

# The Utrecht Approach to Exercise in Chronic Childhood Conditions: The Decade in Review

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**Purpose:** To summarize and discuss current evidence and understanding of clinical pediatric exercise physiology focusing on the work the research group at Utrecht and others have performed in the last decade in a variety of chronic childhood conditions as a continuation of the legacy of Dr Bar-Or. **Key Points:** The report discusses current research findings on the cardiopulmonary exercise performance of children (and adolescents) with juvenile idiopathic arthritis, osteogenesis imperfecta, achondroplasia, hemophilia, cerebral palsy, spina bifida, cystic fibrosis, and childhood cancer. Exercise recommendations and contraindications are provided for each condition. Implications for clinical practice and future research in this area are discussed for each of the chronic conditions presented. **Clinical Implications:** The authors provide a basic framework for developing an individual and/or disease-specific training program, introduce the physical activity pyramid, and recommend a core set of clinical measures to be used in clinical research. (*Pediatr Phys Ther* 2011;23:2–14) **Key words:** achondroplasia, adolescent, cancer, cerebral palsy, child, chronic disease, cystic fibrosis, exercise, exercise therapy, hemophilia, juvenile idiopathic arthritis, osteogenesis imperfecta, spina bifida

## INTRODUCTION

Dr Oded Bar-Or, one of the founding fathers of pediatric exercise physiology, recognized the need to study the benefits and risks of exercise for children with chronic diseases. His textbooks *Pediatric Sports Medicine for the Practitioner*<sup>1</sup> and *Pediatric Exercise Medicine*<sup>2</sup> have served and inspired many clinical pediatric exercise experts in

continuing his scientific legacy. As a result, pediatric health professionals now acknowledge the utility of exercise and exercise testing in diagnosis, treatment, and the primary and secondary prevention of chronic childhood conditions. Exercise testing has also been acknowledged as a useful tool in the monitoring of disease states and in assessing response to therapy.

Physical fitness is a principal concept in clinical exercise physiology and is a multidimensional concept that has been defined as a set of attributes that people possess or achieve to perform physical activity.<sup>3</sup> In current pediatric research, physical fitness has become synonymous with cardiorespiratory or aerobic fitness. In general, aerobic fitness is expressed as maximal oxygen uptake ( $\dot{V}O_{2max}$ ) and is widely recognized as the best single measure of a person's aerobic fitness.<sup>4</sup> Maximal oxygen uptake conventionally implies the existence of a  $\dot{V}O_2$  plateau. However, this response is not typical of children and adolescents<sup>5,6</sup> and so it has gradually become more common to use the term  $\dot{V}O_{2peak}$ , being the highest  $\dot{V}O_2$  elicited during an exercise test to voluntary exhaustion, to describe the aerobic fitness of children.<sup>7</sup>

As opposed to children without disease or chronic illness, children with chronic illness are often restricted in their participation in physical activities and sports

0898-5669/110/2301-0002

Pediatric Physical Therapy

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**Grant Support:** Over the past 10 years, support for the work reported here was provided by Dutch Arthritis Association, Stichting BIO kinderrevalidatie, Johanna Kinderfonds, Baxter Netherlands BV, Dr W. M. Phelps Foundation, The Wilhelmina Children's Hospital Foundation, Scientific College Physiotherapy of the Royal Dutch Society for Physical Therapy, Stichting National Fonds Tegen Kanker, Stichting ROPARUN, and ACARE/Alpe d'Hu6 (Dutch Cancer Foundation).

DOI: 10.1097/PEP.0b013e318208cb22

programs as a consequence of real or perceived limitations imposed by their condition. The chronic condition itself often causes hypoactivity, which leads to a deconditioning effect, a reduction in functional ability, and a downward spiral of further hypoactivity.<sup>2</sup> Children who are hypoactive are also felt to be at high risk of a variety of health conditions associated with a sedentary lifestyle (eg, cardiovascular conditions, obesity, and pre-diabetes). However, still little is known about physical fitness and response to exercise interventions in chronic pediatric conditions.

The aim of this article is to summarize and discuss some of the current evidence and understanding of clinical pediatric exercise physiology focusing on the work our research group and others have performed in the last decade in a variety of chronic conditions as a continuation of Dr Bar-Or's legacy. In addition, implications for clinical practice and future research in this area are discussed.

## JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis (JIA) is one of the most common chronic illnesses of childhood, characterized by joint swelling, pain, stiffness, and fatigue. Juvenile idiopathic arthritis is a disease of unknown etiology that begins before 16 years of age and persists for at least 6 weeks. Research concerning exercise in children with rheumatic conditions, such as JIA, supports the inclusion of exercise capacity as an outcome measure for pediatric rheumatology research and clinical practice. An increasing body of research indicates significant impairment in aerobic fitness and muscle strength in children with JIA compared with peers who are healthy, presumably as a result of the direct effect of disease on the body and subsequent decreased physical activity.<sup>8</sup>

Recent studies from our group investigated measures of fitness in a large cohort ( $n = 87$ ) of children with JIA.<sup>9,10</sup> These studies, which are the largest yet published in JIA, showed significant impairments in aerobic (69.8% of predicted  $\dot{V}O_{2peak}$ ) and anaerobic capacity (66.7% and 65.5% of predicted mean and peak power, respectively) in most patients with JIA compared with peers who do not have the condition. In the cohort of children with JIA, 95% of all subjects had a lower aerobic capacity and 94% had a lower anaerobic capacity compared to age- and sex-matched reference values, suggesting that deconditioning is an almost universal problem in JIA.<sup>10</sup>

