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Benjamin Crain April 9, 2020

Interrelationships Between Body Composition, Physical Functioning, and Quality of Life in Adults with Cystic Fibrosis

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a thesis submitted to the Faculty of Emory College of Arts and Sciences
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Abstract

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Background and Objectives: Maintaining lean mass, a higher level of physical activity, and peripheral muscle strength are associated with more favorable outcomes and increased lifespans for individuals with Cystic Fibrosis (CF). This study aimed to compare physical activity, muscle strength, and muscle quality in individuals with CF compared to healthy controls. We also assessed the relationships between body composition, peripheral muscle strength, muscle quality, and physical activity with quality of life.

Study design and Methods: This was an observational, cross sectional study design in adults (ages 18 - 50) with CF (n = 27) and age-matched healthy controls (n = 25). Body composition was assessed with dual energy X-ray absorptiometry, physical activity by a self-reported questionnaire, peripheral strength by handgrip dynamometry, and quality of life by the Cystic Fibrosis Quality of Life-Revised (CFQ-R) questionnaire. Muscle quality was determined by handgrip strength divided by arm lean mass. Statistical analyses included t-tests and Pearson's or Spearman's correlations.

Results: Demographics, body composition, handgrip strength, and muscle quality were similar between individuals with CF and healthy controls. Among adults with CF, hand grip strength was positively, significantly associated with lean mass and bone mineral density. Higher levels of physical activity were positively associated with higher quality of life scores, and more total body fat and body fat percent were associated with lower quality of life scores.

Discussion: This study provides further evidence of the need to maintain lean mass and engage in physical activity for increased quality of life among individuals with CF. Results also indicated that hand grip strength may be a clinically useful surrogate for body composition. Future studies should determine if exercise interventions to increase lean mass and fitness levels can improve quality of life for individuals with CF.

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Introduction

Cystic fibrosis (CF) is an autosomal recessive inherited trait caused by a mutation of the cystic fibrosis transmembrane protein (CFTR) on the long arm of chromosome 7. CF is the most common life-shortening autosomal recessive disease among individuals of European descent, and it affects approximately 1 in 2,500 Caucasian newborns. [1] As of 2018, there were more than 30,000 people living with CF in the U.S. [2,3]

There are over 2,000 known CFTR mutations, with almost 300 identified as disease-causing mutations. The delta F508 mutation (caused by a deletion of the codon for phenylalanine at position 508) is the most common CFTR gene mutation. This mutation affects approximately 80% of all individuals with CF, and causes abnormal folding of the secondary and tertiary CFTR protein. [4] The delta F508 mutation, as well as the other mutations that cause CF, lead to a wide variety of health complications that impact the entire body. The main life-limiting health complications are lung function decline leading to pulmonary failure and pancreatic insufficiency which causes malabsorption issues and malnutrition. Major improvements in CF diagnostics and disease management have increased the lifespan and quality of lives for people with CF; therefore, it is increasingly important to understand the disease process, comorbidities, and ways to manage the disease to optimize quality of life in an aging population.

1.1 CF Pathophysiology

The mutations that cause CF occur on the CFTR gene which encodes the CFTR protein, an ATP-regulated chloride ion channel. These CFTR proteins are located on the surface cells of the lungs, gastrointestinal tract (GI), and pancreas. [5]

The primary cause of death in CF is due to pulmonary complications. Lung disease that is associated with the later stages of CF occurs largely from changes in the composition of the

airway surface liquid (ASL). In healthy airways, the respiratory epithelium is lined by ASL which lies under a mucus layer and is secreted by goblet and Clara cells. The ASL is important for homeostasis in the airway. The volume, pH, and ionic and nutrient content of the ASL are all important for its antimicrobial activity and mucociliary transport. [6]

In CF patients, the ASL becomes dehydrated and acidic due to various dysfunctional proteins. For people who have the delta F508 mutation, the altered protein structure of the CFTR inhibits chloride and bicarbonate ion transport in response to elevated cAMP levels in epithelial cells (which would normally activate the ion transport) (**Figure 1**). The lack of bicarbonate acidifies the ASL, decreasing the antimicrobial abilities of the mucus layer. The abnormal chloride transport causes increased sodium and water absorption into the epithelial cells which dehydrates the airway. When the airway becomes dehydrated the osmotic gradient is disrupted, and water is pushed out of the ASL causing mucociliary transport to decrease. This reduction of mucociliary transport leads to mucus stasis, airway infection and inflammation, narrowing of the airway lumen (**Figure** 2), and ultimately CF lung disease. [7]

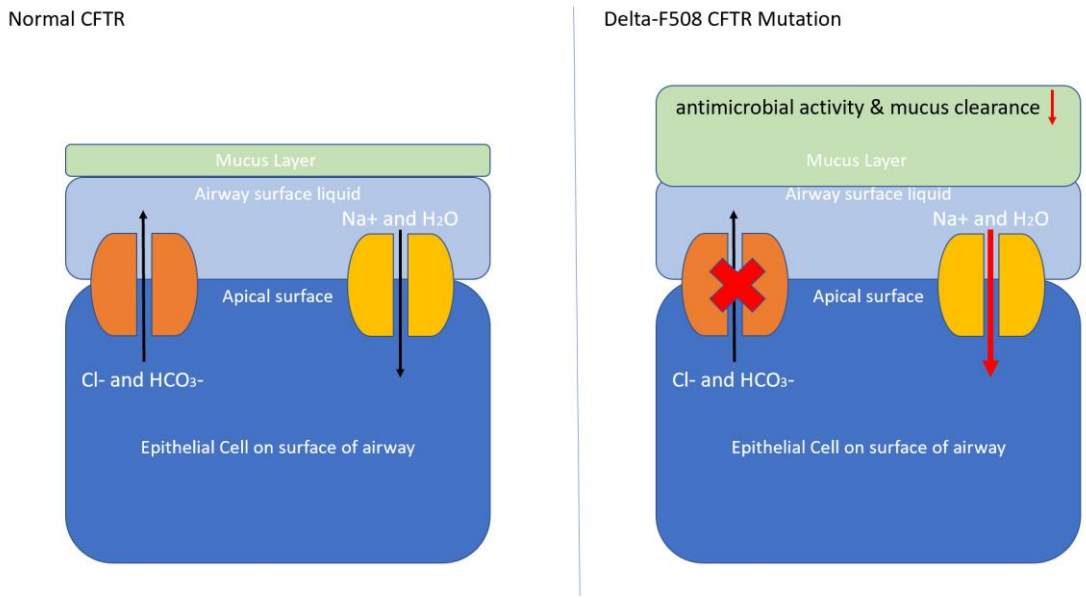

Figure 1: The Pathophysiology of the Delta F508 Mutation on the CFTR Protein

This image illustrates how the Delta F508 mutation creates thicker mucus, less mucus clearance, and a decrease in the antimicrobial properties of the mucus layer in the airway.

