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Handgrip Strength in Children with Cystic Fibrosis

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A thesis submitted to the faculty of
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Master of Science

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ABSTRACT

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Background: Body mass index (BMI) is the primary accepted method to determine nutrition status in children with cystic fibrosis (CF); however, lean body mass (LBM) is more strongly associated with pulmonary function. Handgrip strength (HGS) measures muscle function and is reflective of LBM. The aims of this study were to assess if there was a relationship among HGS, nutrition status, and pulmonary function, to assess if HGS changed after hospitalization, and to assess if there was a relationship between HGS and nutrient intake. ***Methods***: Twenty-three children with CF ages 6-18 years participated. BMI z-scores, nutrition risk scores, and pulmonary function were assessed about five months before, day 5-7 of, and about six weeks after hospitalization. HGS z-scores and arm anthropometrics were measured during and after hospitalization. Nutrient intakes were assessed during hospitalization. ***Results***: Mean dominant HGS z-score was -1.95 ± 0.92 at hospitalization and -1.59 ± 1.06 at follow-up (p=0.007). Mean BMI z-score was -0.09 ± 0.64 at hospitalization and 0.06 ± 0.54 at follow-up (p=0.178). No significant relationship was found between HGS z-scores and BMI z-scores (p=0.892) or HGS z-scores and pulmonary function (p=0.340). ***Conclusions***: HGS z-scores were lower than the standard even though mean BMI z-scores classified participants as normal nutrition status. Further research should be done utilizing a larger sample size in order to better examine HGS's potential as a nutrition assessment tool in this population.

Keywords: handgrip strength, cystic fibrosis, children, BMI z-scores, pulmonary function

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

MANUSCRIPT

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INTRODUCTION

Cystic Fibrosis (CF) is a life-threatening genetic disorder that can lead to significant lung damage, malnutrition, and other complications. Nutrition plays a critical role in the overall health status of individuals with CF.[1, 2] There is a longitudinal relationship between nutrition status, growth, pulmonary function, and survival.[2, 3, 4] Identifying individuals at risk for undernutrition as timely as possible is necessary for prevention and early intervention of nutritional failure. Strong evidence suggests that early interventions, such as increasing energy intake, result in improved weight gain and nutrition status in children with CF.[2] Adequately monitoring nutrition status and growth is critical to maintain and improve pulmonary function.

Nutrition status in children with CF is monitored by a variety of methods including: anthropometric measurements, nutrition risk score, and nutrient intake.[5] Body mass index (BMI) is the primary accepted method to determine nutrition status in children with CF.[6, 7] The CF Foundation Nutrition Guidelines recommend children between the ages of 2-19 years maintain a BMI above the 50th percentile or a BMI z-score above zero.[6] BMI is a measure of weight adjusted for height (kg/m^2) and does not distinguish between lean body mass (LBM) and fat mass. Nutrition risk score is a risk-based classification system used to determine individuals who may benefit from more extensive medical nutrition therapy.[5]

Nutrient intake addresses how many calories a child is consuming and if that child is meeting their recommended energy and protein needs. Children with CF require about 1.5 to 2 times more energy than those without CF to breathe normally, fight infection, and compensate for poor digestion. [2, 8] Traditionally, nutrition interventions focused on increasing fat intake in order to increase energy consumption, but there is concern that this approach is not promoting LBM.[2]

Stronger associations have been found between LBM and pulmonary function than BMI and pulmonary function in CF patients.[9, 10] Decreases in LBM are associated with decreases in pulmonary function; however, LBM is not being assessed routinely and BMI is used to gauge nutrition status in clinical settings.[6]

There are several methods used to examine LBM. Dual-energy X-ray absorptiometry (DXA) scans are one of the most accurate ways to measure LBM and are commonly used in research; however, they are expensive and impractical for everyday use in a clinic. Bioelectrical impedance is another method to assess LBM but has been found to be inaccurate in persons with CF due to an imbalance in electrolytes.[11, 12] Arm anthropometry measurements including triceps skinfolds (TSF), mid-upper arm circumference (MUAC), and arm muscle area (AMA) have been reviewed as possible methods to assess LBM, yet these methods have led to inconsistent results in the CF population.[12, 13] It has been concluded that neither skinfold measurements nor bioelectrical impedance should be included in the standard nutrition assessment of CF patients.[14]

The Jamar® Plus Hand Dynamometer is a validated tool used to measure handgrip strength (HGS), is suitable for a clinical setting, and has been used to measure muscle function in a variety of populations, including adults with CF.[15, 16, 17] The Jamar® Plus Hand Dynamometer has established reliability based on test-retest reproducibility and excellent inter-rater reliability.[18] Muscle function determined by HGS is reflective of LBM and responds earlier to changes in nutritional status than muscle mass.[19, 20] Significant positive associations were found between HGS, LBM, and pulmonary function in adults with CF.[17] To our knowledge, associations among HGS, nutrition status, and pulmonary function have not been studied in children with CF nor have changes in HGS overtime in children with CF been examined. Earlier detection of reductions in LBM would allow for earlier interventions, and likely prevent further

deterioration of pulmonary function. HGS may be a more sensitive way to measure changes in LBM in children with CF and may be a valuable measurement to assess nutrition status in children with CF.

The primary purposes of this study were to assess if there was a relationship among HGS z-scores, nutrition status (BMI z-scores, nutrition risk scores, and AMA z-scores), and pulmonary function (FEV_1) in children ages 6-18 years with CF and to assess if HGS z-scores changed between hospitalization and after hospitalization at an outpatient CF clinic follow-up appointment. The secondary purpose was to assess if there was a relationship between HGS z-scores and nutrient intake, specifically energy and protein intake.

METHODS

Study Setting and Design

A convenience sample of 23 children, ages 6-18 years, with CF participated in a longitudinal study from August 2016 to April 2017. Eligible participants were admitted to 289-bed pediatric specialty hospital within three days of their outpatient CF clinic appointment, able to read and understand verbal directions in English, and able to perform the HGS measurement. Children positive for *Burkholderia cepacia* were excluded. The researcher obtained consent from each subject's guardian(s) and assent from subjects seven years and older and took measurements on day 5-7 of hospitalization and about six weeks after hospitalization. Participants were compensated $5.00 at the initial appointment and $10.00 at the follow-up appointment. The Intermountain Healthcare and Brigham Young University Institutional Review Boards (IRB) approved the study.

Data Collection

Prior to data collection, members of the research team were trained on proper sanitation practices, how to use the Jamar® Plus Hand Dynamometer, and how to take anthropometric measurements using National Health and Nutrition Examination Survey (NHANES) protocol.[21] All measurements were taken by a single member of the research team or by trained outpatient CF clinic staff. Weight during hospitalization was measured by the researcher using a mobile mechanical scale (Seca 882) and before/after hospitalization by clinic staff using a stationary mechanical scale (Scale-Tronix 5002) in the outpatient CF clinic; both were recorded to the nearest 0.1 kg. Height was measured by clinic staff for all three time periods using a wall-mounted stadiometer and was recorded to the nearest 0.1 cm. HGS was measured by gripping the Jamar® Plus Hand Dynamometer with the subject in a seated position, maintaining an unsupported elbow at the side of their body with the forearm stretched to a 90° angle. MUAC was measured with a flexible, non-stretchable tape on the right arm halfway between the acromion process of the scapula and olecranon process at the tip of the elbow following NHANES procedures to the nearest 0.1 cm.[21] Measurement of TSF also followed NHANES procedures and were taken using a skinfold caliper to the nearest 0.1 mm.[21] MUAC and TSF measurements were used to calculate AMA z-scores.

Researchers examined data from three different periods: approximately five months before hospitalization, day 5-7 of hospitalization, and approximately six weeks after hospitalization at an outpatient CF clinic follow-up appointment. Weight, height, pulmonary function (FEV_1), and nutrition risk score were obtained from electronic medical records for all three time periods (See Figure 1). Respiratory therapists measured pulmonary function as forced

expiratory volume at 1 second (FEV_1). Nutrition risk scores were calculated by the registered dietitian nutritionist (RDN) based on BMI percentile, daily weight gain, and annual height gain; children with a score of 0-1 were no-low risk, 2-3 were moderate risk, and 4+ were high risk.[5] The researcher measured HGS, TSF, and MUAC during hospitalization and at follow-up (See Figure 1). Additionally, during hospitalization, the researcher reviewed a 3-day calorie count conducted by the RDN to assess nutrient intake. Mean energy and protein intakes were calculated in order to find what percentage of the child's CF specific recommended energy and protein needs were consumed. The researcher also recorded if the child was receiving nutrition support and if the child had CF related diabetes (CFRD).

