

SIENIAWSKA, Julia, KAMIZELA, Angelika, MADOŃ, Magda, PROSZOWSKA, Patrycja and SIENIAWSKA, Daria. The Benefits of Physical Activity for Patients with Cystic Fibrosis: A Literature Review. *Quality in Sport*. 2024;18:53457. eISSN 2450-3118. <https://dx.doi.org/10.12775/QS.2024.18.53457>  
<https://apcz.umk.pl/QS/article/view/53457>

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.

Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).

Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.

Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

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The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 15.07.2024. Revised: 01.08.2024. Accepted: 02.08.2024. Published: 05.08.2024.

## **The Benefits of Physical Activity for Patients with Cystic Fibrosis: A Literature Review**

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## **Abstract**

### **Introduction**

Cystic fibrosis (CF) is a complex and progressive genetic disorder that significantly impacts multiple organ systems, particularly the lungs and digestive tract. Despite advances in treatment and improved life expectancy, CF remains incurable, necessitating ongoing research and comprehensive management strategies. One of the key components in managing CF is the incorporation of physical activity (PA).

### **Aim of the study**

The aim of the study is to investigate the role of physical activity in in the management of cystic fibrosis.

### **Materials and methods**

This study underscores the critical role of physical activity (PA) in the management and overall well-being of individuals with cystic fibrosis (CF). It provides a comprehensive review of the multifaceted benefits of PA for CF patients, highlighting its positive impact on exercise tolerance, pulmonary function, cardiorespiratory fitness, muscle strength, and quality of life. PubMed and Google Scholar database was searched for articles written in English. The search included the keywords.

### **Results**

The data suggest that while CF patients face unique challenges, including muscle weakness and exercise intolerance, regular PA can mitigate these effects and improve overall health outcomes. Supervised exercise programs have demonstrated significant improvements in exercise tolerance and respiratory muscle endurance without adverse effects, indicating their feasibility and safety for CF patients. Studies have shown that patients with CF who engage in regular PA experience slower declines in lung function, fewer hospitalizations, and better nutritional status. Specific types of exercise, such as anaerobic training, have been particularly effective in increasing muscle strength and body weight.

**Key words:** Cystic fibrosis; Exercise; Physical activity

### **Introduction**

Cystic fibrosis (CF) is the prevailing hereditary condition among Caucasian people, occurring in approximately 1 out of every 2,500-3,500 live births. Upon its initial description in 1938, the majority of infants afflicted with CF succumbed to the disease during infancy. Despite recent advancements, cystic fibrosis remains an incurable condition. Early diagnosis and treatment by multidisciplinary teams are crucial for maximising both short- and long-term results. Neonatal doctors must be informed on the latest research, therapy, and management of CF in order to achieve optimal outcomes[1].

Child-centered health education and counselling treatments are crucial as they can foster healthy lifestyle patterns and perhaps reduce health-compromising behaviours. Moreover, the health-related behaviours shown throughout infancy might build long-term lifestyle habits that can either safeguard or jeopardise individuals throughout their adult lives[2].

### **Cystic fibrosis (CF)**

Cystic Fibrosis (CF) is a genetic systemic illness that is present from birth and is passed down as an autosomal recessive disorder. It is characterised by persistent and worsening symptoms. Cystic Fibrosis is a result of genetic abnormalities in the CFTR gene, which codes for a protein mostly found in epithelial cells. This protein is responsible for controlling the movement of chloride ions across the cell membrane. Genetic mutations in the CFTR gene result in the degradation, malfunction, or incorrect localization of the CFTR protein[3,4].

The CFTR protein facilitates the passage of chloride ions through the cells responsible for mucus production, resulting in the subsequent movement of water and the thinning of the mucus. Nevertheless, the presence of faulty CFTR leads to the formation of dense and adhesive mucus that blocks the airways[5], resulting in severe lung infections, particularly pseudomonas. Neutrophils are infiltrating in large numbers and producing elastase, which overwhelms the lung's antiproteases and causes tissue destruction[6]. In addition, neutrophils that undergo degranulation release significant amounts of nucleic acids and cytosol matrix proteins, which contribute to the increased thickness of mucus[7].

