

# Are exercise programs an effective treatment for children with cystic fibrosis?



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## Why could exercise be beneficial in cystic fibrosis?

Cystic fibrosis (CF) is a genetically inherited, autosomal recessive disease that is caused by a mutation in the gene encoding the cystic fibrosis transmembrane conductance regulator protein. As a result of this deficit, multiple organs, primarily the lungs, pancreas and digestive system, become congested with thick, sticky mucus resulting in infections and inflammation. Despite advances in medical care, life expectancy remains shortened, with 85% of CF-related deaths caused by lung disease [1]. Exercise capacity in this population may be limited by reduced lung function, nutritional status, metabolic deficits and peripheral muscle function.

Extensive research into the effect of exercise training and physical activity in the healthy child has demonstrated physiological and quality-of-life benefits. Guidelines for exercise testing, prescription and training for healthy children are

also well documented. However, by comparison, there is much less evidence demonstrating that children with CF achieve the same level of benefits as their healthy peers, and guidelines for exercise are still being developed. Most available evidence relates to short-term benefits of exercise, with a particular dearth of good-quality longitudinal studies.

Current guidelines for the physiotherapy management of children and adults with CF suggest that regular exercise and physical activity be prescribed in conjunction with airway clearance and inhalation therapy (ACT) [2]. The rationale is that exercise may enhance sputum clearance [3], improve or maintain lung function [4], reduce breathlessness [5], increase aerobic capacity and muscle strength [6], and improve bone health [7] and quality of life [8]. Regular adherence to exercise and ACT is variable in both adults [9,10] and children [11], with time required to complete ACT, nutritional status and progression of the

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disease the key factors that influence exercise capacity, and willingness to participate in any form of exercise or physical activity.

A 2008 Cochrane review by Bradley and Moran evaluated the effects of exercise training in seven randomized controlled trials that involved 231 adults and children with cystic fibrosis [12]. They identified studies that examined either the short- and long-term effects of aerobic or anaerobic exercise, or a combination of both. The authors concluded that there was an insufficient number of studies published to date to clearly define the benefits of exercise in CF. However, exercise was acknowledged to be an important component of the current management of individuals with CF and should not be discouraged.

Two nonsystematic reviews have examined the effects of supervised, unsupervised and part-supervised exercise programs in children with CF in hospital-, outpatient- and home-based settings [13,14]. In addition to evaluating the effects of aerobic exercise on peak oxygen consumption ( $VO_{2Peak}$ ), high intensity anaerobic training and muscle strength training programs were also evaluated. Exercise programs produced similarly beneficial results in males and females. Endurance training was the most popular intervention, and was found to be effective at increasing lung function and  $VO_{2Peak}$ , and improving breathlessness and quality of life, while strength training improved muscle strength and size, and weight gain. High intensity anaerobic training or interval training, which involved short periods of intense exercise followed by short recovery periods, showed improvements in  $VO_{2Peak}$  and power output. The reviewers suggested that a comprehensive exercise-training program should include a combination of modalities. Supervised and in-patient programs for children with CF produced the most improvements in exercise parameters, with less dramatic effects noted in part-supervised or unsupervised programs.

#### How should exercise be prescribed in CF?

Exercise programs by design should include three core components: exercise testing, exercise prescription and exercise training. Comprehensive maximal and/or submaximal exercise tests, such as a cardiopulmonary exercise test (CPET) or functional field-based incremental walk/run tests (ISWT), should be performed to monitor for exercise-induced limitations before exercise

is prescribed, and exercise training is implemented in children with CF [15]. However, a survey of exercise testing and training programs in UK-based CF centers reported that exercise tests, such as CPET, are limited to a few specialist centers, and even they are underused [16].

The advantage of using CPET to determine a safe, individualized exercise prescription in children with CF is that the test measures gas flow,  $VO_{2Peak}$ ,  $CO_2$  production, respiratory exchange ratio, pulse oximetry and heart rate during exercise. When combined with the estimated work rate achieved during the test, variables such as anaerobic threshold and minute ventilation relative to  $CO_2$  exhalation can be calculated [17]. These outcomes are useful in determining exercise limitations such as pulmonary hypertension, exercise induced hypoxemia and cardiac arrhythmias. The results should then be used to determine target heart rates and/or ventilatory threshold exercise training ranges for the child. In the absence of CPET, field-based test results should be performed.

