2021

Nutritional and Metabolic Effects of Elexacaftor/Tezacaftor/ Ivacaftor in Adults and Adolescents with Cystic Fibrosis

Julianna Bailey
University Of Alabama At Birmingham

NUTRITIONAL AND METABOLIC EFFECTS OF ELEXACAFTOR/TEZACAFTOR/IVACAFTOR IN ADULTS AND ADOLESCENTS WITH CYSTIC FIBROSIS

by

JULIANNA BAILEY

KEVIN FONTAINE, COMMITTEE CHAIR
JESSICA ALVAREZ
GREGORY PAVELA
DAVID REDDEN
MICHAEL STALVEY

A DISSERTATION

Submitted to the graduate faculty of The University of Alabama at Birmingham,
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

BIRMINGHAM, ALABAMA

2021

NUTRITIONAL AND METABOLIC EFFECTS OF ELEXACAFTOR/TEZACAFTOR/IVACAFTOR IN ADULTS AND ADOLESCENTS WITH CYSTIC FIBROSIS

JULIANNA BAILEY

HEALTH EDUCATION AND HEALTH PROMOTION

ABSTRACT

Background: Since malnutrition is a main clinical consequence of CF, a high-calorie, high-fat diet is recommended. Highly effective cystic fibrosis transmembrane conductance regulator (CFTR) modulators promote improved growth and weight gain in subsets of the CF population. Recently Elexacaftor/Tezacaftor/Ivacaftor (ETI) was approved for use in up to 90% of people with CF. Our single center open-label observational cohort study aimed to explore the changes in dietary and metabolic outcomes with use of ETI.

Methods: Participants underwent baseline (V1) measurements prior to taking their first dose of ETI. Follow-up measurements were obtained at 28 days (V2) on ETI and > 6 months on drug (V3). Measurements at each time point included: weight, BMI, lung function, resting energy expenditure (REE%), hand grip strength (HGS), dietary intake, and enzyme dosage. Wilcoxon sign rank tests were used to compare changes in outcomes at each time point.

Results: A total of 22 participants enrolled and completed baseline assessments. V2 was completed by 20 participants and 17 participants completed V3. Participants were 16-54 years of age (mean 26 years), and 50% were not previously taking CFTR modulators. Mean (± SD) BMI increased by 0.46 ± 0.93 kg/m² ($p < 0.05$) at V2 and 0.92 ± 0.88 kg/m² at V3 compared to V1 ($p < 0.0001$). REE% decreased by 6.6 ± 15.3 from V1 to V3 ($p <$

0.05). Total caloric intake increased by 297 ± 766 kcal/day ($p < 0.05$) and total fat intake increased by 19 ± 37 grams/day between V1 and V3 ($p < 0.05$).

Conclusions: ETI increased BMI rapidly and this was sustained through at least 6 months. Decreased REE% combined with increased caloric intake are potential mechanisms of weight gain on ETI. Findings highlight the need for individualized nutritional counseling to improve diet quality and manage weight changes on ETI in the clinical setting.

DEDICATION

This dissertation is dedicated to Clay, Ashlee, Ellis, and Kat. Without their overwhelming love, support, and patience, I would not have been able to accomplish this.

ACKNOWLEDGMENTS

I am eternally grateful for all my friends and family who have served as mentors and motivators and cheered me on while completing this dissertation.

I would like to acknowledge my committee. Kevin Fontaine, for eagerly diving into the world of CF research and his leadership in chairing this committee. Jessica Alvarez, who encouraged me to pursue this degree, conduct CF nutrition research, and for being a true inspiration, friend, and mentor throughout this process. Michael Stalvey, who has been a constant source of support, wise counsel, unwavering encouragement, mentorship, and CF expertise. David Redden, who spent countless hours working with me on the statistics, empowering me to believe in myself, and asking the important questions. Greg Pavela, for his enthusiasm for this work and willingness to brainstorm with me.

I would also like to acknowledge my classmates in this doctoral cohort, who have continually encouraged me, particularly Alison Footman. I cannot thank enough the CF Research Center: Steve Rowe, for providing the necessary support to make this study a possibility and for his thoughtful feedback at each juncture. Heather Hathorne, for answering my many regulatory questions and her infinite patience and flexibility. Justin Wade, my PROMISE study partner in crime, for coordinating with me at every level and making the execution of this project not only possible, but fun. His phenomenal communication and positivity during even the most challenging times was an inspiration

throughout the process. I also am incredibly grateful for the entire UAB Adult CF Clinic Team for their support and encouragement while I completed this work.

Mostly, I would like to acknowledge the individuals with CF who took the time to participate in this study. Their enthusiasm for being a part of CF research and their hope for the future is a constant inspiration and it was an honor to get to know and work with each of them.

TABLE OF CONTENTS

Page

APPENDICES

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1: INTRODUCTION

Cystic Fibrosis (CF) is a life threatening, rare genetic disease that primarily affects the lungs and the GI tract. CF is caused by a defective cystic fibrosis transmembrane regulator (CFTR) gene that causes an imbalance of salt in the epithelial cells (Quon & Rowe, 2016). The faulty CFTR protein causes electrolyte abnormalities that result in thick, sticky secretions from epithelial cells (Rowe, Miller, & Sorscher, 2005). Malnutrition is a common consequence of CFTR dysfunction, and is associated with lower lung function and poorer survival (V. A. Stallings, L. J. Stark, K. A. Robinson, A. P. Feranchak, & H. Quinton, 2008a). For this reason, it has been historically recommended that people with CF consume a high-calorie, high fat, high-protein diet to meet elevated metabolic demands of the disease. However, little guidance has been provided on diet quality or nutrient density in the setting of these elevated metabolic needs (McDonald et al., 2021). Over the past 2 decades, life expectancy has dramatically increased in people with CF due to advances in research, clinical care, and new drug development ("Cystic Fibrosis Foundation Patient Registry: 2019 Annual Data Report.," 2019). New drugs, known as CFTR modulators, can improve nutritional status as well as pulmonary outcomes. As longevity increases, it is imperative to understand long-term nutritional implications of these new therapies and update nutrition recommendations to promote optimal health and wellbeing in people with CF as they age.

The purpose of this chapter is to (1) introduce the problem of limited knowledge on how highly effective CFTR modulators will impact nutritional status in people with CF (2) provide background and significance of the problem, (3) state the purpose of this dissertation study, and (4) list the research questions and aims.

Problem, Background, and Significance

Over the past two decades, life expectancy in CF has doubled. In 1990, the median life expectancy for people with CF was 29 years of age, and in 2019, the life expectancy had improved to 47 years of age in the United States ("Cystic Fibrosis Foundation Patient Registry: 2019 Annual Data Report.," 2019). Now that life expectancy has significantly increased in a short period of time, new clinical consequences have emerged including osteoporosis, abnormal blood lipids, macrovascular consequences of CF related diabetes, and the emergence of overweight/obesity (P. A. Flume, Fernandez, G.S., Schechter, M.S, Fink, A., 2019).

While CF is primarily known as a pulmonary disease, the GI tract is also adversely affected. In 85-90% of people with CF, the exocrine portion of the pancreas becomes clogged with thick secretions and destroyed, leading to an inability to absorb fat, carbohydrates, protein, and fat-soluble vitamins A, D, E, and K (Wilschanski & Novak, 2013). Malnutrition is a common problem in CF due to malabsorption caused by exocrine pancreatic insufficiency, increased work of breathing, chronic inflammation, and chronic lung infection (Stallings et al., 2008a). Nutritional status is closely associated with lung function in CF, in that with higher body mass index (BMI) is

associated with better lung function, while malnutrition and low BMI are associated with poorer survival (Stallings et al., 2008a).

Over the past decade, pharmaceutical companies have developed several genetic mutation specific drugs to treat the CF, known as CFTR modulators that treat the underlying cause of CF – a faulty gene that codes for the CFTR protein. Phase 3 trials were completed for a new CFTR modulator, which is a combination of two existing CFTR modulators, and a new corrector known as elexacaftor/tezacaftor/ivacaftor (ETI). Data suggest that ETI is highly effective in treating CF and improving CF clinical outcomes including lung function and quality of life and can improve nutritional status as measured by BMI (Heijerman et al., 2019; Middleton et al., 2019). ETI is designed for people with CF who have at least one copy of the most common mutation (F508del), which accounts for 85% of the US CF population (Middleton et al., 2019). ETI received FDA approval in October 2019 and became available to patients for clinical use. A multi-site prospective observational cohort study (PROMISE - IRB 300002244) is currently being conducted to understand how this drug impacts CF outcomes over time with real-world clinical use. Primary outcomes of the parent PROMISE study include lung function, weight, BMI, sweat chloride levels, and quality of life.

While malnutrition has been a common problem in CF and is associated with poorer clinical outcomes and poorer survival (Wells et al., 2008), CFTR modulator therapies have the potential to improve nutritional status in addition to other CF clinical outcomes. Data suggest that the CFTR modulator, Ivacaftor, increases BMI, linear growth, and is associated with an increase in fat mass and fat free mass (D. Borowitz et al., 2016; Ramsey et al., 2011; Stalvey et al., 2017). The mechanism behind this effect is

not fully understood. Decreases in resting energy expenditure in relation to improved pulmonary function on CFTR modulation may play a role in metabolic and nutritional changes observed in patients with gating mutations who begin the highly effective CFTR modulation therapy, ivacaftor (Stallings, Sainath, Oberle, Bertolaso, & Schall, 2018). *The effect of dietary intake on growth and metabolic parameters in the setting of CFTR modulator therapy is unknown.* Exploring mechanisms of weight gain and dietary changes on new, highly effective CFTR modulation therapy is crucial to understanding how these drugs affect patients in the real-world clinical setting. Elucidating reasons for weight gain can provide foundation for clinical care decisions and future interventions for weight management in CF. Currently, no studies have examined the dietary or metabolic outcomes of ETI.

This single-center observational cohort sub-study (IRB 300003442) to PROMISE aims to explore the changes in nutritional intake and metabolism in a subset of patients with cystic fibrosis who begin a new, highly effective CFTR modulator, elexacaftor/tezacaftor/ivacaftor (ETI), as part of the larger PROMISE cohort study.

Research Questions and Hypotheses

Research Questions

1) What are the effects of starting ETI on nutrition and metabolic parameters, including weight change, BMI change, REE, handgrip strength, dietary intake, and enzyme dosage in adolescents and adults with CF?
2) Are changes in nutrition and metabolic parameters associated with improvements anthropometric measurements and lung function on ETI?

Hypothesis

We hypothesize that ETI will decrease resting energy expenditure in adolescents and adults with CF, and that this will be associated with increased BMI.

CHAPTER 2: BACKGROUND AND REVIEW OF LITERATURE

Cystic Fibrosis

CF is a life limiting genetic multi-system organ disease caused by the defective CFTR protein that causes a salt imbalance in the cells. This leads to thick, sticky secretions from epithelial cells in the lungs, digestive tract, reproductive tract, skin, sinuses, and liver (Rowe et al., 2005). The defect in CFTR can also cause intestinal obstructions, biliary cirrhosis, and infertility. CF is caused by a defective CFTR gene that causes abnormal chloride ion transport across epithelial cells (Quon & Rowe, 2016). This electrolyte imbalance causes thick, sticky secretions from epithelial cells, which leads to chronic lung infection and inflammation as well as fibrosis of the pancreas cells. CF occurs in one in every 4,000 live births (Palomaki, FitzSimmons, & Haddow, 2004) and affects 30,000 in the United States and 70,000 across the world (Foundation, 2019). The gold standard for diagnosis CF is the sweat chloride test with levels ≥ 60 mmol/dL indicating CF. Newborn screening for CF is now in all 50 states since 2010. If IRT levels are elevated on newborn screening, a confirmatory sweat chloride test is completed (Farrell et al., 2017) . The CF Foundation recommends that anyone with a positive sweat chloride test undergo CF genetic sequencing. Individuals with CF-causing genetic mutations on two alleles will likely have CF, which must also be confirmed by sweat chloride testing if this, was not completed initially (Farrell et al., 2017).

CF was often described as a fatal disease, but has more recently been referred to "limiting" and "chronic" as life expectancy has steadily increased over the past 60 years, with a rapid acceleration in the past decade (Link & Nayak, 2020). In 1938, children typically did not live beyond 6 months of age. In the 1980s, few people with CF lived past their teenage years ("Cystic Fibrosis Foundation Patient Registry: 2019 Annual Data Report.," 2019). However, improved clinical care provided by interdisciplinary teams at accredited CF Care Centers as well as advances in drug therapies have led to an improvement in the median life expectancy to 48.4 years of age ("Cystic Fibrosis Foundation Patient Registry: 2019 Annual Data Report.," 2019; Lebecque et al., 2009). Once thought of as a disease of childhood, the most recent CFF Patient Registry (CFFPR) data report revealed that 56% of people with CF in the United States are adults ("Cystic Fibrosis Foundation Patient Registry: 2019 Annual Data Report.," 2019). While this improvement and care and extended longevity is promising, adults with CF now face additional challenges and comorbidities associated with aging including CF related diabetes, low bone mineral density ("Cystic Fibrosis Foundation Patient Registry: 2019 Annual Data Report.," 2019), and the emergence of overweight and obesity (P. A. Flume, Fernandez, G.S., Schechter, M.S, Fink, A., 2019).

Complications and Treatment of Cystic Fibrosis

Pulmonary

While multiple organ systems are affected, the primary cause of death in patients with CF remains respiratory failure ("Cystic Fibrosis Foundation Registry Report," 2017). Imaging evidence suggests that damage to the lungs begins in infancy, even in the

absence of pulmonary symptoms (Mott et al., 2013). The CFTR defect causes reduced airway surface liquid, which leads to increased viscosity of liquids causing abnormally thick mucus in the lungs. Unusually thick mucus causes the cilia in the airway to collapse and impairs the clearance of mucus from the lungs. The mucus is trapped in the lungs, which leads to a chronic cycle of bacterial infection and inflammation (Tang et al., 2014).