Mucous clogs in the gastrointestinal tract block the canaliculi of the pancreas and gall bladder duct, restricting the passage of enzymes and bile into the duodenum. This obstruction leads to malabsorption and irregularities in digestion. As a result, disruptions in the movement of sodium and chloride ions across cell membranes cause the formation of thick secretions. These secretions then gradually block the ducts of many organs and systems, including the respiratory system, exocrine glands, and intestines. Furthermore, individuals with cystic fibrosis (CF) with pancreatic insufficiency may experience a specific condition called Distal Intestinal Obstruction Syndrome (DIOS). This condition is defined by the blockage of the ileo-cecal region due to thickened intestinal contents[8]. The presence of chronic sickness in CF is strongly linked to the gradual decline of the respiratory system caused by the buildup of thick mucus. This leads to the development of long-term inflammation and the colonisation of certain bacteria [9,10].

Gruenert et al. highlighted that advancements in mutation detection and the increased accessibility of genetic testing now enable the diagnosis of individuals with unusual symptoms or inconclusive sweat test findings [11]. The CFTR gene is situated in the chromosomal locus 7q31.2. Over 1900 mutations have been discovered, with the most prevalent being 'F508del', which involves the loss of three bases that code for phenylalanine at the 508th position. There are six distinct categories of mutations that have been documented. Class I mutations result in a deficiency in the generation of CFTR protein, causing its full absence. These mutations are seen in 2-5% of cases globally, except among Ashkenazi Jews, where 60% of patients possess at least one copy of these mutations. Class II mutations result in protein processing abnormalities, which cause the protein to be incorrectly localised. The F508del mutation is the predominant genetic alteration, responsible for 70% of disease-causing alleles in the United States.

Around half of the CF patients are homozygous for this mutation, whereas around 90% are heterozygous. Class III mutations result in protein regulatory anomalies, which in turn cause a reduction in activity. Additionally, it encompasses many alterations, particularly in the regulatory domain. The G551D mutation is the most prevalent class III mutation. Class IV mutations cause disruptions in protein conduction, resulting in changes to the rate of ion flow. The most prevalent mutation is R117H. Class V mutations result in a decreased quantity of functional CFTR protein, while class VI mutations lead to an increased rate of protein turnover. Patients with Class I–III mutations exhibit a more severe manifestation of the illness [13-15].

Remarkable progress has been made in enhancing the chances of surviving during the last few decades, resulting in a present average lifespan. The significant improvement in life expectancy and quality of life can be credited to the comprehensive care provided in CF centres, early screening of newborns, provision of proper nutrition, administration of antibiotics (such as eradicating *Pseudomonas aeruginosa* and promptly treating acute pulmonary exacerbations), rigorous physiotherapy for clearing mucus, use of drugs that help with mucus, and management of complications associated with CF[16]. Treatment for respiratory illness involves the use of medications that can be taken orally, inhaled using a nebulizer, or delivered intravenously. The medications encompass antibiotics, mucolytics, bronchodilators, and corticosteroids [17]. The modification of the chloride channel using pharmacology and the substitution of genes have shown results in laboratory experiments, but have not yet been tested on animal or human subjects. Confirmation of interpatient transmission of microorganisms provides a valid justification for implementing patient segregation programmes. The mechanism of transmission and variables affecting host susceptibility have not been defined. Anti-inflammatory drugs can inhibit the immune response to long-term infection in the bronchial tubes. Ultimately, despite advancements in surgical methods, lung transplantation is still only available to a restricted group of patients [18]. Consequently, the demographic makeup of individuals with CF has undergone significant transformations. CF is no longer exclusively classified as a disease affecting children, since adults aged 18 and above now make up 50% to 60% of patients in nations with established CF healthcare systems[19]. There has been a notable increase in survival rates in recent decades, with the average life expectancy now exceeding 50 years of age[20].

CFTR modulators have significantly transformed clinical treatment, bringing about a fundamental change of perspective for individuals with cystic fibrosis (pwCF) and those who take care of them. There are now four CFTR modulators that have been authorised for use in individuals with cystic fibrosis (pwCF). However, it is important to note that the criteria for accessing and being eligible for these medications may differ among countries. Ivacaftor (IVA), a CFTR potentiator and the pioneering drug in its category, has received approval for patients aged 4 months and above with gating mutations (class III) in Europe. It has been in use for more than 10 years[21]. The positive outcomes of IVA have stimulated the advancement of CFTR correctors lumacaftor (LUM) and tezacaftor (TEZ), which are used in conjunction with IVA to specifically address F508del[22].

