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Dietary Nutrient Intake in Children With Cystic Fibrosis: A Comparative Study With Unaffected Siblings

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Abstract

Children with cystic fibrosis (CF) typically suffer from gastrointestinal (GI) issues, including gut inflammation, poor digestion, and poor nutrient absorption. These symptoms can affect the gut microbiome, contributing to malnourishment and poor growth in children with CF. To combat malnutrition, patients with CF are advised to consume high-calorie diets and increase their intake of key micronutrients, including fat-soluble vitamins. Research has demonstrated that adequate nutritional status during childhood can improve lung function, reduce the severity of CF symptoms, and reduce the likelihood of lung transplantation later in life. This study assessed the dietary intake of children with CF and their unaffected siblings at a pediatric CF center from 2017 to 2021. All 33 participants completed a food frequency questionnaire, while a subset of 17 CF participants contributed serum fat-soluble vitamin measurements. Twenty of 23 CF participants (87%) met their calorie goal, 19 of 23 (83%) met their fat goal, and 22 of 23 (96%) met their protein goal; all 10 unaffected siblings met all three goals. Fiber intake was below target in 13 of 23 CF participants (57%) and six of 10 unaffected siblings (60%). Among CF participants, intake was below target for vitamin K in 23 of 23 (100%), vitamin E in 22 of 23 (96%), vitamin A in 11 of 23 (48%), and vitamin D in six of 23 (26%); six of 10 unaffected siblings (60%) also had vitamin D intake below target. Although calorie and macronutrient intake was generally adequate, fiber and several fat-soluble vitamins remained below target.

Categories: Nutrition, Pediatrics, Pulmonology
Keywords: cystic fibrosis, fiber, genetics, microbiome, micronutrients, nutrition, pancreatic insufficiency, pediatrics, vitamins

Introduction

Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene create a defective protein that poorly regulates chloride ions across the cell membrane [1]. The result is viscous secretions throughout multiple organ systems [2]. In the intestines, these thick viscous secretions lead to several gastrointestinal issues, including poor digestion, poor nutrient absorption, increased inflammation, and abnormalities in the gut microbiota [3]. Due to mucous blockage of the pancreatic ducts, pancreatic insufficiency is present in approximately 90% of CF patients and leads to failure of crucial digestive enzyme release [3]. Chronic infections and inflammation in people with CF lead to much higher energy demands, further increasing their need for calorie intake. Without intervention for these issues, malnutrition results [4].

Pancreatic enzyme replacement therapy (PERT) in people with pancreatic insufficiency is instrumental in providing the necessary enzymes for digestion of consumed macronutrients, including fats, carbohydrates, and proteins [5]. Despite PERT, CF patients still can struggle with absorption of appropriate fats and fat-soluble vitamins as well as maintaining a healthy weight for age and body mass index [6]. Due to the scope of nutritional issues in CF, CF experts, along with the Cystic Fibrosis Foundation (CFF), developed guidelines for nutritional care and management [7]. These guidelines recommend routine monitoring of growth, diet, fat-soluble vitamins, and caloric intake in people with CF, along with early intervention when needed [7,8]. Children with CF generally have higher energy requirements than children without CF of the same age [9]. To account for this, guidelines recommend that children with CF have higher dietary reference intake (DRI) goals than children without CF [7,10]. On average, it is recommended that children with CF consume 1.2 to 2 times the recommended dietary allowance (RDA) of calories compared to an individual without CF [7]. Approximately 35% to 40% of calories consumed should come from fat [7,11]. Children with CF should also consume 1.5 to 2 times the RDA of protein compared to someone without CF [7].

Given all these factors, adequate nutritional intake and growth can be hard to achieve. Children with CF often struggle with insufficient weight gain, failure to thrive, negative gastrointestinal symptoms, and vitamin deficiencies [3,12]. Adequate nutritional status is important in the short term, as it can improve the severity of symptoms and the ability to resist infection [13]. It is also important in the long term, as measures of growth and nutrition in early life are linked to important outcomes later in life, including lung function, morbidity, and the likelihood of lung transplant [3,14].

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The objective of this study was to compare food frequency questionnaire (FFQ)-estimated macronutrient and micronutrient intake between children with CF and their unaffected siblings and to assess intake relative to applicable age- and sex-specific reference values and CF-specific targets. We hypothesized that children with CF would have dietary fat and fat-soluble vitamin intakes below the applicable targets.

Materials And Methods

Inclusion criteria

Participants were eligible if they were children with cystic fibrosis (CF) or unaffected siblings of enrolled CF participants. CF participants had a diagnosis based on a sweat chloride concentration of at least 60 mmol/L and/or two known CF-causing CFTR variants [15].