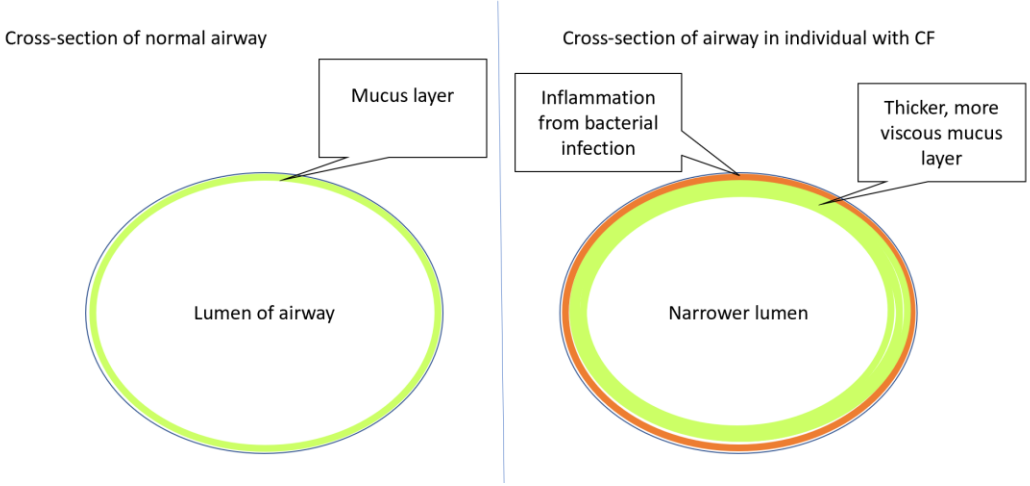

Figure 2: Effects of CF on the airway

This image illustrates how the lumen of the airway narrows from the thickened mucus that results from CFTR mutations. The thickened mucus leads to bacterial infections which causes inflammation in the airway.

In addition, there are many non-pulmonary complications in CF that cause morbidity and can eventually lead to mortality. Pancreatic insufficiency (PI) is a key characteristic of CF that affects approximately 85% of people with CF early in their lives.[8] Some individuals with CF have pancreatic disease beginning in the fetus. Infants with CF have shown decreased development of pancreatic acinar tissue compared to age-matched controls.[9] The lack of exocrine pancreatic enzymes necessary for digestion leads to malabsorption issues. Some common symptoms of PI are weight loss, excess gas, bloating, dyspepsia, and steatorrhea (loose and smelly stools).[10] Malabsorption of fat in CF often leads to fat soluble vitamin deficiencies (A, D, E, and K). Additional gastrointestinal issues experienced by individuals with CF include constipation, appendicitis, cholecystitis, meconium ileus in infants, and distal obstruction syndrome.

Other co-morbidities experienced by individuals with CF include CF-related diabetes (CFRD), CF-related bone disease, and infertility. CFRD occurs in up to 50% of individuals with CF and occurs due to endocrine pancreatic damage, although exact mechanisms leading to damage are yet to be elucidated.[10] CFRD increases the likelihood of mortality and decreases quality of life for people with CF. Common causes of CF-related bone disease are malabsorption of vitamins and minerals to maintain bone health, and elevated pro-inflammatory cytokines from chronic lung infections which can promote bone loss. Lack of weight-bearing exercise and frequent prescription of steroidal medications can also lead to a progressive loss of bone mass.[11] Additionally, individuals with CF may experience infertility. For men, this is caused by congenital bilateral absence of the vas deferens which leads to obstructive azoospermia. Overall, people diagnosed with CF must constantly act in a health-conscious manner as CF can create a wide range of health issues throughout the body.

1.2 CF Screening

Screening for CF has now become routine for newborns. [12] The National Institute for Health and Care Excellence (NICE) have created guidelines to increase the diagnosis and management of CF earlier in patients' lives. The UK created a neonatal screening program in 2007 that tested every newborn for CF, so the median age of diagnosis is now 2 months old. The screening considers the following domains: family history, congenital intestinal atresia, meconium ileus, undernutrition, malabsorption, recurrent pulmonary disease, rectal prolapse, pseudo-Bartter syndrome, a chloride sweat test, and a genetic test. The sweat test measures chloride levels in the patient's sweat, and if the chloride concentration is above 60 mmol/L then a diagnosis of CF is made. The genetic test is a simple blood test that gets analyzed by a genetic lab which looks at any possible mutations in chromosome 7. Widespread newborn screening and subsequent early CF treatment has contributed to improved survival and increased lifespan among individuals with CF.

1.3 Treatments for CF

Before 1980, children that were diagnosed with CF had low life expectancy and lifespan. Since then, research on treatments and therapies have extended the median lifespan of people diagnosed with CF to 47. [13] Chest physiotherapy is a well-established treatment which consists of 15 minutes of percussive therapy on the patient's back and chest. This is intended to loosen thick layers of mucus inside the patient's airway. Antibiotics are also used to treat airway infections.

Therapeutic medications designed to target the mutation in the CFTR gene and cure the disease have been in development over the past decade. New drugs such as CFTR modulators target defects in the protein made by the mutated CFTR gene and significantly improve

pulmonary complications of CF.[14,15,16,17,18] In 2019, the FDA approved a new combination of CFTR modulators that is expected to reach approximately 90% of the CF population.[19] Such new therapies will likely further improve lifespan in patients with CF, although their effects on co-morbidities or among patients with already advanced disease is unknown. Researchers are looking towards gene therapy as a future technology that will be able to put functional CFTR directly on lungs, essentially curing CF. [10] Until then, management of the disease, including the non-pulmonary GI and nutrition-related complications, is critical.

Achievement and maintenance of adequate nutrition status is a critical goal for patients of all ages with cystic fibrosis. Malnutrition in CF is associated with decreased survival and higher morbidity compared to individuals with CF who are adequately nourished.[20] Body mass index (BMI) also is strongly correlated to lung function, and increased survival.[21] An increase in body weight is associated with an increase in survival in the first 5 years of life. [22] Current Cystic Fibrosis Foundation guidelines recommend that CF patients achieve or maintain specific BMI goals. It is recommended that children and adolescents with CF maintain a BMI above the 50th percentile for their age on the growth chart and that women and men maintain a BMI above 22 kg/m^2 and above 23 kg/m^2, respectively. [23] High calorie, high-fat diets are recommended to counteract the malabsorption and ensure sufficient calorie and fat intake for normal growth and function.

1.4 Physical Activity

While physical activity (PA) is important for the general population to prevent chronic illness, PA is especially important for maintaining lung function, muscular strength, and a high quality of life for patients with CF. Arikan et al. (2015) showed that people with CF have a decreased exercise capacity and physical fitness than a healthy control group.[24] Pianosi et al.

(2005) showed that children with CF who have higher peak oxygen uptake demonstrate longer survival.[25] A longitudinal, randomized controlled trial of a 3-year home exercise program showed that aerobic physical activity can extend lifespan for adults with CF by delaying lung function decline.[26] In addition to increasing respiratory function, PA can increase physical and psychosocial health.[27] By engaging in exercise, patients with CF can maintain their muscular strength, lean muscle mass, and lung function which leads to healthier and longer lives.

Physical activity can be measured in many ways. Self-reported PA is a common way to track metabolic equivalent (MET) minutes per week for a given person. The International Physical Activity Questionnaire (IPAQ) is frequently used and is the measure employed in this study. Other self-reported measures are the Modifiable Activity Questionnaire and the Habitual activity estimation scale. [28,22]

1.5 Body Composition

Body composition is an under-utilized indicator of health among individuals with CF. Body composition assesses the different constituents of weight in the body: fat-free mass (FFM) and fat mass. Muscle, bone, connective tissue, and the organs are the different components of body weight within FFM. While BMI is a major indicator of nutritional status in CF, it cannot be used to assess body composition, as it does not distinguish between fat mass and FFM. Reports of a hidden depletion of FFM have been published in CF, where individuals have a "normal" BMI, but FFM is low compared to controls.[29] In addition, our lab has identified a relatively high prevalence (30%) of normal weight obesity among adults with CF; these individuals have a normal BMI but a high body fat percent. Compared to those who were appropriately categorized as lean or who were overweight, individuals with normal weight obesity had decreased lung function. Furthermore, in this study, whereas FFM was positively associated with lung function,

fat mass was inversely associated with lung function.[30] Other studies have shown that FFM was a stronger correlate of lung function compared to BMI or fat mass.[31] Papalexopoupou et al. found that for people with CF, FFM is a stronger predictor for pulmonary function, respiratory muscle function, and level of aerobic exercise than BMI. This study showed that FFM was inversely associated with exercise tolerance and the amount of antibiotics a subject took the past year, and FFM was positively (and significantly) associated to lung function.[22] In another lung disease, chronic obstructive pulmonary disease (COPD), a study showed that FFM is a stronger predictor of mortality than BMI or fat mass.[32] Thus, FFM is important to incorporate when assessing nutritional status in individuals with CF.

