Compensatory Changes in Physical Activity and Sedentary Time in Children and Adolescents with Cystic Fibrosis

Kelly A. Mackintosh[a*], Nicola D. Ridgers[b] & Melitta A. McNarry[a]

[a] *A-STEM, College of Engineering, Swansea University, SA1 8EN, Wales, UK.*

[b] *Institute for Physical Activity and Nutrition Research, School of Exercise and Nutrition Sciences, Deakin University, 221 Burwood Hwy, Burwood, VIC, Australia*

*Dr K. A. Mackintosh

College of Engineering, Swansea University

Bay Campus

Fabian Way

Swansea, SA1 8EN

Tel 01792 295075

Fax 01792 295676

Email: k.mackintosh@swansea.ac.uk

Dr Nicola Ridgers Email: nicky.ridgers@deakin.edu.au

Dr Melitta McNarry Email: m.mcnarry@swansea.ac.uk

Running Title: Physical Activity Compensation in Cystic Fibrosis Youth

Word count: 2,736

Keywords: accelerometry; chronic disease; respiratory health; youth; paediatric

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Physical activity (PA) is a key element in Cystic Fibrosis (CF) treatment strategies, yet little is known as to whether activity compensation occurs. This study examined whether PA and/or sedentary time on one day were temporally associated with time spent in these intensities the following day in youth with CF. Time spent sedentary and in different PA intensities were objectively-measured for seven consecutive days in 50 youth (22 boys; 12.0±2.7 years); 25 with mild-to-moderate CF and 25 age- and sex-matched controls. Multilevel analyses (day and child) were conducted using generalised linear latent and mixed models. On any given day, every additional 10 minutes spent in sedentary time or moderate-to-vigorous physical activity (MVPA) were associated with 1.9 (95%CI: -3.6 to -1.2) and 12.4 (95%CI: -22.1 to -2.9) minutes less sedentary time the following day, respectively. These temporal associations were also observed when split by group (3.1 vs. 1.9 minutes for healthy and CF, respectively). These findings indicate that youth do not compensate their PA, irrespective of disease status, between days, but may compensate their sedentary time between days. Experimental studies are warranted to fully elucidate whether compensatory responses to PA and sedentary time occur, which is fundamental for informing PA promotion strategies.

Keywords: accelerometry; chronic disease; respiratory health; youth; paediatric

Introduction

Cystic fibrosis (CF), currently affecting over 10,000 people in the UK (Cystic Fibrosis Trust, 2017), is the most prevalent inherited genetic disorder in the Caucasian population (Quinton, 1990). CF is a multi-system disease, which primarily affects the lungs and digestive system through mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene that lead to malfunctioning or absent CFTR proteins and impaired mucosal clearance mechanisms (Davies, Alton, & Bush, 2007; National Institute for Health and Care Excellence, 2017; Ratjen, 2009). Despite therapeutic advances and an increased life expectancy to 47 years for those born in 2017 (Cystic Fibrosis Trust, 2017), CF remains incurable, highlighting the need to enhance patient well-being.

Regular participation in physical activity (PA) is an important component in the therapeutic management of individuals with CF (Williams & Stevens, 2013) and is recommended in internationally-recognised guidelines, irrespective of age or disease severity (Radtke, Nevitt, Hebestreit, & Kriemler, 2017; Smyth et al., 2014). In addition to the extensive benefits of leading an active lifestyle in healthy populations (Janssen & Leblanc, 2010), being active elicits further health benefits for those with CF (Hulzebos, Dadema, & Takken, 2013; National Institute for Health and Care Excellence, 2017; Radtke et al., 2017). Specifically, high levels of PA may lead to improved airway clearance by increasing transepithelial fluid transport and reduce, or even prevent, lung function decline (Schneiderman et al., 2014). Furthermore, PA and exercise improve aerobic capacity (Selvadurai et al., 2002), bone mineral density (Buntain et al., 2004), quality of life (Selvadurai, Blimkie, Cooper, Mellis, & Van Asperen, 2004), and ion channel function (Hebestreit,

Kersting, Basler, Jeschke, & Hebestreit, 2001), which not only improves mucus hydration and clearance, but reduces hospital admissions (Wilkes et al., 2007).