Until recently, several research questions remained unanswered, including the influence of disease activity, severity, duration, and JIA subtype on exercise capacity. In the studies mentioned earlier, we found little difference in fitness levels between patients with active disease requiring ongoing therapy and those who were in clinical remission and off medication.<sup>9,10</sup> These findings support the current opinion that exercise capacity is not significantly related to disease status in JIA. The results of the studies mentioned earlier also suggest that gender

and disease subtype seem to be more critical than either disease activity or duration with the largest deficits in exercise capacity in children with rheumatoid factor positive polyarticular-onset JIA, and the smallest impairments in those with persistent oligoarticular-onset JIA.<sup>10</sup> In addition, our results show that aerobic and especially anaerobic capacity are more impaired in girls than in boys compared to age- and sex-matched peers, making girls with JIA an important target group for exercise interventions. Furthermore, our findings of significant impairment of exercise capacity in adolescent patients challenge any notion that children "outgrow" their arthritis or recover their functional ability simply by getting older.<sup>9</sup>

The most recent systematic review concerning the efficacy of exercise therapy in children with JIA yielded no clinically important or statistically significant evidence that exercise therapy can improve functional ability, quality of life, aerobic capacity, or pain ( $P = .036$ ,  $P = .12$ ,  $P = .59$ , and  $P = .09$ , respectively).<sup>11</sup> Both included and excluded studies of exercise interventions in JIA identified through this systematic review were all consistent regarding the finding that short-term detrimental effects of exercise therapy, particularly a flare of arthritis, were not seen in any study. Another important observation from the review was the large variety of outcome measures used by authors of the included studies making interpretation and comparison difficult and indicating the need for standardization of outcome measures used in trials.

When defining individual training programs, it is important to know whether a patient's aerobic or anaerobic capacity is most affected. One tool that may offer valuable insight into this question for an individual patient is the anaerobic-to-aerobic power ratio. We studied this ratio in 62 patients with JIA and determined whether there were differences based on disease-onset type and compared age-related changes in the power ratio.<sup>12</sup> The results indicated that although both aerobic and anaerobic capacities were significantly reduced ( $P = .000$  and  $P = .003$ , respectively), both mean and peak anaerobic-to-aerobic power ratios were no different between children with JIA and a control group of children without JIA, indicating that aerobic and anaerobic capacity were equally impaired in this population. Moreover, there were no statistically significant differences between subgroups of JIA in mean and peak ratios.<sup>12</sup> This indicates that training programs need to include a combination of aerobic and anaerobic training to provide the greatest benefit. This study also confirmed a normal age-related increase in the power ratios in the JIA population.

In conclusion, we feel that there is no universally accepted approach for the assessment and exercise management of children with JIA. We first need to understand the effect of each disease subtype on the different components of physical fitness and the effects of these impairments on functional performance. Furthermore, a standardized core set of outcome measurements for exercise research in JIA is needed. Exercise recommendations and contraindications are provided in Table 1.

**TABLE 1**

Exercise Recommendations and Contraindications for Children With JIA

Recommendations for Children With JIA	Contraindications for Children With JIA
May safely participate in physical activities or sports without risking disease exacerbation. <sup>13</sup>	Should not participate in any physical activity while febrile.
Those with moderate to severe impairment should tailor their activities to lie within their own pain limits.	Should not participate in physical activities or sports that temporally increase joint pain and/or excessive swelling.
May benefit from a combination of moderate aerobic as well as anaerobic, flexibility, and strengthening training. <sup>12,13</sup>	Children who experience severe osteoporosis should avoid contact sports.
Those prescribing exercise programs to children with JIA must appreciate the differences between JIA subtypes as there is large variability in fitness between subtypes. <sup>10</sup>	

Abbreviation: JIA, juvenile idiopathic arthritis.

## OSTEOGENESIS IMPERFECTA

Osteogenesis imperfecta (OI) is a congenital connective tissue disorder characterized by bone fragility and osteopenia. The biochemical basis of the disorder in most cases involves a quantitative abnormality, a qualitative abnormality, or both in the biosynthesis of type I collagen, the principal organic component of the skeleton.<sup>14</sup> Very little work has been undertaken in the field of physical fitness in patients with OI to date. Our research group was the first to study the physical fitness in children with OI type I (the mildest form of OI)<sup>15</sup> and found that aerobic capacity (expressed in  $\dot{V}O_{2peak}$  and  $\dot{V}O_{2peak}/kg$ ) as well as muscle strength was significantly lower than that of peers without OI. ( $P \leq .01$  for all values). Muscle atrophy and deconditioning are probably the primary causes of the decreased aerobic capacity in this population. However, it is not clear whether the reduced aerobic capacity is a consequence of a hypoactive lifestyle or a specific consequence of the impaired muscle collagen synthesis.<sup>15</sup>

Children with mild to moderate forms of OI seem to be primarily restricted by a reduced aerobic capacity and reduced ability to generate muscle force,<sup>15,16</sup> rather than by cardiopulmonary limitations. Evidence for circulatory abnormalities was not found in our studies<sup>15,16</sup> even though symptomatic mitral and aortic valve insufficiency in OI has been reported incidentally; the incidence and prevalence of heart disease in at least OI type I have not been published.<sup>16,17</sup>

In addition to the direct effects of the disease, for example, impaired bone development and impaired skeletal, cardiac, and pulmonary muscle tissue, there are striking indirect factors. Fear of fractures is the most frequently heard explanation for not participating in sports

and other physical activities, often promoted by parents and physicians in the interests of safety.<sup>18</sup> This protective attitude may result in an unnecessarily hypoactive lifestyle and physical deconditioning. Van Brussel et al<sup>16</sup> found a 12-week individual and supervised exercise training program in children with OI types I and IV to be safe and effective. They observed statistically significant improvements in aerobic capacity by 18%, muscle strength by 12%, and clinically relevant improvements in perceived fatigue ( $P = .068$ ).<sup>16</sup>

The general recommendation for children and young people with these types of OI is to actively encourage a physical active lifestyle, although contact sports and physical activities with sudden rotation moments of the joints are strongly discouraged. Further studies are needed to address the safety and efficacy of exercise testing and training in children with other (more severe and/or wheelchair bound) types of OI. Exercise recommendations and contraindications are provided in Table 2.