There are several methods available for the assessment of body composition, ranging in accuracy, clinical feasibility, and cost. A gold-standard tool that accurately assesses body composition is dual energy x-ray absorptiometry (DXA). DXA is an enhanced x-ray device that sends low levels of ionizing radiation through the subject, and differentiates between fat, muscle (lean mass), and bone. DXA allows for a better assessment of risk for sarcopenia (muscle loss), obesity, or osteoporosis (low bone mineral density).[33]

1.6 Peripheral Muscle Strength

Peripheral muscle strength is an important predictor for quality of life, level of physical activity, and the degree of lung function in a CF population.[34,35] Peripheral muscle strength is defined as strength from either the upper or lower extremities. For people with CF, malnutrition, treatments, and reductions in lung function can result in decreases of physical activity, muscle strength, and quality of life. Studies have found that hand grip strength is associated with respiratory muscle strength, peripheral muscle strength, and exercise intolerance, which are important predictors for premature mortality for adults with CF.[36,37] Rovedder et al. (2019)

conducted a prospective, cross-sectional study on a cohort of adults with CF (mean age = 24.6). The study tested peripheral muscle strength through isometric elbow flexor (biceps) and knee extensor (quadriceps) using 1-repetition maximum strength tests. The study demonstrated that subjects who had greater peripheral muscle strength, in both lower and upper extremities, had a greater exercise tolerance and had a greater FEV_1% (forced expiratory volume in 1 second, percent predicted). FEV_1% is a common assessment of lung function for people with CF. The study did not track daily physical activity levels, so it is not clear if people with CF had less muscular strength because of their disease or because they engaged in less physical activity.[34]

Arikan et al. (2015) conducted a comparative, cross-sectional study with a group of patients with CF that were aged matched with a healthy control group (ages 7-25). They examined peripheral muscle strength through an isometric knee extensor (quadriceps) test, a shoulder abductor test, and a hand grip (HG) strength test with a hand-held dynamometer. They also measured pulmonary function, respiratory muscle strength, exercise tolerance via the 6-minute walk test (6MWT), and physical activity with both the Glittre-ADL test and the Munich fitness test. The study showed that while hand grip strength was similar between groups, shoulder abductor and quadriceps strength was significantly lower in patients with CF than the healthy control group. Additionally, the CF group performed worse on the 6MWT (had less exercise tolerance) which was directly related to quadriceps strength.[24]

Troosters et al. (2009) conducted a similar study that was a comparative, cross-sectional study with a group of CF patients and aged matched controls. Troosters et al. (2009) examined upper peripheral muscle strength with a hand grip dynamometer and measured quadriceps strength with a seated dynamometer. This study tracked exercise tolerance using an incremental cycle ergometer test (cycled to exhaustion) as well as the 6MWT. Troosters et al. (2009) also

tracked physical activity by using an accelerometer (an armband with many sensors) to estimate their weekly METS. Consistent with Arikan et al. (2015), the CF group displayed less peripheral muscular strength, muscle mass, and exercise tolerance compared to controls. The study attributed this reduction to the CF group engaging in a significantly lower amount of moderate and intense physical activity. A limitation of this study was that their control group included trainers, therefore the control group was much more physically active, introducing bias to the study.[35]

1.7 Muscle Quality

Longitudinal studies of aging and sarcopenia have shown that muscle strength and muscle mass are not synonymous and do not change in a linear relationship.[38] Muscle quality can be quantified as the muscle strength, or power, per unit of muscle mass.[39] Muscle quality is an important factor in determining muscle function for adults.[40] Muscle quality may be able to serve as an additional assessment tool for sarcopenia, therefore it can aid in identifying individuals at risk for mobility impairments in older adulthood.[41] Since patients with CF are at a higher risk for sarcopenia, it's important to focus on ways to not only increase muscle mass, but also muscle quality. A randomized controlled trial study showed that upper limb resistance exercises can improve upper body muscle strength, inspiratory muscle strength, and quality of life for people that have COPD.[42] To our knowledge, there are no studies available to describe muscle quality in a CF population.

1.8 CF Quality of Life

Health Related Quality of Life (HRQoL) measures have become important to characterize the severity and timeline of chronic illnesses and can potentially decrease health care costs. HRQoL can be measured using a variety of methods but is generally assessed through

self-reported questionnaires. HRQoL is multidimensional and has four core domains: 1) disease state and its physical symptoms; 2) functional status; 3) psychological and emotional state; and 4) social functioning. HRQoL questionnaires must focus around the patient and their subjective daily experience. Further, HRQoL measures may be used for describing primary or secondary outcomes in a clinical trial, understanding how an illness impacts the daily function of a patient, aiding clinical decision making, and evaluating the effectiveness of an intervention.[43] The Cystic Fibrosis Questionnaire-Revised (CFQ-R) is widely used and validated HRQoL measurement tool that is specific for individuals with CF. The CFQ-R is a 12-domain and 50-item self-reported questionnaire that assesses the degree of the participant's physical, mental, and psychosocial symptoms for teens and adults (aged 14 and older).[44] The CFQ-R is scored from 0 to 100, with 100 representing the best quality of life and 0 representing the worst. Quittner et al. (2005) demonstrated that in terms of disease severity, people with mild severity CF score higher than those with moderate severity and late-stage CF patients, thus making the questionnaire practical to understand the progression of the disease.[43]

Quality of life measures are increasingly being recognized as important outcomes in clinical research, in addition to objective measures of health. Gancz et al. (2018) conducted a cross-sectional study in an outpatient clinic for young adults with CF (aged 14-21). This study examined the relationship of each CFQ-R domain with BMI, lung function (FEV_1), and the Shwachman-Kulczyki Score (SKS) which rates an individual's disease severity for CF. The study illustrated that BMI had significant associations with weight and eating disturbances, FEV_1 had significant associations with physical functioning and treatment burden, and SKS scores were significantly associated with health perception, physical functioning and role limitations.[45]

Abbott et al. (2013) conducted a prospective, longitudinal study to see how HRQoL measures and lung function change over time. The study illustrated that both lung function and HRQoL measures decreased over time at similar rates, concluding that HRQoL data provides an additional value of measuring disease severity for CF.[46] Abbott et al. (2013) noted that psychosocial domains, including career concerns, concerns for the future, and treatment burdens, decreased the most, indicating that HRQoL scores may have more to do with how an individual copes with their disease. If they optimistically cope (focused, determined, optimism for the future) they will have higher HRQoL measures than distraction coping (staying busy to keep mind off of disease).[47]

Solé et al. (2016) conducted a prospective, longitudinal study that aimed to validate the CFQ-R by testing whether lower scores correlated with people on the waitlist for lung transplantation (a procedure needed for survival in late-stage CF). The study illustrated that people with lower physical functioning scores and lower FEV_1 values had the highest inclusion on the waitlist for lung transplantation. This finding notably shows that the CFQ-R can help validate other measures, like FEV_1, which is commonly used to get a patient with CF on the waitlist for a new lung. Additionally, lower health perception scores and lower physical functioning scores correlated strongly with mortality. This shows that the CFQ-R validates the notion that how someone feels about their own health can be worthwhile for clinical outcomes.[48]

Dunnink et al. (2009) conducted a cross-sectional study to assess how BMI, respiratory muscle strength, lung function, peripheral muscle strength, and exercise capacity were correlated to the CFQ-R for stable adolescents and adults.[36] The study primarily showed a significant association between respiratory muscle strength and many of the CFQ-R domains.