Pulmonary rehabilitation is an essential element of cystic fibrosis treatment. Pulmonary rehabilitation include methods such as airway clearing procedures, exercise training, education, and behaviour modification.

This comprehensive approach can enhance patients' exercise capacity, muscular strength, quality of life, and nutritional status. Airway clearance procedures have advantageous advantages in eliminating mucus. In recent years, there has been an increasing amount of research supporting the positive impact of exercise training on both exercise capacity and general lung health. Cystic fibrosis is characterised by many causes that lead to a decrease in exercise capacity. Pulmonary rehabilitation should be provided to individuals with cystic fibrosis, since the advantages generally surpass the drawbacks. However, the most effective treatment plans still need to be determined[23].

The evolution of CF is characterised by exacerbations, which can lead to heightened coughing, increased energy consumption, decreased body mass index (BMI), and diminishing pulmonary function [24]. The evidence indicates that physical activity (PA) in adults with CF is basically similar to that of individuals without CF, but it falls short of meeting the recommended levels of global PA. A majority of individuals with CF tend to have occupations that require little physical activity or entail light work. About two-thirds of CF patients consider CF as a hindrance to their employment, with over half indicating that CF limits their ability to work effectively[25]. Consequently, individuals with cystic fibrosis (CF) may choose to abstain from or restrict their engagement in physical activity (PA) due to variables including exhaustion and difficulty breathing. This can lead to a gradual decline in lung function, as well as impairments in the aerobic and anaerobic capacity and muscular strength of the skeletal muscles [26].

### **Physical activity (PA)**

The physiological ramifications of CF are analogous to those of de-conditioning, encompassing compromised cardiovascular function, reduced muscle mass, and decreased strength and power[27]. In addition, children with CF may exhibit a higher level of physical inactivity[28] as a result of the load imposed by their chronic illness[29]. Consequently, they may be susceptible to the compounding effects of chronic disease and lack of physical exercise. CF patients often experience frequent illness exacerbations, which can result in a general lack of physical activity. This sedentariness is accompanied by a significant decrease in exercise tolerance, which is partially due to poor muscle function and malnutrition. These factors, together with lung disorders, contribute to the reduced ability to engage in physical exercise among CF patients[30].

Physical activity (PA) refers to any movement of the body that involves the contraction of skeletal muscles and leads to a significant increase in the amount of calories burned compared to when the body is at rest. There is extensive research supporting the immediate health benefits, such as increased energy levels, enhanced focus, and better emotional well-being, as well as the long-term advantages, such as reducing the risk of chronic illnesses and death, that come from regularly engaging in physical activity in a healthy population [31]. In addition to these advantages, research has indicated that there are distinct health benefits for CF.

Increased levels of physical activity have been linked to a decelerated deterioration in lung function, decreased hospitalisation rates, enhanced quality of life, improved nutritional status, and a more favourable prognosis in both paediatric and adult patients with CF[32].

Physical activity (PA) therapies in cystic fibrosis (CF) can be implemented in several ways, such as personalised exercise programmes, interventions to promote behaviour change, supervised or unsupervised training, telehealth interventions, education, or self-monitoring [33]. There is a lack of definitive ideal ways for incorporating exercise into the therapy of CF [34]. The positive impact of CFTR modulators on health outcomes for individuals with CF has been significant and may influence physical activity (PA) and aerobic capacity in this population [35].

The choice of exercise (aerobic versus anaerobic) used during training can have varying impacts on the enhancement of exercise tolerance. There is no guarantee that aerobic exercise training will consistently enhance the initial lung function or promote weight gain in persons with CF [36]. Weight lifting, which is a type of anaerobic exercise training, resulted in notable enhancements in both body weight and muscular strength [37]. The observed effects are to be expected as interval training, a method that involves repeated periods of intense activity without oxygen, ultimately results in notable enhancements in aerobic exercise capacity for both athletes and those with obstructive lung disease [38]. Therefore, enhancements in the ability to do anaerobic exercises may result in an increase of aerobic capacity in individuals with CF.

The significance of exercise and habitual physical activity (HPA) for individuals with chronic illness has been recognised as a crucial aspect for healthcare providers, doctors, researchers, and especially patients[39]. Increased levels of exercise ability have been found to be crucial for the survival of people with CF. Research has shown a connection between the ability to perform aerobic exercises and the overall health condition of children with CF. Nixon and colleagues discovered a notable association between aerobic fitness (VO<sub>2</sub>) and survival[40], which persisted even after accounting for other factors that may predict outcomes, such as age, sex, lung function, nutritional status, and bacterial colonisation.