## ACHONDROPLASIA

Achondroplasia is the most common and well-known skeletal dysplasia, with an incidence of 1 in 25 000 to 40 000 births.<sup>19</sup> This type of dwarfism is characterized by a disproportional shortening of the proximal limbs in combination with a near-normal trunk length. The disturbed growth related to achondroplasia can influence functional ability and aerobic capacity. To our knowledge, the work of Takken et al<sup>20</sup> is the only study of physical fitness in children with achondroplasia. The authors found that the aerobic capacity and muscle strength in this population were significantly reduced compared to age- and sex-matched reference values ( $P < .001$  and  $P < .01$ , respectively).<sup>20</sup> This reduction in aerobic capacity cannot be easily explained by short stature as no significant correlation was found between these 2 variables. In fact, these children showed a significant higher aerobic capacity compared with height-matched reference values, as a result of a higher muscle mass for a given height compared to subjects without achondroplasia. Furthermore, the authors observed that subjects with

**TABLE 2**

Exercise Recommendations and Contraindications for Children With OI

Recommendations for Children With OI Type I and IV	Contraindications for Children With OI
Promote a physical active lifestyle in which participation in safe activities is encouraged and sidelining due to unnecessary fear of injury is reduced. <sup>16</sup>	Should not participate in contact sports.
Supervised moderate aerobic training in combination with strengthening training without weights (or only weights < 1 kg). <sup>16</sup>	Should not participate in physical activities with sudden rotation moments.
	Should not participate in any forms of intense interval training.

Abbreviation: OI, osteogenesis imperfecta.

achondroplasia required a higher breathing rate for the uptake of 1 L of oxygen compared to age- and sex-matched reference values, which is most likely the result of a reduced vital capacity<sup>21,22</sup> and lower tidal volume being compensated by a higher breathing frequency with higher ventilation of alveolar dead space resulting in lower ventilatory efficiency. Subjects with achondroplasia also had a higher heart rate for a given oxygen uptake compared to age- and sex-matched reference values, implying that they may have a reduced cardiac stroke volume during exercise as a result of their small thoracic volume. In addition, children with achondroplasia showed reduced muscle strength in almost all muscle groups compared with peers probably as a result of a combination of abnormal musculoskeletal proportion and altered biomechanics coupled with reduced neuromuscular coordination. Children with achondroplasia are at high risk of obesity<sup>23,24</sup> and other long-term effects of excess weight (eg, cardiovascular effects). In fact, cardiovascular disease has been identified as a major risk factor for mortality in young adults with achondroplasia and life expectancy is reduced by 10 years in subjects with achondroplasia as a result.<sup>25</sup> Thus, careful attention needs to be paid to the energy balance of children with this condition. Future studies should develop an appropriate activity program with acceptable physical activities to increase energy expenditure and improve the physical fitness in this population.<sup>20</sup> Improving physical fitness and physical activity levels as well as reducing obesity may help to reduce cardiovascular risk factors and thus improve survival in these subjects. Exercise recommendations and contraindications are provided in Table 3.

## HEMOPHILIA

Hemophilia is an x-linked inherited recessive bleeding disorder that is characterized by a deficiency of clotting factor VIII (classic hemophilia or hemophilia A) or IX (hemophilia B). The severity of the disease is graded according to the level of clotting factor present (mild 5%-40%, moderate 1%-5%, and severe <1%). Patients with low levels of clotting factors are at risk of spontaneous bleeds, particularly into muscles and joints; the latter may result in hemophilic arthropathy especially if there are repeated haemarthroses.<sup>26</sup> Where available, treatment with

replacement clotting factors has become the standard therapy in patients with severe disease or moderate disease in certain cases. Modern clotting factors are produced by recombinant techniques and their widespread use has led to a significant reduction in the development of arthropathy. Along with this advancement in treatment, there has been an improvement in function with treated patients showing near-normal physical ability and motor performance.<sup>27,28</sup> Despite this advancement, aerobic capacity ( $\dot{V}O_{2peak}$ ) is still slightly reduced in this group of children<sup>27</sup> but is significantly better than that reported in the study of Koch et al<sup>29</sup> published 25 years ago before routine prophylactic therapy.

Patients treated prophylactically are generally less restricted in their participation in sports and physical activities, some of which were previously perceived as being dangerous (such as soccer). As a result, these patients engage more and more in diverse sports activities<sup>30,31</sup> and obtain the expected benefits in physical fitness. The consequences of this increased participation might be an increase in sports-related injuries; however, data on the number of bleeds as a result of sports participation are scarce. A recent study by Tiktinsky et al<sup>32</sup> showed that participation in vigorous activities increased the proportion of bleeds resulting from trauma (eg, a collision) but did not increase the total number of bleeds. More data are needed to determine the level of risk to which children engaging in vigorous physical activity such as competitive soccer might be subjected.

Nonetheless, the protective effects of exercise and training are postulated to include the possibility that physical activity could improve muscle strength consequently protecting patients from bleeding episodes.<sup>33</sup> Furthermore, exercise has been shown to acutely increase levels of clotting factors in moderately affected patients.<sup>34</sup> While promising, these last 2 studies consisted only of small sample sizes, making additional research in this area warranted. Exercise recommendations and contraindications are provided in Table 4.

**TABLE 3**

Exercise Recommendations and Contraindications for Children With Achondroplasia

Recommendations for Children With Achondroplasia	Contraindications for Children With Achondroplasia
Promote a more physical active lifestyle. May benefit from moderate aerobic training. <sup>19</sup>	Should not participate in individual physical activities when suffering from severe neurological complications.