Statistical Analysis

Descriptive statistics including means and standard deviations were used to describe patient demographics. HGS values were reported as z-scores based on means and standard deviations published by and specific to the Jamar® Plus Hand Dynamometer.[22] Dominant HGS z-scores were assessed in all analyses. Differences between the three periods for BMI z-scores, nutrition risk scores, and FEV_1 were examined using a mixed models analysis. A similar mixed models analysis was used to determine if HGS z-scores, BMI z-scores, and FEV_1 differed between hospitalization and follow-up. Regression analysis and analysis of variance (ANOVA) were used to determine if there was a relationship among HGS z-score at hospitalization and the following variables: BMI z-score, nutrition risk score, FEV_1, MUAC z-score, TSF z-score, AMA z-score, percent energy intake, and percent protein intake. All analyses were done using the Statistical Analysis Systems statistical software package, version 9.4 (SAS Institute, Inc, Cary, NC). Results were considered significant when $p<0.05$.

RESULTS

Demographics

A total of 23 children with CF enrolled in the study and 22 completed the follow-up appointment. Participants were primarily female (66%) ranging from 6-18 years with a mean age of 12.4 years ± 4.0 at hospitalization. Four participants had CFRD and eight participants were receiving nutrition support. Other demographic information is summarized in Table 1.

Outcomes

FEV_1 values were significantly lower during hospitalization compared to before and after hospitalization (p=0.001). No significant difference was found in BMI z-scores between the three periods. HGS z-scores significantly improved after hospitalization (p=0.007); mean HGS z-scores at hospitalization were -1.95 ± 0.92 and at follow-up were -1.59 ± 1.06 (Table 2). Eighty-two percent of participants experienced gains in HGS at their follow-up appointment. HGS z-scores at hospitalization were not significantly related to BMI z-scores, FEV_1, nutrition risk scores, MUAC z-scores, TSF z-scores, or AMA z-scores at hospitalization. No significant correlations were found between HGS z-scores and percent energy intake (p=0.913) or percent protein intake (p=0.489).

DISCUSSION

This study used sex and age-adjusted HGS z-scores to indirectly measure LBM, which has a stronger association with pulmonary function than BMI. [9, 10] Mean HGS z-scores of persons with CF at hospitalization were very low compared to the standard (-1.95 ± 0.92), whereas mean BMI z-scores at hospitalization were much closer to the standard (-0.09 ± 0.64) with 91% of participants being classified as normal nutrition status.[19] Mean BMI z-scores from this study were very similar to those observed in another study of 75 children with CF (-0.09 ± 0.95).[23] Our

study suggested participants may have deficits in LBM that were not detected by assessing BMI alone. It is possible for children with CF to have reduced LBM and be classified as normal nutrition status based on BMI. A study of 77 children with CF found LBM depletion undetectable when using BMI percentile as the screening method.[9] Additionally, LBM values were found to be decreased in children with CF compared to healthy children with the same BMI.[10] BMI also failed to identify poor nutrition status in stunted children with CF.[24] HGS may be useful in identifying LBM depletion that is not apparent with BMI.

This study also found a significant change in HGS z-scores occurred from hospitalization to follow-up (p=0.007). Eighty-two percent of individuals experienced increases in HGS at follow-up. BMI z-scores, however, did not significantly change between hospitalization and follow-up (p=0.178). HGS measures muscle function and has been shown to detect changes in muscle mass sooner than BMI and other anthropometric measures in children >6 years.[25, 26] Measuring muscle function allows for a more dynamic indicator of muscle mass compared to BMI which takes longer to change.[20] Additionally, the correlation between HGS and LBM is stronger than the correlation between BMI and LBM in children ages 6-18 years.[27] These previous findings serve as a potential explanation for the observed change in HGS and lack of change in BMI.

Researchers also wanted to identify whether or not meeting recommended energy and protein needs would impact HGS z-scores. The majority of participants met their recommended energy needs (74%) and their recommended protein needs (89%) based on a 3-day calorie count during hospitalization. Little variation in regards to nutrient intake was present, and no significant correlations with HGS z-scores were found. Thirty-five percent of participants were

receiving nutrition support through enteral tube feedings; those receiving nutrition support had significantly lower HGS z-scores (p=0.02).

This study included several limitations. The most notable being the small sample size. Participants were recruited from one CF clinic that serves approximately 280 pediatric patients ranging from infants to 18 years.[28] To be included in the study, participants had to be between ages 6-18 years and hospitalized following their outpatient CF clinic appointment. These two factors alone did not allow for a large number of potential participants. Portions of our statistical analyses were under powered, making it difficult to detect statistical significance. This may have contributed to the lack of significant correlations found among HGS z-scores, nutrition status (BMI z-scores, nutrition risk scores, and AMA z-scores), and pulmonary function (FEV_1) at hospitalization. Nevertheless, all statistical and meaningful findings were reported.

Additional limitations of the study included incomplete data for some participants. Four participants were missing energy and protein intake values at hospitalization and three participants were missing FEV_1 values at follow-up. These participants were excluded from analysis that incorporated their missing data. In an effort to obtain a reasonable sample size, participants receiving nutrition support and those with CFRD were included. These conditions have been shown to influence nutrition status and pulmonary function.[2, 29, 30, 31] Although no significant difference in HGS z-scores was observed in those with CFRD, those on nutrition support did have significantly lower HGS z-scores. Females tend to have lower HGS compared to males of the same age; the high percentage (66%) of female participants may have influenced the results. [22, 32, 33] However, sex and age-adjusted HGS z-scores were used.

CONCLUSION

In conclusion, HGS z-scores at hospitalization were much lower than the standard even though mean BMI z-scores classified participants as normal nutrition status. HGS z-scores and FEV_1 significantly increased at follow-up; however, no significant relationship among HGS, nutrition status (BMI z-scores, nutrition risk scores, and AMA z-scores), and pulmonary function (FEV_1) was found. Further research should be done utilizing a larger sample size of children with CF in order to better examine HGS's potential as a nutrition assessment tool in this population.

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FIGURES

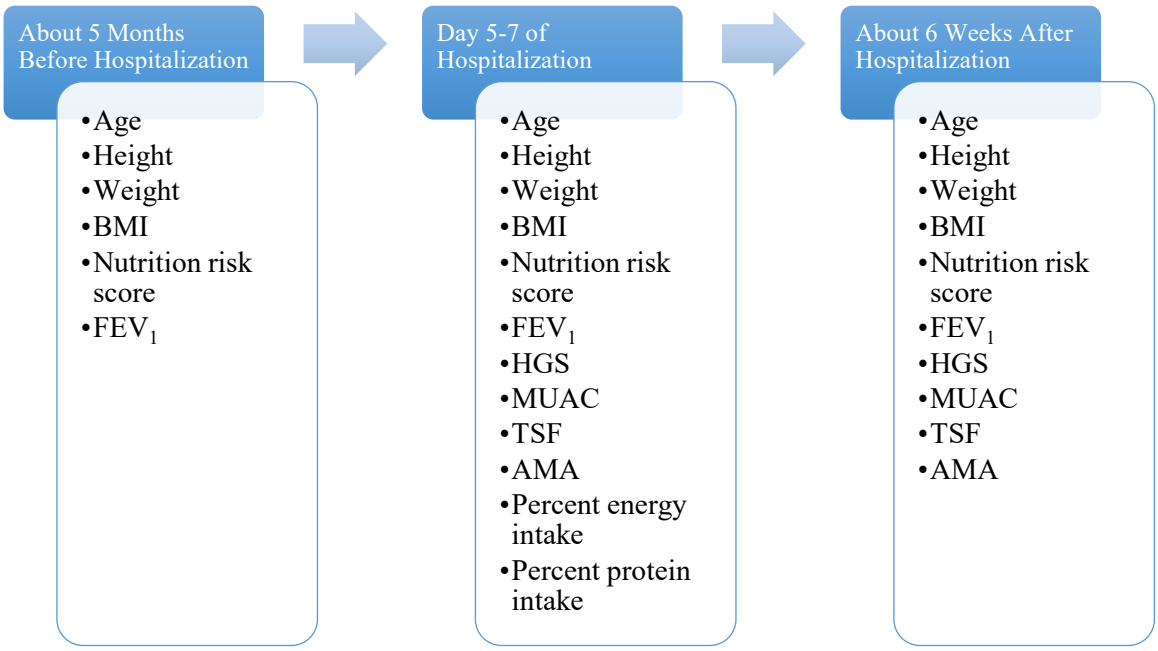

Figure 1: Data Collection Timeline. BMI = body mass index, FEV_1 = forced expiratory volume at 1 second, HGS = handgrip strength, MUAC = mid-upper arm circumference, TSF = triceps skinfolds, AMA = arm muscle area

