Physical activity and physical fitness in children with chronic conditions

Joyce Bos

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CONTENTS

CHAPTER 1

Introduction

Physical activity (PA), defined as 'any bodily movement produced by skeletal muscles that requires energy expenditure'[1], has health benefits as it reduces the risk of cardiovascular diseases, stroke and diabetes. PA also contributes to prevention of risk factors like hypertension, overweight and obesity in adults[2]. In children PA lowers the risk of depressive symptoms[2], reduces body mass index (BMI) and fat mass in children with overweight and obesity[3]. Therefore global recommendations for PA were made by the World Health Organization (WHO) for adults as well as for children[4]. The Committee for the Dutch Physical Activity Guideline advises children (age 4-18 years) to engage in moderate to high-intensity PA for at least one hour every day[2,5]. With this advice the Committee for the Dutch Physical Activity Guidelines follows the international advise of the WHO.

In 2017 the Committee added to this advice; 'PA is good for you - the more the better, the longer you are physically active, and the more frequent and/or more vigorous the activity, the more your health will benefit'. 'Do activities that strengthen your muscles and bones at least three times a week and avoid spending long periods sitting down' (sedentary behaviour)[1].

Despite these recommendations on PA for health, only 40% of the Dutch children engage in PA at moderate to vigorous intensity of one hour every day and in muscle and bone-strengthening activities at least three days a week[6]. On average Dutch children spent between the 4.1 and 5.9 hours a day on sedentary behaviour[6]. Sedentary behaviour is defined as 'any waking behaviour characterized by an energy expenditure ≤ 1.5 metabolic equivalents, while in a siting, reclining or lying posture'[7]. So despite health benefits of PA Dutch children do not reach the recommendations on PA for health.

These PA guidelines are for children in general, but children with a chronic disease like juvenile idiopathic arthritis (JIA), juvenile dermatomyositis or a history of liver transplantation are less physical active compared to controls[8–11] as has been attributed to parental overprotection, medication, fear of being too active, social isolation and ignorance of the health benefits of PA[12]. For example in the past children with JIA were given restrictions on PA as it was assumed that PA could damage joints. Activity is more encouraged by physicians and physical therapists in these children in the last decade[13] but in clinical practice it is still seen that children, parents and some caregivers are still cautious.

In some chronic diseases, such as JIA and liver transplantation motor development is delayed [14,15], which might influence PA of the child. Children with less motor abilities might be less physically active, but on the other hand motor abilities develop through PA. It is known that better motor abilities are positively associated with PA and inversely associated with sedentary behaviour[16].

To determine PA different measurement can be used each with their advantages and disadvantages[17,18]. Doubly labelled water method is the gold standard to objectively measure PA[19] but is not suitable in clinical practice. Activity diaries and accelerometers are commonly used[20]. In general activity diaries tend to overestimate PA[21,22], since not all activities are written down directly but by recall and in young children parents are writing down the activities, while they are not always around to objectively register the activities as during school time. Besides this, filling in an activity diary can be time consuming. On the other hand accelerometers are easy to use. Once the accelerometer is put on correctly, nothing needs to be done. Unfortunately accelerometers underestimate PA, because they do not record certain types of activity like cycling[23]. So it is quite a challenge to measure PA objectively and on a child friendly manner.

In general it is assumed that children with a chronic disease will experience the same health benefits of PA as healthy children. Hence it is important to stimulate PA. Effects of such stimulating programs in children with a chronic disease are scantly available. It is evident that different factors contribute to the impact of increasing PA. For health benefits it is a challenge to find the right strategy on increasing PA especially in children with a chronic disease.

In addition to PA it is known that the aerobic fitness in children with a chronic disease is less compared with controls[10,11,24–26]. Aerobic fitness is expressed as the maximal peak oxygen uptake ($VO_{2\,peak}$) and is a component of physical fitness. Physical fitness is defined as 'a set of attributes that people have or achieve to perform PA' and can be divided into health-related fitness like aerobic (or cardiorespiratory) fitness, muscular endurance and strength, body composition and flexibility and skill-related fitness, like agility, balance, coordination, speed, power and reaction time[1]. Through exercise one can improve on physical fitness.

The relationship between PA, health-related fitness and health is illustrated in Figure 1[27]. The relationship between PA and health is complex, but it is assumed that by increasing PA, components of health-related fitness, such as body weight, muscle power, motor development, cardiorespiratory fitness and metabolic state can be influenced positively, resulting in increased quality of life, lowered morbidity and mortality. Physical activity can influence health-related fitness, but a higher health-related fitness level may increase the level of PA. Health-related fitness also influences health and health status also influences both health-related fitness and PA level. Health-related fitness is not only influenced by PA. Factors such as life-style behaviour, physical and social environmental conditions, personal attributes and genetic characteristics also affect PA, health-related fitness and health.

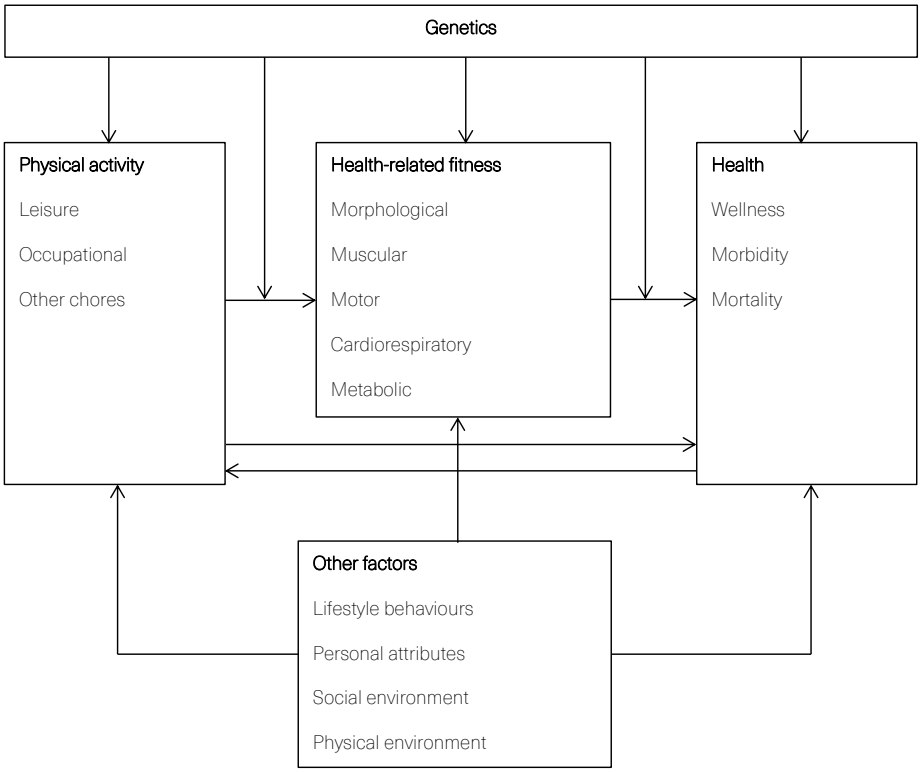

Figure 1. Associations between physical activity, health-related fitness and health (model according to Bouchard[27]).

AIMS AND OUTLINE OF THIS THESIS

Children with liver failure have to acquire their motor abilities within different circumstances, like frequent hospitalization, surgery, less prone position, and medication as compared to healthy children. Data about motor development of children post liver transplantation is limited. Insight in motor development may help to develop interventions to improve motor abilities in these children as better motor abilities are positively associated with PA and inversely associated with sedentary behaviour[16].

The first aim of this thesis was to study motor development in young children pre transplantation and to determine if one year post liver transplantation motor development was similar to controls. In *chapter 2* the motor development in children pre and post liver transplantation was determined and compared with norm values.

Current treatment of JIA improves with medication like biologic drugs and due to insights in pathogenesis. It can be assumed that the effect of better treatment of JIA and these medications has influence on the outcome of PA and the difference between healthy controls is reduced.

The second aim of this thesis was to analyse PA levels in children with JIA compared with controls. In *chapter 3* PA in children with JIA were compared to controls regarding PA, sedentary behaviour and meeting PA guidelines. Besides this the effect of disease specific factors of JIA on PA were analysed.

Improved surgical techniques and use of medication with fewer side effects in children after liver transplantation have improved the survival in these children. It is assumed that better outcome also influences the outcome of PA. Physical activity at young age is important for growth and development. It is assumed that PA established during the young years may provide the greatest likelihood of health benefits at the long term. In general children are more active before puberty than after puberty[6]. Therefore more insights in the PA levels of young children after liver transplantation in particular are needed. Knowledge about PA in young children is limited and sedentary behaviour is not always determined. Since only 40% of the Dutch children engage in activities as recommended in the activity guidelines, insight in children after liver transplantation meeting PA guidelines is also needed.

The third aim of this thesis was to get these insights in children after liver transplantation. In *chapter 4* PA and physical fitness in children after liver transplantation are compared with norm values.

The forth aim of this thesis (*chapter 5*) was to analyse, convergent validity of the two most common instruments used in clinical practise for measuring PA, the activity dairy and the accelerometer in children with JIA. Besides validity we analysed how many days in a week gave reliable results and the effects of combining both instruments for the correction of non-wear.

The final aim of this thesis was to determine the effects of intervention programs to stimulate PA. In *chapter 6* the effects of an exercise-training program in children and adolescents with juvenile dermatomyositis based on a randomized controlled trail are described. In *chapter 7* the effects of an internet program based on cognitive behavioural intervention to stimulate PA and aerobic fitness in children with JIA is described. C*hapter 8* is the general discussion.

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CHAPTER 2

Motor development in children 0 to 2 years pre and post liver transplantation, a prospective study

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Revision required

ABSTRACT

Objective

To determine prospectively gross and fine motor development of children less than two years of age, who undergo liver transplantation.

Methods

In this prospective study, children aged less than two years who undergo liver transplantation, were tested using the motor scale of the Bayley scales of infant and toddler development, 3rd edition Dutch version. Testing was done during screening pre liver transplantation and post liver transplantation: at the time of hospital discharge (2-6 weeks), at 3 months, 6 months and one year. Z-scores were calculated.

Results

Twenty-nine children participated in this study, 14 boys, median age 6 months, at screening for liver transplantation. Gross motor skills were delayed pre liver transplantation (Z-score -1.3). Fine motor skills were normal (Z-score 0.3). Immediately post liver transplantation both skills reduced and at one year post liver transplantation gross motor skills Z-score was -1.0 and fine motor skills Z-score 0.0.

Conclusion

Both gross and fine motor skills Z-scores decline post liver transplantation and tend to recover after one year; gross motor skills to low normal and fine motor skills to normal levels. Monitoring of gross motor development and attention on stimulating gross motor development post liver transplantation remains important, to enable participation in physical activity and sport for health benefits later in life.

INTRODUCTION

Liver transplantation is the standard care for children with a life-threatening liver disease. New surgical techniques and immune-suppressive medication have improved survival of these children[1]. In The Netherlands the 5-year survival has increased in the last 2 decades from 71% to 83%. Living-related liver transplantation in The Netherlands has a 5-year survival of 95%[2]. Given this high survival rate it is important to focus on the long-term outcomes. Beside hypertension, atherosclerosis, reduced growth, obesity, lowered bone density, osteoporosis, increased cardiovascular risk factors, reduced aerobic exercise capacity, a reduced motor development has been reported in these children[3–11]. Children with liver diseases are at risk in all neurodevelopmental domains; cognitive, behavioural and motor outcomes[11].

Although most studies showed impaired motor development in children pre and post liver transplantation[9,10,12–14], one study showed motor scores improved and children reached the norm for their age within 4 years post liver transplantation[15]. In another study, 2 year follow up showed low normal motor development scores following pediatric liver transplantation[10]. Studies do not always distinguish between gross and fine motor skills. In one study in children with biliary atresia pre liver transplantation, gross and fine motor skills were studied separately[12]. It was shown that gross motor skills were delayed, while fine motor scores were relatively preserved[12]. One can imagine that by scoring motor development as a single score low scores on gross motor skills may be compensated by better fine motor skill scores or vice versa.

Insight in the separate scores of gross and fine motor skills are needed pre and post liver transplantation as motor skill development during early childhood may have health benefits on the short term as well as on the long-term[16]. In addition, for clinical relevance insight is needed, in order to be able to refer more specifically to a pediatric physical therapist for stimulating motor development in case of a delayed motor development.

The aim of this study was to evaluate gross and fine motor development in children, aged 0-2 years, pre liver transplantation (screening), at the time of hospital discharge (2-6 weeks), and at 3 months, 6 months and one year post liver transplantation, to determine the extent and the course of the motor development over time.

PATIENTS AND METHODS

All children aged 0 to 2 years, who were screened for liver transplantation and put on the waiting list for a liver transplantation at the University Medical Center of Groningen (UMCG) were eligible for this prospective study. Patients were included between May 2015 and November 2017.

Assessments of the motor development were performed pre liver transplantation at the time of screening and post liver transplantation around discharge (2-6 weeks), at 3 months, 6 months and one year post liver transplantation. Assessments were combined with a visit to the outpatient clinic of the UMCG or during a short hospital stay for medical evaluation.

Exclusion criteria were related to secondary diagnosis that might intervene with the assessment not associated with liver transplantation such as Down syndrome. The Medical Ethical Committee of the UMCG stated that this study fulfilled all requirements for patients' anonymity and it is in agreement with regulations of the UMCG for publication of patient data (M19.227796).

Motor development

We assessed motor development using the motor scale of the Bayley scales of infant and toddler development, 3rd edition (Bayley III)[17]. For this study we used the Dutch version (Bayley III-NL)[18]. The Bayley scales of infant and toddler development is widely used in the clinical evaluation of young children with developmental delay and provides age-standardized composite scores for cognitive, language, and motor skills. Motor development is divided in gross and fine motor skills with a mean score of 10 and a standard deviation of 3. The Bayley III-NL is a valid and reliable instrument[18].

Patient characteristics

Weight (kilogram) and height (centimeters) were measured using an electronic scale and a stadiometer (Seca, Germany). Body mass index was calculated (weight (kilogram)/ height (meters) squared.

All the other study variables like type of liver disease, type, date and number of liver transplantation(s), length of hospitalization post liver transplantation, length of intensive care unit (days), medication, laboratory values (PT, INR, Bilirubin, Albumin,

AST, ALT, gamma GT and cholesterol), pediatric physical therapy or other treatment on stimulating motor development were asked for or retrieved from the medical files.

STATISTICAL ANALYSIS

Sample size

As all pediatric liver transplantations in The Netherlands are performed in our hospital (UMCG), all Dutch children that underwent liver transplantation were eligible for this study. Data was checked for normality and Z-scores for gross and fine motor development were calculated. Z-scores were calculated as ($value_{patient}$ - $mean_{norm}$) / Standard deviation $(SD)_{norm}$.

Differences in motor development between children with or without pediatric physical therapy and children with a living donor and children with deceased donors were calculated using the Mann Whitney U test.

RESULTS

One child was excluded from the study because of the exclusion criteria. Twenty-nine children, 14 boys (48%), median age 6 months (interquartile range (IQR) 4.0 ; 6.0), were eligible and participated in this study (Table 1). In total 6 assessments of the Bayley III-NL were missing pre liver transplantation because of logistic reasons. At time of analyzing this study, one child was waiting for a liver transplantation and 1 child died on the waiting list for liver transplantation. In total 27 children had a liver transplantation. One child died post liver transplantation (Figure 1). In total 23 children were assessed at time of screening for liver transplantation (Table 2).

Table 1. Transplantation and patient characteristics.

Characteristics (n=29)	
Type of liver disease	
Biliary atresia	26 (83%)
Acute liver failure	2 (3%)
Familiar hypercholesterolemy	1 (3%)
Transplantation (n=27)	
Age at liver transplantation (months)	8.0 [6.0 ; 10.0]
Time between screening and liver transplantation (months)	3.0 [1.0 ; 3.0]
Type of liver transplantation	
Partial living donors	19 (70%)
Partial deceased donors	7 (26%)
Full size	1 (4%)
Number of liver transplantations	
1	25 (93%)
2	2 (7%)
Number of days on intensive care unit (days)	10.0 [6.0 ; 15.5]
Hospital stay post liver transplantation (days)	38.0 [22.0 ; 64.0]

Data are presented as numbers (percentages) or as medians and [interquartile range].

n: number of valid observations.

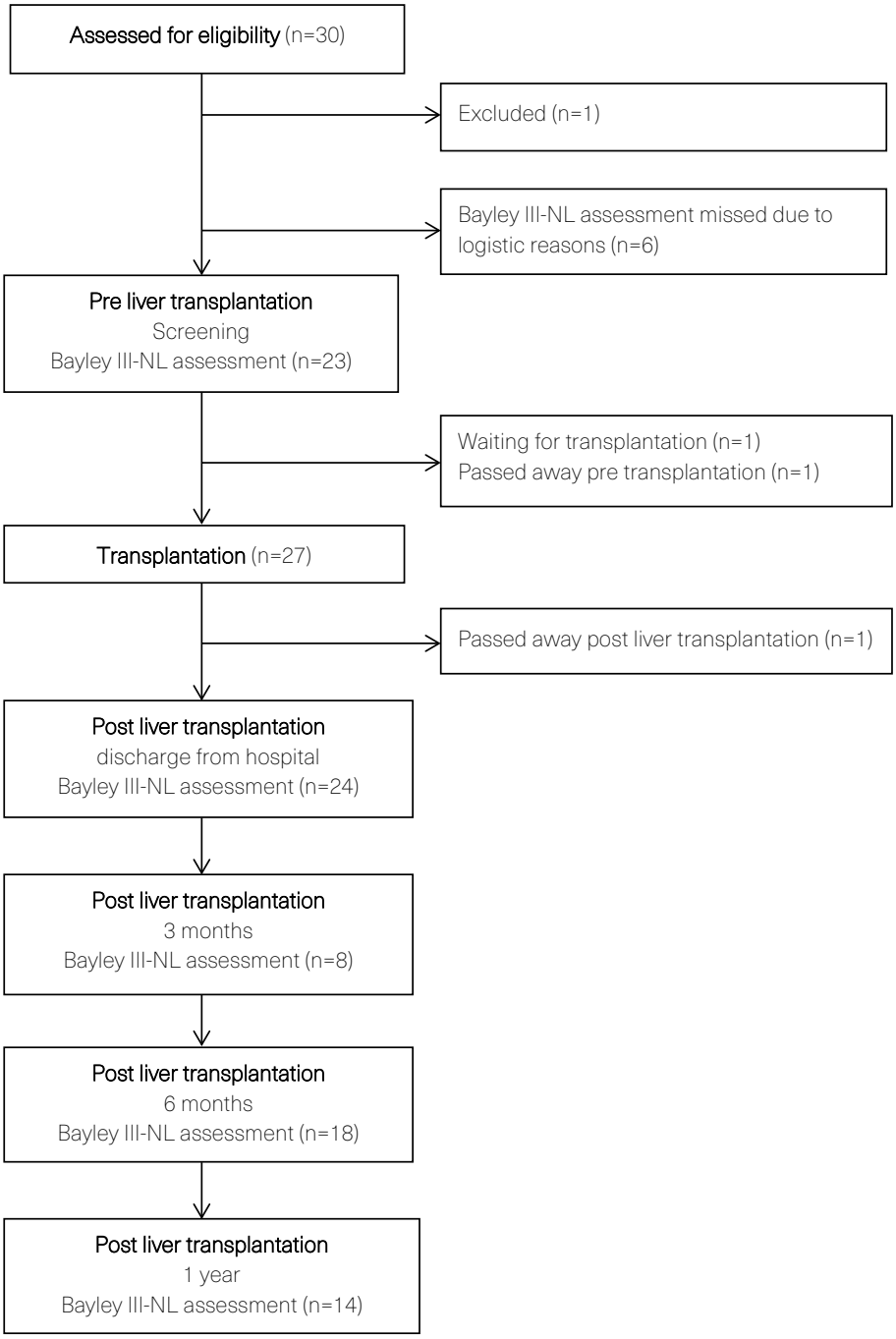

Figure 1. Flow chart of the number of patients involved in evaluation.

Table 2. Patient characteristics pre and post liver transplantation screened for Bayley III-NL.

	Pre LTX (screening) median (IQR) n=23	**Post LTX (discharge) median (IQR)** n=24	**Post LTX (3 months) median (IQR)** n=8	**Post LTX (6 months) median (IQR)** n=18	**Post LTX (1 year) median (IQR)** n=14
Gender, boys (%)	11 (48%)	13 (54%)	4 (50%)	9 (50%)	9 (64%)
Age (months)	6.0 (4.0 ; 6.0)	9.0 (7.3 ; 11.8)	11.5 (11.0 ; 15.0)	13.5 (12.8 ; 16.0)	20.0 (19.8 ; 24.8)
Height (centimeters)	65.0 (62.0 ; 67.0)	73.5 (68.0 ; 78.0)[‡]	76.8 (72.6 ; 83.4)	78.5 (74.3 ; 82.5)[+]	86.5 (81.0 ; 89.3)
Z-score	-0.3 (-1.2 ; 0.4)	-0.1 (-0.6 ; 0.8)[‡]	0.0 (-0.3 ; 0.4)	0.0 (-1.0 ; 0.8) [+]	-0.3 (-1.2 ; 0.4)
Weight (kilogram)	7.5 (6.6 ; 8.4)	8.8 (8.4 ; 10.6)	9.9 (9.6 ; 11.9)	10.4 (9.6 ; 10.9) [>]	12.2 (11.4 ; 14.2)
Z-score	0.1 (-0.6 ; 0.6)	0.2 (-0.5 ; 0.6)	0.0 (-0.3 ; 0.7)	-0.3 (-0.6 ; 0.5) [>]	-0.1 (-1.3 ; 0.5)
BMI	16.8 (15.6 ; 18.1)	17.2 (15.9 ; 18.3)[§]	16.8 (16.3 ; 17.8)	16.9 (16.0 ; 17.3) [+]	16.6 (15.8 ; 18.1)
Z-score	0.4 (-0.3 ; 1.2)	0.3 (-0.7 ; 1.1) [§]	0.2 (-0.3 ; 0.9)	-0.1 (-0.6 ; 0.3) [+]	-0.1 (-1.0 ; 1.3)
Physical therapy (%)	1 (4%)	10 (42%)	5 (63%)	9 (50%)	6 (43%)
Frequency					
< 1 x (week)			1 (20%)	2 (22%)	3 (50%)
1x (week)		5 (50%)	3 (60%)	7 (78%)	3 (50%)
2 x (week)	1 (100%)	5 (50%)	1 (20%)		
Laboratory value					
PT (sec)	11.9 (11.4 ; 13.8)	12.0 (10.5 ; 13.4) [<]	-	-	11.6 (11.1 ; 12.1)[&]
INR	1.1 (1.1 ; 1.3)	-	-	-	1.1 (1.0 ; 1.2)[&]
Total bilirubin (umol/L)	144.0 (115.0 ; 220.0)	6.5 (5.3 ; 9.0)	6.0 (5.3 ; 11.5)	7.5 (6.0 ; 10.8)	5.5 (3.0 ; 8.5)
Albumin (g/L)	35.0 (32.0 ; 39.0)	36.5 (32.0 ; 39.0)	41.0 (37.0 ; 42.8)	40.5 (36.8 ; 41.3)	43.0 (41.8 ; 44.0)
AST (U/L)	218.0 (156.0 ; 343.0)	41.5 (33.0 ; 52.0)	56.5 (49.5 ; 97.8)	52.0 (42.3 ; 63.8)	47.5 (39.8 ; 55.3)
ALT (U/L)	184.0 (100.0 ; 210.0)	48.0 (35.8 ; 65.8)	103.5 (54.3 ; 110.8)	45.5 (36.8 ; 65.3)	31.5 (23.0 ; 39.8)
Gamma GT (U/L)	427.0 (199.0 ; 536.0)	154.5 (91.0 ; 246.0)	72.0 (21.0 ; 140.8)	41.0 (22.8 ; 92.5)	22.0 (15.0 ; 48.3)
Cholesterol (mmol/L)	4.4 (3.6 ; 7.1)[†]	2.9 (2.5 ; 4.2)[¶]	3.1 (2.7 ; 4.6)[¶]	3.2 (2.8 ; 4.0) [}	3.2 (2.7 ; 3.6)

Table 2. Continued
LTX: liver transplantation; BMI: body mass index; PT: prothromin time; INR: international normalized ratio; AST: aspartate aminotransferase; ALT: alamine aminotransferase; GT glutamyl transferase [†]n: 21 valid observations; [‡]n: 23 valid observations; [§]n:20 valid observations; [<]n: 19 observations; [¶]n: 7 valid observations; [+]n: 16 valid observations; [>]n: 17 valid observations; [}]n: 14 valid observations; [&]n: 13 valid observations.

The median time of the assessment of the Bayley III-NL at discharge was 3.5 weeks (IQR 2.0 ; 5.8). At 3 months post liver transplantation not all the children were seen in our outpatient clinic due to a short period between discharge and this evaluation moment or evaluation in a local hospital and therefore not all Bayley III-NL scores were available (Table 2).

Gross motor development was delayed pre liver transplantation, Z-score -1.3, and reduced post liver transplantation, and reduced further 3 months post liver transplantation (Table 3 and Figure 2). After 6 months Z-scores were still lower compared to pre liver transplantation and one-year post liver transplantation gross motor skill Z-scores were low normal (Z-score -1.0). Figure 3 shows the trajectories of individual children on gross motor Z-scores.

Fine motor development was normal pre liver transplantation, Z-score 0.3 (Table 3 and Figure 2). Z-scores reduced post liver transplantation around discharge, at 3 and 6 months post liver transplantation, but were one-year post liver transplantation on the level of pre liver transplantation (Z-score 0.0).

Table 3. Standard scores and Z-scores of gross and fine motor development.

	Pre LTX Screening n=23	**Post LTX discharge** n=24	**Post LTX 3 months** n=8	**Post LTX 6 months** n=18	**Post LTX 1 year** n=14
Gross motor development					
Standard score	6.0 (5.0 ; 8.0)	3.0 (2.0 ; 5.0)[†]	3.0 (2.3 ; 4.0)	4.5 (3.0 ; 9.3)	7.0 (4.0 ; 8.3)
Z-score	-1.3 (-1.7 ; -0.7)	-2.3 (-2.7 ; -1.7)[†]	-2.3 (-2.6 ; -2.0)	-1.8 (-2.3 ; -0,3)	-1.0 (-2.0 ; -0.6)
Fine motor development					
Standard score	11.0 (8.0 ; 13.0)	9.0 (7.0 ; 10.0)	8.0 (7.0 ; 12.0)	8.5 (6.8 ; 10.3)	10.0 (8.8 ; 11.5)
Z-score	0.3 (-0.7 ; 1.0)	-0.3 (-1.0 ; 0)	-0.7 (-1.0 ; 0.7)	-0.5 (-1.1 ; 0.1)	0.0 (-0.4 ; 0.5)

LTX: liver transplantation; n: number of valid observations; [†]n: 23 valid observations.

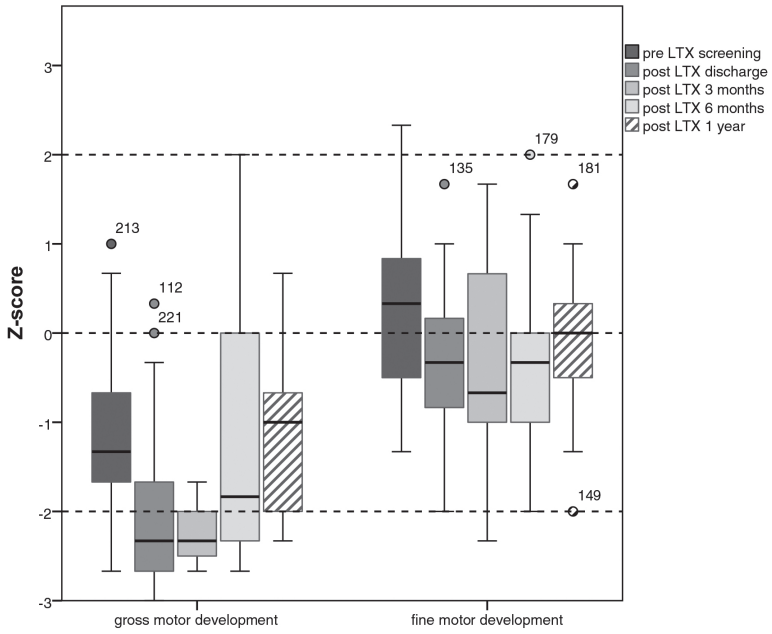

Figure 2. Box and whiskerplots of Z-scores of gross and fine motor development.

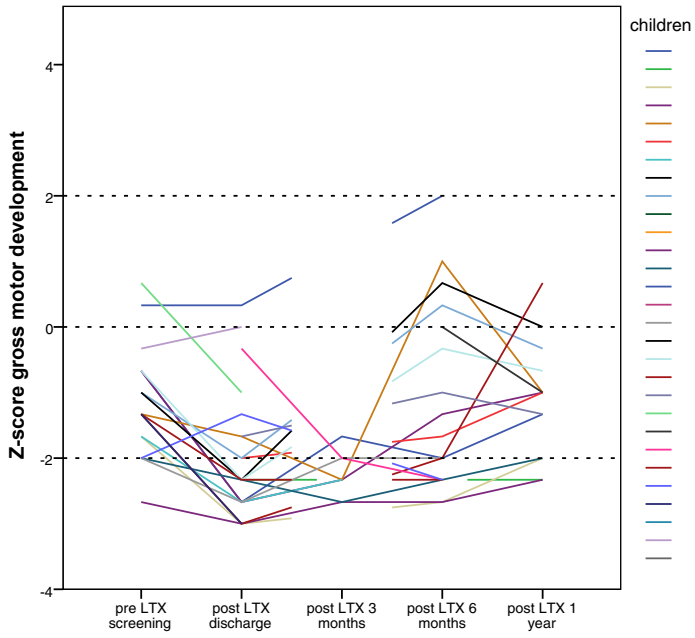

Figure 3. Z-scores of gross motor development over time of each child participating in the study.

Pre liver transplantation one child received pediatric physical therapy. Post liver transplantation 10 out of 24 children received pediatric physical therapy, because of a delayed motor development. Children receiving pediatric physical therapy more often showed significant lower gross motor scores compared to children without pediatric physical therapy (Figure 4a and b). Post liver transplantation around discharge gross motor skills were significantly lower ($p<0.01$) in the pediatric physical therapy group and at 6 months post liver transplantation gross motor skills were still significantly lower in this group ($p=0.02$). At all other evaluation moments no significant differences were found between the group with or without pediatric physical therapy. No significant differences were found in motor development scores between children with transplants of living donors and deceased donors (details not provided, available upon request to corresponding author).

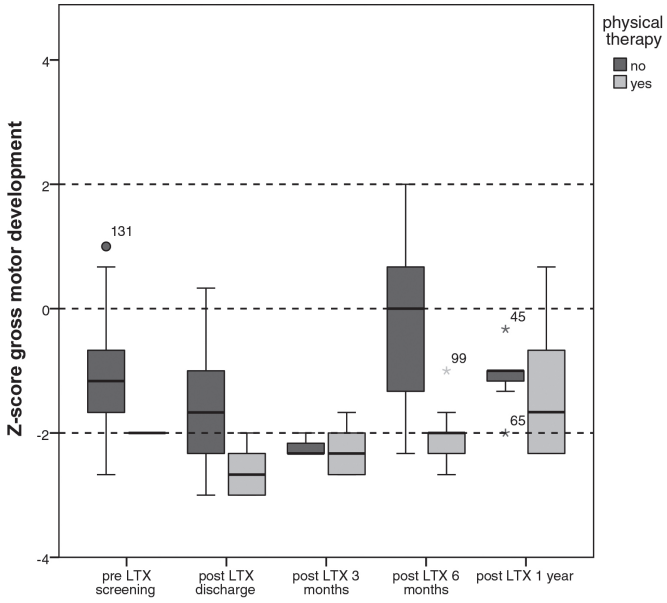

Figure 4A. Box and whiskerplots of Z-scores of gross motor development in children with and without physical therapy.

