 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 minutes or more MVPA per day had higher lung function than those engaging in less than 30 minutes 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-reported PA [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 ((ß=0.59, *P*=0.002, (R^2=0.32)), (R=0.44 p=0.01)) [5,12,30]) and exercise capacity ($VO2_{peak}$ [5,12,30] and 6-minute 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 IAPQ 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.

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 hours 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.

FUNDING

This research was funded by a Liverpool John Moores University PhD scholarship.

REFERENCES

[1] Jeffery Charman, S., Cosgriff, R., Carr, S. A. UK Cystic Fibrosis Registry Annual Data Report 2016. 2017.

[2] Schneiderman JE, Wilkes DL, Atenafu EG, Nguyen T, Wells GD, Alarie N, et al. Longitudinal relationship between physical activity and lung health in patients with cystic fibrosis. Eur Respir J 2014;43. doi:10.1183/09031936.00055513.

[3] Dwyer TJ, Alison JA, McKeough ZJ, Daviskas E, Bye PTP. Effects of exercise on respiratory flow and sputum properties in patients with cystic fibrosis. Chest 2011;139:870–7. doi:10.1378/chest.10-1158.

[4] Garcia ST, Sanchez MAG, Cejudo P, Gallego EQ, Dapena J, Jimenez RG, et al. Bone Health, Daily Physical Activity, and Exercise Tolerance in Patients With Cystic Fibrosis. Chest 2011;140:475–81. doi:10.1378/chest.10-1508.

[5] Cox NS, Alison JA, Button BM, Wilson JW, Morton JM, Holland AE. Physical activity participation by adults with cystic fibrosis: An observational study. Respirology 2016;21:511–8. doi:10.1111/resp.12719.

[6] Hebestreit H, Kieser S, Rüdiger S, Schenk T, Junge S, Hebestreit A, et al. Physical activity is independently related to aerobic capacity in cystic fibrosis. Eur Respir J 2006;28:734–9. doi:10.1183/09031936.06.00128605.

[7] Nixon PA, Orenstein DM, Kelsey SF, Doershuk CF. The prognostic value of exercise testing in patients with cystic fibrosis. N Engl J Med 1992;327:1785–8. doi:10.1056/NEJM199212173272504.

[8] Bradley J, O'Neill B, Kent L, Hulzebos EHJ, Arets B, Hebestreit H, et al. Physical activity assessment in cystic fibrosis: A position statement. J Cyst Fibros 2015;14. doi:10.1016/j.jcf.2015.05.011.

[9] Cystic Fibrosis Trust. Standards of Care and Good Clinical Practice for the Physiotherapy Management of Cystic Fibrosis. Third edition 2017. 2017.

[10] Moola FJ. "CF chatters": the development of a theoretically informed physical activity intervention for youth with cystic fibrosis. Open J Prev Med 2011;01:109–24. doi:10.4236/ojpm.2011.13016.

[11] Howley ET. Type of activity: resistance, aerobic and leisure versus occupational physical activity. Med Sci Sports Exerc 2001;33:S364–9. doi:10.1097/00005768-200106001-00005.

[12] Troosters T, Langer D, Vrijsen B, Segers J, Wouters K, Janssens W, et al. Skeletal muscle weakness, exercise tolerance and physical activity in adults with cystic fibrosis. Eur Respir J 2009;33:99–106. doi:10.1183/09031936.00091607.

[13] Owen N, Healy GN, Matthews CE, Dunstan DW. Too much sitting: the population health science of sedentary behavior. Exerc Sport Sci Rev 2010;38:105–13. doi:10.1097/JES.0b013e3181e373a2.

[14] Swisher Hebestreit, H., Mejia-Downs, A., Lowman, JD., Gruber, W., Nippins, M., Alison, J., Schneiderman, J. AK. Exercise and habitual physical activity for people with Cystic Fibrosis Expert-consensus, evidence-based guide for advising patients. Cardiopulm Phys Ther J 2015;0:1–14. doi:10.1097/CPT.0000000000000016.