Despite the benefits of PA for youth with CF, few engage in moderate-to-vigorous physical activity (MVPA) for 60 minutes every day (Aznar et al., 2014; Mackintosh, Ridgers, Evans, & McNarry, 2018), highlighting the need to develop and implement population-specific PA intervention strategies. However, a significant challenge for CF multi-disciplinary teams is how to promote and encourage MVPA (Cox, Alison, & Holland, 2013) and how to ensure sustained behavior change is achieved. It has been hypothesised that even if interventions are successful at increasing children's PA levels on one day, they may decrease their PA levels on subsequent days to compensate (i.e., the "activitystat" hypothesis; Dale, Corbin, & Dale, 2000; Rowland, 1998; Wilkin, Mallam, Metcalf, Jeffery, & Voss, 2006). Such compensation is thought to occur due to the central nervous system's homeostatic regulation of total PA but the existence and nature of an activitystat in healthy populations has been debated (Gomersall, Rowlands, English, Maher, & Olds, 2013) and little is known about the presence of such behaviours in clinical populations. Specifically, as the activitystat may be considered a homeostatic mechanism, and given the treatment burden and elevated energetic costs in those with CF, one may postulate that they are more likely to display compensatory behaviours than their healthy counterparts (Ridgers, Barnett, et al., 2018). Indeed, even the set-point itself may differ to healthy counterparts, therefore, identifying compensatory behaviours could provide critical information for treatment strategies and on-going care.

The aim of the current study was therefore to examine whether PA and sedentary time on one day are temporally associated with their activity levels on the

following day in children and adolescents with mild-to-moderate CF compared to age- and sex-matched healthy controls.

Materials and Methods

Participants

Twenty-five children and adolescents aged 7 to 17 years with mild-to-moderate CF, confirmed by a sweat chloride >60 $mmol \cdot l^{-1}$ and genotyping (11 Homozygote; 14 Heterozygote; 3 CF-related liver disease; 1 CF-related diabetes), were recruited from a UK CF outpatient clinic. Children with CF were eligible to participate if they had no increase in symptoms or weight loss two weeks prior to testing and had a stable lung function (defined as within 10% of their best in the previous six months). Unstable non-pulmonary comorbidities or acute infections warranted exclusion. All participants with CF were instructed to continue routine prescribed medications. Twenty-five age- and sex-matched apparently healthy counterparts were recruited from local schools. Ethical approval was granted by the Bromley NHS research ethics committee (REC reference: 13/LO/1907). Written informed consent and assent were obtained from parents/guardians and participants, respectively.

Measures

Anthropometry:

Body mass (Seca 220; Hamburg, Germany) and standing and seated stature (Seca 220; Hamburg, Germany) were measured to the nearest 0.01 kg and 0.01 m, respectively. Maturity offset was subsequently estimated as years from peak height velocity using the equations developed by Mirwald et al. (2002). For those with CF, all data was collected during a routine visit to the clinic; healthy age- and sex-

matched counterparts were asked to attend one laboratory session. All measures were taken by trained staff using standardised procedures.

Lung Function:

Forced vital capacity (FVC) and forced expiratory volume in 1s (FEV_1) were assessed using flow-volume loop spirometry (Vitalograph, UK), with the best of three consistent exhalations (<5% variability) used in further analyses. All participants were thoroughly familiarised with the manoeuvre and undertook practice attempts prior to those considered for inclusion. All lung function measurements were expressed as percentage predicted normal according to appropriate reference data (Stanojevic et al., 2009).

Physical Activity and Sedentary Time:

Physical activity and sedentary time were measured at 100 Hz using a hip-mounted ActiGraph GT3X+ accelerometer (ActiGraph LLC, Pensacola, FL). Participants were instructed to wear the monitor for seven consecutive days and advised to remove it for water-based activities (e.g., bathing, swimming) or contact sports. Data were downloaded using ActiLife software (v6.10.4; ActiGraph LLC), processed into 15-second epochs, and reduced using a customised Excel macro. Non-wear time was defined as intervals with at least 20 minutes of consecutive zero's, which is commonly used in youth studies examining compensation (Ridgers, Lamb, Timperio, Brown, & Salmon, 2018; Ridgers, Timperio, Cerin, & Salmon, 2015). Sedentary time was defined as 100 counts·min^{-1} (Ridgers et al., 2012), with time spent in moderate- (MPA; 4-5.99 METs) and vigorous-intensity (VPA; ≥6 METs) physical activity determined using age-adjusted cut-points (Freedson, Pober, & Janz,

2005). MPA and VPA were summed to obtain MVPA. Time spent in light-intensity physical activity (LPA) was defined as >100 counts·min^{-1} to the MPA cut-point. A valid day was defined as at least 9 hours of wear time. Participants with at least 3 valid days of data, irrespective of week or weekend day, were included in the analyses (Mattocks et al., 2008).

