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Shelley, J, Boddy, L, Knowles, Z, Stewart, C, Frost, F, Nazareth, D, Walshaw, M and Dawson, E (2022) Physical activity assessment and vascular function in adults with cystic fibrosis and their non-CF peers. *Journal of Sports Sciences*. 40 (16). pp. 1837-1848. ISSN 1466-447X

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

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

33
34 **ABSTRACT**

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

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

43 Average Euclidean norm minus one (ENMO) (total PA) was significantly lower ($p =$
44 0.005) in pwCF ($35.09 \pm 10.60\text{mg}$), than their non-CF peers ($44.62 \pm 13.78\text{mg}$). PwCF
45 had PA profiles (intensity gradient) indicative of more time in lower intensity activity ($-$
46 2.62 ± 0.20 , -2.37 ± 0.23).

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

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

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

56
57 **Keywords:** cardiovascular; exercise; respiratory disease; endothelial function; flow-
58 mediated dilatation; FMD

59 **1. INTRODUCTION**

60 Physical activity (PA) is of clear benefit for the general population [1], and a small
61 increase in PA is positively associated with clinically relevant changes in health
62 outcomes in a number of clinical and/or inactive populations [1]. Sedentary behaviour
63 (SB) includes activities in a sitting or reclined posture with low energy expenditure (1.0-
64 1.5 metabolic equivalents) and is not merely the absence of PA, it is therefore possible
65 for individuals to engage in sufficient levels of PA whilst also engaging in a high volume
66 of sedentary behaviours [2]. The association between SB and increased risk for
67 cardiometabolic disease and mortality, independently from PA, is well documented [2].
68 There is less evidence available regarding the health associations of PA in individuals
69 with Cystic Fibrosis (CF) [3], though PA has been associated with beneficial effects on
70 lung function [4], hospitalisation frequency [5] and quality of life (QoL) [3]. Despite
71 these potential benefits of PA, beyond those in the general population, there are
72 currently no recommended guidelines for PA devised specifically for individuals with
73 CF [6], or evidence to demonstrate a requirement for such guidelines [3]. Additionally,
74 there is no consensus regarding the monitoring or reporting of PA or SB in this
75 population [7].

76 Understanding of PA-health associations in adults with CF remains limited due to the
77 variety of PA assessment methods and outcome measures reported in the literature
78 [8]. Accelerometry is the most widely used method for the assessment of PA in adults
79 with CF [8]. Traditionally, using accelerometry to quantify PA relied on device specific
80 proprietary algorithms to collect, process, filter, and scale raw signal data to produce
81 device-specific counts [9]. Recent advancements in accelerometer technology have
82 resulted in accelerometers capable of collecting and exporting raw acceleration data,
83 which allows researchers greater control of data processing. It has therefore been
84 proposed that standardised raw data analysis techniques should be utilised with
85 meaningful, interpretable and comparable outputs reported [10]. Proposed outcomes
86 include a measure of the volume of PA (average acceleration, corrected for gravity)
87 and the intensity gradient, which provide an overall PA profile for individuals, rather
88 than focussing on minutes of activity spent in discrete intensity categories alone [11].
89 These novel metrics have not yet been applied in a CF population and may offer the
90 potential to improve the quality of PA assessment and increase understanding of PA
91 in CF.

92 Whilst cardiovascular disease (CVD) is the leading cause of mortality in Europe
93 (accounting for 45% of all deaths) [12], it is uncommon in individuals with CF and
94 typically secondary to severe pulmonary disease [13]. However, with increased life
95 expectancy, individuals with CF have greater exposure to traditional CVD risk factors
96 including ageing, diabetes and metabolic disturbances [14]. Furthermore, CF is also
97 associated with chronic inflammation, altered fatty acid metabolism and abnormal lipid
98 profiles which may pose even further risk of CVD [15] [16]. Endothelial (dys)function,
99 assessed using flow-mediated dilatation (FMD), is a strong predictor of future
100 cardiovascular events [17] and is evident in young people with CF despite preserved
101 lung function and exercise capacity [18]. The relationship between PA and vascular
102 function is yet to be explored in individuals with CF, however PA may be associated
103 with reduced CV risk, not only through the modification of traditional risk factors but
104 also via direct effects on vasculature [19].

