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Original Research Article

Natural variability of daily physical activity measured by accelerometry in children with a mitochondrial disease

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ABSTRACT

In this exploratory study we aimed to select the most valid and feasible accelerometer to measure daily physical activity at home in 10 children with mitochondrial disease. Using the experimentally-selected GENEActiv, good to excellent short- and long-term test-retest reliability of daily physical activity was found. Especially in children with more severe limitations daily physical activity seemed more stable and less susceptible to weather conditions. Moreover, small standard errors of measurement were found, indicating high precision of this measuring method. We conclude that measuring daily physical activity using accelerometry is a promising outcome measure for future studies in this unique population.

1. Introduction

Mitochondrial disorders are the most prevalent inherited metabolic diseases with an estimated prevalence of 1 in every 5000 live births (Schaefer et al., 2004). For most mitochondrial diseases, no treatment has shown a clear benefit on a clinically relevant outcome measure (Pfeffer et al., 2012; Kerr, 2013), but multiple phase 2 studies are currently being conducted in adults with a mitochondrial disease (Koopman et al., 2016; ClinicalTrials.gov identifier, NCT02909400; NCT02976038; NCT01370447). One of the major challenges for clinical trials in rare diseases, is the selection of clinically relevant and robust outcome measures.

Since the most burdensome symptoms that children with mitochondrial disorders and their parents experience are fatigue and lack of energy (Koene et al., 2013), measuring these symptoms could be a clinically relevant endpoint. However, fatigue and lack of energy are often subjective and difficult to measure objectively. This is especially true for children with a mitochondrial disease, since most questionnaires and endurance tests are not feasible or too burdensome for children with a mitochondrial disorder due to intellectual and physical disabilities. Moreover, measuring physical activity in a test situation at one time point does not reflect physical activity performance in daily life (Jimenez-Moreno et al., 2017).

We previously showed that accelerometry is able to detect differences in physical activity in daily life between children with a mitochondrial disorder and their healthy peers (Koene et al., 2017). However, the device used in our previous study (the MOX-accelerometer) was not suitable for future studies, mainly due to labor-intensity and technical difficulties. Some commercially-available activity monitors are expected to be more easy-to-use and stable, but may offer less detailed activity monitoring. However, there are commercially-available research-focused accelerometers that are both user-friendly and offer highly detailed activity monitoring, allowing researchers to focus on the clinically relevant aspects for the specific population.

The aim of this study is two-fold, first to select a single valid and feasible commercially-available accelerometer for future studies in children with mitochondrial disorders (part 1) and secondly to determine the short- and long-term test-retest reliability and standard error of measurement of measuring daily physical activity with this accelerometer, using a tailored analysis (part 2).

2. Methods

This exploratory, observational study is divided into two parts (see Fig. 1). First we selected the most suitable accelerometer from a preselected group of three commercially-available accelerometers based on

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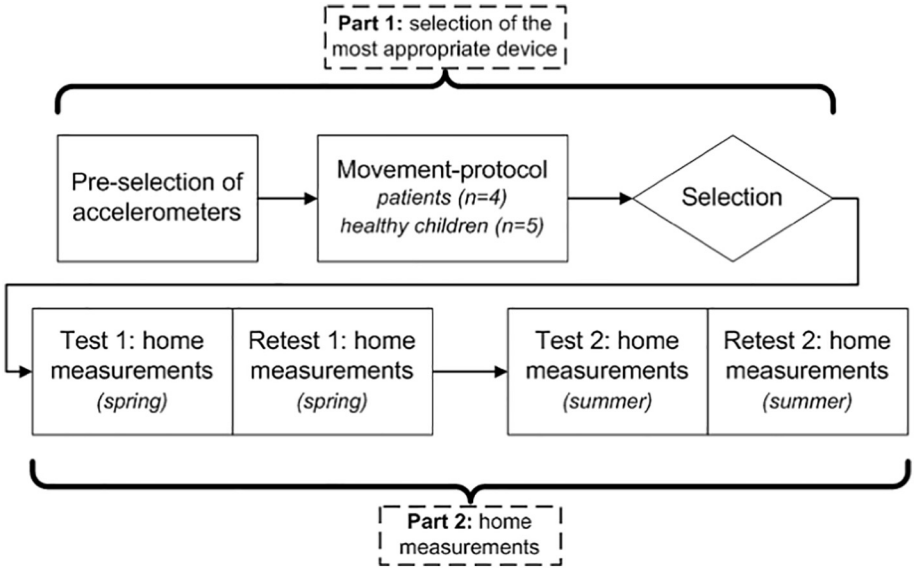

Fig. 1. Flowchart of the complete study protocol, separating part 1 (selection of the most appropriate device) and part 2 (home measurements).

their validity and feasibility during a structured movement-protocol in a laboratory setting. Secondly, we studied the short- and long-term test-retest reliability and standard error of measurement of the selected accelerometer during two home situation measurements of 2 weeks in spring and in summer.

