*Physical therapy*

# Exercise and physical training in cystic fibrosis

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## Background

Recently exercise has been considered a substitute for traditional ACTs by some people with CF; however yet there is no agreed recommendation for this. Systematic reviews will help to confirm exercise as a safe strategy when incorporated into ACT . Physical training is already part of the care package offered to most people with CF and there is no evidence to discourage this. 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 previously performed.

Physical activity refers to any movement of the body generated by the muscles and which burns energy. Physical activity includes exercise, but also includes activity as a part of work, chores or transport. Participation in regular physical activity is important for health and well-being. In CF the progress of lung disease leads to abnormal breathing during exercise. This limits people exercising, which in turn affects health and body image. Physical activity and exercise have become an accepted and valued component of CF care. Regular physical activity and exercise can slow the rate of decline of pulmonary function, improve physical fitness, and enhance quality of life. Furthermore, regular exercise may modify progression of lung disease by improving mucus clearance, increasing ventilation and peak expiratory flow, and perhaps altering some physical properties of the mucus so that expectoration is easier.

Physical training is defined as participation in a program of regular vigorous physical activity designed to improve physical performance or cardiovascular function or muscle strength or any combination of these three elements.

Two different types of physical training are mainly identified: aerobic training or anaerobic training.

Aerobic training usually involves periods of continuous training for a length of time at a target intensity (for example cycling or running).

Anaerobic training involves training at a high intensity for a short duration (for example weight or resistance training or sprinting).

## Issues

To identify the best available evidence on the effects of physical training versus no physical training on exercise capacity, FEV1, quality of life and other outcomes in people with CF.

## What is known

One CDSR (Radtke T, 2022) included 24 parallel RCTs (875 participants) in which a prescribed regimen of physical training (aerobic and anaerobic training, and combined aerobic and anaerobic training) is compared to no physical training in people with cystic fibrosis of any age, and any degree of disease severity, diagnosed on the basis of clinical criteria and sweat testing or genotype analysis. The number of participants in the studies ranged from nine to 117, with a wide range of disease severity. The active training programme lasted up to and including six months in 14 studies, and longer than six months in the remaining 10 studies. Of the 24 included studies, seven implemented a follow?up period ranging from one to 12 months. Studies employed differing levels of supervision. Current evidence shows little or no effect on lung function and HRQoL (low?certainty evidence). Over recent decades, physical activity has gained increasing interest and is already part of multidisciplinary care offered to most people with CF. Adverse effects of physical activity appear rare and there is no reason to actively discourage regular physical activity and exercise. The benefits of including physical activity in an individual's regular care may be influenced by the type and duration of the activity programme as well as individual preferences for and barriers to physical activity. Further high?quality and sufficiently?sized studies are needed to comprehensively assess the benefits of physical activity and exercise in people with CF, particularly in the new era of CF medicine.

One CDSR (Patterson DK, 2022) selected randomised controlled studies (RCTs) and quasi-RCTs to compare the effect of exercise to other ACTs for improving respiratory function and other clinical outcomes in people with CF and to assess the potential adverse effects associated with this ACT. Four RCTs included 86 participants with a wide range of disease severity (forced expiratory volume in one second ($FEV_1$) ranged from 54% to 95%) and age 7 to 41 years old. Two RCTs were cross-over and two were parallel in design. Mainly results did not allow to conclude whether or not exercise is a suitable alternative ACT, and the diverse design of included trials did not allow for meta-analysis of results.

One CDSR (Stanford G, 2020) compared 10 randomised or quasi-randomised clinical controlled trials comparing different inspiratory muscle training regimens with each other or a control in people with cystic fibrosis. 238 patients with CF, of any age, diagnosed by clinical criteria, sweat test or genotyping or both were involved. Primary outcomes were: 1. Health-related quality of life - Chronic Respiratory Disease Questionnaire (emotion); Chronic Respiratory Disease Questionnaire (mastery); 2. Pulmonary function tests (performed at rest): i) forced expiratory volume at one second (FEV1) ii) forced vital capacity (FVC) 3. Exercise tolerance: i) field-based

tests ii) laboratory-based tests. Authors concluded that there is insufficient evidence to suggest whether respiratory muscle training is beneficial or not. Healthcare practitioners should consider the use of this intervention on a case?by?case basis. Further research of reputable methodological quality is needed to determine the effectiveness of respiratory muscle training in people with cystic fibrosis. Researchers should consider the following clinical outcomes in future studies; respiratory muscle function, pulmonary function, exercise capacity, hospital admissions, and health?related quality of life. Sensory?perceptual changes, such as respiratory effort sensation (e.g. rating of perceived breathlessness) and peripheral effort sensation (e.g. rating of perceived exertion) may also help to elucidate mechanisms underpinning the effectiveness of respiratory muscle training.

