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Testing Physical Function in Children Undergoing Intense Cancer Treatment  
– A RESPECT Feasibility Study

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## **Abstract**

Children with cancer exhibit reduced physical function during and following treatment that can compromise quality of life and increase the risk for chronic medical conditions. The “REhabilitation, including Social and Physical activity and Education in Children and Teenagers with cancer” Study (Clinicaltrials.gov:NCT01772862) examines multimodal rehabilitation strategies at diagnosis and includes interventional physical activity. This article discusses the feasibility of and obstacles to evaluating physical function in these children.

**Methods:** The intervention group comprised 46 boys and 29 girls aged 6-18 years (mean±SD: 11.3 ±3.1yrs), diagnosed with cancer from 1/2013-4/2016. Testing at diagnosis and after three months included Timed-Up-and-Go, Sit-To-Stand, flamingo balance, handgrip strength and the bicycle ergometer CardioPulmonary Exercise Test (CPET).

**Results:** Of the children 92% completed a minimum of one test; two children declined testing. CPET completion was low (25%) due to diagnosis-specific obstacles but high for handgrip strength (81%). Children with extracranial solid tumors and CNS tumors completed significantly fewer tests than those with leukemia and lymphoma. Tumor location and treatment related side-effects were barriers for evaluating physical function. Children with leukemia demonstrated reduced lower extremity function, i.e. 24% reduction at three-months testing in Timed-Up-and-Go ( $p=0.005$ ) and Sit-To-Stand ( $p=0.002$ ) in contrast with no reductions observed in the other groups.

**Conclusion:** Children with cancer are motivated to participate in physical function evaluation. Future studies should address diagnosis-specific obstacles and design intervention modalities that facilitate physical function evaluation.

## **Introduction**

Physical function evaluation in children with cancer is gaining increased interest as reports of physical function impairment during and after treatment become more prevalent. Function disabilities include reductions in cardiopulmonary function [1-3] and muscle strength [4-6] and general physical weakness [3, 6, 7] that impact quality of life [3, 5, 8]. Existing topic related studies include limited numbers of children (n= 15-128) as well as restricted diagnostic groups and inclusion criteria. Furthermore, the testing methodologies used in these studies during the treatment trajectory were not standardized. In particular, studies on physical function at diagnosis or at various points during initial cancer treatment are sparse, leaving unclear when the optimal time would be for evaluating physical function in different cancer diagnostic groups.

A 39% reduction in cardiopulmonary function within two weeks of diagnosis of childhood cancer has been recently reported[1]. Ness *et al.* similarly reported that children with Acute Lymphoblastic Leukemia (ALL) show 15% reduced lower extremity muscle strength 7-10 days after diagnosis [4]. These impairments persist years after treatment [9-11] and result in an increased risk for a variety of chronic medical conditions, including metabolic syndrome and cardiovascular disease [12-14]. These findings suggest that preemptive measures such as exercise should be initiated from the point of diagnosis and preliminary intervention results in this respect look promising [15, 16]. In an effort to support expanding these interventions to include a wider diagnostic group of children with cancer, this study aims to: i) elucidate the feasibility of physical function evaluation during the first three months of treatment in children with different cancer diagnoses; ii) compare development in physical function across cancer diagnostic groups participating in physical activity; and iii) identify barriers and promoting factors to physical function evaluation.

## **Methods**

### **Design and setting**

This study forms an integral part of the overall “REhabilitation, including Social and Physical activity and Education in Children and Teenagers with cancer” (RESPECT) Study (Clinical Trial registration NCT01772849 and NCT01772862); a nationwide, prospective and controlled multi-intervention program targeting children aged 6-18 years who are newly diagnosed with cancer or cancer-like diseases and treated with chemotherapy and/or radiation therapy. The RESPECT Study is imbedded in the work structure of the Center for Integrated Rehabilitation (CIRE). This multi-interventional approach was initiated to simultaneously address the academic, social and physical

deficits experienced by children with cancer [17]. The working purpose of the RESPECT Study is to establish whether classmate (ambassador) co-admissions, in conjunction with regular physical activity at the hospital and throughout the initial intensive treatment period, can improve academic and physical function monitored one year after treatment cessation. We hypothesize that maintaining the children's physical function from the point of diagnosis is preferable to physical rehabilitative efforts later in the treatment trajectory. The feasibility of the academic and social components of RESPECT is reported elsewhere.