Exclusion criteria

Individuals with an uncertain diagnosis of CF were excluded, including those with CFTR-related metabolic syndrome, an intermediate sweat chloride concentration of 30-59 mmol/L, atypical CF, or CFTR-related disease [16,17]. Participants were also excluded if they did not complete the required study procedures.

Participant characteristics

Children with CF aged 3-19 years and their unaffected siblings were recruited for this study. The analysis included 33 children from 21 families: 23 participants with CF and 10 unaffected siblings. All CF participants received care at the Nebraska Regional CF Center and were recruited during a scheduled CF clinic visit. Participants represented a subset of a larger study examining the relationship between dietary intake and the gut microbiome. CFTR modulator use at enrollment was recorded for participants with CF. All 33 participants completed the Youth/Adolescent Questionnaire (YAQ), a standardized food frequency questionnaire (FFQ), and were included in the dietary analyses [18]. The YAQ was previously validated in youths aged 9-18 years [18]. The cited validation study did not include children younger than 9 years or specifically establish validity in children with CF.

Food frequency questionnaire and laboratory analyses

Dietary adequacy was assessed by comparing FFQ-derived nutrient estimates with the age- and sex-specific reference values and intake ranges presented in the Appendices, for unaffected siblings and participants with CF, respectively. The numerical targets, reference standards, and supporting sources for each nutrient are provided in the Appendices. CF-specific targets incorporated Cystic Fibrosis Foundation guidance [7]. Nutrient estimates included reported intake from both food and supplements. BMI percentile was used as the primary measure of growth. Total dietary fiber was assessed using the Association of Official Analytical Chemists (AOAC) method [19]. Additional clinical variables included height, weight, BMI percentile, sweat chloride concentration, CFTR genotype, CFTR modulator use, and pancreatic fecal elastase. For this analysis, pancreatic insufficiency was defined solely by a fecal elastase concentration <200 mcg/g. Values <100 mcg/g and 100 to <200 mcg/g were grouped together, without separate analysis by fecal elastase concentration. For participants with CF, serum vitamin A, vitamin D, vitamin E, and prothrombin time/international normalized ratio as a surrogate for vitamin K status were recorded from the medical record. Blood samples were obtained from a subset of 17 of the 23 CF participants who consented to blood collection; only these 17 participants were included in the serum vitamin analyses. Blood samples were collected during winter (24%), spring (18%), summer (24%), or fall (35%). The University of Nebraska Medical Center Institutional Review Board approved the study (Approval No. 811-17-EP).

Mathematical and statistical analyses

Continuous variables were compared between participants with CF and unaffected siblings using Friedman tests to account for sibling relationships within families. Categorical variables were compared using Cochran-Mantel-Haenszel tests stratified by family. Associations between BMI percentile and macronutrient intake were evaluated using Spearman rank correlation coefficients; Pearson correlation coefficients were also displayed for comparison. The p-values displayed for these analyses correspond to two-sided Spearman rank correlation tests. Partial Spearman correlation coefficients were used when adjusting for sibling relationships. Associations between reported fat-soluble vitamin intake and serum vitamin levels in the 17-participant CF subset were evaluated using Pearson correlation coefficients. All tests were two-sided, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria), and Microsoft Excel for Microsoft 365, Version 2311 (Microsoft Corporation, Redmond, WA, USA), was used for data organization.

Results

Demographic data and clinical characteristics

Demographic and clinical characteristics of patients enrolled in this study are shown in Table *1*. Twenty-three patients had CF. The median age of all patients was 7 years old (ranging in age from 3 years old to 14). Over half of the CF participants were male (57%). The CF group had a median sweat chloride of 84.25

mmol/L. The most frequent genetic mutation was F508del (56% of CF participants were homozygous and 39% were heterozygous for F508del); all homozygous F508del participants used CFTR modulators. Approximately 87% of CF participants expressed exocrine pancreatic insufficiency (EPI). Median body mass index (BMI) percentile was slightly lower in CF participants (56th percentile) compared to non-CF participants (58th percentile).