One CDSR (Oliveira V, 2020) evaluated the physical therapies for postural abnormalities in people with cystic fibrosis who have thoracic kyphosis or scoliosis regardless of age and degree of disease severity. 2 RCTs were included. Interventions consisted in any modality of physical therapy considered relevant for treating postural disorders such as manual therapy (e.g. massage, spinal manipulation, and mobilisation), educational programs, exercise training (individualised or group-based or home-based), Pilates, stretching, GPR, IMT, and yoga. Each intervention of physical therapy has been compared with each other, to no physical therapy, sham treatment or usual care. Authors concluded that there is limited evidence about the benefits of physical therapies on postural abnormalities in people with CFd due both to methodological limitations in the included trials and to the low quality of the current data. Therefore, further well?conducted trials with robust methodologies are required considering a prior inclusion criterion to identify the participants who have postural abnormalities.

A CDSR protocol (Patterson KD, 2019) compared exercise versus airway clearance techniques in people with cystic fibrosis is under review.

One Cochrane Protocol (Pereira NP, 2021) is investigating the use of the digital technology for delivering and monitoring exercise programs for people with cystic fibrosis.

A CDSR (Hilton N, 2018) reviewed the literature to establish the effectiveness of respiratory muscle training (either inspiratory or expiratory muscle training) on clinical outcomes in CF. Among 19 identified studies, nine studies including 202 participants met the review's inclusion criteria. A wide variation in the study design and interventions were registered, including the duration of intervention, the sample size and the age of enrolled patients. No significant improvement was reported in the primary outcome of FEV1. In one study a 10% improvement in exercise duration was found when working at 60% of maximal effort (n=20) (very low-quality evidence). In a further study (n=18), when working at 80% of maximal effort, health-related quality of life improved in the emotion domains (very low-quality evidence). No relevant results were found as secondary outcomes. As there is insufficent evidence to suggest whether respiratory muscle training is beneficial or not in people with CF its use should be considered on a case-by-case basisconcluded that there is insufficient evidence that Inspiratory muscle training is beneficial in CF. Healthcare practitioners should consider this intervention on a case-by-case basis.

1 CDSR updated 2017, 7 DARE, 1 NHSEED updated 2012 and more than one hundred primary studies evaluated whether a prescribed regimen of physical training produces improvement or prevents deterioration in physiological and clinical outcomes in cystic fibrosis compared to no training.

Regarding to CDSR updated to 2017 15 studies, including 487 participants, were evaluated among 83 studies identified. The numbers ranged from nine up to 72 participants in each study; two studies were in adults, seven were in children and adolescents and six studies included all age ranges. Four studies of hospitalised participants lasted less than one month and 11 studies were outpatient-based, lasting between two months and three years. The studies included participants with a wide range of disease severity and employed differing levels of supervision with a mixture of types of training. There was also wide variation in the quality of the included studies.

Both short- and long-term studies showed a limited evidence of a positive effect on aerobic exercise capacity, pulmonary function and health-related quality of life in people with CF exposed to aerobic or anaerobic physical exercise training or a combination of both. Although improvements are not consistent between studies and ranged from no effects to clearly positive effects, the most consistent were found for maximal aerobic exercise capacity with unclear effects on $FEV_1$ and health-related quality of life.