[15] World Health Organization. Global Recommendations on Physical Activity for Health. 2012.

[16] Tudor-Locke C, Bassett DR. How many steps/day are enough? Preliminary pedometer indices for public health. Sport Med 2004;34:1–8. doi:Doi 10.2165/00007256-200434010-00001.

[17] Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U, et al. Global physical activity levels: Surveillance progress, pitfalls, and prospects. Lancet 2012;380:247–57. doi:10.1016/S0140-6736(12)60646-1.

[18] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1. doi:10.1186/2046-4053-4-1.

[19] Popay J, Roberts H, Sowden A, Petticrew M, Arai L, Rodgers M, et al. Guidance on the Conduct of Narrative Synthesis in Systematic Reviews. A Prod from ESRC Methods Program 2006:211–9. doi:10.1111/j.1523-536x.1995tb00261.x.

[20] Ruf KC, Fehn S, Bachmann M, Moeller A, Roth K, Kriemler S, et al. Validation of activity questionnaires in patients with cystic fibrosis by accelerometry and cycle ergometry. BMC Med Res Methodol 2012;12:43. doi:10.1186/1471-2288-12-43.

[21] Tejero S, Cejudo P, Sañudo B, Quintana-Gallego E, Sañudo B, Oliva-Pascual-Vaca A. The role of daily physical activity and nutritional status on bone turnover in cystic fibrosis: a cross-sectional study. Braz J Phys Ther 2016;20:206–12. doi:10.1590/bjpt-rbf.2014.0154.

[22] Hebestreit H, Schmid K, Kieser S, Junge S, Ballmann M, Roth K, et al. Quality of life

611 is associated with physical activity and fitness in cystic fibrosis. BMC Pulm Med
612 2014;14:26. doi:10.1186/1471-2466-14-26.

613 [23] Jantzen A, Opoku-Pare M, Bieli C, Ruf K, Hebestreit H, Moeller A. Perspective on
614 cystic fibrosis and physical activity: Is there a difference compared to healthy
615 individuals? Pediatr Pulmonol 2016;51. doi:10.1002/ppul.23532.

616 [24] Higgins Green S (editors) JPT. Cochrane Handbook for Systematic Reviews of
617 Interventions version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011.

618 [25] Hills AP, Mokhtar N, Byrne NM. Assessment of Physical Activity and Energy
619 Expenditure: An Overview of Objective Measures. Front Nutr 2014;1:1–16.
620 doi:10.3389/fnut.2014.00005.

621 [26] Paffenbarger RS, Hyde RT, Wing AL, Lee IM, Jung DL, Kampert JB. The Association
622 of Changes in Physical-Activity Level and Other Life-Style Characteristics with
623 Mortality among Men. N Engl J Med 1993;328:538–45. doi:Doi
624 10.1056/Nejm199302253280804.

625 [27] Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of
626 habitual physical activity in epidemiological studies. Am J Clin Nutr 1982;36:936–42.
627 doi:10.14814/phy2.12883.

628 [28] Savi D, Simmonds N, Di Paolo M, Quattrucci S, Palange P, Banya W, et al.
629 Relationship between pulmonary exacerbations and daily physical activity in adults
630 with Cystic Fibrosis. BMC Pulm Med 2015;15:151. doi:10.1186/s12890-015-0151-7.

631 [29] Ziai S, Coriati A, St-Pierre D, Chabot K, Desjardins K, Leroux C, et al. Glucose
632 Fluctuations are Not Modulated by the Proportion of Calories from Macronutrients or
633 Spontaneous Total Energy Expenditure in Adults with Cystic Fibrosis. Can J Diabetes
634 2016;40:389–92. doi:10.1016/j.jcjd.2016.05.007.

635 [30] Savi D, Di Paolo M, Simmonds N, Onorati P, Internullo M, Quattrucci S, et al.
636 Relationship between daily physical activity and aerobic fitness in adults with cystic
637 fibrosis. BMC Pulm Med 2015;15:59. doi:10.1186/s12890-015-0036-9.