Clinical and demographic features	Non-CF (n=10)	CF (n=23)	Statistical test	Test statistic	p-value
Age, median (years)	8.19	6.88	Friedman	$\chi^2(1) = 0.65$	0.42
Age, minimum (years)	4.16	3.08	N/A	N/A	N/A
Age, maximum (years)	14.64	14.16	N/A	N/A	N/A
Sweat chloride, median (mmol/L)	18.75	84.25	Friedman	$\chi^2(1) = 6.63$	0.01*
Sweat chloride, minimum (mmol/L)	13.5	32	N/A	N/A	N/A
Sweat chloride, maximum (mmol/L)	48.5	105	N/A	N/A	N/A
BMI percentile, median	58	56	Friedman	$\chi^2(1) = 2.18$	0.14
BMI percentile, minimum	11	13	N/A	N/A	N/A
BMI percentile, maximum	84	97	N/A	N/A	N/A
Age 3–8 years (%)	50	73.91	CMH	$\chi^2(2) = 1.64$	0.44
Age 9–13 years (%)	40	17.39	N/A	N/A	N/A
Age 14–18 years (%)	10	8.70	N/A	N/A	N/A
Gender (male) (%)	90	56.52	CMH	$\chi^2(1) = 3.74$	0.053
CFTR modulator (%)	0	86.96	CMH	$\chi^2(1) = 5.02$	0.025*
Pancreatic insufficient (%)	N/A	86.96	N/A	N/A	N/A
CF genotype: homozygous F508del (%)	N/A	56.52	N/A	N/A	N/A
CF genotype: heterozygous F508del (%)	N/A	39.13	N/A	N/A	N/A
CF genotype: other (%)	N/A	4.35	N/A	N/A	N/A

TABLE 1: Demographic and clinical characteristics of participants (n = 33)

Values are displayed as percentages for categorical variables and as separate median, minimum, and maximum values for continuous variables. Friedman tests were used for continuous comparisons and Cochran-Mantel-Haenszel (CMH) tests for categorical comparisons, as applicable.

*Statistically significant difference between CF and non-CF groups ($p < 0.05$).

N/A, not applicable.

Evaluation of nutritional intake

No difference was observed in percent macronutrient intake between CF and non-CF groups (Figure *1*). For both children with CF and non-CF siblings, 33% of their total caloric intake came from fats. When compared with age- and CF-specific intake targets, 20 of 23 CF participants (87%) met their calorie goal, 19 of 23 (83%) met their fat goal, and 22 of 23 (96%) met their protein goal. All 10 unaffected siblings met their calorie, fat, and protein goals.

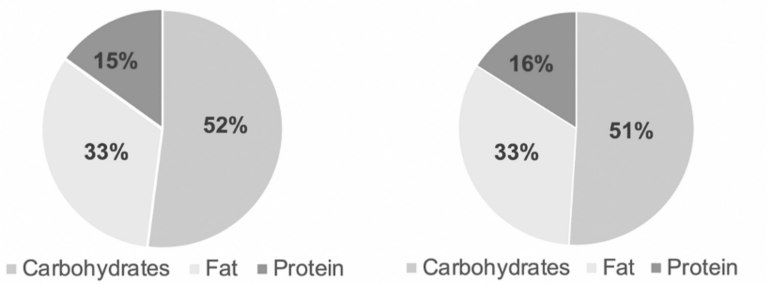


FIGURE 1: Overall macronutrient intake

The left panel shows children with cystic fibrosis (CF), and the right panel shows unaffected siblings. Percentages represent the mean proportion of total caloric intake contributed by carbohydrates, fat, and protein.

Comparison of FFQ-reported intake and DRIs

Compared to DRIs, most participants achieved sufficient dietary intake of macronutrients, including carbohydrates, fat, and protein (Table 2). Fiber intake was below target in 13 of 23 CF participants (57%) and six of 10 unaffected siblings (60%).

Nutrient	CF (n=23)			Non-CF siblings (n=10)		
	Age 3-8 n=17	Age 9-13 n=4	Age 14-18 n=2	Age 3-8 n=5	Age 9-13 n=4	Age 14-18 n=1
Calories (kcal)	94%	75%	50%	100%	100%	100%
Carbohydrates (grams)	94%	100%	100%	100%	100%	100%
Total fat (grams)	88%	100%	0%	100%	100%	100%
Total protein (grams)	100%	100%	50%	100%	100%	100%
Total fiber (grams)	53%	25%	0%	60%	25%	0%

TABLE 2: Evaluation of macronutrient intake for CF and non-CF participants

Percentage of participants with sufficient intake is displayed. Sample sizes are provided in the column headings. Each age group represents the approximate age range corresponding to similar dietary reference intake values. Specific dietary reference intake ranges are provided in the Appendices.

CF, cystic fibrosis.

Most micronutrients were consumed in sufficient amounts, with many of the CF participants consuming more than recommended (Table 3). Among CF participants, intake was below target for vitamin K in 23 of 23 (100%), vitamin E in 22 of 23 (96%), and vitamin A in 11 of 23 (48%). Vitamin D intake was below target in six of 23 CF participants (26%) and six of 10 unaffected siblings (60%). Friedman tests demonstrated differences between CF and non-CF nutrient intakes for zinc ($\chi^2(1) = 3.88$, $p = 0.049$), iron ($\chi^2(1) = 4.22$, $p = 0.040$), vitamin A ($\chi^2(1) = 4.71$, $p = 0.030$), vitamin E ($\chi^2(1) = 8.81$, $p = 0.003$), and vitamin B-12 ($\chi^2(1) = 4.71$, $p = 0.030$). The difference in vitamin C intake was not statistically significant ($\chi^2(1) = 3.71$, $p = 0.054$).