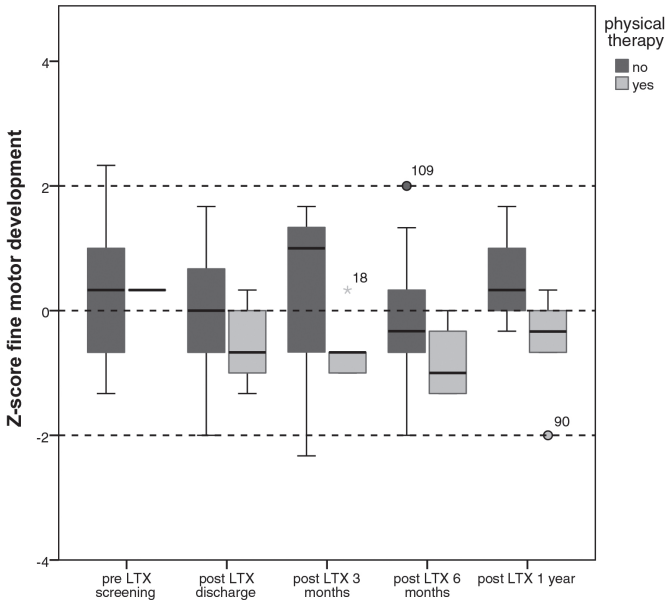

Figure 4B. Box and whiskerplots of Z-scores of fine motor development in children with and without physical therapy.

DISCUSSION

This study showed that children pre liver transplantation had delayed gross motor skills and normal fine motor skills. Both Bayley III-NL Z-scores on gross and fine motor skills reduced post liver transplantation and at one-year post liver transplantation motor development tend to recover; gross motor skills to low normal and fine motor skills stayed within the normal range.

Our findings of delayed motor development pre liver transplantation and recovering of motor development to low normal post liver transplantation was also found previously in a study in children with liver based metabolic disorders[10]. In that study low normal motor development scores were found 2 years post liver transplantation[10], but motor development was assessed with the Bayley scales of infant development 2nd edition, where no distinction is made in gross and fine motor skills and motor development scores are a combination of both. As found in our study, but also previously, fine motor skills scores pre liver transplantation were within normal

values[12]. A delayed gross motor development might not be recognized when gross and fine motor development is presented as a combined score.

Another study showed no improvement of motor scores with time post liver transplantation[9], while yet another study showed improvement of motor scores to normal within 4 years post liver transplantation[15]. In that study the Griffiths Mental Ability Scales (Griffiths-II) was used to determine motor development, but this assessment tool seems to give higher motor scores compared with the Bayley scales of infant development, 2nd edition[19]. Children with multi-visceral transplantations had significant motor development delays both pre and post multi-visceral transplantation[13]. Even children who were not delayed pre multi-visceral transplantation most often showed a decrease in motor or cognitive functioning post multi-visceral transplantation, as assessed with the motor and mental developmental index of the Bayley scales of infant development 2nd edition, despite they were doing medically well[13]. When parents, of children with a liver transplantation, score their children, they also score significantly more motor developmental problems compared to norm values[14].

Delayed motor development in children pre liver transplantation can be understood due to their illness. These children also have growth failure, abdominal distension and therefore are less in prone position[15,20]. One might expect that one-year post liver transplantation children catch up on their motor development as there are fewer limitations, but unfortunately they do not fully recover. Although Z-scores are -1.0, one-year post liver transplantation, one might find this within the low normal range, but still 50% of these children has a delayed gross motor development. It has been suggested that educating parents regarding appropriate developmental expectations (both mental and motor) might increase the parents compliance with developmental interventions as parents often believe and wish their children will be normal post liver transplantation[13].

In our study children receiving pediatric physical therapy showed lower Z-scores on gross motor skills. Probably only the children who are delayed in their motor development were referred for pediatric physical therapy. The percentage of children receiving pediatric physical therapy increased post liver transplantation since in our hospital children with delayed motor development pediatric physical therapy is advised, and motor development decreased post liver transplantation. Gross

motor scores post liver transplantation around discharge were probably underestimated as prone position scores were generally difficult to score due to the effects of surgery. The median time of this assessment was 3.5 weeks post liver transplantation at which prone position was not recommended. Since we could not observe the prone items of the Bayley III-NL, items were scored negative. But this underestimation cannot explain the delayed gross motor development at 3 months post liver transplantation. Only 8 of the possible 26 were seen at 3 months assessment. Of these children, 5 received pediatric physical therapy for delayed motor development. It could be that the motor development not assessed in our hospital was higher.

For long-term outcomes a normal motor development appears to be important as studies in children with high compared to low motor scores suggested that children with low motor scores have low scores on physical fitness as well[21,22]. Therefore the findings of our study suggest the importance to identify the level of motor development in young children and during follow-up as for long-term outcome normal motor development is necessary to prevent low physical fitness later in life, but also to be able to participate in physical activities. When children are unable to run, jump, catch and throw etc. they have limited opportunities to participate in physical activities because they lack the necessary skills. It is of clinical importance to continue to monitor the motor development of these children in order to be able to refer the children to a pediatric physical therapist, because still little is known about long-term motor development in these children and therefore the possible limitations in participation in sports and physical activity for health benefits later in life. Despite the fact that many children received physical therapy, the gross motor development post liver transplantations were low normal after one-year. However we did not systematically monitor the content and frequency of the pediatric physical therapy interventions and therefore no conclusions can be made about the effect of physical therapy on motor development in these children. In general, in a systematic review, it was found that interventions with a task oriented framework is effective in increasing motor development in children with developmental coordination disorders or cerebral palsy[23]. Future study of the interventions of pediatric physical therapy in stimulating gross motor outcome in children post liver transplantation is needed.

This study has some limitations. It was a small sample, but all available cases in The Netherlands were analyzed in this study. We were not able to assess Bayley III-NL at all the control visits for logistic reasons and assessments were postponed to the next visit. The 3-month post liver transplantation evaluation was the most difficult regarding the assessment with the Bayley III-NL, because of recent discharge or check-up was done at a local hospital. Ideally we would have performed statistical analysis, but given the small sample size and missing data we only provided a figure shown the changes over time of each child on gross motor Z-scores (Figure 3). As earlier mentioned prone position especially for the assessment around discharge was not recommended and therefore prone position items were scored as negative as we could not observe these items and therefore gross motor skills were underestimated.

In conclusion both gross and fine motor skills Z-scores decline post liver transplantation and tend to recover after one year; gross motor skills to low normal and fine motor skills to normal levels. Monitoring of gross motor development and attention on stimulating gross motor development post liver transplantation remains important, to enable participation in physical activity and sport for health benefits later in life.

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CHAPTER 3

Physical activity in children with juvenile idiopathic arthritis compared to controls

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ABSTRACT

Objective

To compare physical activity (PA) in children with juvenile idiopathic arthritis (JIA) with controls and to analyze the effect of disease specific factors on PA in children with JIA treated according current treatment regimes.

Methods

Physical activity was measured with a 7-day activity diary and expressed as physical activity level (PAL). Moderate to vigorous physical activity (MVPA) (hours/day) and sedentary time (hours/day) was determined. In children with JIA, medication, the number of swollen and/or painful joints, disease activity, functional ability, pain and well-being was determined. Multivariate regression analysis was performed to analyze differences in PA between JIA and controls, adjusted for influences of age, gender, season, body mass index (BMI) and to analyze predictors of PA in JIA patients.

Results

Seventy-six children with JIA (26 boys and 50 girls, mean ± SD age 10.0 ± 1.4 years) and 131 controls (49 boys and 82 girls, mean ± SD age 10.4 ± 1.2 years) participated in this study. Children with JIA had a significantly lower PAL (0.10, p=0.01) corrected for age, BMI, gender and season. They spent less time in MVPA (0.41 hours/day, p=0.06) and had a significantly higher mean time spent in sedentary activities (0.59 hours/day, p=0.02) compared to controls. The activity level of children with JIA was related to age, gender, season, feeling of well-being and pain.

Conclusion

Children with JIA have a lower PAL, spent less time in MVPA and spent more time on sedentary activities compared to controls despite current medical treatment and PA encouragement.

INTRODUCTION

The treatment of juvenile idiopathic arthritis (JIA) has changed in the past decade, due to insights in pathogenesis and the availability of new medication biologic drugs[1]. The present aim of treatment is to achieve remission within 3 to 6 months[2] and therefore it is current practice in our institutions to administer a top down medication regime. It is expected that the new treatment options reduce the burden of having JIA including improved physical activity (PA) levels. Studies conducted a number of years ago showed a lower level of PA in children with JIA than controls[3,4]. A low level of PA in healthy individuals is related to a higher incidence of overweight and hypertension in later life. This low level of PA might even be more dangerous for children with JIA, as they also have signs of inflammation, perhaps increasing the risk of cardiovascular diseases in later life[5–7].

In children with JIA, it was previously assumed that PA could damage joints and as a consequence rest was often prescribed especially when there were indications of disease activity. More recently, activity is more encouraged in children with JIA and PA is considered to be safe[8–10]. In The Netherlands, there is consensus to encourage children with JIA to be physically active even when there are signs of active disease. However, some care providers remain concerned about the level of PA and competitive sports are often not recommended when there is damage or inflammation of the joints even though exercise does not exacerbate arthritis[11].

It is unknown if the treatment advances in children with JIA and the encouragement of PA has led to PA in children with JIA similar to that of healthy controls. The aim of this study was to compare PA in children with JIA who have been treated according to the latest guidelines[12] to controls and to analyse the effect of disease specific factors on PA in children with JIA.

PATIENTS AND METHODS

Patients

This study is part of a larger study to measure and promote PA in children with JIA. In total 308 children, aged 8 up to 13, from the Beatrix Children's Hospital of the University Medical Center Groningen, the Wilhelmina Children's Hospital of the University Medical Center Utrecht and Amsterdam Rehabilitation Center Reade, all in The Netherlands, were asked to participate in the Rheumates@Work study (ISRCTN92733069). Rheumates@Work is an internet-based cognitive behavioural

intervention to promote PA in children with JIA[13,14]. All subtypes of JIA, according to the international league association of rheumatology, were eligible[15]. Other inclusion criteria beside age and JIA diagnosis were good comprehension of the Dutch language and the availability of a computer with internet connection. Exclusion criteria were high disease activity, defined as visual analogue scale (VAS) as assessed by the pediatric rheumatologist of more than 2 (on a scale of 0 to 10), receiving cognitive behavioural therapy, or patients with physical disability caused by secondary chronic conditions that limited the patients motor and or exercise performance. Children were recruited by the pediatric rheumatologist and received a patient information letter between January 2011 and September 2012. Data of children with JIA were collected twice a year (January and September). Therefore January was labeled as 'winter' and data collected in September as 'summer'.

Eighty-two (27%) children agreed to participate and parents signed informed consent. Reference data were collected in the summer of 2009 from a control group of 131 children, age 8 to 13 years, without a mental or physical disability. All children attended one of the last four grades of two Dutch primary schools. One school was located in the countryside and the other in the city. Healthy children were recruited by physiotherapy students. Children and parents received an information letter and a folder. Informed consent was given by the parents.

Disease activity

Disease activity was assessed according to the core set established by the American College of Rheumatology[16]. Laboratory measures of inflammation were not determined. JIA patients were assessed by a pediatric rheumatologist. Joints were counted as having active disease when they were swollen and/or painful. The pediatric rheumatologist gave a total assessment of disease activity on a VAS, range 1 to 10 centimeter (a higher score corresponded with more disease activity).

Data collection of this study is from the Rheumates@Work study in which we have chosen to use VAS to assess disease activity in order to have a measurement of disease activity in major joints instead of the overall measure of the juvenile arthritis disease activity score (JADAS). The VAS was used to separate children who might be able to increase PA from those who might not be able to do so.

In our study we were also interested in how major joint activity might have an effect on PA and therefore also used VAS as measure of disease activity in our analysis.

Functional ability

To assess functional ability, the childhood health assessment questionnaire (CHAQ-38) was used[17], a revised version of the CHAQ-30 with 8 additional items[18,19]. It assesses 9 domains: dressing, grooming, arising, eating, walking, hygiene, reach grip, activities and extra-curriculum activities. The scores are converted to a CHAQ disability score with a range between 0 to 3 (a higher score corresponds to more disability). The CHAQ-38 includes a VAS (0-10 cm) for assessment of pain and a VAS (0-10 cm) for evaluation of well-being (a higher score corresponds to more pain and worse overall well-being). The VAS score of pain and well-being were scored by the children themselves.

Activity diary

The diary of Bouchard was used to record the level of daily PA[20]. Children and parents received an oral and written explanation how to fill in the diary for 7 consecutive usual days during a school week and weekend. Activities are divided into 9 categories according to their average energy cost, 1 representing the lowest activity category (lying, sleep or rest in bed) and 9 representing the highest activity category (competitive sports). For each 15 minutes the dominant activity was scored. A total of 96 data points were collected per day in the activity diary that was given to the children on paper; for each day one paper bound together with the instructions on top. The children and parents were instructed to fill in the diary during the day period, in case it was not possible to do so, they had to fill in the diary whenever they had the opportunity, but at least once every day. Parents received instructions also on how to support their children in filling in the diary. If the number for the activity was unclear, the instruction given was to describe the activity so the investigators could assign the correct category for the activity. In case of missing data, children were contacted and asked to fill in the missing data. If children could not recall the activity, missing data from 9 pm until 7 am were imputed as a sleeping activity (code 1). Some children filled in 2 values for the same 15 minute period. In that case, the first and second values were chosen alternately throughout the diary. In case of less than 4 missing values, the missing values were imputed by a 2 (sitting activities). If more than 4 values were missing in the diary for one day, that day was excluded for further analysis. In case the same

weekday was recorded twice in one diary (for instance 2 Mondays), one day was excluded and totals were divided over 6 instead of 7 days. An activity diary had to include at least 3 weekdays and 1 weekend day to be used in this study. Lying and sitting (code 1 and 2) were considered as sedentary activities. Light PA was defined as codes 3-5, moderate to vigorous PA (MVPA) by codes 6-9.

Physical activity in this study was defined as PA level (PAL), MVPA and as sedentary time. PAL is an average value, which includes the energy cost of all activities over a 24-hour period[21]. PAL is calculated by dividing total energy expenditure by basic metabolic rate (Appendix 1)[22]. The basis of PAL was formulated in the FAO/WHO/UNU expert committee on energy requirements[21]. Mean time spent in MVPA (hours/day) and mean sedentary time (hours/day) was calculated over 7 days. The number of days obtaining the PA guidelines of at least 1 hour of MVPA each day were counted.

Statistical analysis

For the statistical analysis IBM SPSS statistics version 22 was used. The effect of the season on PA in children with JIA was analyzed using an independent samples t-test. Multivariate regression analysis (method enter) was performed to analyze differences in PA between JIA and controls, adjusted for influences of age, gender, seasonal influence, and body mass index (BMI) and to analyze predictors of PA in children with JIA. Potential predictors of PA in children with JIA were BMI, gender, age, season, functional ability, medication and global assessment of disease activity. The pediatric rheumatologist assessed the global assessment of disease activity and each child pain and overall well-being. Data about BMI and age were centered on their means. Results while on and off medication were entered in the regression model. A p-value of 0.05 or less was considered significant. In the regression analyses, interaction effects were explored if main effects were significant. Residuals were checked for a normal distribution.

RESULTS

A total of 82 children with JIA and 131 controls filled in the activity diary. Data of 6 children with JIA were excluded from the analysis because of missing data. Seven diaries of children with JIA and 2 diaries of controls included data for 6 days. One diary of a child with JIA included 5 days (Table 1).

Of the 76 children with JIA included, 9% (7) had systemic JIA, 33% (25) had persistent oligoarticular JIA, 13% (10) extended oligoarticular JIA, 36% (27) were classified as having polyarticular JIA (of which 11% (3) with a positive rheumatoid factor), 5% (4) had psoriasis related JIA and 4% (3) had enthesitis related JIA.

Of the children with JIA 75% (57) were on medication, 36% (27) did not have any disease activity according to the assessment by the pediatric rheumatologist and 46% (35) of the children with JIA did not have any swollen and/or painful joints.

Children with JIA had a lower PAL, spend less time in MVPA and spend more time on sedentary activities as shown in Table 1. In children with JIA, 4% (3) met the PA recommendations of spending at least 1 hour a day in MVPA. In controls 16% (21) achieved that standard (Table 1). On average, children with JIA had close to 4 days of meeting this PA recommendation compared to 5 days a week in controls.

Table 1. Characteristics of children with juvenile idiopathic arthritis and controls.

	JIA (n=76)	Controls (n=131)	95% CI lower	95% CI upper	p
Gender, boys (%)	26 (34%)	49 (37%)			
Age (years)	10.0 ± 1.4	10.4 ± 1.2	-0.75	-0.02	0.04
Weight (kg)	35.6 ± 9.0	38.5 ± 9.1	-5.47	-0.34	0.03
Height (cm)	143.3 ± 10.1	148.5 ± 9.7	-7.93	-2.31	<0.01
BMI (kg/m^2)	17.1 ± 2.9	17.3 ± 2.6	-0.89	0.64	0.75
Physical activity					
Physical activity level (per day)	1.6 ± 0.2	1.8 ± 0.2	-0.25	-0.14	<0.01
Time spent in MVPA (hours/day)	1.3 ± 0.8	2.1 ± 1.2	-1.02	-0.47	<0.01
Sedentary time (hours/day)	19.3 ± 1.3	18.2 ± 1.3	0.69	1.43	<0.01
Total days per week meeting public health recommendations	3.9 ± 1.7	4.9 ± 1.6	-1.45	-0.54	<0.01
Time since diagnosis (years)	3.6 ± 2.7				
Disease activity					
VAS physicians global assessment (cm)	0.3 (0-0.9)				
Number of active joints	1.0 (0-1.0)				
Upper extremity	0 (0-0)				
Lower extremity	1.0 (0-1.0)				
Number of limited joints	1.0 (0-2.0)				
Functional ability (CHAQ)	0.3 (0.1-0.8)				
VAS pain (cm)	1.5 (0.2-3.9)				
VAS well-being (cm)	0.8 (0.2-2.6)				

Values are the mean ± standard deviation. For disease activity, number of limited joints, functional ability, VAS pain and VAS well-being values are in median (25th and 75th percentiles). Number of valid observations for age in controls n=127, height and BMI in controls n=129. Number of days per week meeting public health recommendations were counted per day of which at least 1 hour of MVPA was present. JIA: juvenile idiopathic arthritis; CI: confidence interval; MVPA: moderate to vigorous physical activity; BMI: body mass index; CHAQ: childhood health assessment questionnaire; VAS: visual analogue scale; cm: centimeter; kg: kilogram; m: meter.

Data of children with JIA was collected twice a year. A difference in data collected in the summer and winter was found. The children whose data was collected in the summer had a significantly higher PAL and spent significantly less time in sedentary activities compared to the winter. No difference in seasonality was found in time spent in MVPA (Table 2). Seasonality was entered in the regression analyses. Residuals of the regression analyses were normally distributed. The multivariate

linear regression analysis, when corrected for the effects of age, BMI, gender and season, showed that children with JIA have a significantly lower PAL (0.10, p=0.01), spend significantly more time on sedentary activities (0.59 hours/day, p=0.02) and less time in MVPA (0.41 hours/day, p=0.06) (Table 3).

Table 2. Seasonal influence on physical activity in children with juvenile idiopathic arthritis.

	Summer n=34	**Winter** n=42	**95% CI lower**	**95% CI upper**	**p**
Physical activity					
Physical activity level (per day)	1.7 ± 0.1	1.6 ± 0.2	0.01	0.17	0.03
Time spent in MVPA (hours/day)	1.5 ± 0.7	1.2 ± 0.9	-0.12	0.63	0.18
Sedentary time (hours/day)	18.9 ± 1.2	19.6 ± 1.4	-1.33	-0.13	0.02
Total days per week meeting public health recommendations	4.2 ± 1.6	3.7 ± 1.7	-0.28	1.27	0.21

Values are the mean ± standard deviation. CI: confidence interval; MVPA: moderate to vigorous physical activity.

Table 3. Multivariate linear regression analyses to predict physical activity in children with juvenile idiopathic arthritis and controls.

	B	**95% CI lower**	**95% CI upper**	**p**
PAL				
Reference	1.75	1.67	1.83	<0.01
Controls	0.10	0.03	0.18	0.01
Age centered 10 years	0.04	0.02	0.07	<0.01
BMI centered 17 kg/m^2	-0.01	-0.02	-0.00	0.04
Gender	-0.07	-0.13	-0.01	0.02
JIA season	-0.14	-0.23	-0.05	<0.01
MVPA				
Reference	1.70	1.27	2.13	<0.01
Controls	0.41	-0.02	0.83	0.06
Age centered 10 years	0.20	0.07	0.33	<0.01
BMI centered 17 kg/m^2	-0.02	-0.08	0.04	0.50
Gender	-0.12	-0.43	0.20	0.47
JIA season	-0.50	-1.00	0.01	0.06
Sedentary time				
Reference	18.86	18.36	19.37	<0.01
Controls	-0.59	-1.09	-0.09	0.02
Age centered 10 years	-0.13	-0.28	0.03	0.10
BMI centered 17 kg/m^2	0.15	0.08	0.21	<0.01
Gender	-0.02	-0.38	0.35	0.92
JIA season	0.78	0.18	1.37	0.01

Table 3. Continued
The regression equation for PAL is as follows: PAL= reference + 0.10 * control + 0.04 *age (centered 10) + -0.01 * BMI (centered 17) + -0.07 * gender + -0.14 * season. The reference for this equation is a 10 year old boy with JIA, a BMI of 17kg/m^2 of which the data was collected in the summer. So a healthy girl (no JIA) of 8 years old, a BMI of 20 has a predicted PAL of (1.75 + 0,10 * 1 + 0.04 * (8-10) * + -0.01 * (20-17) + -0.07 * 1= 1.73. JIA: juvenile idiopathic arthritis; BMI: body mass index; PAL: physical activity level; MVPA: moderate to vigorous physical activity expressed in hours/day. Sedentary time expressed in hours/day; CI: confidence interval of B. Reference category: Boy of 10 years, with a BMI of 17, with JIA, who filled in the diary in the summer period.

In Table 4, the results are given of the predicted PA in children with JIA. A lower PAL in children with JIA was associated with young age, seasonality (winter) and worse well-being and less pain. The same associations were found for time spend in MVPA and sedentary time. We found no association between disease activity as accessed by the pediatric rheumatologist as well as use of medication (on/off) with PA in children with JIA. In mean time spend in MPVA, we also found an association with functional ability (CHAQ). A higher CHAQ score was associated with less time spend in MVPA. For sedentary time an association was found in BMI; a higher BMI corresponds with more time spend in sedentary activities. No significant interaction effects were found.

Table 4. Multivariate linear regression analyses to predict physical activity in children with juvenile idiopathic arthritis.

	B	95% CI lower	95% CI upper	p
PAL				
Reference	1.81	1.72	1.90	<0.01
Age centered 10 years	0.06	0.03	0.09	<0.01
BMI centered 17 kg/m^2	-0.01	-0.02	0.00	0.18
Gender	-0.07	-0.14	0.01	0.08
JIA season	-0.16	-0.23	-0.08	<0.01
Medication	-0.01	-0.09	0.07	0.87
Disease activity	-0.005	-0.012	0.003	0.83
Functional ability (CHAQ)	-0.05	-0.15	0.04	0.27
VAS wellbeing	-0.04	-0.07	-0.01	0.01
VAS pain	0.03	0.002	0.05	0.04
MVPA				
Reference	2.00	1.52	2.48	<0.01
Age centered 10 years	0.26	0.10	0.41	<0.01
BMI centered 17 kg/m^2	0.001	-0.07	0.07	0.99
Gender	-0.13	-0.51	0.25	0.51
JIA season	-0.55	-0.96	-0.15	0.01
Medication	0.03	-0.39	0.44	0.90
Disease activity	-0.01	-0.03	0.02	0.60
Functional ability (CHAQ)	-0.50	-0.99	0.01	0.05
VAS wellbeing	-0.16	-0.30	-0.02	0.03
VAS pain	0.13	0.01	0.26	0.03
Sedentary time				
Reference	18.70	17.94	19.46	<0.01
Age centered 10 years	-0.28	-0.53	-0.04	0.02
BMI centered 17 kg/m^2	0.16	0.05	0.27	<0.01
Gender	0.07	-0.54	0.67	0.83
JIA season	1.01	0.38	1.67	<0.01
Medication	-0.29	-0.96	0.37	0.39
Disease activity	0.01	-0.03	0.05	0.69
Functional ability (CHAQ)	0.14	-0.65	0.94	0.72
VAS wellbeing	0.26	0.04	0.48	0.02
VAS pain	-0.19	-0.38	0.00	0.05

The regression equation for PAL is as follows: PAL = reference + 0.06 * age (centered 10) + -0.01 * BMI (centered 17) + -0.07 * gender + -0.16 * season + -0.01 * medication + -0.005 * disease activity + -0.05 * functional ability (CHAQ) + -0.04 VAS well-being + 0.03 * VAS pain. The reference in this equation a 10 year old boy with JIA, a BMI of 17kg/m^2 of which the data was collected in the summer and off medication. JIA: juvenile idiopathic arthritis; BMI: body mass index; PAL: physical activity level; MVPA: moderate to vigorous physical activity expressed in hours/day. Sedentary time expressed in hours/day. CI: confidence interval of B. A lower score in well-being corresponds to a better well-being. CHAQ: childhood health assessment questionnaire.

DISCUSSION

This study shows that the physical activity level of children with JIA, treated according to recent treatment guidelines[12], is lower compared to controls. PA was not associated with medication or disease activity as measured by the pediatric rheumatologist, but with patient's assessment of well-being and pain score.

Previous studies also found that children with JIA are less active compared to controls[3,4,23–25]. The lower level of PA seems to persist in these children, despite education regarding the importance of an active lifestyle, as well as when some signs of disease activity are present.

In this study we found that only a minority of children, with JIA (4%) and healthy children (16%) met the recommendations for normal PA (e.g. spending at least 1 hour in MVPA each day of the week)[26]. Other studies reported that 38% of children with JIA and 60% of controls[23] and 23% of adolescents with JIA and 66% of controls[4] did meet PA recommendations[26]. In a report of Dutch children on PA and health, a trend of decline in meeting the recommendations for normal PA over the years is seen in the period of 2006-2014 in the ages of 4 to 17 year. No specific reason is given as to why this decline occured[27]. It is alarmingly that this level of PA is declining, especially since the levels of PA in children with JIA are even lower compared to controls. For health benefits, it is desirable that more children meet these PA recommendations. Additionally, both children with JIA and controls spend much time in sedentary activities. More time spent sitting during the day is associated with increased risks of mortality and cardiovascular disease and all causes. Even when individuals are very active, an association between sitting time and mortality has still been found[28].

Contrary to our expectations, we found a positive association between pain as indicated by the children with JIA and the level of activity, that PAL and time spend in MVPA increased with more pain, and that sedentary time decreased with more pain. Previous studies showed either that PA was inversely related to pain[29,30] or no relation between PA and pain in children with JIA[23,24]. JIA often alters the perception of pain and causes decreased pain threshold[31]. An explanation for our results might be that children with JIA that are more active experience more pain similar to every other child, like muscle soreness or pain after detraining. In our study no distinctions was made in pain related to JIA or pain due to PA.

We found that children who feel better (well-being score), appear to move more. This association of PA and well-being has been found previously[4].

Higher functional ability (CHAQ score) was related to less time spend in MVPA, while others did not find this relationship[4,24,25]. Children with higher CHAQ score decrease their MVPA, and had less normal activities in daily life. The PAL was mainly dependent on the low to moderate intensity activities, and not so much on MVPA. This might explain that a relation between CHAQ and MVPA was found, but not with PAL[32].

Despite the fact that this study had a larger sample size and data was collected for a week instead of 1 day or 3 days as in other studies[3,4,24,25], there are some limitations. Data collection of children with JIA was over a longer period of time, so data was collected during the summer and winter periods. As for the controls, the collection only occurred during the summer. PA results differed within the group of children with JIA in favor of the summer. Seasonal variation in physical behaviour in children and adolescents has been found previously[33]. Other studies on PA in children with JIA did not report the season of the data collection[3,4,23–25]. Our study was not designed to study the effects of seasonality on PA. Future studies should consider these effects (longitudinal study), or perform measurements in one season.

Another limitation in this study is that data of the control group was collected 2 year earlier than the data collection of the children with JIA. This difference in time might already have resulted in a significant reduction in time spend in MVPA since children tend to become less active over the years. However the percentages of children meeting PA recommendations have been stable over the last few years[27]. No socio-economic variables were available of the controls so we were not able to study effects of these variables, though in The Netherlands healthcare is accessible for all children and all children have equal access to extracurricular sporting activities.

Although an activity diary gives a close estimate of the PAL it still has its limitations[34]. The diary is not an objective instrument and children may under or overestimate their PA[35]. Studies comparing tri-axial activity monitors with diaries are very needed in this respect.

There might have been selection bias in the participants with JIA. The data of children with JIA came from a larger study of children with JIA willing to participate in a study aimed to improve PA. It is unclear which direction this bias leads since it might be that children willing to participate were less physically active and joined the program for improving PA. On the other hand the group might also consist of children who like to participate in PA and therefore were willing to participate in this program. The girls:boys in this study (2:1) differs from the general JIA population (5:1). It might be that boys are more inclined to sign up for the Rheumates@Work program. This difference limits the external validity.

Additionally there were only a few children with disease activity higher than 0.2 centimeters on the physicians' global assessment of disease activity since a high disease activity score was an exclusion criteria for participating in the Rheumates@Work study. Hence a low PA in children with JIA in this study could not be explained by a high disease activity.

The last limitation in this study is the use of the term sedentary. The term is sometimes used as the lack of exercise. Some studies only describe sitting activities. In this study sitting and lying activities were defined as sedentary time and no distinction was made on laying and sleeping activities in the diary. So it was not possible to make a distinction in sedentary time during the day, which would have given better insights in sedentary activity in children with JIA and controls.

CONCLUSIONS

Although medical treatment of JIA has improved over the years, children with JIA still have a poorer PA compared to controls. Despite encouraging PA in most medical care settings and the growing attention of the importance of PA for pleasure and health benefits, this has not led to an equal amount of PA in children with JIA and controls. Children with JIA need extra help in achieving more normal PA.

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APPENDIX 1

Predicted BMR for:

Boys: 0.074 * body weight (kg) + 2.754 MJ/day

Girls: 0.056 * body weight (kg) + 2.898 MJ/day

To determine the total energy expenditure (TEE), all 15 minute periods of each category were summed. Then divided by 96 (total of 15 minute periods in a day) and multiplied by the physical activity ratio of each activity category and the predicted BMR.

PAL=TEE/BMR

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CHAPTER 4

Physical activity and aerobic fitness in children after liver transplantation

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ABSTRACT

Objective

To determine physical activity (PA), aerobic fitness, muscle strength, health-related quality of life (HRQOL), fatigue and participation in children after liver transplantation.

Methods

Children, 6-12 years, at least one year after liver transplantation, participated in this cross-sectional study. Measurements: Time spent in moderate to vigorous PA (MVPA) was measured using an accelerometer, aerobic fitness ($VO_{2\ peak}$) was measured by cardiopulmonary exercise testing. Muscle strength was measured by hand-held dynamometry. Fatigue was measured using the multidimensional fatigue scale, and HRQOL with the pediatric quality of life core scales and leisure activities was measured using the children's assessment of participation and enjoyment. Outcomes (medians and interquartile range (IQR)) were compared to norm values.

Results

Twenty-six children participated in this study (14 boys, age 9.7 years, IQR 7.7 ; 11.4). Children spent 0.8 hours/day (IQR 0.6 ; 1.1) on MVPA. One child met the recommendation of at least one hour of MVPA every day of the week. Aerobic fitness was similar to norms ($VO_{2\ peak}$ 1.4 $_{L/min}$, IQR 1.1 ; 1.7, Z-score -0.3). Z-scores of muscle strength ranged between -1.4 and -0.4 and HRQOL and fatigue between -2.3 and -0.4. Participation was similar to published norms (Z-scores between -0.6 and 0.6).

Conclusions

Young children after liver transplantation have similar MVPA patterns and aerobic fitness compared to published norms. Despite lower HRQOL, more fatigue, and less muscle strength, these children have similar participation in daily activities. Although children do well, it remains important to stimulate PA in children after liver transplantation in the context of long-term management.