The goal of treatment for CF lung disease is to attenuate lung function decline by preventing and treating bacterial infection and colonization. The CF Foundation recommends routine monitoring of lung function and pulmonary disease progression through at least quarterly spirometry and annual chest -rays. Treatment for CF lung disease includes inhaled antibiotics, mucolytics, inhaled hypertonic saline, and twice daily manual airway clearance therapy (ACT) (Mogayzel et al., 2013). Regular cardiovascular exercise is also encouraged as it assists with airway clearance of mucus and has been found to transiently normalize sweat chloride levels (Quon et al., 2015). Treatment for pulmonary infection exacerbations includes increased frequency of ACT combined with oral antibiotics, intravenous antibiotics, and sometimes hospitalization (P. A. Flume et al., 2009). If all treatments, medications, and therapies are completely adhered to, treatments can take up to 2 hours per day (Sawicki, Sellers, & Robinson, 2009).

Gastrointestinal and Pancreatic Involvement

Both the endocrine and exocrine aspects of pancreatic function are impaired by CF. Up to 90% of people with CF have exocrine pancreatic insufficiency (PI) ("Cystic Fibrosis Foundation Patient Registry: 2019 Annual Data Report.," 2019). There is a link

between the endocrine and exocrine pancreatic involvement in CF, with some evidence that worse exocrine pancreatic disease in infancy as measured by immunoreactive trypsinogen (IRT) levels predicts CF related diabetes development later in life (Soave et al., 2014).

PI is one of the earliest features of CF, and there is evidence that damage to the pancreas begins in utero (Sturgess, 1984). Reduced liquid in ductal secretions in the pancreas leads to thick secretions that clog the ducts, cause cyst formation, and ultimately the fibrosis of the pancreas which lead to the original name of the disease - "cystic fibrosis of the pancreas" (Palermo & Szabo, 2014). Consequently, digestive enzymes are not produced in sufficient quantities due to acinar cell damage and fibrosis and cannot reach the small intestine due to thick secretions clogging pancreatic ducts (V. K. Singh & S. J. Schwarzenberg, 2017). This leads to maldigestion and therefore malabsorption of fat, protein, complex carbohydrates, calcium, and fat-soluble vitamins A, D, E, and K. Symptoms of PI include steatorrhea, abdominal pain, and other GI complaints such as flatulence and bloating.

The treatment for pancreatic insufficiency in association with CF is pancreatic enzyme replacement therapy (Wilschanski & Novak, 2013). Before the availability of pancreatic enzyme replacement therapy (PERT), CF mortality was due to malnutrition caused by exocrine pancreatic insufficiency (Palermo & Szabo, 2014). Oral pancreatic enzymes must be taken before each meal and snack that contains fat, protein, or complex carbohydrate to facilitate absorption of nutrients and weight gain and maintenance (V. A. Stallings, L. J. Stark, K. A. Robinson, A. P. Feranchak, & H. Quinton, 2008b). PERT dosing is most often determined by the CF Care Team Registered Dietitian (Vikesh K.

Singh & Sarah Jane Schwarzenberg, 2017) and is typically set meal and snack doses based on body weight, but individualized to each person with CF since response to PERT can be variable. The CF Foundation recommends 500–2500 units of lipase/kg per meal and half of this with snacks for individuals beyond infancy, and no more than 10,000 units of lipase/kg/day as this level has been associated with fibrosis colonopathy (D. S. Borowitz, Grand, & Durie, 1995). PERT therapy must be adjusted frequently to promote optimal growth and development in pediatric patients with CF and is often adjusted based on symptoms in adults.

The endocrine portion of the pancreas is also compromised, and CF Related Diabetes (CFRD) is one of the most common comorbidities of CF, affecting 30% of adolescents and up to 50% of adults with CF ("Cystic Fibrosis Foundation Patient Registry: 2019 Annual Data Report.," 2019). CFRD is distinct from other types of diabetes although it shares features of both type I and type II DM with primary insulin deficiency caused by fibrosis of islet cells leading to decreased insulin production, as well as insulin resistance caused by the inflammatory nature of the disease (Moran et al., 2018). The CF Foundation guidelines on CFRD recommend screening annually in patients aged 10 years and older by oral glucose tolerance test (OGTT) because Hemoglobin A1c can be spuriously low due to higher red blood cell turnover in CF (Moran et al., 2010). The main treatment for CFRD is insulin, most often in a basal bolus regimen with carbohydrate counting to dose insulin based on an insulin to carbohydrate ratio at meals, and a long-acting insulin dose once per day. Oral agents are not approved for the treatment of CFRD (Moran et al., 2010).

PI is the most common GI consequence of CF, but other manifestations include gastroesophageal reflux disease, small intestinal bacterial overgrowth, distal intestinal obstructive syndrome (DIOS), peptic ulcers, gastroparesis, and CF related liver disease (D. Borowitz & Gelfond, 2013). Approximately 6% of people with CF experience CFLD, and this sometimes requires liver transplantation (Morrell, Kiel, & Pilewski, 2019).

Nutrition in Cystic Fibrosis

Nutritional status as measured by BMI is closely associated with lung function in CF (Sheikh, Zemel, Stallings, Rubenstein, & Kelly, 2014). Lower BMI is associated with lower lung function, increased mortality, and poorer survival in this population (Szwed et al., 2018). For this reason, the CF Foundation guidelines recommend BMI goals to be on the higher side of the normal BMI range. The goal for pediatric patients is to achieve a BMI at or above the 50^{th} percentile, and the goal for adults > 20 years of age is a BMI of 22 kg/m2 for females with CF and 23 kg/m2 for men with CF (Stallings et al., 2008a).

CF has historically been a disease of catabolism, and malnutrition has been a common issue due to increased pulmonary demands, malabsorption with CF-related exocrine pancreatic insufficiency, and chronic infection (Stallings et al., 2008b). Additionally, increased resting energy expenditure (REE) is observed in people with CF when compared with healthy controls, and likely plays a role in suboptimal nutrition status observed in CF(T. Moudiou, Galli-Tsinopoulou, & Nousia-Arvanitakis, 2007; Tatiana Moudiou, Galli-Tsinopoulou, Vamvakoudis, & Nousia-Arvanitakis, 2007). Increased REE has also been observed longitudinally in children with CF age 5-18 who have severe genetic mutations and PI (Magoffin et al., 2008).

Due to the propensity for malnutrition in CF and some limited observational evidence, the legacy "CF Diet" is high-calorie, high-protein, and high-fat to help overcome increased work of breathing with CF lung disease, the malabsorption associated with exocrine pancreatic insufficiency, and a chronic cycle of inflammation (Stallings et al., 2008a). There is little evidence for the optimal diet for CF, but the landmark study that led to the recommendation for the high-calorie, high-fat diet in CF was an observational study conducted between two of the largest CF centers in the country at the time, Boston and Toronto. Results revealed that people with CF in Toronto had a better life expectancy than those in Boston (Corey, McLaughlin, Williams, & Levison, 1988). The main difference in clinical care that was associated with survival differences was that Toronto patients were instructed to eat a high-fat diet, and Boston patients were encouraged to follow a fat restricted diet (Corey et al., 1988). The association between fat content of the diet and survival in CF led to the longstanding recommendation to consume a high calorie, unrestricted fat diet (D. Borowitz, Baker, & Stallings, 2002). However, the landscape of nutrition in CF is changing rapidly due to improvements in clinical care, extended longevity, and the introduction of CFTR modulation therapy. In fact, a recent national registry analysis indicated that overweight and obesity have increased substantially in the US CF population, while malnutrition has been declining over the past 2 decades (P. A. Flume, Fernandez, Schechter, & Fink, 2019). While CFTR modulation therapy has the potential to improve nutritional status in the malnourished subset of people with CF, the weight gain associated with highly effective modulators may lead to overweight and obesity in other portions of the population. Given that CFTR modulators are a relatively new therapy, the long-term

metabolic and nutritional effects are unknown. It is important to understand the nutritional and metabolic effects of CFTR modulators as we move into an era of 85% of people with CF being eligible for highly effective modulator therapy. Understanding the mechanisms of weight gain and metabolic consequences of these drugs can inform weight management interventions for the entire spectrum of BMI status in the CF population.

Body Composition

BMI has historically been used as the main indicator of nutritional status in CF due to its strong correlation to lung function (Stallings et al., 2008a). While BMI is a useful screening tool, it does not consider the difference in fat mass and fat free mass (Engelen, Schroder, Van der Hoorn, Deutz, & Com, 2012; Susannah J. King et al., 2010). Body composition has become a topic of interest to provide a more complete assessment of nutritional status in people with CF. Clinicians and researchers are looking beyond BMI to understand how lean mass and fat mass might influence CF outcomes. Evidence suggests that people with CF tend to have lower fat free mass than healthy controls (Ahmad, Ahmed, & Patrizio, 2013; Bianchi et al., 2006; Hauschild et al., 2016; S. King, Wilson, Kotsimbos, Bailey, & Nyulasi, 2005; Susannah J. King et al., 2010; Reix, Bellon, & Braillon, 2010; Sheikh et al., 2014; Stettler et al., 2000). Other body composition abnormalities including central adiposity, visceral adiposity, and normal weight obesity have been observed in CF (Alvarez, Ziegler, Millson, & Stecenko, 2016; Chaves, Cunha, Costa, Costa Rde, & Lacerda, 2015; Haroun, Wells, Lau, Hadji-Lucas, & Lawson, 2006; Moriconi et al., 2006; Panagopoulou, Fotoulaki, Nikolaou, & Nousia-Arvanitakis, 2014).

Lower fat free mass is also associated with lower lung function in people with CF (Alvarez et al., 2016; Calella, Valerio, Brodlie, Donini, & Siervo, 2018; Calella, Valerio, Thomas, et al., 2018; Ionescu et al., 2002; Susannah J. King et al., 2010; Moriconi et al., 2006; Sheikh et al., 2014). These associations between body composition parameters and CF clinical outcomes have driven an interest in expanding assessment of nutritional status beyond just BMI in the CF population. Recent CF Nutrition guidelines recommend body composition assessment in the clinical setting when feasible (McDonald et al., 2020).

Dietary Intake

CF Foundation recommendations state that people with CF should consume 110-120% of the estimated energy requirements (EER). Although CF Foundation recommendations are dated, 35-40% of calories from fat are also recommended in this population due to the presence of fat malabsorption that contributes to malnutrition (D. Borowitz et al., 2002; Stallings et al., 2008b). As treatment for CF has advanced and longevity has extended, BMI has steadily increased in both the adult and pediatric populations over the past decade according to CF Foundation Patient Registry (CFFPR) Data ("Cystic Fibrosis Foundation Patient Registry: 2019 Annual Data Report.," 2019). Additionally, a recent epidemiological study of the CFFPR found rates of malnutrition declining and the proportion of overweight and obesity increasing in both adults and children with CF over the past 15 years (P. A. Flume, Fernandez, G.S., Schechter, M.S, Fink, A., 2019). Along with rising rates of overweight and obesity, recent studies indicate that the longstanding recommendation for an unrestricted high-calorie, high-fat diet has led to poor diet quality in the CF population (Calvo-Lerma et al., 2019; McDonald et al.,

2021; Sutherland et al., 2018). A recent cross-sectional study found that European children and adolescents with CF consume high-energy, nutrient poor diets, with high simple sugar and saturated fat intake, along with poor nutrient profiles (Calvo-Lerma et al., 2019). In another recent study of U.S. adults with CF, participants had overall poor diet quality and consumed higher amounts of trans fatty acids, added sugars and lower amounts of dietary fiber than healthy controls. Additionally, higher added sugar intake was positively associated with visceral fat in participants with CF (Bellissimo et al., 2019). The Academy of Nutrition and Dietetics published new evidence-based guidelines for nutrition in CF recently, and provide updated recommendations that adults and children with CF follow a diet that is recommended for the general population since there is no evidence that deviating from these recommendations results in any health advantages for people with CF (McDonald et al., 2020). Other recent guidelines on nutrition in CF also highlight the need for both an individualized approach to dietary recommendations and a focus on overall diet quality in this population (Saxby N, 2017). However, these guideline recommendations were based on consensus statements and note paucity of evidence for the optimal diet in CF, especially considering the changing landscape of nutrition as longevity increases and health improves with treatment advances in this population.

CFTR Modulator Therapy and Nutrition Outcomes

There are over 2,000 variants of the CFTR mutation, with approximately 350 mutations known to cause CF (Cystic Fibrosis Foundation). The mutations are classified based on the mechanism by which the defective gene disrupts normal CFTR function

(Elborn, 2016). CFTR mutation classes I, II, and III represent the more severe disease phenotypes (Ratchford, Teckman, & Patel, 2018). Over the past decade, several drugs have been developed that specifically target the underlying defective CFTR protein. These drugs are known as CFTR modulators, and their mechanism of action varies based on the CFTR defect. Ivacaftor (a potentiator) acts on cell surface CFTR protein channels allowing for improved chloride transport, while lumacaftor and tezacaftor (correctors) improve the structure of the CFTR protein and its trafficking to the cell surface (Quon & Rowe, 2016). As some mutations have multiple defects, CFTR modulators are often used in combination with each other. CFTR modulator therapy is effective in improving clinical outcomes, such as increased FEV1% predicted, decreased sweat chloride levels, and decreased risk of pulmonary exacerbation (Davies et al., 2013; De Boeck et al., 2014; Ramsey et al., 2011; Ratjen, Hug, Marigowda, Tian, Huang, Stanojevic, Milla, Robinson, Waltz, Davies, et al., 2017; Taylor-Cousar et al., 2017; Wainwright et al., 2015). Nutritional parameters have not been the primary outcome of the clinical trials conducted on CFTR modulation therapy, but modulators have the potential to improve nutritional status as measured by BMI in CF. Previous research suggests that the effect of CFTR modulators on anthropometric and growth parameters is dependent on both the formulation of the CFTR modulator and the genetic mutations of the individual with CF(J. Bailey et al., 2020) (J. Bailey, Garcia, L., Rutland, S., Oates, G., 2020; Elborn et al., 2016; Ramsey et al., 2011).

