Although previous studies have found that higher BMI is correlated with better lung function, newer research highlights that *lean* body mass is associated with good lung function and health [2]. A high percentage of body fat and low skeletal muscle mass is common in individuals with CF at all BMI levels, suggesting that BMI is a suboptimal marker of nutritional status [3]. The effect of modulators on body composition in children with CF has not been comprehensively documented. Based on previous studies, largely in adolescents and adults, we hypothesize that children with CF on modulator therapy will experience a sustained increase in fat mass. The effect of extended modulator therapy on skeletal muscle mass is unknown.
Methods: This abstract uses baseline data from a longitudinal, observational study that assessed the BMI and body composition of children aged 6 to 11 with CF who were poised to initiate elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) therapy and who had ($n = 27$) or had not ($n = 10$) been treated with modulator therapy. Modulator treatment and BMI data were extracted from the medical record, and body composition was assessed using bioelectrical impedance analysis (BIA) using InBody 770 equipment.
Results: Significant differences were noted at baseline assessment between those who were on modulator treatment before enrollment and those naïve to modulator therapy (Figure 1). Children in the previous modulator treatment group had been on therapy for an average of 3.7 years (range 1.9–4.5 years). Those naïve to modulator were younger on average at study enrollment (8.4 vs 9.7 years, $p = 0.05$). Children previously on modulators were noted to have higher BMI (mean BMI percentile 73% vs 54%, $p = 0.07$), fat mass index (5.03 vs 3.15 kg/m^2, $p = 0.01$), and percentage body fat (25.5% vs 16.9%, $p = 0.007$) than those naïve to modulators. Lean BMI (13.9 vs 13.7 kg/m^2, $p = 0.45$) and skeletal muscle mass index (7.1 vs 6.9 kg/m^2, $p = 0.31$) were comparable.

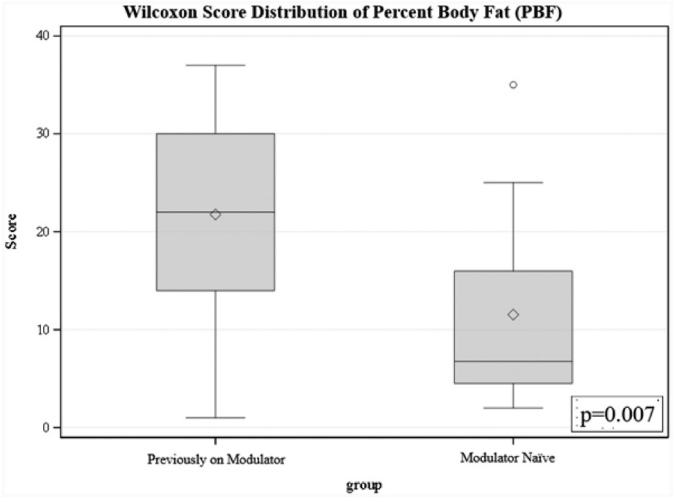

Figure 1. Score distribution of percentage body fat of individuals on modulator therapy and those who were modulator naïve

Conclusions: Our baseline data offered a novel opportunity to identify modulator effects over several years on body weight and composition for children with CF. Data suggest that extended modulator therapy is associated with a persisting increase in body weight and fat mass but not skeletal muscle mass of prepubescent children. These data suggest a need for nutritional and physical activity interventions to optimize overall improvement with modulator therapy. The further effect of ELX/TEZ/IVA therapy on weight, body composition, and muscle strength is being evaluated.
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References

[1] Kutney KA, Sandouk Z, Desimone M, Moheet A. Obesity in cystic fibrosis. *J Clin Transl Endocrinol* 2021;26:100276.
[2] Calella P, Valerio G, Brodlie M, Donini LM, Siervo M. Cystic fibrosis, body composition, and health outcomes: A systematic review. *Nutrition* 2018;55–56:131–9.
[3] King SJ, Nyulasi IB, Strauss BJ, Kotsimbos T, Bailey M, Wilson JW. Fat-free mass depletion in cystic fibrosis: Associated with lung disease severity but poorly detected by body mass index. *Nutrition* 2010;26(7–8):753–9.