One CDSR (Houston BW et al, 2013) identified randomized or quasi-randomized clinical controlled trials to compare different inspiratory muscle training (IMT) regimens with each other or a control group in people with CF and to determine the effect of IMT on health-related quality of life, pulmonary function and exercise tolerance. Among identified studies eight studies with 180 participants met the review inclusion criteria, through a wide variation in the quality of the included studies. No evidence is available to suggest IMT as beneficial effects on pulmonary function. Further longitudinal studies have to take into account to identify specific measures to assess the benefits of IMT, such as PImax and inspiratory muscle strength and endurance, as well as exercise tests such as VO2max.

A CDSR (Cox NS et al, 2013) analyzed studies that evaluated the effect of strategies to increase the continuated participation in physical activity in people with CF. All included studies, recruiting 199 participants, used exercise training to promote participation in physical activity, with the duration of the intervention period ranging from 18 days to three years. No improvement in physical activity participation was reported with any intervention period less than or equal to six months. Improvements in physical activity participation were only seen when follow-up occurred beyond 12 months. There was no significant impact on quality of life from any of the intervention strategies.

Almost 60% of poeple with CF show altered posture as thoracic kyphosis and scoliosis. A CDSR protocol (Oliveira VHB et al, 2018) is ongoing to determine the effects of a range of physical therapies for managing postural abnormalities in people with CF, specifically on qaulity of life, pain, trunk deformity.

Several primary RCTs have been terminated:

one phase-2 randomized controlled clinical trial that showed the positive effect of the exercise guideline on the postural changes preventing the progression of some postural disorders in children and adolescents with CF consisting of a handbook with instructions for aerobic exercise and stretching (Schindel CS et al, 2015). In particular, a decrease in cervical lordosis, thoracic kyphosis, lumbar lordosis, lateral chest distance, and abdominal protrusion, as well as in the baropodometric mean pressure and contact area was registered;

one RCT (Hommerding PX et al , 2015) showed that verbal and written guidelines for aerobic exercise, together with supervision over

the telephone, had a positive impact on the self-reported regular physical exercise practice of children and adolescents with CF. However, no improvement was found in lung function;

one RCT (Rovedder PM et al, 2014) demonstrated that a home exercise programme, based on aerobic training and muscle strength training for a period of 3 months had positive effects in adult patients with CF, including gain in muscle strength in upper limbs. No increase in tolerance to exercise was shown and improvement in the quality of life of the patients who received intervention.

One RCT (Del Corral T, 2018) showed that in 39 children-adolescents with CF a home-based programme using an active video game can improved exercise capacity, musculatr strenght and qyality of life in the short term.

One RCT (Carr SB, 2018) involving 40 children and adults with CF showed that Tai Chi was safe and well tolerated; it was feasible to deliver individual lessons via the internet, reducing concerns regarding cross-infection, and appeared to improve self-reported symptoms.

One RCT (Dwyer TJ, 2019) investigated the effects of treadmill exercise vs resting breathing and PEP therapy on mucus clearance in 14 adults with mild to severe CF lung disease. Mucus clearance was measured using the radioaerosol technique and gamma camera imaging. Treadmill exercise alone was less effective than PEP therapy (mean difference -7%, 95% CI -6- -8). There were no significant differences in mucus clearance from the intermediate and peripheral lung regions, but significantly less clearance from the central lung region.

One RCT (Zeren M, 2019) investigated the effects of inspiratory muscle training (IMT) on postural stability, pulmonary function and functional capacity in 36 children with CF (age range: 8-18 years) through Biodex Balance system (R), spirometry, respiratory muscle strength and 6-min walk distance (6MWD) at baseline and after 8 weeks of training. Authors' conclusions were that combining IMT with chest physiotherapy (PT) failed to provide further improvements, except for maximum inspiratory pressure (MIP), suggesting that a comprehensive chest PT program may be individually effective in improving overall limits of stability (LOS) score, spirometry, respiratory muscle strength and 6MWD.

One RCT (GUPTA S, 2019) investigated the effects of exercise intervention program on bone mineral accretion in children and adolescents with cystic fibrosis. Change in whole body and lumbar spine BMD over 12 mo was non-significant for both parameters in the experimental and in the control group. Experimental group had a significant improvement in their exercise capacity ($p = 0.006$), quality of life, and serum vitamin D ($p = 0.007$) levels. Differences between groups for changes in pulmonary function and habitual activity were non-significant. The authors concluded that exercise regime was not associated with significant improvement in BMD of CF patients, but it had a positive impact on both physical and psychological health of these patients.