Ivacaftor

Six randomized controlled trials, represented by nine articles, examined the effect of ivacaftor on nutritional outcomes including anthropometric and growth parameters (D. Borowitz et al., 2016; Davies et al., 2013; De Boeck et al., 2014; Edgeworth et al., 2017; P. A. Flume et al., 2012; Konstan et al., 2015; Moss et al., 2015; Ramsey et al., 2011; Stalvey et al., 2017). All trials utilized the same dose of ivacaftor: 150 mg every 12 hours or twice per day. While the ENVISION trial targeted pediatric participants, (D. Borowitz et al., 2016; Davies et al., 2013; Konstan et al., 2015; Stalvey et al., 2017) Edgeworth and colleagues included adult participants only (Edgeworth et al., 2017). The remaining studies included both pediatric and adult participants. Sample sizes ranged from 20 (Edgeworth et al., 2017) to 167 (STRIVE) participants (D. Borowitz et al., 2016; Konstan et al., 2015; Ramsey et al., 2011; Stalvey et al., 2017), and trial durations ranged from 8 weeks (KONNECTION) (De Boeck et al., 2014) to 48 weeks (ENVISION and STRIVE) (D. Borowitz et al., 2016; Davies et al., 2013; Konstan et al., 2015; Stalvey et al., 2017). The ENVISION and STRIVE trials and the trial by Edgeworth, et al. (2017) targeted participants with at least one copy of the G551D mutation (Class III), while the KONNECTION (De Boeck et al., 2014) trial targeted CF participants with non-G5511D gating mutations (Class III). Finally, the KONDUCT trial targeted participants with the R117H mutation (Class IV) and the DISCOVER trial targeted participants who were homozygous for the F508del mutation (Class II) (P. A. Flume et al., 2012; Moss et al., 2015). Weight, growth parameters, and body composition were secondary outcomes reported in these phase III trials.

In pediatric participants ≤20 years of age with at least one copy of the G551D mutation (class III), 48 weeks of 150 mg ivacaftor twice daily increased WFA and BMI-for-age z-scores by 0.35 and 0.39, respectively, compared to placebo (mean baseline BMI z-score was -0.199 and WFA z-score was -0.292) (D. Borowitz et al., 2016). The same dose may increase BMI-for-age z-score after 8 weeks in children aged 6-17 years with other class III mutations, but evidence was limited (De Boeck et al., 2014). Stalvey and colleagues conducted post-hoc analysis of the observational GOAL study and randomized, placebo controlled ENVISION trial. They found that ivacaftor significantly improved weight-for-age and height-for-age z-scores in children aged 6-11 years in both studies over 6 months and 48 weeks, respectively (Stalvey et al., 2017). In the ENVISION study, growth velocities for both height and weight were accelerated from baseline to 48 weeks in children taking ivacaftor when compared to placebo (Stalvey et al., 2017). In adults with CF with at least one copy of the G551D mutation (class III) and with optimal (Stallings et al., 2008a) or low mean BMI at baseline, 4-48 weeks of treatment with 150 mg ivacaftor twice daily increased weight and BMI by a mean of 2.9 kg and 0.58-1.2 kg/m^2, respectively (Davies et al., 2013; De Boeck et al., 2014; Edgeworth et al., 2017). In participants ≤20 years of age who were homozygous for the F508del mutation (class II), 16 weeks of 150mg ivacaftor twice daily had no statistically significant effect on WFA or BMI z-scores compared to placebo, though baseline nutritional status for pediatric participants was not able to be determined (P. A. Flume et al., 2012). In adults with CF who had class IV mutations and optimal mean BMI, 150mg of ivacaftor twice daily for 24 weeks had no statistically significant effect on BMI compared to placebo (Moss et al., 2015). The effect of ivacaftor on body composition in

pediatric participants with class III and class II mutations was not described. Only one RCT examined changes in body composition in adults with one copy of G551D (class III mutations) and found that there was no statistically significant effect of CFTR modulation therapy on fat free mass (Edgeworth et al., 2017).

A recent observational study used propensity matching to pair children with gating mutations taking ivacaftor as part of clinical trials for 3 with children with F508del mutations from the CF Patient Registry as a control group. This study revealed that children taking ivacaftor had statistically significant acute improvement in weight-for-age and BMI-for-age z-scores that were durable out to 3 years when compared to the matched control group who did not take ivacaftor (Sawicki et al., 2015). Other observational and retrospective studies support a beneficial effect of ivacaftor on anthropometric parameters among patients with a G551D mutation (Dryden, Wilkinson, Young, Brooker, & Scottish Paediatric Cystic Fibrosis Managed Clinical, 2018; Kirwan et al., 2019; Rowe et al., 2014).

Overall, the literature suggests that in children and adults with at least one copy of the G551D mutation (class III), ivacaftor (150 mg twice daily) increases BMI and growth parameters. Ivacaftor may not have any significant effect on BMI in pediatric patients homozygous for F508del mutation (Class II) or adult patients with at least one copy of the R117H mutation. There is potential for young children taking ivacaftor to restore exocrine pancreatic function, however, this trend has not been observed in adults with gating mutations.

Ivacaftor + Lumacaftor Combination Therapy

Ratjen and colleagues conducted a randomized, double-blind, placebo-controlled, multi-site study was done in patients aged 6–11 years with cystic fibrosis who were homozygous for the *F508del-CFTR* mutation and found that there was not a statistically significant difference in BMI z-score improvement between groups of children taking placebo and the drug (Ratjen, Hug, Marigowda, Tian, Huang, Stanojevic, Milla, Robinson, Waltz, & Davies, 2017). Similar findings were observed in a positive quality RCT conducted by Rowe and colleagues in adult patients with CF who were heterozygous for the F508del mutation (Rowe et al., 2017). There were no between group differences in BMI over the course of the 8-week study (Rowe et al., 2017). The TRAFFIC and TRANSPORT studies were randomized, double blind, placebo-controlled parallel group trials that examined two different dosages of ivacaftor + lumacaftor in adult patients with CF. Both dose groups in the TRANSPORT trial had significant improvement in BMI compared to placebo. However, the difference in absolute BMI change was not significantly different than placebo in either dosage group in the TRAFFIC study (Elborn et al., 2016; Wainwright et al., 2015). Approximately a 1% improvement in BMI was observed with ivacaftor-lumacaftor in the pooled analysis (0.24 to 0.28, $p< 0.001$) (Elborn et al., 2016; Wainwright et al., 2015). In an open label study of ivacaftor-lumacaftor in pediatric patients 2-5 years of age who were homozygous for the F508del mutation, McNamara and colleagues found that BMI z-scores improved significantly from 0.17 to 0.45 ($p < 0.003$) over a 24-weeks (McNamara et al., 2019). However, absence of a control group limits interpretation, and increases in BMI could have in part been affected by clinical trial bias and normal growth. Previous research

supports that ivacaftor + lumacaftor may be effective in improving BMI in adults homozygous for the F508del mutation, but does not have the same effect in children (Ratjen, Hug, Marigowda, Tian, Huang, Stanojevic, Milla, Robinson, Waltz, & Davies, 2017) homozygous for F508del or adults who are heterozygous for F508del mutation (Rowe et al., 2017).

Ivacaftor + Tezacaftor Combination Therapy

In participants with CF, one RCT on the effect of ivacaftor with tezacaftor on weight/growth parameters. A total of 156 participants 12-20 years of age who were homozygous for the F508del CFTR mutation (class II) were randomized to receive either 100 mg of tezacaftor once daily with 150 mg of ivacaftor twice daily or matched placebo for 24 weeks (Taylor-Cousar et al., 2017). Baseline nutritional status was not available for the pediatric population only. There were no significant differences in BMI-for-age z-score change between groups. Body composition and dietary intake were not measured (Taylor-Cousar et al., 2017). In pediatric participants homozygous for the F508del CFTR mutation, tezacaftor (100 mg) plus ivacaftor (150 mg) for 24 weeks did not increase BMI z-scores, although the role of baseline nutritional status is unknown.

Elexacaftor + Tezacaftor + Ivacaftor Therapy

In October 2019, the FDA approved a fixed dosage triple combination therapy of the CFTR corrector tezacaftor, CFTR potentiator ivacaftor, and a next generation, highly effective new corrector known as elexacaftor. Elexacaftor-tezacaftor-ivacaftor (ETI) is

currently approved to treat individuals 12 years of age and older who have one copy of the F508del mutation and is in clinical use. There are two randomized controlled clinical drug studies published on phase 3 trials of ETI. Middleton et al., conducted a double-blind, placebo controlled, randomized trial of ETI in 400 adolescents and adults with minimal function F508del genotypes. BMI was a secondary endpoint in the study, and after 24 weeks on ETI was improved by 1.04 kg/m² ($p < 0.001$) (Middleton et al., 2019). Heijerman et al. conducted a multisite RCT in participants with CF who were F508del homozygous and ≥ 12 years of age comparing ETI with ivacaftor + tezacaftor. Given that dual combination CFTR modulation therapy is standard treatment for people with CF who are F508del homozygous, a 4-week run-in period of ivacaftor + tezacaftor occurred before receiving either ETI or ivacaftor + tezacaftor for a 4-week time period (Heijerman et al., 2019). ETI resulted in a mean increase of 0.60 kg/m² BMI (nominal $p < 0.0001$) and increase of 1.6 kg in weight (nominal $p < 0.0001$) when compared with ivacaftor + tezacaftor (Heijerman et al., 2019). Body composition and dietary intake were not measured in either clinical trial.

There is uncertainty of how the newly approved, highly effective CFTR modulator, ETI, effects nutritional status outside of clinical trials, and how that effect is modified by diet. As individuals with one or two copies of the F508del mutation constitute over 85% of the CF population in the U.S. (Foundation, 2019), there is high potential for the majority of individuals with CF to be treated with ETI. More research is needed to fully understand the effects of ETI on nutrition status in all classes of CFTR mutations.

Dietary Intake and CFTR modulators

The role of diet in modifying study outcomes was not described in any randomized clinical trials of CFTR modulators. Two observational papers have been published that examine dietary intake changes in adolescents and adults taking ivacaftor. In a recent observational cohort study of 22 adolescent and adults with CF and gating mutations, Stallings and colleagues obtained diet records on patients at baseline and after three months on ivacaftor. An increased fat intake was noted and there was no significant difference in total caloric intake after 3 months on ivacaftor (Stallings et al., 2018). An increase in dietary fat intake was also noted in Italians and North American people with CF with gating mutations who took ivacaftor for three months, and this increase was correlated with weight gain (Sainath, Schall, Bertolaso, McAnlis, & Stallings, 2019b). Italian participants also had a significant increase in their total caloric intake as a percent of their estimated energy requirement (EER), however, no change in caloric intake was noted in the North American Cohort. As it is recommended that CFTR modulators are taken with a fat-containing food, this may explain an increase in fat intake, and could also partially contribute to improvements in weight, especially in those who also increased their caloric intake.

Mechanisms of Weight Gain on CFTR Modulation Therapy

Limited research exists that has explored the mechanisms of weight gain on CFTR modulators. In a recent study by Stallings et al., ivacaftor treatment for 3 months significantly decreased resting energy expenditure, improved fat absorption, and reduced gut inflammation in 23 children and adults with class III gating mutations, providing

possible mechanisms for weight gain in the setting of ivacaftor use. Improvements with ivacaftor treatment were more robust in participants with pancreatic insufficiency (Stallings et al., 2018). Additionally, results of open-label trials FIGI and KLIMB described improved pancreatic function as measured by increases in fecal-elastase in 2 to5 year-old children with gating mutations following treatment with ivacaftor (Davies et al., 2016; Rosenfeld et al., 2019). Increased dietary fat and caloric intake helping to create positive energy balance in the setting of improved absorption and decreased resting energy expenditure may also play a role in weight gain on CFTR modulators (Sainath et al., 2019b; Stallings et al., 2018). Currently no published research exists regarding mechanisms of weight gain on ETI. Exploring mechanisms of weight gain in new ETI will help us better understand the nutritional effects of highly effective modulators in adolescents and adults in an expanded profile of CF mutations.

CHAPTER 3: METHODS

Research Design

Using an open-label cohort design, we assessed how metabolic parameters and dietary intake patterns change in patients who initiate ETI in a subset of patients with CF who are participating in the multi-site parent PROMISE cohort observational study. The proposed study is a one-site sub-study of the larger multisite parent PROMISE cohort study.

Specific Aims

Specific Aim 1: Describe changes in metabolic parameters (resting energy expenditure [REE]) and nutritional (caloric intake) and parameters in a subset of patients with CF who are prescribed ETI in the clinical setting. **Hypothesis**: REE will decrease and caloric intake with increase with ETI therapy.

Specific Aim 2: Estimate associations between changes in nutritional and metabolic parameter and CF clinical outcomes including lung function, weight, and BMI. **Hypothesis 1**. Changes in dietary intake and REE will be associated with weight gain and increased BMI with use of ETI. **Hypothesis 2**. Changes in REE will be associated with increases in lung function on ETI.