**TABLE 4**

Exercise Recommendations and Contraindications for Children With Hemophilia

Recommendations for Children With Hemophilia <sup>a</sup>	Contraindications for Children With Hemophilia
Promote participation in regular physical activity and sports, particularly sports considered low risk for hemorrhage (such as swimming, cycling, dancing, or tennis). <sup>2</sup>	Should not participate in high-risk sports (such as boxing, wrestling, competitive soccer, or hockey).
Individualize selection of appropriate physical activities, taking into consideration bleeding tendency, nature of sport, and history of bleeding episodes. <sup>2</sup>	Should not participate in any severe physical activities when not treated prophylactically.

<sup>a</sup>Only applicable when children are treated prophylactically.

## CEREBRAL PALSY

Cerebral palsy (CP) describes a group of nonprogressive disturbances that occur in the developing fetal or infant brain resulting in permanent disorders in movement and posture. The resulting primary motor impairments, such as impaired selective voluntary muscle control, muscle paresis, and spasticity, will limit performance in exercise tests and training exercises.<sup>35</sup> It is known that children with spastic CP often have impaired physical fitness ( $\dot{V}O_{2\text{peak}}$ , anaerobic aerobic muscle power, and muscle strength)<sup>36,37</sup> that compromises their daily function and physical activity.

In a recent systematic review concerning exercise programs for children with CP, the authors found that there were only 5 trials investigating the efficacy of exercise training in this population.<sup>38</sup> Many of the included studies suffered from inadequate control groups. Nonetheless, from these data, it seems that children with CP may benefit from exercise programs that focus on physical fitness with evidence of increased muscle strength and aerobic capacity. Despite these findings, more evidence is necessary to determine whether exercise training will make substantial or sustained improvements in daily function, habitual activity, or the quality of life of children with CP. To our knowledge, the study by Verschuren et al<sup>39</sup> is the first randomized, multicenter, clinical trial studying the effects of “functional exercises,” combining 3 health-related fitness elements in 65 participants with CP. The authors used a circuit training program that contained functional tasks designed to elicit both aerobic and anaerobic training responses. As in other studies, participants in this trial showed significant improvement in aerobic and anaerobic capacity ( $P < .001$  and  $P = .004$ , respectively), as well as in agility and muscle strength (both with  $P \leq .001$ ), as indicated by a series of validated field tests.<sup>40,41</sup> In addition, a significant improvement in participation and health-related quality of life of the subjects in the training group was found compared with the subjects who received standard care only.<sup>39</sup> However, 4 months postintervention, the subjects’ posttraining scores had lowered in most measures but still remained significantly above baseline values.

The same authors investigated the relationship between physical fitness and gross motor capacity in children with CP who were classified in Gross Motor Function Classification System levels I or III.<sup>42</sup> Validated field tests were used to determine physical fitness and moderate to high correlations were found between performance-related fitness components and gross motor activities in these children.<sup>42</sup> In a child with neuromuscular disease, it is muscle function rather than aerobic capacity that is primarily affected, which subsequently limits the child’s physical capacity.<sup>43</sup> For children and adolescents with CP, exercise training interventions are often developed to improve their gross motor capacity. Therefore, when designing an exercise program for this population, it is

important to realize that physical fitness components are related to gross motor capacity.<sup>40</sup> On the basis of the study of Verschuren et al,<sup>39</sup> we recommend considering functional muscle strength, agility, anaerobic components, and balance in the training repertoire of children and adolescents with CP and not just a focus on increasing aerobic capacity. Aerobic capacity remains a strong indicator of health in adulthood<sup>44</sup>; however, for children with CP, we recommend a shift from “adult type” moderate-intensity continuous endurance exercise programs (eg, 20-minute walk/run on a treadmill) to high-intensity interval exercise programs. During high-intensity exercises, short bursts of exercise are interchanged with periods of active rest. It is our experience that children enjoy these activities more than endurance exercises<sup>45</sup> and these interval-training exercises are effective in improving anaerobic and aerobic exercise capacity.<sup>45</sup> Furthermore, we feel that future studies should develop and investigate the effects of (family-based) physical activity promotion programs for children with CP. These programs might be effective in long-term sustained effects of formal exercise programs. Exercise recommendations and contraindications are provided in Table 5.

## SPINA BIFIDA

Spina bifida (SB) is the most common congenital deformity of the neural tube, with an incidence of approximately 1 per 1000 live births.<sup>46</sup> As a result of the neural tube deformity, patients experience a variety of deficits in cognition, motor function, sensory function, and bowel and bladder function. The severity of these deficits is largely determined by both the type and level of lesion of the SB. In 80% of children with the more serious open type of SB (spina bifida aperta), hydrocephalus and a Chiari II malformation (a malformation in the brainstem) is present. Because of advances in medical management, mortality rates have decreased in past decades and 75% to 80% of children with SB now live to be adults. This

**TABLE 5**

Exercise Recommendations and Contraindications for Children With CP

Recommendations for Children With CP	Contraindications for Children With CP
Promote participation in regular physical activity and sports. <sup>39</sup>	Should not participate in physical activities or sport when the child has uncontrolled epilepsy.
General training repertoire should include functional muscle strengthening, agility, anaerobic components, and balance. <sup>39</sup>	Should not participate in physical activities or sport when the child has severe osteoporosis.
The focus of physical training should include high-intensity interval training interchanged with periods of active rest. <sup>39</sup>	

Abbreviation: CP, cerebral palsy.

necessitates a new treatment paradigm for these patients from childhood through adolescence into adulthood with attention not only to the physical disorder but also to the (preventable) health risks, functional and social consequences of the disorder, and lifestyle issues. Several studies have shown that children, adolescents, and young adults with SB are less physically active resulting in obesity, reduced health-related quality of life, and reduced levels of physical fitness.<sup>47-50</sup> A recent study of a large sample of children and adults with SB showed that adolescents with a lower lesion level (sacral level) are faced with an increased obesity risk.<sup>51</sup> Furthermore, the emerging interest in physical fitness, physical activity, and implementation of life-style programs in children, adolescents, and young adults with SB emphasizes the need to develop appropriate outcome measures to monitor change in these areas.