1.9 Sex-Based Differences

There is a sex gap in clinical outcomes among individuals with CF. Females have worse outcomes compared to males.[36] Few studies have described the role of physical function on the disparities in outcomes between males and females. Martinez-Garcia et al. (2019) examined how the sex gap affects peripheral muscle strength for people with CF. In their observational, cross-sectional study design, they utilized an adult population (aged 18-65) with CF, and healthy controls matched for age and BMI. The study used HG strength, a sit-to-stand test (for muscular power), self-selected walking speed, and tested lung function. The study illustrated that while the females with CF had significantly reduced muscular strength and power compared to the female healthy controls, the males with CF had similar HG strength measures and walking speed compared to the male healthy controls. They also showed that females with CF displayed a significant relationship between muscle strength, functional mobility, and lung function.[49] The study argued that more respiratory distress, infections and subsequent inflammation among females causes an increase in resting energy expenditure and a decrease in muscle mass and strength.[50] The study concluded that exercise training may be the most effective intervention to address peripheral muscle weakness and should be recommended for CF patients, especially females.

1.10 Objective and Specific Aims

The objective of this study was to compare peripheral muscle strength and physical inactivity in a cohort of adults with CF to healthy controls, and also examine inter-relationships between PA, body composition, lung function, HG strength and muscle quality (peripheral muscle strength), and quality of life in adults with CF. The three specific aims of this study included:

Specific Aim 1) Compare body composition, peripheral muscle strength, muscle quality, and physical activity levels between the health control group and the CF group.

Null hypothesis: We hypothesized that there would be no difference in these measures between the healthy control and CF groups.

Alternative hypothesis: We hypothesized that the healthy control group would have greater muscular strength, higher muscle quality, and engage in more physical activity.

Specific Aim 2) Determine the relationships of muscle strength and muscle quality with physical activity and lung function in adults with CF.

Null hypothesis: There will be no statistically significant relationships of muscle strength and muscle quality with physical activity and lung function in adults with CF.

Alternative hypothesis: We hypothesized that adults with CF would have a positive, significant relationship between muscle strength and muscle quality with physical activity and lung function.

Specific Aim 3) Determine the relationships of quality of life domains with body composition, physical activity, muscle strength, and muscle quality in adults with CF.

Null hypothesis: Quality of life scores will have no significant relationships with body composition, physical activity, muscle strength, and muscle quality in adults with CF.

Alternative hypothesis: We hypothesized that adults with CF that have higher quality of life scores would have more fat free mass, a higher level of physical activity, more muscular strength, and a higher muscle quality.

Together, the primary goal of the study is to provide evidence for the maintenance of physical activity and peripheral muscle strength in order to improve quality of life for people

with CF. This information can help provide recommendations for engaging in physical activity for people with CF.

Materials and Methods

2.1 Subjects and Study Design

This study was an observational, cross-sectional study design that included 27 clinically stable adults with CF and 25 aged-matched healthy controls. Emory University Institutional Review Board approved this study and every subject provided written informed consent before participating. All testing procedures were conducted at the Emory University Hospital Clinical Research Network unit of the Georgia Clinical and Translational Science Alliance (Atlanta, GA, USA). The inclusion criteria for participants with CF was having a confirmed diagnosis of CF via a chloride sweat test and/or CFTR genetic test, confirmation of any Class I, II, or III CFTR mutation, and a stable medical regimen for at least three weeks (no recent pulmonary exacerbations or administration of oral or intravenous antibiotics or glucocorticoids). The exclusion criteria were pregnancy, inability or not willing to discontinue enteral tube feeds for a night prior to a study visit, most recently measured FEV_1 of less than 40%, or the presence of a recreational or prescription drug or alcohol abuse. Healthy control participants were recruited via flyers and word-of-mouth and had to be age-matched within 18 months of a subject with CF. The inclusion criteria for healthy control volunteers were 18-50 years old and the absence of any hospitalization in the previous year (aside from accidents). The exclusion criteria for controls were the presence of a chronic infection, respiratory disease, cardiometabolic disease, acute illness within the previous two weeks of measurement or recruitment, history of malignancy in the past 5 years, weight instability (+/- 10% of body weight within the previous 6 months), drug or alcohol abuse, or a BMI greater than 30 kg/m^2.

2.2 Lung Function

Measures of lung function were obtained from the electronic medical record. Spirometry testing is performed at the Emory University Hospital Adult CF Clinic which follows the American Thoracic Society/European Respiratory Society guidelines for pulmonary function testing.[51] The healthy control group did not undergo any lung function testing. The absolute values received from spirometry testing were compared to population-based reference values to determine forced expiratory volume in one second (FEV_1) percent predicted (FEV_1% predicted).

2.3 Body Composition

Whole and regional body composition was assessed with DXA using a Lunar iDXA densitometer. Lean mass, fat mass, percent body fat, arm lean mass, and bone mineral density (BMD) were quantified from the DXA measurement.

2.4 Quality of Life

Every participant with CF completed the CFQ-R, which assesses the degree of the participant's physical, mental, and psychosocial symptoms. The CFQ-R is a 50-question self-reported questionnaire that has 12 disease-specific domains. The domains and the number of items in each domain are as follows: physical functioning (8), role limitations (2), vitality (4), emotion (5), social health(5), body image (3), eating disturbances (3), treatment burden (2), health perception (3), weight (1), respiratory symptoms (6), and digestive symptoms (2). Each question is on a 4-point scale (1 = always, a lot of difficulty, or very true; 4 = never, no difference, or very false) and the questionnaire is scored from 0-100, with higher scores representing a better HRQoL. The questionnaire generally takes 15 minutes to complete. Quittner et al. (2005) validated the CFQ-R questionnaire for adolescents and adults (aged 14 and over) for its interrater and test-retest reliability.[43]

2.5 Hand Grip Strength and Muscle Quality

Peripheral muscle strength was estimated by handgrip strength using a Jamar® Plus Hand dynamometer. For the procedure, participants were seated with the arm holding the dynamometer at a 90-degree angle. The participants contracted on the dynamometer at maximum strength 3 times, alternating hands between each measurement, with a 1-minute break in between each hand. The mean of all 6 measurements (3 per hand) was determined and used for analysis. A measure of muscle quality was calculated as the average hand grip strength for both hands divided by the arm lean mass (from DXA).

2.6 Physical Activity

Every participant in the study was given the International Physical Activity Questionnaire (IPAQ). The IPAQ is a self-reported physical activity questionnaire that contains 27-items. It assesses the types of physical activity that person has engaged in the past 7 days as well as the amount of time spent sitting. It categorizes the physical activity as job-related, transportation-related, housework, and recreational physical activity. It additionally asks how much time spent on each level of intensity of physical activity (walking, moderate, or vigorous).

2.7 Statistical Analysis

All data was stored in a RedCap database. Microsoft Excel was used to compile and sort the data. Data was imported into JMP Pro 14 (SAS Institute Inc, Cary, NC) for statistical analysis. Distributions of continuous variables were visually inspected for normalcy. The mean and standard deviations for continuous variables and proportions for categorical variables were determined. A two-tailed t-test was used to assess differences in the mean values of the demographic and clinical measurements between the healthy control group and the CF group. Spearman’s correlation coefficient was used to assess the relationships that included variables

that were not normally distributed, including CFQ-R domains and physical activity scores. Relationships between normally distributed variables were assessed with Pearson correlations. Statistical significance was determined at a p-value <0.05.