This study was approved by the regional Medical Research Ethics Committee (MREC NL59062.091.16). In accordance with the Helsinki agreement, written informed consent was obtained from the subject's legal guardian and, where indicated, the participant.

2.1. Part 1: Selection of most appropriate accelerometer

2.1.1. Study population

Patients were recruited from the Radboud Center for Mitochondrial Medicine, healthy subjects were recruited from sports clubs in Nijmegen and via social media. Patients aged 3–18 carrying a genetic mutation leading to a symptomatic mitochondrial disorder were eligible for inclusion.

2.1.2. Accelerometers

From the different commercially available accelerometers, we pre-selected three accelerometers based on their specifications and availability: the ActiWatch 2 (Phillips Respironics), the GENEActiv Original (ActivInsights) and the SenseWear Mini (BodyMedia Inc.). The ActiWatch 2 is a uni-axial, wrist-worn accelerometer that was set to measure activity counts at 15-second epochs. The GENEActiv is a tri-axial, wrist-worn accelerometer that was set to measure at 20 Hz. Using the GENEActiv Software (V.3.1.) the raw data was converted into 1-second epochs, of which we used the gravity subtracted sum of vector magnitudes (SVMgs) as the activity measure. The SVMgs was calculated using Eq. (1) (Activinsights, 2012). The SenseWear is a tri-axial, upper arm-worn accelerometer using a not publicly available algorithm combining acceleration and heat-related data to calculate energy expenditure at 60-seconds-epochs.

Eq. (1): Calculation of SVMgs

$$SVM_{gs} = \sum \sqrt{x^2 + y^2 + z^2} - 1g \quad (1)$$

2.1.3. Study protocol

All subjects came to the hospital to conduct a movement-protocol while wearing all three accelerometers at the same time, located on the left wrist (GENEActiv), right wrist (ActiWatch) and left upper-arm (SenseWear). The movement-protocol consisted of lying down, sitting (still, while playing a handheld videogame and while catching and throwing a ball), standing (still and while catching and throwing a ball) and walking, running and cycling at different velocities and intensities (see Supplementary Table S2), each for 1 min. Performing the complete protocol took 26 min, but the subjects were allowed to stop if they got too tired to continue. The movement-protocol was designed together with pediatric physiotherapists and rehabilitation specialists, to measure commonly performed basic body positions and to reflect a wide variety of typical daily activities for Dutch children. One researcher instructed all subjects to establish the movements. Moreover, the subjects were filmed while performing the protocol, to correlate the data to the actual movements. Afterwards, the subjects were asked which accelerometer they preferred the most and which the least, based on size, position and comfort.

2.1.4. Analysis

The results of this validity and feasibility study were used to select one accelerometer for the second part of the study. Validity was assessed by calculating the Intraclass Correlation Coefficients for absolute agreement (ICCs) per accelerometer using SPSS (IBM, v22). The activity measured by the accelerometers were compared to the Metabolic Equivalent of Tasks (METs) belonging to each type of movement during the protocol. ICCs of 0.5–0.75 were defined as moderate, of 0.75–0.9 as good and above 0.9 as excellent reliability (Koo and Li, 2016). The MET is a physiological measure expressing the energy cost of physical activities (Compendium of Physical Activities (Ainsworth et al., 2011)). To assess the feasibility, various aspects of the accelerometers were taken into account, including the transparency of data processing, analysis options, water resistance and the subjects' opinions.

2.2. Part 2: Home measurements

2.2.1. Study population

Patients aged 3–18 years carrying a genetic mutation leading to a mitochondrial disorder were eligible for inclusion and were recruited from the Radboud Center for Mitochondrial Medicine.

2.2.2. Study protocol

The aim of the second part of the study was to determine the test-retest reliability and standard error of measurement of daily physical activity using the accelerometer selected in the first part of our study

(the GENEActiv). All subjects wore the accelerometer for 14 consecutive days during spring, of which the first 7 days were the initial test and the second 7 days were the short-term retest (STRT1). A second STRT (STRT2) was conducted by measuring again for 14 days in the same patients during summer. If patients attached the accelerometer late, subjects were excluded from the analysis of the impacted parameters, such as wake time and total activity during the first weekend and week. By comparing the second week (the week with complete measurements for all participants) of each measurement, the long-term retest (LTRT) reliability was assessed as well.

To obtain complete measurements of 14 full days, the children were asked to attach the accelerometer the night before the start of the measurements and remove it the morning after the measurements had ended. Children were instructed to continue with their normal daily life while wearing the GENEActiv for 24 h per day on their non-dominant wrist. The feasibility of this study protocol was determined by reporting the number of patients who were not compliant with the protocol, the number of technical failures and the number of patient reporting discomfort. Since the accelerometer is waterproof, the children were instructed to continue wearing the device while swimming and taking a shower. During both measurement periods, the children or their parents kept a diary in which they had to log their activities during the measurements and could note whether the accelerometer was fitting well or whether the child experienced any burden of wearing the accelerometer. Also, if significant disturbances in activity would be measured, the diaries could help verify the data. After the measurements, the participants sent the accelerometer and the diary back to the researchers for analysis. The accelerometer does not have any display, so the subjects did not receive feedback about their physical activity.