TABLES

Table 1: Demographics of Participants

	Approximately 5 Months Before Hospitalization		**Day 5-7 of Hospitalization**		**Approximately 6 Weeks After Hospitalization**	
	n	%	n	%	n	%
Total participants	23	100	23	100	22	95.7
Gender						
Male	8	34.8	8	34.8	7	31.8
Female	15	65.2	15	65.2	15	68.2
Age						
6 – 11 years	12	52.2	11	47.8	10	45.5
12 – 18 years	11	47.8	12	52.2	12	54.5
Nutrition Support						
Yes	8	34.8	8	34.8	8	34.8
No	15	65.2	15	65.2	15	65.2
CF Related Diabetes						
Yes	4	17.4	4	17.4	4	17.4
No	19	82.6	19	82.6	19	82.6

Table 2: Clinical Characteristics of Participants

	Approximately 5 Months Before Hospitalization	**Day 5-7 of Hospitalization**	**Approximately 6 Weeks After Hospitalization**	
	Mean ± SD (n)	Mean ± SD (n)	Mean ± SD (n)	*p* value
Dominant HGS z-score	n/a	-1.95 ± 0.92 (23)	-1.59 ± 1.06 (22)	0.007*
MUAC z-score	n/a	-0.28 ± 0.81 (23)	-0.12 ± 0.66 (22)	0.361
TSF z-score	n/a	-0.04 ± 0.76 (23)	0.03 ± 0.73 (22)	0.117
AMA z-score	n/a	-0.30 ± 0.92 (23)	-0.22 ± 0.71 (22)	0.966
BMI z-score	-0.17 ± 0.63 (23)[a]	-0.09 ± 0.64 (23)[a]	0.06 ± 0.54 (22)[a]	0.065
Nutrition Risk Score	1.52 ± 1.06 (23) [a]	1.57 ± 1.01 (23) [a]	0.91 ± 1.10 (22)[b]	0.049*
FEV_1	93.52 ± 17.35 (23)[a]	85.65 ± 21.57 (23)[b]	95.63 ± 18.18 (19)[a]	0.001*

HGS z-score = handgrip strength; MUAC z-score = mid-upper arm circumference; TSF z-score = triceps skinfolds; AMA z-score = arm muscle area;
BMI z-score = body mass index: normal nutrition status= >-1, mild malnutrition= -1 to -1.9, moderate malnutrition= -2 to -2.9, severe malnutrition= -3 or less;
Nutrition risk score: 0-1 = no-low nutrition risk, 2-3 = moderate nutrition risk, 4+ = high nutrition risk;
FEV_1 = forced expiratory volume at 1 second, percentage predicted
*$p<0.05$
[a] No significant difference
[b] Significant difference

APPENDIX A: RESEARCH PROPOSAL

Problem Statement

Cystic Fibrosis (CF) is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.[1] The CFTR gene codes for CFTR proteins that reside on the epithelial cells lining the lungs, digestive system, and sweat glands and are responsible for regulating the flow of salts and fluids.[1] CF symptoms occur because the CFTR proteins are altered and cannot channel chloride ions as effectively or at all, resulting in the production of mucus in the lungs, destruction of the pancreas in some individuals, and difficulties with other organs.[2] CF has significant pulmonary and nutrition components; in fact, there is a longitudinal relationship between nutrition status, growth, pulmonary function, and survival.[3, 4, 5] Optimization of both nutrition status and growth are critical for effective treatment.[3]

CF Clinical Care Guidelines recommend maintaining a BMI above the 50th percentile or a BMI z-score above zero for children and a BMI greater than 22-23 in adults.[6] However, BMI is not the best scale for measuring change in nutrition status.[7] BMI is a measure of weight adjusted for height and is incapable of distinguishing between lean body mass (LBM) and fat mass. In individuals with CF a stronger association has been found between LBM and pulmonary function than between BMI and pulmonary function.[8] A depletion of LBM has been associated with increased morbidity and was undetectable using BMI criterion in 48% of patients with CF.[9] Dual-energy X-ray absorptiometry (DXA) scans are often used in research to measure variations in body composition; however, they are expensive and impractical for everyday use in a clinic. Bioelectrical impedance is another method to assess LBM but has been found to be inaccurate in persons with CF due to an imbalance in electrolytes.[10, 11] Arm anthropometric measurements including triceps skinfolds (TSF), mid-upper arm circumference (MUAC), and arm muscle area

(AMA) have been reviewed as possible methods to assess LBM, yet these methods have led to inconsistent results in the CF population.[11, 12] It has been concluded that neither skinfold measurements nor bioelectrical impedance should be included in the standard nutrition assessment of CF patients.[13]

LBM is strongly associated with pulmonary function and is not detectable using BMI, which means that a simple non-invasive method to examine LBM is needed. Handgrip strength (HGS) measures muscle strength and is reflective of LBM.[14] In fact, the correlation between HGS and LBM in children is stronger than the correlation between LBM and BMI.[15] In a cross-sectional study of 25 adults with CF, HGS was reduced in the low LBM group.[14] HGS may serve as a valuable measurement in the CF population based on its association with LBM and potential for earlier detection of muscle depletion. If HGS in children with CF is able to detect changes overtime, it may serve as a more sensitive method for nutrition status assessment and incorporating it routinely may result in improved nutrition status, pulmonary function, and survival.[16, 17]

Purpose Statements

The primary purposes of this research were to:

1) Assess if there was a relationship among HGS z-scores, nutrition status (BMI z-scores, nutrition risk scores, and AMA z-scores), and pulmonary function (FEV_1) in children ages 6-18 years with CF
2) Assess if HGS z-scores changed between hospitalization and after hospitalization at an outpatient CF clinic follow-up appointment

The secondary purpose of this research was:

1) Assess if there was a relationship between HGS z-scores and nutrient intake, specifically energy and protein intake

APPENDIX B: LITERATURE REVIEW

Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.[1] The CFTR gene codes for CFTR proteins that are responsible for regulating the flow of fluids and salts in and out of cells throughout the body, specifically in the lungs, digestive tract, and sweat glands.[1] CF symptoms occur because CFTR proteins are altered and their ability to transport chloride is impaired. There are over 1,800 possible mutations in the CFTR gene that result in CF. Location of the CFTR proteins and type of mutation(s) in the CFTR genes determine where symptoms occur.[2] F508del is the most common mutation occurring in >90% of CF patients and results in the deletion of the codon corresponding to the amino acid phenylalanine at position 508 of the CFTR gene.[18, 19] In order to have CF, a child must receive a copy of the mutated CFTR gene from both parents. Children that only receive one mutated CFTR gene from a single parent will not have CF but will be carriers of the disease. According to the Cystic Fibrosis Foundation Registry Annual Data Report for 2013, there were 28,103 individuals in the United States living with CF, and 373 of those individuals on the registry resided in the state of Utah.[17] Worldwide it has been estimated that there are about 70,000 people with CF.[1] Approximately 1,000 new cases are diagnosed in the US each year, with more than 75% of diagnosis occurring by the age of two years old.[1]

In the lungs mucus clearance is an important defense mechanism against disease.[20] The ability to clear airways through mucociliary clearance strongly depends upon the volume of airway surface liquid (ASL), which consists of a mucus component that traps foreign particles and a periciliary layer (PCL) that maintains optimum mucus distance from the cilia.[21, 22] In those with CF, reduced chloride secretion and increased sodium reabsorption in airway epithelium

leads to reduced water content and reduced volume of PCL, which both contribute to inhibited mucociliary clearance from the airways and to persistent infection.[23, 24] Lung damage may occur each time someone with CF develops a pulmonary infection, so infection control is critical. Multiple precautions must be taken in order to prevent potential infection, including but not limited to prevention of patient-to-patient contact and patient-to-health care worker contact, appropriate hand hygiene for all those around, and sterilization of surroundings, specifically respiratory therapy equipment.[25] Infection control is an essential element of keeping the lungs of CF patients healthy.