Nutrient	CF (n=23)			Non-CF siblings (n=10)		
	Age 3-8 n=17	Age 9-13 n=4	Age 14-18 n=2	Age 3-8 n=5	Age 9-13 n=4	Age 14-18 n=1
Calcium (mg)	88%	100%	50%	100%	75%	100%
Zinc (mg)	100%	100%	100%	100%	100%	100%
Iron (mg)	100%	100%	50%	100%	100%	100%
Magnesium (mg)	100%	100%	0%	100%	100%	0%
Sodium (mg)	88%	100%	100%	100%	100%	100%
Vit A (mcg)	65%	25%	0%	100%	100%	100%
Vit D (IU)	70%	100%	50%	60%	25%	0%
Vit E (mg)	6%	0%	0%	100%	25%	0%
Vit K (mcg)	0%	0%	0%	100%	50%	0%
Vit C (mg)	100%	100%	100%	100%	75%	0%
Vit B-12 (mcg)	100%	100%	100%	100%	100%	100%

TABLE 3: Evaluation of micronutrient intake for CF and non-CF participants

Percentages of participants with sufficient intake are displayed. Sample sizes are provided in the column headings. See Appendices for specific dietary reference intake (DRI) ranges by age group.

CF, cystic fibrosis.

Macronutrient intake and BMI in CF participants

BMI percentile among CF participants was the most direct measure available of growth. Each participant's macronutrient taken from the FFQ was compared to their BMI percentile to determine whether a given macronutrient had a stronger association with BMI percentile overall (Figure *2*). Weak positive Spearman's correlation coefficients (rs) were observed with BMI percentile for carbohydrate and protein intake (0.15 and 0.11, respectively). Total fat had a very weak negative correlation with BMI percentile (-0.07). None of these correlations were significant.

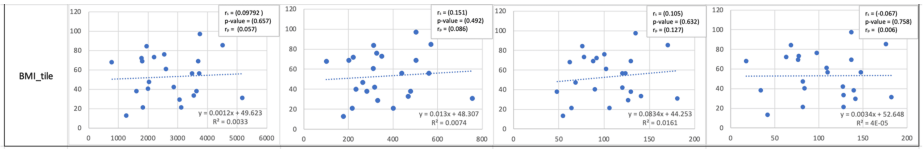


FIGURE 2: BMI percentile correlations with macronutrient intake in CF participants

Panels from left to right show total calories, carbohydrates, protein, and total fat. The Spearman rank correlation test was used for each comparison. The Spearman correlation coefficient (r_s) is reported as the test statistic alongside its corresponding two-sided p-value; the Pearson correlation coefficient (r_p) is also displayed for comparison.

CF, cystic fibrosis.

The corresponding correlations between macronutrient intake and BMI percentile among unaffected siblings are shown in Figure *3*; none were statistically significant.

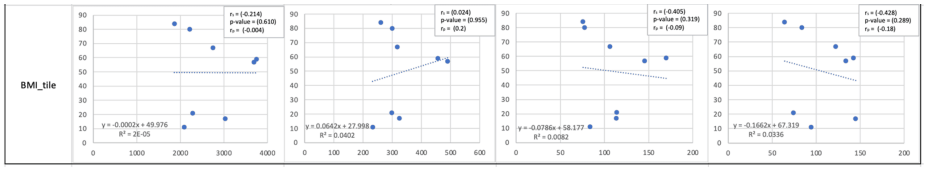


FIGURE 3: BMI percentile correlations with macronutrient intake in unaffected siblings

Panels from left to right show total calories, carbohydrates, protein, and total fat. The Spearman rank correlation test was used for each comparison. The Spearman correlation coefficient (r_s) is reported as the test statistic alongside its corresponding two-sided p-value; the Pearson correlation coefficient (r_p) is also displayed for comparison.

FFQ fat-soluble vitamin intake and vitamin serum levels of CF participants

Next, we examined the association between fat-soluble vitamin intake and vitamin serum levels found in the blood of CF participants (Figure 4). Vitamin intake differed by age and had weak correlations with vitamin serum levels. All correlations between vitamins and their respective serum levels were weak and negative. The strongest correlation observed was the correlation between vitamin D and 25-hydroxyvitamin D, having a Pearson's correlation coefficient (rp) of -0.308. Vitamin E also had a weak -0.248 correlation with alpha-tocopherol, the main isoform of vitamin E found in the blood. Lastly, vitamin A had a -0.203 correlation with retinol found in the blood. The International Normalized Ratio (INR), a surrogate measure of vitamin K in the blood, was not used in this correlation analysis due to lack of data and small sample size. None of these correlations were significant.