Since daily activity in healthy children is subject to weather conditions and seasonal variability (Atkin et al., 2016), different weather parameters were collected during the measurements from weather stations closest to the home of each subject (Koninklijk Nederlands Meteorologisch Instituut).

2.2.3. Analysis

For all measurements, the accelerometers were set to measure at 20 Hz and the raw data was converted into a SVMgs in 1-second epochs. Using a custom designed script in MatLab (MathWorks, R2014b) we calculated over 40 parameters, which were expected to be relevant to children with mitochondrial disease, such as activity after school and sleep time. The moment of waking up and going to sleep were defined by the script and if needed manually corrected based on the measured activity and the diaries kept by the children and their parents. Subsequently, these moments were used to calculate wake times for each day of each subject and parameters were calculated over this wake time. All parameters were expressed per morning, afternoon, evening, full day and the complete 7-day week. Activity was also divided over four intensity categories using the pediatric cut-points established by Phillips et al. (Phillips et al., 2013): sedentary (SVMgs < 7), light (SVMgs 7–19), moderate (SVMgs 20–60) and vigorous (SVMgs > 60). Counts were calculated by multiplying the average activity per timeframe (e.g. waking hours) by the amount of seconds in that timeframe. This way the parameter counts/day reflects both the length and intensity of activity during waking hours.

Several custom designed activity parameters were included, such as the number of sedentary bouts longer than 30 or 60 min and the activity during the first hour after waking up. Finally, we focused on the highest average activity measured over different time-intervals, from 1 s up to 2 h, since a previous study showed that children with mitochondrial disease mainly differ from healthy peers in their peak activity (Koene et al., 2017). All parameters were chosen based on previous studies, experience and clinical expert opinion.

To assess the test-retest reliability of measuring daily physical activity in children with mitochondrial disease, ICCs were calculated for each parameter.

The standard error of measurement (SEM) is an estimate of error to use in interpreting an individual's test score. The SEM can be estimated and may be needed in future research with a low number of children with a mitochondrial disease. The SEM was estimated for the total activity and the most active 5–15 min and 30–120 min of the day.

Using the data of the LTRT, the SEM was estimated using Eq. (2).

Eq. (2): Calculation of SEM

$$SEM = SD\sqrt{1 - ICC} \quad (2)$$

The SEM% was calculated using Eq. (3).

Eq. (3): Calculation of SEM%

$$SEM\% = SEM/mean \quad (3)$$

3. Results

3.1. Part 1: Selection of most appropriate accelerometer

Four patients (one girl) and five healthy children (three girls) aged 3–18 years (mean age 11.6 years) participated in the first part of the study. Detailed patients characteristics are shown in Supplementary Table S1. We included subjects with a broad range of phenotypes, ages and heights to study the validity and feasibility in a diverse population.

The validity was good for almost the complete movement-protocol for all three accelerometers (Fig. 2). The ActiWatch had the lowest validity (ICC = 0.592), mainly due to the overestimation of throwing a ball and the underestimation of cycling on a stationary bicycle. This underestimation was also seen in the GENEActiv, but the overestimation of throwing a ball was much less prominent, resulting in a moderate consistency (ICC = 0.747). The SenseWear had the least over- or underestimation during the movement-protocol and showed a good validity (ICC = 0.889).

No pain or major inconvenience was experienced by any of the subjects while wearing the accelerometers. The wrist-worn accelerometers (ActiWatch and GENEActiv) were preferred most by the subjects. Attaching the SenseWear was not accepted by the 3-year old child and one older child said that she did not want to wear the SenseWear during summertime because of social acceptability. The GENEActiv was the only accelerometer that uses a transparent method of data processing, by offering raw data and using an available formula. The SenseWear uses an algorithm that is not publicly available and is the only non-waterproof accelerometer in our study.

We summarized the validity and feasibility of each accelerometer in Table 1. Based on the moderate validity and good feasibility, we selected the GENEActiv for the second part of our study.