Statistical Analyses

All statistical analyses were conducted using Stata SE v15 (StataCorp, Texas, USA). Independent t-tests were conducted to examine differences between participants who were included and excluded from the analyses and between the CF and healthy groups for all descriptive variables (mean ± SD).

Multilevel analyses were performed using generalised linear latent and mixed models (GLLAMM). This approach accounted for the nested nature of the data arising from multiple days of accelerometer measurements within the same participant (Twisk, 2006). A two-level model was used in all analyses, namely day (level 1) and participant (level 2). GLLAMM was used to estimate associations between temporally adjacent values (i.e., pairs of days) for the outcome variables whilst adjusting for person-level (overall daily mean) sedentary time and/or PA, as appropriate. As GLLAMM can separate participant-level from day-level effects (i.e., within-person changes), these analyses are a more appropriate measure of compensatory changes (Ridgers, Timperio, Cerin, & Salmon, 2014). The analyses examined whether participants activity on one day (day *d* in the model) was associated with their activity from the previous day (day *d-1* in the model). As data were collected over seven consecutive days, each participant provided a maximum of six data points for analysis. In all models, the random structure considered random

intercepts and slopes at the participant level. GLLAMMs were initially performed for the whole sample and adjusted for sex, age, day of measurement, group (CF and healthy), monitor wear time on a given day, and person-level PA and/or sedentary time, as appropriate. To examine whether these associations differed between groups, the analyses were subsequently performed for the CF and healthy groups separately. A two-tailed probability level of 0.05 was used for all analyses.

Results

Forty-three participants (24 boys, 19 girls; 21 CF, 22 healthy controls) met wear time criteria and were included in the analyses. There were no significant differences in the descriptive data of the included or excluded participants, and both CF and healthy participants engaged in similar levels of sedentary time and PA (Table 1). On average, participants provided 6.1 ± 0.9 valid days for analysis.

****Table 1 near here****

The associations between temporally adjacent values for PA and sedentary time for the whole sample are shown in Table 2. On any given day, every additional 10 minutes spent sedentary was associated with 2.1 minutes less sedentary time the following day (95% CI: -3.6 to -1.2). In contrast, on any given day, each additional 10 minutes spent in MVPA was associated with 12.4 minutes less sedentary time the following day (95% CI: -22.1 to -2.9).

****Table 2 near here****

The associations between temporally adjacent values for PA and/or sedentary time for the healthy and CF groups are shown in Tables 3 and 4, respectively. Two statistically significant associations were observed for the healthy group, and one observed for the CF group. Specifically, on any given day, each additional 10 minutes spent sedentary was associated with 3.1 (95% CI: -5.3 to -1.0) and 1.9 (95% CI: -3.6 to -0.3) minutes less sedentary time in the healthy and CF groups, respectively. Lastly, on any given day, each additional 10 minutes that participants in the healthy group engaged in MVPA was associated with 18.1 minutes less sedentary time the following day (95% CI: -33.8 to -2.4).

****Tables 3 and 4 near here****

Discussion

This study examined whether increased PA levels or sedentary time on any given day were temporally associated with these behaviours the following day in children and adolescents with CF and age- and sex-matched healthy controls. Youth, regardless of condition, do not appear to compensate for increased PA, of any intensity, but partially compensated for time spent being sedentary. Furthermore, findings suggest that increased MVPA on any given day was associated with decreased sedentary time the following day. However, this effect was not observed for those with CF when independent group models were utilised.

No associations were found between time spent in PA on any given day and PA on a subsequent day, irrespective of intensity or condition. This suggests that youths do not compensate for increased PA levels on one day by decreasing their PA levels the following day. Whilst this is not consistent with the "activitystat"