Patients increase their minute ventilation to compensate for the enlarged non-functional regions in their lungs. However, this may worsen their pain or sense of being out of breath, which keeps them from engaging in high-intensity activities [41, 42]. Furthermore, decreased lung function has been linked to pulmonary exacerbation, which in turn affects PA [43]. PA decreases in response to pulmonary exacerbations; however, the opposite relationship—that is, PA levels rising in response to fewer exacerbations—might also be true. An acute pulmonary exacerbation and a stable control group were included in a research that followed up on persons with CF for one month. The results indicated a substantial drop in PA in the exacerbation group [44, 45].

A study was conducted in which ten children with cystic fibrosis participated in swimming training over 7 weeks. The patient's respiratory condition, evaluated using spirometry, showed a considerable improvement following the treatment. After a period of 10 weeks following the completion of the training, the majority of measures had reverted back to their original values before to swimming. On most swimming days, children exhibited increased levels of sputum production compared to non-swimming days. Swimming regularly can help children with cystic fibrosis clean mucus from their lungs and improve their ability to breathe [46].

The study assessed exercise tolerance, skeletal muscular strength, and respiratory muscle strength in adult individuals with CF.

The frequency of muscular weakness and the significance of physical inactivity in cystic fibrosis (CF), as well as its correlation with exercise capacity and muscle strength. Quadriceps muscular weakness was observed in 56% of the patients. 89% of patients had below-normal peak oxygen uptake, whereas 75% had below-normal 6-minute walking distance. The strength of the respiratory muscles was within the usual range. The disparities persisted even after adjusting for physical activity. The force exerted by the quadriceps muscles was found to have a correlation with the distance walked in 6 minutes, but not with the maximum amount of oxygen consumed during exercise. Patients with cystic fibrosis (CF) had a similar amount of mild physical activity (PA) compared to the control group, as measured by metabolic equivalents (METs) and the number of steps taken. However, CF patients engaged in less moderate PA, which requires a higher level of exertion (more than 4.8 METs). There was a correlation between moderate physical activity and both peak oxygen consumption and quadriceps force. Cystic fibrosis is commonly associated with skeletal muscular weakness and exercise intolerance. Physical inactivity has a substantial role in reducing exercise tolerance and skeletal muscular power in people with cystic fibrosis. However, it is important to note that these deficits are more than what would be predicted solely from physical inactivity [47].

A group of 109 individuals diagnosed with cystic fibrosis, ranging in age from 7 to 35 years, participated in both pulmonary-function and exercise testing. A longitudinal study was conducted over a period of eight years to ascertain the variables linked to future death. Patients who had the highest levels of aerobic fitness ( $\dot{V}O_{2peak}$ ,  $\geq 82$  percent of predicted) had a survival rate of 83 percent after eight years. In comparison, patients with moderate levels of fitness ( $\dot{V}O_{2peak}$ , 59 to 81 percent of predicted) had a survival rate of 51 percent, while patients with the lowest levels of fitness ( $\dot{V}O_{2peak}$ ,  $\leq 58$  percent of predicted) had a survival rate of 28 percent. After controlling for other risk variables, patients with greater levels of aerobic fitness had a survival rate that was over three times higher than patients with lower levels of fitness. The presence of *P. cepacia* colonisation was linked to a fivefold increase in the probability of mortality. There was no independent correlation found between mortality and age, sex, body-mass index, FEV<sub>1</sub>, and end-tidal PCO<sub>2</sub> during maximal activity. Patients with cystic fibrosis who have higher levels of aerobic fitness have a dramatically reduced chance of mortality. While it is possible that improved aerobic fitness is only an indication of less severe sickness, the assessment of  $\dot{V}O_{2peak}$  seems to be useful in predicting prognosis [48].

A study was conducted on 31 cystic fibrosis patients with varying degrees of pulmonary involvement, ranging from mild to severe. The purpose of the study was to investigate the impact of a closely monitored three-month running programme on the patients' exercise tolerance, pulmonary function, cardiorespiratory fitness (measured by peak oxygen consumption), and respiratory muscle endurance. There were no significant differences between the training and control groups in terms of age, sex, pulmonary function, exercise tolerance, or cardiorespiratory fitness. Following a period of three months of physical conditioning, the exercise group had notable improvements in exercise tolerance and peak oxygen consumption, as well as a substantial decrease in heart rates under submaximal labour loads. In contrast, the nonexercising (control) group did not show any changes in these measures. The Forced Expiratory Volume in 1 second (FEV<sub>1</sub>) shown a significant reduction in the control group.