3.2. Part 2: Home measurements

Ten ambulatory patients aged 3–16 years were included for the second part of the study (see Table 2). The group consisted of five boys and five girls (median age of 12.5 years) with Leigh(− like) syndrome (n = 2), Sengers-like syndrome (n = 1), MELAS syndrome (n = 1), or a non-syndromic mitochondrial disorder (n = 5). The most prevalent symptoms were fatigue and exercise intolerance. During the first measurement, two subjects did not attach their GENEActiv before going to bed on Friday, but during the course of the first Saturday. Four children attached their GENEActiv late during the second measurement, one of which not until Sunday afternoon. These subjects were excluded from the analysis of the first week of the summer measurement. One child was completely excluded for the second measurement due to orthopedic surgery between the two measurements. During measurements, no child removed the accelerometer, resulting in zero non-wear time. A grand total of 265 days were recorded, during which no subject reported any discomfort and no technical problems occurred. Across all measurements, no corrupt or invalid data was detected, thus no removing or replacing of data was needed. This resulted in over

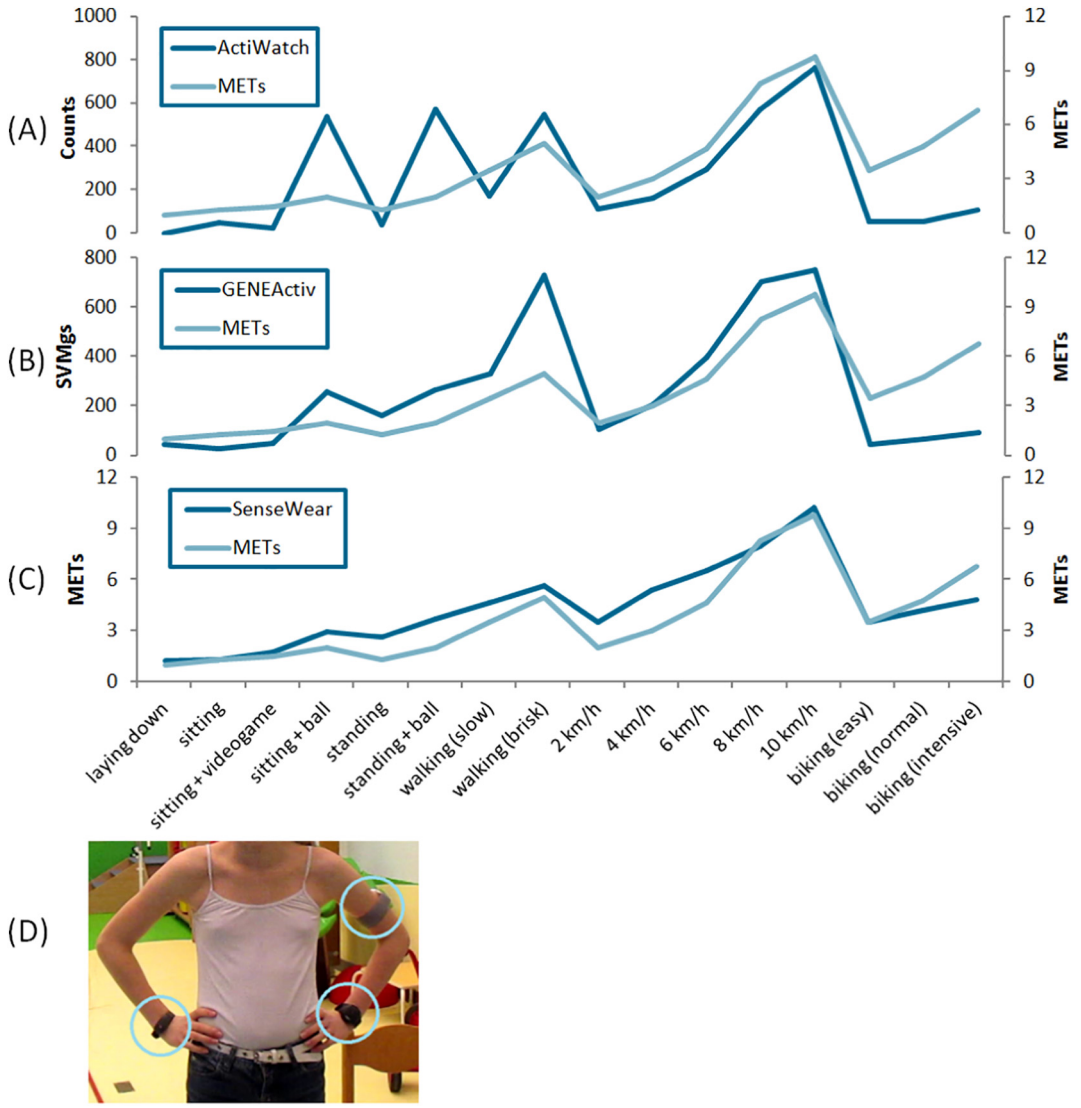

Fig. 2. Movement-protocol activity graphs per accelerometer. The upper panels show the activity measured by the ActiWatch (A), GENEActiv (B) and SenseWear (C), as well as the expected activity in METs. Panel D shows the three devices, as worn during the movement-protocol. METs = Metabolic Equivalent of Task; SVMgs = gravity subtracted sum of vector magnitudes.

20 million data points, from which a wide variety of parameters were calculated. A graphical presentation of 14 days of home measured physical activity from two subjects is shown in Supplementary Fig. S1.