INTRODUCTION

New surgical techniques and immune-suppressive medication have improved treatment and survival of children after liver transplantation[1]. One-year survival of children undergoing liver transplantation is 93% and 5-year survival 88%[2]. In The Netherlands, 5-year survival has increased in the last 20 years from 71% to 83%. Living-related transplantation has a 5-year survival of 95%[3].

Unfortunately, these high survival rates come at the cost of considerable co-morbidities including hypertension, atherosclerosis, reduced growth, obesity, lowered bone density, osteoporosis, delayed motor development, increased cardiovascular risk factors, and a reduced aerobic exercise capacity[4–12]. Most of these co-morbidities are associated with lowered physical activity (PA)[13,14]. Low PA levels and aerobic fitness in childhood are associated with the presence of metabolic syndrome in adolescents after liver transplantation[15].

Several studies were performed to establish that children after liver transplantation have lower PA and aerobic fitness compared to healthy children [4,5,11,16,17]. However, most of these studies have analyzed children in a wider age range or analyzed only adolescents[4,16]. Limited data are available on the PA of young children after liver transplantation. In this study, the focus was put specifically on young children after liver transplantation, since children with a low activity pattern at a young age have a greater chance of a low activity pattern in later life. It is known that children are more active before puberty than after puberty[18]; we therefore studied levels of PA and inactivity in children after liver transplantation before puberty.

Children with a chronic disease are often restricted in their participation in physical activities which may lead to hypoactivity and deconditioning[19]. Therefore, we also studied aerobic fitness, body composition, muscle strength, health-related quality of life (HRQOL), and fatigue in children after liver transplantation.

The aim of this study was to determine the level of PA and aerobic fitness in children, with an age range of 6 - 12 years, who underwent a liver transplantation at least one year prior to participating in this study, and compared outcomes to norm data. Additionally, muscle strength, HRQOL, fatigue, body composition, and participation were determined.

PATIENTS AND METHODS

Children in the age of 6 - 12 years who underwent a liver transplantation at the University Medical Center of Groningen (UMCG), The Netherlands, were eligible for this cross-sectional study. The main immunosuppression regimen for these patients consisted of tacrolimus and prednisolone. One year after transplantation, blood through levels of tacrolimus was aimed at 3-6 µg/L, and all patients continued with a low dose of prednisolone of 0.1 mg/kg/day on alternate days.

Since most complications related to the transplantation occur in the first year[1,20], children were included one year after transplantation, whereby we assumed that children settle in a stable pattern of PA after one year. Other inclusion criteria for this study were a normal graft function, defined as total bilirubine below 10 mmol/L, INR below 1.2, and albumin more than 38 g/L, and being able to follow test instructions. Exclusion criteria for this study were complications that prevented children from performing a maximal exercise test, for example, fractures, or a medical condition that does not allow maximal testing, such as a heart condition. Other exclusion criteria were related to an inability to participate due to cognitive and motor limitations.

The Medical Ethical Committee of the UMCG approved the study (NL48571.042.14). Testing was combined with the regular annual control visit to the outpatient clinic of the UMCG. Children were tested between February 2015 and January 2016.

Physical activity

Physical activity was measured with an Actical accelerometer (Philips-Respironics), during a week in which children went to school. We measured from Saturday to Friday. Physical activity was expressed as time spent in MVPA (mean hours/day), sedentary time (mean hours/day) and mean days meeting recommendations for normal PA, at least one hour of MVPA every day of the week[21].

Children were asked to wear a belt with the accelerometer around the waist at the right side for 7 days. The epoch of the accelerometer was set at one minute. The accelerometer was taken off during sleep and wet activities (like taking a shower or swimming). In case of non-wear during wet activities, the child was asked to write down the time and activity. Data were corrected for non-wear if this influenced the total time spent in MVPA or if it affected sedentary time. Scoring of time

spent in rest, MVPA and days meeting recommendations for normal PA was done according to the cutoff points described previously[22].

In case of non-wear because of gymnastics at school, 37% of the reported time was recorded as time spent in MVPA because study showed that during gymnastics children spent 37% of the total MVPA time reported on actual MVPA[23]. The remaining time was corrected for sedentary time by subtracting this time from time spent in rest, as was also done in case of non-wear because of taking a shower. Correction for other moderate to vigorous sport activities was made by adding the total reported time to the time spent in MVPA, as no observations were available for these sport activities. Sleep time was not included in sedentary time.

In case of non-wear, when children forgot to wear the accelerometer, that day was excluded from the analysis, and totals were divided by the number of valid days. Data had to capture at least one weekend day and 3 weekdays to be included in this study. The wear time on weekdays and weekend days had to be at least 8 and 10 hours, respectively, to be included for analysis. The accelerometer has been validated for children aged 7-18 years[22], and 7-day monitoring provides reliable estimates of PA in children[24]. Only data of children who reported PA for 7 days were included in the analysis for meeting recommendations for normal PA.

Aerobic fitness

Children performed cardiopulmonary exercise testing (CPET) on a cycle ergometer (GE Healthcare) to determine $VO_{2\ peak}$. The Godfrey protocol was used, in which resistance increased every minute depending on height of the child (<120 cm, 10 Watt, 120-150 cm, 15 Watt and >150cm, 20 Watt)[25]. The test ended when the patient had to stop because of exhaustion. Heart rate was monitored continuously during the maximal exercise test. The highest workload (Wmax) and maximal heart rate were recorded.

Breath-by breath minute ventilation (VE), oxygen uptake (VO_2), carbon dioxine output (VCO_2) and respiratory exchange ratio (RER = VCO_2/VO_2) were calculated through gas analysis (Jaeger, Care Fusion). Maximal effort was achieved if the heart rate was above 180 beats per minute and/or RER ≥ 1.0. Peak oxygen uptake ($VO_{2\ peak\ (L/min)}$) was operationalized as the average value of the last 3 measurements during the test. $VO_{2\ peak\ (ml/kg/min)}$ was determined by dividing the $VO_{2\ peak}$ by body weight

in kilogram. The ventilatory anaerobic threshold (AT) was determined by visual inspection of the Wasserman plots (by GB and OL in consensus). An AT above 40% of predicted $VO_{2\ peak\ (L/min)}$ was considered normal.

For children below the age of 8 years, $VO_{2\ peak}$ and Z-scores norm values were calculated by regression analysis from data of children above 8 years[26], since no reference data in children below the age of 8 years were available. Cardiopulmonary exercise testing up to maximal exertion is considered the gold standard for assessing aerobic fitness. Although during CPET the response is measured objectively, the performance of the test is depending on the motivation to reach maximal effort. Young children can validly perform a CPET if the right equipment is available (pediatric cycle ergometer) and the child is able to understand the instructions[27].

Muscle strength

To determine maximal muscle strength (in newton) in 4 muscle groups (elbow flexors, elbow extensors, hip flexors and knee extensors) on the left and right side, a hand-held dynamometer was used (Citec dynamometer CT 3001, C.I.T. Technics). Maximal muscle strength was tested with the break method. In the break method, the child delivers maximal power to the hand-held dynamometer until movement of the joint (eccentric contraction of the muscle). Each muscle group was measured three times, and the highest score was recorded. Reliability and validity of measuring muscle strength in children by hand-held dynamometry vary in the previously conducted studies[28,29]. Hand-held dynamometry was chosen as it is easily applicable clinically and Dutch reference values are available[30]. We therefore used the described method of that study.

Health-related quality of life and fatigue

Health-related quality of life was measured by the paediatric quality of life inventory (PedsQl) core scales, a 4 subscale (physical, emotional, social, and school functioning) modular instrument[31].

Fatigue was measured by the PedsQl multidimensional fatigue scale[32]. The 18 items were divided over the scales: general fatigue, sleep/rest fatigue, and cognitive fatigue. Feasibility, reliability, and validity were found to be good on both the HRQOL[31] and fatigue[32] scales of the Dutch version of the PedsQl.

Both parent and child versions of the HRQOL and fatigue questionnaires were completed. Higher scores indicate higher HRQOL and less fatigue. For this study, we made two comparisons, namely child and/or parent report compared to norm data and child report compared to parent report.

Participation in daily activities

Participation in after-school activities was measured by the children's assessment of participation and enjoyment (CAPE), a child's self-report measure of participation in recreation and leisure activities[33,34]. This questionnaire assesses different domains of participation, namely diversity (which activities does the child do, with a maximum of 55 items), intensity (how often a child does activities, using a 7-point scale ranging from "once in the last 4 months" to "once a day"), and enjoyment (how much does the child enjoy the activity, using a 5-point scale ranging from "not at all" to "love it"). Furthermore, children had to fill in with whom (5-point scale ranging from "alone" to "with others") and where (6-point scale ranging from "at home" to "outside of town") the activities were undertaken. The Dutch version of the CAPE is a reliable and valid instrument for measuring participation in daily activity in children with and without physical disabilities aged 6 through 18 years[35]. A distinction was made in "formal" (15 items) and "informal" (40 items) activities. Formal activities are structured activities with rules and goals, and a coach or instructor is present (like organized sports or music lessons). Informal activities are mostly initiated by the child, whereby no planning of the activities in advance is required (like reading and play). The activities can be further categorized as recreational (12 items), active physical (13 items), social (10 items), skill-based (10 items) and self-improvement (10 items) activities.

Participant characteristics

Age, gender, original liver disease, date of transplantation (for calculation of the time since liver transplantation), type and number of liver transplantations, medication, laboratory values (PT, INR, Bilirubin, Albumin, AST, ALT, gamma GT, cholesterol), model for end-stage liver disease (MELD) score, pediatric end-stage liver disease (PELD) score, type of education, school absenteeism, sport participation, participation in gymnastics at school, and physical therapy were asked or retrieved from the medical files.

Weight (kilogram) and height (centimeters) were measured using an electronic scale and a stadiometer (Seca, Germany). Body mass index was calculated as body weight (kilogram)/ height squared (meters). Skinfold measurement was performed at the right-hand side with a caliper (Holtain T/W). Two to three measurements were taken for the biceps, triceps, subscapular, and suprailiac skinfold, averaging those within 1 millimeter of one another. Skinfold was scored as the sum of the 4 recorded skinfolds to express the percentage of body fat.

Data of aerobic fitness[26], muscle strength[30], HRQOL[36], fatigue[32], and participation[35,37] in this study were compared with published norm data of Dutch children. Data of PA was compared with data from a European study because data from The Netherlands were not available[38].

Statistical analysis

Sample size calculation

All pediatric liver transplantations in The Netherlands are performed in our hospital (UMCG). At the time of the design of our study, about 40 children after liver transplantation in the age of 6 to 12 years were seen in the outpatient clinic. In general, Dutch children are on average active for 40.03 minutes per day (SD 16.78)[39].

The following formula was used for sample size calculation[40]: $n = (u + v)^2 * s^2 / (m-m_0)^2$, where n is the number of participants, u=0.84, v=1.96, s is the standard deviation of the norm group, m is the mean PA of the children after liver transplantation, and m_0 is the mean PA of the norm group. We assumed it would be feasible to include 26 children after liver transplantation for this study, taking into account possible dropout and non-participation of 35%. With this sample size, we would be able to detect a difference of 9.2 minutes/day or more with the available norm data[39].

Data were checked for normal distribution, and Z-scores were calculated as $(value_{patient} - mean_{norm}) / standard\ deviation(SD)_{norm}$.

Wilcoxon signed rank test was performed for differences in child and parent report of the HRQOL and fatigue questionnaire outcome. Wilcoxon signed rank test was also performed for differences in weekdays and weekend days in PA. Mann-Whitney U test was performed for differences in Z-scores of muscle strength

between boys and girls. Kruskal-Wallis was performed for difference between included and excluded children and children who declined. For differences in gender, the chi square test was performed. Spearman's rho test was performed to analyze the association of age with predicted $VO_{2\ peak}$ and age with $VO_{2\ peak}$ Z-scores. IBM SPSS statistics version 23 was used.

RESULTS

We identified 47 children after liver transplantation in the age of 6-12 years who received a liver transplant at least one year earlier (Figure 1). Thirty-six children were eligible for this study. In total 11 children were excluded from the study, 9 boys (82%), median age of 11.5 years (IQR: 9.2 ; 12.6), and median 7.9 years (IQR: 5.9 ; 10.0) post-liver transplantation. Ten children, 5 boys (50%), median age of 11.0 years (IQR: 9.1 ; 12.8), and median 6.0 years (IQR: 2.7 ; 8.9) post-liver transplantation declined to participate. Not all of the declining participants gave a reason for declining to participate in the study but some indicated it would be an extra burden as the visit takes longer, or too stressful. No significant differences were found in gender (p=0.24), age (p=0.20), and time since liver transplantation (p=0.40) between included and excluded children and children who declined. In total, 26 children (72%) participated in this study (Table 1) of whom 7 children (27%) were below the age of 8 years. All patients had a good graft function. Laboratory values are presented in the Appendix (Appendix Table A1).

Four patients had one or more re-transplantations: two within 2 weeks because of vascular problems of the first graft, and 2 after 2 and 6 years respectively because of biliary complications of the first graft.

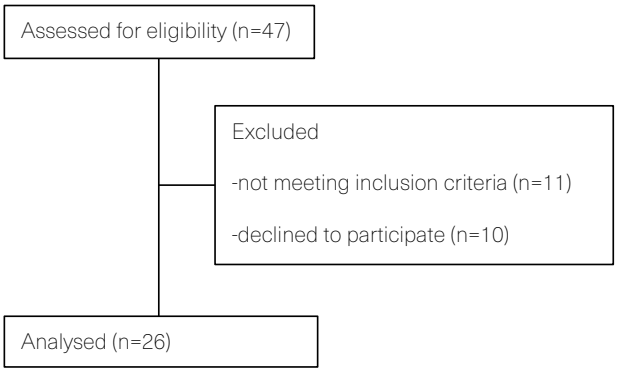

Figure 1. Flowchart patients participating in the study.

Table 1. Patient and transplantation characteristics and medication.

Patient characteristics (n=26)	**Median (IQR)**	**Z-score**
Age, years	9.7 (7.7 ; 11.4)	
Gender, boys, n (%)	14 (54%)	
Height, centimeters	138.7 (125.7 ; 153.1)	-0.4 (-1.2 ; 0,2)
Weight, kilogram	31.9 (27.2 ; 40.2)	0.2 (-0.6 ; 0.9)
Body mass index, kg/m^2	16.7 (15.8 ; 18.4)	0.4 (-0.3 ; 1.1)
Skinfold (sum 4 skinfolds in millimeter)	31.1 (26.0 ; 52.9)	Percentile
Fat%	18.2 (14.9 ; 25.3)	18.2 (14.9 ; 24.3)
Blood pressure, systolic, mmHg†	111.0 (102.5 ; 114.0)	72.0 (52.0 ; 88.0)
Blood pressure, diastolic, mmHg†	63.0 (56.5 ; 70.5)	63.0 (46.5 ; 75.5)
Type of liver disease, n (%)		
Acute liver failure	5 (19%)	
Biliary atresia	14 (54%)	
Alpha 1antitrypsin deficiency	3 (12%)	
Glycogen storages disorders	1 (4%)	
Hepatoblastoma	1 (4%)	
Tyrosimenia	2 (8%)	
Time since liver transplantation, years	7.5 (4.2 ; 9.9)	
Type of liver transplantation, n (%)		
Partial (of which 4 livingrelated)	23 (88%)	
Full size	3 (12%)	
Number of transplantations, n (%)		
1	22 (85%)	
2 or more	4 (15%)	
Medication, n (%)		
Tacrolimus	24 (92%)	
Cyclosporine	1 (4%)	
Prednisolone	21 (81%)	
Anti hypertensive medication	2 (8%)	
PELD	8.0 (1.5 ; 25.8)	
MELD	18.0 (10.0 ; 28.5)	

Norm values for standard deviation for height, weight, and body mass index by TNO[49]. Norm values for percentile Fat% by Deurenberg et al.[50] and blood pressure by national high blood pressure education program working group[51]. †n= 25 valid observations. IQR: interquartile range; PELD: pediatric end-stage liver disease score; MELD: model for end-stage liver disease score.

Physical activity and aerobic fitness

The Actical was worn by 21 children. In 6 children, corrections for non-valid days were made. In 6 other children, data were corrected for MVPA in case of non-wear (in total 5 hours for swimming activities, gymnastics at school, and horse jumping games) (Table 2). In 16 children, sedentary time was corrected for non-wear because of showering during the day (in total 26.9 hours).

No significant differences were found in weekend days and weekdays for duration of MVPA (p =0.17) or sedentary time (p=0.24). One child met public health recommendations for normal PA.

Table 2. Physical activity measured with Actical accelerometer.

Physical activity (n=21)	**Median (IQR)**	**Percentile**
Total MVPA (hours/day)	0.8 (0.6 ; 1.1)	93.0 (75.0 ; 96.0)
MVPA weekday (hours/day)	0.9 (0.7 ; 1.2)*	
MVPA weekend day (hours/day)	0.5 (0.3 ; 1.1)	
Total sedentary time (hours/day)	7.9 (6.5 ; 9.4)	3.0 (1.0 ; 25.0)
Sedentary time weekday (hours/day)	8.3 (6.7 ; 9.4)**	
Sedentary time weekend day (hours/day)	6.9 (6.3 ; 9.4)	
Meeting public health recommendations (days/week)†	2.0 (2.0 ; 5.0)	

†n = 15 valid observations. MVPA and sedentary time were calculated with the cut off points of Puyau[22]. *Difference between weekdays and weekend days p=0.17 and **p=0.24. Percentile scores for physical activity by Konstabel[38]. IQR: interquartile range; MVPA: moderate to vigorous physical activity.

Aerobic fitness

Cardiopulmonary exercise testing was performed in 24 children (92%). One child was afraid of wearing the mask, and one child was not able to perform the test at the right speed; therefore, the $VO_{2\ peak}$ could not be determined. Of the 24 children, 2 children did not reach maximal effort and were excluded for further analysis.

Five children were below the age of 8 years (3 girls and 2 boys). For these children, extrapolated data from norm values[26] were used to calculate Z-scores. Both results of aerobic fitness without extrapolated data and with extrapolated data are shown in Table 3. This is also shown in the appendix (Figure 1A) as we plotted $VO_{2\ peak}$

$_{ml/kg/min}$ Z-scores against age. The correlation coefficient of predicted $VO_{2\ peak\ L/min}$ with age was -0.48 (p=0.02), and that of age and Z-score of $VO_{2\ peak\ L/min}$ was -0.43 (p=0.05). The correlation coefficient of predicted $VO_{2\ peak\ ml/kg/min}$ with age was -0.53 (p=0.01), and that of age and Z-score of $VO_{2\ peak\ ml/kg/min}$ was -0.52 (p=0.01).

Table 3. Aerobic fitness.

Aerobic fitness	Median (IQR)	% predicted	Z-score
$VO_{2\ peak\ (L/min)}$	1.4 (1.1 ; 1.7)†	93 (77 ; 98)‡	-0.5 (-1.6 ; -0.14)‡
Extrapolated		96 (79 ; 101)¶	-0.3 (-1.5 ; 0.1)¶
$VO_{2\ peak\ (ml/kg/min)}$	41.6 (36.2 ; 44.3)†	89 (77 ; 104)‡	-0.9 (-1.8 ; 0.3)‡
Extrapolated		95 (85 ; 107)¶	-0.4 (-1.2 ; 0.6)¶
Anaerobic treshold	0.84 (0.72 ; 0.99)§		
Anaerobic treshold of predicted $VO_{2\ peak}$		52 (46 ; 67)§	
Extrapolated		55 (48 ; 67)†	

Z-scores calculated as ($VO_{2\ peak}$ - $VO_{2\ peak\ norm}$)/standard $deviation_{norm}$. Norm by Bongers[26]. For children younger than 8 years, regression equations were used as described by Bongers[26] and standard deviations were extrapolated by regression analysis. †n=20, ‡n=17, §n=16, ¶n=22 valid observations. IQR: interquartile range.

Muscle strength

Muscle strength was tested in all 26 children (Table 4). Z-scores of muscle strength ranged between the -1.4 and -0.4. No significant differences were found in Z-scores between boys and girls, with the exception of elbow flexion for both sides (p=0.03).

Table 4. Muscle strength in Newton and Z-scores.

Muscle strength (n=26)	**Right side median (IQR)**	**Z-score median (IQR)**	**Left Side median (IQR)**	**Z-score median (IQR)**
elbow flexors (N)	103 (76 ; 132)	-1.3 (-2.3 ; -0.5)	109 (78 ; 132)	-1.4 (-2.2 ; -0.5)
elbow extensors (N)	68 (57 ; 77)	-1.3 (-1.7 ; -0.8)	72 (56 ; 81)	-1.0 (-1.7 ; -0.7)
knee extensors (N)	160 (129 ; 187)	-0.9 (-1.3 ; -0.4)	160 (117 ; 182)	-1.2(-1.5 ; -0.6)
hip flexors (N)	179 (138 ; 226)	-0.4 (-1.4 ; 0.2)	167 (116 ; 219)	-0.8 (-1.6 ; -0.2)

Z-scores calculated (muscle strenght in N – muscle strenght norm in N)/standard $deviation_{norm}$. Norm by Beenakker et al.[30]. N: newton; IQR: interquartile range.

Health-related quality of life and fatigue

Health-related quality of life and fatigue questionnaires was absent for 1 child. All parents filled in both questionnaires. Z-scores of HRQOL could only be calculated for parent report in children aged 5-7 years and for child report in children 8-12 years (Table 5). Z-scores of HRQOL and fatigue ranged between the -2.3 and 0.4.

A significant difference in child and parent report was only found in sleep/rest fatigue (p=0.03), children reported lower scores of sleep/rest fatigue compared to the parents.

Table 5. Health-related quality of life and fatigue.

HRQOL and Fatigue	Child report median (IQR)	Child Z-score median (IQR)	Parent report median (IQR)	Parent Z-score median (IQR)	p
HRQOL	(n=25)	(n=18)†	(n=26)	(n=7)‡	
Total score	75.0 (64.1 ; 80.4)	-1.0 (-2.3 ; -0.5)	71.2 (57.6 ; 84.2)	-2.3 (-3.1 ; -0.2)	0.87
Physical functioning	81.3 (67.2 ; 92.2)	-0.8 (-2.2 ; 0.6)	84.4 (58.6 ; 91.4)	-1.5 (-3.5 ; 0.2)	0.99
Psychosocial functioning	70.0 (60.0 ; 80.0)	-1.0 (-2.2 ; -0.1)	64.8 (55.0 ; 81.7)	-1.8 (-2.4 ; -0.2)	0.57
Emotional functioning	65.0 (57.5 ; 82.5)	-0.9 (-1.6 ; 0.3)	66.9 (50.0 ; 80.0)	-0.6 (-1.9 ; 0.6)	0.37
Social functioning	80.0 (65.0 ; 92.5)	-0.7 (-1.8 ; 0.7)	70.0 (63.8 ; 90.0)	-1.1 (-2.8 ; -0.2)	0.25
School functioning	70.0 (50.0 ; 72.5)	-1.2 (-2.4 ; -0.3)	65.0 (48.8 ; 75.0)	-2.0 (-2.9 ; -1.5)	0.71
Fatigue	(n=25)	(n=25)	(n=26)	(n=26)	
General fatigue	70.8 (58.3 ; 85.4)	-0.9 (-1.8 ; 0.2)	62.5 (47.9 ; 87.5)	-1.4 (-2.8 ; 0.4)	0.64
Sleep/rest fatigue	70.8 (60.4 ; 77.1)	-0.4 (-0.9 ; 0.1)	75.0 (68.8 ; 95.8)	-0.8 (-1.5 ; 0.8)	0.03
Cognitive fatigue	75.0 (47.9 ; 77.1)	-0.4 (-1.5 ; 0.2)	58.3 (41.7 ; 75.0)	-1.0 (-1.8 ; -0.1)	0.48
Total fatigue	66.7 (62.5 ; 81.3)	-0.9 (-1.3 ; 0.3)	64.6 (51.0 ; 83.7)	-1.4 (-2.4 ; 0.2)	0.61

p values for differences between child report and parent report calculated with the Wilcoxon signed rank test. † Only children 8-12 years, ‡ Only parent report of children 5-7 years. Norm values HRQOL by Engelen et al.[36] and fatigue by Gordijn et al.[32]. HRQOL: health-related quality of life; IQR: interquarile range.

Participation

The CAPE questionnaire was missing for one child. Not all sub scores could be calculated of all children because of missing values (Table 6). Diversity Z-scores and intensity Z-scores ranged from -0.6 to 0.6. No differences were found in children after liver transplantation and norm values in formal an informal participation

in daily activities. If participation was divided in different categories, the biggest difference between children after liver transplantation and the published norms was found in social participation, and both diversity and intensity Z-scores were negative, -0.6 and -0.4, respectively.

Education and participation

Nineteen of 26 children (61%) followed regular education, and 7 children (27%) followed special education. None of the children missed school related to the liver transplantation. In total, 17 out of 25 children participated in organized sports, of which 9 for more than 3 times a week. Twenty-three out of 25 children participated in gymnastics at school, and 3 children out of 25 had physical therapy.

Table 6. Participation in all activities, formal and informal activities, and in different types of activities.

Participation	Diversity Median (IQR)	Intensity Median (IQR)	With whom Median (IQR)	Where Median (IQR)	Enjoyment Median (IQR)	Z-scores Diversity Median (IQR)	Z-score Intensity Median (IQR)
Overall	28.0 (25.0 ; 33.5)†	2.4 (2.0 ; 2.7)‡	2.4 (2.25 ; 2.8)‡	2.5 (2.3 ; 2.9)>	4.3 (4.1 ; 4.4)¶		
Formal	4.0 (3.0 ; 5.5)†	1.1 (0.8 ; 1.5)†	4.0 (3.0 ; 4.3)¶	4.0 (3.3 ; 4.6)§	4.5 (4.0 ; 4.8)¶	0.3 (-0.2 ; 1.1)†	
Informal	25.0 (21.0 ; 28.0)†	2.9 (2.4 ; 3.2)‡	2.3 (2.0 ; 2.5)‡	2.3 (2.1 ; 2.7)>	4.3 (3.9 ; 4.4)§	0.2 (0.2 ; 0.8)†	
Recreational	9.0 (8.0 ; 11.0)†	4.0 (3.3 ; 5.1)§	2.1 (1.7 ; 2.4)¶	1.8 (1.5 ; 2.0)¶	4.2 (4.0 ; 4.5)§	0.5 (0.0 ; 1.4)†	0.5 (0.0 ; 1.5)§
Active physical	4.0 (2.0 ; 6.0)†	1.5 (0.9 ; 2.0)†	3.3 (2.7 ; 3.9)§	3.3 (3.0 ; 4.3)§	4.3 (3.6 ; 4.8)§	-0.2 (-1.2 ; 0.8)†	-0.2 (-0.9 ; 0.5)†
Social	6.0 (5.0 ; 8.0)†	2.5 (1.9 ; 2.9)§	2.5 (2.4 ; 2.8)§	2.7 (2.4 ; 3.1)§	4.7 (4.5 ; 4.8)§	-0.6 (-1.1 ; 0.4)†	-0.4 (-0.9 ; 0.3)§
Skill-based	3.0 (2.0 ; 5.0)†	1.5 (0.7 ; 1.9)§	3.5 (2.8 ; 4.3)§	3.0 (2.8 ; 4.2)‡	4.6 (4.3 ; 4.9)§	0.3 (-0.4 ; 1.5)†	0.5 (-0.5 ; 1.0)§
Self-improvement	6.0 (5.0 ; 6.0)†	2.5 (1.9 ; 3.3)¶	1.9 (1.4 ; 2.4)¶	2.8 (2.2 ; 3.4)¶	3.5 (2.9 ; 4.0)†	0.6 (0.1 ; 0.6)†	0.1 (-0.4 ; 0.9)¶

Range of diversity scores: overall 0-55, formal 0-15, informal 0-40, recreational 0-12, active physical 0-13, social 0-10, skill-based 0-10, self-improvement 0-10. Range of intensity scores: 1=once in four months, 2=twice in 4 months, 3=once a month, 4=2-3 times per month, 5=once a week, 6=2-3 times per week, 7=once a day. Range of with whom scores: 1=alone, 2=with family members, 3=with family, 4=with friends, 5=with others. Range of where scores: 1=at home, 2=at family, 3=in the neighborhood, 4=at school (but not during school), 5=in the village of town, 6=outside the village or town. Range of enjoyment: 1=not at all, 2=somewhat, 3=pretty much, 4=very much, 5=love it. Z-score calculated as for diversity: (diversity score / diversity score by Bult et al.[37])/standard deviation by Bult et al.[37] and for intensity: (intensity score/ intensity score by Bult et al[35].)/ standard deviation by Bult et al.[35]. †n=25, ‡n=22, §n=24, ¶n=23, >n=21 valid observations. IQR: interquartile range.

DISCUSSION

This study showed that, at least one year after liver transplantation, children aged 6 to 12 year are similarly physically active compared to published European norms, spend less time on sedentary activities, and have a normal aerobic fitness, but they do not reach the recommendation of one hour of MVPA each day[21]. Parents underestimated the children's experience of sleep/rest fatigue. The participation of children with a liver transplant in out-of-school activities was similar to Dutch norm values, and they enjoyed these activities highly.

The PA levels (time spent in MVPA) of our children are similar to healthy European published norms[38], but are somewhat less active compared to healthy Canadian children (about 1 hour/day)[41]. After liver transplantation, our children spent less time in sedentary time compared to healthy European published norms[38].

Compared to Canadian children after liver transplantation, our group spent more time in MVPA[16]. In that study, only 0.5 hours/day was spent in MVPA and none of the children met the PA recommendations[16], children were on average 14 years old, and PA levels decline with an increasing age[18,42].

In a Dutch questionnaire study in healthy children in the age of 4 to 11 years, 21% met PA recommendations[18]. In the European study, the adherence to the PA recommendations of 1 hour of MVPA each day differed between countries from 2% in Cyprian girls to 34% in Belgian boys[38].

Sedentary time is given increasing attention considering the long-term negative effects on health[19]. In our study, we found that children after liver transplantation spent less time on sedentary activities than European published norms[38]. We found no significant differences in weekdays/schooldays (median 8.3 hours/day) compared to weekend days (median 6.9 hours/day), whereas in the previously mentioned questionnaire study, sedentary time for weekdays was on average 7.3 hours/day and for weekend days 4.1 hours/day[18]. It is known that PA questionnaires have limited reliability and validaty[43].

Aerobic fitness in this study was similar to that of the healthy population. Other studies in children after liver transplantation found lower predicted values for $VO_{2\ peak}$, 90.5%[11] and 77%[16]. These studies were done in children with a mean age 11.6

and 14.0 years. We found that there was an inverse relation between percentage of predicted $VO_{2\ peak}$ and age and Z-scores of $VO_{2\ peak}$ and age. This might explain the difference between our results and the results of previous studies[11,16], our children were younger. As shown in the appendix (Figure A1), Z-scores seem to decrease with age.

Muscle strength in our children was overall lower than that of Dutch norm values. This difference was also found in previous studies[4,5]. We have chosen to measure muscle strength with a hand-held dynamometer, because it is easy clinically applicable and Dutch norm values for children are available. In one study in children after liver transplantation, quadriceps muscle strength was measured with a Biodex (peak torque)[4]. In that study, a difference between boys and girls was found: Girls had 50% lower scores compared to age and sex-predicted norm values for the Biodex measurements and boys achieved 78% of the norm[4]. In our study, we did not find differences in boys and girls in Z-scores of quadriceps muscle strength.

Similar to previous studies, we found both child report (only age 8-12 years) and parent report (only age 5-7 years) on HRQOL was lower in this study compared to published healthy norms[11,44–46]. School functioning showed the largest difference between children after liver transplantation and healthy norms, probably based on frequent school absenteeism. In our study, there was hardly any school absenteeism, but we found the largest difference with healthy published norms in school functioning as in another study[44].

Fatigue is one of the most common complaints in adult liver transplantation patients[47]. Both parent report and child report showed a higher level of fatigue compared to published healthy norms, and these findings are similar to other children after liver transplantation[16,17]. Children in our study reported more sleep/rest fatigue compared to their parents, meaning parents underestimate the children's experience of sleep/rest fatigue. No differences were found between child and parent report on HRQOL in our study, other studies report a moderate ability of caregivers to report on behalf of their children, and it is suggested to gain insight in both the perspective of the child and the parents[44,46]. In a study interviewing both children after liver transplantation and their parents, it was found that children's perspective tended to relate to the present whereas parents reflected more to a future perspective[48]. In the context of long-term management of health benefits,

children need to learn about the importance of a lifelong need for immunosuppression and about the benefits of PA. For health benefits, it is important to be physically active on all days of the week for at least one hour of MVPA.