638 [31] Savi D, Quattrucci S, Internullo M, De Biase R V, Calverley PMA, Palange P.
639 Measuring habitual physical activity in adults with cystic fibrosis. Respir Med
640 2013;107:1888–94. doi:10.1016/j.rmed.2013.09.012.

641 [32] Hollander FM, De Roos NM, De Vries JHM, Van Berkhout FT. Assessment of
642 nutritional status in adult patients with cystic fibrosis: Whole-body bioimpedance vs

643 body mass index, skinfolds, and leg-to-leg bioimpedance. J Am Diet Assoc
644 2005;105:549–55. doi:10.1016/j.jada.2005.01.030.

645 [33] Decorte N, Gruet M, Camara B, Quetant S, Mely L, Vallier JM, et al. Absence of calf
646 muscle metabolism alterations in active cystic fibrosis adults with mild to moderate
647 lung disease. J Cyst Fibros 2017;16. doi:10.1016/j.jcf.2016.05.010.

648 [34] Haworth CS, Selby PL, Webb AK, Dodd ME, Musson H, Mc LNR, et al. Low bone
649 mineral density in adults with cystic fibrosis. Thorax 1999;54:961–7.

650 [35] Gruet M, Peyre-Tartaruga LA, Mely L, Vallier J-M. The 1-Minute Sit-to-Stand Test in
651 Adults With Cystic Fibrosis: Correlations With Cardiopulmonary Exercise Test, 6-
652 Minute Walk Test, and Quadriceps Strength. Respir Care 2016;61:1620–8.
653 doi:10.4187/respcare.04821.

654 [36] Rasekaba TM, Button BM, Wilson JW, Holland AE. Reduced physical activity
655 associated with work and transport in adults with cystic fibrosis. J Cyst Fibros
656 2013;12:229–33. doi:10.1016/j.jcf.2012.09.003.

657 [37] Currie S, Greenwood K, Weber L, Khakee H, Legasto M, Tullis E, et al. Physical
658 Activity Levels in Individuals with Cystic Fibrosis-Related Diabetes. Physiother Can
659 2017;69:171–7. doi:10.3138/ptc.2015-92EP.

660 [38] Enright S, Chatham K, Ionescu AA, Unnithan VB, Shale DJ. Inspiratory muscle
661 training improves lung function and exercise capacity in adults with cystic fibrosis.
662 Chest 2004;126:405–11. doi:10.1378/chest.126.2.405.

663 [39] Elkin SL, Fairney A, Burnett S, Kemp M, Kyd P, Burgess J, et al. Vertebral deformities
664 and low bone mineral density in adults with cystic fibrosis: A cross-sectional study.
665 Osteoporos Int 2001;12. doi:10.1007/s001980170104.

666 [40] Ionescu AA, Evans WD, Pettit RJ, Nixon LS, Stone MD, Shale DJ. Hidden depletion
667 of fat-free mass and bone mineral density in adults with cystic fibrosis. Chest
668 2003;124:2220–8.

669 [41] Street ME, Spaggiari C, Ziveri MA, Volta C, Federico G, Baroncelli GI, et al. Analysis
670 of bone mineral density and turnover in patients with cystic fibrosis: Associations
671 between the IGF system and inflammatory cytokines. Horm Res 2006;66.
672 doi:10.1159/000094143.

673 [42] Bhudhikanok GS, Wang MC, Marcus R, Harkins A, Moss RB, Bachrach LK. Bone
674 acquisition and loss in children and adults with cystic fibrosis: A longitudinal study. J

675 Pediatr 1998;133:18–27. doi:Doi 10.1016/S0022-3476(98)70172-6.

676 [43] Enright S, Chatham K, Ionescu AA, Unnithan VB, Shale DJ. The influence of body
677 composition on respiratory muscle, lung function and diaphragm thickness in adults
678 with cystic fibrosis. J Cyst Fibros 2007;6. doi:10.1016/j.jcf.2007.02.006.