### **Intervention components**

While the RESPECT study approach is described in-depth elsewhere [17], the components of the current study include: introducing cancer and its treatment to classmates of the child with cancer; selecting two classmates as 'ambassadors' who take turns in being co-admitted with the child with cancer to the hospital for the day (i.e. 9 a.m. to 3. p.m.) every 14th in- and out-patient day; conducting a physical activity intervention when the child is admitted to hospital that consists of individually designed activities offered three times weekly (Monday, Wednesday, and Friday). A novel approach to promoting physical activity in children with cancer is to include their healthy classmates as ambassadors in the program. Tuesdays and Thursdays are reserved for potential joint sessions with any admitted children and their ambassadors. The training consists of cardiorespiratory, strength and balance exercises [1] and is often camouflaged as play or games in order to motivate the children; and exercises are adapted daily to ensure variety in physical function.

### **Participants**

Study participants were included between January 2013 and April 2016. Inclusion criteria were: aged 6-18 years; cancer diagnosis; Langerhans cell histiocytosis or myelodysplastic syndrome; treated with chemotherapy and/or radiation therapy; enrolled in school at the time of diagnosis; and able to communicate in Danish. Exclusion criteria were: mental disability (e.g. Down's syndrome) and severe co-morbidity. Data from the first 75 children admitted to the University Hospital of Copenhagen with a cancer diagnosis and accepted in the Study are presented below.

TABLE 1 shows the anthropometric and clinical characteristics of the participants. The inclusion of children in the RESPECT program is ongoing. The children were included in the study if their respective treatment plans involved chemotherapy and/or radiation therapy. Some children experienced a delay in fulfilling this criterium.

### **Anthropometric data**

The participants' height and weight were measured at diagnosis and after three months as required by cancer treatment protocols and medical journals. Body Mass Index (BMI) was calculated by dividing weight by height<sup>2</sup>. The children were separated into four diagnostic groups (Leukemia, lymphomas, extra-cranial solid tumors, and Central Nervous System (CNS) tumors).

### **Physical tests**

Tests conducted are described elsewhere [17] and comprised: a cardiopulmonary exercise test (CPET); Timed-Up-and-Go; Sit-to-Stand; Flamingo balance; and Handgrip strength. The tests were performed within 14 days of diagnosis and three months after diagnosis  $\pm$  14 days and in the absence of any ambassadors to ensure that the child with cancer did not feel exposed or distracted. For feasibility determination, the two testing points per child were collectively labelled as 'early testing'. Inclusion criteria included: thrombocyte count  $>$  10 billion/L; hemoglobin count  $>$  5 mmol/L; and temperature  $<$  38 °. Exclusion criteria (for testing) included: active diarrhea; coughing, cold; and side-effects preventing participation in physical activity.

**CPET** was performed on an electronical brake cycle ergometer (Lode Corival Pediatric or Monark Ergomedic 839 E) using a modified Godfrey protocol [17]. The child was instructed to maintain a steady tempo (80 rpm) while the workload progressively increased by 10 W/min. to the point of exhaustion [18]. Ventilation and gas exchange data were determined breath-by-breath, using a portable INNOCOR ergo spirometry system, INNO00010 (Innovision, DK 5260 Odense, Denmark) and Hans Rudolph Valve (2-wat NRBV, Hans Rudolph inc., Kansas City, MO, USA) or Hans Rudolph mouthpiece and nose clip, if the child was fitted with a gastrointestinal tube.  $VO_2$  peak was determined by calculating the average of the highest values continuously measured over 60 seconds and was expressed in (mL/kg/min) and (L/min). Heart rate and oxygen saturation were continuously measured every 30 seconds (Polar FT2 sport tester Polar Electro, Kempe, Finland).