Our research group studied the fitness levels of 23 ambulatory children with SB and showed impaired aerobic capacity with significantly reduced  $\dot{V}O_{2peak}$  levels ( $P \leq .05$ ) as well as muscle strength ( $P = .01$ ).<sup>50,52</sup> Interestingly, muscle strength was impaired even in muscle groups innervated above the spinal lesion level, indicating generalized muscle weakness. Many children with SB also demonstrated low peak heart rate values, which puts into question the validity of a treadmill test in this population of ambulatory SB patients; however, we recently tested the validity of maximal treadmill testing in children with SB, using a graded treadmill test with an additional supramaximal verification phase,<sup>53</sup> and found treadmill testing to be a valid procedure in these patients.

Our research group also evaluated the test-retest reproducibility of energy cost of locomotion in children with SB during a 6-minute walk test. Intraclass correlations showed good reliability for almost all calculated parameters. However, agreement between the parameters was somewhat lower, meaning that a change of 20% to 25% from baseline may be necessary to obtain a meaningful improvement for an individual patient.<sup>54</sup> Interestingly, walking speed during the 6-minute walk test was one of the most reproducible parameters with the highest agreement, making this parameter extremely suitable for clinicians to use in the examination of children with SB.

To date there are only 2 small nonrandomized studies describing the effects of interventions aimed at improving fitness levels in children and adolescents with SB.<sup>55,56</sup> Therefore, future studies should focus upon large, randomized, controlled studies to permit stronger statements concerning the efficacy of exercise training and energy cost of locomotion in this population. Exercise recommendations and contraindications are provided in Table 6.

## CYSTIC FIBROSIS

Cystic fibrosis (CF) is the most common life-shortening genetic disease in the white population. Cystic fibrosis is inherited as an autosomal recessive disease and has an incidence of 1 in every 2500 white life births, 1 in 17 000 blacks and 1 in 90 000 Asians.<sup>58</sup> With the

**TABLE 6**

Exercise Recommendations and Contraindications for Children With SB

Recommendations for Children With SB	Contraindications for Children With SB
Promote participation in regular physical activity and sports for fitness and prevention of excessive weight. <sup>49</sup>	Should not participate in physical activities or sport when the child has had recent surgery
Aerobic, anaerobic, and strengthening training may all be beneficial. <sup>53</sup>	Should not participate in physical activities or sport when the child has progressive back pain
When aiming to improve ambulation, a home-based treadmill training program has been proven safe and effective. <sup>57</sup>	Should not participate in physical activities or sport when the child has poor fitting orthoses

Abbreviation: SB, spina bifida.

current understanding of the pathology and significant improvements in diagnosis and treatment, the median life expectancy for children born after 1990 is 40 years.<sup>59</sup>

Reduced exercise capacity is a hallmark of disease progression in patients with CF and is associated with many factors including decreased muscle mass, declining lung function, reduced habitual physical activity levels, malnutrition, and/or an inefficient use of oxygen as energy substrate.<sup>60</sup> From the early teenage years, patients with CF demonstrate a continuous decline in aerobic exercise capacity ( $\dot{V}O_{2peak}$ ) compared with subjects who do not have CF. This decline in aerobic exercise capacity is probably related to a delay in maturation and ongoing disease progression.<sup>61</sup> Higher levels of aerobic capacity have been reported to be important for survival in patients with CF,<sup>62</sup> and there is some evidence that both aerobic training and muscle strength training can positively affect pulmonary function, aerobic capacity, and muscle strength.<sup>63,64</sup>

Our research group has investigated the effects of a long-term (6 months) home-based bicycle training program in 14 children, aged 10 to 17 years, with mild to moderate symptoms of CF. Subjects were prescribed an exercise program with 20 minutes of cycling on an exercise bike at a work rate aimed at achieving a heart rate of 140 to 160 beats per minute, 5 times a week. This frequency and moderate intensity are at the level at which health benefits were expected and reflect the traditional adult-based approach to exercise prescription to improve fitness. Although the program was effective in improving fitness, the acceptability of the program was low.

In a follow-up study, we investigated the effects of a 12-week "anaerobic" (interval) training program led by a community pediatric physical therapist.<sup>65</sup> This intermittent high-intensity exercise reflects children's natural physical activity patterns and was more attractive for children and improved exercise adherence. Moreover, significant improvements in aerobic capacity, anaerobic capacity, and health-related quality of life ( $P < .05$ ,  $P < .001$ , and  $P = .001$ , respectively) were observed.<sup>65</sup> These findings

were echoed by a review from van Doorn,<sup>64</sup> indicating that short-term, in-hospital, aerobic, or strength training significantly improves pulmonary function, muscle strength, and aerobic capacity. The review of Bradley and Moran<sup>66</sup> also suggests that exercise training programs are effective in improving physiological measurements and quality of life in children with CF, and evidence is available for improving pulmonary function also. Home-based training with regular contacts with an exercise specialist can produce improvements in exercise testing measures in children with CF.<sup>67,68</sup> However, the improvements become less dramatic as supervision decreases, programs become home-based, and the training period lengthens. Therefore, we recommend formal training programs by community pediatric physical therapists inducing behavior change toward exercise as the main goal and feel that such approaches may reduce the need for “constant supervision.”