Target Population

Participants were adolescents and adults with CF who were at least 16 years of age, clinically prescribed ETI, and were enrolled in the PROMISE study.

Detailed inclusion criteria for the PROMISE study include:

1. All genders within the age limit of the FDA approved indication for elexacaftor, tezacaftor and ivacaftor (ETI) at Day 1.
2. Diagnosis of CF.
3. CFTR mutations consistent with the FDA approved indication for ETI
4. Physician intent to prescribe ETI
5. Willing to fast for 8 hours prior to all study visits (for subjects on overnight enteral tube feedings, willing to hold the feeding for at least 8 hours).
6. Able to perform the testing and procedures required for this study, as judged by the investigator.
7. Enrolled in the Cystic Fibrosis Foundation Patient Registry.
8. Clinically stable with no significant changes in health status within the 14 days prior to Visit 1.

Exclusion criteria: Participants were excluded if they were not enrolled in or declined the PROMISE study or were on supplemental oxygen. Detailed exclusion criteria for the PROMISE study included:

1. Use of any ETI within the 180 days prior to Visit 1, such as in a clinical drug trial.
2. Any acute use of antibiotics (oral, inhaled or IV) or systemic corticosteroids within the 2 weeks prior to Visit 1 for lower respiratory tract symptoms.

3. Initiation of any new chronic therapy (e.g., ibuprofen, Pulmozyme®, hypertonic saline, azithromycin, inhaled tobramycin, Cayston®, Kalydeco, Orkambi®, Symdeko®) within the 4 weeks prior to Visit 1.
4. Use of an investigational agent within the 28 days prior to Visit 1.
5. Use of chronic oral corticosteroids (equivalent to 10 mg. or more per day of prednisone) within the 28 days prior to Visit 1.
6. Treatment for nontuberculous mycobacterial (NTM) infection, consisting of ≥ two antibiotics (oral, IV, and/or inhaled) within the 28 days prior to Visit 1.
7. History of lung or liver transplantation or listing for organ transplantation.
8. Use of supplemental oxygen.

Study Design

Using an open-label cohort design, we assessed how metabolic parameters and dietary intake patterns change in patients who initiate ETI in a subset of patients with CF who are participating in the multi-site parent PROMISE cohort observational study. The proposed study is a one-site sub-study of the larger multisite parent PROMISE cohort study. Participants were clinically prescribed ETI, and baseline visits occurred up to 30 days prior to their first dose of the drug. Visit 2 occurred at 28 days (+/- 3 days) after the first dose of the drug and visit 3 was scheduled to occur at 6 months (+/- 3 days) of taking the first dose of ETI. Outcome measurements were obtained at each of the 3 visits. See Figure 1 for study diagram.

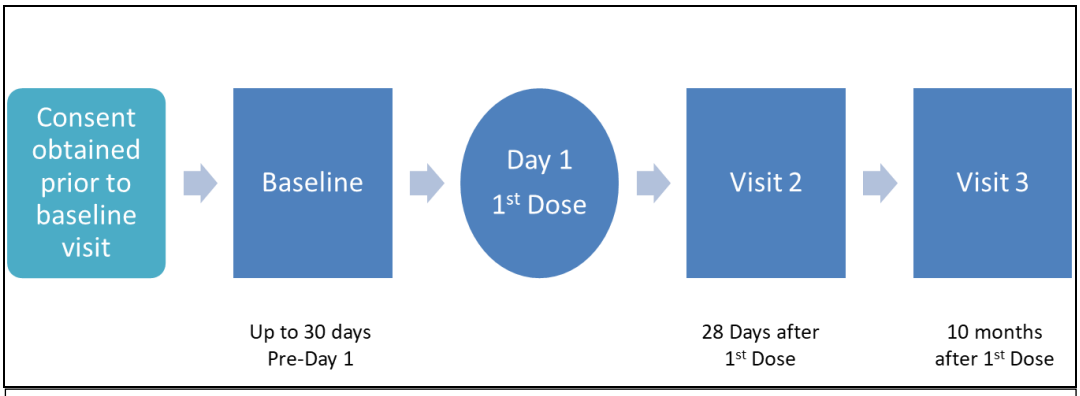

Figure 1: Study Design

Screening and Recruitment

Participants were recruited from patients who consent for the parent PROMISE study at University of Alabama at Birmingham (UAB) Adult CF Center and Children's of Alabama Pediatric CF Center beginning in November 2019. Recruitment and screening occurred in the UAB Adult CF Clinic, UAB Hospital Pulmonary Unit, and the Children's of Alabama Pediatric CF Clinic. Recruitment closed in March 2020. Informed consent was obtained from patients 18 years of age and older, and from patients aged 14-17 years, with parental permission. Patients aged 12-13 provided assent with parental consent. Our recruitment goal was at least 20 participants. Approval to conduct this study was obtained from the UAB Institutional Review Board, protocol #300003442, listed in Appendix A.

Enrollment

A total of 22 participants enrolled and completed baseline assessments at visit 1, 20 participants completed visit 2, and 17 participants completed all assessments through visit 3. Participants signed consent either at their screening visit, or at the beginning of

their first visit before any assessments occurred. We provided flexibility for screening visit vs. first day of visit consents because many patients live > 100 miles from the testing site and we wanted to minimize travel burden on participants.

Data Collection

Participants completed 3 study visits at the CF Research Center and the UAB Nutrition Obesity Research Center Metabolics Core to link with PROMISE parent study visits. Visit 1 (baseline) occurred within 30 days before initiation of ETI and +/-3 days of PROMISE study visit 1. Visit 2 occurred 28 days after initiation of ETI and +/- 3 days of PROMISE study visit 2. Visit 3 was scheduled to occur 180 days (6 months) after initiation of ETI therapy and +/- 3 days of PROMISE study visit 4. Resting energy expenditure (REE), dietary intake, handgrip strength was measured at visit 1(baseline), visit 2, and visit 3. Demographic data was collected at baseline and will included age, sex, race, genetic mutations, and genotype group (F508del heterozygous vs F508del homozygous). Lung function as FEV1 % predicted was measured at each study visit along with height (cm) and weight (kg).

Indirect Calorimetry

Resting energy expenditure (energy/calories burned at rest) was measured through open-circuit indirect calorimetry testing using a metabolic cart (Vmax ENCORE 29N Systems, Sensor Medics Corporation, Yorba Linda, CA). Participants fasted overnight for 10 hours prior to the test. Upon arrival to the Nutrition Obesity Research Center, participants rested awake while lying in the supine position for 30 minutes prior to the

indirect calorimetry test, and then a clear canopy/hood that was connected to the metabolic cart was placed over their head and neck for 30 minutes to measure gas exchange while they breathed normally at rest. The participant was monitored throughout the test to ensure they did not fall asleep or have extraneous movement that could alter respiratory rate.

Dietary Intake

Dietary intake of fat, carbohydrate, protein, and micronutrients were measured through use of 3-day diet, as well as pancreatic enzyme use were recorded by participants on two consecutive weekdays and one weekend day (see Appendix C). Participants were provided blank three-day diet and enzyme records to complete in the 3 days following enrollment but prior to beginning ETI and baseline visit, for 3 days prior to visit 2, and 3 days prior to visit 3. Study staff placed reminder calls 1 week prior to each study visit to have participants fill out 3-day food and enzyme records. The study dietitian reviewed completed diet records with participants at study visits to clarify portion sizes and foods consumed and enters the diet records into Nutrition Data System for Research (NDSR, Nutrition Coordinating Center, University of Minnesota, MN, USA; database version 2018) (Schakel, Sievert, & Buzzard, 1988) for analysis.

The Healthy Eating Index (HEI) was calculated for each participant at each timepoint. The HEI is a validated measurement of diet quality based on the Dietary Guidelines for Americans. The HEI is measured on a scale of 1-100 with 100 being the highest possible score. The HEI and its variable components were calculated using SAS in code provided by NDSR (cite). The HEI is made up of 9 components: moderation

components include saturated fats, refined grains, sodium, and added sugars. Higher scores on these components indicate lower intake of these nutrients that are advised to be consumed in moderation. The adequacy components of the HEI are nutrients and food groups or types of foods that are recommended by the DGA and include: total fruits, whole fruits, total vegetables, beans and greens, whole grain, dairy, total protein foods, seafood, and plant protein, and (unsaturated) fatty acids. Higher scores for adequacy components indicate higher intakes that meet or exceed the standards.

Handgrip Strength

Upper body muscle strength changes were measured using handgrip strength testing (Jamar Hydraulic Hand Dynamometer) at visits 1, 2, and 3. Participants were coached to hold the hand dynamometer with a 90-degree bend in their arm, with forearm parallel to the ground and wrist in a neutral position. Each hand was tested three times and the average is calculated for each hand. The highest HGS measurement on either hand for each visit was also recorded as a secondary way to analyze HGS. The staff obtaining measurements were trained by an experienced Occupational Therapist. The dominant hand and any previous wrist or arm injuries are noted at each test.

Pulmonary Function Testing

Obtained as part of the parent PROMISE study and was measured at each visit. A COVID-19 test was required 24 hours prior to spirometry testing after June 2020. Participants were educated on how to provide best effort on the pulmonary function testing in the standing position with chin elevated. Participants were instructed to breath

in as much air as possible and then to “blast” out their breathe as hard and fast as they can into the mouthpiece of the spirometer. A full 6 seconds of exhalation was required for a valid test.

Statistical Methods

Statistical Analysis Plan

Descriptive statistics and change in outcome variables (anthropometric measurements, REE, dietary intake, and handgrip strength, serum vitamin levels) with treatment for the whole sample using paired t-tests or Wilcoxon sign rank tests. Change and outcome variables within genotype group of F508del homozygous vs heterozygous were calculated using unpaired t-tests or Wilcoxon sum rank tests. Repeated measures non-parametric ANOVA was also used to determine changes in outcome variables with treatment for the whole sample. Correlations between changes in dietary intake and weight gain as well as changes in REE and lung functions improvements were assessed using Pearson Correlations. Analyses were conducted in JMP® Pro software version 16.0.0 (SAS Institute, Cary, NC), using two-sided tests with an alpha significance value of 0.05.

CHAPTER 4: RESULTS

Descriptive Statistics

Participants

Descriptive statistics were calculated on all variables and included frequencies, proportions, means, standard deviations, medians, and ranges depending on the variable type. Normality was assessed by examining normal quantile plots with Sharpiro-Wilke tests. Non-parametric tests were used in cases with outliers and when the assumption of normality was violated. To participate in the study, participants had to be 16 years of age or older, diagnosed with cystic fibrosis, been clinically prescribed ETI, and be participants in the parent PROMISE study. Of the 22 participants enrolled at baseline, 15 (68%) were female and 7 were male (32%), with 21 patients identifying as white (95%) and 1 patient as African American (5%). This is consistent with the U.S. national CF population given that CF primarily affects Caucasians. Patients ranged in age from 16 to 54 years old. All participants were determined to be pancreatic insufficient and were on PERT. All participants were taking CF-specific fat-soluble vitamin preparations that provide additional vitamin A, E, D, and K, and these dietary supplements were not included in dietary analysis. Table 1 provides a full description of demographic data and CF clinical characteristics at baseline.

Table 1
Demographic and CF Clinical Characteristics of Participants

Variable, mean ± SD	**Baseline**
	All *n = 22*
Age	26.2 ± 8.9
Sex	
Female	15 (68%)
Male	7 (32%)
Race	
Caucasian	21 (95%)
African American	1 (5%)
Education Level	
In high school	2 (10%)
High school Graduate	5 (24%)
Some college	7 (33%)
College graduate	7 (33%)
CF Related Diabetes	
Yes	10 (45%)
No	12 (55%)
Genotype	
F508del homozygous	11 (50%)
F508del heterozygous	11 (50%)
Weight, kg	65 ± 11.9
BMI, kg/m2	22.8 ± 3.4
FEV1, % predicted	waiting
REE, % predicted	112.7 ± 10.8
HGS, Left	29 ± 9.7
HGS, Right	28.6 ± 8.3
PERT, units lipase/kg/meal	1502 ± 554
PERT, units lipase/kg/day	5175 ± 2154

Statistical Analysis

Exploratory analyses included determination of changes in dietary intake parameters, muscle strength, weight/BMI, and pancreatic enzyme replacement therapy dosages with use of ETI. Difference scores were calculated by subtracting baseline outcome variable values from visit 2 outcome variable values. This difference score

calculation was repeated for long-term follow up by subtracting baseline outcome variable values from visit 3 outcome variable values. Paired sample t-tests or Wilcoxon signed rank tests were performed to assess for differences in outcome variables between pre- and post-ETI use at two time points of short term and long term follow up on the drug. Results for changes in outcome variables are presented in table 2. Change in outcome variables by group are presented in Table 3. We also examined whether changes in outcome measures associated with changes in CF clinical outcomes on ETI including increased lung function and BMI.