Along with the pulmonary component, 85-90% of individuals with CF suffer from pancreatic insufficiency.[26] The pancreas makes and secretes bicarbonate into the small intestine to neutralize acidic content coming from the stomach. The pancreas also secretes pancreatic enzymes that work to further breakdown carbohydrates, proteins, and fats from foods for absorption. Bicarbonate allows pancreatic enzymes to work more efficiently. Failure of chloride secretion results in mucus build up, which causes duct blockage and prevents bicarbonate and pancreatic enzymes from entering the small intestine and may lead to pancreatitis.[27] Pancreatic insufficiency leads to malabsorption of dietary fat, protein, and other nutrients and has a direct influence on nutrition status.[28] Pancreatic insufficiency is most often treated by oral replacement therapy of pancreatic enzymes to be taken with meals.[19] Even with the addition of pancreatic enzymes, in some cases fat malabsorption, fat-soluble vitamin deficiency, and steatorrhea continue to occur.[29]

Impaired uptake of fat in the presence of pancreatic enzymes may be a result of compromised bile composition and production in the liver.[29] The bile produced in the liver may become dehydrated and more acidic than regular bile. This change in bile can result in gallstones

or total blockage of the liver ducts, which will ultimately influence the body's ability to absorb fat within the small intestine.

As patients age, pancreatic islets containing beta cells that secrete insulin may become damaged resulting in the development of CF-related diabetes (CFRD).[27] In CFRD the pancreas either does not produce enough insulin or the insulin that it does produce does not work properly. Individuals with CF ages ten and older should be tested every year for CFRD with an oral glucose tolerance test.[17] In CF, even if blood glucose levels are fairly normal, insulin deficiency can lead to protein breakdown and malnutrition, which negatively impacts lung function and potentially survival.[17, 30, 31] CFRD is manageable with the addition of insulin, so early detection is critical in order to maintain the upmost nutrition status.

CF can also affect other organs such as the kidneys, skin, and reproductive system. The major CF symptoms include salty skin, continuous lung infections, decline in pulmonary function, malabsorption, and poor weight gain and growth. At the present time, there is not a cure for CF; however, scientists have and are continuing to develop treatments and therapies that may be used to ease symptoms and prolong life. Numerous drugs with different aims such as CFTR modulation, restoring airway surface liquid, mucus alteration, anti-inflammatories, anti-infections, and improved nutrition status are available and contributing to increased lifespan in those with CF.[32]

Screening and Assessment of Children with CF

Early detection and diagnosis of CF plays an important role in improving nutrition status, pulmonary function, and survival.[14, 17] Newborn screening allows for earlier detection and intervention, which has been shown to improve outcomes.[16] Routine newborn screening is fairly

new in the U.S.; as of 2010 all 50 states screen newborns for CF. One study compared health statistics of children aged ≤ 18 years between the U.S. and Australia using the 2003 national data registries for CF.[33] Australia adopted newborn screening much earlier than the U.S., so there was a significant difference in the proportion of individuals diagnosed by newborn screening between the countries: U.S. (7.2%) and Australia (65.8%).[33] The researchers found that Australian children had significantly greater mean height and weight percentiles compared to American children, and that children in both countries diagnosed with CF using newborn screening had improved lung function.[33] Multiple other studies suggest that a delay in diagnosis is associated with worsened disease outcomes such as severe malnutrition and pulmonary infection.[34, 35, 36] Overall earlier detection allows for earlier intervention, which ultimately is associated with improved nutrition status, pulmonary function, and survival. [16, 17, 34]

Once an individual is screened and diagnosed with CF, routine assessment is key in maintaining optimal health. It is recommended by the CF Foundation Care Guidelines that people with CF have four or more clinic visits each year.[17] The CF Foundation Care Guidelines also recommend four or more sputum/throat cultures per year, two or more lung function tests (PFTs) per year, a measurement of fat-soluble vitamins once per year, an oral glucose tolerance test if above ten years of age once per year, and a blood test to measure liver enzymes once per year.[17] These many tests are not completed at every single clinic appointment. However, at each clinic appointment a nutrition screening process should be in place to identify CF patients with poor nutrition status. A critical goal of the CF Foundation Care Guidelines is that children, teens and adults with CF have normal growth and normal nutrition status.[17] Poor nutrition status is associated with reduced pulmonary function measured by forced expiratory volume at 1 second (FEV_1).

BMI is the primary accepted method to determine nutrition status in children with CF.[6, 37] Research has shown that normal weight-for-age, normal weight-for-height, and normal height-for-age percentiles and a BMI greater than the 50th percentile for ages 2-20 years are all associated with better pulmonary function.[3, 38] These anthropometric measurements are often considered when assessing nutrition status in individuals with CF. Primary Children's Hospital in Salt Lake City, Utah uses a CF nutrition risk screening tool based on BMI percentile, daily weight gain, and annual height that assigns each patient to a nutrition risk score category of no-low risk, moderate risk, or high risk. [38]

Although there is a relationship between BMI and pulmonary function, an even stronger relationship has been found between LBM and pulmonary in CF patients with pancreatic insufficiency.[8] It has been found that LBM is an important element of diaphragm strength and longitudinal peak aerobic performance for children and adolescents with CF.[39, 40] BMI is incapable of distinguishing between LBM and fat mass and may not be the best scale for measuring nutrition status changes in children.[7] A depletion of LBM has been associated with increased morbidity and found undetectable using BMI criterion in 48% of adults with CF.[9] BMI has also failed to identify poor nutrition status in stunted children with CF.[41] Dual-energy X-ray absorptiometry (DXA) scans are often used in research to measure variations in body composition; however, they are expensive and impractical for everyday use in a clinic. Bioelectrical impedance is another method to assess LBM but has been found to be inaccurate in persons with CF due to imbalances in electrolytes.[10, 11] Arm anthropometric measurements including triceps skinfolds (TSF), mid-upper arm circumference (MUAC), and arm muscle area (AMA) have been reviewed as possible methods to assess LBM, yet these methods have led to inconsistent results in the CF population.[11, 12] It has been concluded that neither skinfold

measurements nor bioelectrical impedance should be included in the standard nutrition assessment of CF patients.[13] LBM is strongly associated with pulmonary function and is not detectable using BMI, which means that a simple non-invasive method to measure LBM is needed.

Overall improving nutrition status in children with CF is critical, yet challenging because of difficultly absorbing nutrients as well as increased resting energy expenditure and reduced appetite.[42] The CF Foundation recommends energy intakes greater than the standard population to breathe normally, fight infection, compensate for poor digestion, and to support an age-appropriate weight.[3, 43] Improved weight status in both children and adults has been found at energy intakes of 110% to 200% of energy needs for the healthy population of similar age, sex, and size.[3] Historically, nutrition therapy for individuals with CF has focused on increased fat intake due to the malabsorption of fat. Yet, LBM is associated with pulmonary function and survival, and optimal protein intake is important to prevent muscle loss. The median survival age for CF has increased to 40 years, and there is more of a concern with sarcopenic obesity and cardiovascular risk. For patients with a BMI > 25, there was significantly less improvement in FEV_1 with increased BMI compared to patients in the normal weight range.[44] Increases in BMI may be due to increases in fat mass or to increases in LBM; BMI is incapable of deciphering between the two. This incapability illustrates the importance of a tool that is able to examine LBM in children with CF in clinical settings.

Handgrip Strength

Handgrip strength measures muscle function and has been shown to detect changes in muscle mass sooner than BMI and other anthropometric measures in children >6 years.[45, 46] It is a simple, non-invasive tool that is suitable for a clinical setting. HGS has been used to measure

muscle function in a variety of populations, including adults with CF. [14, 47, 48] It has been found that the correlation between HGS and LBM in children is stronger than the correlation between LBM and BMI.[15, 49] In a cross-sectional study of 25 adults with CF, handgrip strength and pulmonary function was reduced in the low LBM.[14] HGS is measured using handgrip dynamometry. The Jamar® Hand Dynamometer is widely used to measure HGS due to its established test-retest, inter-rater, and intra-rate reliability.[50] Children with CF have reduced muscle force, even in the absence of weakened nutrition status, which means that in order to utilize HGS as a nutrition assessment tool, it must first must be studied specifically in children with CF.[51] Multiple studies have shown HGS to be a good indicator of increased postoperative complications, increased length of hospitalization, increased rate of re-hospitalization, and decreased physical status in adults.[49] Silvia et al. looked at the relationship of HGS as an indicator of nutrition status in hospitalized pediatric patients and found that HGS was associated with undernutrition and that HGS decreased during hospital stay in 64% of the children.[52] Minimal research has been done on HGS in children with CF, and no research to our knowledge has been done comparing HGS in children with CF between hospitalization and after hospitalization at a 6-week follow up appointment. Investigating the relationship between HGS during hospitalization and after hospitalization could potentially provide evidence as to whether HGS is capable of detecting changes over time. HGS may serve as a valuable measurement in the CF population based on its ability to detect muscle depletion, accelerating the need for nutrition intervention to reverse muscle loss and pulmonary function decline. As noted previously, earlier detection of nutrition status decline is associated with improved nutrition status, pulmonary function, and survival.[16, 17]