An overview of the activity measured during both measurements is shown in Table 3. There was a significant inverse correlation between physical activity and age ($r = -0.79$, $p \leq .01$). There was no significant difference between activity on weekdays and during the weekends (mean activity weekdays 76,709 counts/day (range 23,034–166,143), mean activity weekends 71,037 counts/day (range 26,114–152,843); $p = .386$). As expected, the amount of measured activity was related to the disease severity of the subjects. The two least active children were diagnosed with Leigh-syndrome and MELAS syndrome, whereas the two most active children are non-syndromic patients with fatigue and (mild) exercise intolerance. This (qualitative)

Table 1
Validity and feasibility scores per accelerometer. ICC = Intraclass Correlation Coefficient for absolute agreement.

		ActiWatch	GENEActiv	SenseWear
Validity		ICC = 0.592 (moderate)	ICC = 0.747 (moderate)	ICC = 0.889 (good)
Feasibility	Wear location	Wrist	Wrist	Upper-arm
	Size	43 × 23 × 10 mm	43 × 40 × 13 mm	55 × 62 × 13 mm
	Weight	16 grams (with strap)	16 gram (without strap)	45 grams (with strap)
	Waterproof	Yes	Yes	No
	Rated as favorite[a]	3 times	2 times	0 times
	Rated as least favorite	0 times	0 times	3 times
	Transparency of data processing	Limited	Good	Limited

[a] Not all children had a preference

Table 2
Patient characteristics for part 2 of the study, showing the most representative symptoms of the patients.

Characteristic	Patients (n = 10)
Age, years (median; range)	12.5; 3–16
Female (n)	5
Genotype	
MT-TL1 (m.3243A > G)	3
MT-ATP6 (m.9185T > C)	1
AGK (c.1131 + 5G > A)	1
SDHA (c.64-2A > G)	1
RARS2 (c.442A > G; c.1519G > A)	1
NDUFS7 (c.364G > A)	1
MTFMT (c.626C > T; c.766C > T)	1
OPA1 (c.910C > T)	1
Symptoms[a]	
Fatigue (n)	8
Exercise intolerance (n)	7
Psychomotor retardation (n)	3
Ataxia (n)	3
Cardiomyopathy (n)	1

[a] Not mutually exclusive and not including all symptoms of all patients

observation was true for total activity, intensity and peak-activity such as highest average activity over 15 min.

3.2.1. Test-retest reliability

The GENEActiv showed overall good STRT reliability in both spring (median of all ICCs 0.910 (range 0.684–0.978)) and summer (median ICC 0.909 (range 0.678–0.986)) and comparable LTRT reliability (median ICC 0.827 (range 0.498–0.963); Table 3). Nearly all parameters calculated over a full week showed good to excellent reliability, both for activity and intensity. Moreover, the ICCs of the maximal average activity showed to be good to excellent for almost all time-intervals.

The SEM% estimated for total activity was 1.7%, for the most active 5–15 min of the day 14–15% and for the most active 30–120 min of the day 20–22%.

Weather conditions differed between the two measurements. During spring, temperatures were lower (spring 14.0 °C, summer 17.5 °C; $p < .01$), and there was less rainfall (spring 1.2 mm/day, summer 3.4 mm/day; $p < .01$) than during summer. Moreover, temperatures were more stable during summer compared to spring (range spring 8–22.1 °C, range summer 15.6–20.7 °C). The duration of sunshine was not significantly different between spring and summer (spring 6.4 h/day, summer 5.2 h/day; $p = .073$). On a group level, the mean activity of all subjects per day showed a moderate positive correlation with the temperature ($r = 0.48$, $p = .01$; $n = 28$; Fig. 3). Individually, this association was most prominent in the two most active children and absent in the two least active children. Despite the differences in weather conditions between spring and summer, there were no significant differences in activity between the two measurements (Table 3).

4. Discussion

The aim of this exploratory study was to determine the feasibility and short- and long-term test-retest reliability of quantification of physical activity in a home situation in children with a mitochondrial disease. Based on validity and acceptability, we selected the GENEActiv as a valid and feasible accelerometer for measuring physical activity in children with a mitochondrial disease. Using this accelerometer in a

Table 3
Results of the home measurements during spring and summer per calculated parameter. Intraclass Correlation Coefficients were calculated to assess the short term test-retest reliability (STRT1 for spring and STRT2 for summer). Long term test-retest reliability (LTRT) was calculated using the second week of both measurements. Parameters with a good to excellent reliability (ICC > 0.75) are shown in bold and were significant.

