Physical activity assessment and vascular function in adults with Cystic fibrosis and their non-CF peers.

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ABSTRACT

An understanding of physical activity (PA) and related health benefits remains limited in adults with Cystic Fibrosis (CF). Raw acceleration data metrics may improve the quality of assessment and further this understanding. The study aimed to compare PA between people with CF (pwCF) and non-CF peers and examine associations between PA, vascular function and health outcome measures.

PA was assessed in 62 participants (31 pwCF) using ActiGraph accelerometers. Vascular function (a marker of cardiovascular disease risk) was assessed using flow-mediated dilatation (FMD) in sub-groups of pwCF (n=12) and matched controls.

Average Euclidean norm minus one (ENMO) (total PA) was significantly lower (p = 0.005) in pwCF (35.09 ± 10.60m*g*), than their non-CF peers (44.62 ± 13.78m*g*). PwCF had PA profiles (intensity gradient) indicative of more time in lower intensity activity (-2.62 ± 0.20, -2.37 ± 0.23).

Vigorous activity was positively associated with lung function (r_s = 0.359) and Quality of Life (r = 0.412). There were no significant differences (p = 0.313) in FMD% between pwCF (5.29 ± 2.76%) and non-CF peers (4.34 ± 1.58%) and no associations with PA.

PwCF engaged in less moderate-to-vigorous PA and demonstrated a steeper PA profile than their non-CF peers.

Highlights: Adults with Cystic Fibrosis engage in less moderate to vigorous physical activity (PA) than their non-CF peers. Average ENMO and intensity gradient metrics provide a comprehensive PA profile that may allow tailored PA advice for adults with CF.

Keywords: cardiovascular; exercise; respiratory disease; endothelial function; flow-mediated dilatation; FMD

1. INTRODUCTION

Physical activity (PA) is of clear benefit for the general population [1], 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 [1]. Sedentary behaviour (SB) includes activities in a sitting or reclined posture with low energy expenditure (1.0-1.5 metabolic equivalents) and is not merely the absence of PA, it is therefore possible for individuals to engage in sufficient levels of PA whilst also engaging in a high volume of sedentary behaviours [2]. The association between SB and increased risk for cardiometabolic disease and mortality, independently from PA, is well documented [2]. There is less evidence available regarding the health associations of PA in individuals with Cystic Fibrosis (CF) [3], though PA has been associated with beneficial effects on lung function [4], hospitalisation frequency [5] and quality of life (QoL) [3]. 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 [6], 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 [7].

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 [8]. Accelerometry is the most widely used method for the assessment of PA in adults with CF [8]. 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 [9]. 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 [10]. 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 [11]. 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) [12], it is uncommon in individuals with CF and typically secondary to severe pulmonary disease [13]. However, with increased life expectancy, individuals with CF have greater exposure to traditional CVD risk factors including ageing, diabetes and metabolic disturbances [14]. Furthermore, CF is also associated with chronic inflammation, altered fatty acid metabolism and abnormal lipid profiles which may pose even further risk of CVD [15] [16]. Endothelial (dys)function, assessed using flow-mediated dilatation (FMD), is a strong predictor of future cardiovascular events [17] and is evident in young people with CF despite preserved lung function and exercise capacity [18]. 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 [19].

2. AIMS

The primary aim of the current research was to compare device-based PA assessment 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 device-based PA assessment and lung function, quality of life and self-reported PA were explored.

3. METHODS

3.1. Participants

Ethical approval was granted by a local National Health Service (NHS) Health Research Authority [17/NW/0360] and Liverpool John Moores University [18/SPS/034]. Adults with CF were recruited from outpatient CF clinics at the regional adult CF Centre (n=340). Participants for the non-CF control group were recruited via advertisements within the University. All participants were screened for eligibility (Figure 1) and invited to attend testing at their clinic (CF) or the university (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.

3.2. Data collection

3.2.1. Health outcome measures

Pulmonary function was assessed according to American Thoracic Society (ATS) /European Respiratory Society (ERS) standard operating procedures [20] 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.

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 [21]. 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 [22].

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 the device-based measure. The GPA-Q was also used in the non-CF group to allow for comparison of self-reported PA between groups. 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 [23].