APPENDIX C: COMPLETE METHODS

Study Setting and Design

A convenience sample of 23 children, ages 6-18 years, with cystic fibrosis (CF) participated in a longitudinal study from August 2016 to April 2017. Eligible participants were admitted to 289-bed pediatric specialty hospital within three days of their outpatient CF clinic appointment, able to read and understand verbal directions in English, and able to perform the HGS measurement. Children positive for *Burkholderia cepacia* were excluded. Eligible participants and/or their guardian(s) were given a flyer explaining the study within 24-72 hours of hospitalization. If the guardian(s) and child were interested, the registered dietitian nutritionist (RDN) set up an appointment for the family to meet with the researcher on day 5-7 of hospitalization. At this appointment, the researcher obtained consent from each subject's guardian(s) and assent from subjects seven years and older and took the appropriate measurements. Participants were compensated $5.00 at the initial appointment and $10.00 at the follow-up appointment. The Intermountain Healthcare and Brigham Young University Institutional Review Boards (IRB) approved the study.

Data Collection

Prior to data collection, members of the research team were trained on proper sanitation practices, how to use the Jamar® Plus Hand Dynamometer, and how to take anthropometric measurements using National Health and Nutrition Examination Survey (NHANES) protocol.[53] All measurements were taken by a single member of the research team or by trained outpatient CF clinic staff. Weight during hospitalization was measured by the researcher using a mechanical scale (Seca 882) and before/after hospitalization by clinic staff using a stationary mechanical scale (Scale-Tronix 5002) in the outpatient CF clinic; both were recorded to the

nearest 0.1 kg. Height was measured by clinic staff for all three periods using a wall-mounted stadiometer and was recorded to the nearest 0.1 cm. HGS was measured by gripping the Jamar® Plus Hand Dynamometer with the subject in a seated position, maintaining an unsupported elbow at the side of their body with the forearm stretched to a 90° angle. Each subject was asked to squeeze the hand dynamometer three times in each hand, alternating hands between each measurement. The mean measurement of all three trials on both the dominant and non-dominant hand was recorded. Mid-upper arm circumference (MUAC) was measured with a flexible, non-stretchable tape on the right arm halfway between the acromion process of the scapula and olecranon process at the tip of the elbow following NHANES procedures to the nearest 0.1 cm.[53] Measurement of triceps skinfolds (TSF) also followed NHANES procedures and were taken using a skinfold caliper to the nearest 0.1 mm.[53] MUAC and TSF measurements were used to calculate arm muscle area (AMA) z-scores. All equipment was disinfected using hospital grade sanitation wipes before and after measurements were taken.

Researchers examined data from three different periods: approximately five months before hospitalization, day 5-7 of hospitalization, and approximately six weeks after hospitalization at an outpatient CF clinic follow-up appointment. Weight, height, pulmonary function, and nutrition risk score were obtained from electronic medical records for all three periods (See Figure 1). Respiratory therapists measured pulmonary function as forced expiratory volume at 1 second (FEV_1). Nutrition risk score was calculated by the RDN based on BMI percentile, daily weight gain, and annual height gain; children with a score of 0-1 were no-low risk, 2-3 were moderate risk, and 4+ were high risk.[38] The researcher measured HGS, TSF, and MUAC during hospitalization and at follow-up (See Figure 1). Additionally, during hospitalization, the researcher reviewed a 3-day calorie count conducted by the RDN to assess

nutrient intake. The researcher was specifically interested in the amount of energy and protein a child consumed and if that child met their recommended energy and protein needs. Mean energy and protein intakes were calculated in order to find what percentage of the child's CF specific recommended energy and protein needs were met. The researcher also recorded if the child was receiving nutrition support and if the child had CF related diabetes (CFRD).

Statistical Analysis

Descriptive statistics including means and standard deviations were used to describe patient demographics. HGS values were reported as z-scores based on means and standard deviations published by and specific to the Jamar® Plus Hand Dynamometer.[54] Differences between the three periods for BMI z-scores, nutrition risk scores, and FEV_1 were examined using a mixed models analysis. A similar mixed models analysis was used to determine if HGS z-scores, BMI z-scores, and FEV_1 differed between hospitalization and follow-up. Regression analysis and analysis of variance (ANOVA) were used determine if there was a relationship among HGS z-score at hospitalization and the following variables: BMI z-score, nutrition risk score, FEV_1, MUAC z-score, TSF z-score, AMA z-score, percent energy intake, and percent protein intake. All analyses were done using the Statistical Analysis Systems statistical software package, version 9.4 (SAS Institute, Inc, Cary, NC). Results were considered significant when $p<0.05$.

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APPENDIX E: IRB APPROVAL

Intermountain Healthcare Research
Institutional Review Board

June 06, 2016

IRB # 1050194 **Study Alias:** Handgrip Strength Cystic Fibrosis
PI: Sarah Bellini
Title: *Handgrip Strength in Children with Cystic Fibrosis*

Initial Application - Expedited Review
IHC IRB (Corporate)
Approved: 06/02/2016
Expiration Date: 06/01/2017
Submission Reference #: 007412

The above referenced Study Application has been reviewed and approved by a member of the IHC IRB (Corporate) via expedited review in accordance with 45 CFR 46.110(f)(4).

The following submission items have been approved:

Title	Version Number	Version Date
Study Protocol Final	Version 2.1	05/10/2016
Appointment Form	Version 1.1	04/01/2016
Recruitment Instructions for RDNs	Version 1.2	04/01/2016
Follow-up Data Collection Sheet	Version 1.2	04/01/2016
Hospitalization Data Collection Sheet	Version 1.4	04/01/2016
Retrospective Data Collection Sheet	Version 1.2	04/01/2016
Recruitment Flyer	Version 1.0	04/01/2016
Assent Form	Version 1.1	04/01/2016
Parental Permission Consent Form	Version 1.1	04/01/2016

The FDA requires that research projects be reviewed yearly, or more often at the discretion of the IRB Committee. You will receive an email notification when it is time for review of this study. It is your responsibility to respond to this notification or approval for this study will be discontinued. In the meantime, please submit any administrative, procedural or clinical changes to the IRB for approval prior to making them effective.

It is your responsibility to notify DHHS and/or the FDA, and the IRB of any occurrence or emergency that seriously increases the risk to or affects the welfare of subjects.

APPENDIX F: RECRUITMENT FLYER

RESEARCH PARTICIPANTS NEEDED

PURPOSE: This study will assess if there is a difference in handgrip strength in children with cystic fibrosis during hospitalization compared their routinely scheduled follow up appointment.

ABOUT: This study will take place from June 2016 until June 2017 OR until enough children have participated in the study. Research data will be collected during your current hospitalization and at your routinely scheduled follow-up appointment. Data collection will only take 15 minutes.

ELIGIBILITY: Participants in this study must be between the ages of 6-18, have cystic fibrosis, be able to follow verbal and written directions in English, and be able to perform the handgrip strength measurement. Participants must have been admitted to Primary Children's Hospital after attending the Intermountain Cystic Fibrosis Center.

COMPENSATION: Participants will be given $15 for participation. $5 will be given to the participant at hospitalization and $10 will be given at the follow-up appointment.

BENEFITS of RESEARCH: Data collected from this research study will add to a better understanding of nutritional status in children with cystic fibrosis.

If you and your child are interested in participating in this study, please let your Registered Dietitian know and provide a specific time that both you and your child are available to meet the researcher on days 5-7 of child's hospital stay:

Researcher Availability for August 2016-December 2016

Monday	8:00 am – 7:00 pm
Tuesday	8:00 am – 7:00 pm
Wednesday	8:00 am – 7:00 pm
Thursday	8:00 am – 7:00 pm
Friday	8:00 am – 7:00 pm
Saturday	8:00 am – 7:00 pm

Please choose a **specific** time within this range to meet with the researcher.