Table 2
Changes in outcome variables over time for total group

Variable, mean ± SD	**Baseline**	**Visit 2**	**Visit 3**	**1 month change**	**10 month change**
	n = 22	*(n=20)*	*(n=17)*	*(n=20)*	*(n = 17)*
Weight, kg	65 ± 12	67 ± 12	68 ± 13	1.26 ± 2.40 *	3.1 ± 3.0 ***
BMI, kg/m2	22.8 ± 3.4	23.4 ± 3.2	23.7 ± 2.7	0.5 ± 0.9 *	0.9 ± 0.9 ***
REE, % predicted	112.7 ± 10.8	110.6 ± 7.7	107.3 ± 11.9	-2.9 ± 11.4	-6.6 ± 15.3 *
HGS, Left	29 ± 9.7	29.7 ± 9.6	30.2 ± 6.9	-0.3 ± 5.4	-0.03 ± 5.7
HGS, Right	28.6 ± 8.3	29.3 ± 2.1	30.5 ± 7.8	0.4 ± 5.6	0.9 ± 6.5
PERT, units lipase/kg/meal	1698 ± 533	1337 ± 546	1397 ± 520	-133 ± 331	-159 ± 432
PERT, units lipase/kg/day	5774 ± 1978	4581 ± 1755	5218 ± 1436	-442 ± 1328	-310 ± 1386
Lung Function	*n = 22*	*n = 19*	*n = 12*	*n = 19*	*n = 12*
FEV1, % predicted	75 ± 27	82 ± 24	98 ± 19	9.9 ± 10.3 ***	11 ± 19.3
Dietary Intake	*n = 22*	*n = 16*	*n = 16*	*n = 16*	*n = 16*
Kcal/day	2932 ± 1068	2896 ± 778	3108 ± 734	81 ± 797	297 ± 766 *
Fat, g/day	134 ± 49	135 ± 43	145 ± 37	7 ± 53	19 ± 36 *
Protein, g/day	119 ± 55	123 ± 37	130 ± 46	9.0 ± 35	8.0 ± 49
Carbohydate, g/day	318 ± 113	303 ± 94	326 ± 79	-5.2 ± 72	22 ± 90
Glycemic Index	88.6 ± 6.3	88.0 ± 5.4	88.6 ± 4.4	-1.1 ± 7.8	-0.9 ± 5.8
Vitamin A, units per day	6167 ± 5250	8042 ± 5913	5899 ± 3217	1775 ± 7436	-184 ± 3361
Vitamin E, units per day	7.8 ± 5.6	12.2 ± 4.1	8.3 ± 5.8	-0.1 ± 7.7	-0.3 ± 6.5
Vitamin D, mcg per day	12.5 ± 5.6	8.7 ± 5.5	12.4 ± 4.4	0.8 ± 5.4	-0.4 ± 5.2
Vitamin K, mcg per day	125 ± 101	120 ± 96	132 ± 107	-18 ± 87	40 ± 115
Healthy Eating Index	52.1 ± 10.7	51.6 ± 11.2	51.2 ± 10.4	-1.5 ± 10	-0.3 ± 9.5

* $P < 0.05$ *** $P < 0.001$

Weight and BMI

Mean (± SD) weight in kilograms significantly increased by 1.26 ± 2.40 kg (t-ratio = 2.371, p = 0.028) at visit 2 and 3.1 ± 3.0 kg (t-ratio = 4.23, p < 0.001). Similarly,

mean BMI significantly increased by 0.46 ± 0.93 kg/m² ($p < 0.05$) at V2 and 0.92 ± 0.88 kg/m² at V3 compared to V1 ($p < 0.001$). Figures 2 and 3 describe weight and BMI changes in the group across the study duration, respectively.

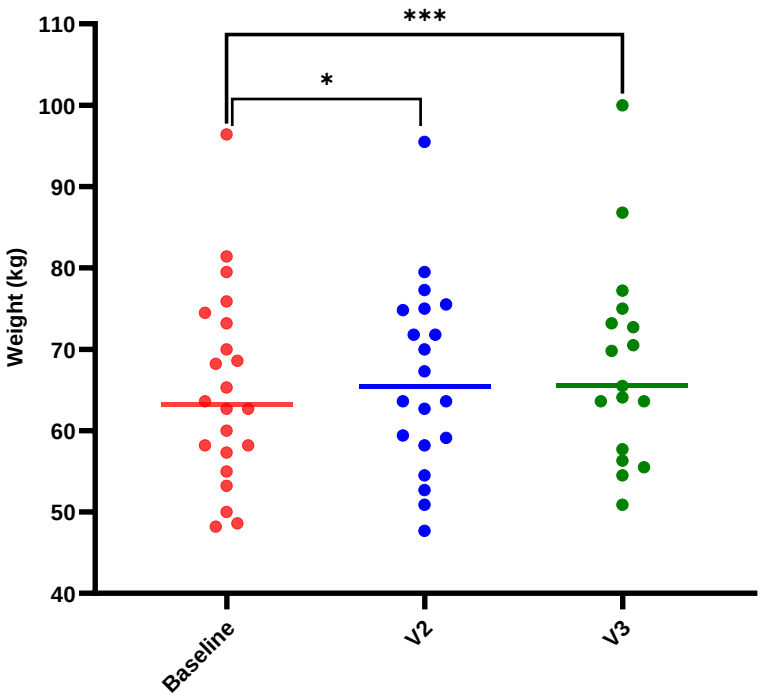

Figure 2: Change in weight over study duration

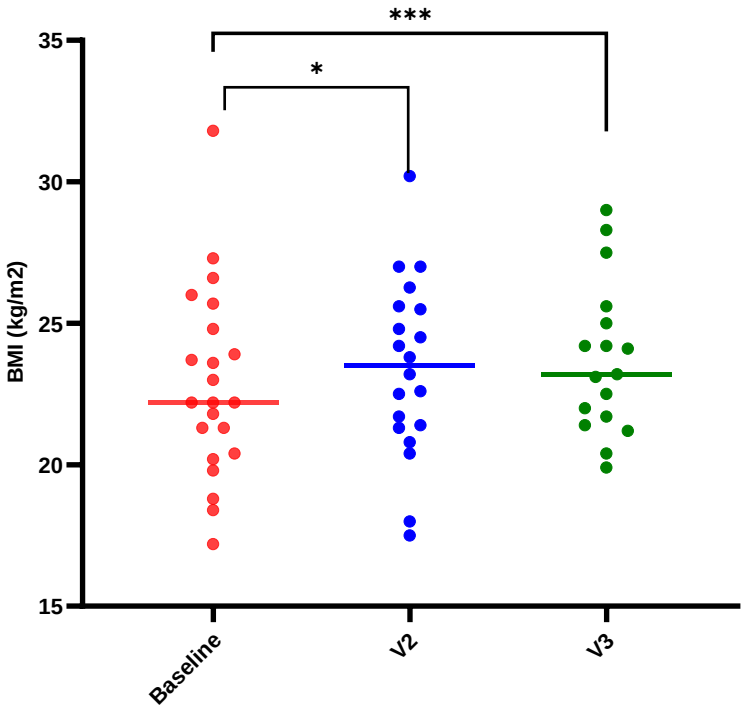

Figure 3: Change in Body Mass Index study duration

While the mean baseline BMI was 22.8 kg/m2, there was a range of 17.2 kg/m^2 to 31.8 kg/m^2 spanning malnutrition to obesity. To understand change in weight status during the study, we categorized participants into underweight (BMI < 22 for women or < 23 kg/m^2 for men), optimal weight per CF Foundation Guidelines (BMI 22 or 23 to 24.9 kg/m^2 for females and males, respectively), overweight (BMI 25-29.9 kg/m^2), and obese (BMI ≥ 30 kg/m^2). The proportion of underweight decreased from 41% to 29% by 10-month follow-up, and the proportion of overweight increased from 18% to 29% in the same amount of time. One participant was obese at baseline and intentionally lost weight during the study, coming down into the overweight category. Changes in BMI category over the course of the study are presented in Figure 4.

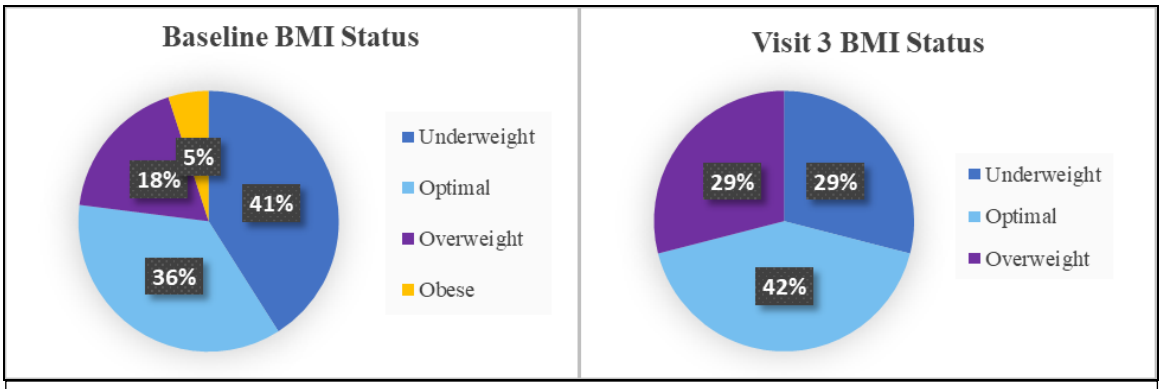

Figure 4: Change in proportion of BMI categories over study duration

Resting Energy Expenditure

The average REE% at baseline was 113 ± 11, indicating hypermetabolism and REE% ranged from 92-137 in our sample. REE% decreased 2.9 ± 11.4 (singed rank = -32.5, p = 0.253) from baseline to short term follow-up at visit 2 and decreased significantly by 6.6 ± 15.3 from V1 to V3 (signed rank = -42.5, $p < 0.05$). Results of changes in REE% at each study visit for the whole cohort are presented in Figure 5.

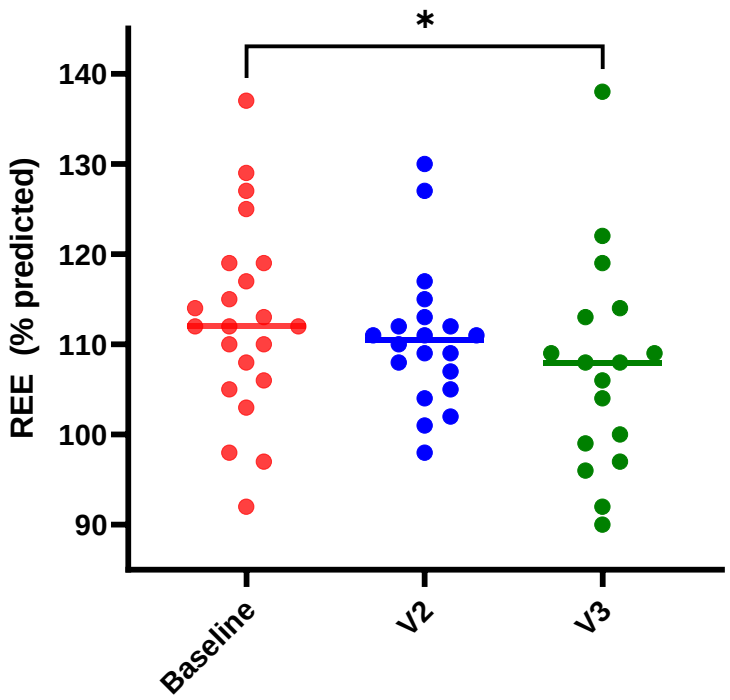

Figure 5: Change in REE Percent Predicted over time

Dietary Intake

Baseline percent estimated energy requirement (EER) was 106% and increased to 108% by visit 3. The mean total calorie intake increased by 297 ± 799 kcal per day (signed-rank = 47, p-value = 0.0131) from baseline to long term follow-up. Daily fat intake increased by a mean of 19 ± 36 grams (signed-rank = 41, p-value = 0.033) between baseline and visit 3. There was not a significant increase in total calories or fat between baseline and short term 28 day follow up. There was also not a significant change in any other dietary parameters measured at either timepoint including protein, carbohydrate, fat soluble vitamins A, D, E, and K or the glycemic index. Graphs of changes over time in non-significant diet variables are presented in Appendix 2.