One RCT (NCT03737630) aimed to evaluate inspiratory muscle training in children and adults with CF.

One RCT (Estévez-González AJ, 2021) investigated the effects of a short-term resistance-training program on heart rate variability in CF children. 19 subjects (13 boys) were included (CON = 11; and EX = 8). Mean age was 12.2 ± 3.3, FEV(1) (forced expiratory volume in the first second) z-score was 1.72 ± 1.54 and peak oxygen consumption (VO(2)peak) 42.7 ± 7.4 mL.Kg(-1).min(-1). Individuals were divided into two groups: control (CON) and resistance-training (EX). Individuals in the EX group completed an individualized guided resistance program (5-RM-60-80%) for 8 weeks (3 sessions of 60 min/week). Upper and lower limbs exercises (seated bench press, seated lateral row, and leg press) were used. Exercise induced significant changes in the frequency-domain variables, including a decrease in LF power ($p = 0.001$, $d = 0.98$) and LF/HF ratio ($p = 0.020$, $d = 0.92$), and an increase in HF power ($p = 0.001$, $d = -0.97$), compared to the CON group. No significant changes were found for time-domain variables, although increases with a moderate effect size were seen for SDNN ($p = 0.152$, $d = -0.41$) and RMSSD ($p = 0.059$, $d = -0.49$) compared to the CON group. A short-term resistance exercise-training program was able to modulate HRV in children and adolescents with CF presenting mild to moderate lung function impairment and good physical condition.

One RCT (Güngör S, 2021) investigated the clinical effects of combining postural exercises with chest physiotherapy in 19 pediatric CF patients. Postural exercises as an adjunct to chest physiotherapy program. Patients were randomly allocated to chest physiotherapy and postural exercise program (Group 1, n=10) or chest physiotherapy program alone (Group 2, n=9). Respiratory functions were improved in both groups; however, these changes were not statistically significant. The MST increased after treatment in both groups ($p<0.001$ and $p=0.003$ respectively), without a significant difference between the groups. Emotional function and treatment difficulties subdomains in CFQR were significantly increased only in the group with postural exercises ($p<0.05$). The postural exercise program in addition to chest physiotherapy in pediatric CF patients whose postural changes were not taken place did not cause significant changes in respiratory function, exercise tolerance, and postural stability; however, it affected the emotional state well and improved the compliance with the treatment.

A parallel arm multicenter RCT (Hebestreit H, 2021) (ACTIVATE -CF) evaluated the effects of a partially supervised conditioning program in Cystic Fibrosis. 117 patients (40% of target sample size) were randomized to an intervention (n=60) or control group (n=57). After 6 months, ?FEV(1) was significantly higher in the control group compared to the intervention group (2.70% predicted, 95% CI 0.13 to 5.26; p=0.04). The intervention group reported increased vigorous PA compared with the control group at each study visit, had higher exercise capacity at 6 and 12 months, and higher physical activity at 12 months. No effects were seen in other secondary outcomes. ACTIVATE-CF increased vigorous PA and exercise capacity, with effects carried over for the subsequent 6 months, but resulted in better FEV(1) in the control group.

An RCT (Kaltsakas G, 2021) evaluated interval exercise (IE) vs constant-load exercise (CLE) training in adults with 24 adult CF patients. Patients were randomised to 30-min IE (100 % peak work capacity (WRpeak) for 30-s alternated with 40 % WRpeak for 30-s; n?=?12) or 30-min CLE (70 % WRpeak; n?=?12) training, 3 times weekly, for 12 weeks. The magnitude of improvement in quadriceps muscle strength was greater (p?=?0.037) in the IE (by 32?±?13 Nm) compared to the CLE (by 23?±?12 Nm) groups. Maximum inspiratory and expiratory mouth pressures were significantly improved only in the IE group (by 30?±?10 cmH(2)O; p?=?0.009 and 13?±?4 cmH(2)O; p?=?0.007, respectively). Arterial oxygen saturation during training was higher (p?=?0.002) for IE (94?±?1%) compared to CLE (91?±?1%), whereas dyspnoea scores were lower (p?=?0.001) for IE (3.8?±?0.7) compared to CLE (5.9?±?0.8). Authors concluded that IE is superior to CLE in improving peripheral and respiratory muscle strength and preferable to CLE because it is associated with lower exercise-induced arterial oxygen desaturation and breathlessness.