One subjective and two objective criteria were required for the CPET test to be considered valid. Subjective criteria included signs of intense effort (e.g. unsteady cycling pattern, facial flushing,

unsteady breathing or inability to maintain tempo). The objective criteria were: heart rate > 180 beats/min; and respiratory exchange ratio >1.05.

**Timed-Up-and-Go** was performed using a chair and allowed the child to flex the legs at a 90° angle. From the start position, with the back resting against the chair and arms on knees, the child was instructed to stand up, walk three meters as fast as possible, turn around and return to the start position. Completion time was recorded in seconds to the nearest two decimals. Strong verbal encouragement was given during the test. The last score of three tries was used in the analysis.

**Sit-To-Stand** was performed using a chair and allowing the child to flex the legs at a 90° angle. The child was instructed to fold his/her arms across the chest or to let them hang to the side, stand straight and then touch the chair with their bottom while returning to a seated position. Strong verbal encouragement was given during the test. The test score equated the number of repetitions during a 30 second period.

**Flamingo Balance:** The child was instructed to stand barefooted and on one leg (preferred) for 60 seconds. As the child lost balance, the timer was stopped and restarted again once balance was regained. The number of restarts was recorded.

**Handgrip strength** was measured using a Saehan hand dynamometer (Glanford Electronics, Scunthorpe, UK). Two attempts per arm were performed either standing or sitting and without use of the elbow or the dynamometer touching anything. Strong verbal encouragement was given during the test and the highest score was used in the analysis.

### **Test feasibility**

Feasibility of the test battery was calculated using: (1) the percentage of eligible patients agreeing to participate in the study (acceptability); (2) the percentage of enrolled patients withdrawing from the study because of the physical testing component (attrition); and (3) the percentage of each test completed by each diagnostic group (adherence; two time-points combined). Furthermore, reasons for uncompleted CPET tests were recorded and categorized: (1) physician decision; (2) treatment related side-effect (e.g. nausea, dizziness, chronic pain); (3) non-motivation (no obvious physical reason); (4) logistical reason; (5) equipment issue; or (6) late inclusion.

### **Ethical approval**

The Regional Ethics Committee for the Capital Region (file. H 3-2012-105) and the Danish Data Protection Agency (file. 2007-58-0015/nr.30-0734) approved the Study and the data protection structure.

## **Statistics**

Analyses of CPET, Timed-Up-and-Go, Sit-To-Stand, Handgrip strength, BMI and body weight were performed using the linear mixed model to evaluate differences in change over time between diagnostic groups (Leukemia, Lymphoma, Extracranial solid tumors and CNS tumors). Paired t-test was used to analyze changes over time in each diagnostic group. Only the children who completed both testing at diagnosis and after three months were included in the analysis. Analysis of the flamingo balance was performed using random effects Poisson regression. The linear mixed model and Poisson regression analyses were adjusted for the effects of age, gender and diagnosis. Differences in completion rates (diagnosis tests + three month tests) of the test battery across diagnostic groups were evaluated using Chi-squared tests. P-values <0.05 were considered statistically significant.

## **Results**

### **Baseline characteristics**

Of the included children 41% were diagnosed with leukemia, 28% with extracranial solid tumors, 19% with lymphomas and 12% with CNS tumors (see TABLE 1). There were no differences in anthropometric characteristics or physical function between the four diagnostic groups, except in the case of borderline inferior flamingo balance scores for children with CNS tumors compared with the three other diagnostic groups at diagnosis ( $p=0.06$ ).