Participation in recreation and leisure activities is important for children, because they learn new skills and competencies. In this study, participation is similar to healthy published norms regarding diversity and intensity scores. Children after liver transplantation scored high on enjoyment. In this study, 68% (n=17) of the children participate in organized sports.

Our study has some limitations. Studying a control group particularly with younger children would have strengthened our results. Unfortunately, no reference data of Dutch children was available for PA in the age of 6 to 12 years measured with the Actical accelerometer; therefore, we used European reference values[38]. In that study, a different accelerometer was used, and although we compared our data with the scores of the same cutoff points as in our study, there might be differences. When designing the study, we intended to use the reference data of Dutch children, but in that study children were on average 13.4 years[39]. Reference data of the European children became available while performing the study. Although we made corrections for non-wear to do justice to the time spent in MVPA, there might be an overestimation of the real time spent in MVPA as we corrected for the full reported time, knowing that studies in gymnastics at school show that only 37% of the reported time is spent in MVPA[23]. One can imagine the same applies for activities reported during non-wear, but since no studies were available for other activities, we have chosen to correct these activities for the reported time. The same applies for sedentary time. If we did not make the corrections by subtracting the reported activities during non-wear from the total sedentary time, we would have overestimated sedentary time, considering that we did not actually know the real intensity of the reported activity. Correction for non-wear was negligible on the total PA time.

No norm values for aerobic fitness were available in children below the age of 8 years. We wanted to get more insight in especially young children and chose to extrapolate available data with all the known limitations of this method.

The last limitation of this study is the small sample. Since our center is the only pediatric liver transplant center in The Netherlands and we wanted to focus on the young children, we were not able to increase the sample, but we had 72% participation. In total, 10 children declined to participate in this study (no significant differences in age, gender and time since liver transplantation) which might cause potential bias. The small group especially applied for calculating Z-scores on HRQOL, since these calculations could not be made for HRQOL child report in the age of 5-7 years and HRQOL parent report in the age of 8-12 year as no norm data was available. The small sample also makes the population somewhat heterogeneous; several participants were well prior to transplantation, while others were chronically ill, which could influence the outcome of the measures.

Despite the limitations of the study and the sample, this study provides insight in PA, aerobic fitness, muscle strength, HRQOL, fatigue and participation in young children after liver transplantation.

In conclusion, young children after liver transplantation have similar MVPA patterns, spend less time on sedentary activities compared to published healthy norms, and have normal levels of aerobic fitness. Both HRQOL and muscle strength are overall lower and children experience more fatigue compared with published norms, but this does not limit these children in participation of daily activities. Participation levels are similar to published healthy norms and are rated highly on enjoyment. Although children do well, in the context of long-term management, it remains important to stimulate PA in children after liver transplantation.

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APPENDIX

Table A1. Laboratory values.

Laboratory value (n=26)		**Mean (SD)**
PT sec (9-12) †		11.71 (0.69)
INR †		1.13 (0.08)
Total bilirubin (umol/L)		9.31 (6.93)
Albumine (g/L)		44.73 (2.30)
AST (U/L)		35.27 (9.76)
ALT (U/L)		23.31 (8.29)
Gamma GT (U/L)		56.08 (109.14)
Cholesterol mmol/L		3.36 (0.58)
Percentile 5	9 (35%)	
Percentile 75	16 (62%)	
Percentile 95	1 (4%)	

n= valid observations, †n=24. Norm value cholesterol by Kliegman et al.[52]. PT: prothromin time; INR: international normalized ratio; AST: aspartate aminotransferase; ALT: alamine aminotransferase; GT: glutamyl transferase.

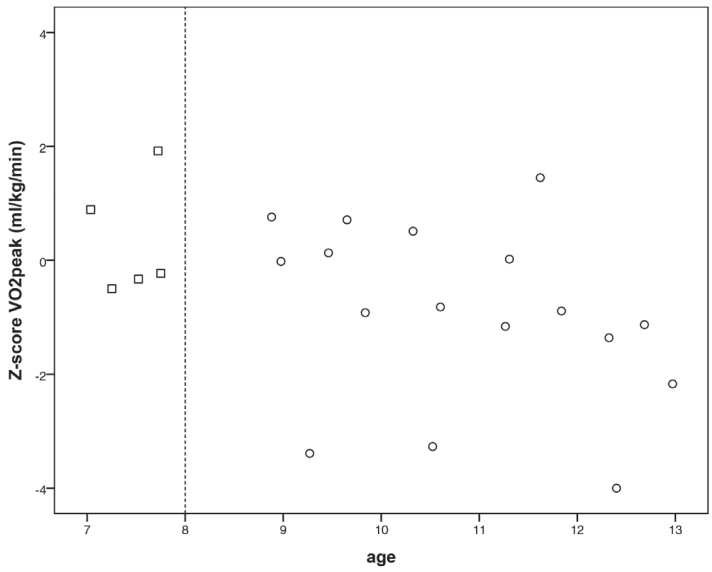

Figure A1. Z-scores of $VO_{2\ peak\ (ml/kg/min)}$ plotted against age.

At the left side of the dotted line the extrapolated data and at the right side Z-scores of norm values.

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CHAPTER 5

Measuring physical activity in juvenile idiopathic arthritis: activity diary versus accelerometer

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ABSTRACT

Objective

(1) To determine convergent validity of an activity diary (AD) and accelerometer (Actical brand/Phillips-Respironics) in measuring physical activity (PA) in children with juvenile idiopathic arthritis (JIA). (2) To determine how many days give reliable results. (3) To analyze effects of correcting accelerometer data for non-wear.

Methods

Children with JIA (8-13 years) were recruited from 3 Dutch pediatric rheumatology centers. Physical activity was assessed for 7 days with an AD and accelerometer, and was expressed as mean minutes/day of rest, light PA (LPA), moderate to vigorous PA (MVPA), and PA level (PAL). To analyze convergent validity, intraclass correlation coefficients (ICC) were calculated and paired sample Student t tests were performed. The required number of days to achieve reliable results was calculated using the Spearman-Brown prophecy formula.

Results

Convergent validity between AD and accelerometer was moderate for rest and PAL (ICC 0.41). ICC for LPA and MVPA were < 0.24. AD overestimated PAL and MVPA compared with the accelerometer. Wearing the accelerometer for 7-19 days gave reliable PA estimates on group and individual levels. For the AD, 13-36 days were needed. Adjusting accelerometer data for non-wear resulted in a clinically relevant higher mean number of minutes/day spent in LPA (effect size 1.12), but not in MVPA (effect size 0.44).

Conclusion

Convergent validity between AD and accelerometer is moderate to poor. In children with JIA, 1-week assessment with an accelerometer is sufficient to measure PA (all levels) reliably. On an individual level and for clinical use, 3 weeks are required. Additional use of an AD enables correction for non-wear of accelerometer data.

INTRODUCTION

Physical activity (PA), increasing energy expenditure above basal metabolic level[1], contributes to prevention of several chronic conditions, improves psychological health, and is associated with longevity and prevention of all-cause mortality[2–5]. For patients with juvenile idiopathic arthritis (JIA), it is equally important to profit from these benefits, because evidence shows PA is safe and does not damage joints[6–8]. PA is reduced in children and adolescents with JIA[9–16].

PA can be expressed as total energy expenditure (TEE) in kilojoules (kj) or kilocalories per day, where TEE is the sum of the basal metabolic rate, diet-induced thermogenesis, and activity-related energy expenditure (AEE). Another way to express PA is by PA level [PAL; TEE (kJ) divided by the basal metabolic rate (kJ)]. PA can be categorized into rest, light PA (LPA), and moderate to vigorous PA (MVPA)[17,18].

To determine PA, many methods can be used[18–20]. In JIA, self and proxy reports, questionnaires, recall diaries, and accelerometers, or combinations of these methods have been used to determine PA[9–15,21–23].

Because PA can vary from day to day, increasing the number of days measured will improve reliability of measurements but will increase the burden for patients and may decrease adherence. The number of days in which PA was measured previously ranged from 1 to 7[9–12,14,15,21–23]. Further, the number of days needed to determine PA reliably depends on the type of instrument used and on patient characteristics[24].

In general, questionnaires and recall diaries tend to overestimate PA[25,26]. However, accelerometers underestimate PA, while they do not or insufficiently record certain types of activity, in particular, nonambulatory PA with arm and or leg movements[27]. The underestimation is enforced by non-wear during activities such as swimming. Therefore, it has been suggested to combine 2 or more techniques to improve the accuracy of measurements[20]. In a study in 13- and 15-year-old adolescents, PA was determined using an accelerometer and an activity diary (AD) to register activities while the accelerometer was not worn. Significantly higher levels of MVPA were found when the results were corrected for non-wear[28].

The aims of our study were to (1) determine convergent validity of a 7-day AD and an accelerometer in children with JIA, (2) determine how many days of PA needed to be assessed to obtain reliable results using an AD and accelerometer, and (3) analyze the effect of combining the 2 instruments by using the AD to correct for non-wear of the accelerometer.

PATIENTS AND METHODS

Study design

Our current study covers a cross-sectional design of a 7-day observation period.

Subjects

Participants were children with JIA, aged 8 to 13 years, participating in the Rheumates@Work study, a multicenter trial to evaluate the effects of an internet-based cognitive behavioural program on PA levels (trial number SRCTN92733069)[29]. For our study, baseline measurements of Rheumates@Work were used. Children were recruited from 3 pediatric rheumatology outpatient clinics in The Netherlands: the Beatrix Children's Hospital of the University Medical Center Groningen; the Wilhelmina Children's Hospital of the University Medical Center Utrecht; and from Reade, Center for Rehabilitation, Amsterdam, from January 2011 until September 2012. The medical ethics research board of all 3 centers approved the study (NL34044.042.10). All patients with JIA diagnosed according to the international league of associations for rheumatology criteria[30] were asked to join in the Rheumates@Work study. Children willing to participate filled in an informed consent form and were invited to participate at their own clinic, where disease activity was scored and comorbidity was registered by a pediatric rheumatologist. On the same day, the accelerometer and AD were handed out. The children and one of their parents were verbally and in writing instructed on how to wear and use the accelerometer and AD, simultaneously. Inclusion criteria for our study were disease activity lower than 2 centimeters on a physician's global assessment scale (0-10). Exclusion criteria were comorbidity that affected maximum exercise capacity and PA, and insufficient proficiency of the Dutch language. Patients without a completed AD and or accelerometer for 7 consecutive days were also excluded from our study.

Accelerometry

An Actical accelerometer (Phillips-Respironics) was worn with an elastic belt over the right hip near the anterior superior iliac spine. This accelerometer has been validated for children aged 7 years up to 18 years of age (sensitivity 86%-97% and specificity 66%-80%)[31]. It contains an omnidirectional accelerometer that measures occurrence and intensity of motion. This information was used to calculate activity counts per time unit (60 seconds in our study) and AEE in kilocalories per day. TEE (MJ) was calculated with the formula ([AEE * 4.1868 ÷ 1000 + BMR] ÷ 0.9), where BMR is the basal metabolic rate[22]. Data from the accelerometer were stored in an Excel file as counts per minute, giving 1440 timepoints per day. Higher counts per minute correspond with higher PA intensity. Cutoff points were used for rest, LPA, and MVPA[31]. Accelerometer data were visually inspected with help of an actogram, a graphic representation of activity counts per minute, and non-wear time was observed and compared with non-wear time in the Excel file. Non-wear time was defined as 60 consecutive minutes of 0 counts, with allowance for 1 or 2 minutes of counts between 0 and 100. Accelerometer measurements were considered valid when the wearing time summed 6 hours on weekends or 8 hours on weekdays.

Activity Diary

The AD is a reliable instrument for measuring PA in children from 10 years of age and up (intraclass correlations 0.86-0.95)[32]. It was validated in 15-year-olds using the doubly labeled water method (gold standard for measuring PA), showing a mean difference of 0.01 in PAL and with limits of agreement between -0.47 and 0.49[33]. Every quarter of an hour, the dominant activity was scored with a number 1-9 (Appendix 1). In case children or parents where in doubt about giving the correct number for the activity, children or parents could contact the investigator or could describe the type of activity in de AD. In cases where a 15-minutes period had more than 1 entry, the first or second entry was chosen alternately.

In case of missing values, children and parents were asked to recall the activity for that period. If there were still missing values present, missing values were corrected to enable the calculation of PAL. Missing values between 9 p.m. and 7 a.m. were imputed with a 1, because this was considered to be sleeping time. Children were instructed to draw a smiley face in the AD at the time the accelerometer was put on in the morning and when it was taken off in the evening. When children forgot to give a number for their activity and only drew a smiley face to

indicate that the accelerometer was worn, missing values were imputed by the activity of the prior 15 minutes. In case of missing data and children had drawn a smiley face indicating that the accelerometer was taken off, data were imputed with the activity of the next 15 minutes. When 4 or fewer missing values remained, they were substituted by activity 2. In cases of more than 4 remaining missing values, the AD was excluded from the analysis.

PA was expressed as PAL and time (minutes) spent at rest, LPA, and MVPA. Corresponding energy expenditure was calculated with known formulas (Appendix 1)[25,33,34]. To calculate TEE, the energy cost of all 15-minutes periods were summed and divided by 96. PAL was calculated by dividing the TEE for each day with the BMR[22,33].

Correction of accelerometer data for non-wear

Rest as measured with the accelerometer was compared to AD data. When LPA or MVPA was reported in the AD and the accelerometer data showed rest, we assumed non-wear. Non-wear was corrected by adding up the number of minutes of LPA or MVPA, reported in the AD, and subtracting the equivalent number of minutes from the total minutes spent at rest. No corrections were made for PAL, because algorithms to calculate energy expenditure use activity counts for each individual minute[35], whereas counts per minute can differ considerably within LPA (from 101 up to 1500) and MVPA (≥1501).

The patient characteristics age, sex, weight, and height were recorded. The diagnosis was taken from the medical chart.

Statistical analysis

Intraclass correlation coefficients (ICC) were calculated for rest, LPA, MVPA, and PAL-based accelerometer and AD to analyze convergent validity. An ICC of ≥ 0.60 was rated as good validity, ≤ 0.3 to < 0.6 was rated as poor to moderate validity, and < 0.3 was rated as no convergent validity[36].

Differences between the AD and the accelerometer were analyzed using paired sample Student t-tests. Bland-Altman plots were drafted, where the difference between AD and accelerometer data was plotted against the average of both methods. Limits of agreement were calculated as mean difference ±1.96 * SD.

Differences between accelerometer and AD were analyzed using linear regression analysis for proportional bias[37,38].

The required number of measurement days to achieve an ICC of 0.75 and 0.9 for PAL, rest, LPA, and MVPA, measured with AD and accelerometer, were calculated using the Spearman-Brown prophecy formula: k=[ICC to achieve ÷ (1 - ICC to achieve)] * [(1-ICC_{single}) ÷ ICC_{single}], where k is the number of required measurement days. Single-day ICC was calculated using repeated measurements of ANOVA by dividing the between-patient variance by the total variance, which is the sum of between-patient between-days and error variance. An ICC of > 0.75 was considered good reliability at group level, and an ICC of 0.9 was considered good reliability at an individual level[39].

Differences between rest, LPA, and MVPA measurements of the accelerometer with and without correction for non-wear were analyzed with paired sample Student t tests. Effect size was calculated by dividing the mean difference by the standard deviation of that difference. Bland-Altman plots were drawn, where the difference between rest, LPA, and MVPA based on accelerometer with and without correction for non-wear was plotted against the mean of both. Median difference was provided with limits of agreement as indicated by 2.5 and 97.5 percentiles. The Statistical Package for Social Sciences (IBM SPSS Statistics 22) was used for statistical analysis.

RESULTS

In 8 AD, parents and children described their activity precisely, but had not assigned a number to it. The authors filled in the number based on that description, consisting in total of 22 hours. Fourteen hours of missing values were imputed based on recall of parents and children. Thirteen diaries contained double numbers for a total of 17 hours. Missing values adjacent to smiley faces in the AD were imputed in 10 AD for a total of 8.5 hours. In 17 diaries, missing values were imputed by sitting activities for a total of 5 hours.

Eighty-three children participated in the Rheumates@Work study. After data imputation, 73 children (88%) had a complete AD. Sixty-six children (80%) had complete accelerometer data. In total, 61 children (73%) had a complete AD [consisting a

total of 10,248 hours, of which 21 hours were imputed (0.2%)] and accelerometer data on 7 consecutive days (Table 1).

Table 1. Patient characteristics.

Characteristics (n=61)	**Values**
Age, years	10.1 (1.4)
Boys/girls, n	24/37
Height, cm	144 (10)
Weight, kg	35.8 (8.7)
JIA subtype, n	
Persistent oligoarticular	22
Extended oligoarticular	10
Polyarticular	17
Psoriasisrelated	3
Enthesitisrelated	3
Systemic	6

Values are mean (SD) unless otherwise specified.
JIA: juvenile idiopathic arthritis; cm: centimeters; kg: kilogram; n: number.

Number of hours spent on MVPA were mostly based on AD, followed by corrected accelerometer data and non-corrected accelerometer data (Table 2). Number of hours spent at rest was calculated mainly with accelerometer data (Table 2). The ICC between the AD and accelerometer indicate moderate convergent validity or worse (Table 2). The differences between AD and accelerometer depended on the means of both for all PA categories (Figure 1 and Table 3). For all PA categories for lower means, AD data were lower than those of the accelerometer, and in the higher means, AD data were higher than those of the accelerometer (Figure 1). Regression lines all run from lower left border to upper right border, indicating proportional bias.

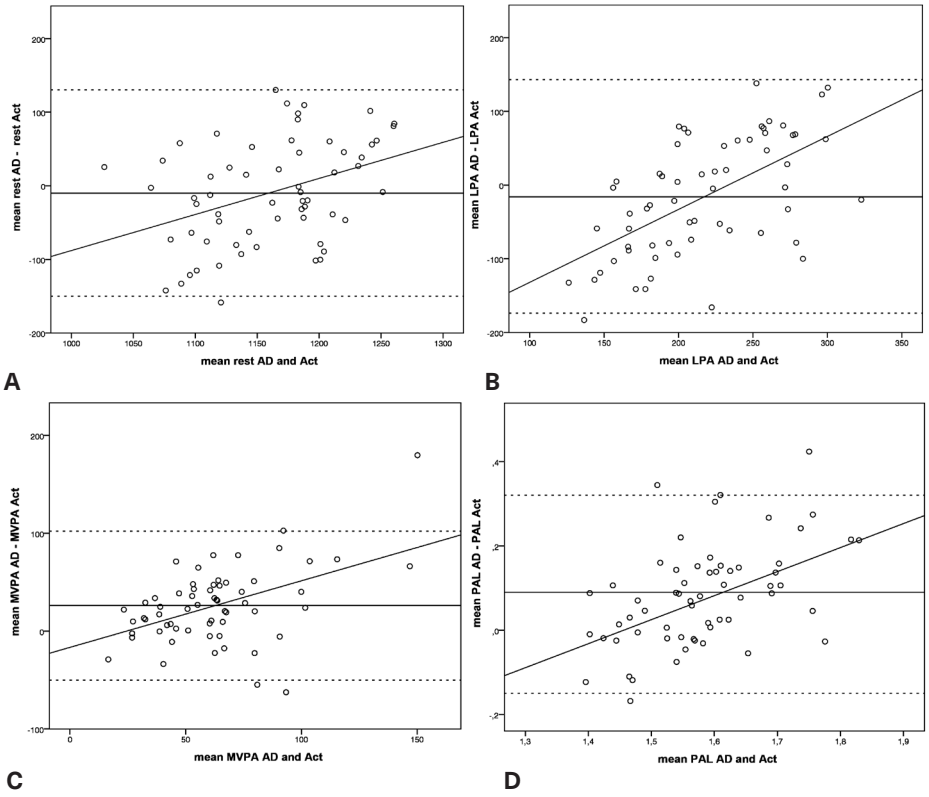


Figure 1. Bland-Altman plots of differences in time spent in physical activity based on AD and accelerometer (Act) data (Y axis) plotted against the means of AD and accelerometer data (X axis). Solid horizontal lines: mean differences. Dotted lines: limits of agreement (LOA). **(A)** Minutes/day spent at rest (mean difference: -10, LOA -150.1; 130.3). **(B)** Minutes/day spent in LPA (mean difference: -16, LOA -173.9; 141.3). **(C)** Minutes/day spent in MVPA (mean difference: 26, LOA -50; 102.1). **(D)** PAL (mean difference: 0.09, LOA-0.15; 0.32). All regression lines run from lower left to upper right, indicating proportional bias. AD: activity diary; LPA: light physical activity; MVPA: moderate to vigorous physical activity; PAL: physical activity level.

Table 2. ICC between physical activity (minutes/day) and physical activity level based on data of AD and accelerometer, and differences between physical activity based on data of accelerometer and accelerometer corrected for non-wear.

Variables	AD	Accelerometer	AD-Accelerometer, Mean Difference (95% CI), Significance*	ICC (95% CI)	$Actical_{cor}$	$Actical_{cor}$ – Accelerometer, Mean Difference (95% CI), Significance*	$Actical_{cor}$ – Accelerometer, ES
Rest†	1156 (77)	1166 (53)	-10 (28.2 - 8.4), p=0.29	0.41 (0.19 - 0.60)	1145 (52)	-21(-25 to -16), p<0.01	1.11
LPA†	209 (79)	225 (40)	-16 (-36.8 to 4.4), p=0.12	0.17 (-0.08 to 0.40)	243 (41)	18 (14 - 22), p<0.01	1.12
MVPA†	76 (40)	50 (25)	26 (16.1 - 36.0), p<0.01	0.24 (-0.01 to 0.46)	52 (25)	2 (0.9 - 3.8), p<0.01	0.44
PAL	1.63 (0.14)	1.54 (0.09)	0.09 (0.05 - 0.11), p<0.01	0.41 (0.09 - 0.63)	NA	NA	NA

Values are mean (SD) unless otherwise specified. †Minutes/day. *Results of paired sample Student t test. ICC: intraclass correlation coefficient; AD: activity diary; LPA: light physical activity; MVPA: moderate to vigorous physical activity; PAL: physical activity level; $Actical_{COR}$: Actical (accelerometer) data corrected for non-wear time; ES: effect size (mean difference/ $SD_{difference}$); NA: not applicable.

Table 3. Results of the linear regression analyses to predict the difference between the AD and accelerometer, with the mean of the AD and accelerometer as predictors for assessing proportional bias.

Variables	Constant	b	95% CI	p	R^2
Rest	-578	0.49	0.18 - 0.80	<0.01	0.15
LPA	-231	0.99	0.64 - 1.35	<0.01	0.35
MVPA	-17	0.68	0.35 - 1.01	<0.01	0.22
PAL	-0.83	0.57	0.31 - 0.84	<0.01	0.25

AD: activity diary; LPA: light physical activity; MVPA: moderate to vigorous physical activity; PAL: physical activity level; CI: confidence interval.

To reach an acceptable reliability for determining MVPA, 5 days of accelerometer measurements were enough, and measured by means of AD, 13 days were necessary (Table 4). For clinical application for individual decision making, 14 days of measurement using the accelerometer and 36 days of measurement using the AD are needed (Table 4).

Table 4. ICC of AD and accelerometer, and number of days to reach an ICC of 0.75 and 0.90.

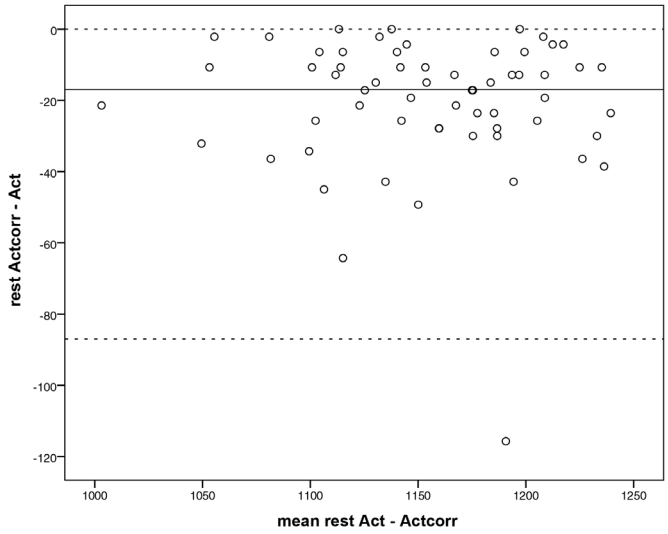
Activity		ICC (95% CI)	No. days needed to reach: ICC 0.75	ICC 0.90
Activity diary				
PAL	0.21	(0.12 - 0.32)	11.4	34.3
Rest	0.32	(0.23 - 0.44)	6.3	18.8
LPA	0.36	(0.26 - 0.48)	5.3	16.1
MVPA	0.20	(0.11 - 0.31)	12.3	36.0
Accelerometer				
PAL	0.33	(0.23 - 0.47)	6.2	18.6
Rest	0.37	(0.27 - 0.49)	5.1	15.1
LPA	0.37	(0.27 - 0.49)	5.2	15.5
MVPA	0.39	(0.29 - 0.51)	4.6	13.9

ICC: intraclass correlation coefficient; PAL: physical activity level; LPA: light physical activity; MVPA: moderate to vigorous physical activity; CI: confidence interval.

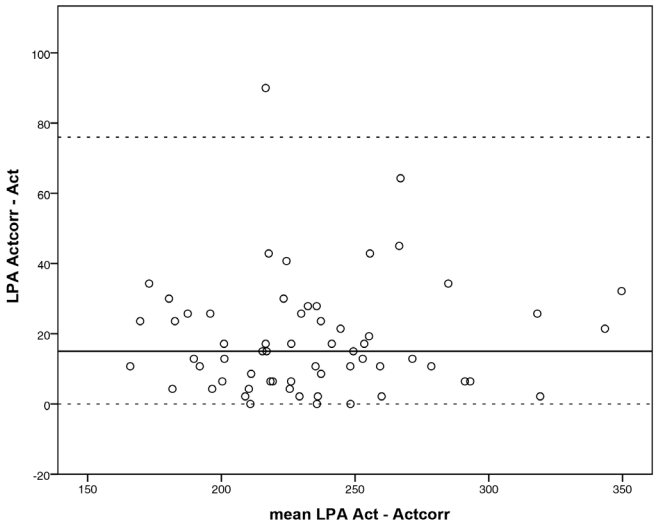
When accelerometer data were corrected for non-wear, significant differences were found in mean time spent at rest, LPA, and MVPA (Table 2). The effect size for MVPA was small for non-wear. For rest and LPA, effect sizes were large.

Bland-Altman plots showed that corrections for non-wear of the accelerometer in MVPA could differ up to 25 minutes for individual patients (Figure 2).

A



B



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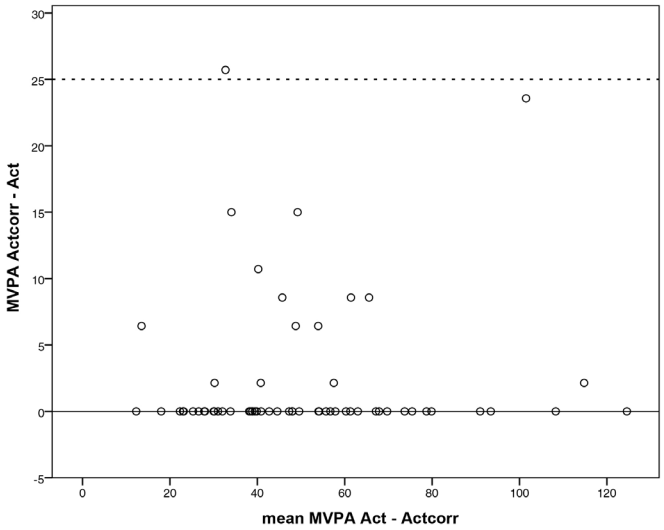

Figure 2. Bland-Altman plots of differences in time spent in physical activity based on accelerometer (Act) and accelerometer corrected for non-wear (Act_{corr}) data (Y axis) plotted against the means of Act and Act_{corr} (X axis).

Solid horizontal lines: median differences. Dotted lines: 2.5 percentile to 97.5 percentile. **(A)** Minutes/day spent at rest (median difference: -17, 0; -87). **(B)** Minutes/day spent in LPA (median difference: 15, 0; 76). **(C)** Minutes/day spent in MVPA (median difference: 0, 0; 25). LPA: light physical activity; MVPA: moderate to vigorous physical activity.

DISCUSSION

Our study showed that the AD and accelerometer have a moderate or poor convergent validity in patients with JIA aged 8 to 13 years. One-week measurement with an accelerometer and 13 days of measurements with an AD are sufficient to obtain reliable estimates of PA at group level. In individual cases and for clinical purposes, almost 3 weeks of accelerometer and > 5 weeks of AD measurements are required. Correction for non-wear of the accelerometer resulted in a significant increase in LPA and MVPA. The effect size for LPA was substantial, and for MVPA it was small. In studies where LPA is one of the outcome variables, correcting for non-wear is relevant. Correcting MVPA for non-wear is relevant for individual patients.

The poor to moderate convergent validity between AD and accelerometer was also found previously[40–42]. Two-thirds of parents of healthy children, aged between

5 to 7 years, overestimated their children's PA when PA was measured with an electronic diary compared to the activity counts of the accelerometer. A moderate correlation (0.44) was found between both instruments[41]. Correlations of 0.33 for girls and 0.44 for boys were found, controlled for body mass, between estimated AEE measured with a 3-day AD and an accelerometer in 403 healthy adolescents[40]. In healthy Spanish adolescents, a moderate correlation of 0.36 was found in MVPA between the ActiGraph brand activity monitor and the Bouchard AD[42]. In general, correlations between any self-report and an objective instrument were found to be low to moderate at best[25].

The poor to moderate convergent validity can be explained in 2 ways. First, in AD, participants usually tend to overestimate the intensity and duration of different types of activities and sports because of the intermittent characteristics of activities and sports[25]. When a child reports 1 hour of physical education classes, normally classified as MVPA, in reality only 37% of the time will be actual MVPA while the rest of the time will be spent on sedentary or LPA[26]. Additionally, accelerometers underestimate intensity and duration of certain types of activities because they are less sensitive to registering activities such as walking up stairs, cycling, and activities that mainly involve arm movements[43]. Moreover, compliance with wearing an accelerometer for a whole 7-day period remains a concern, and non-wear will again underestimate PA[43]. Second, intensity thresholds of AD are based on metabolic equivalents of tasks performed, while thresholds of accelerometers are measured in the laboratory, where body movement and energy expenditure are concurrently measured[25].

For children with JIA, disease-specific arguments may account for the poor to moderate convergent validity between AD and accelerometer. Children with JIA have higher AEE compared with healthy peers when performing similar activities[44,45]. This difference not only affects thresholds for activity counts for categories of PA, but it also affects the classification of the activities 1-9, as used in the AD. Additionally, children with JIA have different activity counts compared with healthy peers when performing the same activities[44]. To what extent both arguments affect convergent validity has not been studied, to our knowledge, but should be taken into account.

Our study showed that in children with JIA aged 8-13 years, 1 week of measurements with an accelerometer was sufficient, but for an AD, at least 13 days of measurements were needed to reach sufficient reliability. This finding is in line with a previous study that showed that the number of measurement days for reliable assessment of PA depended on the type of instrument, purpose of the study, and the characteristics (including age) of the population[24]. Healthy younger children exhibited less day-to-day variability than healthy adolescents and therefore required fewer days to assess PA reliably. In healthy 5-year-old preschool children, 5-6 days of accelerometer monitoring were needed, compared to 4-5 days in 7- to 12-year-old children, and 8-9 days of monitoring in 13- to 16-year-olds[46,47]. For adults, 3-5 days of monitoring appeared to be sufficient to assess PA[27]. In healthy and chronically ill children, as far as we know, the number of days required for the AD has never been assessed. Our results indicate that in children with JIA on an individual level and for clinical purposes, almost 3 weeks of accelerometer monitoring is needed and 5 weeks of the AD. This number of weeks is not realistic, considering the effort this would require from children and their parents.