Results

3.1 Demographic and Clinical Characteristics

Demographic and clinical characteristics are presented in **Table 1** for the healthy controls and CF patients. There were 51 total subjects included in this study (24 healthy controls and 27 CF patients). Mean age was 26.6 ± 7.8 years in the healthy control group and 27.7 ± 8.9 years in the CF group. Participants were predominantly Caucasians, with the control group consisting of 22 Caucasians and 2 African Americans, and the CF group consisting of 22 Caucasians, 4 African Americans, and 1 Hispanic. BMI for both groups was in the normal weight range.

Measures of physical function and activity (hand grip strength, muscle quality, and IPAQ) are presented in **Table 2** for the healthy controls and CF group. There were no statistically significant differences in these measures between the groups.

Table 1: Clinical Characteristics and Demographics of Healthy Controls and Individuals with Cystic Fibrosis

	Healthy Controls (n= 24)	CF (n = 27)	p-value
Sex	62.5% Female	51.9% Female	0.57
Age	26.6 ± 7.8	27.7 ± 8.9	0.62
Race	88% Caucasian	81% Caucasian	0.67
FEV_1%	NA	74.6 ± 21.0	NA
FEV1/FVC	NA	0.703 ± 0.104	NA
Height (cm)	171.1 ± 10.0	167.5 ± 9.7	0.20
Weight (kg)	64.6 ± 10.5	61.6 ± 13.7	0.38
BMI (kg/m^2)	22.0 ± 2.8	21.8 ± 4.2	0.85
Lean mass (kg)	45.7 ± 9.7	43.8 ± 9.5	0.48
Fat mass (kg)	16.5 ± 4.4	15.6 ± 8.5	0.62
Percent Body Fat (%)	25.7 ± 6.6	24.5 ± 9.4	0.59
Arm Lean mass (kg)	5.1 ± 1.8	4.8 ± 1.6	0.53
Total BMD (g/cm^2)	1.2 ± 0.1	1.2 ± 0.2	0.19
Z score	0.8 ± 0.7	0.3 ± 1.2	0.11

Abbreviations: BMI = body mass index; BMD = bone mineral density; FEV_1% = forced expiratory volume in 1 second (% predicted); FVC = forced vital capacity

Table 2: Peripheral Muscle Strength and Physical Activity in Healthy Controls and Individuals with Cystic Fibrosis

	Healthy Controls (n = 24)	CF (n = 27)	p-value
Hand Grip Strength (kg)	32.2 ± 9.5	30.0 ± 9.8	0.42
Muscle Quality	6.6 ± 1.3	6.4 ± 1.2	0.53
Total IPAQ score	4608.5 ± 2926.4	6386.2 ± 8385.9	0.31
Walking IPAQ score	1774.4 ± 1565.1	1774.7 ± 2274.2	0.99
Moderate IPAQ score	1660.2 ± 1325.9	2771.5 ± 4962.8	0.27
Vigorous IPAQ score	1158.3 ± 973.5	1840 ± 2865.4	0.25

Data presented as the mean ± standard deviation
Abbreviations: CF = cystic fibrosis; IPAQ = International Physical Activity Questionnaire

Demographic and clinical characteristics are presented in **Table 3** for the healthy controls and CF patients stratified by sex. Of the 24 healthy controls, 9 were men and 15 were women. Of the 27 CF patients, 13 were men and 14 were women. Healthy control males had a significantly higher body weight ($p = 0.006$), BMI ($p = 0.02$), lean mass ($p = 0.03$), fat free mass ($p = 0.03$), and arm lean mass ($p = 0.01$) compared to the men with CF. There were no significant differences between females in the healthy control group vs. those in the CF group. In comparing the CF men to the CF women, the men had a significantly higher handgrip strength ($p = 0.001$) than the women.

Table 3: Healthy Control and CF Patients Clinical Characteristics and Demographics Stratified by Sex

Characteristic	Men			Women		
	Healthy Controls	Cystic Fibrosis	p-value	Healthy Controls	Cystic Fibrosis	p-value
N	9	13		15	14	
Age	28.6 ± 10.9	26.1 ± 9.2	0.58	25.4 ± 5.3	29.3 ± 8.7	0.16
Race	100% Caucasian	76.9% Caucasian	0.49	86.67% Caucasian	85.71% Caucasian	1.00
Height (cm)	179.8 ± 6.5	174.7 ± 7.1	0.10	165.9 ± 7.9	160.8 ± 6.3	0.07
Weight (kg)	74.8 ± 5.5	64.2 ± 10.4	**0.006***	58.4 ± 7.4	59.1 ± 16.1	0.89
BMI (kg/m^2)	23.1 ± 1.5	20.9 ± 2.4	**0.02***	21.4 ± 3.2	22.7 ± 5.3	0.42
FEV_1%	NA	75.1 ± 21.9	NA	NA	74.2 ± 20.9	NA
FEV_1/FVC	NA	0.7 ± 0.1	NA	NA	0.7 ± 0.1	NA
Lean Mass (kg)	56.3 ± 4.9	50.0 ± 7.9	**0.03***	39.4 ± 5.1	38.1 ± 6.9	0.57
Percent Body Fat (%)	20.9 ± 4.9	17.8 ± 6.4	0.22	28.6 ± 5.8	30.8 ± 7.2	0.39
Fat Mass (kg)	15.7 ± 4.2	11.7 ± 5.2	0.06	16.9 ± 4.7	19.1 ± 9.5	0.44
ALM (kg)	7.2 ± 0.7	5.9 ± 1.4	**0.01***	3.8 ± 0.8	3.7 ± 0.9	0.82
BMD (g/cm^2)	1.3 ± 0.1	1.2 ± 0.2	0.10	1.2 ± 0.1	1.1 ± 0.1	0.30
Total IPAQ	4737.9 ± 2573.1	5072.4 ± 3676.8	0.81	4539.4 ± 3183.1	7606.1 ± 11173.2	0.34
Walking IPAQ	1681.2 ± 1448.8	1490.1 ± 1656.9	0.78	1830.4 ± 1678.0	2038.9 ± 2766.5	0.81
Moderate IPAQ	1533.8 ± 1270.8	1662.3 ± 1537.6	0.84	1727.7 ± 1393.2	3801.4 ± 6686.1	0.27
Vigorous IPAQ	1453.3 ± 845.2	1920.0 ± 2674.3	0.57	981.3 ± 1029.2	1765.7 ± 3131.5	0.39
HG strength (kg)	41.8 ± 5.8	36.9 ± 8.5	0.13	26.4 ± 5.7	23.5 ± 5.5	0.17
Muscle Quality	5.9 ± 0.8	6.4 ± 1.4	0.24	7.1 ± 1.4	6.4 ± 1.0	0.13

Values are expressed as the mean ± the standard deviation. P-values represent differences between CF vs controls among men and women, respectively.

Abbreviations: ALM = arm lean mass; BMD = bone mineral density; BMI = Body mass index; CF = Cystic Fibrosis; FEV_1% = forced expiratory volume in 1 second (expressed as percentage of expected value for age, race, and sex); FEV_1/FVC = forced expiratory volume in 1 second divided by forced voluntary capacity; HC = healthy control group; IPAQ = International physical activity questionnaire;

3.2 CFQ-R Results

The mean, standard deviation, median, minimum, and maximum scores for each domain of the CFQ-R are presented in **Table 4**. Eating disturbances had the highest mean score (91.0 ± 19.5) and median score (100). Treatment burden had the lowest mean score (56.4 ± 15.4) and median score (55.6).