Parameter	Spring			Summer			Spring vs. summer	
	Median	Range	ICC STRT1 (n = 10)	Median	Range	ICC STRT2 (n = 9)	Spring compared to summer (p-value)	ICC LTRT (n = 9)
Wake time (h/day)	14.8	13–15.6	**0.828**[a]	14.7	13–16.2	**0.909**[b]	0.374	**0.906**
Total activity (counts/day)	75,480	37,407–133,932	**0.800**	78,717	37,928–135,797	**0.978**	0.859	**0.879**
Average activity (counts/s)	1.41	0.67–2.66	**0.918**	1.52	0.65–2.66	**0.981**	0.515	**0.900**
Sedentary (average % per day)	76.1	58.6–91.2	**0.884**	74.2	57.8–91.4	**0.951**	0.953	**0.825**
Light (average % per day)	19.2	8.3–29.3	**0.868**	18.5	8.0–30.0	**0.927**	0.515	**0.798**
Moderate (average % per day)	4.7	0.5–11.3	**0.910**	5.1	0.6–13.2	**0.977**	0.859	**0.866**
Vigorous (average % per day)	0.3	0.02–2.3	**0.926**	0.3	0.02–1.8	**0.986**	0.260	**0.963**
Bouts of 30 min sedentary (n/week)	31	8–62	**0.911**	29	6–64	**0.902**	0.233	**0.758**
Bouts of 60 min sedentary (n/week)	4	0–31	**0.907**	6	1–35	**0.922**	0.063	**0.877**
Sleep time (h/night)	9.1	8–11.1	**0.795**	9.3	7.3–11	**0.897**[b]	0.953	**0.871**
Total activity during sleep (counts/night)	7508	5785–12,714	**0.978**	8026	5919–12,605	**0.896**	0.859	**0.769**
Average activity during sleep (counts/s)	0.23	0.18–0.36	**0.967**	0.25	0.18–0.36	**0.929**	0.859	**0.795**
Maximal average activity (counts/s)								
1 s	70.1	34.9–105.1	**0.949**	69.8	50.5–115.1	0.686	0.859	0.626
5 s	45	23.1–65	**0.843**	40.8	18.7–75	**0.875**	0.441	**0.801**
15 s	33.5	15.1–39.3	**0.843**	27.1	12.3–48.4	**0.901**	0.173	0.643
30 s	22.5	9.5–31.3	**0.874**	20.1	11.1–40	0.678	0.859	0.498
1 min	16.9	7.4–27.8	0.684	11.5	6.4–30.5	**0.840**	0.652	0.665
5 min	8.2	3.1–14.9	**0.927**	7.1	3.1–18.5	**0.932**	0.314	**0.894**
10 min	6.3	2.6–13.7	**0.923**	6.4	2.7–16	**0.942**	0.515	**0.925**
15 min	5.4	2.4–12.9	**0.907**	5.9	2.6–13.7	**0.947**	0.515	**0.926**
30 min	4.2	1.9–9.4	**0.912**	4.9	2.4–9.5	**0.885**	0.260	**0.827**
60 min	3.2	1.4–7	**0.934**	4.4	2–6.7	**0.902**	0.314	**0.834**
120 min	2.8	1.2–5.7	**0.913**	3.7	1.6–5.4	**0.871**	0.515	**0.780**

[a] $n = 8$.
[b] $n = 5$.