We found a significant but small increase of about 4% between MVPA, measured with and without correction for non-wear. In a study including 513 healthy children, aged 13-15 years, correction for non-wear using ActiGraph accelerometers and a non-wear diary resulted in an increased mean MVPA of 43% (23-33 minutes/day increase)[28]. In the study, the increase was mainly related to non-wear during aquatic activities and ball games. In our study, a smaller correction for non-wear for MVPA was found, perhaps because of the instructions given to the children to wear the accelerometer all the time, except for water activities. Another explanation might be the younger age of our patients, which could lead to more compliance to wear the accelerometer. However, at individual level, MVPA was corrected for 10 minutes up to 25 minutes per day in 5 children, and for 5–10 minutes in 6 patients. This correction is clinically relevant because it results in an increase of 35-175 min of MVPA per week. These findings indicate that the relevance of correcting for non-wear can vary between samples and that, in studying MVPA in JIA clinical trials, correction leads to small differences at the group level. For clinical use in children with JIA individually, the use of an AD in combination with an accelerometer is recommended, because in individual cases non-wear can be considerable.

Our study has limitations. Only children with JIA with no or mild disease activity were selected. Patients with high disease activity may show lower and less variable PA, and are more likely to engage in exercise activities such as swimming, resulting in more non-wear of the accelerometer. However, measuring PA in low disease activity states is more useful, because it is during this phase that PA is especially resumed. Another form of selection bias was caused by the willingness of children to participate in a program aimed at improving PA. These children may have overestimated their PA, leading to higher AD scores, or those who were less active were willing to improve their PA level. In our study, boys were relatively more represented as compared with the general population of patients with JIA. Boys may have different activity patterns that could have influenced our results. The age of the patients may have also influenced results. Children in our study were 8-13 years old, but the reliability of the AD has only been assessed in children 10 years of age and older[32]. We tried to overcome this by instructing parents to help their children fill in the diary. Another limitation was that the AD was validated only in children aged 15 years[33]. Imputing missing values could cause errors, although this was only necessary in a very small proportion of the AD. An epoch of 1 minute for the accelerometer could be another limitation because it underestimated MVPA in preschool children and adolescents compared with an epoch of 15 seconds[48,49]. In a recent study in healthy children, aged 8-11 years, a small clinically irrelevant underestimation of MVPA (1.9 minutes/day) was found when using an epoch of 1 minute[50]. Another limitation is that we measured for 7 days and used these data to calculate the number of days needed for reliable estimates. By measuring and using a single ICC, compound symmetry is assumed, meaning that the correlations among days are similar[24]. However, because of day-to-day variability, actual correlations between days will most likely differ, thus violating the compound symmetry assumption leading to underestimation of the days required[24].

There is poor to moderate convergent validity between the AD and accelerometer. To compare PA between groups of patients with JIA, a 1-week assessment with the accelerometer is sufficient. For individual decision making, 2-3 weeks are required. To be able to correct for non-wear (for instance swimming), use of an AD is recommended.

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APPENDIX

Appendix 1. Categories of activities and the formulas for energy expenditure.

Categories of activities for the activity diary

1= sleeping or resting in bed; 2= sitting, eating, writing, etc.; 3= standing, washing, combing, etc.; 4= walking indoors (< 4 km/hour), light home activities; 5= walking outdoors (4-6 km/hour), cleaning bedroom, easy outdoor playing; 6= recreational sports and leisure time activities with low intensity; 7= recreational sports and leisure time activities with moderate intensity; 8= recreational sports and leisure time activities with high intensity; and 9= sports competitions.

Equations to calculate energy expenditure

Rest time refers to activities that do not increase energy expenditure substantially above resting level, such as sleeping, lying down, and seated activities[34]. These are represented by categories 1 and 2, and the energy costs are 0,98*basal metabolic rate (BMR) and 1.5*BMR, respectively[33]. Intensity thresholds between light physical activity (LPA) and moderate to vigorous physical activity (MVPA) are around 4 metabolic equivalents of tasks[25]. Therefore, LPA is represented by categories 3, 4, and 5, with a cost of 2.0, 2.8, and 3.3*BMR, respectively. MVPA is category 6 and higher, with an energy cost of 4.4, 6.5, 10.0, and 15.0*BMR, respectively.

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CHAPTER 6

Muscles in motion: a randomized controlled trial on the feasibility, safety and efficacy of an exercise training programme in children and adolescents with juvenile dermatomyositis

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ABSTRACT

Objective

To study for the first time in a randomized controlled trial the feasibility, safety and efficacy of an exercise training programme in children and adolescents with juvenile dermatomyositis (JDM).

Methods

Patients were randomly assigned to the intervention group (IG; n=14) or waiting control group (WCG; n=12). The intervention comprised an individually tailored 12-week home-based exercise programme of treadmill interval training and strength exercises. The efficacy of the IG over usual care (WCG) was examined with mixed linear regression (intention-to-treat). Effect sustainability during 12 weeks follow-up was also examined.

Results

Seventy-five percent of the participants completed the intervention. Reasons for discontinuation were motivation/fatigue, recurrent infections and increasing physical complaints. No hospitalizations occurred and immune suppressive therapy remained stable or decreased in the patients who participated in the intervention. The estimated marginal means after the intervention period were significantly in favour of the IG compared to WCG for standing long jump distance [difference between groups (95%CI): 13 cm (2 - 23)], the 30-seconds number of push-ups [8 (3 - 13)] and sit-ups [4 (0.4 – 8)], and the parent childhood health assessment questionnaire 30+8 score [-0.13 (-0.24 to -0.01)] and effects sustained at follow-up. A trend was seen for the maximal oxygen uptake divided by body mass during maximal exercise treadmill testing; the IG scored 3.0 ml/kg/min (-1.3 to 7.3) higher compared to the WCG. Other outcomes (e.g. isometric muscle strength and perception of fatigue) did not differ between IG and WCG.

Conclusion

Exercise training is of value in the clinical management of JDM.

INTRODUCTION

Juvenile dermatomyositis (JDM) is a rare systemic autoimmune vasculopathy characterized by capillary inflammation affecting predominantly the musculoskeletal and cutaneous system[1]. Prominent clinical features are significant muscle weakness[2], reduced tolerance for anaerobic and aerobic exercise[3–7] and fatigue[8]. Despite pharmacological improvements, these clinical features frequently persist in patients with JDM, even when the disease is in remission[9–12].

In the past, exercise was not recommended as part of treatment for JDM and other idiopathic inflammatory myopathies due to consideration of triggering or amplifying the inflammatory response in the affected muscles[13,14]. Nowadays, exercise (training) is increasingly utilized in the clinical management of patients with an idiopathic inflammatory myopathy because several studies show no increases of muscle damage or inflammation after either a single exercise session[15] or after an exercise training programme[16–21]. Additionally, various studies in patients with adult dermatomyositis and other idiopathic inflammatory myopathies indicate that exercise training enhances muscle strength, aerobic fitness and functional outcomes[17,18,22,23].

Recently, two studies to exercise training in patients with JDM were performed: one study included 10 children with active and non-active mild or chronic JDM[20] and one included 10 adolescents and adults who had recovered from JDM[21]. Both studies showed positive effects of exercise training on muscle strength, functional outcomes, aerobic fitness, bone mass, and health-related quality of life. However, they comprised small patient groups and did not include a control group.

Therefore, we performed a multicentre randomized controlled trial to study the feasibility, safety, and efficacy of an individually tailored 12-week home-based exercise training programme in the largest group of patients with JDM studied to date. The sustainability of the effects of this training programme after 12 weeks follow-up was also examined.

PATIENTS AND METHODS

Study design

This was a multicentre (four academic hospitals), stratified (age and gender), parallel-group study conducted in The Netherlands with a balanced randomization performed by an independent and blinded person using computergenerated lists of random numbers with randomly varying block sizes (2 or 4)[24]. Analyses of the data were performed blinded for group allocation.

Between baseline and follow-up 1, patients in the intervention group (IG; n=14) performed the intervention, while patients in the waiting control group (WCG; n=12) received usual care. Usual care was defined as pharmacological and non-pharmacological routine care received by the patients for treatment of JDM (see Table 1 for details). The patients in the WCG performed the intervention after their usual care period was completed. To determine the effect sustainability of the intervention, all participants who completed the intervention were measured 12 weeks after completing the programme (Figure 1). Measurements were conducted at the University Medical Center (UMC) Utrecht and the UMC Groningen by trained assessors.

Table 1. Baseline clinical characteristics of the intervention group and waiting control group.

	Baseline	
Characteristics	**IG (n=14)**	**WCG (n=12)**
Age at inclusion, median (range) years	11.6 (8.3 - 17.5)	12.6 (8.7 - 17.6)
Gender, girls%	64	58
Anthropometrics		
Maturity offset, median (range) years	-1.5 (-4.8 - 3.9)	0.7 (-4.3 - 2.9)
Height, median (range) metres	1.47 (1.18 - 1.74)	1.64 (1.30 - 1.82)
Height, median (range) Z-score	-0.7 (-3.2 - 0.8)	-0.6 (-1.7 - 1.5)
Body mass, median (range) kg	40.5 (21.6 - 65.0)	58.4 (27.9 - 79.8)
Body mass, median (range) Z-score	0.6 (-2.5 - 1.4)	0.5 (-1.9 - 2.3)
Body mass index, median (range) kg·meter^2	20.5 (14.8 - 24.9)	20.0 (14.9 - 26.2)
Body mass index, median (range) Z-score	1.1 (-0.6 - 1.9)	0.6 (-1.6 - 2.1)
Fat free mass, median (range) kg [a]	34.2 (16.1 - 61.0)	40.3 (17.4 - 51.7)
Fat free mass, median (range) % of body mass [a]	73 (56 - 77)	75 (62 - 82)
Disease characteristics		
Age at diagnosis, median (range) years	8.4 (3.6 - 12.1)	6.3 (3.1 - 7.4)

Table 1. Continued

Characteristics	Baseline IG (n=14)	Baseline WCG (n=12)
Disease duration at inclusion, median (range) years	3.2 (0.8 - 9.1)	7.0 (2.8 - 11.5)
Usual care		
Accumulative duration corticosteroids, median (range) years	1.3 (0.7 - 6.1)	2.8 (1.0 - 9.3)
Off immunosuppressive medication, n	4	6
Time since last medication, median (range) years	0.5 (0 - 2.5)	3.9 (1.7 - 6.0)
On immunosuppressive medication, n	10	6
Corticosteroids, oral, n; median (range) mg/day/kg	5; 0.2 (0.1 - 0.3)	2; 0.2 (0.2 - 0.3)
Methotrexate, n; median (range) mg/week/kg	9; 0.3 (0.2 - 0.8)	4; 0.2 (0.1 - 0.7)
Intravenous immunoglobulin, n; g/month	0	2; 16 and 36
Azathioprine, n; mg/day	0	1; 50
Mesalazine, n; mg/day	0	1; 1500
Hydroxychloroquine, n; mg/day	1; 200	2; 100 and 200
Tacrolimus, n; mg/day	1; 6	2; 5 and 10
Autologous stem cell transplantation, n; years before inclusion	0	1; 4.3
Participation in outpatient exercise rehabilitation, n	1	5
Participation in gymnastics at school		
Full participation, n	10	5
Partial participation, n	2	4
No participation, n	2	3[b]
Physical transportation		
No problems, n	10	5
Problems, without adjustments, n	1	0
Problems, with adjustments (step/electrical bike), n	3	6
No physical transport, n	0	1
Additional sport participation, (n); frequency median (range) week[1]	(10); 2.3 (1 - 3)	(4); 1.3 (1 - 3)

[a]Fat free mass was not measured in the patients from Groningen (n=8). Data of other parameters were complete. [b]In one patient, gymnastics was not offered at school. IG: intervention group; WCG: waiting control group; g: gram; kg: kilogram; mg: milligram; n: number.

PARTICIPANTS

Patients were eligible if they were diagnosed with JDM by a paediatric rheumatologist/immunologist according to the Bohan and Peter criteria[25,26], and were between the ages of 8 and 18 years at time of enrolment in this study.

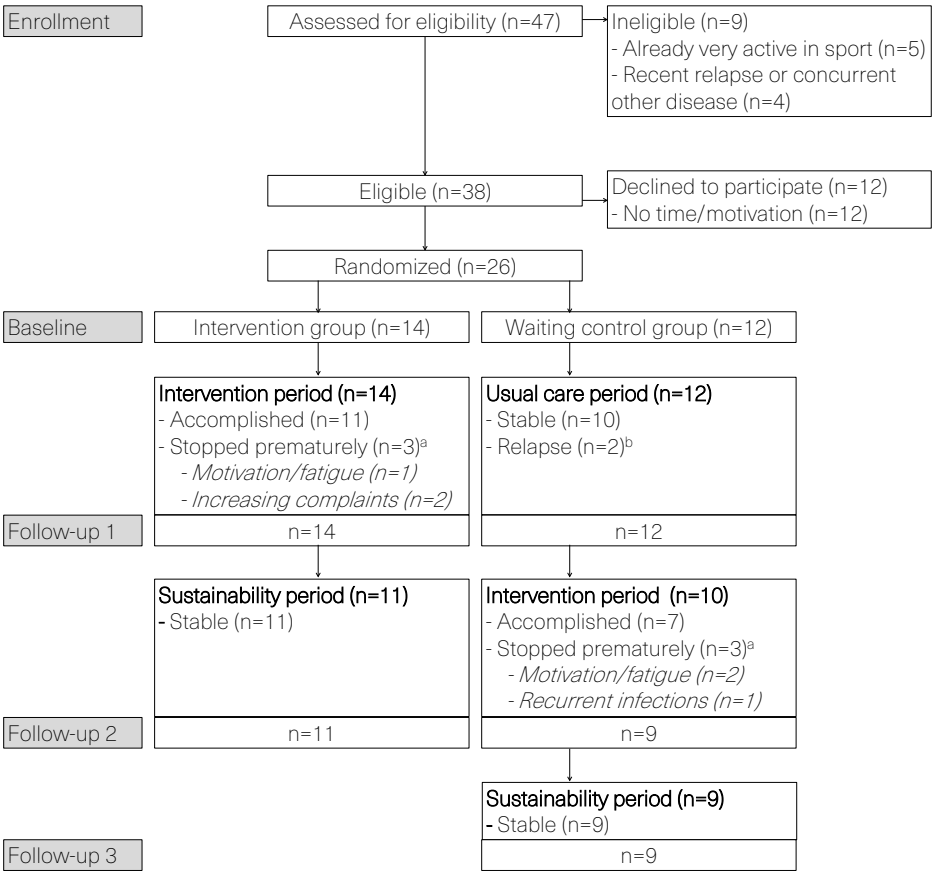

Figure 1. Flowchart for participants according to the CONSORT guidelines.

The time between two consecutive follow-up measurements was 12 weeks. [a]These patients left the study after follow-up 1 (intervention group) or follow-up 2 (waiting control group) and were removed in the per-protocol analyses. [b]These patients left the study after follow-up 1 and were included in the per-protocol analyses.

Patients were excluded: if medical status contra-indicated exercise testing; the patient and/or the parents/caregivers had an insufficient understanding of the Dutch language; a medical event that might interfere with the outcome of testing and/or the trial was present (such as a planned surgery); the rheumatologist advised against participation based on a recent relapse or concurrent existence of other disease; and/or the patient was already very active in sports without any restrictions and without a subjectively diminished exercise capacity. Figure 1 depicts a flowchart of the patients.

Forty-seven patients were assessed for eligibility, which is approximately three-quarter of the total JDM population in The Netherlands between the ages of 8 and 18 years. Of these patients, four had negative advice with respect to participation from their rheumatologist and five were already very active in sports. The other 38 patients were invited to participate; of these, 12 patients declined to participate due to lack of time/motivation. The remaining 26 patients were randomly assigned to the IG or the WCG. The included patients were all diagnosed between 2000 and 2012. Participants were included from 2012 to 2014. Medical histories of the included patients were extracted from the patients' records from each associated medical centre. This muscles in motion study (including statistics) was approved by the Medical Ethics Committee of the UMC Utrecht, The Netherlands. The Medical Ethics Committee was informed of the improved statistical analysis techniques compared to those included in the original design[24]. All parents/caregivers as well as participants >12 years of age provided informed consent and assent before enrolment in the muscles in motion study.

INTERVENTION

The intervention consisted of an individually tailored home-based exercise training programme of interval training on a treadmill and strength exercises (Table 2). Participants received a treadmill at home together with a detailed and individualized description of the exercise programme and were asked to keep track of every completed stage. Heart rate during the training was measured with a heart rate monitor and recorded at three fixed moments during the training. Training was supervised by a researcher every other week. A design paper extensively describes the rationale and details of the intervention[24]. Patients were allowed to perform other physical activities during the intervention period, the usual care period and sustainability period.

Table 2. Description of the intervention.

Factor	Weeks 1-4	Weeks 5-8	Weeks 9-12
Frequency, week^{-1}	3	3	2
Time, minutes	40-60	45-60	50-60
Interval training on treadmill			
Intensity, heart rate as % of peak heart rate	65-70	70-80	80-90
Interval duration, minutes	3	2-2.5	1-2
Number of intervals	4-7	6-10	10-12
Strength training			
Number of different exercises and type	3: squats/sit-ups/push-ups		
Number of sets/exercise	3		
Number of repetitions/set	Week 1: 3 Week 2-12: as much as possible in 20 or 30-s		

Baseline clinical characteristics

Baseline clinical characteristics included age at inclusion, gender, anthropometrics (maturity offset, height, body mass, body mass index and fat-free mass), disease characteristics (age at diagnosis and disease duration at inclusion) and usual care (medication usage and participation in physical activities). Maturity offset was determined with gender-specific equations including age, height, body mass, and sitting height[27]. Fat-free mass was measured with BODYSTAT QuadScan 4000 (EuroMedix, Leuven, Belgium). The disease duration at inclusion was defined as the time from diagnosis to inclusion.

OUTCOME MEASURES

Feasibility

Feasibility was assessed by examining the tolerability of and adherence to the exercise intervention.

Safety

Safety was assessed by evaluating signs of disease relapse during the intervention period, reflected by intensification of immune suppression or hospitalization.

Efficacy

Primary efficacy outcome measures

Aerobic fitness was assessed with a treadmill-based (RAM, Accuramed BVBA, Lummen, Belgium; or GE Healthcare) incremental maximal exercise test according the Dubowy protocol set out by the German Society for Pediatric Cardiology[28], together with gas analysis (ZAN 600, Accuramed BVBA, Lummen, Belgium; or Carefusion, Masterscreen CPX, GE Healthcare, Cardiosoft). Briefly, the test was started at a speed of 2 kilometers/hour with a 0% grade; the speed increased by 0.5 kilometers/hour and the grade by 3% every 90 seconds up to a maximum of 21%. The test was terminated upon voluntary exhaustion despite strong verbal encouragement.

The parameters related to aerobic fitness that were assessed were: endurance time [minutes]: time from the start to the end of the protocol; VO_{2peak} (l/min): the average volume of oxygen uptake during the last 30-seconds period of the test; $VO_{2peak/kg}$ (ml/kg/min): VO_{2peak} divided by body mass; and $VO_{2VAT/kg}$ (ml/kg/min): the VO_2 eliciting the ventilatory anaerobic threshold divided by body mass. The ventilator anaerobic threshold was defined by an increase in both the ventilatory equivalent of oxygen (=VE/VO_2) and end-tidal pressure of oxygen with no concurrent increase in the ventilatory equivalent of carbon dioxide (=VE/VCO_2). These values were also expressed as percentage of gender-and age-based predicted values[28]. Other primary efficacy outcome measures were isometric muscle strength (hand-held dynamometer)[29] and perception of fatigue (Dutch translated version of the PedsQL Multidimensional Fatigue Scale[30–32] as described in the design paper[24].

Secondary efficacy outcome measures

Secondary outcome measures were previously described in a design paper[24] and included: muscle pain [10-centimeter visual analogue scale (VAS)]; muscle function [Subscale 8 (Strength) of the Bruininks-Osteretsky test of motor proficiency, second edition (BOT-2)[33] and childhood myositis assessment scale[34]; functional capacity (6-minute walk test[35]; distance was analysed and expressed as absolute value and as percentage of predicted distance based on gender, age, and height)[36]; physical activity enjoyment (Physical Activity Enjoyment Scale)[37]; quality of life (Dutch translated PedsQL generic core scale)[31,38,39]; functional ability [childhood health assessment questionnaire (CHAQ) 30+8[40–42]; questions completed by parents, with scores ranging from 0 to 3 (with lower score representing less disability)]; VAS pain

and VAS global disease activity (completed by patients); habitual levels of physical activity (accelerometry, monitored by Actical for seven days[43] and processed using cutoff points of Puyau et al.[44]; and activity journal (for three days)[45].

Statistical analysis

Statistical analysis was performed using SPSS Statistics for Windows (Version 21.0, IBM Corporation, Armonk, NY, USA). Efficacy outcome measures were analysed with a mixed linear model involving the variables Follow-up (follow-up 1, 2 and 3), Group (IG and WCG), Follow-up x Group interaction and Baseline value of the outcome measure that was analysed. P values < 0.05 were considered statistically significant.

The primary end point was the difference between the IG and WCG at follow-up 1 in estimated marginal means of the primary efficacy outcome measures (sample size calculation was based on $VO_{2peak/kg}$)[24] using an intention-to-treat approach (i.e. all participants were included in the groups to which they were randomly assigned and the researchers made efforts to obtain outcome data for all participants, even if the intervention was not completed)[46]. Power analyses indicated a required sample of 11 patients in each group, excluding missings and drop-outs[24].

As a secondary endpoint, per-protocol (PP) analyses were performed. Patients that stopped prematurely with the intervention in the IG (n=3) or WCG (n=3) were excluded from analysis (Figure 1). Results of the PP analyses were only reported if statistically significant. As another secondary end point, the effect sustainability of the intervention was assessed by analysing the within-subjects effect of Follow-up (follow-up 1 and 2 in the IG, together with follow-up 2 and 3 in the WCG). All statistical tests were also performed for the secondary efficacy outcome measures. Feasibility and safety measures were only described and not statistically analysed.

RESULTS

The baseline clinical characteristics of the patients in each group are depicted in Table 1. The median (range) age at inclusion was 12.3 (8.3-17.6) years and 62% were girls. The median (range) age at diagnosis was 7.1 (3.1 -12.1) years. The median (range) disease duration at inclusion was 4.4 (0.8-11.4) years.

STUDY OUTCOMES

Feasibility

Two patients were unable to start the intervention after the 12 weeks of usual care as a consequence of a relapse that occurred during the waiting control period. Of the remaining 24 patients, six patients (25%) started the intervention and stopped prematurely as a consequence of: lack of motivation/fatigue (n=3; after 3, 7, and 11 sessions); recurrent infections (n=1; after 9 sessions); and increasing complaints at the heel or knee (n=2; both after 16 sessions). The other 18 patients (75%) completed the intervention and performed a median of 30 (interquartile range: 27-31) of the 32 sessions. Reasons for missing some of the sessions in this latter group included other sport activities, holiday, fatigue, illness, and transient physical complaints.

Safety

No hospitalization occurred in the patients that participated in the intervention. In all patients that started the intervention, immune suppressive therapy remained stable or decreased during the study period.

Efficacy

Table 3 shows the baseline values of the outcome measures for both groups. Table 4 depicts the estimated marginal means for follow-up 1 for both groups, and their differences are described below.

Table 3. Baseline values of the efficacy outcome measures in the intervention group and waiting control group.

Outcomes	Baseline, mean (SD)	
	IG (n=14)	**WCG** (n=12)
Aerobic fitness (maximal exercise on treadmill)		
$VO_{2peak/kg}$, ml/kg/min	38.6 (9.7)	33.9 (6.9)
$VO_{2peak/kg}$, % of predicted	91 (21)	79 (16)
VO_{2peak}, l/min	1.73 (0.62)	1.71 (0.62)
VO_{2peak}, % of predicted	87 (14)	78 (19)
Endurance time, minutes	11.9 (1.8)	10.1 (1.9)
Endurance time, % of predicted	87 (14)	78 (19)
$VO_{2VAT/kg}$, ml/kg/min	22.3 (4.9)	20.0 (4.8)
$VO_{2VAT/kg}$, % of predicted	75 (14)	67 (17)
Maximal isometric muscle strength (Hand-held dynamometry –break method)[a]		
Left knee extensors, N	250 (156)	250 (104)
Right knee extensors, N	255 (137)	261 (112)
Left hip flexors, N	218 (110)	220 (82)
Right hip flexors, N	225 (97)	223 (56)
Perception of fatigue (PedsQL multidimensional fatigue scale – patient form; range 0-100)		
Total score	76 (9)	70 (14)
Subscale general fatigue	77 (13)	71 (13)
Subscale sleep/rest fatigue	72 (8)	63 (16)
Subscale cognitive fatigue	77 (11)	76 (22)
Muscle pain (10-cm visual analogue scale muscle pain)		
Score, mm	7 (14)	9 (12)
Muscle function (BOT-2 subscale 8 –strength)		
Distance of standing long jump, cm	107 (30)	112 (22)
Number of push-ups in 30 s	16 (10)	13 (9)
Number of sit-ups in 30 s	18 (5)	16 (8)
Time wall sit (max: 60), s	43 (17)	41 (19)
Time V-up (max: 60), s	52 (11)	39 (22)
Muscle function (childhood myositis assessment scale; max: 52)		
Total score	49.3 (2.7)	49.6 (2.8)
Functional capacity (6-Minute walk test)[b]		
Distance, metres	559 (49)	545 (62)
Distance, % of predicted	85 (9)	81 (8)
Physical activity enjoyment (physical activity enjoyment scale)[b]		

Table 3. Continued

Outcomes	Baseline, mean (SD)	
	IG (n=14)	**WCG** (n=12)
Total score	78 (13)	72 (10)
Quality of life (PedsQL generic core scale–patient form; range 0-100)[c]		
Total score	78 (6)	71 (14)
Subscale physical functioning	80 (10)	68 (22)
Subscale emotional functioning	76 (9)	71 (15)
Subscale social functioning	87 (7)	77 (18)
Subscale school functioning	67 (16)	71 (15)
Functional ability (childhood health assessment questionnaire 30+8)		
Disability score (0-3) (parents)	0.22 (0.27)	0.37 (0.30)
10-cm VAS pain, mm (patients)	9 (12)	11 (15)
10-cm VAS global disease severity, mm (patients)	13 (12)	6 (9)
Physical activity (Actical–7 days)[d]		
Inactivity, % of the day	82 (3)	83 (4)
Light activity, % of the day	15 (1)	14 (3)
Moderate activity, % of the day	2.9 (1.8)	2.6 (1.6)
Vigorous activity, % of the day	0.1 (0.2)	0.1 (0.3)
Physical activity (Activity journal–3 days)[e]		
Inactivity, % of the day	85 (5)	86 (9)
Light activity, % of the day	8 (4)	10 (9)
Moderate activity, % of the day	6.9 (4.2)	3.9 (3.6)
Vigorous activity, % of the day	0.9 (1.2)	1.0 (1.3)

[a]One patient missing for knee extensors because measurements were not valid. [b]One patient did not have enough energy to perform all tests during a test day. Hence, this patient did not perform the 6-minute walk test and physical activity enjoyment scale. [c]One patient did not fill in the PedsQL generic core scale at baseline. [d]Three patients missing (Actical not worn/data not available). [e]Five patients missing [not (adequately) filled in]. BOT: Bruininks-Osteretsky test of motor proficiency, second edition; CI: confidence interval; cm: centimeters; kg: kilogram; l: liters; min: minutes; ml: millilitres; mm: millimeters; n: number; N: Newton; s: seconds; SD: standard deviation; IG: intervention group; WCG: waiting control group.

Table 4. Baseline values and estimated marginal means for follow-up 1 from the mixed linear model in the intervention group and waiting control group for the intention to-treat-analyses.

Outcomes	Baseline Mean (SD) **Total** (n=26)	Follow-up 1 Estimated marginal means (95%CI) **IG** (n=14)	**WCG** (n=12)	Follow-up 1 p-values IG vs WCG
Aerobic fitness (maximal exercise test on treadmill)[a]				
$VO_{2peak/kg}$, ml/kg/min	36.5 (9.0)	38.6 (35.9 ; 41.4)	35.7 (32.5 ; 38.8)	0.2
$VO_{2peak/kg}$, % of predicted	85 (20)	90 (83 ; 96)	83 (76 ; 91)	0.2
VO_{2peak}, l/min	1.72 (0.59)	1.92 (1.76 ; 2.07)	1.77 (1.60 ; 1.95)	0.2
VO_{2peak}, % of predicted	82 (16)	88 (82 ; 94)	83 (76 ; 90)	0.3
Endurance time, min	11.2 (2.0)	11.8 (11.0 ; 12.7)	11.2 (10.2 ; 12.1)	0.3
Endurance time, % of predicted	82 (16)	86 (80 ; 92)	81 (75 ; 88)	0.3[g]
$VO_{2VAT/kg}$, ml/kg/min	21.3 (5.0)	23.2 (21.1 ; 25.3)	22.1 (19.9 ; 24.3)	0.5
$VO_{2VAT/kg}$, % of predicted	71 (16)	77 (70 ; 84)	73 (66 ; 80)	0.4
Isometric muscle strength (Hand-held dynamometry –break method)[b]				
Left knee extensors, N	250 (133)	263 (240 ; 287)	246 (219 ; 273)	0.3
Right knee extensors, N	258 (124)	286 (259 ; 313)	256 (225 ; 286)	0.1
Left hip flexors, N	219 (96)	227 (196 ; 258)	223 (190 ; 257)	0.9
Right hip flexors, N	224 (79)	221 (187 ; 254)	228 (191 ; 264)	0.8
Perception of fatigue (PedsQL multidimensional fatigue scale–patient form; range 0-100)				
Total score	73 (12)	75 (71 ; 79)	74 (69 ; 78)	0.8
Subscale general fatigue	74 (13)	78 (72 ; 84)	75 (69 ; 82)	0.5
Subscale sleep/rest fatigue	68 (13)	70 (65 ; 75)	71 (66 ; 76)	0.8
Subscale cognitive fatigue	77 (22)	77 (69 ; 84)	75 (67 ; 83)	0.8
Muscle pain (10-cm visual analogue scale muscle pain)				
Score, mm	8 (13)	4 (-3 ; 11)	13 (5 ; 20)	0.1
Muscle function (BOT-2 subscale 8 –strength)[c]				
Distance standing long jump, cm	109 (27)	120 (113 ; 127)	107 (99 ; 114)	0.017[g]
Amount of push-ups in 30 s	14 (9)	22 (19 ; 25)	14 (10 ; 18)	0.004[g]

Table 4. Continued

Outcomes	Baseline Mean (SD) Total (n=26)	Follow-up 1 Estimated marginal means (95%CI) IG (n=14)	WCG (n=12)	Follow-up 1 p-values IG vs WCG
Amount of sit-ups in 30 s	17 (7)	23 (20 ; 25)	18 (15 ; 21)	0.030[g]
Time wall sit (max: 60), s	41 (18)	44 (38 ; 50)	45 (38 ; 52)	0.8
Time V-up (max: 60), s	47 (17)	50 (43 ; 57)	47 (39 ; 54)	0.5
Muscle function (childhood myositis assessment scale; max: 52)[c]				
Total score	49.4 (2.8)	49.8 (49.1 ; 50.5)	49.9 (49.1 ; 50.7)	0.9
Functional capacity (6-minute walk test)[d]				
Distance, meters	553 (54)	561 (526 ; 596)	554 (514 ; 594)	0.8
Distance, % of predicted	84 (9)	85 (79 ; 90)	83 (77 ; 89)	0.7
Physical activity enjoyment (physical activity enjoyment scale)[d]				
Total score	75 (12)	70 (63 ; 76)	72 (65 ; 79)	0.6
Quality of life (PedsQL generic core scale–patient form; range 0-100)[e]				
Total score	75 (11)	75 (71 ; 79)	76 (71 ; 81)	0.8
Subscale physical functioning	75 (17)	79 (74 ; 83)	73 (67 ; 78)	0.1
Subscale emotional functioning	74 (12)	74 (67 ; 81)	79 (71 ; 87)	0.4
Subscale social functioning	83 (14)	77 (71 ; 83)	82 (76 ; 89)	0.2
Subscale school functioning	69 (15)	72 (65 : 79)	71 (63 ; 79)	0.8
Functional ability (childhood health assessment questionnaire 30+8)				
Disability score (0-3) (parents)	0.29 (0.29)	0.18 (0.10 ; 0.25)	0.30 (0.22 ; 0.39)	0.028[g]
10-cm VAS pain, mm (patients)	10 (13)	16 (4 ; 28)	15 (3 ; 27)	0.9
10-cm VAS global disease severity, mm patients)	10 (11)	10 (2 ; 18)	9 (0 ; 17)	0.8
Physical activity (Actical–7 days)[f]				
Inactivity, % of the day	83 (4)	80 (76 ; 85)	83 (81 ; 85)	0.3
Light activity, % of the day	14 (3)	15 (12 ; 19)	13 (11 ; 15)	0.3

Table 4. Continued

Outcomes	Baseline Mean (SD) **Total** (n=26)	Follow-up 1 Estimated marginal means (95%CI) **IG** (n=14)	**WCG** (n=12)	Follow-up 1 p-values IG vs WCG
Moderate activity, % of the day	2.8 (1.7)	4.6 (2.5 ; 6.8)	3.8 (2.6 ; 4.9)	0.5
Vigorous activity, % of the day	0.1 (0.3)	0.1 (-0.1 ; 0.3)	0.1 (0.0 ; 0.2)	0.9
Physical activity (Activity journal–3 days)[f]				
Inactivity, % of the day	85 (7)	85 (81 ; 89)	84 (80 ; 89)	0.9
Light activity, % of the day	9 (7)	8 (5 ; 11)	8 (5 ; 11)	0.7
Moderate activity, % of the day	5.1 (3.8)	5.6 (2.8 ; 8.4)	6.3 (3.5 ; 9.2)	0.7
Vigorous activity, % of the day	1.0 (1.2)	1.3 (0.4 ; 2.2)	1.0 (0.1 ; 1.9)	0.6

[a]One patient was not able to maximally perform on the maximal exercise test at follow-up 1 as a consequence of knee complaints; one patient was not able to reach maximal values at the maximal exercise test at follow-up 1, 2, and 3; the ventilatory anaerobic threshold was determined in this patient. [b]One patient is missing for knee extensors because measurements were not valid. [c]One patient was not able to perform the childhood myositis assessment scale and BOT-2 for the follow-up 1 measurement as a consequence of a relapse during the control period. [d]One patient did not have enough energy to perform all tests during a test day. Hence, this patient did not perform the 6-minute walk test and physical activity enjoyment scale. [e]One patient did not fill in the PedsQL generic core scale at baseline. [f]Six patients missing (Actical not worn/journal not (adequately) filled in/data not available). [g]p <0.05 in per protocol analysis. BOT: Bruininks-Osteretsky test of motor proficiency, second edition; CI: confidence interval; cm: centimeters; kg: kilogram; l: liters; min: minutes; ml: millilitres; mm: millimeters; n: number; N: Newton; s: seconds; SD: standard deviation; IG: intervention group; WCG: waiting control group.