hypothesis (Rowland, 1998) and contrasts previous research that used the same analytical approach in healthy children (Ridgers, Barnett, et al., 2018; Ridgers et al., 2014), the present findings are consistent with others who reported that healthy youths do not compensate between days (Baggett et al., 2010; Goodman, Mackett, & Paskins, 2011). Such discrepancies may, at least in part, be attributed to methodological differences in PA measurement analyses (e.g., wear time criteria), thereby limiting inter-study comparability. Nonetheless, a possible explanation may be that populations, or indeed individuals, compensate total PA levels in different ways, though there is a lack of consensus regarding the time frame over which this occurs. Specifically, some research suggests that youths can tolerate discrete bouts of activity (Ridgers, Lamb, et al., 2018), whilst others have demonstrated *within-day* compensation (Ridgers et al., 2015). Gomersall et al. (2013) contend that it is unlikely to be demonstrated on a day-to-day basis, citing previous interventions that have reported compensatory responses which ranged from approximately 1 to 3 months, due to the period of the homeostatic regulatory response (Baggett et al., 2010; Goodman et al., 2011). Indeed, it may be that compensatory effects take longer to emerge in clinical populations such as those with CF and that even the specific innate 'set-point' may vary between individuals depending on biological, psychosocial and physical environment-related factors (Eisenmann & Wickel, 2009; Rowland, 1998). It is also important to highlight that the intensity of physical activity may be a key determinant in whether compensatory responses are observed, although this remains to be elucidated, along with the potential interaction between an activitystat and health and environmental-related parameters.

In this study, temporal associations were found between time spent in MVPA on any given day and time spent being sedentary the subsequent day. Specifically,

for every additional ten minutes spent in MVPA, children and adolescents engaged in 12.1 minutes less sedentary time the following day, although this was only statistically significant in the healthy youth. Whilst this may be a spurious finding as suggested in a previous study (Ridgers et al., 2014), if replicable, the current results refute the notion of a compensatory PA response, irrespective of clinical condition. In contrast, the present study suggests that youth may demonstrate a regulatory homeostatic mechanism for sitting time (i.e., a "sedostat"; Olds, Maher, Ridley, & Kittel, 2010). Specifically, for every ten additional minutes spent being sedentary on any given day, youth spent 2.1 minutes less time being sedentary the following day. Caution is required when interpreting this potential compensatory response given the small sample size and magnitude of the response. Furthermore, the day-to-day variability in sedentary time largely remains to be determined, although the limited evidence available appears to suggest that sedentary behaviours are fairly stable (Basterfield, Adamson, Pearce, & Reilly, 2011). However, it is nonetheless interesting to note that the magnitude of compensation was greater in healthy participants compared to those with CF. Given that previous research has questioned whether such homeostatic mechanisms are physiological or predominantly reflect environmental and sociological elements (Epstein, Paluch, Kilanowski, & Raynor, 2004), the partial compensation in those with CF could be due to their high treatment burden, inhibiting time available for a greater compensatory response. It is therefore possible that the exhibited compensation may not be evidence of an activitystat, or even a sedostat, *per se*. Nonetheless, given that daily treatment duration remains relatively consistent, excluding treatment associated with exacerbations, it could be argued that activity opportunities for those with CF also remain constant. It could therefore be postulated that healthy populations are less tolerant to increased

sedentary time, or those with CF have a smaller relative amount of time to compensate. Future research is required to verify the apparent disease-related differences observed in the present study; future studies may wish to consider moderator analyses to help further elucidate these differences.

Additionally, or perhaps alternatively, discrepancies between health conditions may be related to the cut-points used to define activity intensities. Whilst the cut-points utilised have demonstrated acceptable classification accuracy in youth (Trost, Loprinzi, Moore, & Pfeiffer, 2011), the lack of cut-points developed and validated for CF populations may have resulted in misclassifications of time spent in relative intensities (Mackintosh et al., 2018). However, it should be noted that there were no significant differences in PA levels between those with CF and their age- and sex-matched healthy controls. Indeed, 47.6% of our CF population met recommended guidelines, which is a considerably higher proportion than previously reported (Aznar et al., 2014). It could be speculated that greater compensatory responses would have been apparent in less active individuals, who may have a lower innate activitystat and thus an increase of 10 minutes MVPA would be a greater percentage of their overall daily activity levels. Alternatively, more active youth may have a greater tolerance around the 'set-point'. However, Ridgers et al. (2018) found few variables which moderated such compensatory effects. Although research suggests that youths may be able to tolerate isolated increases in PA (Ridgers, Lamb, et al., 2018), the threshold required to trigger a compensatory response is presently unknown. It could be postulated that the reduced exercise capacity characteristic of the CF population may lower such a threshold, though further experimental work is required to identify the smallest meaningful

compensatory response. Such research should account for factors such as fitness and lung function (FEV_1), which may moderate any compensatory responses.