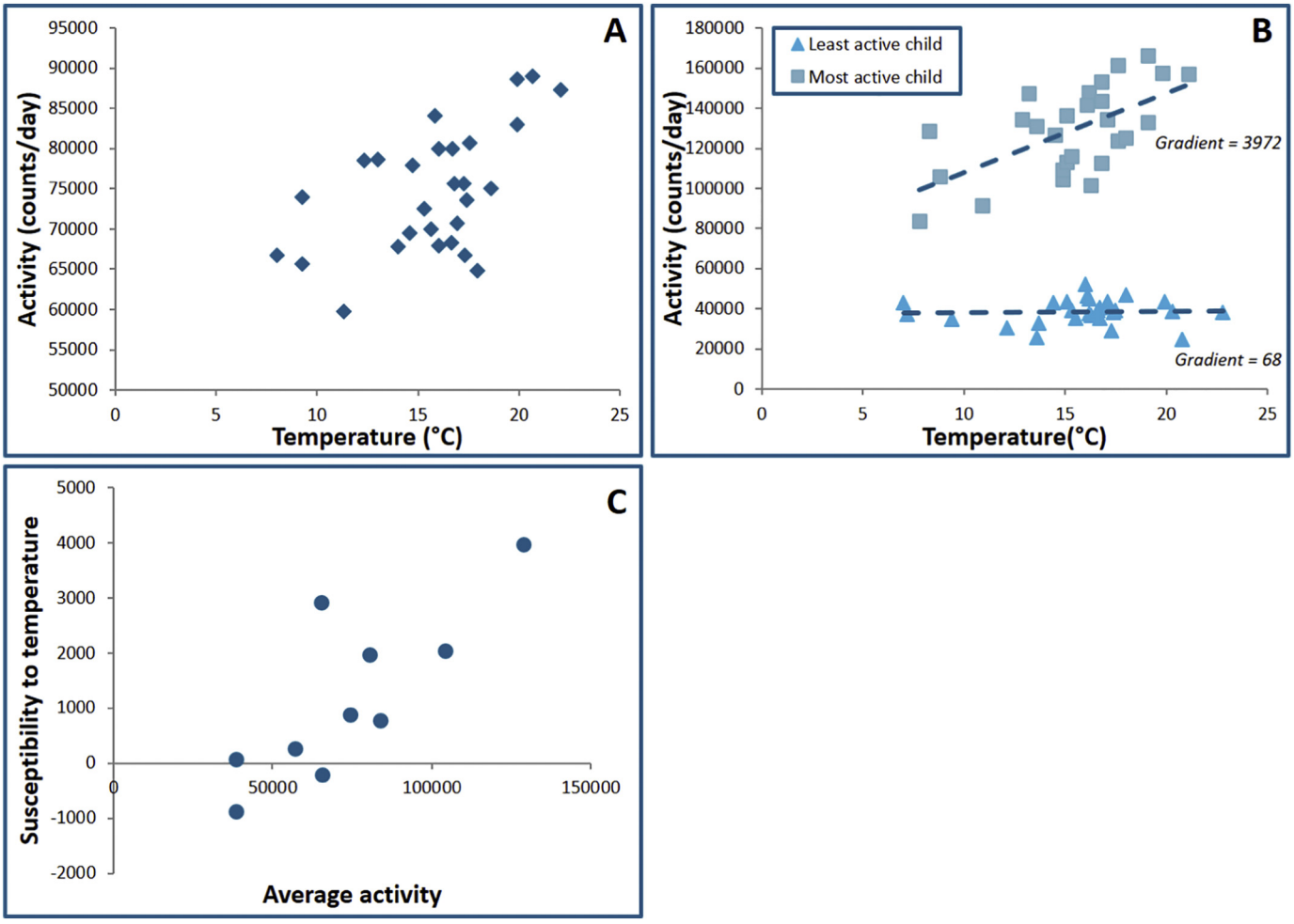

Fig. 3. Activity related to outside temperature. (A) Correlation between mean activity of all children and the mean temperature for each day ($r = 0.48$, $p = .01$; Spearman's correlation coefficient). (B) Correlation between total activity and individual temperature for each day for the least active child and most active child. The most active child is more susceptible to variability in temperature than the least active child, resulting in a higher gradient of the correlation line. (C) Correlation between the average activity of each subject and its susceptibility to the variability in temperature, using the gradients as shown in (B) for each individual. Children with a higher activity level tend to be more susceptible to variability in temperature, where the physical activity of inactive children is regardless of the temperature.

home measurement situation was feasible and showed good to excellent test-retest reliability of physical activity on both short term (two subsequent weeks) and on long term (spring versus summer). The standard error of measurement for total activity in 1 week is 1.7%, for the peak activities the standard error of measurement is higher (14–22%). By focusing on the validity, feasibility, reliability and acceptability, our study meets the recommendations for measuring habitual physical activity in neuromuscular disorders (Jimenez-Moreno et al., 2017).

4.1. Selection of most appropriate accelerometer

We found good validity for most activities in the first part of the study, but several activities showed low validity for all devices. The physical activity during catching and throwing a ball while sitting or standing was generally overestimated by all accelerometers, whereas the physical activity of cycling on a stationary bicycle was greatly underestimated. These discrepancies are to be expected since all devices are worn at the arm/wrist and therefore measure arm/wrist-activity, which is not representative for these specific movements. Other studies also faced these difficulties: Welch et al. found a similar misclassification of stationary cycling by the GENEActiv in healthy adults (Welch et al., 2013). We observed the lowest discrepancies in both 3D-accelerometers (SenseWear and GENEActiv), most likely due to their ability to measure more sophisticated than a 1D-accelerometer such as the ActiWatch. Moreover, the physical activity during outdoor cycling is expected to be less underestimated than during stationary cycling, since the bicycle itself would accelerate relative to its surrounding. Although cycling and throwing are in general not very common or long-lasting activities for most children with a mitochondrial disease, the impact of these misclassifications on individual measurements may be significant. All accelerometers studied were upper-limb worn and therefore our findings may not directly translate to devices that were designed to be worn on different body parts.

4.2. Home measurements

We determined the test-retest reliability of the GENEActiv for two times 7 days in two different seasons, since previous studies in healthy children showed that a 7-day measurement is acceptable for participants and provides enough data for analysis (Matthews et al., 2012; Ridgers et al., 2016; Bjornson, 2005). Moreover, 7 days cover both week- and weekend days, which are expected to show different physical activity-patterns (Atkin et al., 2016). Importantly, we found good reproducibility of physical activity on the short- and long-term on a group level, despite the variability in weather conditions. This may be caused by the "lack of energy" in children with a mitochondrial disorder, which is hypothesized to make their daily physical activity less susceptible to external factors. On an individual level, the activity of

children who are clinically less affected by the disease is more susceptible to weather conditions such as temperature compared to severely affected children. This is in line with our clinical observations and experience, that the activity of less severely affected children is more comparable to healthy children.