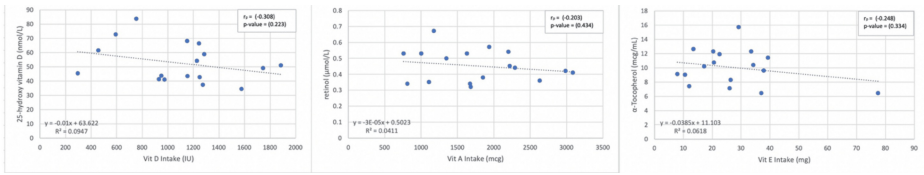


FIGURE 4: Fat-soluble vitamin intake and serum levels in CF participants

Associations between reported fat-soluble vitamin intake and serum vitamin levels among the 17 CF participants in the serum-analysis subset. Panels from left to right show vitamin D intake versus serum 25-hydroxyvitamin D, vitamin A intake versus serum retinol, and vitamin E intake versus serum alpha-tocopherol. Pearson correlation tests were used. The Pearson correlation coefficient (r_p) is reported as the test statistic alongside its corresponding two-sided p-value.

CF, cystic fibrosis.

Discussion

The dietary intake of CF participants and their siblings was better than expected. Most participants had balanced diets that were meeting their caloric and macronutrient goals as measured by the FFQ. However, the majority of both groups were deficient in AOAC fiber. CF participants were deficient in fat-soluble vitamins disproportionately more often than their non-CF siblings. Also, we found statistically significant differences in intake between CF and non-CF participants in zinc, iron, vitamin A, vitamin E, and vitamin B-12. No significant associations existed between macronutrient intake and BMI percentile or vitamin intake and serum vitamin levels. No significant trend was observed for the non-CF participant group either.

In our participants, the majority were meeting their caloric intake and macronutrient goals. A small proportion were deficient, but this was only a few participants. No significant association existed between macronutrient intake and BMI percentile. According to the FFQ data and the evaluation of macronutrient intake, most participants consumed balanced diets. However, recommended intake for fat and protein is higher for CF patients compared to non-CF patients. CF patients, aged 4-18 years, are recommended to obtain 35-40% of their total calories from fat intake. Recommended protein intake follows a similar trend, with CF patients suggested to obtain 16-20% of their calories from protein. Fat intake and protein intake for CF patients are 140% and 160% of the recommended RDA for non-CF patients, respectively [20-22]. The goal of these macronutrient recommendations for CF patients is to achieve a daily energy (kcal) intake of 110-200% of the recommended dietary allowance (RDA) for their age group, which functions to promote optimal

growth [23].

Sufficient dietary intake for individuals is often evaluated based on several anthropometric measurements. For children under the age of 2, weight-for-length is the standard assessment. BMI percentile is the most common evaluation for individuals between the ages of 2 and 20 years old. CF adults above the age of 20 are assessed through numerical BMI values [24]. CF participants in our study had a median BMI at the 56th percentile (ranging from the 13th to 97th percentile). Their non-CF siblings had an average BMI around the 58th percentile (ranging from the 11th to 84th percentile). Guidelines from the Cystic Fibrosis Foundation recommend that CF patients maintain their BMI above the 50th percentile, which is often considered a marker of sufficient nutrition [24]. Many studies have shown that individuals with a BMI above the 50th percentile have better outcomes associated with improved lung function and increased lifespan [25-27].

Previous research suggests that BMI percentile may be particularly informative when screening for extreme weight concerns such as critical malnourishment or obesity. In people with CF, patients within the overweight and obesity BMI ranges may experience better clinical outcomes than patients within the normal BMI range, including higher FEV1 measurements and reduced risks of exocrine pancreatic insufficiency and CF-related diabetes [28]. Research involving children and adolescents has also found that obesity, defined as BMI above the 97th percentile, could be predicted when food frequency questionnaire data demonstrated elevated fat intake while the intake of other macronutrients remained average [29]. However, the average BMI among participants in the present study was approximately at the 50th percentile, so these extremes were not a factor.