Conclusions about the efficacy of physical training in CF are limited by the small size, short duration, and incomplete reporting of most of the studies.<sup>66</sup> Further research is needed to assess comprehensively the benefits of exercise programs in people with CF and the relative benefits of the addition of aerobic and anaerobic exercise programs. There is great potential for future research focused on designing exercise programs for children with CF using a combination of modalities as well as the inclusion of respiratory muscle training.<sup>69</sup> Different types of exercise programs and/or increasing habitual physical activity should become an integral part of the treatment regimen for CF. Physical therapists should consider factors that are related to exercise compliance including social support, perceptions of competency and self-esteem, enjoyment of activity, and availability of a variety of activities to facilitate successful long-term participation. Exercise recommendations and contraindications are provided in Table 7.

**TABLE 7**

Exercise Recommendations and Contraindications for Children With CF

Recommendations for Children With CF	Contraindications for Children With CF
Promote a physical active lifestyle. <sup>13</sup>	Should not participate in any physical activity while febrile.
Individualized exercise programs including moderate strength training. <sup>64,65</sup>	Should not continue in physical activities when oxygen saturation falls below 90%.
Exercise testing to identify maximal heart rate, levels of oxygen desaturation, and ventilation limits should be undertaken before and during any training program to assess efficacy. <sup>13</sup>	Should not participate in moderate- to high-intensity activities in case of cardiac dysfunction. Should not participate in scuba diving. Children with enlarged spleen or diseased liver should avoid contact or collision sports.

Abbreviation: CF, cystic fibrosis.

## CHILDHOOD CANCER

*Childhood cancer* is defined as cancer developed among children aged 0 to 19 years. Statistically the occurrence of cancer during childhood is uncommon, but overall childhood cancer incidences are almost similar worldwide.<sup>70</sup> The latest epidemiology study of Linabery and Ross<sup>71</sup> describes the overall age-adjusted incidence rate of childhood cancer to be 158 per 1 000 000 person years. The 2 most common childhood cancers are leukemia (incidence rate: 41.9 per 1 000 000 person years) and central nervous system tumors (27.6 per 1 000 000 person years).

Many children, adolescents, and even young adults who have survived childhood cancer are reported to have lower aerobic capacity than subjects who haven't had the disease.<sup>72-74</sup> In addition to aerobic capacity, muscle strength and motor performance are reduced compared with those of subjects who are healthy not only during treatment of leukemia but also years after completion of therapy.<sup>73,75-77</sup> Several studies have reported lower physical activity levels in survivors of pediatric cancer than peers with no history of cancer.<sup>75,78,79</sup> A recent study that measured physical activity by accelerometry found significantly lower levels of activity ( $P \leq .001$ ) in 80 children who underwent cancer therapy when compared with peers without cancer.<sup>80</sup> Factors contributing to reduced physical activity include disease and treatment-related limitations in exercise capacity (neuromotor abnormalities, decreased pulmonary function, and cardiac dysfunction).<sup>72,81</sup> Other studies have reported impaired motor performance during and after cancer therapy.<sup>73,76,82</sup> The exact cause of this impairment is not elucidated yet.

The evidence of increased body weight and obesity in patients with and survivors of leukemia is overwhelming, while obesity also has been described in survivors of pediatric brain tumors.<sup>81,83-85</sup> In recent years, a few small studies have emerged reporting that patients and survivors of childhood cancer can safely engage in physical activities to promote physical fitness.<sup>86,87</sup>

As in the general population, prevention and treatment of excessive weight and obesity in children with cancer during and after treatment are important to reduce related physical and psychosocial morbidity and mortality. These are considered even more important in childhood cancer survivors as previous disease and treatment exposures already place them at increased risk for numerous adversities later in life, effects that may be aggravated by excessive weight. Only a few studies involving exercise in patients with childhood cancer have been performed and study groups were small. Three studies were performed, 1 during and 2 after chemotherapy treatment.<sup>86-91</sup> It is expected that children will have lower fitness levels during chemotherapy than during remission and have less energy to perform exercise because of the chemotherapy. However, when in remission, many children wish to be free of the disease and its treatment and thus lack interest in

participating in organized exercise therapy. Therefore, the feasibility of exercise programs seems to be the highest during the last phase of therapy (maintenance phase) or as soon as possible when the disease moves into remission.

Very recently a pilot study was conducted by our group, studying the feasibility of an outpatient exercise training program in children who survived cancer. For this study, a special 12-week exercise training program, “the FITstrong” training program, was developed.<sup>92</sup> From this study it was concluded that it is possible to perform exercise training in community pediatric physical therapy practices; however, several patients dropped out of the training program because they experienced an increased fatigue level after several training sessions. Moreover, parents were very protective of their children. On the basis of these findings, it was recommended to include a psychosocial program for parents and children in addition to the exercise training program. Currently, we are investigating the effects of a combined exercise training and psychosocial program for children who survive cancer in the so-called “Quality of Life in Motion” study. The available studies<sup>87–93</sup> suggest that structured, supervised exercise training might increase the functional capacity of patients with childhood cancer and children who survive cancer, with subsequent improvement of their aerobic capacity, muscle strength, functional mobility, and health-related quality of life. Limited data are available on the effects of physical exercise on bone mineral density or fat mass in children with leukemia.<sup>94</sup> Exercise recommendations and contraindications are provided in Table 8.