Overall, we found very low physical activity in our population. The percentage of sedentary behavior was far more than found in comparable studies in healthy children (Hildebrand et al., 2015; Keane et al., 2017). Moreover, only two children (20%) with a mitochondrial disorder exceeded the threshold of an average 60 min of MVPA per day, which was set by the WHO as the recommended level of physical activity for children aged 5–17 years old (WHO Guidelines Approved by the Guidelines Review Committee, 2010). This is in line with findings in other neuromuscular diseases (Heutinck et al., 2017; Bratteby Tollerz et al., 2015). In healthy Dutch children, over 40% of parents reported that their child performed > 60 min of MVPA per day (CBvdSismRvVe, 2016). High percentages of sedentary behavior and insufficient duration of MVPA are related to high risk of cardiovascular diseases, mental health and obesity in healthy children (Poitras et al., 2016). Especially in mildly affected children who have the same life expectancy as their peers, optimizing life habits is expected to reduce future morbidity significantly (Apabhai et al., 2011). We showed that monitoring the daily physical activity of children with a mitochondrial disease during 1 week is valid, feasible and sufficient to reflect their usual activity level and may help their practitioner to offer better lifestyle advise. However, when interpreting the data it is important to take into account that mildly affected children are more susceptible to seasonal variations than severely affected children.

4.3. Strengths and weaknesses

We included 10 ambulatory children with genetically proven mitochondrial disease in this exploratory study. Although this number is quite small due to the rare nature of this disease, the protocol design of the second part of the study allowed us to draw conclusions on the suitability of accelerometry as an outcome measure for children with mitochondrial disease. Except for some children who attached the accelerometers late, all children were compliant with the quite intense longitudinal protocol, suggesting a low burden of the measurement.

4.4. Recommendations for future studies

These first results on the validity, feasibility and reliability of measuring daily activity with the GENEActiv in children with a mitochondrial disease, show that measuring daily physical activity using the GENEActiv is a promising outcome measure for future intervention studies. Before these studies start, preferably a training-measurement (or pre-baseline measurement) should be performed to indicate the stability and baseline activity level of physical activity in the individual child. In our cohort of 10 patients, we found good feasibility and test-retest reliability of a 1-week measurement.

Based on our results, we would recommend future studies to focus on total activity as it showed good to excellent reliability, low standard error of measurement and covers both the wake time and average activity. Also, peak-parameters such as the highest average activity over 10 or 15 min are recommended, since we previously found that these highly reliable parameters were significantly different between children with a mitochondrial disease and their healthy peers (Koene et al., 2017). Since the percentage of vigorous activity was negligible in all children, this parameter is not expected to be susceptible to change during future trials. Establishing suitable intensity cut-points for children with a mitochondrial disorder may help to overcome this issue. Otherwise, merging the moderate and vigorous intensities into a MVPA-category is suggested.

The device used is a personal choice, but requires a pilot study to test feasibility of measurements and data processing (Koene et al., 2017). During our study, no technical difficulties were encountered and no discomfort was experienced by the participants, making the GENEActiv a feasible alternative to the previously used MOX-accelerometer. However, some children attached their devices too late, forcing us to exclude them partially from our analysis. Although the percentage of non-compliance is comparable to other studies (Koene et al., 2017; Keane et al., 2017; Bratteby Tollerz et al., 2015), future studies should consider strategies to encourage compliance in advance.

We found that the activity measured in the more severely affected children was more stable over time and less susceptible to seasonal variations compared to less severely affected children, suggesting that measuring daily activity at home is a more suitable outcome measure for future intervention studies in more severely affected children. Larger studies involving more seasonal variations (e.g., in winter) are indicated to draw more solid conclusions about the activity pattern and whether the influence of weather conditions can be corrected for. Still, the heterogeneity between patients will still dictate a personalized approach when drawing conclusions about the stability of physical activity patterns on an individual level.

5. Conclusions

In this exploratory study, we showed that measuring daily physical activity in a home situation in children with a mitochondrial disease is feasible and shows good short- and long-term test-retest reliability. Activity intensity was categorized using cut-points validated for healthy children. Establishing disease-specific intensity cut-points for children with a mitochondrial disorder is expected to result in data that better reflects their physical activity. The GENEActiv is a user-friendly, feasible, valid and reliable device for custom designed analysis for this pediatric disease. We suggest that quantification of physical activity is a suitable outcome measure for future intervention studies in this unique population, especially in children with more severe disabilities.

Conflict of interest

The authors declare no commercial or financial conflict of interest. Jan Smeitink is the CEO of Khondrion BV.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mito.2019.04.005.

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