Primary outcome measures

Aerobic fitness. $VO_{2peak/kg}$ was higher in the IG compared with the WCG; however, this difference was not statistically significant either when expressed in ml/kg/min [difference between the two groups in estimated marginal means at follow-up 1 [Δ (95%CI); 3.0 ml/kg/min (-1.3, 7.3)] or when expressed as percentage of the predicted value [Δ (95% CI); 6% (-4, 16); Figure 2B].

Endurance time on the maximal exercise test showed a trend to be higher in the IG compared with in the WCG when either expressed in minutes [Δ (95%CI): 0.7 min (-0.7, 2.0)] or when expressed as percentage of the predicted value [Δ (95%CI): 5% (-4, 14)]. This latter analysis reached statistical significance in the PP analysis [Δ (95%CI): 12% (1, 23)], and the effect was sustained during the 12 weeks after the intervention (Figure 2A). The absolute VO_{2peak} and the ventilatory anaerobic threshold during the maximal exercise test did not show significant differences in the IG compared to the WCG (Table 4).

Isometric muscle strength. The IG and WCG were at follow-up 1 not statistically different for the left knee extensors [Δ (95%CI): 17 N (-18, 53)], the right knee extensors [Δ (95%CI): 31 N (-10, 72)], the left hip flexors [Δ (95%CI): 3 N (-42, 49)], and the right hip flexors [Δ (95%CI): -7 N (-56, 42)] (Table 4). No significant differences were found in the PP analyses either.

Perception of fatigue. The IG and WCG were at follow-up 1 not statistically different for the total score on the PedsQL multidimensional fatigue scale [Δ (95%CI): 1 (-5, 7)] and the subscales (Table 4). No significant differences were found in the PP analyses either.

Secondary outcome measures

Muscle function as assessed with BOT-2 subscale strength was greater in the IG compared with the WCG for three individual items: distance from standing long jump [Δ (95%CI): 13 cm (2, 23)], number of push-ups in 30 seconds (one patient performed full push-ups; all others knee push-ups) [Δ (95%CI): 8 (3, 13)], and number of sit-ups in 30 seconds [Δ (95%CI): 4 (0.4, 8)]. These differences in favour of the IG became even more significant in the PP analysis. The effects of the intervention on these scores were sustained during the 12 weeks after the intervention (Figures 2C-E).

Functional ability as assessed with the disability score from the CHAQ 30+8 was significantly better in the IG compared with the WCG [Δ (95%CI): -0.13 (-0.24, -0.01)], this was also reflected in the PP analysis. The effect of the intervention on the disability score was sustained during the 12 weeks after the intervention (Figure 2F). VAS pain and VAS global disease severity did not differ significantly between the groups.

The following secondary outcomes were not significantly different in the IG compared with the WCG: VAS muscle pain, muscle function as assessed with the childhood myositis assessment scale, distance on 6-minute walk test (absolute and as percentage of predicted), physical activity enjoyment, quality of life (total and subscale scores), and physical activity (Actical and activity journal).

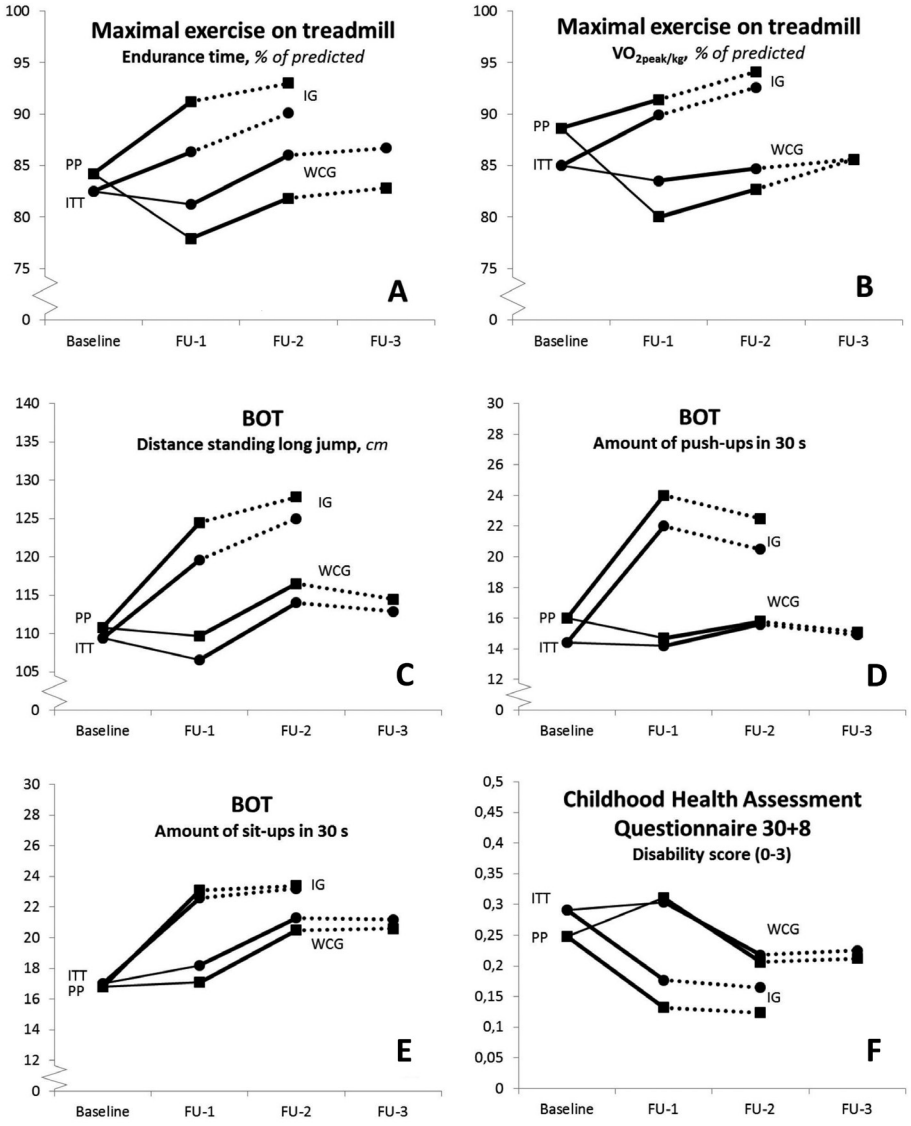

Figure 2. Mean baseline values of the total group and estimated marginal means at follow-up 1, follow-up 2 and follow-up 3 of the IG and WCG.

Figure 2. Continued

The circles represent the ITT and the squares represent the PP analyses. The thin continuous lines represent the usual care period in the WCG, the thick continuous lines represent the intervention period, and the dotted lines represent the sustainability period. **(A)** Endurance time as percentage of predicted at the maximal exercise test. **(B)** $VO2_{peak/kg}$ as percentage of predicted at the maximal exercise test. **(C)** Distance reached with standing long jump. **(D)** Number of push-ups in 30 seconds. **(E)** Number of sit-ups in 30 seconds. **(F)** Disability score at the childhood health assessment questionnaire 30+8. Estimated marginal means of both groups in the ITT at follow-up 1 are mentioned in Table 4. ITT: intention-to-treat analyses; FU-1: follow up 1; FU-2: follow-up 2; FU-3: follow-up 3. IG: intervention group; BOT: Bruininks-Osteretsky Test of Motor Proficiency, Second Edition; WCG: waiting control group; PP: per-protocol.

DISCUSSION

This is the first multicentre randomized controlled trial that studied the feasibility, safety, and efficacy of an individualized exercise programme in children and adolescents with JDM. The programme was feasible, showing high adherence and toleration. Exercise training, as conducted in this study, was safe since no hospitalizations or intensifications of immunosuppression occurred during the intervention period. This is in line with earlier studies in both adults and children with JDM and other idiopathic inflammatory myopathies[16–21]. The efficacy of exercise training was demonstrated because aerobic fitness, muscle function and functional ability were (significantly) higher after the intervention compared with after usual care. The findings of this study indicate the value of a training programme in the clinical management of patients with JDM.

The feasibility of the programme differed for individual patients, which is not surprising given the heterogeneity in phenotype of the JDM population[47]. Some patients became energized by the programme and adhered to all sessions, whereas others missed some sessions or stopped prematurely as a consequence of motivation and/or fatigue issues, worsening of pre-existing physical complaints or transient physical complaints. The home-based nature with every other week supervision may more likely facilitate exercise in the long-term and probably contributed to a high adherence in some patients; however, it may have made the programme less attractive and lowered the adherence in others.

There are several possible reasons why we did not find (large) statistically significant effects of the intervention in some outcome measures. First, our patients had

on average high baseline values and active lifestyles. Compared to the two previously published uncontrolled trials examining a 12-week aerobic (and strength) training programme in JDM[20,21], our patients had higher initial $VO_{2peak/kg}$ levels and more active lifestyles; our patients had an initial $VO_{2peak/kg}$ of 36.5 ml/kg/min and showed high participation at gymnastics at school and in sport, whereas the patients in the other two studies had an initial $VO_{2peak/kg}$ of 31 and 23 ml/kg/min, respectively, and were inactive, did not engage in any form of exercise for at least 6 months prior to and during the study, or were exercising at a low intensity. Consequently, less room for improvement would be expected in our study.

Also, the high activity level of many of the participants in the control group decreased the opportunity for the intervention to be beneficial compared with usual care. Higher efficacy of our intervention would be expected when participants in the control group were less physically active than they were in our study. However, due to ethical reasons, it would be impossible to prohibit participants in the control group being physically active.

Futhermore, in our study, there was a high variation between participants at the baseline as well as in follow-up outcomes. The difference in $VO_{2peak/kg}$ in the IG compared with WCG [Δ 3.0 (intention-to-treat) and 5.0 ml/kg/min (PP)] was comparable with the improvements seen in $VO_{2peak/kg}$ the other two studies[20,21] (4 and 6 ml/kg/min, respectively). However, the high variation in $VO_{2peak/kg}$ at baseline and in follow-up in our participants (compared with the other two studies) could partly explain why our findings were not statistically significant whereas their findings were statistically significant. In this context, a larger sample size would have been beneficial- although difficult to obtain in this rare disease.

Moreover, despite of the randomization, higher average baseline values were found in the IG compared with the WCG for several outcome measures (e.g. aerobic fitness, perception of fatigue and quality of life, and functional ability). This reduces the possibility for improvement in the IG as compared with the control group, thus decreasing the opportunity to measure significant benefits from our intervention. Presumably related to that, the IG and WCG seem to be different for several disease and usual care characteristics at baseline. On average, patients in the IG had shorter disease duration, showed more participation in gymnastics at school, had fewer limitations with physical transportation, and participated more frequently in additional sports

compared with patients in the WCG. Due to the small sample size of the study, it was not possible to analyse subgroup of patients with more comparable disease and usual care characteristics. Future studies should stratify for factors like disease duration and baseline performance.

Significant improvements were observed in muscle function in the IG compared with the WCG as assessed by the items of BOT-2 subscale strength. However, we found no improvements in muscle function as assessed by the childhood myositis assessment scale. This latter is partly or totally due to the ceiling effect of this latter tool in combination with the high baseline values in our patients. We also found no improvement in muscle strength measured by hand-held dynamometry; this may be partly explained by the low reliability of this instrument[48,49]. In contrast, Omori et al.[20] did observe an increase in muscle strength; however, in their study the muscle strength measurement was matched with the training programme, which was not the case in our study.

Presumably related to the improved muscle function, subjective measurements indicated improvements in performance on physical activities of daily living. First, functional ability assessed with the CHAQ 30+8 (completed by parents) significantly improved after the intervention. Second, the subscale physical functioning of the PedsQL generic core scale showed a trend towards improvement in the IG compared with the WCG. This score was not statistically significant, possibly because the questionnaire is not sensitive enough for this specific topic. However, the anecdotal reports of many participants and their parents indicated improved subjective physical functioning. More sensitive outcome measures for examining changes in physical function are recommended for future studies. A qualitative study to gain insight into the patients' experiences might be of interest. Although physical activity measurements did not quantify an increased exercise level after the intervention was finished, some patients reported that they maintained an increased exercise level. This latter illustrated our findings that the significant improvements were sustained during the 12 weeks after the intervention.

Generalizability

In this study, approximately three-quarter of the patients with JDM in The Netherlands were assessed for eligibility. Furthermore, the inclusion criteria for this study were very broad, which resulted in a high variation in disease characteristics, usual care, and scores on baseline measurements for the patients. Therefore, the results of

this study are applicable to a large group of patients with JDM. The downside of this broad range is that patients with a (near) normal physical fitness level were included. Most of our patients already commenced exercise directly after diagnosis and start of pharmacological treatment as part of their usual care. This high starting level could have reduced the efficacy of the intervention as mentioned above. In patients with high initial physical fitness level, a higher training intensity might be more suitable. As this study involved only patients with clinically stable disease (with and without medication), no extrapolation of the present findings can be made to patients with active inflammation early in disease course.

Future directions

The heterogeneity observed in the feasibility and efficacy highlight the importance of an individualized approach for prescribing an exercise training programme in patients with JDM. Future research should explore how the programme should be adjusted for each individual patient to further optimize the feasibility and efficacy [e.g. by adjusting type (walking vs cycling) and intensity of training].

Furthermore, future research should examine the feasibility, safety, and efficacy of exercise training in the active phase of JDM. Adult studies in idiopathic inflammatory myopathies indicate that exercise can be safely used in addition to immunosuppressive medication in active disease and also improved muscle performance[50].

Only a small number of studies in patients with idiopathic inflammatory myopathies have examined outcomes that assess the physiological basis of improvements observed during exercise training. These studies, all in adults, indicate an improved aerobic metabolism[50–52]. Future research should further explore the within-muscle adaptations after an exercise training programme; this should be undertaken for juvenile patients and patients with active disease, because this adds important information about underlying mechanisms for treatment effects.

In conclusion, this randomized controlled trial showed that an individually tailored 12-week home-based exercise training programme in children and adolescents with JDM was feasible in most patients, safe in all patients and effective for some aspects of aerobic fitness, muscle function, and functional ability. The effect sustained during the 12 weeks follow-up after the intervention. Exercise training is therefore of value in the clinical management of patients with JDM.

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CHAPTER 7

Internet program for physical activity and exercise capacity in children with juvenile idiopathic arthritis: a multicenter randomized controlled trial

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ABSTRACT

Objective

To determine the effects of Rheumates@Work, an internet-based program supplemented with 4 group sessions, aimed at improving physical activity, exercise capacity, health-related quality of life (HRQOL), and participation in children with juvenile idiopathic arthritis.

Methods

Patients were recruited from 3 pediatric rheumatology centers in The Netherlands for an observer-blinded, randomized controlled multicenter trial. Physical activity level, time spent in rest, light, and moderate to vigorous physical activity (MVPA) were recorded in a diary and with an accelerometer, before intervention, after intervention, and at follow-up after 3 and 12 months (intervention group only). Exercise capacity was assessed using the Bruce treadmill protocol, HRQOL was assessed with the pediatric quality of life inventory generic core scale, and participation in school and in physical education classes were assessed by questionnaire.

Results

The intervention group consisted of 28 children, and there were 21 children in the control group. MVPA, exercise capacity, and participating in school and physical education classes improved significantly in the intervention group. HRQOL improved in the control group. No significant differences were found between groups. The effect of Rheumates@Work on physical activity and exercise capacity lasted during the 12 months of follow-up. Improvements in physical activity were significantly better for the cohort starting in winter compared to the summer cohort.

Conclusion

Rheumates@Work had a positive, albeit small, effect on physical activity, exercise capacity, and participation in school and physical education class in the intervention group. Improvements lasted for 12 months. Participants who started in winter showed most improvement. Rheumates@Work had no effect on HRQOL.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a chronic, relapsing autoimmune disease that exerts a negative impact on a child's daily life, irrespective of disease status[1,2]. Although the primary goal of treatment is to achieve remission, negative psychosocial and physical consequences of JIA are cause for considerable concern. The physical consequences include an increased risk of atherosclerosis, obesity, and diminished bone mineral density[3–6]. Furthermore, children with JIA experience chronic fatigue, pain, functional impairments[1,7], and decreased health-related quality of life (HRQOL)[8]. Additionally, low physical activity levels and impaired exercise capacity are common[9,10].

Physical activity (PA) is essential for physical health and mental well-being for children in general[11,12]. For children with JIA, PA has the same health benefits as it has for healthy children, i.e., reducing blood pressure and weight and increasing bone mineral density[12–14]. Moreover, PA improves general health and HRQOL in these children and reduces disease-specific symptoms, such as pain and disability[14–16]. Exercise does not exacerbate arthritis[17]. Despite the potentially positive effects of PA, children with JIA are less active in comparison to healthy controls, as well as less involved in physical and social leisure activities, and they have a high rate of absenteeism[18]. School absenteeism, next to PA, is an indicator of disease burden. Considering the impact of JIA on daily life, the long-term health risks of the disease, the sedentary habits that come with it, and the potentially favorable effect of PA, promoting an active lifestyle in children with JIA is important. Nevertheless, interventions aimed at promoting PA in children with JIA are limited.

Physical activity varies according to season and, in general, it is higher during favorable weather conditions. We therefore analyzed the effect season had on our results[19,20]. Physical activity is the type of behaviour that is determined by a combination of physical and psychosocial factors[21,22]. Children and parents are not always aware of the benefits of PA and fear the potential damaging effect of PA. A cognitive behavioural program could change behaviour, and thus it could help overcome barriers and teach children about the benefits of PA[21]. In adult patients with rheumatoid arthritis, internet interventions to promote PA have shown high scores on satisfaction, and they are effective and reach many patients[23,24]. Combining internet intervention with individually tailored supervision, exercise equipment, and group sessions is more effective in adults with rheumatoid arthritis than an

intervention without these ingredients[25]. Keeping in mind these findings, we developed a 14-week, cognitive behavioural program, Rheumates@Work. This program is a combination of internet-based personal instruction, supplemented with 4 group sessions, to improve PA in children with JIA[26]. The results of the pilot study showed that PA and exercise capacity increased in children with low PA levels (PALs)[27]. To confirm these results, we analyzed the effects of Rheumates@Work in a multicenter, randomized controlled trial. The objective of this study was to analyze the effects of Rheumates@Work on PA, exercise capacity, and HRQOL directly after the intervention, and after 3 and 12 months. Additionally, we analyzed the effects on the participation in physical education classes and on school absenteeism.

PATIENTS AND METHODS

Design and participants

The design is a multicenter, observer-blinded, randomized controlled trial. The study was conducted in The Netherlands. Based on the eligibility criteria, we included children who had been diagnosed with JIA according to the criteria established by the International League of Associations for Rheumatology[28], were ages 8-13 years, had good comprehension of the Dutch language, had a computer with access to the internet, and had an exercise capacity below or equal to the 5th percentile for age and sex or had a sedentary lifestyle, defined as <60 minutes of PA of moderate-to-vigorous intensity for at least 4 days in a 7-day period as recorded in an activity diary[27]. We excluded children who had a physical disability caused by a condition other than JIA and that limited motor and/or exercise performance, received cognitive behavioural therapy, and had a high disease activity as defined by a physician's score of > 2 cm on a visual analog scale (VAS; range 0-10).

All eligible children were recruited from the pediatric rheumatology departments of Beatrix Children's Hospital, University Medical Center Groningen (by WA), and Wilhelmina Children's Hospital, University Medical Center Utrecht (by NMW), and from the Reade Center for Rehabilitation and Rheumatology in Amsterdam (by JC and MAJvR) and received a written invitation to participate in the study. Testing and group sessions took place at the department where the children had been recruited. At each center, approval was obtained from the local medical ethics committee.

Intervention

Rheumates@Work is a 14-week, cognitive behavioural program. It consists of a combination of internet-based and individual instruction, supplemented with 4 group sessions, and it aims to improve PA in children with JIA. A detailed description of Rheumates@Work is provided elsewhere[26]. Rheumates@Work contains the following elements: health education related to JIA and PA, information on barriers that prevent someone from being active, explanation of the benefits of PA, and self-efficacy towards becoming more physically active. The children's families as well as schools were involved to stimulate the children to become more active. The program supports children to remain active even during a relapse of JIA. The children had to set themselves an attainable goal based on their current PA, as recorded in an activity diary, and by their exercise capacity. All elements were based on Pender's health promotion model[21] and were provided through cartoons, puzzles, and brain teasers, supplemented with 4 group sessions[26]. At the time of finishing the intervention(T1), the results of the PA and exercise capacity were discussed with the participants in an effort-affirming way. Children randomized in the control group received standard care and were not restricted in any activities.

Outcomes

All participants, i.e., both the intervention and control group, were tested at baseline (T0), and after 14 weeks, when the intervention was completed by the intervention group (T1). Testing was performed blinded. To evaluate long-term effects, the intervention group was followed up and retested after 3 months (T2) and 12 months (T3). For the control group, the study ended at T1. The intervention started either in September (the summer group) or in January (the winter group). Patient characteristics, collected at T0, included age, sex, weight, and height. Body mass index was calculated using weight (kg)/height^2(meter). Type of JIA, disease duration, and a list of current medications were collected from the children's medical charts.

Primary outcome

PA was expressed as PA level (PAL) and as time spent in 3 different categories of PA: rest, light PA, and moderate to vigorous PA (MVPA). PA was assessed with a 7-day activity diary[29] and an accelerometer (Actical, Phillips Respironics), during 7 days. Both measurements were used because the diary provides a subjective record of PA, and it was part of the intervention[26,30]. The accelerometer served as an objective measurement of PA[31]. More details regarding the measurements are

described in Supplementary Appendix A (Appendix A; Description of the activity diary, accelerometer, and exercise capacity). Arbitrarily, we defined clinically relevant improvements and differences between groups as a change in PAL of 0.1, and for MVPA and rest as an improvement of 20 minutes.

Secondary outcomes

Exercise capacity, expressed as maximum endurance time, was measured with the Bruce Treadmill protocol[32] and presented as a Z-score of the Dutch population norm, to evaluate the long-term effects of Rheumates@Work[33]. Z-scores were calculated as patients' exercise capacity - population mean/population SD. An increase of endurance time of 10% or more was considered clinically relevant[34]. More details regarding the exercise capacity are described in Supplementary Appendix A (Appendix A; Description of the activity diary, accelerometer, and exercise capacity).

Health-related quality of life was measured using the pediatric quality of life inventory (PedsQL), version 4.0, a modular instrument for measuring HRQOL in children and adolescents ages 2-18 years. The PedsQL generic core scales may be used in healthy populations as well as in populations with acute or chronic health conditions. The questionnaire consists of 23 items and 4 subscales: physical, emotional, social, and school functioning[35]. Higher scores mean better HRQOL.

Disease activity was assessed by a pediatric rheumatologist and expressed on a 0-10-centimeter VAS at commencement and during the intervention, to monitor exacerbations (where 0= no disease activity and 10= maximum disease activity). Functional ability was measured using the Dutch version of the childhood health assessment questionnaire 38[36], which measures functional impairment in 9 domains. Pain and well-being were measured on a 0-10-centimeter VAS (where 0= no pain or optimal well-being and 10= the maximum amount of pain possible or the worst well-being possible).

Participation in school and physical education classes were measured during 3 months prior to the test. School absenteeism was defined as being absent from school for 1 or more days as a consequence of JIA, and not as a result of an infection or regular hospital visits. Participation in physical education classes was rated as full when children did not miss any classes due to JIA. Partial participation was

defined as missing a class every now and then, or if the activities were adjusted because of the disease. No participation was defined as no participation whatsoever due to JIA.

Sample size and randomization

Calculating the sample size was based on the results of the pilot study, where the baseline PAL and the PAL after the intervention of the sedentary participants (both recorded in the activity diary) were mean ± SD 1.53 ± 0.12 and 1.82 ± 0.24), respectively[27]. The SD of the change, assuming r=0.5, was estimated to be 0.21. To measure a difference in change of 0.105 in PAL, a sample size of 51 for each group is required. Randomization was performed in SPSS software per center by investigators not involved in recruiting the children (GJFJB and OTHML) in a computer-generated way. Patients received a letter informing them whether they could start right away or had to wait for 6 months.

Statistical analysis

Statistical analysis was performed using SPSS software, version 22. Changes within the intervention and control groups from baseline were analyzed using the Wilcoxon's test. Differences in median change in outcome parameters from baseline between groups and effect sizes were analyzed with the Mann-Whitney-U test according to an intention-to-treat analysis. For this analysis, missing data on T1 were imputed according to the last observation carried forward principle. Within the intervention group, longitudinal effects of the program were analyzed using a Friedman's test. For this analysis, no data were imputed. A linear, mixed-effects model analysis was performed with autoregressive first-order covariance, to analyze seasonal and intervention effects on outcome measures of PA in the intervention group. Residuals were checked for normal distribution. A p value less than 0.05 was considered significant.

RESULTS

Of the 308 children who received an invitation, 83 (27%) agreed to participate (Figure 1). The participation rate in the different centers was 88% for Beatrix Children's Hospital, 19% for Wilhelmina Children's Hospital, and 14% for Reade. A total of 49 children proved eligible and were included in the study; 28 of these children were randomly assigned to the intervention group and 21 to the control group. The 49 participants were divided into 6 cohorts spread over 2.5 years from

January 2011 until September 2012; 25 were categorized as the winter group and 24 as the summer group. Of the 28 participants in the intervention group, 22 were followed up and analyzed after 1 year. The reasons for loss at follow-up are shown in Figure 1.

At baseline (T0), no substantial differences were present between the intervention and control groups regarding patient characteristics and outcome variables (Table 1). During the study period none of the participants received physiotherapy or participated in an organized sports group under medical supervision.

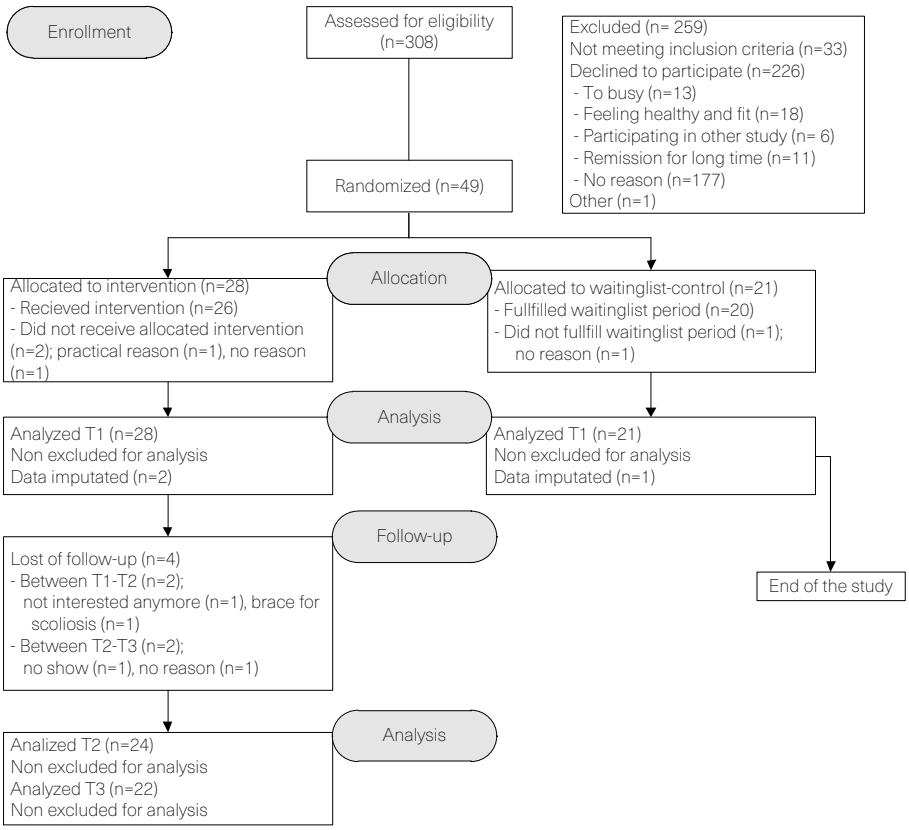

Figure 1. Participant flow diagram.

Analysis at the time of completion by intervention (T1) with the Mann-Whitney U test according to an intention-to-treat analysis. Missing data on T1 were imputed according to last observation carried forward principle. Within the intervention

group, longitudinal effects of the program were analyzed using a Friedman's test. For this analysis no data were imputed. T2=3 months after completion; T3=12 months after completion.

Table 1. Baseline characteristics of the intervention group and control groups.