There were no notable changes in pulmonary function seen in either the control or exercise group. The exercise patients saw a considerable increase in respiratory muscle endurance, while there was no change observed in the control patients. The results indicate that implementing a supervised running programme can enhance the exercise tolerance and cardiorespiratory fitness of patients with CF. This improvement may be attributed, at least partially, to an increase in the tolerance of the respiratory muscles[49].

The study involved persons diagnosed with CF and individuals of the same age without CF, serving as controls. The study evaluated the levels of physical activity (PA), exercise tolerance, and the strength of skeletal and respiratory muscles in a group of patients and a control group. The primary discovery is the high occurrence of skeletal muscle weakness and exercise intolerance in adult CF patients who have moderate impairment in lung function. While the majority of patients saw a decline in both peak and functional exercise capacity, only 35% of patients met the criteria for being categorised as insufficiently active. While individuals with CF still exhibited acceptable levels of physical activity at a mild intensity, their participation in physical activities above a moderate intensity was considerably lower compared to the control group [50].

The study found that there was a positive correlation between changes in lung function and, to a lesser degree, nutritional status, and changes in the aerobic capacity of children with CF. While 'exercise' implies planned and regulated physical activity based on intensity and duration, habitual physical activity (HPA) focuses on incorporating physical activity into everyday routines and includes a wider range of possibilities for staying active. Research has demonstrated that engaging in physical activity plays a distinct role in improving the well-being of those diagnosed with cystic fibrosis. Hence, the significance of physical exercise and hypothalamic-pituitary-adrenal (HPA) axis in individuals with cystic fibrosis is crucial. This provides healthcare professionals with a chance to incorporate regular activity guidelines as a standard component of therapeutic treatment [51,52].

## **Conclusion**

Cystic fibrosis (CF) remains a challenging genetic disorder with significant implications for the respiratory and gastrointestinal systems, among others. Despite advances in treatment and management, CF is still incurable, highlighting the need for ongoing research and innovative therapeutic approaches. Multidisciplinary care, early diagnosis, and intervention are essential to improving both the quality of life and life expectancy of individuals with CF.

The role of physical activity (PA) in managing CF is particularly crucial. Regular PA has been shown to offer numerous benefits for individuals with CF, including improved exercise tolerance, cardiorespiratory fitness, respiratory muscle endurance, and overall quality of life. Studies have demonstrated that higher levels of PA are associated with slower lung function decline, reduced hospitalization rates, and better nutritional status. Additionally, specific forms of exercise, such as anaerobic training, have been found to significantly enhance muscle strength and body weight.

The beneficial effects of exercise and habitual physical activity (HPA) for CF patients underscore the importance of integrating these activities into routine care.



Exercise interventions, whether supervised or unsupervised, can lead to substantial improvements in physical capacity and health outcomes. However, the optimal strategies for incorporating PA into CF management are still being explored.

In summary, while CF poses significant challenges, the incorporation of regular physical activity into the management plans of CF patients offers a promising avenue for improving their overall health and prognosis. It is vital for healthcare providers to promote and facilitate PA and HPA as part of comprehensive CF care, ensuring that patients can achieve the best possible outcomes.

After conclusions

**Author's contribution:**

Conceptualization: Julia Sieniawska, methodology: Magda Madoń, Patrycja Proszowska, software, Daria Sieniawska, check: Angelika Kamizela, formal analysis: Patrycja Proszowska, investigation: Magda Madoń, Julia Sieniawska, resources, Daria Sieniawska, Angelika Kamizela, data curation, Patrycja Proszowska, writing-rough preparation, Daria Sieniawska, visualization, Angelika Kamizela, supervision, Julia Sieniawska, project administration, Magda Madoń

All authors have read and agreed with the published version of the manuscript

**Disclosure**

**Funding statement**

The study did not receive special funding.

**Informed Consent Statement**

Not applicable

**Acknowledgments**

Not applicable

**Conflict of Interest Statement**

The authors report no conflicts of interest.

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