3.2.4. Vascular function

Vascular function was assessed in sub-groups of both CF and non-CF groups using Flow Mediated Dilatation (FMD). 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 cases participants did not want to be fasted for their clinic visit. FMD is a non-invasive assessment of nitric-oxide dependent endothelial function [24] and has recently been shown to be reliable and repeatable in individuals with CF [25]. 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 [24]. 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 in artery diameter and blood flow were then recorded for a further 3 minutes.

3.3. Data analysis

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 [26]. Signals were then converted into gravity-corrected vector magnitude units, termed the Euclidean norm minus one (ENMO) [27], 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 [27]. 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 [28]. 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) [29]. The PA intensity gradient (IG) is a novel metric to describe the distribution of PA intensity, calculated from raw acceleration data [30]. 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 2). The R^2 value, gradient and constant were used to describe individuals' PA profiles (IG) [30]. A lower gradient (steeper slope) represents a 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.

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 [23]. EQ-5D-5L was analysed using the questionnaire specific scoring and analysis guidance to provide an overall index for QoL [22].

3.3.3. Flow-Mediated Dilatation (FMD)

FMD was assessed in accordance with recent guidelines [24]. Assessment of brachial artery diameter was done using custom edge-detection and wall-tracking software [24]. 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% [31].

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 1). 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.

4. RESULTS

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 1).

Table 1. 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.*

4.2. Physical activity & sedentary time

Device-based PA assessment 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 2).

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 2). Adults with CF had a steeper gradient and lower constant representing a 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 2).

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 3).

Higher levels of device-based VPA were positively correlated with lung function (Table 4). Higher device-based MVPA and mean ENMO values were also positively correlated with FEV_1%, but no other measures of lung function (Table 4). Device-based sedentary time assessment was not significantly correlated with any measures of lung function.

Pearson's and Spearman's correlation analyses were used to assess the relationship between device-based and self-reported PA. Self-reported sedentary time and MPA were significantly correlated with device-based 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 device-based VPA, r_s 0.178 (p = 0.171). There were no significant correlations observed when analysing the CF group separately (all $p > 0.05$). Device-based and self-reported sedentary time were correlated for the non-CF group when analysed separately (r = 0.498, p = 0.004), but device-based and self-reported MPA and VPA were not significantly correlated (p >0.05).

Table 2. Physical activity variables assessed using 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 3. 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 4 – Correlations between device-based physical activity assessment 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].*

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 = 0.313). 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 5).

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 6).

Table 5. 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 dilatation (uncorrected); SRAUC, shear rate area under the curve.

Table 6 – Correlations between vascular function, physical activity and lung function.

	Age		BMI		FEV1 L		FVC L		ENMO		MVPA		Vig		Mod		Light		Sed	
FMD%	r_s = 0.460	***p* = **0.027**	r_s = - 0.281	*p* = 0.194	r_s = - 0.203	*p* = 0.354	r_s = - 0.180	*p* = 0.412	r_s = 0.089	*p* = 0.687	r_s = 0.165	*p* = 0.452	r_s = 0.039	*p* = 0.861	r_s = 0.135	*p* = 0.538	r_s = 0.172	*p* = 0.433	r_s = - 0.030	*p* = 0.893
Baseline diameter	r_s = - 0.324	*p* = 0.132	r_s = 0.631	***p* = 0.001**	r = 0.445	***p* = 0.033**	*r* = 0.423	***p* = 0.044**	*r* = 0.329	*p* = 0.125	r_s 0.502	***p* = 0.015**	*r* = 0.296	*p* = 0.170	r_s = 0.481	***p* = 0.020**	*r* = - 0.097	*p* = 0.659	*r* = - 0.118	*p* = 0.593
Peak diameter	r_s = - 0.268	*p* = 0.217	r_s = 0.554	***p* = 0.006**	*r* = 0.410	*p* = 0.052	*r* = 0.387	*p* = 0.068	*r* = 0.358	*p* = 0.093	r_s 0.548	***p* = 0.007**	*r* = 0.302	*p* = 0.161	r_s = 0.519	***p* = 0.011**	*r* = - 0.070	*p* = 0.752	*r* = - 0.134	*p* = 0.541
SBP	r_s = - 0.135	*p* = 0.538	r_s = - 0.080	*p* = 0.716	*r* = - 0.135	*p* = 0.538	*r* = - 0.067	*p* = 0.760	*r* = 0.004	*p* = 0.986	r_s 0.193	*p* = 0.379	*r* = - 0.105	*p* = 0.633	r_s = 0.173	*p* = 0.430	*r* = - 0.093	*p* = 0.674	*r* = - 0.093	*p* = 0.675
DBP	r_s = - 0.101	*p* = 0.646	r_s = - 0.118	*p* = 0.593	r_s - 0.450	***p* = 0.031**	r_s = - 0.371	*p* = 0.082	r_s = - 0.323	*p* = 0.133	r_s - 0.165	*p* = 0.452	r_s = - 0.226	*p* = 0.299	r_s = - 0.167	*p* = 0.445	r_s = - 0.190	*p* = 0.386	r_s = 0.194	*p* = 0.376