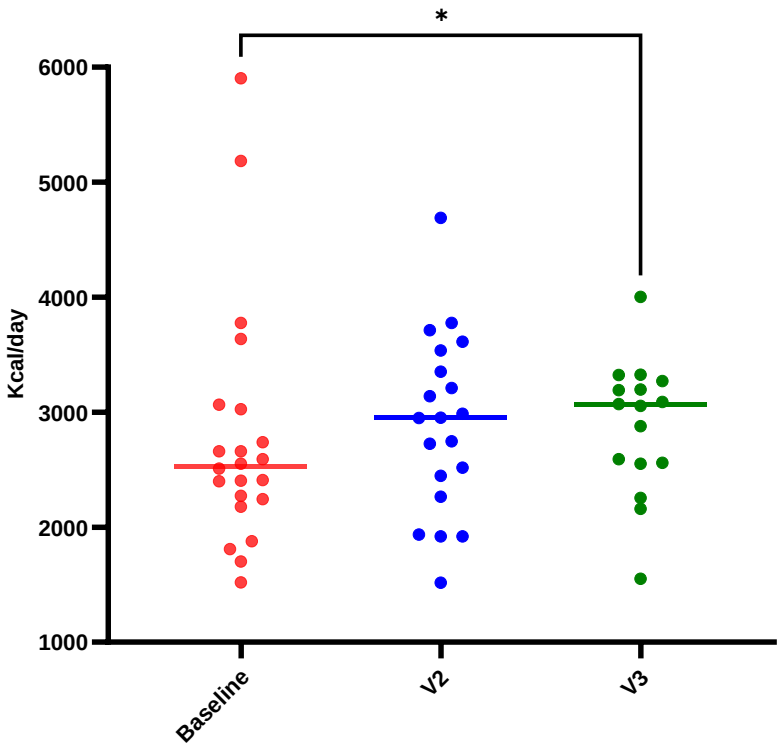

Figure 6: Change in Calorie Intake over time

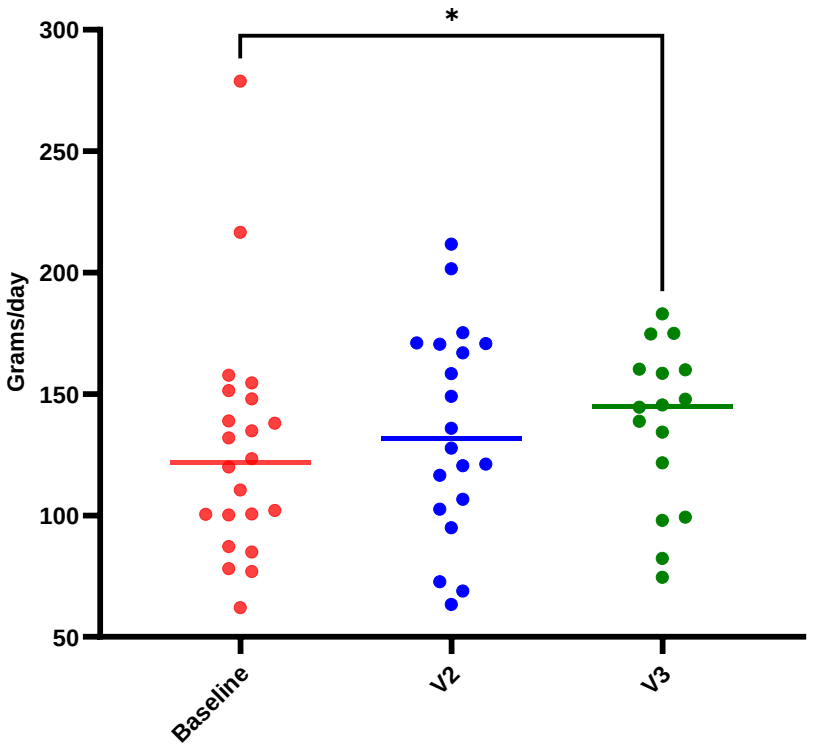

Figure 7: Change in Total Fat Intake over time

Healthy Eating Index

The mean HEI at baseline was 52.1 ± 10.7 which indicates poor diet quality on the 1 to 100 scale (i.e., 100 indicating the best possible diet quality based on the Dietary Guidelines for Americans). The global HEI did not significantly change at either time point. Components of the HEI that are recommended to consume in moderation include refined grains, added sugars, and saturated fatty acids. For moderation components, lower scores indicate a higher intake. Fatty acids are an "adequacy component" of the HEI meaning that higher scores indicated higher intake of this desirable nutrient. Examination of the moderation components of the HEI revealed that people with CF in our cohort consumed significantly more refined grains and saturated fats than the U.S. adult population, but less added sugars and unsaturated fatty acids. Added sugar intake

significantly decreased by 2 points over the course of the study (signed-rank = 87.5, p-value < 0.001) and refined grain intake decreased by 1.6 points (p-value = 0.0362). Trends in fatty acids and saturated fat HEI rank components did not reach statistical significance. Changes in components of the HEI and a comparison to the U.S. National Averages compared with participant component scores at each time point in the study are presented in Table 3 below.

Table 3

HEI Components within group over time compared with U.S. National Average for Adults

	Baseline		**Visit 2**		**Visit 3**		**U.S. Average**
	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean
Refined Grains	1.38 ± 2.9	1.7-4.5	1.3 ± 2.9	0 - 2.6	3.4 ± 4.5	1.4-5.3	6.3
Fatty Acids	3.1 ± 3.1	1.7-4.5	2.8 ± 3.3	1.3-4.2	1.7 ± 2.7	0.5-2.9	4.6
Added Sugars	6.7 ± 2.6	5.5-7.9	8.0 ± 3.0	6.7-9.3	8.3 ± 2.5	7.2-9.4	6.4
Saturated Fats	2.4 ± 2.4	1.3-3.5	3.4 ± 3.6	1.7-4.9	4.0 ± 4.2	2.2-5.9	6

Handgrip Strength

There were no significant changes in HGS on either the left or right hand between baseline and either visit 2 or visit 3 when using the average of 3 measurements on each hand. We also assessed HGS by taking the highest 3 measurements on both hands for each visit, and this form of measurement also revealed no significant change in HGS with ETI treatment over the duration of the study. Figures of HGS changes for both the left and the right hand are shown in Appendix B.

Pancreatic Enzyme Replacement Therapy Dosage

PERT dosing was measured by calculating the units of lipase per kilogram per meal and per day as is common in clinical practice. Neither meal PERT nor daily PERT dosing changed significantly over the course of the study. One outlier for low PERT

dosage was observed at visit 2 and visit 3 and was determined to be accurate given that this patient endorsed self- decreasing their enzyme dosage due to gastrointestinal side effects experienced on ETI. Since the outlier was verified, it remained in the analysis and a non-parametric test was used for the analysis. Graphs of changes in PERT dosage over the study by both daily and mealtime dosing can be found in Appendix B.

Pulmonary Function

The mean pulmonary function expressed as FEV1 percent predicted (FEV1%) was 75 ± 27, which indicates mild to moderate CF lung disease. Pulmonary function increased by 9.9 ± 11 between baseline and visit 2 (signed-rank = 80, p-value = 0.0005), and increased by 11 ± 19.3 between baseline and visit 3 (signed-rank = 24, p-value = 0.064). Improvement was noted in FEV1% at our long term follow up timepoint and approached statistical significance. We were unable to obtain visit 3 long-term follow up spirometry on 10 of the participants due to restrictions with the COVID-19 pandemic and some participants were not able to complete a COVID test 24 hours prior to their study visit spirometry procedure. Change in FEV1% for the whole group over the study duration is presented in Figure 6.

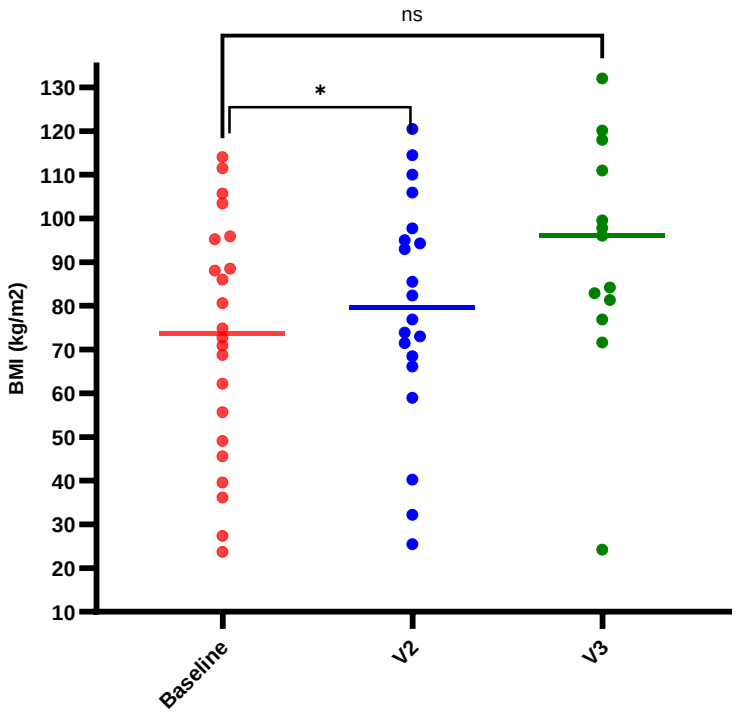

Figure 8: Change in FEV1 Percent Predicted

Correlations

Spearman's correlations were calculated to determine if there were significant associations between increases in fat and calorie intake and a decrease in REE% and weight gain between baseline and visit 3 among enrolled participants. The correlation between the decrease in REE and increase in lung function was also examined. As shown in Table 4, these associations were not significantly significant. The correlation between the decrease in REE% and weight gain between baseline and visit 3 approached statistical significance.

Table 4
Correlations between outcome parameter changes and weight gain

Factors	**r^2**	**p-value**
Increase in caloric intake and weight gain	-0.19	0.475
Increase in fat intake and weight gain	0.06	0.828
Decrease in REE and weight gain	-0.43	0.083
Decrease in REE and lung function	0.18	0.604

Genotype Group Analysis

Differences in certain variables between genotype groups, representing if patients had previously been on another CFTR modulator before, were also of interest. To assess differences between genotype groups, pooled t-tests or Wilcoxon rank sum tests were used. There were no significant differences between genotype groups at baseline for any variable listed. Weight and BMI were higher in heterozygous patients at baseline, but this was not statistically significant. Average BMI for heterozygous patients of 25.1 kg/m2 at visit 3 is classified as overweight. There were no significant differences in variable changes between group for any variable at either follow up time point. Homozygous patients experienced both a larger decrease in REE and a larger increase in fat intake between baseline and visit 3 than did heterozygous patients, however, these changes did not achieve statistical significance. Changes in outcome measures over time for each genotype group are presented in Table 5. Changes in outcome variables across the study by genotype group are also presented in Figures 7-10.

Table 5
Change in outcome variables over time by genotype group

	Baseline		**Visit 2**		**Visit 3**	
Variable, mean differen	**Heterozygous**	**Homozygous**	**Heterozygous**	**Homozygous**	**Heterozygous**	**Homozygous**
	n = 11	*n = 11*	*n = 7*	*n = 10*	*n = 7*	*n = 10*
Weight, kg	66.8 ± 10.7	63.3 ± 13.6	68.9 ± 9.7	64.2 ± 13.3	70.8 ± 10.2	66.1 ± 14.1
BMI, kg/m2	23.7 ± 3.8	22 ± 2.7	24.5± 3.28	22.4 ± 2.72	25.1 ± 2.4	22.8 ± 2.6
REE, % predicted	112.5 ± 6.9	113 ± 14	110.7 ± 9.00	110.5 ± 6.8	109.3 ± 16.2	105.9 ± 8.6
Dietary Intake	*n = 11*	*n = 11*	*n = 7*	*n = 9*	*n = 7*	*n = 9*
Caloric Intake, kcal/day	2848 ± 1169	2714 ± 984	2715 ± 809	3076 ± 741	2636 ± 657	3069 ± 467
Total Fat Intake, kcal/day	132 ± 57	137 ± 43	124 ± 42	147 ± 43	129 ± 36	157 ± 35