If you have any questions or would like to participate, please contact one of the following individuals:

Sarah G. Bellini, PhD, RD, CD
Assistant Professor
Department of NDFS
ESC 141
Brigham Young University
Provo, UT 840602-4602
801-422-0015
sarah_bellini@byu.edu

Primary Children's Hospital
Catherine McDonald, Phd, RD, CD
Clinical Dietitian
Food & Nutrition Services
801-662-5314
katie.mcdonald@imail.org

Primary Children's Hospital
Jennifer Derrick MS, RD, CD
Administrative Dietitian, Research & Education
Food & Nutrition Services
801-662-5310
jennifer.derrick@imail.org

Parental Permission Form

What Handgrip Strength in Children with Cystic Fibrosis

Where

Primary Children's Hospital
Jennifer Derrick MS, RDN
100 Mario Capecchi Dr.
Salt Lake City, UT 84132

Intermountain Cystic Fibrosis Center
Catherine McDonald PhD, RDN, CD
100 Mario Capecchi Dr.
Salt Lake City, UT 84132

Who Primary Investigator: Sarah Gunnell Bellini PhD, RDN, CD (801)-422-0015

Co-investigators:
Jennifer W. Derrick MS, RDN, CD (801) 662-5310
Amanda Nederostek MS, RDN, CD (801)662-5303
Robin Aufdenkampe MS, RDN, CD (801) 662-5313
Catherine McDonald PhD, RDN, CD (801) 662-5314
Julie Spelman MBA, RDN, CD (801) 662-1404
Fadi Asfour MD (801) 213-3599
Hannah Gibson (801)-422-0015

When During your child's hospital stay and at your child's follow-up appointment.

Why This study will assess if there is a difference in handgrip strength in children with cystic fibrosis during hospitalization compared to a 6-week follow-up appointment.

How If you agree to have your child participate, we will do the study during your child's current hospital stay and at your child's routinely scheduled follow-up appointment. During hospital stay, the researcher will measure weight, mid-upper arm circumference, triceps skinfolds, and handgrip strength. Weight will be measure by having you step onto a scale. The researcher will also measure mid-upper arm circumference with a tape measure and triceps skinfolds using a skinfold caliper. The researcher will then measure handgrip strength by asking your child to squeeze a special tool with his/her hand. The researcher will record the numbers of all measurements. At the routinely scheduled follow-up appointment, a researcher will again measure mid-upper arm circumference and triceps skinfolds. The researcher will also again ask you to squeeze the tool used to measure handgrip strength. The researcher will record the measurements.

Why is this study being done?
We are asking you to give permission for your child to take part in a research study to see if there is a difference in handgrip strength in children with CF during hospitalization compared to a 6-week follow-up appointment. Handgrip strength is a simple measurement that may be used to assess nutritional status if a relationship is found in this study. There is little information about using handgrip strength to measure nutritional status in children with cystic fibrosis.

Why are you asking my child to take part in the study?
We are asking for your child to take part in this study because the study focuses on the handgrip strength of children with cystic fibrosis aged 6-18 years to measure nutrition health. Your child is a patient at Primary Children's Hospital and meets the study's inclusion criteria. Approximately *30* people will take part in this study at Primary Children's Hospital.

Please read this form and ask any questions you may have before giving permission for your child to be in this research study.

Who can be in the study?
We want to enroll children who…
- are between 6-18 years of age
- have cystic fibrosis
- are admitted to Primary Children's Hospital
- are able to understand verbal and written directions in English
- have the ability to perform handgrip strength measurements

Who cannot be in the study?
Your child cannot participate in this study if s/he…
- is not between the ages of 6-18 years of age
- is unable to squeeze the handgrip strength tool
- is unable to read or understand directions in English
- is not currently admitted to Primary Children's Hospital
- is positive for *Burkholderia cepacia*

If you agree for your child to be in this study, it will take about 15 minutes to collect the measurements that will be done today. The researcher will measure your child's weight, mid-upper arm circumference, triceps skinfolds, and ask them to squeeze the handgrip strength tool. The tool that your child will be squeezing is similar to the one pictured below. The second measurements of mid-upper arm circumference, triceps skinfolds, and handgrip strength will be collected at the follow-up appointment that you schedule and will also take about 15 minutes. A researcher will only measure mid-upper arm circumference, triceps skinfolds, and handgrip strength at the follow-up appointment. The tool used to measure handgrip strength is pictured below.

Do I have to give permission for my child to be in the study?
No, you do not have to give permission. Your decision for your child to take part in this study is completely voluntary.

What if I decide not to give permission?
You can choose not to have your child take part in this study and nothing about your child's care will change.

Can I change my mind later?
Yes. If you decide to give permission for your child to join the study, you can change your mind and decide to stop at any time.

How long will my child be in the study?
Your child will be in the study for approximately 15 minutes at Primary Children's Hospital and for approximately 15 minutes at their follow-up appointment in the Intermountain Cystic Fibrosis Center.

What will happen if I decide to let my child take part?
If you agree for your child to be in this study, the researcher will measure your child's weight and handgrip strength during their hospital stay. It will take about 15 minutes. The researcher will also be present at your child's follow-up appointment to measure handgrip strength, which will take about 15 minutes.

What are the risks to my child if s/he is the study?
There are minimal risks for participation in this study. However, some children may experience anxiety and discomfort from having his/her measurements taken. Your child may also potentially have pain associated with squeezing the handgrip strength tool. If your child does experience either of these issues, counseling and medical attention will be provided.

Are there any benefits to my child if s/he takes part in the study?
This study may help your child in the future. We hope to learn more about nutritional status in children with CF by doing this research study. There are no anticipated benefits now.

What happens if my child is injured because s/he was in the study?
If your child becomes injured while taking part in this study, Intermountain Healthcare can provide medical treatment. We will bill you or your insurance company in the usual way. Because this is a research study, some insurance plans may not pay for the treatment. If you believe your child has been injured as a result of being in this study, please call the Principal Investigator right away. You may also call the Office of Research at 1-800-321-2107.

Who do I ask if I have questions about the study or my child's rights?
If you have questions about the study please do not hesitate to call either Sarah Bellini at (801) 422-0015, Jennifer Derrick at (801) 662-5310 or Katie McDonald at (801) 662-5314.

If you have questions regarding your child's rights as a research subject or if problems arise which you do not feel you can discuss with the Investigator, please contact **Intermountain's Office of Research at 1-800-321-2107.**

What are the costs of taking part in the study?
There will be no cost for participation in this study.

Will my child be paid to take part in the study?
Each participant will be given $5 during hospitalization and $10 at follow-up for participation in this study.

If my child takes part in this study, what health information about him/her will you use?

Below is the health information from your child's medical records that will be used in the study:

- Nutritional risk score
- Pulmonary Function
- Height
- Weight
- BMI
- 3-day calorie count (energy and protein intake)
- CF related diabetes, yes or no
- Currently on nutrition support, yes or no
    - If yes, how long

Below is the health information that the researcher will measure directly from your child:

- Weight
- Mid-upper arm circumference
- Triceps skinfolds
- Handgrip Strength

The above health information will come from the information given to the researchers and from your child's medical records at hospitals and clinics where they've been treated.

The researchers will need to share your child's information with others. This information will **not** identify your child.

Important: You need to know that laws protect your child's health information when it is held by hospitals and healthcare providers. But if your child's health information goes to someone else, your child's health information may not be protected by those laws.

- Your child's health information may be viewed for the following purposes, and laws protect the confidentiality of your health information when used by these groups for these purposes: Intermountain's IRB (Institutional Review Board) to oversee the safety and ethics of the study
- Intermountain employees to do their job (such as give treatment, for billing matters, or to make sure the research is done correctly).
- The Food and Drug Administration and others to comply with law.

If you decide to allow your child to take part in this study and sign this form, you permit researchers to use your child's health information for this study. If you **want** your child to take part in this study, please **sign** this form. If you **don't** want your child to participate, please **don't** sign this form.

You can always ask to see your child's medical information at any time; however, you will not be able to see your child's health information that is used in this study until the study is finished.

Your agreement —which is called an authorization—to share your child's health information as part of this study will end when the study ends.

Consent

I confirm that I have read and understand this consent and authorization document and have had the opportunity to ask questions. I understand that my child's participation is voluntary and that I am free to withdraw my child at any time, without giving any reason, without my medical care or legal rights being affected. I will be given a signed copy of the consent and authorization form to keep.

I agree to allow my child to participate in this research study and permit you to use and disclose health information about my child for this study, as you have explained in this document.

_____
Child's Name

(Please Note: Both parents must give their permission unless one parent is deceased, unknown, incompetent, not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. If both parents are not able to sign, please list the name of the parent and the reason why they are not able to sign in the signature line.)