One RCT (Emirza C, 2021) investigated the effect of Expiratory Muscle Training on Peak Cough Flow (PCF) in Children and

Adolescents with CF. 30 CF patients were enrolled. Patients were randomized as training and sham groups. Both groups were trained with the EMT protocol, which involved twice per day for at least five days per week for six weeks. The training intensity in the training group was 30% of the maximal expiratory pressure (MEP). In the sham group, it remained at the lowest pressure (5cmH(2)O). Twenty-eight patients completed the study. Changes in PCF (p=0.041) and MEP (p=0.003) were higher in the training group than the sham group. Also, treatment burden (p=0.008), digestive symptoms (p=0.019), and vitality (p=0.042) in QoL were more improved in the training group. Maximal inspiratory pressure (MIP) (p=0.028) and 6MWD (p=0.035) changed significantly only in the training group. Spirometric measurements did not change (p>0.05). The results of the study show that EMT could improve PCF, MEP, treatment burden, digestive symptoms, and vitality domains of QoL in patients with CF. Moreover, MIP and functional exercise capacity improved in the training group with EMT.

By a crossover design (Salonini E et al, 2015), 30 young subjects were randomized to 2 intervention groups: Xbox Kinect and a traditional stationary cycle. Heart rate, SpO2, dyspnea, and fatigue were measured. Xbox Kinect has the potential to be employed as an exercise intervention in young subjects with CF, but investigation over longer periods is needed.

A recently observational study (Wheatley CM et al, 2015) suggested that a moderate intensity exercise is the optimal intensity for individuals with CF, as low intensity exercise increases EPI less than 50% can promote greater improvements in gas diffusion and comparable bronchodilation when compared to albuterol.

The Steep Ramp Test (SRT) (Bongers BC et al, 2015) has been recently proposed as a quick, convenient, and low-cost exercise test that is well-tolerated in patients with CF with mild-to-moderate airway obstruction and can potentially be used when exercise testing using gas exchange measurements is not possible.

Although increasing anecdotal study including a parallel, randomized controlled Australian trial suggested that singing may support lung function and enhance quality of life of people with CF (Irons JY et al, 2012) as an adjunct to physiotherapy, as well as gaming console exercise could be included in CF exercise program, a CDSR updated 2014 showed that there is insufficient evidence to determine the effects of singing on quality of life or on the respiratory parameters in people with CF. However, there is growing interest in non-medical treatments for CF and researchers may wish to investigate the impact of this inexpensive therapy on respiratory function and psychosocial well-being further in the future.

5 clinical trials performed have been completed or terminated:

1. to test the hypothesis whether a home-based peripheral muscle training program (Five Basic Exercises program-5BX) is more effective in increasing exercise capacity (e.g. peak work rate) and patients preferred occupational performance when it is preconditioned by IMT (NTR2092- Netherlands);
2. to assess whether, when subjects with CF are admitted to the hospital for a pulmonary exacerbation, a comprehensive exercise program (moderate to high intensity aerobic, resistance, flexibility and balance exercises) was superior to usual care intervention (30 min/day of self selected mode and intensity of exercise) in improving aerobic capacity, muscle strength/power, flexibility and balance (NCT01759342);
3. to evaluate the effect of Pulmozyme on exercise tolerance in patients with severe, stable patients with CF whose routine treatment included Pulmozyme compared to a placebo group (therapy withdrawn for 2 weeks)(NCT00434278)
4. to assess the role of exercise coupled to self drainage in pediatric CF patients as an open label cross-over RCT (NCT01509235)
5. to evaluate the use of quadriceps electrostimulation as an additional retraining procedure in patients with CF in an add-on, randomized, open label, clinical trial (NCT00391703). The study has been terminated for enrollment difficulties.
6. A phase 4 randomized controlled parallel study (NCT02875366) has been performed in order to evaluate the effects of lumacaftor/ivacaftor on exercise tolerance and traning in subjects with CF, homozygous for the F508del-CFTR.
7. In adults homozygous for Phe508del with severe disease, treated with LUM/IVA a clinically significant improvement in 6MWT was evident at 4?weeks and maintained at 52?weeks (ACTRN12619000708156) (Wark PAB et al , 2019).
8. A further study showed that incremental cardiopulmonary exercise testing (CPET) improved after two years of lumacaftor-ivacaftor therapy in three adults homozygous for Phe 508del in treatment with LUMA/IVA for 2 years (Savi D et al, 2019).