Table 4: CFQ-R Results

CFQ-R Domains	Mean ± SD	Median	Min	Max
Physical functioning	81.6 ± 19.3	87.5	37.5	100
Vitality	60.5 ± 16.6	66.7	25	83.3
Emotion	77.3 ± 23.4	86.7	13.3	100
Eating Disturbances	91.0 ± 19.5	100	22.2	100
Treatment Burdens	56.4 ± 15.4	55.6	22.2	100
Health Perceptions	70.0 ± 21.5	66.7	11.1	100
Social Functioning	71.8 ± 15.8	72.2	38.9	94.4
Body Image	65.8 ± 29.1	77.8	0	100
Role Limitations	81.5 ± 17.0	83.3	50	100
Weight	66.7 ± 33.3	66.7	0	100
Respiratory Symptoms	72.0 ± 16.9	72.2	44.4	100
Digestive Health	77.4 ± 16.2	77.8	44.4	100

3.3 Correlations of Physical Activity and Lung Function vs. Muscle Function and Quality

The relationships between body composition and muscle quality vs. physical activity and hand grip strength for adults with CF are presented in **Table 5**. Muscle quality was positively and significantly related to total IPAQ ($\boldsymbol{\rho}$ = 0.49, p = 0.009) and walking IPAQ scores ($\boldsymbol{\rho}$ = 0.60, p = 0.0001). Moderate IPAQ score had no significant relationships with body composition, hand grip strength, or muscle quality. Vigorous IPAQ score was inversely and significantly related to fat mass ($\boldsymbol{\rho}$ = -0.38, p = 0.05). BMI showed no significant associations with physical activity and hand grip strength measures. Our lab has previously shown that lean mass is positively and significantly correlated to lung function (FEV_1%).[52]

Table 5: Correlations of Physical Activity vs. Body Composition and Physical Functioning among Adults with CF

	Walking IPAQ	**Moderate IPAQ**	**Vigorous IPAQ**	**Total IPAQ**
BMI (kg/m^2)	-0.14 (0.50)	0.14 (0.49)	-0.31 (0.12)	-0.04 (0.84)
Body Weight (kg)	-0.11 (0.58)	0.18 (0.36)	-0.28 (0.15)	-0.05 (0.82)
Lean Mass (kg)	-0.07 (0.73)	0.05 (0.79)	-0.10 (0.61)	-0.02 (0.91)
Fat Mass (kg)	-0.18 (0.36)	0.13 (0.51)	**-0.38 (0.05*)**	-0.16 (0.44)
Body Fat Percent	-0.08 (0.70)	0.16 (0.42)	-0.31 (0.12)	-0.08 (0.70)
BMD (g/cm^2)	-0.15 (0.44)	0.02 (0.93)	0.05 (0.79)	0.07 (0.72)
Hand grip Strength (kg)	0.17 (0.41)	0.23 (0.26)	0.17 (0.39)	0.30 (0.13)
Arm Lean Mass (kg)	-0.07 (0.72)	0.15 (0.46)	-0.06 (0.77)	0.05 (0.83)
Muscle Quality	**0.60 (0.001*)**	0.15 (0.45)	0.28 (0.16)	**0.49 (0.009*)**

Values are reported as Spearman's $\boldsymbol{\rho}$ (p)
Abbreviations: BMD = bone mineral density; BMI = body mass index; CF = Cystic Fibrosis; DXA = dual x-ray absorptiometry; IPAQ = International Physical Activity Questionnaire
* Denotes significant correlation ($p < 0.05$)

3.4 Correlations of Body Composition and Muscle Quality to Physical Activity and Hand Grip Strength

The relationship between hand grip strength and body composition measures are shown in **Figure 3**. Hand grip strength was positively and significantly correlated to body weight ($r = 0.46$, $p = 0.02$), lean mass ($r = 0.76$, $p = 0.0001$), arm lean mass ($r = 0.86$, $p = 0.0001$), and total BMD ($r = 0.64$, $p = 0.004$). Hand grip strength is inversely associated with percent body fat ($r = -0.48$, $p = 0.01$). Hand grip strength was not significantly associated with fat mass ($r = -0.16$, $p = 0.43$).

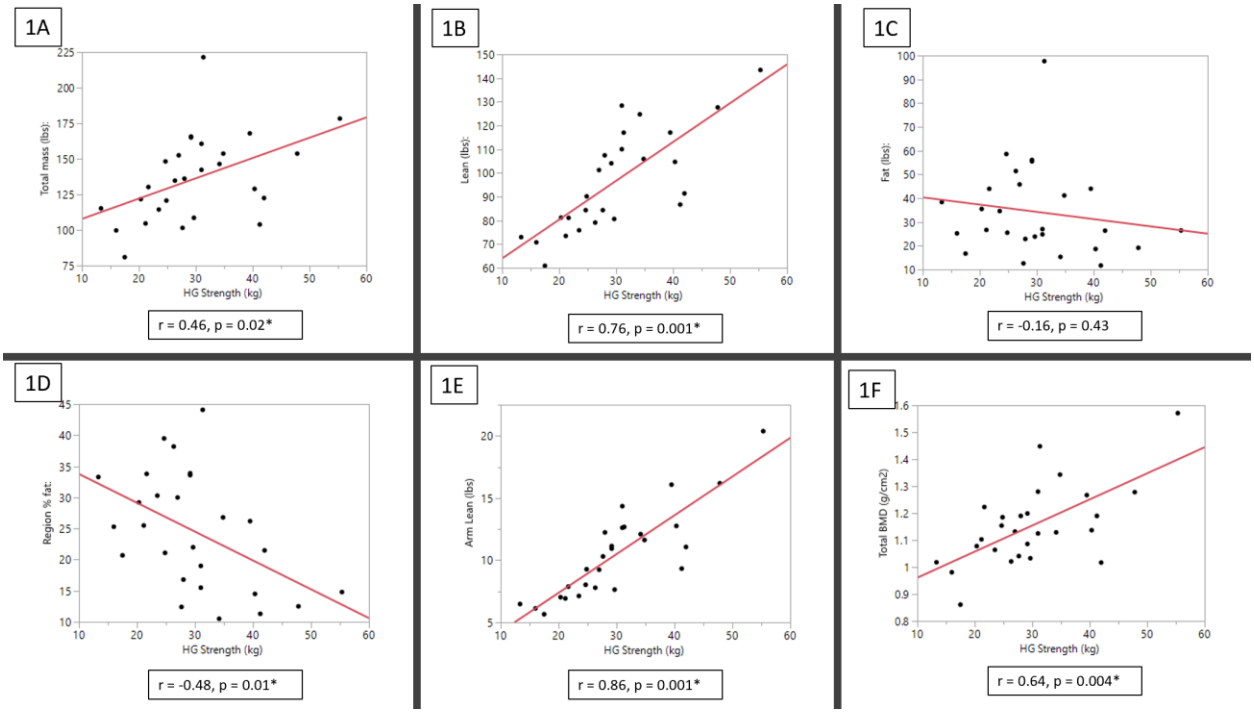

Figure 3. Associations between Hand Grip Strength and Body Composition

Values for Figure 1 (A-F) are expressed as Pearson's correlation (r, p)

Abbreviations: BMD = bone mineral density; HG = hand grip; DXA = dual x-ray absorptiometry

* Denotes a statistically significant p-value (<0.05)

3.5 Relationships between Quality of Life and Body Composition/Physical Outcomes

Spearman's correlations between CFQ-R domains and physical activity, hand grip strength, and muscle quality measures are presented in **Table 6**. Physical functioning was positively and significantly associated with intense physical activity ($\rho = 0.57$, $p = 0.002$). Health perceptions were positively and significantly associated with total physical activity score ($\rho = 0.38$, $p = 0.049$) and intense physical activity score ($\rho = 0.45$, $p = 0.02$). The weight domain was inversely and significantly associated with muscle quality ($\rho = -0.44$, $p = 0.02$). Vitality, eating disturbances, role limitations, and respiratory symptoms had no significant correlations.

