













# Effects of a remotely supervised resistance training program on muscle strength and body composition in adults with cystic fibrosis: Randomized controlled trial

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## Abstract

**Introduction:** Among the limited studies on physical exercise interventions in adults with cystic fibrosis (CF), few have specifically addressed the improvement of peripheral muscle strength and body fat-free mass. The aim of this study was to examine the impacts of a remotely supervised, individualized 8-week resistance training program of moderate to high intensity on strength and body composition in these subjects.

**Methods:** This was a randomized controlled trial performed in adults with CF. The exercise group (EX) performed three 1-h resistance training sessions per week over 8 weeks. The control group (CON) followed the physical activity recommendations of their physician. The main outcomes were muscle strength and body composition, with secondary measures including pulmonary function and quality of life. Two-way repeated measures analysis was used.

**Results:** In 23 participants (age  $32.13 \pm 7.72$  years), the intervention showed a significant beneficial effect on leg press strength, with a large effect size, both in absolute ( $p=0.011$ ;  $\eta_p^2=0.281$ ) and relative ( $p=0.007$ ;  $\eta_p^2=0.310$ ) terms. Large intervention effects were observed on total fat mass ( $p<0.001$ ;  $\eta_p^2=0.415$ ), body adiposity index ( $p<0.001$ ;  $\eta_p^2=0.436$ ), and fat mass index ( $p<0.001$ ;  $\eta_p^2=0.445$ ), all

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showing reduction in the EX group. In addition, significant large size effects were detected on total fat-free mass ( $p=0.046$ ;  $\eta_p^2=0.177$ ), trunk fat-free mass ( $p=0.039$ ;  $\eta_p^2=0.188$ ), and fat-free mass index ( $p=0.048$ ;  $\eta_p^2=0.174$ ), all favoring exercise. No significant effects were observed on pulmonary function and quality of life.

**Conclusions:** An 8-week remotely supervised resistance training program, with moderate to high intensity, effectively improved lower limb muscle strength and body composition.

#### KEYWORDS

body composition, cystic fibrosis, resistance training, strength

## 1 | INTRODUCTION

Cystic fibrosis (CF) is a recessive autosomic hereditary disease caused by more than 2000 different mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.<sup>1</sup> The defect in the resultant protein affects several epithelia, and lung involvement is the main cause of death in these patients.<sup>2</sup> In the last 30 years, life expectancy has increased to today's 50 years,<sup>3</sup> leading to an increased prevalence of age-related comorbidities such as a greater risk of sarcopenia.<sup>4</sup>

In addition, individuals with CF present exercise intolerance due to several factors related directly and indirectly to the CFTR defect in the different tissues involved in exercise, including muscle.<sup>5</sup>

Muscle dysfunction is due in part to muscle mass loss, malnutrition, and chronic inflammation present in these patients,<sup>4</sup> but also to failure of the CFTR receptor in this tissue. CFTR is located in the sarcoplasmic reticulum and regulates calcium release from ryanodine and inositol triphosphate receptors. Defective CFTR function increases calcium mobilization, and thus impairs muscle contraction and relaxation.<sup>6</sup> Given the importance of maintaining good muscle health, especially in the adult patient, resistance exercise becomes an essential component of treatment.

While the importance of exercise is recognized by patients, the lack of free time because of treatments and the high rate of transmission of respiratory infections makes it difficult for patients to come together for sessions. This also affects motivation and adherence to exercise programs.<sup>7</sup>

Both in lung disorders and other chronic diseases, the benefits of remote exercise and rehabilitation are starting to emerge as comparable to those of in situ programs.<sup>8,9</sup> There is, however, a need for more good quality randomized controlled trials designed to analyze the impacts of these physical exercise programs in adults with CF. In addition, few studies have focused on their benefits for muscle strength and body composition.<sup>10–12</sup> Consequently, the

main aim of this study was to determine the effects of a remotely supervised, individualized 8-week resistance training program of moderate to high intensity on strength and body composition in adults with this disease.

## 2 | METHODS

### 2.1 | Study design

This was a randomized controlled trial conducted in adult CF outpatients of the Hospital Universitario La Princesa (HU La Princesa), Madrid, Spain. The study protocol was approved by this hospital's *Comité de Ética de la Investigación con Medicamentos* (registry no. 4318, act CEIm 25/20 dated 22/12/2020), and by the Research Committee of the *Universidad Europea de Madrid* (ref: CIPI/21/007). The trial was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (ID: NCT05173194). Written informed consent was obtained from each participant. Consolidated Standards of Reporting Trials recommendations were followed.<sup>13</sup> Participants were randomized 1:1 to two parallel groups: exercise (EX) and control (CON). All participants were examined by the same investigators at baseline (T1) and at the end of the 8-week program (T2).