A NHSEED study updated 2012 (Urqhard D et al, 2012) supervised outpatient exercise and physiotherapy program in subjects with CF aged ?10 years who had received ?4 courses of IV antibiotics in 2009 compared to 2010. Main results showed improvements in QOL and exercise tolerance, a reduction in IV antibiotic days, and a trend towards reducing lung function decline in children with CF. The cost of IV antibiotics was also reduced in 2010 when compared with 2009.

One NCT (NCT01744561) has been completed with the primary objective to evaluate the effects of a 6-months partially supervised exercise intervention along with regular motivation on FEV1 in a large international group of CF patients. Secondary endpoints reported quality of life, as well as levels of anxiety and depression, and control of blood sugar. A total of 292 patients with CF 12 years and older with a FEV1 ?35% predictedhave been recruited.

One NCT (NCT03190031) has been performed to evaluate Respiratory Muscle Training in CF Patients (having to following outcomes: respiratory muscle endurance, respiratory muscle strength, maximal cycling performance, quality of life).

One pilot, open-label, randomized crossover trial (Spoletini G, 2021) investigated nasal high-flow therapy (NHFT) as an adjunct to exercise in patients with cystic fibrosis. 23 CF participants completed two treadmill walking test (TWT) with and without NHFT at 24-48 h interval. No adverse events caused by NHFT were observed. Tolerability was good and data completion rate was 100%. Twenty subjects (91%) were included in the exploratory study. Mean difference in TWTD on NHFT was 19 m (95% CI [4.8 - 33.1]). S(p)O(2) was similar, but respiratory rate and mean tcCO(2) were lower on NHFT (mean difference = -3.9 breaths/min 95% CI [-5.9 - -1.9] and -0.22 kPa 95% CI [-0.4 - 0.04]). NHFT reduced exercise-induced dyspnoea and discomfort. In conclusion NHFT appears to improve walking distance, control respiratory rate, CO(2), dyspnoea and improve comfort. A larger trial with a longer intervention is feasible and warranted to confirm the impact of NHFT in training programmes for patients with CF.

One RCT (Kenis-Coskun Ö, 2022) aimed to investigate the effect of telerehabilitation (exercise program three times a week via Zoom for 12 weeks) on quality of life, anxiety and depression in 14 children (6-13 years) with cystic fibrosis and caregivers (28) showed

that a short-term telerehabilitation program improved patients' anxiety and depression levels, body image and functional status. However caregiver anxiety and depression levels did not change significantly.

One RCT ( Donadio MVF, 2022 ) explored if exercise and electrostimulation is effective in improving muscle strength and cardiorespiratory fitness in children with cystic fibrosis and mild-to-moderate pulmonary impairment. Twenty-seven patients, aged 12.6 ± 3.0 years, were enrolled. Subjects were evaluated at baseline and at the end of an 8-week individualized exercise-program (3 days/week, 60min/session). No significant interactions were found for cardiorespiratory fitness. Functional capacity presented significant differences, indicating a better performance in both exercise (EX) group and exercise and neuromuscular electrical stimulation (EX + NMES) group. No significant changes between groups were seen for quality of life and lung function. As for muscle strength, EX and EX + NMES presented large effect sizes and significant differences, compared to the control (CON) group, for quadriceps (p = 0.004, ?(2)(p) = 0.401), pectoral (p = 0.001, ?(2)(p) = 0.487), dorsal (p = 0.009, ?(2)(p) = 0.333) and handgrip (p = 0.028, ?(2)(p) = 0.278). Authors concluded that a resistance exercise-training program led to improvements in muscle strength and functional capacity in CF patients with mild-to-moderate pulmonary impairment. The addition of NMES to the training program resulted in no extra favorable effects.