Based on the results of exercise tests, frequency, intensity, time and type exercise principles should be used to guide an age-appropriate, individualized exercise training program for the child. Dependent on the aims of the training program, clinicians could prescribe aerobic, anaerobic or muscle strength training or a combination of these for the child [14]. It should be noted that guidelines for exercise prescription and training in children with CF require further development.

#### What is new in children with more severe disease, and where do we go from here?

In the last 5 years there have been three novel, 12-month observational studies that have explored an alternative model of physiotherapy care in small groups of sicker children with moderate-to-severe CF. Children who have required >40 days of intravenous (iv.) antibiotic treatment in the previous year were included in the programs, and data from the intervention year were compared with the previous year's data. Each program provided regular supervised, individualized exercise training in an outpatient [18] or outreach setting [19,20], in addition to current specialist CF care.

In the 2008 Brisbane study, Black *et al.* (n = 10) demonstrated a 48% reduction in iv. antibiotic requirement, and a significant increase in lung function and 20 m ISWT scores [18]. Urquhart *et al.* (n = 12) demonstrated a 17%

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reduction in iv. antibiotic requirement and cost savings of approximately UK£66,384 to the hospital. In addition, children improved their ISWT scores, quality of life scores measured by the disease-specific Cystic Fibrosis Questionnaire (CFQ), and there was a trend towards improved lung function [19].

In our own CF unit at Great Ormond Street Hospital for Children (London, UK), the Frequent Flyer Programme (n = 16) was undertaken as a quality improvement initiative [20]. Our program showed a 25% reduction in iv. antibiotic requirement and approximately UK£113,570 cost benefit to the hospital. CPET and ISWT scores were significantly improved and the majority of children on the program maintained their lung function and growth outcomes. The children's CFQ scores showed only marginal improvements in quality of life, although an end of program questionnaire suggested that quality of life had been improved. Feedback from both children and parents was very encouraging, with families reporting that their children had been able to spend more time at home and school and experienced less of a dip in their general quality of health. Children reported they were now able to exercise at the same level or sometimes even higher than their peers.

These programs present an interesting new model of physiotherapy care focused on incorporating structured, supervised exercise programs into children's CF management. As observational studies, they should not be overinterpreted, particularly with regard to mechanism. It is plausible that the pilot programs offered clinicians an opportunity to monitor children more closely for subtle changes in their clinical status, and that it was this closer monitoring rather than the exercise intervention that led to improved outcomes. Nonetheless, the key findings from these three studies are that most subjects had a quantifiable improvement in health outcomes while on the exercise program and that a concurrent reduction in other therapies generated

savings that outweighed the cost of the exercise intervention.

The above three programs all focused on individuals with moderate-to-severe lung disease. The question then arises regarding the impact a structured program could have on subjects with milder disease, and here the evidence is currently lacking. A number of randomized trials are currently collecting data, including one European collaborative study and another study at our own center. The aim of these studies is to quantify both health improvements and the overall cost impact of extending such initiatives more widely across pediatric CF care.

In conclusion, most current evidence regarding the benefit of regular exercise in children with CF has focused on the impact of exercise upon defined surrogate variables over relatively short timescales. More recent pilot studies in subjects with more advanced disease, where the exercise intervention runs over a longer period, have implied marked improvements in a variety of outcomes, and crucially a reduction in other healthcare needs that suggest exercise could be a cost-neutral or even cost-saving intervention in selected individuals. Well-structured randomized trials in a broader range of subjects are ongoing, but until then, a CF clinician/physiotherapist is required to make a clinical judgment on the value of exercise prescription in the CF clinic. The balance of evidence currently suggests that an exercise prescription is likely to be of benefit to at least some of these patients.

#### Financial & competing interests disclosure

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