### 2.2 | Participants

Participation in this trial was voluntary. Inclusion criteria were (i) age >18 years; (ii) clinical and genetic diagnosis of CF defined as compatible clinical symptoms or positive neonatal screen and chlorine in sweat  $\geq 60$  mEq/L and/or two pathogenic variants of the *CFTR* gene. Exclusion criteria were (i) lung transplant recipients; (ii) pregnancy; (iii) any musculoskeletal abnormality preventing physical exercise. Of 48 eligible patients invited to participate, 32 agreed to participate in this study. Assessments were carried out in HU La Princesa and Universidad Europea de Madrid.

## 2.3 | Familiarization and reliability of outcome assessment

Before the study outset, all participants completed a session of familiarization with the assessment and training exercise techniques.

## 2.4 | Exercise intervention

The EX group performed three 1-h training sessions per week over 8 weeks. Each 1-h session included warmup, resistance training exercises, and cool down. Sessions were guided remotely by trainers with experience with this type of patient. Participants were assigned to one of three levels according to pulmonary function and physical condition. Each of these three levels was subdivided into subgroups of two to three individuals.

The exercises included were triceps extensions, biceps curls, lunges, front and side planks, back extensions, shoulder abductions, femoral biceps curls, knee extensions, situps, glute bridges, and seated wide and narrow grip row. Resistance bands were used. Intensity was moderate to high and equivalent to a Borg perceived effort of seven to eight on a scale of zero to ten, performing two to three sets of eight to fifteen repetitions of exercises (Data S1). Intensity was increased as deemed by the trainer. Each trainer completed an exercise session attendance diary. Subjects in the CON group followed the physical activity recommendations of their physician.

## 2.5 | Outcomes

### 2.5.1 | Descriptive variables

#### *Clinical and demographic variables*

The following variables were recorded at the study outset: age, sex, genotype, modulator therapy, clinical diagnosis, and microbiology. Genotype was recorded as (i) homozygous for F508del, (ii) heterozygous for F508del, and (iii) other mutations. Some participants were started on the compassionate use of CFTR channel modulating agents and this was recorded as (i) none, (ii) ivacaftor, (iii) tezacaftor/ivacaftor, and (iv) elexacaftor/lumacaftor/ivacaftor. Clinical diagnoses considered the presence or absence of (i) exocrine pancreatic insufficiency, (ii) CF-related liver disease, and (iii) CF-related diabetes mellitus. We also considered the presence or absence of chronic bronchial infection by (i) *Pseudomonas aeruginosa*, (ii) methicillin-sensitive *Staphylococcus aureus*, and (iii) *Burkholderia cepacia*.

#### *Peak oxygen consumption ( $VO_{2peak}$ )*

After a 3-min walking warmup, a maximal exercise test was completed on a treadmill using an incremental ramp protocol with increases set according to pulmonary function.

#### *Lifestyle variables*

Physical activity levels and adherence to the Mediterranean diet were assessed through Rapid Assessment of Physical Activity (RAPA), and *Prevención con Dieta Mediterránea* (PREDIMED), respectively.

The RAPA has two parts: RAPA1, which measures aerobic exercise, and RAPA2, which assesses muscle strengthening and flexibility exercise. RAPA 1 has seven items. Scores equal to or above 6 indicate fulfillment of recommendations. RAPA 2 is divided into two items: Item 1 determines whether the subject undergoes strength training; and Item 2 whether flexibility sessions are carried out.

The questionnaire PREDIMED has 14 items and is scored from 0 to 14. A score of 9 or more was considered a good adherence to the Mediterranean diet.

### 2.5.2 | Primary outcomes

#### *Muscle strength variables*

Hammer Strength machines were used for leg press and Cybex Eagle NX pulley machines for chest press and lat pulldown. The protocol consisted of two warmup sets with 1-min breaks between sets. From the third set onward, we determined the maximum load for five repetitions (5RM) with 2-min rests between sets. One repetition maximal strength (1RM) was then calculated using the Baechle and Earle equation.<sup>14</sup> The muscle strength variables recorded were 1RM estimated as absolute (kg) and relative to body weight values for the exercises: leg press, chest press, and lat pulldown.

#### *Anthropometric data and body composition*

Body composition was assessed with a dual x-ray absorptiometry (DXA) system (Hologic QDR Discovery, Bedford, MA, USA). The anthropometric and body composition data collected were weight (kg), height (cm<sup>2</sup>), BMI (kg/m<sup>2</sup>), total fat mass (kg), body adiposity index (BAI) (%), fat mass index (FMI) (kg/m<sup>2</sup>), visceral adipose tissue (VAT) area (cm<sup>2</sup>), VAT mass (g), total fat-free mass (kg), trunk fat-free mass (kg), mean arms fat-free mass (kg), mean legs fat-free mass (kg), fat-free mass index (FFMI) (kg/m<sup>2</sup>), skeletal muscle index (SMI) (kg/m<sup>2</sup>), and appendicular skeletal muscle index (ASMI) (kg/m<sup>2</sup>).