Table 6: CFQ-R Correlations with Physical Activity, HG Strength, and Muscle Quality

CFQ-R Domain	Total IPAQ	Walking IPAQ	Moderate IPAQ	Vigorous IPAQ	Hand Grip Strength	Muscle Quality
Physical functioning	0.22 (0.26)	-0.04 (0.85)	-0.17 (0.41)	**0.57 (0.021*)**	0.28 (0.16)	-0.12 (0.54)
Vitality	0.19 (0.35)	0.25 (0.21)	-0.36 (0.07)	0.30 (0.13)	0.24 (0.23)	-0.08 (0.69)
Emotion	0.17 (0.39)	0.05 (0.81)	0.01 (0.99)	0.17 (0.40)	0.27 (0.18)	-0.30 (0.13)
Eating Disturbances	-0.21 (0.29)	0.13 (0.52)	-0.31 (0.11)	-0.23 (0.25)	-0.28 (0.16)	0.10 (0.63)
Treatment Burdens	0.17 (0.40)	0.31 (0.12)	-0.03 (0.88)	0.16 (0.43)	0.20 (0.31)	0.12 (0.56)
Health Perceptions	**0.38 (0.049*)**	0.11 (0.58)	0.09 (0.67)	**0.45 (0.02*)**	0.06 (0.77)	-0.14 (0.47)
Social Functioning	0.20 (0.32)	0.21 (0.30)	-0.04 (0.84)	0.22 (0.28)	0.20 (0.32)	-0.14 (0.49)
Body Image	0.18 (0.38)	0.26 (0.20)	0.05 (0.79)	-0.05 (0.82)	0.26 (0.19)	-0.13 (0.52)
Role Limitations	0.13 (0.50)	-0.03 (0.90)	-0.03 (0.86)	0.36 (0.06)	0.35 (0.07)	-0.05 (0.79)
Weight	-0.20 (0.32)	-0.17 (0.40)	-0.12 (0.57)	-0.36 (0.06)	-0.32 (0.10)	**-0.44 (0.02*)**
Respiratory Symptoms	0.35 (0.08)	0.14 (0.48)	0.10 (0.61)	0.36 (0.07)	0.14 (0.49)	-0.18 (0.38)
Digestive Health	-0.18 (0.36)	-0.24 (0.24)	-0.25 (0.22)	-0.06 (0.75)	0.22 (0.27)	-0.16 (0.43)

Data are presented as Spearman's rho (p-value)

Abbreviations: CFQ-R: Cystic Fibrosis Questionnaire-Revised; IPAQ: International Physical Activity Questionnaire

* Denotes a statistically significant association ($p < 0.05$)

Spearman's correlations between CFQ-R domains and body composition measures are presented in **Table 7**. Physical functioning was inversely and significantly associated with total body fat (ρ = -0.63, p = 0.004) and percent body fat (ρ = -0.66, p = 0.002). Emotion was positively and significantly associated with lean mass (ρ = 0.41, p = 0.03), fat free mass (ρ = 0.42, p = 0.03), and arm lean mass (ρ = 0.43, p = 0.03). Treatment burdens were inversely and significantly associated with total body fat (ρ = -0.49, p = 0.009) and percent body fat (ρ = -0.47, p = 0.01). Social limitations were inversely and significantly associated with total body fat (ρ = -0.45, p = 0.02) and percent body fat (ρ = -0.47, p = 0.01). Body image was positively and significantly associated with body weight (ρ = 0.58, p = 0.001), lean mass (ρ = 0.41, p = 0.03), fat free mass (ρ = 0.42, p = 0.03), and arm lean mass (ρ = 0.40, p = 0.04). Weight was positively and significantly associated with total body fat (ρ = 0.55, p = 0.003) and percent body fat (ρ = 0.59, p = 0.001). Digestive health was inversely and significantly associated with total body fat (ρ = -0.45, p = 0.02) and percent body fat (ρ = -0.53, p = 0.004).

Table 7: CFQ-R Correlations with Body Composition Measures

CFQ-R Domain	Body Weight	Lean Mass	Arm Lean Mass	Total Body Fat	Percent Body Fat
Physical functioning	-0.10 (0.61)	0.26 (0.19)	0.32 (0.11)	**-0.63 (0.004*)**	**-0.66 (0.002*)**
Vitality	0.17 (0.40)	0.29 (0.14)	0.26 (0.19)	-0.14 (0.48)	-0.21 (0.28)
Emotion	0.32 (0.10)	**0.41 (0.03*)**	**0.43 (0.03*)**	0.03 (0.90)	-0.13 (0.52)
Eating Disturbances	-0.19 (0.35)	-0.23 (0.26)	-0.29 (0.14)	-0.05 (0.80)	0.03 (0.89)
Treatment Burdens	-0.04 (0.84)	0.14 (0.48)	0.13 (0.53)	**-0.49 (0.01*)**	**-0.47 (0.01*)**
Health Perceptions	0.20 (0.31)	0.13 (0.50)	0.16 (0.43)	0.05 (0.81)	0.01 (0.99)
Social Functioning	-0.04 (0.86)	0.21 (0.30)	0.24 (0.22)	**-0.45 (0.02*)**	**-0.47 (0.01*)**
Body Image	**0.58 (0.001*)**	**0.41 (0.03*)**	**0.40 (0.04*)**	0.31 (0.12)	0.16 (0.43)
Role Limitations	0.13 (0.51)	0.28 (0.16)	0.32 (0.11)	-0.28 (0.16)	-0.35 (0.07)
Weight	0.29 (0.15)	-0.05 (0.80)	-0.04 (0.86)	**0.55 (0.003*)**	**0.59 (0.001*)**
Respiratory Symptoms	0.11 (0.58)	0.23 (0.25)	0.26 (0.19)	-0.32 (0.10)	-0.34 (0.09)
Digestive Health	-0.18 (0.36)	0.16 (0.42)	0.21 (0.28)	**-0.45 (0.02*)**	**-0.53 (0.004*)**

Data are presented as Spearman's rho (p).

* Denotes a significant association ($p < 0.05$)

Discussion

The objective of this study was to characterize peripheral muscle strength and physical activity in a population of adults with CF to an age-matched healthy control group. We additionally sought to assess the inter-relationships between PA, body composition, hand grip strength and muscle quality (peripheral muscle strength), and quality of life in adults with CF. We found that: 1) Adults with CF had similar hand grip strength, muscle quality, and physical activity levels as our control group; 2) Hand grip strength was highly associated with body composition measures among adults with CF; and 3) Self-reported quality of life measures were associated with body composition and physical activity among adults with CF.