Parent/ Guardian Name	Parent/ Guardian Signature	Title	Date

_____
Name of Person Obtaining Authorization and Consent

_____ _____
Signature of Person Obtaining Authorization and Consent Date

APPENDIX H: PARTICIPANT ASSENT FORM

Assent Form

What Handgrip Strength in Children with Cystic Fibrosis

Where

Primary Children's Hospital Jennifer Derrick MS, RDN CD 100 Mario Capecchi Dr. Salt Lake City, UT 84132	Intermountain Cystic Fibrosis Clinic Catherine McDonald PhD, RDN, 100 Mario Capecchi Dr. Salt Lake City, UT 84132

Who Primary Investigator: Sarah Gunnell Bellini PhD, RDN, CD (801) 422-0015

Co-investigators:
Jennifer W. Derrick MS, RDN, CD (801) 662-5310
Amanda Nederostek MS, RDN, CD (801)662-5303
Robin Aufdenkampe MS, RDN, CD (801) 662-5313
Catherine McDonald PhD, RDN, CD (801) 662-5314
Julie Spelman MBA, RDN, CD (801) 662-1404
Fadi Asfour MD (801) 213-3599
Hannah Gibson (801) 422-0015

When During your hospital stay and at your follow-up appointment.

Why This study will assess if there is a difference in handgrip strength in children with cystic fibrosis during hospitalization compared to a 6-week follow-up appointment.

How This is a summary of what we will be doing, described on the next few pages.

If you agree to participate, we will do the study during your current hospital stay and at your follow-up appointment. During hospital stay, the researcher will measure weight, mid-upper arm circumference, triceps skinfolds, and handgrip strength. Weight will be measure by having you step onto a scale. The researcher will also measure mid-upper arm circumference with a tape measure and triceps skinfolds using a skinfold caliper. The researcher will then measure handgrip strength by asking you to squeeze a special tool with your hand. The researcher will record the numbers of all measurements. At the routinely scheduled follow-up appointment, a researcher will again measure mid-upper arm circumference and triceps skinfolds. The researcher will also again ask you to squeeze the tool used to measure handgrip strength. The researcher will record the measurements.

What is a research study?
A research study is a way to find out new information about something. You do not need to be in a research study if you do not want to.

Why are you asking me to be in this research study?
We are asking you to take part in this research study because we want to learn more about using handgrip strength to measure nutrition health in children with cystic fibrosis.

Do my parents/guardian know about this study?
Yes. We have explained the study to your parents/guardian, and they said that we could ask you if you want to be in this research study. Please talk about this with your parents before you decide if you want to be in the study.

We will also ask your parents to give their permission for you to take part in this study. But even if your parents say "yes" you can still decide not to be in this study.

Do I have to be in the study?
No, you do not have to be in this study. Being in this study is your choice and no one will be upset if you don't want to be in the study.

What will happen if I decide I want to be in the study?
If you agree to be in this study a researcher will measure your weight, mid-upper arm circumference, triceps skinfolds, and ask you to squeeze the handgrip strength tool. Then when you return to the hospital for your follow up appointment (in approximately 6 weeks) the researcher will again measure mid-upper arm circumference, triceps skinfolds, and ask you to squeeze the handgrip strength tool.

Can I get hurt if I join the study?
It is not likely that you will be hurt if you join this study. You have to have your weight, mid-upper arm circumference, and triceps skinfolds measured, and then squeeze a tool to measure how strong you are. The tool you squeeze is similar to the one pictured below.

Could this research study help me?
This study may help you in the future. We hope to learn more about nutrition in people with CF by doing this research study. There are no anticipated benefits now.

Can I stop being in the study if I change my mind later?
Yes. Being in this study is up to you and no one will be upset if you change your mind later and want to stop.

Who will see the information you collect about me?
All of your records about this research study will be kept locked up so no one else can see them. The files will be kept in a locked filing cabinet and in a locked office. Information kept in the computer will be password protected.

What if I have questions?
You can ask Katie McDonald in person or by telephone at 801-662-5314 any questions that you have about the study. If you have a question later that you didn't think of now, you can call Sarah Bellini at 801-422-0015.

You can take more time to think about being in the study. Please also talk with your parents or guardian about it. If you want to be in this research study, please write your name on the 'participant' lines below.

- **Remember, you can change your mind and stop being part of this study at any time**
- You and your parents will be given a copy of this paper to keep

_____
Name of participant (Please Print)

_____ _____
Participant signature Date

APPENDIX I: RECRUITMENT INSTRUCTIONS FOR RDNS

Recruitment Instructions for RDNs

Handgrip strength in Children with Cystic Fibrosis

Step 1: Provide flyer to parents of children that are eligible for this study. If the parent is not there when you assess the child, please leave a flyer with the nurse.

Step 2: If the parent and child express interest in the study, have the parent select a time from the flyer availability to meet with the researcher. If none of the times on the flyer work for the parent, obtain a time that does work for the parent.

Step 3: Notify Hannah Gibson by email. Include date and time for her to come meet with the parent and child. Do not include any patient information.

Hannah Gibson's email: hannah.gibson@byu.net

Step 4: Record appointment time, potential subject name, and room number on the provided appointment form posted in the dietitian office.

The researcher will call once a week to check to see if she has any upcoming appointments.

Who can be in the study?
We want to enroll children who…
- are between 6-18 years of age
- have cystic fibrosis
- are admitted to Primary Children's Hospital
- are able to understand verbal and written directions in English
- have the ability to perform handgrip strength measurements

Who cannot be in the study?
A child cannot participate in this study if s/he…
- is not between the ages of 6-18 years of age
- is unable to squeeze the handgrip strength tool
- is unable to read or understand directions in English
- is not currently admitted to Primary Children's Hospital
- is positive for *Burkholderia cepacia*

APPENDIX J: APPOINTMENT FORM

HGS in Children with Cystic Fibrosis Appointment Form

Potential Subject Name	Room Number	Date of Appointment	Time of Appointment

APPENDIX K: RETROSPECTIVE DATA COLLECTION SHEET

Retrospective

Q1 Date of Retrospective Data Collection

Q2 Study ID Number

Q3 Birthdate

Q4 Gender
- ❍ Male (1)
- ❍ Female (2)

Q5 Nutrition Support
- ❍ No (1)
- ❍ Yes (2) _____

Q6 CF Related Diabetes
- ❍ No (1)
- ❍ Yes (2)

Q7 Height

Q8 Weight

Q9 Pulmonary Function (FEV1 % Predicted)

Q10 Nutrition Risk Score
- ❍ No-low Risk (0-1) (1) _____
- ❍ Moderate Risk (2-3) (2) _____
- ❍ High Risk (4+) (3) _____

APPENDIX L: HOSPITALIZATION DATA COLLECTION SHEET

Hospitalization

Q1 Date of Data Collection

Q2 Study ID Number

Q3 Birthdate

Q4 Gender
- ❍ Male (1)
- ❍ Female (2)

Q5 Dominant Hand
- ❍ Right (1)
- ❍ Left (2)
- ❍ Both (3)

Q6 Right HGS

Q7 Left HGS

Q8 Weight

Q9 MUAC

Q10 Triceps Skinfolds

Q11 Nutrition Support
- ❍ No (1)
- ❍ Yes (2) _____

Q12 CF Related Diabetes
- ❍ No (1)
- ❍ Yes (2)

Q13 Height

Q14 Pulmonary Function (FEV1 % Predicted)

Q15 Nutrition Risk Score
- No-low Risk (0-1) (1) _____
- Moderate Risk (2-3) (2) _____
- High Risk (4+) (3) _____

Q16 Estimated Energy Needs from RDN

Q17 Mean Energy Intake

Q18 Percent Energy Intake

Q19 Estimated Protein Needs from RDN

Q20 Mean Protein Intake

Q21 Percent Protein Intake

APPENDIX M: FOLLOW-UP DATA COLLECTION SHEET

Follow-up

Q1 Date of Follow-up

Q2 Study ID Number

Q3 Birthdate

Q4 Gender
- ❍ Male (1)
- ❍ Female (2)

Q5 Cystic Fibrosis Related Diabetes
- ❍ No (1)
- ❍ Yes (2)

Q6 Nutrition Support
- ❍ No (1)
- ❍ Yes (2) _____

Q7 Right HGS

Q8 Left HGS

Q9 Height

Q10 Weight

Q11 MUAC

Q12 Triceps Skinfolds

Q13 Pulmonary Function (FEV1 % Predicted)

Q14 Nutrition Risk Score

- No-low Risk (0-1) (1) _____
- Moderate Risk (2-3) (2) _____
- High Risk (4+) (3) _____

BUDGET & JUSTIFICATION

Trainee's Salary or Stipend	$ 1,200
Supplies (itemize by major category)	$ 0
Other Expenses (itemize) Incentives	 $ 300
Total (Direct Costs only. No Indirect Costs allowed.)	$ 1,500

Justification of supplies or other expenses, if applicable: (Note: A maximum of $300 may be requested for project- related research supplies and other expenses.)