679 [44] Cox NS, Alison JA, Button BM, Wilson JW, Morton JM, Holland AE. Physical activity
680 participation by adults with cystic fibrosis: An observational study. Respirology
681 2016;21. doi:10.1111/resp.12719.

682 [45] Tremblay MS, Aubert S, Barnes JD, Saunders TJ, Carson V, Latimer-Cheung AE, et
683 al. Sedentary Behavior Research Network (SBRN) - Terminology Consensus Project
684 process and outcome. Int J Behav Nutr Phys Act 2017;14:1–17. doi:10.1186/s12966-
685 017-0525-8.

686 [46] Laborde-Castérot H, Donnay C, Chapron J, Burgel PR, Kanaan R, Honoré I, et al.
687 Employment and work disability in adults with cystic fibrosis. J Cyst Fibros
688 2012;11:137–43. doi:10.1016/j.jcf.2011.10.008.

689 [47] Ridgers ND, Fairclough S. Assessing free-living physical activity using accelerometry:
690 Practical issues for researchers and practitioners. Eur J Sport Sci 2011;11:205–13.
691 doi:Pii 93735128910.1080/17461391.2010.501116.

692 [48] Heil DP, Brage S, Rothney MP. Modeling physical activity outcomes from wearable
693 monitors. Med Sci Sports Exerc 2012;44:50–60.
694 doi:10.1249/MSS.0b013e3182399dcc.

695 [49] Hildebrand M, Van Hees VT, Hansen BH, Ekelund U. Age group comparability of raw
696 accelerometer output from wrist-and hip-worn monitors. Med Sci Sports Exerc
697 2014;46:1816–24. doi:10.1249/MSS.0000000000000289.

698 [50] Wieboldt J, Atallah L, Kelly JL, Shrikrishna D, Gyi KM, Lo B, et al. Effect of acute
699 exacerbations on skeletal muscle strength and physical activity in cystic fibrosis. J
700 Cyst Fibros 2012;11:209–15. doi:10.1016/j.jcf.2011.12.001.

701 [51] Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al.
702 International physical activity questionnaire: 12-Country reliability and validity. Med
703 Sci Sports Exerc 2003. doi:10.1249/01.MSS.0000078924.61453.FB.

704 [52] Johnson-Koslow M, Sallis JF, Gilpin EA, Rock CL, Pierce JP. Comparative validation
705 of the IPAQ and the 7-day PAR among women diagnosed with breast cancer. Int J
706 Behav Nutr Phys Act 2006. doi:10.1186/1479-5868-3-7.

[53] Fillipas S, Cicuttini F, Holland AE, Cherry CL. The International Physical Activity Questionnaire Overestimates Moderate and Vigorous Physical Activity in HIV-Infected Individuals Compared With Accelerometry. J Assoc Nurses AIDS Care 2010. doi:10.1016/j.jana.2009.11.003.

[54] Kaleth AS, Ang DC, Chakr R, Tong Y. Validity and reliability of community health activities model program for seniors and short-form international physical activity questionnaire as physical activity assessment tools in patients with fibromyalgia. Disabil Rehabil 2010. doi:10.3109/09638280903166352.

[55] Wells GD, Wilkes DL, Schneiderman-Walker J, Elmi M, Tullis E, Lands LC, et al. Reliability and validity of the Habitual Activity Estimation Scale (HAES) in patients with cystic fibrosis. Pediatr Pulmonol 2008;43:345–53. doi:10.1002/ppul.20737.

[56] Matthews CE, Hagströmer M, M PD, Bowles HR. Best Practices for Using Physical Activity Monitors. Med Sci Sports Exerc 2013;44:1–17. doi:10.1249/MSS.0b013e3182399e5b.BEST.

[57] Hebestreit H, Arets HGM, Aurora P, Boas S, Cerny F, Hulzebos EHJ, et al. Statement on Exercise Testing in Cystic Fibrosis. Respiration 2015;90:332–51. doi:10.1159/000439057.