### **Feasibility**

*Acceptability:* From January 2013 to April 2016, 75 of 78 (96%) eligible children were included in the RESPECT Study. None of the three children who declined participation did so because of the physical activity intervention or evaluation of physical function. Two children declined as they did not desire that their classmates participate in the intervention and one declined, finding the intervention to be irrelevant in the out-patient setting. *Attrition:* after three months of treatment, no child withdrew from the study. Of the enrolled children, 69 (92%) completed at least one physical function test. Of the six children who did not complete any test, two (2.7%) were not motivated to participate in physical function evaluation, despite having participated in preceding physical activities. In four children (5.3%) testing at diagnosis and three months could not be performed due to delayed (approx. one year) diagnosis. *Adherence:* The Overall CPET completion rate was 25.3% (range: 19-36 %) with no significant difference between diagnostic groups, however, remaining test differences were observed (see TABLE 2). Children with CNS tumors completed significantly



fewer tests than the three other diagnostic groups ( $p < 0.05$ ). Similarly, children with extracranial solid tumors completed significantly fewer Sit-To-Stand and Timed-Up-and-Go tests than children with lymphoma or leukemia ( $p < 0.05$ ).

### **Barriers for completing the CPET**

Of the 150 CPETs, 38 of these tests (25%) were completed. Six major barriers for test completion include: (1) physician decisions (tumor location prohibited strenuous activities of the affected extremity). This was the case in 52.4% of the tests scheduled for children with extracranial solid tumors; (2) therapy related side-effects (e.g. nausea, dizziness, pain; overall 41.3% of the scheduled tests); (3) motivational reasons (no obvious physical reasons not to perform the CPET; overall 6%); (4) logistical reasons (treatment abroad, concurrent medical treatment/examinations or hospital discharge; overall 3.3% of scheduled tests); (5) equipment failures or maintenance (overall 2% of scheduled tests); and (6) late inclusion (28% of scheduled CPET for children with CNS tumors). The children were included only when treatment plans involved chemotherapy and/or radiation therapy.

### **Impact of the initial phase of treatment with physical activity**

After three months of promoting daily physical activity in the diagnostic groups, all participants maintained their baseline levels of handgrip strength, BMI and body weight (TABLE 3). CPET analysis could not be interpreted due to low completion rates and too few paired tests (25% completion rate). Sit-To-Stand performance decreased by 24% after three months ( $p = 0.006$ ) in the leukemia group. This change was significantly worse ( $p = 0.005$ ) compared with the three other diagnostic groups that maintained their baseline levels. Timed-Up-and-Go performance also decreased by 24 % after three months ( $p < 0.001$ ) in the leukemia group. This change was significantly worse ( $p = 0.002$ ) compared with the three other diagnostic groups that maintained their baseline levels. Furthermore, significant differences were observed between the diagnostic groups ( $p < 0.001$ ) with respect to the flamingo balance performance. In the leukemia group, 20% faced difficulties standing on one leg for 60 seconds at diagnosis and, after three months, 67% had difficulties standing on one leg.

### **Discussion**

The intervention demonstrates that children with cancer are generally motivated to participate in physical function evaluation; however, diagnostic group specific obstacles exist. In particular, the