4.1 Body Composition, Muscle Strength and Quality in Adults with CF Compared to Healthy Controls

Historically, BMI has been the predominant indicator of nutritional status. BMI, however, does not distinguish between muscle, bone, and fat. Lean mass is a more important predictor of lung function in CF compared to BMI and other body composition components;[30,31,52] thus, there has been a recent push within the research community to assess body composition measures in individuals with CF. However, only relying on the quantity of lean mass is limiting because it does not provide information about muscle function, strength, or quality. Studies in non-CF aging populations have suggested that handgrip strength as a measure of muscle function is a better predictor of clinical outcomes compared to lean mass.[53]

Contrary to our hypothesis, there was not a statistically significant difference in hand grip strength between adults with CF and the healthy control group. Older studies have suggested that hand grip strength is lower in adults with CF compared to healthy controls.[54] Elkin et al. (2000) reported significantly lower hand grip strength, as well as other muscle strength outcomes, in their CF group compared to age- and sex-matched healthy controls. The decreased muscle mass

for the CF group was consistent with lower BMI. As previously reported by Bellissimo et al. (2019), our CF participants had similar lean mass and BMI compared to healthy controls, thus null findings in hand grip strength difference likely reflect similarities in lean mass between our groups. Indeed, the mean hand grip strength of participants with CF in our study were above European Sarcopenia Consensus guideline cut-points to define risk for sarcopenia.[41,53] Our findings, compared to previous studies, are consistent with widespread improvements in nutritional status in the CF population as a whole.[55]

To our knowledge, this is the first study to characterize muscle quality in adults with CF. Our measurement of muscle quality, which assesses hand grip strength per unit measure of lean mass, did not differ between the individuals with CF and the healthy controls. Other factors should be considered in the assessment of muscle quality, such as muscle tissue composition which includes fat infiltration and cellular characterization of muscle fibers.[56] We have previously shown in this cohort that, despite similar total body composition between adults with CF and healthy controls, visceral adipose tissue deposition was significantly higher in individuals with CF and this was positively associated with fasting glucose levels.[52] Future studies in CF should assess deposition of fat between muscles (intermuscular fat), which has been shown in non-CF populations to correlate with visceral adiposity and other predictors of metabolic health.[57]

4.2 Muscle Strength and Quality, Body Composition, and Physical Activity Correlations

Researchers believe that inactivity, chronic inflammation, and metabolic abnormalities promote muscular weakness in people with CF (especially women).[58] Our study showed no significant relationships of hand grip strength with physical activity and lung function. Previous studies have shown a positive relationship of hand grip strength and lung function in CF. A

recent cross-sectional study examined the relationship between hand grip strength, functional mobility, and lung function and found that adults with CF had significant associations between muscle strength and lung function.[49] Another study, performed in young males with CF, illustrated a positive and significant relationship between knee flexor and extensor strength and FEV_1%.[28] The lack of association with lung function in our study may be attributed to only assessing peripheral muscle strength with a single hand grip strength test (no quad or biceps strength testing was performed) and a small sample size.

In our study, hand grip strength was significantly associated with several body composition measures, including lean mass and BMD. A previous study found that lower body strength was significantly associated with BMI for young males with CF, although it did not assess more specific body composition measures.[28] Consistent with our findings, another study found that in adult patients with CF, lean body mass was positively and significantly associated with hand grip strength.[59] The strong positive correlations between hand grip strength and DXA-derived body composition measures of lean mass and bone mineral density suggest that hand grip strength may be clinically useful as a proxy for body composition assessments. While DXA is considered a gold-standard for assessment of body composition, it's expense and radiation exposure (albeit relatively minimal) limit its feasibility as a tool to regularly monitor body composition. Future studies should determine if changes in body composition over time correlate with changes in hand grip strength in a CF population.

Muscle quality was significantly associated with self-reported physical activity in this study, suggesting that CF patients who engage in a higher level of physical activity have better muscle quality. It is important for CF patients to engage in a high level of physical activity in order to maintain their muscular strength. Martinez-Garcia et al. (2019) suggested that muscle

power decreases sooner than muscle mass and muscle strength in CF patients. Since people with CF have more respiratory distress and infections, which causes an increase of pro-inflammatory cytokines, CF patients often show strength deficits.[49] While our study did not find significant differences in muscle strength between the group with CF and the healthy controls, the significant positive association between muscle quality and physical activity reflects the importance of people with CF staying active.

4.3 Correlations with the Self-Reported Cystic Fibrosis Questionnaire

Self-reported physical activity score and body composition measures were associated with several CF quality of life questionnaire domains. Vigorous IPAQ score was significantly and positively associated with the physical functioning and health perceptions CFQ-R domains. Thus, those who report engaging in a higher level of physical exercise rate their physical functioning and health perceptions higher. In addition to self-reported activity (via 7-day physical activity recall questionnaire), Hebestreit et al. (2014) also found significant and positive correlations between aerobic fitness and physical functioning, both cross-sectionally and longitudinally, in a German cohort of individuals with CF.[60] A cross-sectional study of healthy men in the US Navy found that higher levels of cardiorespiratory fitness is associated with improved HRQoL scores.[61] Perceived well-being is an important aspect of clinical care in individuals with CF; thus, our data in combination with others', supports the promotion of physical activity in this population.

Higher levels of DXA-derived lean mass were positively associated with a higher body image and emotion scores in this study. Olveira et al. (2010) similarly reported a positive relationship between CFQ-R domains and fat free mass estimated by skinfold assessments in a Spanish cohort of adolescents and adults with CF.[62] In our study, higher levels of adiposity were

inversely associated with several quality of life domains, including physical functioning, treatment burden, social functioning, and digestive health. This inverse relationship suggests that perceived quality of life is lower with higher adiposity in CF. Previous studies assessing body composition against CFQ-R have not shown these inverse relationships with adiposity. In contrast, and also shown by Olveira et al. (2010) and Hebestreit et al. (2014) with skinfold measurements, body fat was positively associated with the weight domain, suggesting less perceived problems gaining weight with higher adiposity.[60,62] Together, these studies highlight key differences in the relationship of varying body composition components with perceived quality of life domains in CF.

4.4 Study Strengths

A major strength of the study was the use of an age- and sex-matched healthy control group to make comparisons for clinical characteristics with the CF patient population. Similarities in several body composition components between CF and healthy controls minimized the level of confounding in between-group comparisons. In addition, gold standard DXA enabled accurate body composition assessment, in comparison to measures that have been more traditionally used, such as BMI and skinfolds.

4.5 Limitations and Future Directions

This study's main limitation is the small sample size, which limited our ability to assess complex regression models and adjust for potential confounding variables. It is possible that we did not have sufficient power to determine statistical significance for some relationships; thus, a lack of statistical relationship does not mean two variables are definitively not related.

Another limitation of this study was that we only used hand grip strength as the measure for peripheral muscle strength and function. Rovedder et al. (2019), Arikan et al. (2015), and Troosters et al. (2019), conducted studies that utilized other ways to measure peripheral muscle strength in their CF study populations, such as quadricep and biceps isokinetic flexor/extensor exercises. Rovedder et al. (2019) found that quadriceps strength was a better predictor for exercise capacity, nutritional status, and BMI than upper extremity strength.[34] Arikan et al. (2015) also found that while the hand grip strength of their CF group was similar to their healthy control group, the CF group had a significantly lower quadriceps strength. They also illustrated that quadriceps strength was a better predictor for exercise capacity than hand grip strength.[24] Additionally, our study relies on self-reported data for physical activity. Similar to food intake often being under-reported, a social desirability bias may promote a tendency for participants to over-estimate their physical activity.[63] Future studies should employ objective measures of physical activity (such as accelerometers) and exercise capacity and function (such as submaximal cycle ergometer testing and 6 minute walking tests).

Finally, a major limitation was the cross-sectional nature of the study, which inhibited the ability to make cause-effect inferences. Longitudinal studies are needed to determine if there are relationships for outcomes that change over time. Importantly, future studies should determine if interventions to improve body composition and/or physical activity lead to improvements in physical function, fitness, and perceived quality of life.

4.6 Conclusion

Overall, this study found that hand grip strength had many significant correlations with body composition measures. Additionally, physical activity and body composition measures were significantly correlated with self-reported CF quality of life domains. These findings are

important as it suggests that hand grip strength may serve as a surrogate measure for body composition, as it is inexpensive and easy to measure. Additionally, the association between vigorous physical activity and improved quality of life reiterates the importance of engaging in physical activity and increasing lean mass to maintain a high quality of life in people living with CF.

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