No other studies have investigated the activitystat hypothesis in those with CF, thereby precluding specific population comparisons. In healthy populations, the literature is dominated by observational studies, which have reported mixed findings; few experimental studies have been conducted. This lack of consensus regarding compensatory changes may be explained, at least in part, by inter-study methodological differences, including, but not limited to, previous studies failing to account for person-level variation in responses. Indeed, Selvadurai et al. (2004) reported significant influences of maturity on PA levels in those with CF, and a failure to account for this, as well as disease severity, may limit interpretation. Nonetheless, the concept of a biological control of PA and the activitystat for those with CF has significant implications; given the numerous additional health benefits for those with CF (National Institute for Health and Care Excellence, 2017; Schneiderman et al., 2014), over and above those identified in healthy children (Janssen & Leblanc, 2010), the present study highlights that it may be feasible to increase total physical activity without compensatory responses to discrete bouts of PA.

The present findings have potential implications for the development and delivery of PA interventions for youth with CF. Whilst specific PA and exercise recommendations remain in their infancy, HIIT has been specifically identified as a potential strategy to enhance PA levels in those with CF (Cox & Holland, 2017). However, Kriemler et al. (1999) suggest that high-intensity exercise may be associated with compensation when other intensities are not, questioning the potential applicability of this exercise modality to increasing overall physical activity

levels. Future studies should therefore specifically examine whether compensation occurs as a result of participating in prescribed PA or exercise interventions and its interaction with exercise intensity. Moreover, such research should seek to measure total energy expenditure, as well as total PA levels, as, whilst PA is likely to be the predominant contributory factor to total energy expenditure, it could be argued that disease severity may have significant implications on energy expenditure. Indeed, Gomersall et al. (2013) identified that researchers should clearly distinguish between an 'activitystat' and 'energystat'.

This is the first study to examine compensatory changes in objectively-measured PA levels and sedentary time between days in children and adolescents with CF. Nonetheless, several limitations should be acknowledged and the present results should be interpreted with caution. Specifically, this study was observational in nature; future experimental research should aim to increase or decrease PA during specific periods of inactivity or activity, respectively, to ascertain *if*, and indeed *when*, compensatory effects occur (Ridgers, Lamb, et al., 2018). The sample size also restricted the number of person-level variables that could be investigated, which may potentially moderate the compensatory effect (Ridgers, Barnett, et al., 2018). Furthermore, given that no CF-specific cut-points are currently available, those developed for healthy children were applied to those with CF. This may have resulted in the misclassification of sedentary time and activity intensities which limits the interpretation of the present results. It is also pertinent to note that further research is required to identify the duration required to classify as clinically meaningful compensatory behaviour.

Conclusions

In conclusion, these findings are inconsistent with the activitystat hypothesis, regardless of population. However, youth may compensate for sedentary time, albeit to a lesser extent in those with CF. These findings highlight that it may be possible to enhance PA levels in youth CF populations, without concomitant increases in deleterious sedentary time.

Acknowledgements

We would like to thank Dr Rachel Evans, Michelle Barry and Julie Clarke from the Department of Child Health at Morriston Hospital, Swansea, for their assistance in conducting this study and the volunteers for their participation. The authors acknowledge Eoin O'Connell for the development of the customised Excel macro. NDR is supported by a National Heart Foundation of Australia Future Leader Fellowship (ID 101895).

Declaration of Interest

The authors have no competing interests to declare.

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468 **Table 1: Participant characteristics and activity levels (mean ± SD)**

	Whole Sample	**Cystic Fibrosis**	**Healthy Controls**
	n = 43	***n = 21***	***n = 22***
Participant Characteristics			
Age (years)	11.9 ± 2.6	12.1 ± 2.6	11.7 ± 2.7
Stature (cm)	147.4 ± 13.7	146.0 ± 13.5	148.8 ± 14.1
Body mass (kg)	43.0 ± 12.6	41.9 ± 11.5	44.1 ± 13.7
BMI ($kg \cdot m^{-2}$)	19.3 ± 3.2	19.3 ± 2.8	19.4 ± 3.6
Maturity Offset (yrs)	-1.04 ± 2.3	-1.04 ± 2.4	-1.04 ± 2.3
FVC (% predicted)	85 ± 13	82 ± 12	88 ± 14
FEV_1 (% predicted)	86 ± 13	80 ± 10	92 ± 14
ActiGraph Data			
Sedentary time ($min \cdot day^{-1}$)	566.4 ± 65.3	555.8 ± 59.9	576.5 ± 69.9
LPA ($min \cdot day^{-1}$)	222.9 ± 50.8	225.5 ± 50.4	220.6 ± 52.3
MVPA ($min \cdot day^{-1}$)	60.7 ± 33.4	58.9 ± 36.9	62.2 ± 30.3
Wear time ($min \cdot day^{-1}$)	848.6 ± 44.0	840.3 ± 48.9	856.7 ± 38.2