## 2.5.3 | Secondary outcomes

### *Pulmonary function*

For spirometry, we followed the recommendations of the American Thoracic Society and European Respiratory Society,<sup>15</sup> using the MGC Diagnostics Spirometer (CPFS/D USB, MGC Diagnostics, St. Paul, MN, USA). The pulmonary function variables recorded were forced expiratory volume in 1 s (FEV<sub>1</sub>), forced vital capacity (FVC), both in milliliters and percentage predicted value, and the ratio between them (FEV<sub>1</sub>/FVC).

### *Quality of life*

To assess quality of life, the Cystic Fibrosis Questionnaire-Revised (CFQR 14+) was used. CFQR 14+ consists of 50 items classified into 12 domains: physical functioning, role, vitality, emotional functioning, social, body image, eating disturbances, treatment burden, health perceptions, weight, respiratory symptoms, and digestive symptoms. As results, a score for each domain is obtained, where 100 points indicate the best quality of life for the different domains.

## 2.6 | Sample size

A convenience sample was obtained comprising adults with CF registered at the Pneumology outpatient's clinic at the HU La Princesa. Sample size was calculated using

the package GPower v3.11. Based on repeated measures ANOVA and assuming a Type 1 error of 5%, a power of 80% and an effect size  $\eta_p^2=0.08$  from moderate ( $\eta_p^2=0.06$ ) to large ( $\eta_p^2=0.14$ ) on the variable leg strength, the sample size calculated was 26 patients. Allowing for 20% expected losses, the number of participants needed was 32. Leg strength was used for sample size calculation, as quadriceps muscle dysfunction is an important variable in the prognosis of pulmonary diseases,<sup>16</sup> and the most affected musculature in CF patients.<sup>17</sup>

## 2.7 | Randomization

The 32 participants were randomly assigned to the groups EX and CON ( $n=16$  each). For randomization, an investigator not involved in this study used individual codes and the randomization function of Microsoft Excel.

## 2.8 | Blinding

The investigator conducting the data analysis and the physician responsible for clinical assessments were unaware of participant allocation to the groups. As this was an intervention based on exercise, the responsible investigators could not be blind to the training protocol. Participants were explicitly informed of their group allocation, and were instructed to not disclose it to the investigation staff.

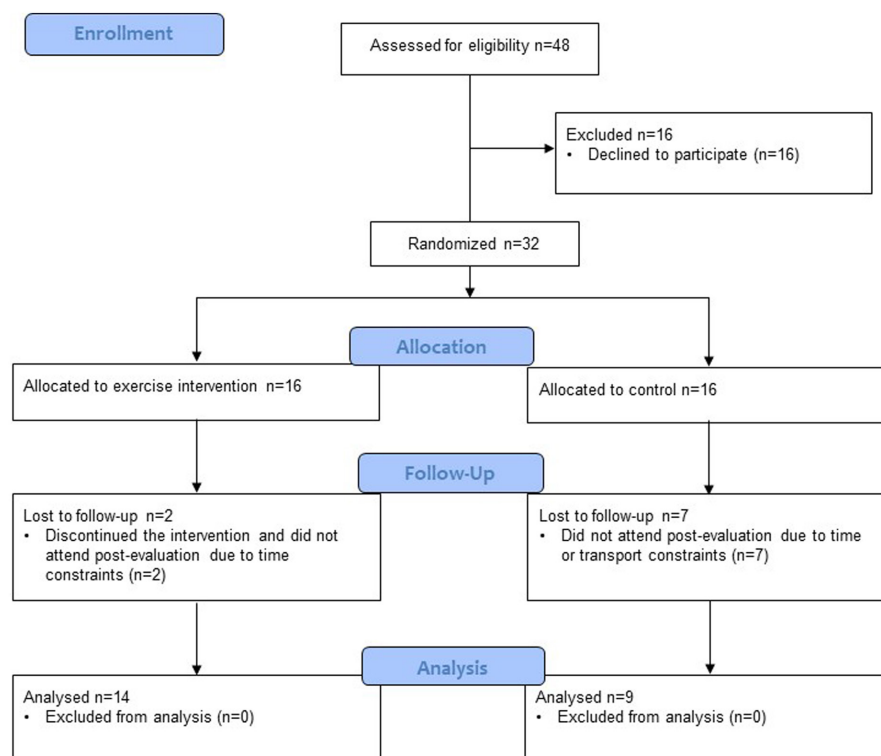


FIGURE 1 Participant flow.

TABLE 1 Baseline characteristics of the study participants.