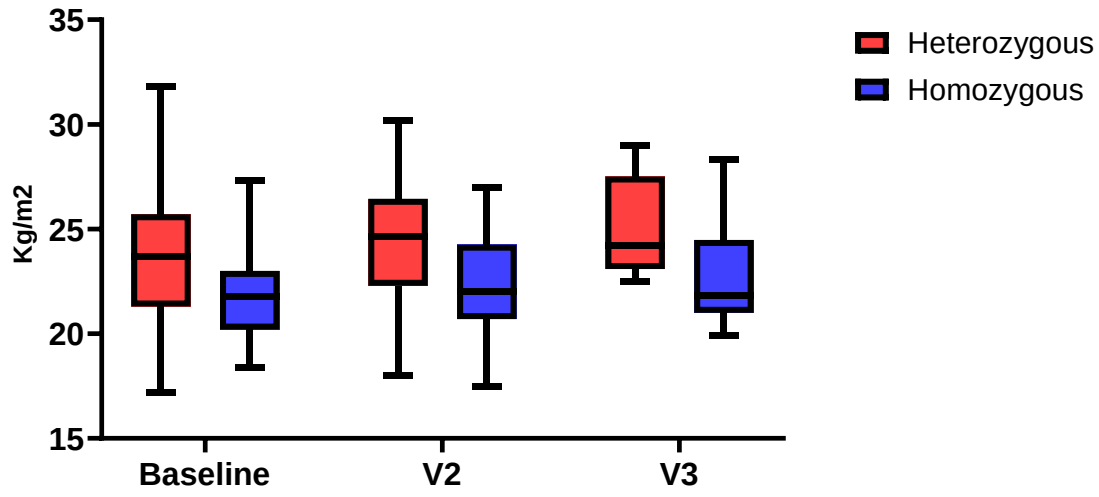

Figure 9: Change BMI over time by genotype group

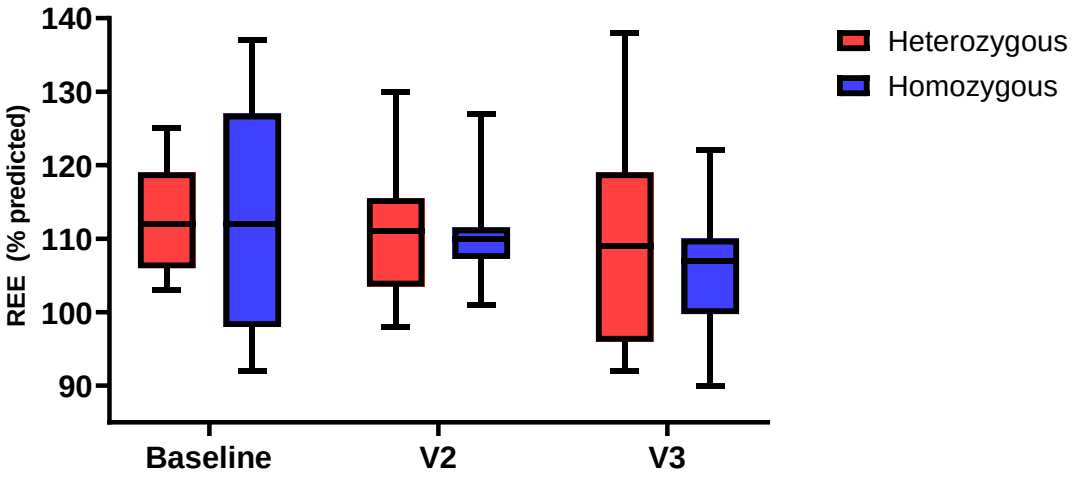

Figure 10: Change REE over time by genotype group

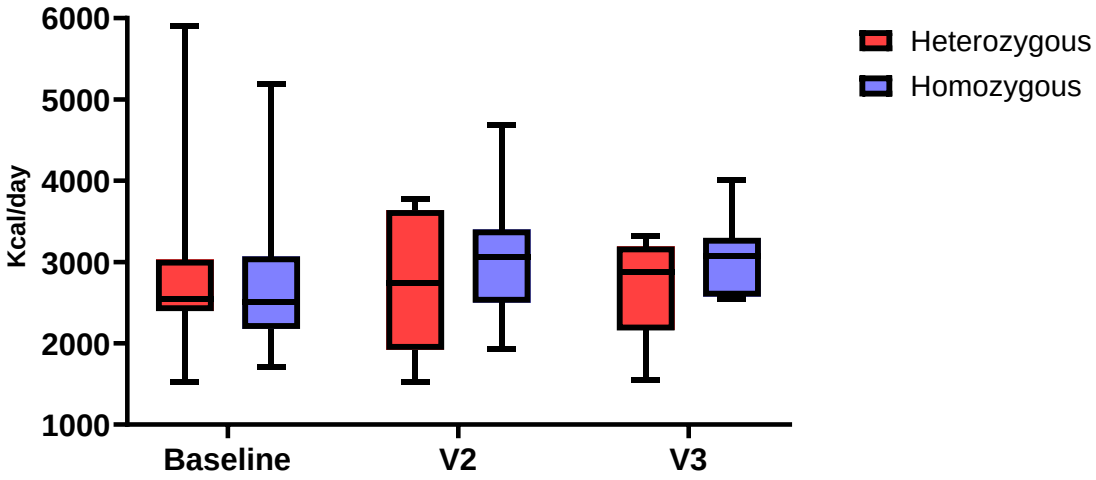

Figure 11: Change total calorie intake over time by genotype group

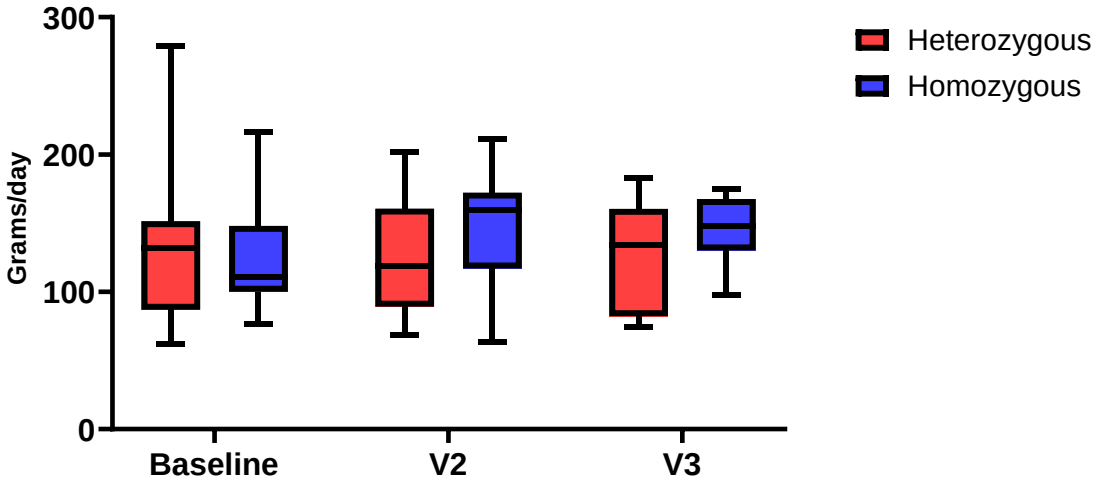

Figure 12: Change total fat intake over time by genotype group

CHAPTER 5: DISCUSSION

Summary of Major Findings

The objective of our study was to determine the effects of ETI on nutritional and metabolic outcomes in adults and adolescents with CF. We hypothesized that REE would decrease on this drug, and that this could be a potential mechanism of weight gain. Consistent with clinical trials, we found that weight (kg) and BMI (kg/m^2) significantly increased with ETI therapy. A significant increase in weight and BMI was observed at our short-term follow-up timepoint of 28 days, and this was sustained throughout long term follow-up of 6 months or longer. REE significantly decreased in our sample with long term ETI treatment. This is similar to the results of a prior study of ivacaftor alone in adults and adolescents with gating mutations (Stallings et al., 2018).

Regarding dietary intake, we noted a significant increase in both total calorie and fat intake at our long-term follow up of > 6 months. Of note, patients are instructed to take ETI with a "fat containing food," per the ETI drug package insert, however, there are no specific recommendations provided on how much fat to consume with the drug every 12 hours. This recommendation could account for increases in fat intake specifically, and this finding is consistent with what was observed in a study of both Italians and North Americans who took ivacaftor only (Stallings et al., 2018). Total caloric intake increases may contribute to the weight gain observed on ETI in this study. Interestingly, while North Americans who took Ivacaftor only significantly increased their fat intake, their

total calorie intake remained stable in contrast to Italians who also increased their total calories consumed per day (Stallings et al., 2018). Macronutrient balance, glycemic index and fat-soluble vitamin intake remained stable over the course of the study. The HEI in our participants indicated poor diet quality when compared with the Dietary Guidelines for Americans and is similar to both the U.S. General Population (NHANES data, HEI website) and what has been observed in another cross sectional study on diet quality in adults with CF (Bellissimo et al., 2019). Further, despite decreases in added sugar and refined grain intake over the course of the study in our sample, the HEI was stable and overall diet quality remained consistent at each time point.

Pancreatic enzyme replacement therapy dosages did not change over the course of the study. This is important because there have been many anecdotal reports of adults with CF stopping or decreasing their PERT once they stop ETI. The stable doses observed in this patient population may reflect a concerted clinical effort that encouraged patients in our CF Center to maintain their PERT dosing when taking ETI due to insufficient evidence to recommend changes with the use of this new drug. This study did not examine absorption or GI symptoms, but these end-points are being assessed in the multi-center PROMISE study.

Handgrip strength (HGS) did not significantly change over the course of the study, even when assessed using two different methodologies. This indicates that upper body muscle strength was stable on ETI, which contrasts with what was observed in a study of ivacaftor alone where weight gain was also associated with increases in HGS and other measures of muscle strength (Stallings et al., 2018). Of note, a large portion of the study occurred during the COVID-19 pandemic, and the associated quarantine and

restricted access to public spaces may have impacted patient's physical activity levels and lead to a more sedentary lifestyle. Body composition assessments were not obtained as part of this sub-study but are being assessed by an endocrine sub-study to PROMISE.

Finally, there was not a significant correlation between the increases in caloric and fat and the observed weight gain on ETI, nor was there a significant correlation between reduction in REE and increases in pulmonary function. The correlations may not have reached statistical significance due to the small sample size of our study and should be assessed in larger observational cohorts.

Significance and Implications

To our knowledge, this is the first study to examine the impact of ETI on dietary and metabolic outcomes in adults with CF. While larger studies are needed, this study confirms increases in BMI observed in phase III clinical trials of ETI and demonstrates both reduction in energy expenditure and increases in total caloric and fat intake with long term use of ETI in the clinical setting. Despite the increase in total calories and fat, diet quality remained poor throughout the duration of the study. The high-calorie, high-fat diet recommendation in CF needs to be re-evaluated given rising BMI, increased intake, and poor diet quality observed.

Limitations

This study is subject to several limitations. Small sample size may lead to the study being underpowered, particularly when examining differences in outcome variables between genotype groups. As with all studies of patient reported dietary intake, we had to

rely on patient recall to report their home diets accurately. To minimize this risk of bias, reminder calls to fill out 3-day diet records were one week before each study visit, and the study RD went through each diet record with patients to obtain clarity on portion sies and amounts consumed. Other limitations include the lack of a comparator/control group and the inability to measure body composition and GI absorption changes on TCT as part of this study protocol. Other factors such as physical activity and absorption were not measured as part of this study and could be other potential mechanisms of weight gain on this drug. Finally, the COVID-19 pandemic altered the study schedule, timeline, and led to the drop out of 2 participants who had not yet completed baseline visits as well as the drop out of 5 participants who declined to complete the final study visit citing concerns over the spread of COVID-19 prior to the availability of vaccinations.

Future Directions/Recommendations for Future Studies

This study investigated the impact of both short- and long-term ETI use in the clinical setting on nutritional and metabolic parameters in adults and adolescents with CF and at least one copy of the F508del CFTR mutation. We reported an increase in weight and BMI, increase in total caloric intake and total daily fat intake, as well as a decrease in REE. Weight gain occurred quickly and continued through follow-up. Weight gain was not accompanied by increases in muscle strength, measured by handgrip strength in this study. No significant differences were observed between genotype groups; however, this may be due to the study being underpowered.

In a phase 3, randomized, double blind placebo-controlled trial to confirm the efficacy and safety of ETI in patients 12 years of age or older with cystic fibrosis one

copy of F508del, a significant increase in BMI of 1.04 kg/m^2 over the 24-week study period. In another phase 3 RCT of ETI in participants who were homozygous for F508del, results indicated a significant average weight gain of 1.6 kg and least squares mean increase of 0.6 kg/m^2 in BMI. In the present study, participants gained an average of 3.1 kg over the 10-month study time period. This study demonstrated that ETI treatment increased weight and BMI, however, the proportion of overweight increased as well, and almost one third of patients fell into the overweight category at long term follow up on the drug. Increased caloric intake, combined with decreases in REE could be potential mechanisms of weight gain, but future research with a larger sample is needed to explore correlations between these factors and weight gain on ETI.

Diet quality was poor and remained poor throughout the duration of the study. Although the Academy of Nutrition and Dietetics and Australia/New Zealand Nutrition Guidelines for CF both have consensus recommendations for people with CF to consume a diet comprised of age-appropriate healthful foods that are associated with positive health outcomes in the general population (McDonald et al., 2020; Saxby N, 2017), CF Foundation Nutrition Guidelines are over 10 years old and still recommend a diet high in calories and high in fat, but with little guidance related to the type of fat or nutritional density of foods consumed (Stallings et al., 2008b). More research is needed to determine the optimal diet for people with CF as the landscape of nutrition changes with ETI available to up to 90% of the population with CF. Future studies should focus on exploring strategies to maintain a healthy weight and improve nutrient density of the diet on ETI given the metabolic and dietary intake changes on the drug observed in this study.

We were not able to measure body composition or fat absorption as part of this nutrition sub-study to PROMISE. Exocrine pancreatic insufficiency was present in all participants and is a known factor that contributes to malnutrition and the elevated metabolic needs of people with CF. Improvements in intestinal absorption have been noted in ivacaftor, and it is possible that ETI could cause similar increases in absorption of fat and other macro and micro nutrients (Stallings et al., 2018). Future work should add additional measures of absorption to more fully understand the mechanisms of weight gain on this drug. Further, it is unknown what percentage of weight gain on ETI during this study was fast mass or fat free mass. FFM has been positively associated with increased lung function in adults and children with CF independent of BMI, and normal weight obesity has also been observed in people adults with CF. A recent systematic review indicates that there is limited evidence from randomized controlled trials on the effect of CFTR modulators on body composition (J. Bailey et al., 2020). Evidence from open-label observational cohort studies suggests that both fat mass and fat free mass increase with short term ivacaftor treatment in adults with CF who have gating mutations (S. J. King et al., 2021; Sainath, Schall, Bertolaso, McAnlis, & Stallings, 2019a; Stallings et al., 2018). A recent study also found that increases in weight and fat mass as measured by BIA were sustained at long term follow up out to 2 years in adults with gating mutations who took ivacaftor (S. J. King et al., 2021). Clinical and metabolic consequences of body composition changes associated with CFTR modulator use are yet to be determined. Body composition assessment is becoming increasingly more important as the CF community begins to look beyond BMI as the main marker of nutritional status. Studies are needed to determine body compositional changes with the weight gain

observed on ETI, particularly since the proportion of overweight increased with ETI use in our sample.

Finally, we found that participants heterozygous for F508del had more pronounced weight gain and BMI improvement and that those who were homozygous for F508del had a larger reduction in REE and dietary fat intake. However, these trends did not reach statistical significance potentially due to the small sample size of genotype groups in this study. Further, pediatric patients were not assessed in this study due to ETI only being approved for those 16 years of age and older at the time of recruitment. It will be important to understand if findings from this study of adolescents and adults extend to the younger pediatric population, especially because children with CF receive extensive and frequent nutritional counseling and dietary habits are formed early in life. Future work should explore longitudinal nutritional and metabolic trends between genotype groups in larger sample sizes as well as expand into the pediatric population with added measures of body composition and absorption. Further investigation of the long-term nutritional and metabolic effects of ETI is necessary to determine optimal nutritional strategies and recommendations for people with CF in this new era of highly effective CFTR modulators.

REFERENCES

Ahmad, A., Ahmed, A., & Patrizio, P. (2013). Cystic fibrosis and fertility. *Curr Opin Obstet Gynecol, 25*(3), 167-172. doi:10.1097/GCO.0b013e32835f1745

Alvarez, J. A., Ziegler, T. R., Millson, E. C., & Stecenko, A. A. (2016). Body composition and lung function in cystic fibrosis and their association with adiposity and normal-weight obesity. *Nutrition, 32*(4), 447-452. doi:10.1016/j.nut.2015.10.012

Bailey, J., Garcia, L., Rutland, S., Oates, G. (2020). Prevalence and correlates of overweight and obesity in a national cohort of children and adolescents with cystic fibrosis. *Pediatric Pulmonology Supp, 56,* 144.