105

106 **2. AIMS**

107 The primary aim of the current research was to compare device-based PA assessment
108 in adults with CF to their non-CF peers. The secondary aim was to determine the
109 association between PA and vascular function in a sub-sample of participants. In
110 addition to this, the relationships between device-based PA assessment and lung
111 function, quality of life and self-reported PA were explored.

112

113 **3. METHODS**

114 **3.1. Participants**

115 Ethical approval was granted by a local National Health Service (NHS) Health
116 Research Authority [17/NW/0360] and Liverpool John Moores University
117 [18/SPS/034]. Adults with CF were recruited from outpatient CF clinics at the regional
118 adult CF Centre (n=340). Participants for the non-CF control group were recruited via
119 advertisements within the University. All participants were screened for eligibility
120 (Figure 1) and invited to attend testing at their clinic (CF) or the university (non-CF),
121 during which informed written consent was obtained and all procedures were carried
122 out as outlined below. Vascular function was assessed in a sub-group of individuals

123 with CF who were then matched on sex, age and ethnicity with a non-CF control
124 participant.

125 **3.2. Data collection**

126 3.2.1. Health outcome measures

127 Pulmonary function was assessed according to American Thoracic Society (ATS)
128 /European Respiratory Society (ERS) standard operating procedures [20] using a
129 standard laboratory based spirometer (Spirostik, Geratherm, Germany) or a portable
130 handheld spirometer (Micro Medical Ltd, Rochester, UK) for the CF and non-CF
131 groups respectively. Height and body weight were measured to the nearest 0.1 cm
132 and 0.1 kg respectively using a digital scale and stadiometer (Seca, Birmingham, UK),
133 with body-mass index (BMI) subsequently calculated ($\text{weight}/\text{height}^2$). Blood pressure
134 was measured using an Omron M2 (Omron Healthcare, Hoofddorp, Netherlands) or
135 Dinamap Pro 300V2 (Dinamap, GE Healthcare, Chicago, IL) automated
136 sphygmomanometer, placed around the left upper arm, for the CF and non-CF groups
137 respectively. Medical notes were reviewed to obtain microbiology status, current
138 medications and genotype for participants with CF.

139

140 3.2.2. Quality of life

141 Health related quality of life was assessed using the Cystic Fibrosis Questionnaire-
142 Revised (CFQ-R). The CFQ-R is a validated disease-specific patient-reported
143 outcome tool providing assessment of QoL and health status, covering a range of
144 physical, emotional and social factors [21]. To control for a confounding influence of
145 QoL on PA, QoL was also assessed in the non-CF group using the EQ-5D-5L health
146 questionnaire, which provides a simple descriptive profile and a single index value for
147 health status [22].

148

149 3.2.3. Physical activity

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

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

154 The Global Physical Activity Questionnaire (GPA-Q) was already used as part of
155 routine clinical care and was therefore used alongside the monitors to compare self-
156 reported PA and SB with the device-based measure. The GPA-Q was also used in the
157 non-CF group to allow for comparison of self-reported PA between groups. The GPA-
158 Q comprises of 16 questions collecting information on PA participation in three
159 domains (at work, travel and recreational activities) as well as SB [23].