low completion rate of CPET (25%) suggests that alternative ways to evaluate cardiopulmonary function must be explored. The study data show that physical activity and testing in children with cancer is feasible, albeit to variable extents between the diagnostic groups. It is worth pursuing the RESPECT study aim, i.e. physical activity from the time of diagnosis may prevent deterioration of physical function in children with cancer, however as the current study lacks inclusion of control group data, proving this aim will be attempted in a future RESPECT study. Supervised training in children with cancer has been shown to be safe and feasible and children with cancer are generally motivated to participate in physical activity [1]. The present study findings show that evaluating physical function during initial cancer treatment is found acceptable, with 69 (92%) of the children having completed at least one physical function test and only two children (2.7%) having refused testing. Several diagnosis-specific barriers to physical function evaluation were identified. In particular, children with extracranial solid tumors were instructed by their treating physicians to refrain from certain physical function tests (e.g. tests that impact the affected extremity) and CPET completion rates were poor due to side-effects across all of the diagnostic groups. Likewise, delayed final diagnosis of CNS tumors was an obstacle for testing. Although several barriers are present when performing CPET in children with cancer, their cardiopulmonary function remains an important factor as they experience reduced cardiopulmonary function during and after treatment [1, 2] and, consequently, increase their risk for metabolic syndrome and cardiovascular disease [12-14]. It can be argued that barriers of severe and treatment related side-effects can be avoided by ensuring more flexible test timing, improved logistics and communication with physicians. If tests can be scheduled and performed directly prior to the start of chemotherapy courses, then side-effects would be less likely to prevent evaluating physical function. It is noted, however, that this would come at the cost of less stringent time points for testing. Furthermore, including different equipment options such as demonstrated in the study by Fiuza-Luces *et al.* [19] may also improve completion rates. That study used a treadmill and arm crank ergometer simultaneously to perform the CPET. The only drawback to using different equipment options for performing the CPET is the limited comparability between the results obtained from the varied equipment used. The present study recommends: instilling more flexibility with test points; pursuing the option of evaluating physical function prior to the start of chemotherapy courses; and including various equipment options for performing CPET in order to improve overall completion rates. The study hoped to recruit more children diagnosed with CNS tumors as this diagnosis represent approximately 33% of childhood cancer cases and, in the present study, children with CNS tumors represent 12% of the

cohort. However, the number of participants from this diagnostic group may have been limited by the Study's inclusion criteria, i.e. inclusion of children receiving chemotherapy and/or radiation therapy; thus children undergoing operations only were excluded.

A study by Hartman *et al.* that included 51 children with leukemia randomized into either a group with a home-based exercise intervention with parent supervision or to a control group, reported significantly decreased physical function at diagnosis compared with healthy peers. However, that study showed no change over time or effect of intervention [20]. The current study data confirm physical function reduction during intense leukemia treatment.

Other studies show significant improvements in physical function when interventions were initiated at the start of childhood ALL maintenance therapy [21-25]. However, the children showed markedly lower physical function at that later baseline than the children in the present study [21, 24]. In a study by Tanir *et al.*, the children used 8.5 seconds and 6.6 seconds (start of maintenance therapy and at three months, respectively) to complete the Timed-Up-and-Go compared with 3.8 and 5.0 seconds (at diagnosis and at three months, respectively) for the children with leukemia in the present study[21]. Although methodological effects cannot be excluded, the better end-point performance scores in the current study compared with baseline performance scores in the Tanir study suggest that the present study's children with leukemia may have benefitted from the intervention.

## **Conclusion**

Children with cancer are motivated to participate in physical function evaluation. Future studies should address diagnosis-specific obstacles and design intervention modalities that facilitate physical function evaluation.

## **Conflict of interest**

The authors declare no conflict of interest.

## **Acknowledgements**

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TABLE 1: Anthropometric characteristics

Diagnosis	All participants	Leukemia	Lymphoma	Extracranial solid tumors	CNS tumors	p
<b>Gender (n=75)</b>	29 girls (38.7%) 46 boys (61.3%)	n=31 (41 %) 18 boys and 13 girls	n=14 (19 %) 9 boys and 5 girls	n=21 (28 %) 13 boys and 8 girls	n=9 (12 %) 4 boys and 5 girls	n.s
<b>Age (yrs)</b>	11.3 ± 3.1	10.7 ± 2.9	11.7± 2.7	12.2 ± 3.0	10.8 ± 3.4	n.s
<b>Height (m)</b>	1.54 ± 0.19	1.50 ± 0.18	1.59 ± 0.2	1.59 ± 0.19	1.49 ± 0.23	n.s
<b>Weight (kg)</b>	46 ± 16.8	42.9 ± 15.3	47.8 ± 15.7	49.8 ± 16.4	45.6 ± 18.7	n.s
<b>BMI</b>	18.8 ± 4	18.5 ± 4.3	18.4 ± 2.9	19.2 ± 3.9	19.7 ± 4.4	n.s

Data is presented as mean ± SD. n.s. = not significant.