	Intervention group (n=28)	**Control group** (n=21)
Male, n (%)	7 (25)	9 (43)
Age, years	9.7 (8.7 ; 11.3)	10.2(9.0 ; 10.8)
BMI	17.2 (15.8 ; 19.0]	18.7 (15.1 ; 21.4)
Diagnosis, n%		
Persistent oligoarticular JIA	8 (29)	4 (19)
Extended oligoarticular JIA	3 (11)	4 (19)
Polyarticular JIA	10 (36)	8 (38)
Polyarticular rheumatoid factor+	1 (4)	1 (5)
Enthesitis-related JIA	2 (7)	0 (0)
Psoriasis-related JIA	1 (4)	1 (5)
Systemic JIA	3 (11)	3 (14)
Disease duration, years	3.50 (1.31 ; 6.42)	2.03 (0.84 ; 5.08)
Disease activity VAS (range 0-10 cm)	0.0 (0.00 ; 0.98)	0.20 (0.05 ; 0.80)
Pain VAS (range 0-10 cm)	0.85 (0.20 ; 5.6)	1.60 (0.60 ; 4.0)
Well-being VAS (range 0-10 cm)	1.65 (0.60 ; 4.83)	1.10 (0.20 ; 4.35)
Functional ability	0.50 (0.11 ; 0.78)	0.44 (0.22 ; 0.94)
Activity diary, minutes		
Rest	1,166 (1,109 ; 1,226)	1,151 (1,099 ; 1,214)
Light	195 (153 ; 247)	204 (150 ; 261)
MVPA	48.2 (38.6 ; 87.3)	68.6 (55.7 ; 87.9)
PAL	1.57 (1.47 ; 1.66)	1.59 (1.48 ; 1.68)
Actical device, minutes		
Rest	1,185 (1,156 ; 1,203)	1,180 (1,131 ; 1,207)
Light	213 (194 ; 236)	215 (204 ; 255)
MVPA	46.4 (31.3 ; 54.9)	39.7 (29.0 ; 54.7)
PAL	1.53 (1.46 ; 1.58)	1.53 (1.48 ; 1.63)
Exercise capacity, seconds	525 (472 ; 599)	559 (460 ; 615)
HRQOL		
Physical functioning	71.9 (63.3 ; 81.3)	68.8 (54.7 ; 81.3)
Emotional functioning	75.0 (61.3 ; 85.0)	75.0 (67.5 ; 92.5)
Social functioning	80.0 (75.0 ; 90.0)	80.0 (65.0 ; 95.0)
School functioning	75.0 (65.0 ; 80.0)	75.0 (60.0 ; 85.0)
Total score	76.1 (67.7 ; 83.2)	69.6 (60.9 ; 88.0)

Table 1. Continued

	Intervention group (n=28)	**Control group** (n=21)
School absenteeism, n (%)	12 (43)	5 (24)
PE participation, n (%)		
Complete	16 (57)	13 (62)
Partial	9 (32)	7 (33)
No	3 (11)	1 (5)
Start in summer, n (%)	15 (54)	10 (48)
EC category ≤5th percentile, n (%)	18 (64)	16 (76)
% days MPVA by activity diary†	42.9 (28.6 ; 57.1)	42.9 (42.9 ; 71.4)

Values are the median (interquartile range) unless indicated otherwise .†Median percentage of days that fulfilled 60 minutes or more for MVPA as measured by activity diary. BMI: body mass index; JIA: juvenile idiopathic arthritis; VAS: visual analog scale; MPVA: moderate to vigorous physical activity; PAL: physical activity level; HRQOL: health-related quality of life; PE: physical education; EC: exercise capacity; n: number.

Results of the primary outcome

At T1, in the intervention group, the median time spent in MVPA in the activity diary ($MVPA_{AD}$) had increased by 31 minutes (p=0.04) and $rest_{AD}$ had decreased by 18 minutes (p=0.12)(Table 2). In the intervention and control group, the median PAL_{AD} increased by 0.06 (p=0.08) and 0.03 (p=0.04), respectively. None of the PA outcomes measured with the Actical device had changed significantly after the intervention. Changes in $MVPA_{AD}$, $rest_{AD}$, and PAL_{AD} did not differ significantly between the intervention and control group.

In the intervention group, the results of the longitudinal analysis showed a positive and significant effect on 3 of the 4 PA outcomes. This effect was most visible until T2; median time spent in $rest_{AD}$ was reduced by 81 minutes, median $MVPA_{AD}$ time increased by 50 minutes, and median PAL_{AD} improved by 0.17. Thereafter, the values decreased slightly, but a median improvement compared to baseline was still present: $rest_{AD}$ 47 minutes, $MVPA_{AD}$ 32 minutes, and PAL_{AD} 0.08 (Figure 2 and Supplementary Appendix B (Appendix B; Results of longitudinal follow-up of the intervention group). Outcomes measured with the Actical did not change significantly over time.

Table 2. Effect of Rheumates@Work in the intervention and control groups on T=0 and T=1.

Variable	**Intervention**(n=28) **T0**	**T1**	**Control**(n =21) **T0**	**T1**	**r**
Disease activity VAS (range 0-10 cm)	0.44 (0.00 ; 0.98)	0.00 (0.00 ; 0.38)	0.20 (0.05 ; 0.80)	0.10 (0.00 ; 0.65)	-0.13
Pain VAS (range 0-10 cm)†	0.85 (0.20 ; 5.61)	3.11 (0.23 ; 6.23)	1.60 (0.60 ; 4.02)	0.50 (0.10 ; 2.65)	0.13
Well-being VAS (range 0-10 cm)†	1.65 (0.60 ; 4.83)	2.43 (0.58 ; 4.83)	1.10 (0.20 ; 4.35)	0.90 (0.10 ; 3.20)	0.07
Functional ability†	0.50 (0.11 ; 0.78)	0.39 (0.22 ; 0.78)	0.44 (0.22 ; 0.94)	0.44 (0.11 ; 0.94)	-0.09
Activity diary, minutes					
Rest†	1,166 (1,109 ; 1,226)	1,148 (1,111 ; 1,204)	1,151 (1,099 ; 1,214)	1,148 (1,115 ; 1,213)	-0.07
Light	195 (153 ; 247)	197 (159 ; 235)	204 (150 ; 261)	210 (135 ; 247)	0.02
MVPA	48.2 (38.6 ; 87.3)	79.3 (51.4 ; 117) ‡	68.6 (55.7 ; 87.9)	64.3 (41.8 ; 124)	0.14
PAL	1.57 (1.47 ; 1.66)	1.63 (1.52 ; 1.78)	1.59 (1.48 ; 1.68)	1.62 (1.54 ; 1.81) ‡	0.02
Actical device, minutes					
Rest	1,185 (1,156 ; 1,203)	1,184 (1,153 ; 1,220)	1,180 (1,131 ; 1,207)	1.163 (1,112 ; 1,208)	0.01
Light	213 (194 ; 236)	215 (174 ; 236)	215 (204 ; 255)	220 (192 ; 259)	0.06
MVPA	46.4 (31.3 ; 54.9)	42.3 (29.4 ; 53.0)	39.7 (29.0 ; 54.7)	57.1 (35.8 ; 63.4)	-0.18
PAL	1.53 (1.46 ; 1.58)	1.54 (1.48 ; 1.62)	1.53 (1.48 ; 1.63)	1.57 (1.50 ; 1.69)	-0.10
Exercise capacity, seconds	525 (472 ; 599)	582 (524 ; 609) §	559 (460 ; 615)	513 (447 ; 627)	0.14
HRQOL					
Physical functioning	71.9 (63.3 ; 81.3)	75.0 (65.6 ; 84.3)	68.8 (54.7 ; 81.3)	75.0 (67.2 ; 92.2) ¶	-0.16
Emotional functioning	75.0 (61.3 ; 85.0)	72.5 (61.3 ; 88.8)	75.0 (67.5 ; 92.5)	80.0 (72.5 ; 87.5)	-0.10
Social functioning	80.0 (75.0 ; 90.0)	85.0 (75.0 ; 95.0)	80.0 (65.0 ; 95.0)	80.0 (75.0 ; 97.5)	-0.13
School functioning	75.0 (65.0 ; 80.0)	75.0 (65.0 ; 88.8)	75.0 (60.0 ; 85.0)	80.0 (65.0 ; 85.0)	-0.12
Total score	76.1 (67.7 ; 83.2)	77.7 (68.5 ; 85.6)	69.6 (60.9 ; 88.0)	79.3 (73.4 ; 86.7)#	-0.11

Table 2. Continued
Values are the median (interquartile range) unless indicated otherwise. Results are not significant except for within-group changes as noted. No significant differences between groups were found. A positive effect size indicates a favorable outcome of the intervention group compared to the control group, except as noted. T0: baseline measurement; T1: measurement immediately after completing the intervention; VAS: visual analog scale; MPVA: moderate to vigorous physical activity; PAL: physical activity level; HRQOL: health-related quality of life.[L]Negative effect size indicate a favorable outcome for the intervention group, [‡]p=0.04, [§]p=0.02, [¶]p< 0.01, [#]p =0.01.

Results of the linear mixed-effects model analysis on the long-term effects of treatment and season on $MVPA_{AD/Actical}$, $PAL_{AD/\ Actical}$, and $rest_{AD/Actical}$ showed that starting in winter (treatment-season interaction) reduced $rest_{AD}$ and $rest_{Actical}$ time significantly more compared to starting in summer (54.17 and 24.25 minutes, respectively). Additionally, starting the program in winter improved $MVPA_{Actical}$ and $PAL_{Actical}$ significantly more compared to starting in summer (12.72 and 0.07 minutes, respectively) (Table 3).

Table 3. Results of the linear mixed model analysis for rest, MVPA, and PAL to analyze changes over time in the intervention group.

	Intercept	Time	Intervention	Season	Intervention* season
Activity diary					
-Rest	1,143 (1,096 ; 1,189)	-0.33 (-0.86 ; 0.19)	-37.39 (-0.68. ; -6.43)	39.99 (-14.75 ; 94.74)	54.17 (11.99 ; 96.35)
-p	<0.01	0.21	0.02	0.15	0.01
-MVPA	86.38 (59.96 ; 12.81)	0.12 (-0.29 ; 0.52)	9.15 (-14.49 ; 32.79)	-3.38 (-33.94 ; 27.19)	-13.45 (-45.49 ; 18.59)
-p	<0.01	0.57	0.44	0.82	0.40
-PAL	1.61 (1.49 ; 1.73)	0.00 (-0.00 ; 0 .00)	0.07 (-0.01 ; 0.14)	0.00 (-0.16 ; 0.15)	-0.09 (-0.19 ; 0.02)
-p	<0.01	0.15	0.09	0.95	0.11
Actical device					
-Rest	1,193 (1,167 ; 1,220)	0.07 (-0.31 ; 0.44)	-8.87 (-26.71 ; 8.97)	-27.70 (-62.39 ; 7.00)	24.25 (0.02 ; 48.47)
-p	<0.01	0.72	0.32	0.11	0.05
-MVPA	39.22 (31.09 ; 47.35)	-0.03 (-0.15 ; 0.09)	5.05 (-3.11 ; 13.21)	11.71 (1.53 ; 21.89)	-12.72 (-23.81 ; -1.63)
-p	<0.01	0.63	0.21	0.03	0.03
-PAL	1.52 (1.47 ; 1.57)	0.00 (-0.00 ; 0.00)	0.02 (-0.02 ; 0.07)	0.04 (-0.03 ; 0.10)	-0.07 (-0.13 ; -0.01)
-p	<0.01	0.15	0.31	0.32	0.02

Values are the regression coefficient (95% confidence interval) unless indicated otherwise. Seasons: winter, 0: summer, 1: MVPA: moderate to vigorous physical activity; PAL: physical activity level.

Results of the secondary outcomes

In the intervention group, median exercise capacity showed a significant increase of 57 seconds compared to the baseline measurement. It decreased by 46 seconds (not statistically significant) in the control group. The difference in exercise capacity between the 2 groups was not significant. In the intervention group, longitudinal follow-up showed that Z-scores for exercise capacity improved until T2, and then declined until T3. In comparison to T0 values, however, the Z-scores had improved by 0.65 (see Supplementary Appendix B). Rheumates@Work had no effect on HRQOL in the intervention group between T0 and T1. In the control group, HRQOL improved with regard to the physical subscale and total score. In the intervention group, longitudinal follow-up showed that all scales of the HRQOL questionnaire improved, except the school subscale. Only the emotional scale showed a significant change over time. Rheumates@Work had no significant effect on functional ability, pain, well-being, and disease activity (Table 2) in the 2 groups. In the intervention group no exacerbation occurred that required adjustment of medication.

Participation in school activities increased. The percentage of children in the intervention group (n= 26 valid measurements), who missed at least 1 day of school due to JIA during the preceding 3 months, decreased significantly from 43% to 14% (p=0.02) at T1. In the control group (n= 20 valid measurements), this percentage increased from 24% to 29% (p=0.60). The difference between groups was not statistically significant. Participation in physical education classes increased from 57% to 71% (p<0.01) and from 62% to 67% (p=0.01) in the intervention and control groups, respectively. The difference between the intervention and control groups was not statistically significant.

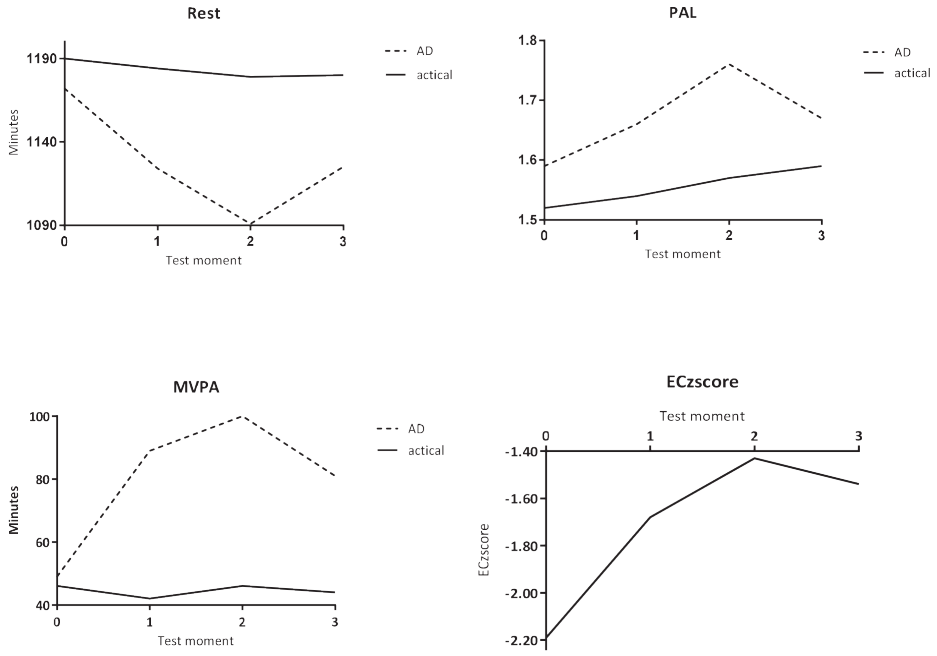

Figure 2. Development of physical activity and exercise capacity in the intervention group over time.

PAL: physical activity level; AD: Activity diary; actical: Actical accelerometer; MVPA: moderate to vigorous physical activity. ECzscore: Z-score of the exercise capacity.

DISCUSSION

Rheumates@Work, an internet-based intervention program for children with JIA, proved to be instrumental in improving PA, exercise capacity, and participation in school and physical education classes in the intervention group. In both the intervention and control group children's PAL increased as recorded in the activity diary. The change in PAL, time spent resting, and MVPA did not differ between the intervention and control groups. Improvements in PA and exercise capacity were still present in the intervention group at follow-up after 1 year. Rheumates@Work did not induce exacerbations and it did not influence HRQOL in the intervention group.

Baseline data of the participants showed lower PAL (1.53-1.59) compared to healthy Dutch children of the same age, who have a PAL_{AD} of 1.8 in summer[37]. MVPA at baseline was 48-69 minutes, which is lower compared to healthy Dutch peers, who

are moderately to vigorously active for up to 108 minutes (median)[37]. MVPA in the intervention group improved, with 35 minutes up to >1 hour per day and fulfilled the recommendations on PA for healthy individuals[38]. This effect in the intervention group is clinically relevant and is consistent with the results found in the pilot study[27]. MVPA in the control group did not change.

Interventions aimed at improving PA in other chronic conditions have shown variable results. In healthy children, the effects of school-based interventions showed improvements of MVPA ranging from 5 to 45 minutes[39]. A meta-analysis in obese children showed that walking and running activities increased by 4 minutes more in the intervention group compared to the control group[40]. A Cochrane review of patients with cystic fibrosis did not find convincing effects of interventions to improve PA[41]. In patients with cerebral palsy, PA measured by self-reports did increase after an intervention. This effect, however, did not last beyond 12 months[42]. The results of our longitudinal follow-up on PA showed ongoing improvement up to 3 months after completing the Rheumates@Work program. Even though all outcome variables deteriorated slightly after 1 year, the improvement remained evident compared to the baseline measurements. This finding may imply that a 14-week intervention period is too short, or that refreshment is needed after a certain interval to achieve lasting changes in PALs. We found that the effects of the intervention were significantly better in the winter group. This effect was not significant for the intervention or season alone, except for $rest_{AD}$ and $MVPA_{Actical.}$ Favorable weather conditions and the summer season are well-known contributors to higher PALs in the general population[19,20]. An explanation for the favorable outcome of the winter compared to the summer group could be that participants who started in winter were confirmed in their effort to improve. All participants received feedback on their PA outcome measures at T1. Although the improvement found at T1 in the winter group may partly be due to season, it might also have served as reinforcement for their healthy behaviour. In the summer group, the lack of seasonal effect led to smaller personal milestones compared to the results of the winter group. Positive experiences are known to be of major importance in cognitive behavioural theory[22]. So for participants who started in winter, the natural seasonal effects might have resulted in long-term consolidation of the improvement from PA outcome measures.

Other studies showed that interventions only have a small positive effect on PA in children[40]. Rheumates@Work addressed barriers and benefits associated with PA in children with a chronic disease, by means of education about fatigue and energy management[26], fear of being active, lack of time, and lack of joy in being active, along with health benefits[42]. During the intervention, children were stimulated to increase their PA, but no specific exercise instructions were given. Such general stimulation of their activity pattern may have been too abstract for children of this age to be able to have a major change in their behaviour. In the evaluation, participants did mention that they had appreciated receiving more explicit exercise assignments[26]. A recent review demonstrated that interventions which reduced sedentary time by using TV-limiting devices were shown to be effective for children, and that interventions featuring exercise equipment like games and dance mats were able to improve PA[43]. One suggestion might be to include an exercise training element in a cognitive behavioural program like Rheumates@Work This inclusion might also help to overcome the seasonal influence on PA, since exercise devices can be used at home during all seasons.

Discrepancies between the outcomes of the activity diary compared to those of the Actical, have been found previously, where MVPA was overestimated when measured with the activity diary compared to the Actical[44]. An activity diary may not be valid for this age group, despite thorough explanations and attempts to involve the parents. Another reason might be that in the intervention group children and their parents were eager to improve and overestimated themselves. Filling in diaries is very time-consuming; although there were no invalid activity diaries at T3, participants might have become more negligent in rating their activities. On the other hand, the Actical has not been validated in children with JIA for measuring PA or change in PA. The Actical has proven to detect changes in PA in healthy children[45], but that study was performed in a laboratory setting and not in daily life as was our study. Rheumates@Work stimulated patients to be more active in daily life, for example, walking up the stairs, going to school by bike, and swimming. These are precisely the activities that are difficult to measure with the Actical[46] or that are registered as non-wear, as in the case of swimming[47]. Patients with JIA may possibly have different activity patterns compared to their healthy peers. Therefore, results from the Actical should also be interpreted with caution. Further studies are needed to validate methods for measuring PA in the daily life of patients with JIA[48,49].

Even though Rheumates@Work is not a training program, exercise capacity improved significantly in the intervention group. Results were consistent with those of the pilot study[27]. The 10% improvement in our study is clinically relevant, especially since exercise capacity is needed to perform strenuous activities. With regards to exercise capacity, longitudinal follow-up showed the same patterns as the outcome measures of PA, i.e., an increase until T2, followed by a slight decrease. This finding would indicate that also from an endurance point of view, an adjustment to the program is required to achieve a more persistent effect.

Rheumates@Work had no effect on HRQOL, and improving HRQOL was not the primary aim of Rheumates@Work. In our study, baseline HRQOL might also have been higher compared to other studies on HRQOL in patients with JIA[8]. The children in our study were willing to change their physical behaviour. This willingness possibly resulted in higher HRQOl scores and a ceiling effect. Participating in the Rheumates@Work program improved the children's school attendance and their taking part in physical education classes at school. This behaviour is an important finding, since school attendance is important for acquiring an education as well as for social acceptance.

Since the participants in our study had already experienced JIA for a considerable length of time and become sedentary as a result, offering Rheumates@Work in the first year after JIA is diagnosed might be advisable. Thus, early information about the benefits of PA, followed up by introducing children to the intervention program, could prevent them from becoming sedentary. A program like Rheumates@Work can be applied in every center where multidisciplinary teams are present for the care of children with JIA like hospitals or rehabilitation centers.

Our study showed that PAL improved in both the intervention group and the control group. Possibly this improvement was an effect of the waiting list design. Perhaps the willingness to participate had already induced a behavioural change. In addition, baseline testing might have created awareness in the participants of the need to become more active. Improvement in HRQOL in the control group might also have been due to the fact that the children felt better at the prospect of participating in the intervention even though they had been allocated in the control group.

This study has limitations, some of which have already been discussed. The rate of participation was low and different for the 3 centers participating in the study. The Medical Ethics Committees did not allow us to collect patient characteristics and reasons for declining the invitation to participate in the program. We are unable, therefore, to assess whether our sample was representative. Participation was highest in the Beatrix Children's Hospital, most likely because it was the initiating center and patients knew the study leaders. We chose to include only patients with inactive disease status because patients with active disease could reach remission within the period of the intervention. This possibility could affect PA positively, irrespective of the intervention. We did not reach our inclusion target, most likely due to our strict inclusion criteria, and consequently, the relatively small sample size might have influenced the outcome. A post hoc analysis revealed that a minimum of 1,100 participants would be needed to show a significant effect on MVPA between the intervention and control groups. For endurance, the number was 125. We had not calculated the size of the sample required for the longitudinal analyses prior to starting the study.

We conclude that Rheumates@Work, a cognitive behaviour, internet-based program aimed at improving PA in the daily life of children with JIA ages 8-13 years, results in improved MVPA levels as measured with a diary. It also results in an increase in exercise capacity and does not exacerbate disease status. The effects are small and should be interpreted with caution due to their low power. Further studies are needed to establish whether or not our findings are generalizable. Levels of PA continued to improve for 3 months after completing the intervention program, and the effect lasted for 12 months. Participants who started the intervention program in winter benefitted most. Rheumates@Work did not affect HRQOL in the intervention group. Nevertheless, participation in school and physical education classes did increase.

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SUPPLEMENTARY APPENDIX A.

Description of the activity diary, accelerometer, and exercise capacity.

The activity diary

The participants were asked to keep an activity diary (AD). In this diary they recorded their physical activity (PA) every 15 minutes, for 24 hours, during 7 consecutive days. This was done by assigning a code to the activity on a scale from 1 through 9. Parents were asked to help their children to complete the diary, since the validity of such a record in children attending primary school may be questionable *(Sallis JF. Self-Report Measures of Children's Physical Activity. J Sch Health 1991;61:215-219)*.

In case of missing data, children were first asked to try to recall their activity as correctly as possible. If they had forgotten what they had been doing between 9 p.m. and 7 a.m., they were considered to have been asleep (Code 1). In case of four or fewer missing values outside this time frame they were scored as having been sitting (Code 2). If the children were lying and sitting (Codes 1 and 2) they were considered to have been resting. Light physical activity (LPA) was scored as Codes 3 through 5, and moderate to vigorous PA (MVPA) as Codes 6 through 9. The mean times for resting, LPA, and MVPA were calculated by adding up the outcomes of the different activity categories for each valid day, divided by the number of valid days. A day was excluded from analysis if five or more values were missing for that day.

Thresholds for resting, LPA, and MVPA were in accordance with the literature. Resting refers to any activity that does not increase energy expenditure substantially above resting level and includes activities such as sleeping, lying down, and sitting *(Pate RR, O'Neill JR, Lobelo F. The evolving definition of "sedentary". Exerc Sport Sci Rev. 2008 Oct;36(4):173–178)*. These activities are represented by Codes 1 and 2, with an energy cost of (0.98* basal metabolic rate) (BMR) and (1.5*BMR), respectively *(W.N. Schofield. Predicting basal metabolic rate, new standards and review of previous work Human nutrition; clinical nutrition 1985, 39C, Suppl. 1 5-41)*. Intensity thresholds between LPA and MVPA are around four metabolic equivalents of tasks *(Ekelund, et al. What proportion of youth are physically active? Measurement issues, levels and recent time trends. Br J Sports Med*

2011 Sep;45(11):859–865). LPA is, therefore, represented by Codes 3, 4, and 5, with energy costs of 2.0, 2.8, and 3.3* BMR, respectively. MVPA is represented by Codes 6, 7, 8, and 9, with energy costs of 4.4, 6.5, 10.0, and 15.0*BMR, respectively.

To calculate the child's physical activity level (PAL), all 15-minute periods for each category 1-9 were added up and divided by 96 and multiplied by PA *(Bratteby LE et al. G. A 7-day activity diary for assessment of daily energy expenditure validated by the doubly labeled water method in adolescents. Eur J Clin Nutr 1997;51:585–591)*. Mean PAL per day was calculated by adding up the physical activity levels for valid days, divided by number of valid days.

The accelerometer

The accelerometer (Actical, Phillips Respironics, Bend, OR, USA) was validated for children aged 7 through 18 years. It measures accelerations in any plane of movement, translates them into activity counts, which in turn reflect PA. *(Puyau MR, et al. Prediction of activity energy expenditure using accelerometers in children. Med Sci Sports Exerc 2004;36:1625-1631)*. The Actical was worn by participants on the right hip for seven consecutive days. Counts were added up in 1-minute periods. Cutoff points were used to determine thresholds for being sedentary (0-100 counts per minute), or for being engaged in light (101 -1500 counts per minute), moderate (1501 -6500 counts per minute), or vigorous activities (more than 6500 counts per minute). The mean time spent in sedentary, light, and, MVPA was calculated by adding up the length of time spent in various PA categories, divided by the number of valid days. The Actical produced activity-related energy expenditure (AEE) in Kcal per day. PAL was computed using the formula: ((AEE * 4.1868)/1000 + BMR)/0.9.)/BMR). BMR was computed using the formula: 0.074 * kg bodyweight + 2.754 Mj/ day for boys and 0.056 x kg bodyweight + 2.898 Mj/ day for girls, where Mj/day stands for Megajoule per day *(Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr 1985;39C:5-41)*. In order to count as a valid measurement, the length of time the Actical was worn during week days had to amount to at least 8 hours per day and at least 6 hours during each day of the week. This criterion was less stringent than the 10-hour wearing-time previously suggested *(Colley R, et al. Quality control and data reduction procedures for accelerommetry-derived measures of physical activity. Stat Canada, Cat 2010;21:1-7)*. A shorter wearing-time was accepted since our participants were young and went to bed earlier than adults and, as a result,

had fewer hours of activity during the day. Initially, we aimed at at least three valid weekdays and one valid weekend day for each patient, for every test moment. Results were analyzed with valid data only, and with all available data. No clinically relevant differences were found between the outcomes of these analysis, hence all data were included in the analysis of the trial.

Exercise capacity

To measure maximum exercise capacity we used the Bruce treadmill protocol. During rest, heart rate was recorded by a Polar chest belt. During the test, participants were encouraged to reach maximum exertion, i.e. a maximum heart rate of 180 or higher *(Bongers BC, Van Brussel M, Hulzebos EH, Takken T. Pediatric norms for cardiopulmonary exercise testing. Second edition; 2014:1-201, ISBN 978-90-8891-998-5)*. During the test, walking speed and inclination increases every three minutes until the child is exhausted (and critical power is exceeded) *(Palange et al. Recommendations in the use of exercise testing in clinical practice Eur Resp J 2007; 29; 185-209)*. The workload for that moment must remain stable during three minutes. The test is terminated at the patient's or the observer's discretion. The test should be interpreted as a combination of a symptom-limited, incremental exercise and a high intensity, constant-load endurance test. Changes in endurance of > 10% were considered clinically relevant.

SUPPLEMENTARY APPENDIX B.

Results of longitudinal follow-up of the intervention group.

	T0 Median (IQR)	T1 Median (IQR)	T2 Median (IQR)	T3 Median (IQR)	p
AD*					
rest	1172(1094 ; 1231)	1124 (1083 ; 1196)	1091 (1063 ; 1158)	1125 (1068 ; 1174)	0.03
light	184 (150 ; 260)	199 (160 ; 239)	227 (158 ; 273)	221 (167 ; 305)	0.56
MVPA	49.3 (38.6 ; 89.5)	88.9 (61.1 ; 123)	99.6 (85.7 ; 132)	81.4 (52.5 ; 145)	0.02
PAL	1.59 (1.46 ; 1.69)	1.66 (1.56 ; 1.84)	1.76 (1.61 ; 1.87)	1.67 (1.55 ; 1.87)	<0.01
Actical **					
rest	1190 (1156 ; 1206)	1184 (1164 ; 1222)	1179 (1138 ; 1224)	1180 (1147 ; 1225)	0.83
light	210 (191 ; 235)	214 (168 ; 235)	200 (178 ; 246)	209 (168 ; 242)	0.85
MVPA	45.9(30.8 ; 55.5)	42.3 (32.6 ; 55.2)	45.7 (30.0 ; 68.8)	43.6(31.9 ; 55.5)	0.81
PAL**	1.52 (1.46 ; 1.56)	1.54 (1.47 ; 1.60)	1.57 (1.46 ; 1.65)	1.59 (1.47 ; 1.67)	0.17
ECzscore*	-2.19 (-2.52 ; -1.33)	-1.68 (-2.6 ; - 0.97)	-1.43(-2.30 ; -0.78)	-1.54 (-2.68 ; -0.84)	0.66
HRQOL**					
Physical	71.9 (65.6 ; 81.3)	78.1 (65.6 ; 85.9)	78.1 (67.2 ; 85.9)	78.1 (64.1 ; 90.6)	0.12
Emotional	75.0 (62.5 ; 87.5)	75.0(62.5 ; 90.0)	95.0 (65.0 ; 100)	80.0 (70.0 ; 97.5)	0.05
Social	80.0 (75.0 ; 90.0)	85.0 (80.0 ; 95.0)	90.0 (72.5 ; 97.5)	90.0 (80.0 ; 97.5)	0.16
School	75.0 (67.5 ; 80.0)	75.0 (62.5 ; 90.0)	80.0 (60.0 ; 85.0)	75.0 (72.5 ; 82.5)	0.98
Total	76.1 (67.9 ; 82.6)	80.4 (69.0 ; 85.9)	82.6 (71.7 ; 89.1)	82.6 (73.4 ; 88.0)	0.17

*n=22; **n=21. T0: baseline measurement; T1: measurement immediately after completing the intervention; T2: measurement three months after completing the intervention; T3: measurement one year after completing the intervention. p values represent the results of Friedman's 2-way ANOVA. IQR: inter quartile range; AD: activity diary; MPVA: moderate to vigorous physical activity; PAL: physical activity level; HRQOL: health-related quality of life; EC Z-score: Z-score of exercise capacity.

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CHAPTER 8

General Discussion

In this chapter the most remarkable findings will be summarized and the clinical and scientific relevance will be discussed. Thereafter the limitations of the studies will be summarized and finally perspectives of future research will be discussed.

In infants with a liver transplant fine motor skills are normal pre transplantation compared to norm values, while gross motor skills are delayed pre liver transplantation. Both skills decline post liver transplantation and tend to recover after one year; gross motor skills to low normal and fine motor skills to normal levels *(chapter 2)*.

Children with Juvenile Idiopathic Arthritis (JIA) have a lower physical activity (PA) level, they spent less time in moderate to vigorous PA (MVPA) and spent more time on sedentary activities compared to controls despite current medical treatment and PA encouragement *(chapter 3)*.

Children post liver transplantation have similar MVPA patterns and aerobic fitness compared to norm values and they participate in recreational and leisure activities similar to norm values *(chapter 4)*. But both children with JIA *(chapter 3)* and children post liver transplantation do not meet the recommendations of PA. In children with JIA 4% and in children post liver transplantation 7% meets PA recommendations while in healthy Dutch children 16% meets recommendations of PA *(chapter 4)*.

Convergent validity between an activity diary (AD) and an accelerometer (Actical) in children with JIA is moderate to poor. To reliably establish PA on a group level one week measurements of the accelerometer are needed and for AD 13 days. For an individual level 3 weeks of the accelerometer are needed and more than 5 weeks of AD measurements *(chapter 5)*.

A home-based exercise trainings program of interval training on a treadmill and strength exercises in children with Juvenile Dermatomyositis as well as an internet-based cognitive behavioural treatment program Rheumates@Work in children with JIA are safe, showing high adherence but have no positive effect on PA *(chapter 6 and 7)*.

RELEVANCE

Motor development

The delayed gross motor development in infants pre liver transplantation can be explained by their illness. They are less in prone position, because most of the time these children have abdominal distension, are frequent hospitalized, have growth failure before transplantation[1,2] and might use medication through infusion which limits them in their gross motor activities. Prior to our research we assumed that gross motor development in children post liver transplantation would have recovered after one year, although gross motor development improved to low normal values, still half of these children have a delayed gross motor development. Delayed motor development will influence PA, since better motor development is positively associated to level of PA and physical fitness in later life[3–5].