*Pearson's and Spearman's correlation analysis displayed, *Indicates statistical significance (<0.05).*

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 6. Device-based 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 7).

Table 7. 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. DISCUSSION

The aim of the current research was to compare levels of device-based PA assessment in adults with CF to their non-CF peers and to determine the association between PA and vascular function. Overall, 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 were associated with higher QoL. Average ENMO (a measure of total PA) was significantly lower in adults with CF, who also had a PA profile (intensity gradient) reflecting more time spent in lower intensity activity and less time across the range of intensities 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.

5.1. 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 for adults with CF. 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 [30]. 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 [30]. This would enable comparison to normative values and longitudinal tracking of PA [30] which could be advantageous in CF populations. Data from a large scale population level assessment of PA, employing similar methods, suggests that the levels of PA reported in the current study are broadly comparable to the wider UK adult population. Average acceleration for 45-54 year olds was 35.09 mg compared with 34.21 mg for individuals with CF in the current study, although the average age was lower (29 years old) and an average decline of 7.5% or 2.35 mg can be expected per decade [32]. Furthermore, a study which assessed PA using raw acceleration data cut points in 43 adults with CF reported mean MVPA of 113.3 ± 83.6 mins per day, which is higher than both CF (86.02 ± 36.21) and non-CF (114.12 ± 39.34) groups in the current study [33].

Use of these methods may improve the quality of PA assessment in this population and supports earlier research suggesting that individuals with CF engage in less MVPA than their non-CF peers [34], despite engaging in similar amounts of LPA. These differences were only evident when using device-based 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 [35] 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 [7], though this tool was validated for use in adolescents [36] and it has subsequently been suggested that the tool is not accurate enough to be used for individualised activity counselling in adolescents or adults [37].

5.2. Flow-mediated dilatation

Given that previous research has demonstrated impaired FMD response in young people with CF [18] 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 [38]. 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 Cystic Fibrosis Related Diabetes (CFRD) status.

5.3. Associations between PA and other variables

Increased total acceleration (average ENMO), VPA and MVPA were positively associated with lung function, suggesting that higher levels of PA at moderate intensity

or greater may be associated with higher lung function, providing support for interventions to promote PA in individuals with CF. Additionally, only VPA was associated with improved QoL. This is in contrast to previous research which was unable to find an association between MVPA and QoL, although change in PA was positively associated with QoL [39]. The authors acknowledged that the accelerometer data analysis and cut-offs for MVPA may have obscured the relationship between PA and QoL [39]. 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.

5.4. Limitations

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 [40] , as such these methods may be more appropriate as research tool at present. Sedentary behaviour is categorised by posture (sitting or reclining) and low energy expenditure [41]. 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 recent method, termed the Sedentary Sphere makes it possible to identify, analyse and visualise posture from wrist-worn accelerometry data [42], 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.

Exercise capacity was not assessed as part of this study. Exercise capacity is known to be an independent predictor of mortality [43] and is also associated with lung function [4] 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 [44].

Participants were tested at different locations and whilst the same ultrasound machine was used different blood pressure monitors and spirometers were used which may have resulted in some variation between groups. 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. Furthermore, both the overall group and sub-group consisted of predominately male participants and were not sufficiently powered to explore any potential sex differences. Finally, the researcher performing all FMDs also conducted the analysis and was therefore not blinded for the analysis.

6. CONCLUSION

Adults with CF engaged in less moderate to vigorous PA and demonstrated a PA profile reflecting more time spent in lower intensity activity and less time across the range of intensities 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.

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.

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LIST OF FIGURES