	EX (n = 14)	CON (n = 9)	Total (n = 23)	p
<b>Demographics</b>				
Sex, men, n (%)	8 (57.1)	3 (33.3)	11 (47.8)	0.400
Age (years), mean (SD)	31.57 (7.34)	33.00 (8.66)	32.13 (7.72)	0.675
<b>Anthropometrics, mean (SD)</b>				
Weight (kg)	59.94 (8.75)	57.50 (11.31)	58.98 (9.66)	0.566
Height (cm)	163.71 (7.36)	166.67 (9.86)	164.87 (8.34)	0.420
BMI (kg/m <sup>2</sup> )	22.29 (2.18)	20.51 (2.19)	21.60 (2.31)	0.070
<b>Pulmonary function, mean (SD)</b>				
FEV <sub>1</sub> (mL), median (Q1–Q3)	2328.00 (1807.50–2710.00)	2040.00 (1611.00–3240.00)	2286.00 (1611.00–3240.00)	0.781
FEV <sub>1</sub> (%)	67.50 (21.00)	66.56 (16.82)	67.13 (19.07)	0.911
FVC (mL)	3814.29 (832.88)	3720.00 (1574.52)	3777.39 (1146.13)	0.852
FVC (%)	89.93 (13.18)	84.56 (16.30)	87.83 (14.371)	0.394
FEV <sub>1</sub> /FVC	62.07 (13.79)	65.11 (6.53)	63.26 (11.41)	0.486
<b>Cardiorespiratory capacity, mean (SD)</b>				
VO <sub>2peak</sub> (mL/kg/min)	32.61 (6.93)	31.14 (13.43)	32.03 (9.72)	0.733
VO <sub>2peak</sub> (%predicted)	86.71 (18.61)	87.33 (29.66)	86.96 (22.91)	0.951
<b>Genotype, n (%)</b>				
F508del homozygous	6 (42.9)	2 (22.2)	8 (34.8)	0.496
F508del heterozygous	3 (21.4)	4 (44.4)	7 (30.4)	
Other mutations	5 (35.7)	3 (33.3)	8 (34.8)	
<b>Modulator therapy, n (%)</b>				
None	6 (42.9)	5 (55.6)	11 (47.8)	0.831
Ivacaftor	1 (7.1)	0 (0)	1 (4.3)	
Tezacaftor/ivacaftor	5 (35.7)	3 (33.3)	8 (34.8)	
Elexacaftor/lumacaftor/ ivacaftor	2 (14.3)	1 (11.1)	3 (13)	
<b>Clinical diagnoses, n (%)</b>				
Exocrine pancreatic insufficiency	13 (92.9)	6 (66.7)	19 (82.6)	0.260
CF-related liver disease	3 (21.4)	1 (11.1)	4 (17.4)	1.000
CF-related diabetes mellitus	5 (35.7)	2 (22.2)	7 (30.4)	0.657
<b>Microbiology, n (%)</b>				
Chronic <i>Pseudomonas aeruginosa</i>	2 (14.3)	3 (33.3)	5 (21.7)	0.890
Chronic <i>Staphylococcus aureus</i>	4 (28.6)	3 (33.3)	7 (30.4)	0.827
Chronic <i>Burkholderia cepacia</i>	2 (14.3)	1 (11.1)	3 (13.0)	1.000
<b>Lifestyle questionnaires, n (%)</b>				
RAPA, physically active	10 (71.4)	8 (88.9)	18 (78.3)	0.611
RAPA, strength training	9 (64.3)	6 (66.7)	15 (65.2)	1.000
PREDIMED, good adherence	8 (57.1)	4 (44.4)	12 (52.2)	0.680

Note: Data are presented as mean (SD), median (Q1–Q3) or n (%). Differences between groups were detected using the Student's *t*-test, Mann–Whitney *U*-test, chi-squared<sup>2</sup> test, or Fisher's exact tests, as appropriate. Significance was set at *p* < 0.05.

Abbreviations: BMI, body mass index; cm, centimeters; CON, control group; EX, exercise group; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; g, grams; kg, kilograms; m, meters; ml, milliliters; PREDIMED, Prevention with Mediterranean Diet; Q1, first quartile; Q3, third quartile; RAPA, Rapid Assessment of Physical Activity; SD, standard deviation; VO<sub>2peak</sub>, peak oxygen uptake.

## 2.9 | Statistical methods

Results were analyzed per protocol. The normality of the distributions of variables were checked using the tests Shapiro–Wilk and Levene and by constructing P–P and Q–Q plots. Variables are provided as the mean and standard deviation, median, and interquartile range (Q1–Q3), or as the frequency and percentage as appropriate. To compare baseline variable means between the EX and CON groups we used the Student's *t*-test for parametric variables, the Mann–Whitney *U*-test for nonparametric variables and the Fisher's exact test for categorical variables. Two-way repeated measures analysis was used for the different groups (EX and CON), time points (T1 and T2), and their interaction effects (group×time). To minimize the risk of Type 1 errors, we only considered this interaction. Statistical tests were performed using the IBM SPSS Statistics 28.0 package for MAC (28.0.1.1 version 14). Significance was set at  $p < 0.05$ .

## 3 | RESULTS

### 3.1 | Recruitment and retention

Of a total sample of 48 eligible patients, 32 were randomly assigned to two groups. Two patients in the EX group and seven in the CON group were lost to follow-up. Patients of the EX group discontinued the intervention and did not attend post-evaluations due to time constraints. The reasons given by patients of the CON group were time or transport constraints to attend post-evaluation, leaving a final study

population of 14 patients in EX and 9 patients in CON. Participant flow is depicted in Figure 1. The training program was well tolerated and the compliance was 80%. Study was conducted between October and December 2021.