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Persistent immaturity of the developing gut microbiome in infants with cystic fibrosis

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Background: The gut microbiome of infants with cystic fibrosis (CF) is characterized by the altered abundance of beneficial bacterial taxa coincident with a developmental delay in maturation in the first year of life [1]. There is an inflection point of microbiome stability after 12 months of age in healthy infants [1,2]. We sought to explore the functional capacity of the CF gut past the first year of life to understand how gut microbiome dysbiosis affects long-term health in CF.
Methods: We performed whole-genome shotgun sequencing on 192 stool samples from 40 infants with CF through 3 years of age and compared metagenomic taxonomic and functional profiles with published data including 4003 samples from 714 infants [1–6]. We then used supervised and unsupervised machine learning methods to understand the developmental trajectory and key contributing taxa [1,7,8].
Results: Our analysis revealed persistent delays in microbiome development in CF through 36 months of life. We identified distinct developmental community states through which the CF microbiome failed to transition, defined by depleted levels of immune-modulatory taxa including *Bacteroides* and members of the phylum *Firmicutes* known to produce short-chain fatty acids [9].
Conclusions: We identified key developmentally delayed microbiome states in the gut of infants with CF that could be targeted using future microbiota-directed therapeutic interventions to improve gut and systemic health in CF.
Acknowledgements:

References

[1] Hayden HS, Eng A, Pope CE, Brittnacher MJ, Vo AT, Weiss EJ, *et al.* Fecal dysbiosis in infants with cystic fibrosis is associated with early linear growth failure. *Nat Med* 2020;26(2):215–21.
[2] Yassour M, Vatanen T, Siljander H, Hämäläinen A-M, Härkönen T, Ryhänen SJ, *et al.* Natural history of the infant gut microbiome and impact of antibiotic treatment on bacterial strain diversity and stability. *Microbiome* 2016;8(343).
[3] Backhed F, Roswall J, Peng Y, Feng Q, Jia H, Kovatcheva-Datchary P, *et al.* Dynamics and stabilization of the human gut microbiome during the first year of life. *Cell Host Microbe* 2015;17(5):690–703.
[4] Kostic AD, Gevers D, Siljander H, Vatanen T, Hyotylainen T, Hamalainen AM, *et al.* The dynamics of the human infant gut microbiome in development and in progression toward type 1 diabetes. *Cell Host Microbe* 2015;17(2):260–73.
[5] Stewart CJ, Ajami NJ, O'Brien JL, Hutchinson DS, Smith DP, Wong MC, *et al.* Temporal development of the gut microbiome in early childhood from the TEDDY study. *Nature* 2018;562(7728):583–8.
[6] Vatanen T, Kostic AD, d'Hennezel E, Siljander H, Franzosa EA, Yassour M, *et al.* Variation in microbiome LPS immunogenicity contributes to autoimmunity in humans. *Cell* 2016;165(4):842–53.
[7] Holmes I, Harris K, Quince C. Dirichlet multinomial mixtures: Generative models for microbial metagenomics. *PLoS One* 2012;7(2):e30126.

[8] Beghini F, McIver LJ, Blanco-Miguez A, Dubois L, Asnicar F, Maharjan S, *et al.* Integrating taxonomic, functional, and strain-level profiling of diverse microbial communities with bioBakery 3. *Elife* 2021;10.
[9] Parada Venegas D, De la Fuente MK, Landskron G, Gonzalez MJ, Quera R, Dijkstra G, *et al.* Short chain fatty acids (SCFAs)-mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. *Front Immunol* 2019;10:277.

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Efficacy of cyproheptadine for appetite stimulation in children with cystic fibrosis

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Background: Cystic fibrosis (CF) is an autosomal-recessive disease that results in progressive lung disease and may lead to poor nutritional status secondary to pancreatic insufficiency (PI). Because of impaired digestion and malabsorption, weight loss and malnutrition are complications of CF, and have been linked to declining lung function and increased infection. This study aims to evaluate the impact of cyproheptadine on nutritional status and lung health in children with CF and PI.
Methods: A retrospective chart review was conducted on patients aged 1 to 21 with CF and PI initiated on cyproheptadine for appetite stimulation between 2013 and 2019. Fifty-two patients with poor nutritional status were analyzed, comparing changes in body mass index (BMI) z-scores or weight for length based upon age, lung function (forced expiratory volume in 1 second [FEV_1]), and pulmonary exacerbations for 1 year before and 1 year after starting cyproheptadine or until discontinuation.
Results: Patients initiated on cyproheptadine realized an improvement in BMI z-scores of 0.363 ($p = 0.002$) and weight-for-length z-scores of 0.96 ($p < 0.001$) after 12 months. Reduction in the number of exacerbations was demonstrated, with 1.41 fewer exacerbations per calendar year ($p < 0.001$) 12 months after cyproheptadine initiation. There were no significant changes in FEV1.
Conclusions: The results of this study indicate a clinical benefit with cyproheptadine for appetite stimulation based on use for at least 12 months. Cyproheptadine was found to be an appropriate therapy to improve nutritional status, as demonstrated by significant increase in BMI and weight-for-length z-scores, and was correlated with fewer exacerbations. These findings suggest that cyproheptadine is an effective treatment addition for providing alternative nutritional support in people with CF and PI as young as 1 year old.