**TABLE 8**

Exercise Recommendations and Contraindications for Children With Cancer

Recommendations for Children With Childhood Cancer	Contraindications for Children With Childhood Cancer
Before starting physical training, extensive exercise testing by an experienced exercise physiologist is recommended for detecting and assessing potential anthracycline cardiomyopathy.	Should not participate in any physical activity while febrile and when dramatic drops in counts of hematological parameters
Follow gender- and age-specific hematological parameters (eg, white blood cells, platelets, hemoglobin, hematocrit) to establish whether physical training is safe or not (values should be in normal ranges and show no dramatic drops in counts)	Significant increased fatigue levels during training
When training is thought to be safe, start physical training in the maintenance phase of chemotherapy <sup>85</sup>	Strict assessment and monitoring in case cardiomyopathies
Moderate aerobic fitness training, combined with strength training, is safe and may be of benefit. <sup>85</sup>	Avoid exercise if severe nausea is experienced during exercise/physical training

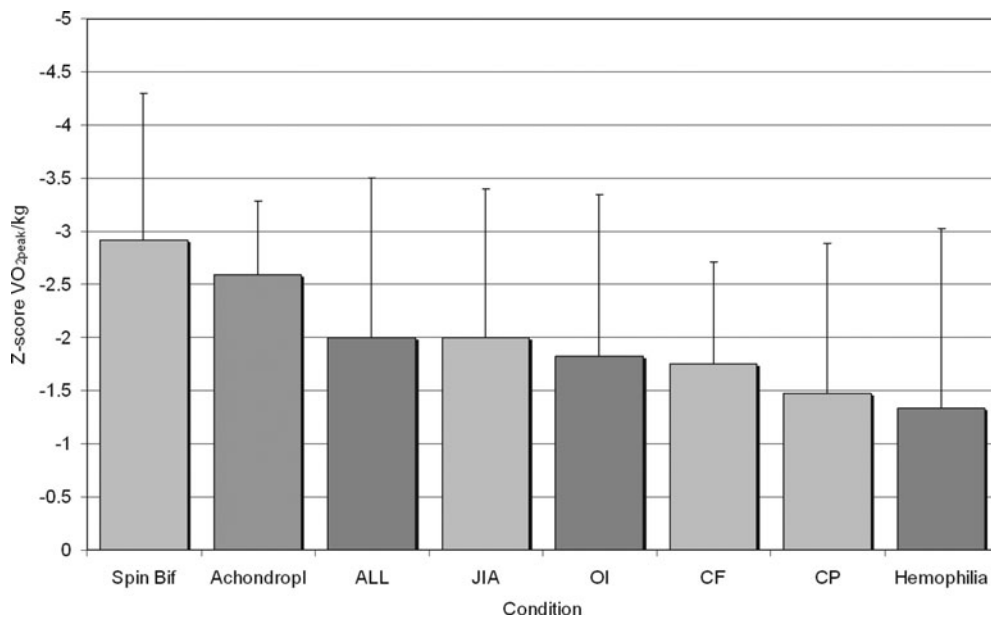
## WHAT WE HAVE LEARNED SO FAR AND FUTURE DIRECTIONS

As pediatric health professionals, we must understand the effect of each chronic condition on specific components of physical fitness and, in turn, the effects of these impairments on functional capacity. As described in this article, many children with chronic conditions have reduced levels of aerobic fitness (expressed as  $\dot{V}O_{2peak}/kg$ ). See Figure 1 for an overview. These reductions are caused by a combination of condition-related pathophysiology itself, treatment of the condition (such as certain medications), hypoactivity, and deconditioning.

Determining physical fitness levels in children with chronic medical conditions is of great clinical relevance, as this variable is a powerful predictor of mortality in people with or without disease.<sup>44,95</sup> For example, in patients with CF, reduced physical fitness is a strong predictor of mortality.<sup>96</sup> Whether the level of physical fitness during childhood also predicts the mortality in adult life remains unknown. It can be determined only by performing longitudinal studies tracking into adulthood. To date, these studies have not been performed.

Evidence demonstrates that exercise training is important for children with chronic conditions.<sup>97,98</sup> Several intervention studies show significant improvements in the physical fitness domain; however, little information is yet available on the clinical characteristics of children that may be used to predict who is likely to benefit with improvements in exercise capacity. The clinician would benefit from prediction rules for identifying which children might benefit from an exercise program and exercise guidelines on how to design a disease and child-tailored training program. The first step in this process is to determine whether the particular individual is actually physically deconditioned. When deconditioning is objectively determined possibly through exercise testing, the next step (and possibly the most important one) is to determine whether deconditioning is either due to inactivity, medication, nutritional status, or disease-related pathophysiology or due to a combination of these factors. In other words, the therapist should determine all the real and/or perceived limitations imposed by the child’s chronic condition.

It is important to realize that there are no universally accepted guidelines for children with chronic diseases. Therefore, we recommend using the so-called factors—Frequency, Intensity, Time, and Type—as a basic framework for developing an individual and/or disease-specific training program. As variations between the different factors determine the efficacy of training, the key is to determine the most important contributing factors for each child taking into account all the various anthropometric and disease-specific limitations. Nonetheless, in many children with chronic conditions, the following general pediatric factors—Frequency, Intensity, Time, and Type—can be used. Training frequency should be minimally 2 times per week; intensity should be higher than 66% of peak heart rate, lasting for 20 to 60 minutes per session, in



**Fig. 1.** Observed levels of aerobic capacity (expressed in Z scores of  $VO_{2peak}/kg$ ) from several studies from our group. Data obtained from references 10, 15, 21, 28, 41, 53, 64, and 74. For details about the populations, we refer the reader to the original publications.

which the large muscle groups have to be used. Training programs should continue for about 12 consecutive weeks. After these 12 weeks, a comprehensive reevaluation should be made.

It is important to keep in mind the possibility of higher fatigue values, slower recovery times, and slower adaptation times in these populations. Some patients may benefit from longer exercise programs, such as those with obesity for weight management or in other cases where training may help to slow down the progression of their disease.<sup>99</sup>

Type of activity should always be suited to the specific chronic condition. Furthermore, exercise should be developmentally and age-appropriate and enjoyable and involve a variety of activities.<sup>100</sup> Adherence to exercise programs depends on individual motivation and on a variety of activities. Children and adolescents are more likely to enjoy short-term, high-intensity exercises, because they usually offer the necessary variety and better mimic the usual daily activity pattern of children.<sup>101</sup> Such activities may not be appropriate for all patient groups, such as children with congenital cardiac disease. In addition to developing exercise intervention prescriptions, it is important to educate and motivate the children to be physically active and to reinforce that assessment of behavioral change characteristics is eminent.