469 FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second.

470

Table 2: Associations between time (min) spent in different physical activity intensities and sedentary time variables between pairs of days (all participants; n=43)

	Between-days model[a]	
	b (95% CI)	***p* value**
$SED_{D1} \rightarrow SED_{D2}$	-0.24 (-0.36 to -0.12)	**<0.001**
$LPA_{D1} \rightarrow LPA_{D2}$	-0.05 (-0.20 to 0.11)	0.57
$MVPA_{D1} \rightarrow MVPA_{D2}$	-0.01 (-0.49 to 0.47)	0.96
$SED_{D1} \rightarrow LPA_{D2}$	0.01 (-0.09 to 0.09)	0.97
$SED_{D1} \rightarrow MVPA_{D2}$	0.02 (-0.04 to 0.08)	0.61
$LPA_{D1} \rightarrow SED_{D2}$	-0.20 (-0.42 to 0.03)	0.08
$LPA_{D1} \rightarrow MVPA_{D2}$	0.03 (-0.09 to 0.14)	0.68
$MVPA_{D1} \rightarrow SED_{D2}$	-1.24 (-2.21 to -0.29)	**0.01**
$MVPA_{D1} \rightarrow LPA_{D2}$	-0.12 (-0.76 to 0.53)	0.72

[a]Analyses adjusted for: sex, decimal age, condition, measurement day, wear time, person-level physical activity and/or sedentary time

Table 3: Associations between time (min) spent in different physical activity intensities and sedentary time variables between pairs of days (healthy matched controls)

	Between-days model[a]	
	b (95% CI)	***p* value**
$SED_{D1} \rightarrow SED_{D2}$	-0.31 (-0.53 to -0.10)	**<0.01**
$LPA_{D1} \rightarrow LPA_{D2}$	0.11 (-0.15 to 0.37)	0.40
$MVPA_{D1} \rightarrow MVPA_{D2}$	-0.23 (-1.02 to 0.57)	0.58
$SED_{D1} \rightarrow LPA_{D2}$	0.11 (-0.04 to 0.25)	0.15
$SED_{D1} \rightarrow MVPA_{D2}$	-0.01 (-0.13 to 0.09)	0.81
$LPA_{D1} \rightarrow SED_{D2}$	-0.31 (-0.70 to 0.09)	0.13
$LPA_{D1} \rightarrow MVPA_{D2}$	-0.03 (-0.23 to 0.17)	0.77
$MVPA_{D1} \rightarrow SED_{D2}$	-1.81 (-3.38 to -0.24)	**0.02**
$MVPA_{D1} \rightarrow LPA_{D2}$	0.56 (-0.48 to 1.59)	0.29

[a]Analyses adjusted for: sex, age, measurement day, wear time, person-level physical activity and/or sedentary time

Table 4: Associations between time (min) spent in different physical activity intensities and sedentary time variables between pairs of days (CF patients)

	Between-days model[a]	
	b (95% CI)	***p* value**
$SED_{D1} \rightarrow SED_{D2}$	-0.19 (-0.36 to -0.03)	**0.02**
$LPA_{D1} \rightarrow LPA_{D2}$	-0.10 (-0.30 to 0.10)	0.33
$MVPA_{D1} \rightarrow MVPA_{D2}$	0.25 (-0.37 to 0.86)	0.43
$SED_{D1} \rightarrow LPA_{D2}$	-0.43 (-0.16 to 0.07)	0.46
$SED_{D1} \rightarrow MVPA_{D2}$	0.04 (-0.04 to 0.12)	0.38
$LPA_{D1} \rightarrow SED_{D2}$	-0.14 (-0.42 to 0.15)	0.36
$LPA_{D1} \rightarrow MVPA_{D2}$	0.06 (-0.08 to 0.21)	0.41
$MVPA_{D1} \rightarrow SED_{D2}$	-1.01 (-2.27 to 0.24)	0.11
$MVPA_{D1} \rightarrow LPA_{D2}$	-0.38 (-1.23 to 0.46)	0.38

[a]Analyses adjusted for: sex, age, measurement day, wear time, person-level physical activity and/or sedentary time