### 3.2 | Participant characteristics

The main features of the participating patients can be seen in Table 1. No significant differences were detected between groups at baseline in terms of demographics and anthropometrics, pulmonary function, cardiorespiratory capacity, genotype, modulator therapy, clinical diagnoses, microbiology, quality of life, physical activity level, and adherence to the Mediterranean diet.

### 3.3 | Outcome variables

There were no significant differences in baseline primary and secondary outcome variables between groups.

#### 3.3.1 | Primary outcome variables

##### *Peripheral muscle strength*

In response to the intervention, a significant effect of the interaction (group×time) was observed on the variable 1RM leg press both absolute ( $p=0.011$ ) and relative ( $p=0.007$ ) with a large effect size ( $\eta_p^2=0.281$  and  $\eta_p^2=0.310$ , respectively), increasing 38% in the EX group (Figure 2). However,

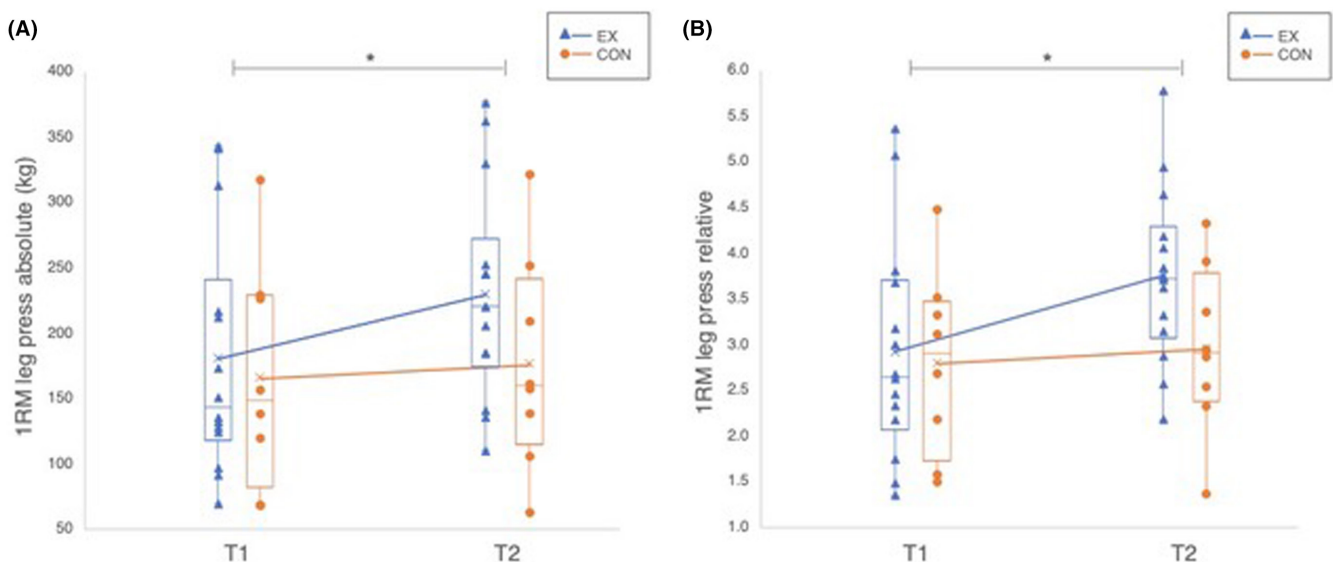


FIGURE 2 Effects of the strength training intervention on peripheral muscle strength in adults with cystic fibrosis. (A) 1RM leg press in kg (absolute); (B) 1RM leg press in kg (relative). Kg: kilogram; EX: exercise group; CON: control group; T1: study outset or baseline; T2: 8 weeks. Data presented as the mean and standard deviation. Differences were assessed by two-way repeated measures ANOVA. \*indicates significant differences for the interaction group×time ( $p < 0.05$ ).

TABLE 2 Effects of the strength training intervention on body composition. EX ( $n = 14$ ), CON ( $n = 9$ ).