160

161 3.2.4. Vascular function

162 Vascular function was assessed in sub-groups of both CF and non-CF groups using
163 Flow Mediated Dilatation (FMD). All participants were invited to take part in both the
164 PA assessment and vascular assessment, however the vascular assessment required
165 participants to arrive fasted and extended the length of their routine clinic appointment.
166 A proportion of participants therefore opted out of the sub-group, participating in the
167 main study group only. The reason given (if any) for opting out of the sub-group was
168 primarily a lack of time owing to the additional burden of the test and in some cases
169 participants did not want to be fasted for their clinic visit. FMD is a non-invasive
170 assessment of nitric-oxide dependent endothelial function [24] and has recently been
171 shown to be reliable and repeatable in individuals with CF [25]. Participants were
172 asked to arrive for testing having fasted for 8 hours and avoided vigorous activity for
173 24 hours, all participants were non-smokers. In accordance with guidelines, after 10
174 minutes rest in the supine position ultrasound images of the brachial artery were
175 captured to measure artery diameter and blood flow velocity [24]. A Hokanson cuff
176 (Hokanson, Bellevue, WA) placed around the participants forearm was inflated to
177 suprasystolic pressure (>220 mmHg) to induce ischemia. Following the 5-minute
178 period of downstream-occlusion, the cuff was released, resulting in increased blood
179 flow velocity through the brachial artery. Changes in artery diameter and blood flow
180 were then recorded for a further 3 minutes.

181 3.3. Data analysis

182 3.3.1. Physical activity data

183 ActiGraph data were downloaded using ActiLife (version 6.13.3), saved in raw format
184 as .gt3x files and converted to .csv files for data processing. The raw ActiGraph data
185 files were processed in R (<http://cran.r-project.org>) using the GGIR package (version
186 1.9-0) which autocalibrated the raw triaxial accelerometer signals [26]. Signals were
187 then converted into gravity-corrected vector magnitude units, termed the Euclidean
188 norm minus one (ENMO) [27], which were expressed as the average ENMO values
189 per 1 second epoch. Accelerometer wear time inclusion criteria were a minimum of 10
190 h·day⁻¹, with non-wear estimated on the basis of the standard deviation and value
191 range of each accelerometer axis, calculated for moving windows of 60 min with 15
192 min increments [27]. For each 15 min period detected as non-wear time over the valid
193 days, missing data were replaced by the mean value calculated from measurement
194 on other days at the same time of day [28]. Sleep logs were used to determine the
195 average waking period, which was used to standardise the analysis window at 08:52
196 – 23:45 to correct for sleep in all participants. Hildebrand *et al.*'s adult non-dominant
197 wrist cut-points were used for classifying activity into sedentary time, light intensity PA
198 (LPA), moderate intensity PA (MPA), moderate-vigorous intensity PA (MVPA) and
199 vigorous intensity PA (VPA) [29]. The PA intensity gradient (IG) is a novel metric to
200 describe the distribution of PA intensity, calculated from raw acceleration data [30]. To
201 calculate the IG, intensity (*mg*), classified using 25*mg* categories and time (mins)
202 accumulated at each intensity were log transformed and used to calculate a linear
203 regression for each participant (Figure 2). The R² value, gradient and constant were
204 used to describe individuals' PA profiles (IG) [30]. A lower gradient (steeper slope)
205 represents a PA profile reflecting more time spent in lower intensity activity, whereas
206 a higher gradient (shallower slope) represent a better profile with more time across the
207 range of intensity.

208

209 3.3.2. Questionnaires

210 GPA-Q data was manually cleaned and analysed to provide estimates for moderate,
211 vigorous and sedentary time, including travel, recreation and work domains as well as

212 calculating a total weekly metabolic equivalence (MET) value [23]. EQ-5D-5L was
213 analysed using the questionnaire specific scoring and analysis guidance to provide an
214 overall index for QoL [22].

215

216 3.3.3. Flow-Mediated Dilatation (FMD)

217 FMD was assessed in accordance with recent guidelines [24]. Assessment of brachial
218 artery diameter was done using custom edge-detection and wall-tracking software
219 [24]. Peak velocity was calculated from analysis of the Doppler signal. Duplex
220 ultrasound-derived velocity and diameter were used to calculate shear rate area under
221 the curve up to peak diameter. Analysis of covariance (ANCOVA) using an allometric
222 approach was performed to analyse change in brachial artery diameter and estimate
223 mean difference in endothelial function between groups, adjusted for baseline
224 diameter to produce covariate-adjusted FMD% [31].