Fiber intake was below target in 57% of CF participants and 60% of unaffected siblings. The interaction between dietary fiber intake and GI symptoms is quite complex, as the role of fiber in the gut microbiome is not completely understood. One study has suggested that increased fiber intake in the CF diet may diminish GI symptom severity [30]. However, other evidence has suggested that no significant link exists between fiber intake and incidence of GI symptoms [31]. Many clinical trials and epidemiological studies have suggested that use of probiotic and prebiotic supplements along with modulated dietary fiber intake may beneficially improve the gut microbiome, having potential to treat GI symptoms in CF patients. However, the data supporting this are highly variable, as dietary intervention with prebiotics and probiotics depends heavily upon the patient's existing diet, existing microbiota, and current medications that can complicate cultivating a healthy gut microbiome [32]. A meta-analysis of 64 studies found that dietary fiber intervention significantly increased the abundance of several microbes, including Bifidobacterium and Lactobacillus spp., which have been found to alleviate symptoms of constipation, promote regularity, and decrease inflammation in the gut [33,34].

CF participants were deficient in fat-soluble vitamins disproportionately more often than their non-CF siblings, which is not unexpected. CF patients commonly experience exocrine pancreatic insufficiency (EPI), which can lead to decreased fat-soluble vitamin absorption [35]. Despite the use of PERT, undernourishment can still occur [36]. To compensate for this malabsorption, DRIs are much higher for those with CF than those without CF across all age groups. CF DRIs for vitamin E and vitamin K are approximately 10 times and 6 times higher than non-CF individuals, respectively. Vitamin A DRIs for CF patients are 4 times higher than non-CF DRIs, and vitamin D DRIs are 1.3 times higher in CF patients (see Appendices).

Locally, our general dietician recommendations are that children with CF follow a structured eating pattern of 3 meals and 2-3 nutrient-dense snacks daily, which avoids a grazing-type eating pattern. This rationale is intended to encourage patients to take their pancreatic enzymes 5-6 times/day. Pancreatic enzyme replacement therapy (PERT) helps patients meet their calorie needs [5]. In those who are having difficulty gaining weight simply by food, we also recommend the consumption of high-calorie nutrition supplements anywhere from 1-4 daily, or more if needed. Another option that is utilized to help improve and maintain adequate nutrition status when needed is the use of enteral nutrition support providing macronutrients and micronutrients through a gastrostomy tube [7].

For CF participants, 100% were deficient in vitamin K, while 96% were deficient in vitamin E intake. Vitamin K supplementation is important in the CF diet as it acts as a clotting factor in the bloodstream and may increase bone density. In CF patients, some evidence suggests that supplementation of 10 mg/day may promote increased bone formation over a 12-month period [37]. Vitamin E works primarily as an antioxidant in its many roles in the body [38]. Vitamin E deficiency may promote incidence of several types of disorders in the nervous system, especially disorders of the eye [39]. It is assumed that vitamin E supplementation may diminish the chance of CF patients acquiring these disorders. However, prevention of these outcomes through supplementation have yet to be supported by strong experimental evidence [40].

In our study, vitamin A and vitamin D intake was below target in 48% and 26% of CF participants, respectively. Vitamin D intake was also below target in 60% of unaffected siblings. Vitamin A plays significant roles in vision, reproduction, cell development, and the immune system [41]. Previous studies have identified that up to 40% of CF patients are deficient in vitamin A [42]. A study found that administering a high dose of serum beta-carotene, a derivative of vitamin A and retinol, had a significant association with decreased number of days of systemic antibiotic treatment for patients battling pulmonary

exacerbations compared to controls [43]. Vitamin D plays significant roles in the musculoskeletal system, immune system, glucose metabolism, and the cell cycle [44]. Calcium and vitamin D work together to promote bone growth and repair. Patients with more extreme cases of vitamin D deficiency may suffer from osteoporosis, but it is more common among adult populations than pediatric populations [44]. Though Vitamin D can be synthesized from sun exposure, supplementation may deliver the most effective dosage for CF patients [45]. Previous CF and chronic lung disease studies have suggested that vitamin D may act to preserve lung function by improving the health and immune response of the airway by promoting convalescence from inflammation or injury, while also making airways a less hospitable environment for bacterial growth [46].

Our study identified statistically significant differences in zinc, iron, vitamin A, vitamin E, and vitamin B12 intake between CF participants and unaffected siblings; the vitamin C comparison was not statistically significant. Zinc and iron deficiencies are common among the CF population. Zinc deficiencies may lead to immunosuppression and failure to thrive. Also, associations exist between zinc deficiency and hypogeusia, which may lead to loss of appetite [47]. Iron deficiency is a common risk for CF patients, due to malabsorption and insufficient intake being common issues. Furthermore, iron deficiency may result from chronic inflammation or blood loss experienced by CF patients [47]. Vitamin C and B-12 deficiencies are typically not common in the CF population. However, one study has shown that daily 1000 mg supplementation of vitamin C may decrease respiratory tract inflammation by enhancing the antioxidant effects of vitamin E [48]. Vitamin B-12 metabolism is thought to be dysregulated due to malabsorption and pancreatic insufficiency. An experimental study demonstrated that increased supplementation leads to higher B-12 serum levels than normal in CF children with pancreatic insufficiency. However, the effects of long-term vitamin B-12 supplementation are currently unknown [49].