Variables	Group	T1	T2	p-Value for group effect	p-Value for time effect	p-Value for interaction (group $\times$ time) effect	$\eta^2_p$
Body composition, mean $\pm$ SD							
Weight (kg)	EX	59.94 (8.75)	59.79 (8.14)	0.647	0.210	0.087	0.133
	CON	57.50 (11.31)	58.41 (11.29)				
BMI (kg/m <sup>2</sup> )	EX	22.29 (2.18)	22.25 (2.06)	0.097	0.166	0.079	0.140
	CON	20.51 (2.19)	20.85 (2.24)				
Total fat mass (kg)	EX	17.81 (3.98)	16.83 (3.69)	0.790	0.990	<0.001*	0.415 (power = 0.957)
	CON	16.39 (4.24)	17.36 (3.74)				
BAI (%)	EX	29.88 (5.92)	28.34 (5.86)	0.861	0.694	<0.001*	0.436 (power = 0.970)
	CON	28.93 (6.49)	30.19 (5.77)				
FMI (kg/m <sup>2</sup> )	EX	6.66 (1.48)	6.30 (1.43)	0.573	0.981	<0.001*	0.445 (power = 0.974)
	CON	5.95 (1.59)	6.30 (1.44)				
VAT area (cm <sup>2</sup> )	EX	78.44 (31.88)	73.06 (27.37)	0.179	0.285	0.143	0.099
	CON	60.23 (20.75)	61.11 (14.24)				
VAT mass (g)	EX	378.20 (153.71)	352.26 (131.94)	0.179	0.285	0.143	0.099
	CON	290.40 (100.04)	294.61 (68.64)				
Total fat-free mass (kg)	EX	42.13 (7.58)	42.96 (7.48)	0.689	0.076	0.046*	0.177 (power = 0.526)
	CON	14.58 (2.09)	14.57 (2.08)				
Trunk fat-free mass (kg)	EX	20.86 (3.19)	21.44 (3.25)	0.740	0.072	0.039*	0.188 (power = 0.558)
	CON	41.11 (10.44)	41.05 (10.30)				
Arm fat-free mass (kg)	EX	20.65 (4.09)	20.61 (4.31)	0.536	0.092	0.827	0.002
	CON	2.29 (0.73)	2.33 (0.63)				
Leg fat-free mass (kg)	EX	2.08 (0.90)	2.13 (0.87)	0.810	0.313	0.299	0.051
	CON	6.62 (1.43)	6.70 (1.43)				
FFMI (kg/m <sup>2</sup> )	EX	6.48 (2.15)	6.48 (2.05)	0.162	0.062	0.048*	0.174 (power = 0.518)
	CON	15.61 (1.86)	15.93 (1.87)				
SMI (kg/m <sup>2</sup> )	EX	14.58 (2.09)	14.57 (2.08)	0.161	0.051	0.055	0.164
	CON	14.83 (1.77)	15.15 (1.78)				
ASMI (kg/m <sup>2</sup> )	EX	13.84 (1.99)	13.83 (1.98)	0.273	0.098	0.598	0.013
	CON	6.18 (1.11)	6.27 (1.05)				
	CON	5.64 (1.36)	5.69 (1.28)				

Note: Differences between groups, time, and group  $\times$  time were assessed through two-way repeated measures ANOVA. Effect size ( $\eta^2_p$ ) is reported for all variables, and statistical power is reported for significant  $p$ -values recorded for the interaction (group  $\times$  time).

Abbreviations: ASM, appendicular skeletal muscle index; BAI, body adiposity index; BMI, body mass index; cm, centimeters; CON, control group; EX, exercise group; FFMI, fat-free mass index; FMI, fat mass index; g, grams; kg, kilograms; m, meters; SD, standard deviation; SMI, skeletal muscle index; VAT, visceral adipose tissue.

\*Significance was set at  $p < 0.05$ .

no upper body strength gains in the chest press and lat pull-down exercises, neither absolute nor relative were found. One participant from CON group could not perform leg press assessment and another participant in CON group could not perform upper body strength assessments.

### Body composition

The intervention led to significant (group  $\times$  time) changes with a large effect size in total fat mass, BAI, and FMI (Table 2), with a mean reduction of 5.23%, 5.12%, and 5.23%, respectively in the EX group. Significant effects of the interaction with a large effect size were also observed in total fat-free mass, trunk fat-free mass, and FFMI (Table 2), consisting of mean increases of 2.04%, 2.83%, and 2.04%, respectively for the EX group (Table 2).

### 3.3.2 | Secondary outcome variables

#### Pulmonary function

No impacts of the intervention were produced on any of the pulmonary function variables (Table 3).

#### Quality of life

No impacts were produced on the quality of life scores for any domain of the CFQR 14+ questionnaire (Table 4).

## 4 | DISCUSSION

This study was designed to assess the effects of a remotely supervised 8-week resistance training program of moderate to high intensity and individualized progressions in

adult patients with CF. This intervention resulted in improved leg muscle strength and body composition in terms of reduced fat mass and increased fat-free mass. This main result suggests that despite carrying a CFTR defect at the muscular level, the adult CF patient responds to training, improving both muscle function and structure.

Abnormal muscle CFTR protein could compromise potential strength gains due to contractile and metabolic alterations.<sup>6</sup> While physical exercise could be the most effective tool to manage muscular dysfunction, it should be stressed that responses depend on an adequate exercise modality and dose. As patients with CF show most marked weakness in the legs,<sup>17</sup> improvements in this musculature are an important clinical target.