Bailey, J., Rozga, M., McDonald, C. M., Bowser, E. K., Farnham, K., Mangus, M., . . . Alvarez, J. A. (2020). Effect of CFTR Modulators on Anthropometric Parameters in Individuals with Cystic Fibrosis: An Evidence Analysis Center Systematic Review. *J Acad Nutr Diet*. doi:10.1016/j.jand.2020.03.014

Bellissimo, M. P., Zhang, I., Ivie, E. A., Tran, P. H., Tangpricha, V., Hunt, W. R., . . . Alvarez, J. A. (2019). Visceral adipose tissue is associated with poor diet quality and higher fasting glucose in adults with cystic fibrosis. *J Cyst Fibros, 18*(3), 430-435. doi:10.1016/j.jcf.2019.01.002

Bianchi, M. L., Romano, G., Saraifoger, S., Costantini, D., Limonta, C., & Colombo, C. (2006). BMD and body composition in children and young patients affected by cystic fibrosis. *J Bone Miner Res, 21*(3), 388-396. doi:10.1359/jbmr.051023

Borowitz, D., Baker, R. D., & Stallings, V. (2002). Consensus report on nutrition for pediatric patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr, 35*(3), 246-259. doi:10.1097/00005176-200209000-00004

Borowitz, D., & Gelfond, D. (2013). Intestinal complications of cystic fibrosis. *Curr Opin Pulm Med, 19*(6), 676-680. doi:10.1097/MCP.0b013e3283659ef2

Borowitz, D., Lubarsky, B., Wilschanski, M., Munck, A., Gelfond, D., Bodewes, F., & Schwarzenberg, S. J. (2016). Nutritional Status Improved in Cystic Fibrosis Patients with the G551D Mutation After Treatment with Ivacaftor. *Dig Dis Sci, 61*(1), 198-207. doi:10.1007/s10620-015-3834-2

Borowitz, D. S., Grand, R. J., & Durie, P. R. (1995). Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. *J Pediatr, 127*(5), 681-684. doi:10.1016/S0022-3476(95)70153-2

Calella, P., Valerio, G., Brodlie, M., Donini, L. M., & Siervo, M. (2018). Cystic fibrosis, body composition, and health outcomes: a systematic review. *Nutrition, 55-56*, 131-139. doi:10.1016/j.nut.2018.03.052

Calella, P., Valerio, G., Thomas, M., McCabe, H., Taylor, J., Brodlie, M., & Siervo, M. (2018). Association between body composition and pulmonary function in children and young people with cystic fibrosis. *Nutrition, 48*, 73-76. doi:10.1016/j.nut.2017.10.026

Calvo-Lerma, J., Hulst, J., Boon, M., Martins, T., Ruperto, M., Colombo, C., . . . Ribes-Koninckx, C. (2019). The Relative Contribution of Food Groups to Macronutrient

Intake in Children with Cystic Fibrosis: A European Multicenter Assessment. *J Acad Nutr Diet, 119*(8), 1305-1319. doi:10.1016/j.jand.2019.01.003
Chaves, C. R., Cunha, A. L., Costa, A. C., Costa Rde, S., & Lacerda, S. V. (2015). Nutritional status and body fat distribution in children and adolescentes with Cystic Fibrosis. *Cien Saude Colet, 20*(11), 3319-3328. doi:10.1590/1413-812320152011.03242015
Corey, M., McLaughlin, F. J., Williams, M., & Levison, H. (1988). A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. *J Clin Epidemiol, 41*(6), 583-591.
Cystic Fibrosis Foundation, J. H. U., Hospital for Sick Children. . CFTR2. Clinical and functional translation of CFTR. . Retrieved from http://www.cftr2.org
Cystic Fibrosis Foundation Patient Registry: 2019 Annual Data Report. (2019).
Cystic Fibrosis Foundation Registry Report. (2017). Retrieved from https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2017-Patient-Registry-Annual-Data-Report.pdf
Davies, J. C., Cunningham, S., Harris, W. T., Lapey, A., Regelmann, W. E., Sawicki, G. S., . . . Group, K. S. (2016). Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2-5 years with cystic fibrosis and a CFTR gating mutation (KIWI): an open-label, single-arm study. *Lancet Respir Med, 4*(2), 107-115. doi:10.1016/S2213-2600(15)00545-7
Davies, J. C., Wainwright, C. E., Canny, G. J., Chilvers, M. A., Howenstine, M. S., Munck, A., . . . Ahrens, R. (2013). Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. *Am J Respir Crit Care Med, 187*(11), 1219-1225. doi:10.1164/rccm.201301-0153OC
De Boeck, K., Munck, A., Walker, S., Faro, A., Hiatt, P., Gilmartin, G., & Higgins, M. (2014). Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. *J Cyst Fibros, 13*(6), 674-680. doi:10.1016/j.jcf.2014.09.005
Dryden, C., Wilkinson, J., Young, D., Brooker, R. J., & Scottish Paediatric Cystic Fibrosis Managed Clinical, N. (2018). The impact of 12 months treatment with ivacaftor on Scottish paediatric patients with cystic fibrosis with the G551D mutation: a review. *Arch Dis Child, 103*(1), 68-70. doi:10.1136/archdischild-2015-310420
Edgeworth, D., Keating, D., Ellis, M., Button, B., Williams, E., Clark, D., . . . Wilson, J. (2017). Improvement in exercise duration, lung function and well-being in G551D-cystic fibrosis patients: a double-blind, placebo-controlled, randomized, cross-over study with ivacaftor treatment. *Clin Sci (Lond), 131*(15), 2037-2045. doi:10.1042/cs20170995
Elborn, J. S. (2016). Cystic fibrosis. *Lancet, 388*(10059), 2519-2531. doi:10.1016/s0140-6736(16)00576-6
Elborn, J. S., Ramsey, B. W., Boyle, M. P., Konstan, M. W., Huang, X., Marigowda, G., . . . Wainwright, C. E. (2016). Efficacy and safety of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis homozygous for Phe508del CFTR by pulmonary function subgroup: a pooled analysis. *Lancet Respir Med, 4*(8), 617-626. doi:10.1016/s2213-2600(16)30121-7

Engelen, M. P., Schroder, R., Van der Hoorn, K., Deutz, N. E., & Com, G. (2012). Use of body mass index percentile to identify fat-free mass depletion in children with cystic fibrosis. *Clin Nutr, 31*(6), 927-933. doi:10.1016/j.clnu.2012.04.012

Farrell, P. M., White, T. B., Ren, C. L., Hempstead, S. E., Accurso, F., Derichs, N., . . . Sosnay, P. R. (2017). Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. *J Pediatr, 181s*, S4-S15.e11. doi:10.1016/j.jpeds.2016.09.064

Flume, P. A., Fernandez, G. S., Schechter, M. S., & Fink, A. (2019). Prevalence of obesity in people with cystic fibrosis over a 20-year period. *Pediatr Pulmonol, 54*, 263.

Flume, P. A., Fernandez, G.S., Schechter, M.S, Fink, A. (2019). Prevalence of obesity in people with cystic fibrosis over a 20-year period. . *Pediatr Pulmonol, Supp 54*, 263.

Flume, P. A., Liou, T. G., Borowitz, D. S., Li, H., Yen, K., Ordonez, C. L., & Geller, D. E. (2012). Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. *Chest, 142*(3), 718-724. doi:10.1378/chest.11-2672

Flume, P. A., Mogayzel, P. J., Jr., Robinson, K. A., Goss, C. H., Rosenblatt, R. L., Kuhn, R. J., & Marshall, B. C. (2009). Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. *Am J Respir Crit Care Med, 180*(9), 802-808. doi:10.1164/rccm.200812-1845PP

Foundation, C. F. (2019). *Cystic Fibrosis Foundation Patient Registry 2018 Annual Data Report*. Retrieved from Bethesda, Maryland:

Haroun, D., Wells, J. C., Lau, C., Hadji-Lucas, E., & Lawson, M. S. (2006). Assessment of obesity status in outpatients from three disease states. *Acta Paediatr, 95*(8), 970-974. doi:10.1080/08035250600702586

Hauschild, D. B., Barbosa, E., Moreira, E. A., Ludwig Neto, N., Platt, V. B., Piacentini Filho, E., . . . Moreno, Y. M. (2016). Nutrition Status Parameters and Hydration Status by Bioelectrical Impedance Vector Analysis Were Associated With Lung Function Impairment in Children and Adolescents With Cystic Fibrosis. *Nutr Clin Pract, 31*(3), 378-386. doi:10.1177/0884533615627157

Heijerman, H. G. M., McKone, E. F., Downey, D. G., Van Braeckel, E., Rowe, S. M., Tullis, E., . . . Group, V. X. T. (2019). Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *Lancet, 394*(10212), 1940-1948. doi:10.1016/S0140-6736(19)32597-8

Ionescu, A. A., Nixon, L. S., Luzio, S., Lewis-Jenkins, V., Evans, W. D., Stone, M. D., . . . Shale, D. J. (2002). Pulmonary function, body composition, and protein catabolism in adults with cystic fibrosis. *Am J Respir Crit Care Med, 165*(4), 495-500. doi:10.1164/ajrccm.165.4.2104065

King, S., Wilson, J., Kotsimbos, T., Bailey, M., & Nyulasi, I. (2005). Body composition assessment in adults with cystic fibrosis: comparison of dual-energy X-ray absorptiometry with skinfolds and bioelectrical impedance analysis. *Nutrition, 21*(11-12), 1087-1094. doi:10.1016/j.nut.2005.04.005

King, S. J., Nyulasi, I. B., Strauss, B. J. G., Kotsimbos, T., Bailey, M., & Wilson, J. W. (2010). Fat-free mass depletion in cystic fibrosis: Associated with lung disease

severity but poorly detected by body mass index. *Nutrition, 26*(7), 753-759. doi:https://doi.org/10.1016/j.nut.2009.06.026

King, S. J., Tierney, A. C., Edgeworth, D., Keating, D., Williams, E., Kotsimbos, T., . . . Wilson, J. W. (2021). Body composition and weight changes after ivacaftor treatment in adults with cystic fibrosis carrying the G551 D cystic fibrosis transmembrane conductance regulator mutation: A double-blind, placebo-controlled, randomized, crossover study with open-label extension. *Nutrition, 85*, 111124. doi:10.1016/j.nut.2020.111124

Kirwan, L., Fletcher, G., Harrington, M., Jeleniewska, P., Zhou, S., Casserly, B., . . . Jackson, A. D. (2019). Longitudinal Trends in Real-World Outcomes after Initiation of Ivacaftor. A Cohort Study from the Cystic Fibrosis Registry of Ireland. *Ann Am Thorac Soc, 16*(2), 209-216. doi:10.1513/AnnalsATS.201802-149OC

Konstan, M. W., Plant, B. J., Elborn, J. S., Rodriguez, S., Munck, A., Ahrens, R., & Johnson, C. (2015). Efficacy response in CF patients treated with ivacaftor: post-hoc analysis. *Pediatr Pulmonol, 50*(5), 447-455. doi:10.1002/ppul.23173

Lebecque, P., Leonard, A., De Boeck, K., De Baets, F., Malfroot, A., Casimir, G., . . . Leal, T. (2009). Early referral to cystic fibrosis specialist centre impacts on respiratory outcome. *J Cyst Fibros, 8*(1), 26-30. doi:10.1016/j.jcf.2008.07.005

Link, S. L., & Nayak, R. P. (2020). Review of Rapid Advances in Cystic Fibrosis. *Mo Med, 117*(6), 548-554.

Magoffin, A., Allen, J. R., McCauley, J., Gruca, M. A., Peat, J., Van Asperen, P., & Gaskin, K. (2008). Longitudinal analysis of resting energy expenditure in patients with cystic fibrosis. *J Pediatr, 152*(5), 703-708. doi:10.1016/j.jpeds.2007.10.021

McDonald, C. M., Alvarez, J. A., Bailey, J., Bowser, E. K., Farnham, K., Mangus, M., . . . Rozga, M. (2020). Academy of Nutrition and Dietetics: 2020 Cystic Fibrosis Evidence Analysis Center Evidence-Based Nutrition Practice Guideline. *J Acad Nutr Diet*. doi:10.1016/j.jand.2020.03.015

McDonald, C. M., Bowser, E. K., Farnham, K., Alvarez, J. A., Padula, L., & Rozga, M. (2021). Dietary Macronutrient Distribution and Nutrition Outcomes in Persons with Cystic Fibrosis: An Evidence Analysis Center Systematic Review. *J Acad Nutr Diet, 121*(8), 1574-1590.e1573. doi:10.1016/j.jand.2020.03.016

McNamara, J. J., McColley, S. A., Marigowda, G., Liu, F., Tian, S., Owen, C. A., . . . Sawicki, G. S. (2019). Safety, pharmacokinetics, and pharmacodynamics of lumacaftor and ivacaftor combination therapy in children aged 2-5 years with cystic fibrosis homozygous for F508del-CFTR: an open-label phase 3 study. *Lancet Respir Med, 7*(4), 325-335. doi:10.1016/s2213-2600(18)30460-0

Middleton, P. G., Mall, M. A., Dřevínek, P., Lands, L. C., McKone, E. F., Polineni, D., . . . Group, V. X. S. (2019). Elexacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. *N Engl J Med, 381*(19), 1809-1819. doi:10.1056/NEJMoa1908639

Mogayzel, P. J., Jr., Naureckas, E. T., Robinson, K. A., Mueller, G., Hadjiliadis, D., Hoag, J. B., . . . Marshall, B. (2013). Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *Am J Respir Crit Care Med, 187*(7), 680-689. doi:10.1164/rccm.201207-1160oe