Negative correlations were observed between all fat-soluble vitamins and their respective serum levels, which was unexpected. Although none of the correlations were statistically significant, some positive correlations between vitamin intake and serum levels were expected. The fact that vitamin serum levels were measured experimentally on a different day than the completion of the FFQ is the most probable explanation for these weak negative correlations. To properly understand the relationship between fat-soluble vitamin intake and absorption, food must be consumed and accounted for several hours before the serum levels are measured to ensure accurate measurements of absorption in the blood.

The YAQ was validated in youths aged 9-18 years [18]; however, 22 of 33 participants in this study were younger than 9 years. Use outside the age range evaluated in the cited validation study may affect the accuracy of dietary estimates and should be considered when interpreting the findings.

Other limitations of this study include slight variations in DRI values across nutritional literature. The main limitation of our study came from the ambiguity of RDA values found for healthy individuals and individuals with cystic fibrosis. Inconsistencies in RDA values from various sources led to choosing wider adequate intake ranges to accommodate most values found in the literature. Lastly, the small sample size of the study may have limited observation of significant trends between both CF and non-CF groups.

Conclusions

FFQ-estimated dietary intake generally met macronutrient targets in this sample, whereas fiber and several fat-soluble vitamin intakes were below the applicable targets in a substantial proportion of participants. These findings suggest that dietary assessment in children with CF should consider micronutrient and fiber intake alongside energy and macronutrient intake. Interpretation is limited by the small sample size, uncertainty associated with FFQ-based estimates, and the availability of serum vitamin measurements in only a subset of participants. Nutritional assessment should remain an integral component of CF care as treatment approaches evolve. However, this has also revealed additional comorbidities, including obesity and chronic eating disorders. In the future, more research should investigate the effects of CFTR modulators on nutritional status. This highlights the ongoing need for the CF community to re-evaluate clinical care guidelines over time to ensure we are providing the most up-to-date recommendations for our patients.

Appendices

Dietary reference intakes (DRIs) for non-CF and CF patients

Appendix A and Appendix B reflect dietary reference intakes (DRIs) for non-CF and CF patients, respectively. These data include recommended nutritional intake from the Cystic Fibrosis Foundation (CFF) for children of several age groups [7]. Nutrient recommendations from various nutrition professionals were collected to construct Appendix A and Appendix B [50-57].

Appendix A

Variable	DRI standard	Males and females	Males and females	Males	Females	Males	Females
Nutrient	DRI measurement	Age 1-3 (children)	Age: 4-8 (children)	Age: 9-13	Age: 9-13	Age 14-18	Age: 14-18
Calories (kcal)	EER: (low to high activity)	(1000 – 1400)	(1200 – 1600)	(1800 – 2200)	(1600 – 2000)	(2200 – 2800)	(1800 – 2000)
Carbohydrates (g)	(RDA – ND)	(130 – ND)	(130 – ND)	(130 – ND)	(130 – ND)	(130 – ND)	(130 – ND)
Total fat (g)	RDA: (low to high activity)	(22 – 54)	(26 – 62)	(40 – 85)	(35 – 78)	(49 – 108)	(40 – 78)
Total protein (g)	(RDA – ND)	(13 – ND)	(19 – ND)	(34 – ND)	(34 – ND)	(52 – ND)	(46 – ND)
Total fiber (g)	(AI – ND)	(19 – ND)	(25 – ND)	(31 – ND)	(26 – ND)	(38 – ND)	(26 – ND)
Calcium (mg)	(RDA – UL)	(700 – 2500)	(1000 – 2500)	(1300 – 3000)	(1300 – 3000)	(1300 – 3000)	(1300 – 3000)
Zinc (mg)	(RDA – UL)	(3 – 7)	(5 – 12)	(8 – 23)	(8 – 23)	(11 – 34)	(9 – 34)
Iron (mg)	(RDA – UL)	(7 – 40)	(10 – 40)	(8 – 40)	(8 – 40)	(11 – 45)	(15 – 45)
Magnesium (mg)	(RDA – ND)	(80 – ND)	(130 – ND)	(240 – ND)	(240 – ND)	(410 – ND)	(360 – ND)
Sodium (mg)	(AI – UL)	(1000 – 1500)	(1200 – 1900)	(1500 – 2200)	(1500 – 2200)	(1500 – 2300)	(1500 – 2300)
Vit A (mcg)	(AI – UL)	(300 – 600)	(400 – 900)	(600 – 1700)	(600 – 1700)	(900 – 2800)	(700 – 2800)
Vit D (IU)	(AI – UL)	(600 – 2520)	(600 – 3000)	(600 – 4000)	(600 – 4000)	(600 – 4000)	(600 – 4000)
Vit E (mg)	(AI – UL)	(6 – 200)	(7 – 300)	(11 – 600)	(11 – 600)	(15 – 800)	(15 – 800)
Vit K (mcg)	(AI – ND)	(30 – ND)	(55 – ND)	(60 – ND)	(60 – ND)	(75 – ND)	(75 – ND)
Vit C (mg)	(AI – UL)	(15 – 400)	(25 – 650)	(45 – 1200)	(45 – 1200)	(75 – 1800)	(65 – 1800)
Vit B-12 (mcg)	(RDA – ND)	(0.9 – ND)	(1.2 – ND)	(1.8 – ND)	(1.8 – ND)	(2.4 – ND)	(2.4 – ND)