225

226 3.3.4. Statistical analysis

227 Descriptive statistics are displayed as mean \pm SD unless otherwise stated.
228 Independent t-tests were used to compare baseline characteristic between groups
229 (Table 1). Analysis of covariance (ANCOVA) and multivariate analysis of covariance
230 (MANCOVA) were used to compare variables between groups and to control for
231 covariates (age and sex). Pearson's correlation analyses were performed to explore
232 the relationship between variables and Spearman's correlation were performed where
233 the assumptions of normal distribution were violated.

234 **4. RESULTS**

235 **4.1. Baseline characteristics**

236 The groups were well matched for age, height and BMI but lung function was
237 significantly lower ($p < 0.001$) in individuals with CF when compared to their non-CF
238 peers (Table 1).

239

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			
<i>Pseudomonas Aeruginosa</i> (n, %)	17 (55%)		
<i>Pseudomonas Aeruginosa</i> (LES+)* (n, %)	3 (10%)		
<i>Staphylococcus aureus</i> (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

241 Values are displayed as mean±SD or n(%). P-value refers Pearson Chi-square for categorical data and
 242 independent t-tests for all other variables. BMI indicates body mass index; CFRD, Cystic Fibrosis
 243 related diabetes; FEV₁, forced expiratory volume in 1 second; FVC, Forced vital capacity; *LES+,
 244 Liverpool Epidemic strain of *Pseudomonas Aeruginosa*.

245

246 4.2. Physical activity & sedentary time

247 Device-based PA assessment was significantly different between groups when
 248 controlling for age and sex ($p < 0.001$). Separate univariate analysis of variance
 249 indicated no significant difference between groups for wear time ($p = 0.881$), total PA

250 ($p = 0.741$), sedentary time ($p = 0.551$), or light PA ($p = 0.097$), but all other variables
251 (average ENMO, MVPA, MPA, VPA) were significantly lower in individuals with CF
252 when compared to their non-CF peers ($p < 0.05$) (Table 2).

253 PA intensity gradient was significantly different between groups when controlling for
254 age and sex ($p = < 0.001$). Differences between groups were significant ($p < 0.05$) for
255 each of the three variables used to describe the PA profile (Table 2). Adults with CF
256 had a steeper gradient and lower constant representing a PA profile, reflecting more
257 time spent in lower intensity activity and less time across the range of intensities when
258 compared to their non-CF peers (Figure 2).

259 When assessed using the GPA-Q questionnaire there was no significant difference in
260 self-reported PA between groups when controlling for age and sex ($p = 0.089$).
261 Univariate analysis of variance highlighted significantly less PA reported in the travel
262 domain in individuals with CF when compared to their non-CF peers ($p = 0.004$) but
263 no other significant differences were observed between groups using the GPA-Q
264 (Table 3).

265 Higher levels of device-based VPA were positively correlated with lung function (Table
266 4). Higher device-based MVPA and mean ENMO values were also positively
267 correlated with FEV₁%, but no other measures of lung function (Table 4). Device-based
268 sedentary time assessment was not significantly correlated with any measures of lung
269 function.

270 Pearson's and Spearman's correlation analyses were used to assess the relationship
271 between device-based and self-reported PA. Self-reported sedentary time and MPA
272 were significantly correlated with device-based sedentary time and MPA, $r = 0.372$ (p
273 $= 0.003$), $r = 0.272$ ($p = 0.034$), respectively. There was no significant correlation
274 between the remaining item assessed using the GPA-Q (VPA) and device-based VPA,
275 $r_s 0.178$ ($p = 0.171$). There were no significant correlations observed when analysing
276 the CF group separately (all $p > 0.05$). Device-based and self-reported sedentary time
277 were correlated for the non-CF group when analysed separately ($r = 0.498$, $p = 0.004$),
278 but device-based and self-reported MPA and VPA were not significantly correlated (p
279 > 0.05).