TABLE 2: Overview of completion rates for the test battery

<b>CPET</b>	35.7%	25.8%	22.2%	19%
<b>Sit-To-Stand</b>	92.9%	77.4%	64.3% <sup>#</sup>	33.3% <sup>*</sup>
<b>Timed-Up-and-Go</b>	89.3%	69.4%	61.9% <sup>#</sup>	33.3% <sup>*</sup>
<b>Flamingo balance</b>	96.4%	80.3%	80.9%	33.3% <sup>*</sup>
<b>Handgrip strength (right)</b>	96.4%	87.1%	76.2%	44.4% <sup>*</sup>
<b>Handgrip strength (left)</b>	96.4%	87.1%	81%	44.4% <sup>*</sup>

Completion rates were calculated using all planned tests (diagnosis tests + three months tests)

CPET= Cardiopulmonary exercise test. <sup>\*</sup>Significantly fewer completed tests compared with the three other diagnostic groups. <sup>#</sup> Significantly fewer completed tests compared with the lymphoma and leukemia groups

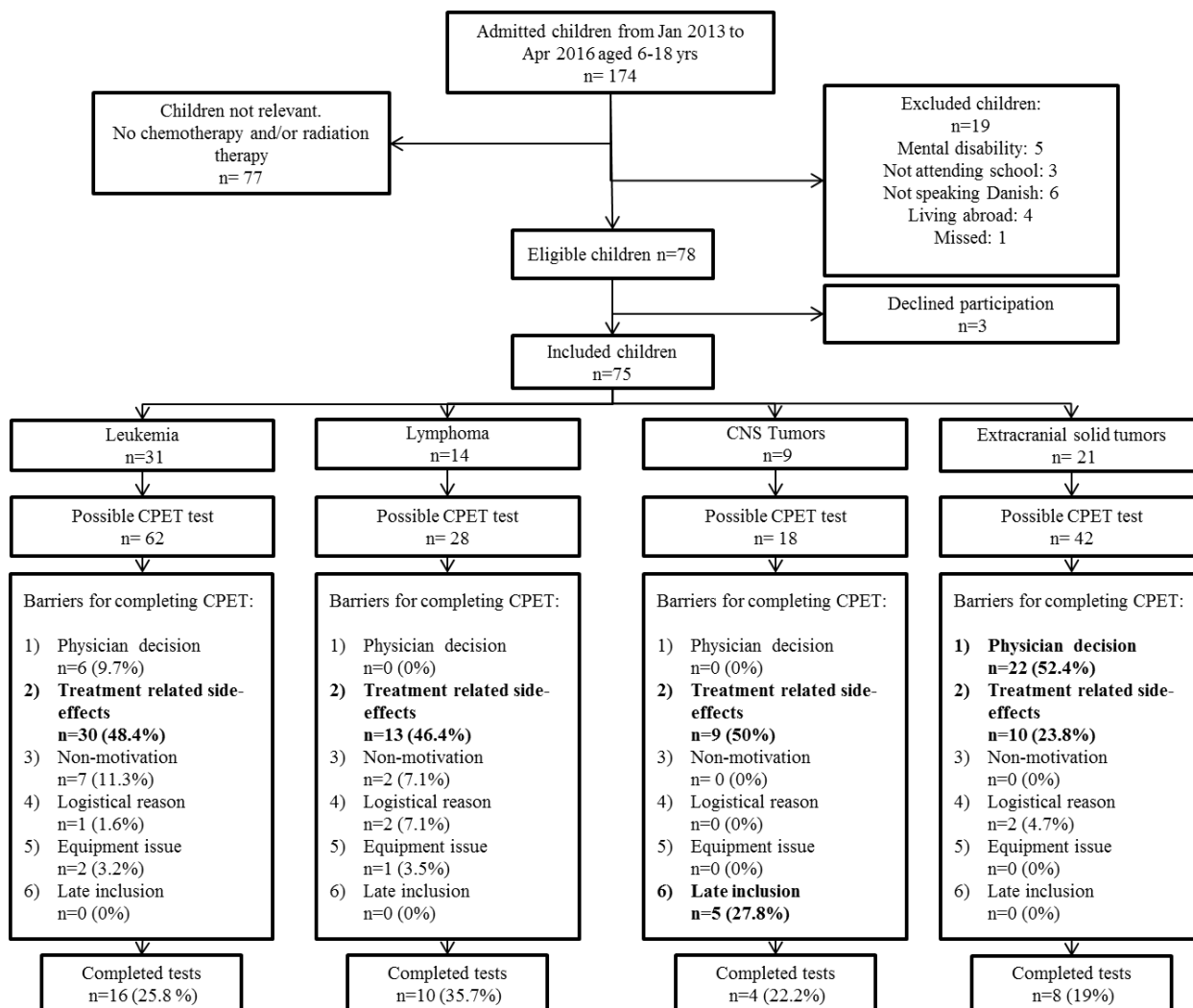


FIGURE 1 Flow chart of included patients and barriers for uncompleted CPET tests.

**TABLE 3 Impact of initial phase of treatment with physical activity**

	Lymphoma			Leukemia			Extracranial solid tumors			CNS tumor		
	Diagnosis	3 months	P	Diagnosis	3 months	P	Diagnosis	3 months	P	Diagnosis	3 months	P
VO <sub>2</sub> peak (mL/kg/min)	28.4±3.1	28.9±3.0	n.s	27.8±2.2	21.9±2.5	n.s	31.7±4.8	29.0±2.6	n.s	26.8±4.6	29.4±4.8	n.s