Despite the delay in gross motor development in the initially year, median 7.5 years post liver transplantation children have a MVPA and aerobic fitness similar to norm values. But there still may be a delayed gross motor development resulting in less MVPA as these children experience more fatigue and lower health related quality of life (HRQOL) compared to norm values. Additionally, these children have less muscle strength than norm values and only 4% meets recommendations for PA. Although the children participated in recreational and leisure activities as norm values, only some of these activities reach the recommended intensity of MVPA for health benefits[6].

Young children post liver transplantation should be screened on gross motor development and during follow up. As most previous studies have shown that motor development did not improve post liver transplantation[7–9]with exception of one study[2]. That study showed that motor scores, determined with the Griffiths mental ability scales (Griffiths-II), improved and children reached the norm for their age within 4 years post liver transplantation. This finding might be based on the instrument used since, the Griffiths locomotor subscale (gross motor skills) results in higher scores compared with the Bayley scales of infant development, second edition, (BSID-II)[10], used in other studies[8,9]. One should be aware of the assessment tool used to determine motor development. In case of delayed gross motor development children should be referred to a pediatric physical therapist, for assessment and stimulation of gross motor skills, so these children have the appropriate skills to be physical active and with it the health benefits of an active lifestyle.

Physical activity

In the JIA study children spent on average more than one hour a day on MVPA, suggesting that they are sufficiently active, but when correcting MVPA per day only a few children reach the minimum of one hour of MVPA every day of the week. However, PA is challenging to evaluate as it is a complex behaviour, especially in children. Conflicting findings of meeting PA guidelines[11, 12] are due to differences in samples, study design, and PA determination in these different studies. Instruments to determine PA all have some limitation[13]. This thesis shows that on individual level almost 3 weeks of the accelerometer and more than 5 weeks of AD measurements are required to obtain reliable estimates of PA in children with JIA. It is impossible to ask children to fill in an AD or to wear an accelerometer for such a long time and it is easily forgotten.

The AD has the advantage for children that it also educates children about the intensity of an activity; a higher intensity of the activity is associated with a higher number of coding in the AD. In this way children gain insight in their activity pattern. The disadvantage of the AD is that it overestimates PA as the dominant activity per 15 minutes is entered in the AD. If children are moderate to vigorous physically active for 10 minutes, 15 minutes of MVPA is recorded in the AD. One might expect that this overestimation is compensated at times the child is less active for most of the 15 minutes and only had a few minutes of MVPA and light activity is entered in the AD, but if this truly happens is unknown. Another source of information bias might be that children fill in the AD more favorable regarding PA than they actually perform and errors based on recall if the diary is not immediately filled in.

The advantage of an accelerometer is that it monitors PA more objectively. It provides information about the intensity and duration of the activity and is easy to wear[13]. The disadvantage of an accelerometer is that some movements are difficult to detect like cycling and data analyses must be performed before gaining insight into intensity and duration of the activities. Combining both methods, AD and accelerometer, provides better insight in PA and allows correcting the accelerometer for activities they do not detect or correct for non-wear during wet activities as not all accelerometers are waterproof. The disadvantage of double assessment is the burden for the child and parent.

For clinical and scientific relevance it is important to be aware of the advantages and disadvantages of PA measurements and the purpose of the measurement as not all instruments can be used to evaluate against PA guidelines[6]. No specific method can be considered as best option. The choice of the most appropriate instrument depends on the research question, or reason for evaluation of PA. This thesis showed that on group level one week measurement of the accelerometer and 13 days of AD is needed for reliable estimates of PA in children with JIA, which is less compared to individual level, but still a considerable burden for the child. Suggestions have been made to simplify data collection by focusing assessments to key times or places when children are active, like after school time[14].

Regarding health benefits it is important to get insight in intensity and duration of the activity to evaluate against PA guidelines as the description of the activity itself is insufficient. For instance in a football game some children are very active and run around over the field while others wait for the ball to reach them. Both children are 'playing football'. Especially activities with a moderate to vigorous intensity are important for health benefits in the long term. For this purpose an instrument must therefore be chosen that can display MPVA as objectively as possible. By combining the accelerometer with a non-wear time AD provides a more complete representation of the PA of the children.

In the context of long-term management, it remains important to stimulate PA, in children with or without chronic conditions. Dutch children in general are not active enough[15], their motor skills are deteriorating and childhood obesity is increasing[16]. As previously mentioned, this thesis shows that a low normal gross motor development is present in children one year after liver transplantation. A declined motor development, especially gross motor development, might affect PA later in life. When children are unable to run, jump, catch and throw etc. they have limited opportunities to participate in physical activities because they lack the necessary skills. If children are not physical active at a young age the likelihood of them being physical active in later life is less as participation in sports at a younger age increases the probability of a higher level of PA in later life[17,18].

In the Netherlands, the government offers all kinds of PA programs to simulate children to be physical active. Everyone must be able to opt for an active and healthy lifestyle (Dutch government) and therefore financial support is available

for children growing up in low-income families[19]. The Committee for the Dutch Physical Activity Guidelines advices; 'PA is good for you - the more the better, the longer you are physically active, and the more frequent and/or more vigorous the activity, the more your health will benefit. Do activities that strengthen your muscles and bones at least three times a week and avoid spending long periods sitting down'[20]. However, too much PA might result in injuries[15]. A child must be ready for certain sports activities as physical growth and development of motor skills are important in order to learn sports skills. In goal setting and expectations of sports activities, variation of both cognitive and motor skill development must be taken into account[21].

Physical activity interventions

It is assumed that children with chronic conditions will experience the same health benefits from PA as healthy children. Children in general are hard to activate and for children with a chronic condition it is sometimes difficult to let them participate in regular sports activities which may lead to hypo activity and deconditioning[22]. Several attempts have been made to develop sports groups for children with a chronic condition. These sports groups are most often associated with a rehabilitation center or with a hospital and transportation is the biggest problem. To overcome barriers to participate in PA, home based programs have been developed so that one does not have to travel and can chose a suitable time to perform the activities of the home based program. In this thesis 2 individual home-based programs were evaluated to improve PA; an exercise trainings program of interval training, on a treadmill and strength exercises in children with dermatomyositis and an internet based cognitive behavioural program in children with JIA. Both programs are safe, feasible and had a high adherence but they had no effect on PA.

It is unclear as to why both interventions had no effect on PA. In the internet-based cognitive behavioural intervention in children with JIA, the intervention group significantly improved in time spend in MVPA measured with the AD, but not when measured with the accelerometer and no significant differences were found between the intervention and control group in PA. In this intervention children had to set an attainable goal based on the baseline findings of their PA and physical fitness, but no specific exercises were given on how to reach that goal. Therefore the goal setting might have been too abstract for these children. In the exercise training study in children with juvenile dermatomyositis all exercises were well

described and that study showed increased endurance time and improvement on standing long jumps, push-ups and sit ups, which were also partially exercises of the training intervention. Endurance time also significantly increased in the intervention group in the internet-based intervention, but no significant differences were found between the intervention and control group. In general PA interventions show little effect on the overall activity of children[23]. Possible explanations are that the PA component was not sufficiently intense or poor delivery of the activity sessions. Another explanation might be that the exercise sessions of the intervention replaced the periods at which children are normally active at the same intensity level[23]. For example organized sports replace the period that children usually spend in outdoor playing activities.

Combining both interventions (physical training and cognitive behavioural intervention) might be more effective in increasing PA; it gives variety in training and education, but also clear exercises to achieve the final goal. Both the exercise training program of interval training, on a treadmill and strength exercises in children with dermatomyositis and the internet based cognitive behavioural program in children with JIA showed to have good components, like home based, well defined exercises, guidance, health education related to the chronic condition and PA, information on barriers that prevent someone from being active, explanation of the benefits of PA and self-efficacy towards becoming more physical active[24,25]. The acceptance and satisfaction of the internet intervention were high and the costs low[24]. The exercise intervention showed high adherence and toleration. For further optimization of the combined program, one might consider to make the education more age specific as suggested during evaluation[24] and taking into account the motor skills in setting goals, as the age range in both studies was wide.

LIMITATIONS

The studies described in this thesis have some limitations. Small groups were studied in all studies. For the study of motor development pre and post liver transplantation assessments post liver transplantation of gross motor development was limited because children could not be assessed in prone position as it is not recommended until 4-6 weeks post-surgery. Additionally assessments were sometimes not possible for logistic reasons. In our hospital children with a delayed motor development are referred to a pediatric physical therapist, but it is not clear what the content, duration and frequency of this treatment was.

In the study comparing PA in children with JIA and controls, the PA data of the control group were assessed 1.5 years earlier. This might result in an overestimation of PA in the control group as sedentary activities in children increases over time, possibly by increased screen-time. Another limitation in that study was that PA data in the control group were assessed in the summer probably overestimating PA since children are less active in autumn and winter when sedentary time is greater[26].

In the study comparing children after liver transplantation on PA and aerobic fitness with norm values, no comparison could be made with Dutch norm values, as these were not available in the age group studied. Additionally no norm data are available on physical fitness in children below the age of 8 years. Data was extrapolated from norm values to be able to compare study findings, which may have resulted in under- or overestimating aerobic fitness.

In comparing the AD with the accelerometer data was imputed in the AD in case of missing values if it was not possible to enter data by recall of the children/ parents. Children had to enter a smiley in the AD at the time they put on the accelerometer. Some children forgot to enter a number of the activity at that given time point. Missing data was imputed by light activity, assuming that the moderate to vigorous activities will be remembered well, but no data is available to substantiate this assumption.

Controls in the juvenile dermatomyositis study showed high levels of PA and in the intervention group children had already high levels of aerobic fitness at baseline, which reduced a priory chance for improvements in aerobic fitness. Although the intervention group and the control group were stratified for age, and gender, both groups differed in disease activity and disease duration which might have influenced outcomes.

Although the Reumates@Work intervention consisted largely of education, improved knowledge was not evaluated as outcome measure, in the sense of detecting change in knowledge about the chronic condition and the importance of PA, knowledge evaluation might do more justice to evaluate the effect of this intervention.

FUTURE RESEARCH

For future studies assessing PA in a more structured way (in all seasons) in both healthy children and children with a chronic condition improves comparison of outcomes and detect changes over time. Now many methods are used like questionnaires, AD and accelerometers. If settings of the accelerometers and outputs are processed in standardized way, comparing data would be much more realistic. New techniques in improving accelerometer devices are needed for better detection of the activity and the use of smartphone apps might help as reminders for filling in data at times of non-wear.

Expressing PA as physical activity level is not always a clear concept, expressing PA in categories as light, moderate and vigorous PA is easier to understand, but different cut-off points are used in expressing these categories, which make comparison with other studies more difficult. Future studies should express PA concepts like light, moderate and vigorous PA similarly and consensus should be reached regarding definitions and cut-off points in categorizing these activities. Norm data on PA and aerobic fitness is needed in young children.

Evaluation of motor development, especially gross motor development, more structured during follow up of the chronic condition is needed, to detect early delayed gross motor development, to help prevent from less PA and physical fitness in later life.

In addition, the intervention of the pediatric physical therapist, content and assessment of the effect of the intervention, should be studied regarding gross motor development, to improve referral to the pediatric physical therapist in children after liver transplantation. Also the impact of delayed motor development on PA in later life should be explored.

For the intervention of increasing PA and aerobic fitness in children with chronic conditions it is interesting to study the effects of combining an internet based cognitive behavioural and exercise trainings intervention program as this intervention seems easy applicable as it is home based and the concept might be applicable for all kind of different chronic conditions.

CONCLUSION

Children with chronic conditions experience a lower quality of life than healthy children, which might be improved through improving PA and health-related fitness. The medical treatment of several chronic conditions in children continues to improve, and PA is generally safe in chronic conditions. Physical activity has benefits on growth, development and general health of children. Therefore, PA should not be overlooked in the treatment of children with chronic condition. Stimulating PA for health benefits is a challenge because intensity and activity duration are important, but are difficult to measure objectively. One must take into account that physical activities require the appropriate motor skills for any children to participate. The best way of improving PA in children with chronic conditions is still not clear, but methods and interventions have to be focused on the specific problems and circumstances of the target population. Improving motor deficiencies of children with a liver transplant is important, but might be less relevant for other chronically ill populations. Combining an internet-based cognitive intervention program with an exercise training program – and taking into account the age of the children - might improve PA for health benefits, but further evaluation of such a program is needed.

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SUMMARY

Physical activity is beneficial for human beings. Therefore, governments and organisations develop physical activity guidelines for both adults and children. The Dutch Physical Activity Guideline advises children to engage in moderate to high-intensity physical activity for at least one hour every day. It is generally assumed that children with a chronic condition experience the same health benefits from physical activity as healthy children, which is why there is a strong shift towards initiating physical activity in children with a chronic condition.

Previously, people were reluctant to stimulate physical activity in chronic conditions, and bed rest was often advised. For children with juvenile idiopathic arthritis (JIA), it was similarly assumed that physical activity would cause damage to the joints; however, research shows that physical activity is safe.

Survival of children with a livertransplant has improved through improved medicinal and surgical treatment options. Medical treatment for children with JIA has also improved. For both groups, the focus has increasingly shifted to long-term outcomes. For these children, important long-term outcomes include quality of life as well as participation in sport and play activities.

Typical motor development is important for one's ability to participate in sport and play activities with peers. Motor abilities are positively associated with physical activity and negatively associated with sedentary behaviour.

Chapter 2 describes a study of motor development, both gross and fine motor skills, on pre- and post-liver transplant paediatric patients. The study compared outcomes with norm values of healthy children. This study shows that both gross and fine motor skills decline in post-liver transplant young children. This decline continues until three months after a liver transplant. Skills recover after one year: gross motor skills are low normal and fine motor skills are normal. Monitoring the gross motor development remains particularly important for participation in sport and play activities as well as for the benefits of physical activity throughout life.

One would expect for differences in physical activity, as described in various studies, between children with a chronic condition and healthy children to decrease as treatment and guidelines improve. **Chapter 3** describes a study that

compared the physical activity of children with JIA with a control group. The study involved children with JIA according to the current treatment regime. This treatment encourages children to be physical active and it includes a top-down medication routine that achieves remission within 3–6 months. The study also analysed the disease-specific factors of JIA that may affect physical activity. By doing so, this study showed that children with JIA spend less time on moderate to vigorous physical activity and demonstrate more sedentary behaviour when compared to the control group. Medication or disease activity do not affect the physical activity of children with JIA, but appear, instead, to be related to the patient's well-being and pain. Children with JIA who experienced more pain were more active, which was not in line with expectations; however, we were able to explain this outcome by acknowledging that those subjects experienced pain (e.g. muscle pain or post-training pain) just like the other children did. In addition, we found that children who feel better (higher score of well-being) were more physically active.

Chapter 4 describes a similar study that measured the physical activity and physical fitness of children who had received a liver transplant in the past. This study found that these children perform at the same level of moderate to vigorous physical activity and enjoy an aerobic fitness comparable to norm values. Despite a lower health-related quality of life, more fatigue, and reduced muscle strength, children with a liver transplant participate as much as healthy children in daily activities outside school hours. The study thus concluded that these children are doing well despite their chronic condition. Nevertheless, it appeared that both groups (children after a liver transplant (**chapter 4**) and children with JIA (**chapter 3**)) scored poorly for a key marker of sufficient physical activity (i.e. one hour of moderate to vigorous physical activity 7 days each week). There were hardly any children in these two groups who met this criterion.

It is difficult to measure physical activity objectively even though various methods exist. **Chapter 5** determines the convergent validity of an activity diary and an accelerometer and appeared as moderate in children with JIA. The outcomes of the activity diary suggest a higher activity level than outcomes of the accelerometer. In the activity diary, every 15 minutes a number is given for the most dominant activity performed in that time segment. When children are moderately active for 10 minutes and sit down for 5 minutes, the diary records moderately intensive activity for those 15 minutes. This approach risks overestimating moderate physical

activity. Accelerometers, on the other hand, are unable to properly register all movements, such as cycling. As a result, accelerometers are prone to registering certain activities lower than their actual intensity. A diary alongside the accelerometer could supplement it and improve measurement accuracy, but this procedure remains vulnerable to the previously described overestimation and may burden children by doubling the tasks of recording. The advantage of filling in the activity diary is that children receive education and feedback about the intensity of the activity. An accelerometer is easy to use because one does not have to do anything after one attaches it.

To reliably measure physical activity at group level, this study shows a one-week period of accelerometer measurements and a period of at least 13 days for a diary is required. On an individual level, the accelerometer must be worn for almost 3 weeks, and the activity diary must be filled in for 5 weeks. One can imagine that this is difficult to maintain and that days are easily forgotten. As the physical activity patterns differ over the week, it is important to measure different days of the week (both weekdays and weekend days).

To enjoy the long-term effects of physical activity, children with chronic conditions need to be encouraged to be physically active. **Chapters 3 and 4** report that only a small percentage of children with JIA and children after a liver transplant meet the Dutch Physical Activity Guideline. For children with a chronic condition, it is sometimes difficult to participate in regular sport programs. Although there are specific training groups for children with chronic conditions, the travel distance is often a limiting factor. **Chapter 6** investigates the feasibility, safety, and effectiveness of a 12-week physical training program in 26 children with juvenile dermatomyositis. The children received a treadmill at home, and the training consisted of walking/running on the treadmill and muscle-strength exercises like push-ups and sit ups. The children trained at their own level and were supervised at home once every two weeks by a researcher. The children were able to execute the program well, and there were no indications that the training provokes disease activity. Overall, aerobic fitness, muscle function, and functional ability improved, and those improvements were still present 12 weeks after the end of the programme. The study concludes that exercise training is of value, but it did not find any effect on improving physical activities.

Chapter 7 describes the study of a cognitive-behavioural internet program to promote physical activity and physical fitness in children with JIA. Accompanied by 4 group sessions for parents and children, it consisted of a 14-week program offered via the internet. The program discussed various themes, such as self-efficacy with regard to physical activity, obstacles that prevent people from being active, education about JIA, as well as physical activity, fatigue, energy management, and the benefits of physical activity.

Children and parents enjoyed the programme and found it educational. The majority of the children completed the programme. No differences were found between the intervention and controls group, but the time spent in moderate physical activity and aerobic fitness improved in the intervention group. In addition, school absenteeism in the intervention group decreased and participation in physical education classes at school improved. The improvements remained 12 months after the program finished, and the children who started the programme in the winter improved more than the group that started in the summer.

In **chapter 8** the most remarkable findings of this thesis are summarized and discussed. Children with chronic conditions experience a lower quality of life than healthy children, which we might improve through improving physical activity and health-related fitness. The medical treatment of several chronic conditions in children continues to improve, and physical activity is generally safe in chronic conditions. Physical activity has benefits on the growth, development, and general health of children. Therefore, physical activity should not be overlooked in the treatment of children with chronic conditions. Stimulating physical activity for health benefits is a challenge because intensity and activity duration are important but are difficult to measure objectively. One must take into account that physical activities require appropriate motor skills for any children to participate. The best way of improving physical activity in children with chronic conditions is still not clear, but methods and interventions have to be focused on the specific problems and circumstances of the target population. Improving motor deficiencies of children with a liver transplant is important, but might be less relevant for other chronically ill populations. Combining an internet-based cognitive intervention program with an exercise training program—and taking into account the age of the children—might improve physical activity for health benefits, but further evaluation of such a programme is needed.

NEDERLANDSE SAMENVATTING

Het is algemeen geaccepteerd dat bewegen gunstig is voor de mens. Daarom ontwikkelen overheden en organisaties richtlijnen voor gezond bewegen voor zowel volwassenen als kinderen. De Nederlandse beweegrichtlijn raadt kinderen aan om dagelijks minimaal een uur matig intensief te bewegen. Er wordt verondersteld dat kinderen met een chronische aandoening dezelfde gezondheidsvoordelen ondervinden van bewegen als gezonde kinderen, vandaar dat er een verschuiving plaatsvindt om kinderen met een chronische aandoening te activeren tot bewegen.

Voorheen was men terughoudend in het geven van beweegadviezen aan kinderen met een chronische aandoening en werd bedrust vaak geadviseerd. Zo werd verondersteld dat bewegen bij kinderen met juveniele idiopathische artritis (JIA) schade aan de gewrichten zou veroorzaken, maar uit onderzoek bleek dat bewegen veilig is.

De overleving van kinderen na levertransplantatie is verbeterd door verbeterde medicamenteuze en chirurgische behandelmogelijkheden. Ook de behandeling van kinderen met JIA is verbeterd. De focus van behandeling is daarom verschoven naar de lange termijn uitkomsten betreffende kwaliteit van leven en participatie in school sport en spelactiviteiten.

Om goed te kunnen bewegen en te participeren in sport- en spelactiviteiten met leeftijdsgenoten is een normale motorische ontwikkeling van belang. Een goede motorische ontwikkeling is positief geassocieerd met fysieke activiteit en negatief geassocieerd met sedentair gedrag.

Hoofdstuk 2 beschrijft een onderzoek betreffende de motorische ontwikkeling, van zowel de grove als fijne motoriek, pre- en post levertransplantatie bij jonge kinderen. De resultaten van deze kinderen werden vergeleken met normwaarden van gezonde kinderen. Deze studie toonde aan dat zowel de grof als fijn motorische vaardigheden afnamen bij jonge kinderen na levertransplantatie. Deze afname zet door tot 3 maanden na transplantatie en leek 1 jaar post operatief te herstellen, de grof motorische vaardigheden naar laag normaal en de fijn motorische vaardigheden naar normaal. Het monitoren van de grof motorische ontwikkeling blijft belangrijk met het oog op fysieke activiteiten en participatie in sport- en spel activiteiten en de voordelen van bewegen op lange termijn uitkomsten.

Doordat de behandeling van chronische aandoeningen verbetert en er een steeds actiever beleid is ten aanzien van stimuleren tot bewegen bij kinderen met een chronische aandoening zou men verwachten dat de verschillen in fysieke activiteit, zoals beschreven in diverse onderzoeken, tussen deze kinderen en gezonde kinderen steeds kleiner worden. **Hoofdstuk 3** beschrijft een onderzoek waarin de fysieke activiteit van kinderen met JIA is vergeleken met een controlegroep. De kinderen met JIA zijn behandeld volgens het huidige behandelregime. Deze behandeling omvat een top down medicatie regime waarin remissie wordt bereikt binnen 3 tot 6 maanden en men kinderen stimuleert tot bewegen. Daarnaast zijn ziekte specifieke factoren bij JIA geanalyseerd die fysieke activiteit kunnen beïnvloeden. Uit dit onderzoek bleek dat kinderen met JIA minder tijd besteedden aan matig intensieve fysieke activiteiten en meer sedentair gedrag vertoonden vergeleken met de controlegroep. Medicatie of mate van ziekte activiteit had geen invloed op de fysieke activiteit van kinderen met JIA. Fysieke activiteit bleek samen te hangen met het welbevinden van het kind en pijnbeleving. Kinderen met JIA die meer pijn ervoeren, waren fysiek actiever, wat niet in lijn was met de verwachting, maar wat mogelijk verklaard kan worden doordat de kinderen pijn ervoeren als gevolg van bewegen (bijvoorbeeld spierpijn of pijn na training) net als elk ander kind. Bovendien werd gevonden dat kinderen die zich beter voelen (hogere maat van welbevinden), fysiek actiever waren.

Hoofdstuk 4 beschrijft een soortgelijk onderzoek, namelijk de fysieke activiteit en fysieke fitheid van kinderen met een levertransplantatie in de voorgeschiedenis. Dit onderzoek wees uit dat deze kinderen evenveel bewegen qua matig intensieve fysieke activiteit en een aerobe fitheid hadden vergelijkbaar met de normwaarden. Ondanks een lagere gezondheid gerelateerde kwaliteit van leven, meer ervaren vermoeidheid en een verminderde spierkracht, participeerden kinderen met levertransplantatie in de voorgeschiedenis evenveel als gezonde kinderen in dagelijkse activiteiten buiten de schooluren. Kortom deze kinderen doen het ondanks hun chronische aandoening goed. Niettemin bleek dat beide groepen (kinderen na levertransplantatie (**hoofdstuk 4**) en kinderen met JIA (**hoofdstuk 3**)) slecht scoorden wat de beweegrichtlijn betreft, namelijk 1 uur matig intensief bewegen 7 dagen per week. Er waren nauwelijks kinderen in deze twee groepen die aan dit criterium voldeden.

Het objectief meten van fysieke activiteit is lastig, hoewel er verschillende methoden bestaan. **Hoofdstuk 5** beschrijft de overeenstemming tussen een activiteitendagboek en een accelerometer (bewegingsmeter). De overeenstemming bleek matig te zijn bij kinderen met JIA. De uitkomsten van het activiteitendagboek waren hoger dan die van de accelerometer. In het activiteitendagboek wordt elk kwartier een getal gegeven voor de meest dominante activiteit die in dat kwartier is uitgevoerd. Wanneer kinderen gedurende 10 minuten matig actief zijn en 5 minuten gaan zitten, wordt er voor 15 minuten matig intensieve activiteit geregistreerd. Op deze manier kan er een overschatting van de matig intensieve fysieke activiteit ontstaan. Accelerometers daarentegen zijn niet in staat om alle bewegingen goed te registeren zoals bijvoorbeeld fietsen. Hierdoor worden dit soort activiteiten lager geregistreerd dan de daadwerkelijke intensiteit en kunnen de activiteiten onderschat worden. Het tegelijkertijd invullen van een activiteitendagboek naast het dragen van een accelerometer kan de schatting van fysieke activiteit verbeteren, maar hierdoor kan ook de eerder omschreven overschatting van activiteiten ontstaan en worden de kinderen dubbel belast met zowel het invullen van het activiteitendagboek als het dragen van de accelerometer. Het voordeel van het invullen van het activiteitendagboek is dat kinderen educatie en feedback krijgen over de intensiteit van de activiteit. Een accelerometer is gemakkelijk te gebruiken, omdat men niets hoeft te doen nadat men deze heeft bevestigd.

Dit onderzoek toonde aan dat 1 week accelerometer metingen nodig zijn en tenminste 13 dagen van een activiteitendagboek om fysieke activiteit betrouwbaar te meten op groepsniveau. Op individueel niveau diende de accelerometer bijna 3 weken gedragen te worden en het activiteitendagboek 5 weken te worden ingevuld. Men kan zich voorstellen dat dit lastig is vol te houden en het gemakkelijk wordt vergeten. Omdat het activiteitenpatroon over de week verschilt is het van belang om verschillende dagen van de week te meten (zowel doordeweekse dagen als weekenddagen).

Voor de lange termijneffecten van bewegen, moeten kinderen met een chronische aandoening meer gestimuleerd worden om fysiek actief te zijn. In de **hoofdstukken 3 en 4** wordt beschreven dat er maar een klein percentage kinderen met JIA en kinderen na levertransplantatie voldoet aan de Nederlandse Beweegrichtlijn. Voor kinderen met een chronische aandoening is het soms lastig om deel te nemen aan reguliere sportprogramma's. Hoewel er specifieke trainingsgroepen zijn voor

kinderen met chronische aandoeningen, is de reisafstand vaak een beperkende factor. In **hoofdstuk 6** wordt de haalbaarheid, veiligheid en de effectiviteit van een fysiek trainingsprogramma beschreven bij 26 kinderen met juveniele dermatomyositis gedurende 12 weken. De kinderen ontvingen thuis een loopband. De training bestond uit wandelen/hardlopen op de loopband en spierkrachttraining door middel van bijvoorbeeld opdrukken en sit ups. De kinderen trainden op hun eigen niveau en zij werden 1 keer per 2 weken thuis begeleid door een onderzoeker. De kinderen konden het programma goed uitvoeren en er waren geen aanwijzingen dat de training ziekteactiviteit uitlokt. Verder verbeterde de aerobe fitheid, de spierfunctie en functionele vaardigheden, welke 12 weken na het beëindigen van het programma nog aanwezig waren. Kortom, training is van toegevoegde waarde, maar er werd geen effect gevonden op het verbeteren van fysieke activiteiten.

Hoofdstuk 7 beschrijft het onderzoek van een cognitief gedragsmatig internet programma om de fysieke activiteit en fysieke fitheid bij kinderen met JIA te bevorderen. Het betrof een 14 weken durend programma welke werd aangeboden via internet en daarnaast bestond uit 4 groepssessies voor de ouders en kinderen. Gedurende het programma kwamen verschillende thema's aan bod zoals zelfeffectiviteit t.a.v. bewegen, obstakels die weerhouden om te gaan bewegen, educatie over JIA en bewegen, vermoeidheid, energie management en de voordelen van bewegen.

Kinderen en ouders vonden het een leuk en leerzaam programma. De meerderheid van de kinderen voltooide het programma. Er werden geen verschillen gevonden tussen de interventie- en controlegroep, maar in de interventiegroep verbeterde de tijd besteed in matig intensieve activiteiten en de fysieke fitheid. Bovendien nam het schoolverzuim af in de interventiegroep en verbeterde de participatie in schoolgym. De verbeteringen bleven 12 maanden nadat het programma was afgelopen, en de kinderen die in de winter aan het programma begonnen, verbeterden meer dan de groep die in de zomer begon.

In **hoofdstuk 8** worden de meest opmerkelijke bevindingen van dit proefschrift samengevat en besproken. Kinderen met een chronische aandoening worden geconfronteerd met een lagere kwaliteit van leven dan gezonde kinderen, wat verbeterd zou kunnen worden door fysieke activiteit en gezondheid gerelateerde fitheid te verbeteren. De medische behandeling van verschillende chronische

aandoeningen bij kinderen blijft verbeteren en fysieke activiteit is over het algemeen veilig bij chronische aandoeningen. Fysieke activiteit heeft voordelen voor de groei, ontwikkeling en algehele gezondheid van kinderen. Daarom moet fysieke activiteit niet over het hoofd gezien worden in de behandeling van kinderen met een chronische aandoening.

Het stimuleren van fysieke activiteit voor gezondheidsvoordelen is een uitdaging waarbij de intensiteit en de duur van bewegen belangrijk zijn, maar moeilijk objectief te meten zijn. Men moet er rekening mee houden dat fysieke activiteiten de juiste motorische vaardigheden vereisen voor alle kinderen om deel te nemen. De beste manier om fysieke activiteit te verbeteren bij kinderen met chronische aandoeningen is nog steeds niet duidelijk, maar methoden en interventies moeten gericht zijn op de specifieke problemen en omstandigheden van de doelpopulatie. Het verbeteren van motorische tekortkomingen van kinderen met een levertransplantatie is belangrijk, maar is mogelijk minder relevant voor andere chronisch zieke populaties. Het combineren van een op internet gebaseerd cognitief gedragsmatig interventie programma met een trainingsprogramma, rekening houdend met de leeftijd van de kinderen, kan de fysieke activiteit verbeteren met de daaraan gekoppelde gezondheidsvoordelen, maar verdere evaluatie van dergelijk programma's is noodzakelijk.

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CURRICULUM VITAE

Joyce Bos werd geboren op 24 februari 1979 te Dronten. In 1997 behaalde zij haar VWO diploma aan het Ichtus College te Kampen. Na het behalen van haar propedeuse Pedagogiek aan de Rijksuniversiteit Groningen in 1998, is ze begonnen met haar studie Bewegingswetenschappen, die ze in 2001 heeft afgerond. Aansluitend heeft ze de opleiding Fysiotherapie gevolgd aan de Hogeschool Utrecht, welke is afgerond in 2004. In 2005 was zij werkzaam als fysiotherapeut op de mythylschool in Zwolle en in 2007 heeft ze de overstap gemaakt om als fysiotherapeut te gaan werken in het Universitair Medisch Centrum te Groningen. Naast haar werkzaamheden heeft zij in de periode 2005 tot 2008 de opleiding tot kinderfysiotherapeut aan de Transfergroep Rotterdam gevolgd en afgerond.

In 2014 is ze begonnen met de opleiding master physician assistant aan de Hanzehogeschool Groningen. In 2017 behaalde zij hiervoor haar diploma (cum laude).

Momenteel is zij werkzaam als physician assistant op de afdeling orthopedie van het Universitair Medisch Centrum Groningen en is zij moeder van twee kinderen.

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* Joint first co-author

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