Other expenses: Each subject will receive an incentive of $15 for participation in the study. The $300 requested will cover 20 of the 30 total subjects. The incentive cost for the remaining 10 subjects will be covered by internal funds.

PROJECT DESCRIPTION

Maximum: Three pages.

Provide a concise description of the proposed project. Briefly state the hypothesis to be studied, its relationship to cystic fibrosis, methods to be used (experimental design), and expected outcomes from the study.

Background and Hypothesis

Optimization of nutritional status and growth in the cystic fibrosis (CF) population is associated with increased pulmonary function and is critical for effective treatment.[1] Body mass index (BMI) is currently the accepted method to determine nutritional status in children with CF.[2] BMI is a measure of weight adjusted for height (kg/m^2) and is incapable of distinguishing between lean body mass (LBM) and fat mass. In the past few years, newer research suggests a stronger association between LBM and pulmonary function than BMI and pulmonary function in CF patients.[3, 4, 5] However, BMI is still being used to measure nutritional status in clinical settings. DXA scans are commonly used in research to measure LBM; however, they are expensive and impractical for everyday use in a clinic. Bioelectrical impedance and triceps skinfolds have been assessed as possible methods to indirectly measure LBM in some populations, yet these methods have led to inconsistent results.[6] Handgrip strength (HGS) is a validated tool that has been used to measure muscle strength in a variety of populations.[7, 8, 9] Research has shown that muscle strength is reflective of LBM and that muscle function responds earlier to changes in nutritional status.[10] More specifically, positive associations have been found between HGS and LBM in adults with CF, and positive associations have also been found between low HGS and undernutrition in hospitalized pediatric patients at admittance.[9, 11] To our knowledge, HGS has not been measured overtime in children with CF. Due to the strong associations between LBM and pulmonary function and between HGS and LBM, HGS serves as a potentially crucial measurement in assessing nutritional status in children with CF.

The specific aim of this research project is to assess if there is a difference in HGS in children with CF during hospitalization compared to HGS at a 6-week follow-up appointment. Differences in HGS between hospitalization and follow-up would indicate changes in LBM. LBM has been found to have a strong association with pulmonary function and is an important element of diaphragm strength. [3, 4, 5, 12] Improving pulmonary function is key in CF treatment. HGS may be a more sensitive way to measure changes in LBM overtime compared to the traditional use of BMI. This study will examine the relationship among HGS, BMI, and pulmonary function. This study will also assess the relationship among HGS, nutrient intake, and nutrition status. Researchers are interested in nutrient intake in order to determine what percentages of each child's estimated energy/protein needs were consumed in a standardized 3-day calorie count. Researchers want to determine if % energy intake and % protein intake are associated with HGS. This information is important in understanding if there is a correlation between what an individual is consuming and their HGS. The relationship between HGS and nutrition status (determined by the nutrition risk score) is important to examine because nutrition risk scores (NRS) are routinely calculated in the CF pediatric population. The score is based on BMI percentile, daily weight gain, and annual height gain and is used to identify children that may benefit from more extensive medical nutrition therapy. The significance of these findings

are to determine whether or not HGS serves as a useful tool to measure nutritional status in children with CF.

We hypothesize that:

1. HGS measurements taken at the 6-week follow-up appointment will differ from measurements taken during hospitalization
2. HGS will be positively associated with BMI, pulmonary function, nutrient intake, and nutrition status

Methods and Experimental Design

A longitudinal study design will be used to examine if there is a difference between HGS in children with CF during hospitalization compared to HGS at a post-hospitalization 6-week follow-up appointment. The study population will consist of approximately 30 children with CF that are admitted to the Primary Children's Hospital (PCH) after attending the Intermountain Cystic Fibrosis Center (ICFC) in Salt Lake City, UT. Children with CF are commonly admitted to the hospital after attending ICFC if they have reduced pulmonary function, a respiratory infection, weight loss, or another complication. The inclusion criteria are: children aged 6-18 years with CF, must be admitted to PCH for 7-14 days after ICFC attendance, must have the ability to perform handgrip strength test, and both parent and child must be able to understand verbal and written directions in English. In an effort to maintain infection control, children with *Burkholderia cepacia* will be excluded. The age range of 6-18 years has been chosen based on the physical ability to have HGS measured and because the HGS tool to be used in the study (Jamar® Plus Hand Dynamometer) has been validated for this range.[13, 14]

Subjects will be recruited during hospitalization within the inpatient wing of PCH. Potential subjects will receive a flyer detailing the study within 24-72 hours of hospital admittance from the registered dietitian nutritionist (RDN) conducting the routine initial nutrition assessment. If the parent/guardian and child are interested, the RDN will set up an appointment for the family to meet with the designated researcher on day 5-7 of hospitalization. At the scheduled appointment, the researcher will explain the study in detail and answer any questions the family may have. If the parent and child wish to participate in the study, the researcher will obtain consent and/or assent and then proceed to taking the appropriate measurements.

On the day the child attended ICFC before hospital admittance, trained ICFC staff will measure/calculate height (cm), pulmonary function (FEV_1), and NRS (range). On day 5-7 of hospitalization the researcher will measure weight (kg) and HGS. The participant's weight will be measured using a mechanical scale (Seca 882) and will be recorded to the nearest 0.1 kg.[15] HGS will be recorded to the nearest 0.01.[13, 14] The researcher will calculate BMI using the weight obtained on day 5-7 and the height measured by ICFC trained staff on the day of hospital admission. A standardized 3-day calorie count will be administered to each subject during hospitalization as routine hospital protocol, and the researchers will use this information to examine the relationship between % energy intake, % protein intake, and HGS.[16] Approximately 6-weeks after hospitalization a routine follow-up appointment will be scheduled in the ICFC. At the follow-up appointment the same researcher that took measurements on day 5-7 of hospitalization will measure HGS. Also at the follow-up appointment, trained ICFC staff will measure/calculate weight, height, pulmonary function, BMI, and NRS. Additionally, researchers will examine the following retrospective data (approximately 6 months before hospitalization)

from subjects' medical records: weight, height, pulmonary function, BMI, and NRS. Medical record access has been requested in the submitted IRB application.

Data Analysis Plan

Means, medians, and standard deviations will be calculated for all variables: HGS, height, weight, BMI, pulmonary function, NRS, % energy intake, and % protein intake. Paired t-tests will be used to compare means of HGS, BMI, and pulmonary function between hospitalization and follow-up. An analysis of covariance and regression models will determine relationships between the dependent variable HGS and the independent variables height, weight, BMI, pulmonary function, NRS, % energy intake, and % protein intake. Relationships will be analyzed for multiple points in time: 6 months before hospitalization, at hospitalization, and 6-weeks post hospitalization. HGS data will only be available at hospitalization and at follow-up; no retrospective data will be available for HGS. Categorical variables include pulmonary function (FEV_1), NRS, % energy intake, and % protein intake. FEV_1 and NRS both have reference ranges that will be used to place these variables into categories.[16, 17, 18] Percent energy intake and % protein intake represent the percentage of estimated energy/protein needs met and will be separated into one of four categories: sufficient nourishment, mild malnutrition, moderate malnutrition, or severe malnutrition.[16] Continuous variables include HGS, BMI, height, and weight. Gender and age will be controlled for in all models because of their influence on HGS.[11] The significance level will be set at $p<0.05$.

Expected Outcomes

Researchers expect HGS measurements taken at the follow-up appointment to differ from HGS measurements taken during hospitalization. Positive associations are anticipated to occur between HGS and the following: BMI, pulmonary function, nutrition status, % energy intake, and % protein intake. Identifying LBM changes in children with CF is critical for effective treatment based on its positive association with pulmonary function.[9] BMI is currently the accepted method to determine nutritional status in children and is incapable of identifying changes in LBM.[2] HGS may serve as a potentially crucial measurement in the pediatric CF population based on its ability to detect muscle depletion; this detection would accelerate the need for nutrition intervention in order to reverse muscle loss and to prevent and/or improve pulmonary function decline.

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