280

281 **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

282 *Values are displayed as mean±SD. P-value refers univariate analysis of variance for all variables.*
 283 *ENMO indicates Euclidean norm minus one; MVPA, moderate-vigorous physical activity; PA, physical*
 284 *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

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

288
289

290 **Table 4 – Correlations between device-based physical activity assessment and**
 291 **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]

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

294

295 **4.3. Vascular function**

296 Vascular function was assessed in a sub-group of adults with CF who were then
297 matched for sex, age and ethnicity with a non-CF control participant, of the fifteen
298 participants tested twelve were successfully matched a with non-CF control. There was
299 no significant difference in FMD% between groups, ($p = 0.313$). Separate univariate
300 analysis of variance revealed that baseline diameter ($p = 0.008$) and peak diameter (p
301 $= 0.012$) were significantly lower in individuals with CF when compared to their non-
302 CF peers. Diastolic blood pressure was also significantly higher in individuals with CF
303 when compared to their non-CF peers, although there was no significant difference in
304 FMD% change ($p = 0.313$), (Table 5).

305 FMD% was positively associated with age for the groups combined (r_s 0.460, $p =$
306 0.027) and the CF group alone (r_s 0.618, $p = 0.043$) but not in the non-CF group when
307 analysed separately. FMD% was significantly positively correlated with BMI in the CF
308 group when analysed separately (r_s -0.645, $p = 0.032$) but not for the whole group or
309 the non-CF group. FMD% was not significantly correlated with any other variable
310 assessed in either group (all $p > 0.05$).

311 Higher baseline artery diameter was positively associated with lung function FEV₁ L (r
312 $= 0.445$, $p = 0.033$), FVC L ($r = 0.423$, $p = 0.044$) and MVPA (r_s 0.502, $p = 0.015$) for
313 the groups combined but not when analysed separately. Peak artery diameter was
314 also positively associated with MVPA (r_s 0.548, $p = 0.007$) but not lung function ($p >$
315 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

317 Values are displayed as mean±SD. P-value refers to univariate analysis of variance. 'corrected FMD' refers to an
318 ANCOVA with baseline diameter as a covariate. BMI indicates body mass index; CFRD, Cystic Fibrosis related diabetes;
319 FEV₁, forced expiratory volume in 1 second; ENMO, Euclidean norm minus one; MVPA, moderate-vigorous physical
320 activity; PA, physical activity. FMD, flow-mediated dilatation (uncorrected); SRAUC, shear rate area under the curve.

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

322

	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

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

324 **4.4. Quality of life**

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

329 Quality of life scores for the CF group are displayed in table 6. Device-based VPA was
330 positively associated with scores for the 'physical' and 'role' domains ($r = 0.412$, $p =$
331 0.024), ($r = 0.395$, $p = 0.038$) respectively. Additionally, sedentary time was negatively
332 associated with the 'role' domain ($r = -0.382$, $p = 0.045$). There were no other
333 significant associations between PA and QoL (Table 7).

334

335 **Table 7. Quality of life data for individuals with CF.**

	<i>Physical</i>	<i>Vitality</i>	<i>Emotion</i>	<i>Eating</i>	<i>Treatment Burden</i>	<i>Health Perception</i>	<i>Social</i>	<i>Body image</i>	<i>Role</i>	<i>Weight</i>	<i>Respiratory</i>	<i>Digest</i>
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

336 *Values are displayed as mean \pm SD. Scoring across each domain ranges from 0-100, with higher scores*
337 *indicating better health.*

338 **5. DISCUSSION**

339 The aim of the current research was to compare levels of device-based PA
340 assessment in adults with CF to their non-CF peers and to determine the association
341 between PA and vascular function. Overall, adults with CF engaged in significantly
342 less MVPA than their non-CF peers. VPA in particular was positively associated with
343 lung function and QoL. Lower levels of sedentary time were associated with higher
344 QoL. Average ENMO (a measure of total PA) was significantly lower in adults with CF,
345 who also had a PA profile (intensity gradient) reflecting more time spent in lower
346 intensity activity and less time across the range of intensities when compared to non-
347 CF peers. There were no significant differences in FMD between adults with CF and
348 their non-CF peers and no association between FMD and PA.