Our intervention led to significant improvements in EX group compared to CON group in terms of the 1RM leg press as also observed by Beaudoin et al. in response to a 12-week combined training program.<sup>18</sup> Conversely, Rovedder et al. observed no leg muscle strength gains following 12 weeks of daily combined training sessions.<sup>19</sup> This could be due to their younger study population or to the importance of individualized training loads and adequate supervision.

In CF, muscle strength correlates positively with pulmonary function and functional capacity<sup>20</sup> making the improvement of muscular strength of great clinical relevance.

In the trial by Rovedder et al. strength gains in the upper limbs were observed,<sup>19</sup> while Beaudoin et al. reported increased strength in the bench press but not the lat pulldown.<sup>18</sup> In our intervention, no significant strength gains were observed in the bench press or lat pulldown, possibly due to the shorter duration.

Body composition studies in patients with CF have highlighted the relevance of this assessment over BMI as

**TABLE 3** Intervention effects on pulmonary function. EX ( $n = 14$ ), CON ( $n = 9$ ).

Variables	Group	T1	T2	p-Value for group effect	p-Value for time effect	p-Value for interaction (group $\times$ time) effect	$\eta_p^2$
Pulmonary function, mean (SD)							
FEV <sub>1</sub> (mL)	EX	2374.00 (785.52)	2269.29 (867.50)	0.671	0.721	0.227	0.069
	CON	2470.22 (1205.80)	2527.78 (1145.31)				
FEV <sub>1</sub> (%)	EX	67.50 (21.00)	66.07 (20.04)	0.912	0.781	0.209	0.074
	CON	66.56 (16.82)	68.78 (14.40)				
FVC (mL)	EX	3814.29 (832.88)	3739.29 (794.96)	0.927	0.595	0.332	0.045
	CON	3720.00 (1574.52)	3742.22 (1551.52)				
FVC (%)	EX	89.93 (13.18)	88.36 (10.22)	0.459	0.720	0.380	0.037
	CON	84.56 (16.30)	85.22 (15.49)				
FEV <sub>1</sub> /FVC	EX	62.07 (13.79)	62.14 (13.89)	0.425	0.216	0.248	0.063
	CON	65.11 (6.53)	67.11 (7.08)				

Note: Differences between groups, time, and group  $\times$  time were assessed through two-way repeated measures ANOVA. Significance was set at  $p < 0.05$ . Effect size ( $\eta_p^2$ ) is reported for all variables, and statistical power is reported for significant  $p$ -values recorded for the interaction (group  $\times$  time).

Abbreviations: CON, control group; EX, exercise group; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; mL, milliliters; SD, standard deviation.



TABLE 4 Effects of the strength training intervention on CFQ-R. EX ( $n=14$ ), CON ( $n=9$ ).

Variables	Group	T1	T2	p-Value for group effect	p-Value for time effect	p-value for interaction (group × time) effect	$\eta_p^2$
The Cystic Fibrosis Questionnaire-Revised, mean (SD)							
CFQ-R physical	EX	79.76 (15.23)	77.38 (11.98)	0.357	0.036	0.227	0.069
	CON	75.46 (22.29)	67.13 (27.83)				
CFQ-R vital	EX	73.21 (19.39)	66.07 (23.90)	0.557	0.202	0.568	0.016
	CON	75.92 (21.02)	73.15 (18.99)				
CFQ-R emotional	EX	88.09 (11.74)	85.71 (13.30)	0.216	0.919	0.385	0.040
	CON	74.81 (31.58)	77.77 (26.67)				
CFQ-R eat	EX	89.68 (15.38)	90.48 (13.68)	0.763	0.880	0.880	0.001
	CON	87.65 (25.72)	87.65 (25.73)				
CFQ-R treat	EX	61.91 (13.58)	61.11 (12.13)	0.405	0.514	0.736	0.006
	CON	55.55 (28.33)	53.08 (29.80)				
CFQ-R health	EX	79.37 (18.42)	76.99 (16.57)	0.440	0.328	0.829	0.002
	CON	72.84 (30.48)	69.14 (27.09)				
CFQ-R social	EX	77.78 (17.02)	78.57 (11.70)	0.335	0.600	0.788	0.004
	CON	70.99 (17.29)	73.46 (17.95)				
CFQ-R body	EX	84.82 (24.11)	83.33 (18.36)	0.227	0.343	0.702	0.007
	CON	74.07 (26.64)	70.37 (25.46)				
CFQ-R role	EX	87.50 (20.61)	92.26 (8.93)	0.333	0.372	0.062	0.156
	CON	90.74 (14.70)	77.78 (21.65)				
CFQ-R weight	EX	73.81 (29.75)	64.29 (40.22)	0.870	0.053	0.442	0.031
	CON	77.78 (37.26)	55.56 (47.14)				
CFQ-R respiratory	EX	78.57 (15.38)	76.19 (10.80)	0.197	0.431	0.921	0.000
	CON	69.13 (23.09)	67.28 (21.42)				
CFQ-R digestive	EX	80.16 (16.98)	80.16 (18.06)	0.786	0.558	0.558	0.017
	CON	80.25 (19.86)	83.95 (17.67)				

Note: Differences between groups, time, and group × time were assessed through two-way repeated measures ANOVA. Significance was set at  $p < 0.05$ . Effect size ( $\eta_p^2$ ) is reported for all variables, and statistical power is reported for significant  $p$ -values recorded for the interaction (group × time).