TABLE 4: Non-CF DRIs by age

Dietary reference intakes (DRIs) include estimated energy requirement (EER), recommended daily allowance (RDA), adequate intake (AI), upper limit (UL), or not determined (ND).

CF, cystic fibrosis.

Appendix B

Variable	DRI standard	Males and females	Males and females	Males	Females	Males	Females
Nutrient	DRI measurement	Age 1-3 (children)	Age: 4-8 (children)	Age: 9-13	Age: 9-13	Age 14-18	Age: 14-18
*Calories (kcal)	CFF recommendations	(1200 – 2800)	(1440 – 3200)	(2160 – 4400)	(1920 – 4000)	(2640 – 5600)	(2160 – 4000)
Carbohydrates (g)	(RDA – ND)	(130 – ND)	(130 – ND)	(130 – ND)	(130 – ND)	(130 – ND)	(130 – ND)
*Total fat (g)	CFF recommendations	(47 – 124)	(56 – 142)	(84 – 195)	(75 – 178)	(103 – 249)	(84 – 178)
*Total protein (g)	CFF recommendations	(19.5 – 26)	(28.5 – 38)	(51 – 68)	(51 – 68)	(78 – 104)	(69 – 92)
*Total fiber (g)	(AI – ND)	(19 – ND)	(25 – ND)	(31 – ND)	(26 – ND)	(38 – ND)	(26 – ND)
Calcium (mg)	(RDA – UL)	(700 – 2500)	(1000 – 2500)	(1300 – 3000)	(1300 – 3000)	(1300 – 3000)	(1300 – 3000)
*Zinc (mg)	(RDA – UL)	(3 – 7)	(5 – 12)	(8 – 23)	(8 – 23)	(11 – 34)	(9 – 34)
Iron (mg)	(RDA – UL)	(7 – 40)	(10 – 40)	(8 – 40)	(8 – 40)	(11 – 45)	(15 – 45)
Magnesium (mg)	(RDA – ND)	(80 – ND)	(130 – ND)	(240 – ND)	(240 – ND)	(410 – ND)	(360 – ND)
*Sodium (mg)	(AI – UL)	(1000 – 1500)	(1200 – 1900)	(1500 – 2200)	(1500 – 2200)	(1500 – 2300)	(1500 – 2300)
*Vit A (mcg)	CFF recommendations	1500	(1500 – 3000)	(2800 – 3000)	(2800 – 3000)	(2800 – 3000)	(2800 – 3000)
*Vit D (IU)	CFF recommendations	(800 – 1000)	(800 – 1000)	(800 – 2000)	(800 – 2000)	(800 – 2000)	(800 – 2000)
*Vit E (mg)	CFF recommendations	(53.6 – 100.5)	(67 – 134)	(134 – 268)	(134 – 268)	(134 – 268)	(134 – 268)
*Vit K (mcg)	CFF recommendations	(300 – 500)	(300 – 500)	(300 – 500)	(300 – 500)	(300 – 500)	(300 – 500)
Vit C (mg)	(AI – UL)	(15 – 400)	(25 – 650)	(45 – 1200)	(45 – 1200)	(75 – 1800)	(65 – 1800)
Vit B-12 (mcg)	(RDA – ND)	(0.9 – ND)	(1.2 – ND)	(1.8 – ND)	(1.8 – ND)	(2.4 – ND)	(2.4 – ND)

TABLE 5: CF DRIs by age

Nutrients marked with an asterisk (*) are recommended to be consumed at higher levels for cystic fibrosis (CF) patients. Dietary reference intakes (DRIs) include estimated energy requirement (EER), recommended daily allowance (RDA), adequate intake (AI), upper limit (UL), or not determined (ND).

CFF, Cystic Fibrosis Foundation.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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