349 **5.1. Physical activity**

350 The average ENMO metric and the IG provide a comprehensive PA profile that may
351 allow tailored PA advice for individuals with CF without requiring CF specific PA cut-
352 points to classify intensity, which are not yet available for adults with CF. The IG metric
353 is relatively independent of overall activity in comparison to traditional intensity
354 categories and is independently associated with health outcomes, highlighting the
355 potential relevance of the distribution of PA for individualised PA interventions [30].
356 Normative values are not yet available and the metric is not compatible with current
357 PA guidelines. However, it can be calculated retrospectively using variables commonly
358 reported, which could allow for age- and sex-specific population-referenced
359 percentiles to be generated [30]. This would enable comparison to normative values
360 and longitudinal tracking of PA [30] which could be advantageous in CF populations.
361 Data from a large scale population level assessment of PA, employing similar
362 methods, suggests that the levels of PA reported in the current study are broadly
363 comparable to the wider UK adult population. Average acceleration for 45-54 year olds
364 was 35.09 mg compared with 34.21 mg for individuals with CF in the current study,
365 although the average age was lower (29 years old) and an average decline of 7.5% or
366 2.35 mg can be expected per decade [32]. Furthermore, a study which assessed PA
367 using raw acceleration data cut points in 43 adults with CF reported mean MVPA of
368 113.3 ± 83.6 mins per day, which is higher than both CF (86.02 ± 36.21) and non-CF
369 (114.12 ± 39.34) groups in the current study [33].

370 Use of these methods may improve the quality of PA assessment in this population
371 and supports earlier research suggesting that individuals with CF engage in less
372 MVPA than their non-CF peers [34], despite engaging in similar amounts of LPA.
373 These differences were only evident when using device-based assessment methods
374 and were not present when using the self-report tool (GPA-Q). The GPA-Q provided
375 useful information relating to PA domains, highlighting that individuals with CF report
376 spending less time engaging in active transport than their non-CF peers. Interventions
377 promoting active travel have the potential to generate substantial health benefits [35]
378 and may therefore be of interest for future research.

379 The correlations between accelerometer assessed PA components and the GPA-Q
380 were weak, particularly for VPA which is positively associated with lung function and

381 QoL. The GPA-Q correlated better with accelerometry for estimating sedentary time,
382 as such utilisation of this tool may be limited to assessment of sedentary time and
383 facilitating discussion around PA behaviour rather than accurately quantifying PA
384 levels. There are no studies that validate the use of the GPA-Q in individuals with CF,
385 consequently the GPA-Q should only be considered as a supplementary assessment
386 tool to use alongside accelerometry to provide context. The habitual estimation scale
387 is currently recommend for self-reported assessment of PA in individuals with CF [7],
388 though this tool was validated for use in adolescents [36] and it has subsequently been
389 suggested that the tool is not accurate enough to be used for individualised activity
390 counselling in adolescents or adults [37].

391 **5.2. Flow-mediated dilatation**

392 Given that previous research has demonstrated impaired FMD response in young
393 people with CF [18] it was somewhat surprising that no difference was observed
394 between groups in the current study. Paradoxically, the older participants with CF had
395 higher FMD% response than younger participants, which possibly results from a
396 selection bias where only relatively 'well' individuals with CF survive to later life. It is
397 also important to note that the confounding effect of pharmaceutical treatments was
398 not controlled for in the current research, the effects of which on FMD are not known.
399 Whilst there was no difference in FMD% change, baseline and peak artery diameter
400 were significantly lower in individuals with CF when compared to their matched non-
401 CF peers. In addition, diastolic blood pressure was also higher in individuals with CF,
402 although BP is within normal range for both groups. These findings may be indicative
403 of inward vascular remodelling [38]. FMD was not correlated with PA but was positively
404 correlated with BMI. Low BMI is a marker of poorer outcome in CF, so it follows that
405 individuals with higher BMI may have less severe disease along with higher FMD. The
406 sub-group was also not sufficiently powered to explore difference between genotype
407 or Cystic Fibrosis Related Diabetes (CFRD) status.