Abbreviations: CFQ-R, Cystic Fibrosis Questionnaire-Revised; CON, control group; EX, exercise group; SD, standard deviation.

an indicator of nutritional status, as it is a good predictor of disease progression.<sup>4</sup> Hence, within a normal BMI, there could be a hidden excess of body fat, which is in turn associated with worse pulmonary function.<sup>21</sup>

When we examined the impacts of our intervention on body fat, we detected improvements in total fat mass, BAI, and FMI. Similarly, Beaudoin et al. observed lowered fat mass. As we did, these authors used DXA for body composition measurements as the gold standard procedure.<sup>22</sup> In contrast, controversial results were obtained in the study by Reuveny et al. in that increased BAI was found in the groups completing the exercise interventions.<sup>23</sup>

It should be stressed that in CF patients, a lower fat-free mass has been associated with worse pulmonary function, a greater number of exacerbations,<sup>24</sup> and increased mortality.<sup>25</sup> The loss of fat-free mass even within a normal range BMI is linked to a greater bone mineral

density loss and systemic inflammation.<sup>26</sup> This means that maintaining an adequate fat-free mass is important at the multisystemic level.

To date, randomized controlled trials of physical exercise interventions in adult CF patients have not detected improvements in fat-free mass.<sup>18,23,27</sup> Our intervention, nevertheless, led to significant improvements in total fat-free mass, trunk fat-free mass, and FFMI. Despite the resistance training component of the intervention assessed by Beaudoin et al.<sup>18</sup> no improvements were produced in fat-free mass. This is possibly due to the importance of supervision of training sessions to achieve the adequate dose. Other studies in which fat-free mass improvements could not be achieved were based on high-intensity interval training,<sup>23,27</sup> not the optimal for muscle strength gains. In our study, besides total fat-free mass, a significant increase was detected specifically in trunk fat-free

mass. This could be attributed to the involvement of the core muscles in the exercises performed. Our study is the first randomized controlled trial to obtain improvements in fat-free mass in adults with CF.

The resistance training modality and the short duration of this trial were not adequate to achieve improvements in lung function in this progressive lung disease, as observed in previous studies.<sup>18,19</sup> In this regard, in adult CF patients, a mainly cardiovascular exercise intervention of 1 year duration has managed to slow the lung function deterioration, but without statistically significant effect.<sup>28</sup>

The participants of our study perceived no improvement in quality of life in any domain of the CFQR 14+ questionnaire. This finding is consistent with those of Beaudoin et al. and Rovedder et al. who also detected no significant changes in quality of life.<sup>18,19</sup> Pulmonary function may be a key factor in achieving significant improvements in quality of life.<sup>29</sup> Additional factors such as anxiety, depression, familiar, social, financial, and educational may also play an important role in these patients.<sup>30,31</sup> Nevertheless, despite finding no statistically significant effects in quality of life for most domains, in this study, a clinically relevant effect was found in the role functioning domain.

In view of the new era of CFTR modulators, improvements in channel functioning will bring about changes in the physiology of CF patients, promoting an increase in the BMI as the consequence of improved nutrient absorption. Considering that any increase in BMI is preferable to be a result of increased muscle mass, physical exercise is a tool to potentiate improvements in this body composition and its clinical consequences.

The present study has certain limitations including a considerable number of losses to follow-up. The reasons given by participants who dropped out of the study were difficulties in getting to the testing sites. The clinical situation of adult patients with CF explains these difficulties. Despite this, significant results were obtained with a large effect size. For the secondary outcomes, it is possible that the sample size falls short of allowing for the detection of significant changes or that a longer intervention duration is warranted.

## 5 | CONCLUSION

A remotely supervised 8-week resistance training program of moderate to high intensity and individualized progressions was able to improve both the strength of the lower limbs and the body composition of adult CF subjects, despite CFTR dysfunction at the muscular level. No changes in pulmonary function or quality of life attributable to the intervention were observed.

## 6 | PERSPECTIVE

Given the favorable response of muscle functionality to a short duration resistance exercise training on a muscle with CFTR failure, we believe that future longer term research with adherence analysis is necessary to know the extent of this effect. Research should also focus on the interaction of exercise with the new CFTR modulating/potentiating drugs, recently implemented in the clinical care of these patients. In terms of practical applications, we suggest implementing muscle function assessments in the specialist physician's clinic to identify the patients at risk of sarcopenia. Additionally, implementing body composition and muscle function analysis as predictors of hospitalization and pulmonary exacerbation.

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### CONFLICT OF INTEREST STATEMENT


The authors declares no conflict of interest.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.


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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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