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Caregiver perceptions of a lifestyle education tool and subsequent behavior changes with elexacaftor/tezacaftor/ivacaftor initiation

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Background: Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) is a cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulator currently approved for persons with CF aged 6 and older with at least one copy of the F508del mutation or another eligible mutation. ELX/TEZ/IVA should be taken every 12 hours with fat-containing (10–20 g) foods and pancreatic enzyme therapy for optimal absorption. In clinical trials, ELX/TEZ/IVA increased body mass index (BMI) by 1 kg/m^2. Some adolescents started on ELX/TEZ/IVA at our center had rapid weight gain leading to overweight or obese status. We developed a proactive educational tool to increase caregiver knowledge about nutrition, physical and mental wellbeing, and anticipated outcomes with ELX/TEZ/IVA use in children aged 6 to 11, with the goal of providing education and avoiding rapid weight gain.
Methods: As part of a quality improvement project, multidisciplinary clinical care team members and family partners created an educational tool (Figure 1) to educate patients and families on the impact of ELX/TEZ/IVA therapy on BMI and potential lifestyle changes. Several months after the ELX/TEZ/IVA educational session, a survey was sent via the patient portal in our hospital's electronic medical record to caregivers of children aged 6 to 11 started on ELX/TEZ/IVA. This survey assessed caregiver perceptions of the educational tool and subsequent behavioral changes at home after ELX/TEZ/IVA initiation.

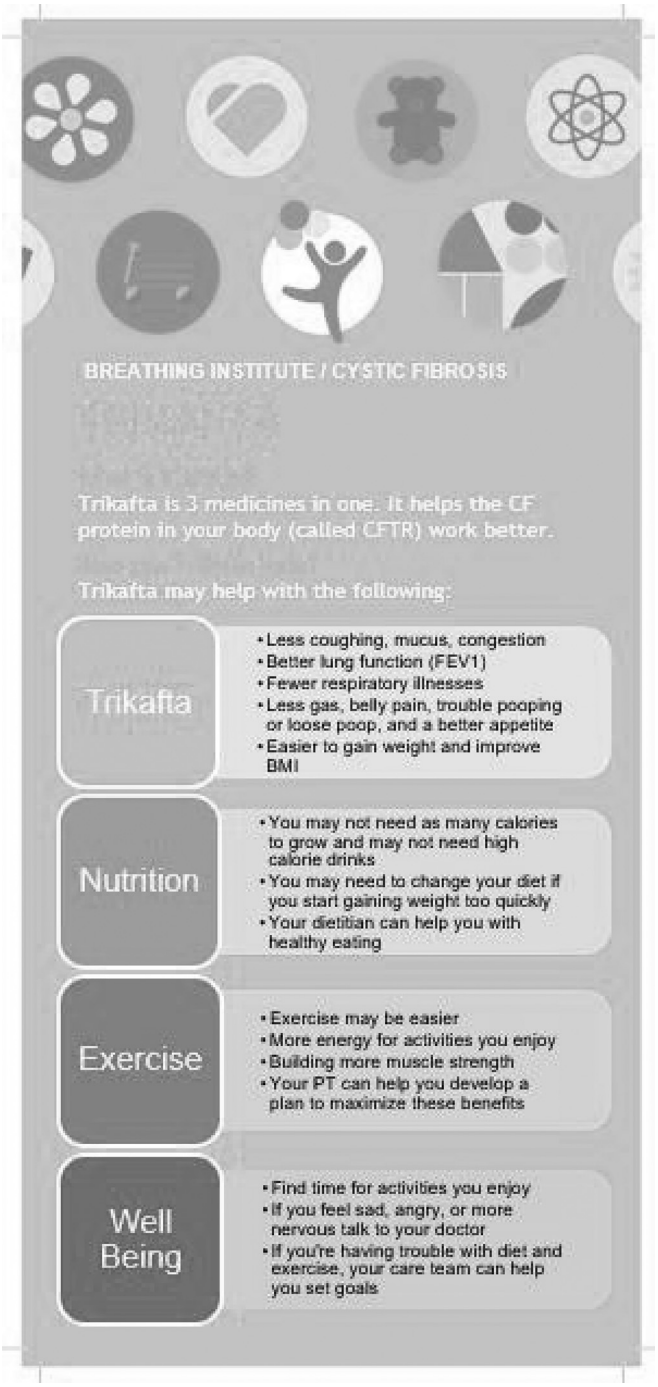

Figure 1. Elexacaftor/tezacaftor/ivacaftor (Trikafta) education tool

Results: We received 37 survey responses. Twenty-eight (76%) remembered receiving the educational tool and found it helpful, seven (19%) did not remember receiving it, and two (5%) did not find it helpful. Two-thirds requested that future educational materials be provided electronically. Caregivers reported potential side effects ($n = 26$) as the biggest concern with ELX/TEZ/IVA initiation, and some were concerned about insurance coverage ($n = 13$) or lack of improvement with treatment ($n = 11$). Nutritional and lifestyle changes that were made after ELX/TEZ/IVA