Most children with chronic conditions will benefit from an increase in habitual activity. We have found the children's physical activity pyramid to be a helpful tool for the general prescription of physical activity in children (the children's physical activity pyramid can be found at [http://www.classbrain.com/artread/publish/article\\_31.shtml](http://www.classbrain.com/artread/publish/article_31.shtml)). The physical activity pyramid is similar to the food pyramid for nutrition. Many sports clubs, physical education classes, or extracurricular physical activity

programs are not fully equipped to have children with chronic conditions participating in their programs. Physical therapists should therefore inform not only coaches and parents about the importance of sufficient and appropriate levels of exercise for children with chronic conditions but also caregivers, health care professionals, sport trainers, and teachers.<sup>98,102</sup>

Pediatric physical therapists and other clinical pediatric exercise experts face a dilemma in prescribing exercise programs for children with chronic conditions because in various conditions exercise may improve health in part by stimulating growth factors and tissue anabolism. However, it is also known that the same process of exercise, if of sufficient intensity, can stimulate inflammatory cytokines and can lead to a catabolic state.<sup>103–106</sup> Finding the optimal level of physical activity in children and adolescents with a chronic (inflammatory) condition is difficult, because the underlying disease often is associated with increased (basal) energy expenditure, malnutrition, and inflammation, all of which can promote tissue catabolism, even at rest.<sup>107</sup> The latter illustrates the problem of implementing exercise therapy in children with a variety of inflammatory/catabolic conditions, such as arthritis, CF, and cancer. However, the role and positive effect of exercise as a therapy in children with a variety of chronic conditions are becoming increasingly recognized.<sup>107</sup>

For future research and clinical application of physical activity, standardization of outcome measures is essential. Thus we propose that a standardized core set of outcome measures be developed for each chronic childhood condition, which should be used in intervention studies. This core set might help investigators compare studies and help identify the optimal type and dose of exercise and activity. A suggestion for this core set is provided in Table 9.

**TABLE 9**

Proposed Core Set for Outcomes in Exercise Training/Activity Promotion Studies

Fitness Component	Proposed Measure
Health-related fitness <sup>a</sup>	Aerobic capacity ( $\dot{V}O_{2peak}$ ), muscle strength
Physical activity/inactivity	Directly measured (eg, pedometers, accelerometry, heart rate monitors, Global Positioning System monitors)
Health-related quality of life	Questionnaire
Fatigue	Questionnaire
Performance-related fitness <sup>b</sup>	6-Minute Walk Test, Shuttle-Sprint Test, Timed Up and Down Stairs, Timed Up and Go

<sup>a</sup>Health-related fitness is associated with the ability to perform daily activities with vigor, and the possession of traits and capacities that are associated with a low risk of premature development of inactivity-related diseases.<sup>110</sup>

<sup>b</sup>Performance-related fitness is linked typically to those attributes that are associated with performance outcomes that vary with the sport.<sup>111</sup>

The text *Physical Activity Assessment for Health-Related Research*<sup>108</sup> provides a more in-depth coverage of many outcome measures and might also be useful for clinical pediatric exercise experts; however, these outcome measures should be translated and validated before being used in studies involving children. Also, the Web site of the COMET-initiative<sup>109</sup> lists conditions for which appropriate outcomes have been identified for use in clinical trials. Furthermore, we believe that studies are needed that identify the facilitators and barriers for implementing exercise training programs and activity promotion programs in children with chronic conditions. This information might help increase adherence to these programs.

Collaboration and dissemination of knowledge is essential and thus we propose that when proven effective and safe, a detailed description of disease-specific exercise programs should be made available by investigators in the public domain (eg, on World Wide Web or a journal Web site), allowing others to synthesize the information and implement the programs freely where appropriate. This might also enhance the ongoing surveillance of these programs and establish the effectiveness of these programs in non-research settings with less highly selected patient groups. Finally, in addition to the short-term benefits, the long-term effects of well-structured exercise and training programs in children with chronic conditions should be studied, so that we can further increase our knowledge about the underlying physiological (and psychological) determinants in these conditions.

## CLINICAL BOTTOM LINES

Children with chronic conditions often show reduced fitness levels and physical activity patterns as a result of cardiovascular or neuromuscular impairment of which the etiology is diverse and often dependent on the childhood

condition involved. Determining the physical fitness levels in these children can be of clinical relevance, as this variable is a powerful predictor of mortality in adults with disease or who are healthy.<sup>44,112</sup> Whether the level of physical fitness during childhood also predicts mortality can be determined only by longitudinal studies, which have not been completed up to now. Until such time, however, it is important to understand and distinguish direct and indirect causes for the decreased levels of fitness, for possible short-, medium-, and long-term treatments. Physical training is effective and safe in most chronic conditions. Individually tailored training programs prescribed by pediatric exercise experts seem warranted, because between and within chronic conditions there can be immense differences in levels of physical stress toleration. However, we must also take factors such as sidelining, misguided fears about worsening of the disease with activity and unwarranted concerns about inability to participate into account, as we know that these factors are major contributors to reduced activity levels in children with chronic conditions. Participation in appropriate physical activities should be a part of the ongoing management of children with chronic disease and is an important part of the “normalization” process for children with chronic disease allowing integration into school and social environments.

## ACKNOWLEDGMENTS

The authors thank all colleagues and students who helped to design, perform, and analyze the cited studies from their department. We also thank Dr Davinder Singh-Grewal for the meticulous editing of the manuscript.

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