Although evidence about the efficacy of physical exercise training is limited exercise training is already part of regular outpatient care in CF. Since there is some evidence for beneficial effects on aerobic fitness and no negative side effects, there is no reason to discourage this, taking into account that benefits may be influenced by the type and duration of the training programme. High quality randomized controlled trials have to be encouraged.

### Unresolved questions

One interventional study (NCT04075864) will evaluate the feasibility of a new model for exercise erescription in cystic fibrosis adult patients.

One RCT (NCT03965832) is ongoing to evaluate HFNT (high flow nasal therapy) during exercise in adult CF patients. HFNT is a device that provides patients with air or a blend of air and oxygen at flows up to 60 L/min. In CF, HFNT is routinely used for patients admitted with acute respiratory failure (inability to maintain adequate oxygenation) with positive results. This is a piolt monocentric study to understand if HFNT can improve the exercise tolerance in patients with CF and advanced lung disease, by reducing breathlessness and avoiding the drop in oxygenation observed during simple training. The Investigators propose a short study to assess if further large clinical trials are feasible and practical, and will therefore collect preliminary data to have some results to use for planning other studie

One ACTRN trial (ACTRN12615001361594) is ongoing to evaluate whether exercise alone versus exercise and positive expiratory pressure is a form to increase airway secretion clearance in adults with mild CF- respiratory disease

An ongoing trial (NCT03653949) aims to evaluate the effect of aerobc exercise on insulin resistance in children aged 6-20 years with CF.

An ongoing RCT (NCT03710538) aims to evaluate the effect of a pre-meal Snack and/or exercise on post-prandial glycemic excursions in adults with CF.

An ongoing RCT (NCT03672058) aims to optimise physical activity and health in adults with CF using fitness trackers and personalised goal-based text messaging support.

An ongoing RCT ( NCT03873688 ) aims to evaluate the effects of expiratory muscle training on cough efficacy in children and adolescents (8-18 years) with Cystic Fibrosis.

An ongoing RCT (NCT04249999) will assess whether three-months use of an online platform (ActivOnline) can help increase physical activity levels in people with CF (age range: 12-35 years) compared to a control group continuing routine treatment.

An ongoing RCT (NCT04543929) will evaluate the effectiveness of standard of care therapy + exercise compared to standard of care only for improving cardiorespiratory-fitness in adult CF patients.

An ongoing pilot RCT phase 2 study (NCT05239611) will compare exercise intervention with usual care. The exercise intervention group will be delivered with a telehealth platform using internet, an app, phone, and email/text support. Participants will be randomly allocated to either an exercise coaching program or a usual care arm. The exercise intervention arm will follow guidelines established by the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) and complement best clinical practices established by the American Thoracic Society/European Respiratory Society (ATS/ERS). The usual care arm will be provided a handout on resources for engaging in physical activity.

An ongoing RCT ( NCT05239611 ) will compare exercise intervention with a usual care group in adult CF patients. The exercise intervention group will be delivered with a telehealth platform using internet (Zoom HIPAA-Compliant video), an app, phone, and email/text support. Participants will be randomly allocated to either an exercise coaching program or a usual care arm.

The benefits obtained from including physical training may be influenced by the type of training programme. Likely training for less than

one month would be not beneficial. Both short and long-term studies show that either aerobic or anaerobic physical training have positive effects on primary outcomes (exercise capacity, strength and lung function). No definite effect on secondary outcomes as mortality, number of hospitalization, quality of life, bone mineral density, compliance with other therapies has been clarified.

Further studies are needed to assess the benefits of exercise programme in people with CF and the relative benefits of the addition of aerobic versus anaerobic versus a combination of both types of physical training to the care of people with CF, as well as further studies could clarify the effects of training intensity (higher versus lower) or type (continuous versus interval training) on lung function.

Further research is needed to determine the effect of strategies such as health coaching or telemedicine applications in promoting the uptake and adherence to regular participation in physical activity.

Open question arises  i the shifting landscape of CF management with the advent of highly-effective small molecule therapies, which are changing the way people with CF care for.

**Keywords**

Exercise; Training;