408

409 **5.3. Associations between PA and other variables**

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

412 or greater may be associated with higher lung function, providing support for
413 interventions to promote PA in individuals with CF. Additionally, only VPA was
414 associated with improved QoL. This is in contrast to previous research which was
415 unable to find an association between MVPA and QoL, although change in PA was
416 positively associated with QoL [39]. The authors acknowledged that the accelerometer
417 data analysis and cut-offs for MVPA may have obscured the relationship between PA
418 and QoL [39]. In the current study, high levels of sedentary time were negatively
419 associated with QoL and interventions which aim to reduce sedentary time, regardless
420 of PA may also be of benefit for individuals with CF.

421 **5.4. Limitations**

422 The novel PA assessment methods used in the current research may have limited
423 clinical application owing to the cost of accelerometers and the level of expertise and
424 time required for data analysis [40] , as such these methods may be more appropriate
425 as research tool at present. Sedentary behaviour is categorised by posture (sitting or
426 reclining) and low energy expenditure [41]. The assessment methods employed in the
427 current study measured acceleration (movement), therefore sedentary time was
428 determined by low or no movement and not by determining posture. A recent method,
429 termed the Sedentary Sphere makes it possible to identify, analyse and visualise
430 posture from wrist-worn accelerometry data [42], which may improve the assessment
431 of sedentary behaviour in future research. Additionally, sleep duration was determined
432 using a self-report diary. Given the good wear time and compliance evident in the
433 current study it may be feasible to employ 24-hour wear protocols in future studies,
434 which would allow for sleep analysis and the determination of a full 24-hour movement
435 profile.

436 Exercise capacity was not assessed as part of this study. Exercise capacity is known
437 to be an independent predictor of mortality [43] and is also associated with lung
438 function [4] in individuals with CF and could therefore be of significance in relation to
439 both PA and FMD. Exploring the relationship between PA and exercise capacity may
440 be beneficial in view of understanding the nature of exercise intolerance seen in CF,
441 which is likely a consequence of inactivity, pulmonary limitation and impaired skeletal
442 muscle function [44].

443 Participants were tested at different locations and whilst the same ultrasound machine
444 was used different blood pressure monitors and spirometers were used which may
445 have resulted in some variation between groups. Vascular function was only assessed
446 using FMD, future research would benefit from including additional risk factors for CVD
447 including analysis of cholesterol (high and low -density lipoproteins), triglycerides,
448 glucose, and high- sensitivity C-reactive protein to provide a more comprehensive
449 profile of cardiovascular health. Given the indications of adapted vascular structure it
450 may also be of interest to assess intima-media thickness (IMT) in addition to FMD to
451 quantify and track the atherosclerotic process. Furthermore, both the overall group
452 and sub-group consisted of predominately male participants and were not sufficiently
453 powered to explore any potential sex differences. Finally, the researcher performing
454 all FMDs also conducted the analysis and was therefore not blinded for the analysis.

455

456 **6. CONCLUSION**

457 Adults with CF engaged in less moderate to vigorous PA and demonstrated a PA
458 profile reflecting more time spent in lower intensity activity and less time across the
459 range of intensities than their non-CF peers. Analysis of raw acceleration data,
460 reporting the average ENMO and IG metrics can provide meaningful, interpretable and
461 comparable analysis of PA in adults with CF. Higher levels of PA, particularly VPA
462 were associated with positive health outcomes in CF, including lung function and QoL.
463 Further research is required to explore vascular function in individuals with CF and
464 provide a more comprehensive understanding of cardiometabolic risk in this
465 population.

466

467 **7. FUTURE RECOMMENDATIONS**

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

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604 LIST OF FIGURES

605 Figure 1 – CONSORT diagram displaying the recruitment, inclusion/exclusion and
606 completion of participants.

607

608 Figure 2 - Displaying the mean intensity gradient for individuals with CF ($y = -2.62x +$
609 14.93 , $R^2 = 0.92$) (circle markers and dashed line) compared to their non-CF peers
610 ($y = -2.37x + 13.99$, $R^2 = 0.87$) (triangle markers and solid line). A steeper (less shallow)
611 gradient represents a PA profile, reflecting more time spent in lower intensity activity
612 and less time across the range of intensities.