VO <sub>2</sub> peak (mL/min)	1230±196	1415±190	n.s	1113±142	942±159	n.s	1102±305	1315±166	n.s	1388±294	1525±305	n.s
Timed-Up-and-Go (s)	4.17±0.27	4.21±0.25	n.s	3.80±0.19	5.00±0.19	P<0.05*#	4.15±0.23	3.62±0.27	n.s	4.38±0.52	3.87±0.52	n.s
Sit-To-Stand (reps)	23.5±2.1	22.3±2.1	n.s	25.0±1.5	19.0±1.6	P<0.05*#	27.5±1.9	29.8±2.3	n.s	22.1±4.4	28.6±4.4	n.s
Handgrip strength R (kg)	20.3±1.7	19.8±1.8	n.s	21.2±1.3	17.2±1.3	n.s	21.6±1.5	22.3±1.7	n.s	18.4±3.2	20.4±3.3	n.s
Handgrip strength L (kg)	18.3±1.7	17.6±1.7	n.s	20.4±1.2	16.2±1.2	n.s	20.4±1.4	20.8±1.7	n.s	16.8±3.1	18.5±3.2	n.s
Weight (kg)	43.7±2.5	46.4±2.5	n.s	44.8±1.7	44.6±1.7	n.s	45.0±2.0	45.4±2.0	n.s	48.1±3.1	48.5±3.1	n.s
BMI (kg/m <sup>2</sup> )	17.6±1.0	18.6±1.0	n.s	18.8±0.7	18.5±0.7	n.s	18.4±0.8	18.4±0.8	n.s	19.7±1.2	19.9±1.2	n.s
Flamingo Balance (number)	0 (0 to 2)	0 (0 to 1)	n.s	0 (0 to 0)	2(0 to 3.5)	p<0.05*#	0 (0 to 0)	0 (0 to 0)	n.s	2 (0 to 6)	0 (0 to 0)	p<0.05*#

Data are presented as means ± SE except for the flamingo test with median (IQR).\*significant change over time # significant change compared to change in the other diagnosis groups. n.s= not significant

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