Nutrition 142 (2026) 112984

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Nutritional outcomes in people with cystic fibrosis receiving elexacaftor/tezacaftor/ivacaftor: A 24-mo real-world study

Gianfranco Alicandro [a,b,*], Laura Zazzeron [b], Valentina Visciola [b], Anna Bulfamante [b], Arianna Biffi [b], Fabiola Corti [b], Andrea Gramegna [a,c], Francesco Blasi [a,c], Valeria Daccò [b]

[a] Department of Physiopathology and Transplantation, Università degli Studi di Milano, Milan, Italy
[b] Mother and Child Department, Cystic Fibrosis Center, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[c] Respiratory Unit and Cystic Fibrosis Adult Center, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

ARTICLE INFO

Article History:
Received 22 May 2025
Received in revised form 5 September 2025
Accepted 29 September 2025

Keywords:
Cystic fibrosis
CFTR modulators
Nutrition
Vitamins

ABSTRACT

Background: The highly effective CFTR modulator elexacaftor/tezacaftor/ivacaftor therapy has revolutionized the care of cystic fibrosis (CF) leading to significant improvement in patient outcomes. However, data on long-term evolution of nutritional outcomes are limited.

Methods: We conducted a prospective study to evaluate changes in nutritional outcomes in people with CF (pwCF), including weight, body mass index (BMI), fat absorption and fat-soluble vitamin levels. Study outcomes were measured before treatment initiation and after 12 and 24 mo. Mean changes and 95% confidence intervals (CI) were obtained using generalized estimating equations.

Results: A total of 84 patients with a median age of 19.9 y (range: 12–32) were enrolled. At the 24-mo follow-up visit, weight increased by 4.7 kg (95% CI: 3.5, 6.0) and BMI increased by 0.40 standard deviation scores (95% CI: 0.27, 0.53). The prevalence of overweight and obesity increased from 4.8% to 10.7%. After 24 mo of ETI therapy, levels of vitamin A and E, as well as international normalized ratio (used as a marker of vitamin K status) were lower than baseline values, while vitamin D did not appreciably change.

Conclusions: ETI has primarily led to significant improvements in the nutritional status of pwCF, resulting in increased BMI. However, a shift from the traditional hypercaloric and high fat diet to a balanced, healthy diet is essential to avoid excessive weight gain. Additionally, our findings underscore the need for ongoing monitoring of fat-soluble vitamin levels and adherence to supplementation.

© 2025 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)

Introduction

Cystic fibrosis (CF) is an autosomal recessive, multiorgan disease caused by mutations in the CF Transmembrane Conductance Regulator (CFTR) gene [1]. Progressive lung disease remains the main cause of morbidity and mortality. However, CF also presents with a wide range of gastrointestinal symptoms that vary in severity and frequency [2,3]. Among these, pancreatic insufficiency affects approximately 80% of people with CF (pwCF). It often develops prenatally and requires lifelong pancreatic enzyme replacement therapy (PERT). Another common feature is chronic intestinal inflammation, linked to dysregulated immune response and mucosal damage. Both conditions impair the absorption of fats and fat-soluble vitamins, increasing the risk of nutritional deficiencies and growth impairment. These nutritional deficits can further worsen pulmonary complications and accelerate disease progression.

The introduction of the CFTR modulator therapy has transformed clinical care. The triple combination of the correctors elexacaftor and tezacaftor with the potentiator ivacaftor (ETI), improves both lung function and nutritional status [4,5]. In a phase 3, randomized, double-blind, placebo-controlled trial of 403 patients with at least one F508del mutation, ETI therapy led to an increase in body mass index (BMI) of 0.34 standard deviation score (SDS) (95% confidence interval, CI: 0.25–0.44) after 24 wk, compared with 0.04 (95% CI: −0.05 to 0.14) in the placebo group [4]. Given the clinical importance of maintaining optimal growth and nutritional status in pwCF, this finding represents a significant clinical achievement. However, it is unclear whether this improvement is sustained over the long term or whether ETI therapy may also lead to excess weight gain [6,7].

*Corresponding author. Tel.: 0039 052032456
E-mail address: gianfranco.alicandro@unimi.it (G. Alicandro).

https://doi.org/10.1016/j.nut.2025.112984
0899-9007/© 2025 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)

BMI has been the main nutritional outcome in clinical trials, given its strong association with improved lung function and survival [8]. Increases in BMI likely reflect both reduced energy expenditure, due to improvements in pulmonary disease, and enhanced intestinal absorption of nutrients, including fat-soluble vitamins [9]. Vitamin levels were not assessed in clinical trials, but they have been investigated in some postapproval studies. These studies have reported increased levels of vitamin A and D during ETI therapy [10–14], while findings on vitamin E levels are conflicting [10,14,15]. Hergenroeder et al. recently measured vitamin levels in 169 pwCF over 12 y of age who received ETI therapy. They observed significant increases in vitamins A and D but no change in vitamin E or in international normalized ratio (INR), a surrogate marker of vitamin K status [15].

Conflicting results across studies may reflect changes in vitamin formulations, adjustment in PERT dosing, differences in adherence, and suboptimal control of malabsorption. These factors must be considered when evaluated the overall impact of ETI on nutritional status of pwCF.

This study aimed to extend the findings from clinical trials by assessing BMI changes in pwCF receiving ETI over a 24-mo period. A secondary objective was to evaluate other nutritional outcomes not examined in clinical trials, including PERT requirements, fat absorption, and fat-soluble vitamin status.

Subjects and methods

Study participants

We conducted a prospective observational cohort study involving pwCF regularly followed at the Regional Reference Center for CF care in Milan. All patients initiated ETI treatment between August 2021 and September 2022 according to the recommended therapeutic regimen. Exclusion criteria included participation in a clinical trial, pregnancy, gastrointestinal disorders (including liver disease, celiac disease or chronic inflammatory bowel diseases), malignancies, and a history of organ transplantation.

Study outcomes

The primary outcome was the change in BMI following ETI initiation, expressed as SDS. Secondary outcomes included changes in body weight, BMI (kg/m^2), PERT (lipase units/kg of body weight), vitamin A, vitamin D, vitamin E levels, international normalized ratio (INR), and steatocrit values.

Study procedures

Baseline data, including sex, CFTR genotype, date of birth, pancreatic insufficiency, cirrhosis, dosage of PERT and vitamin supplementation, and the ETI initiation date, were retrieved from clinical chart forms.

Pancreatic insufficiency (PI) was defined as fecal elastase-1 levels $<$ 200 μg/g of stool.

Patients were assessed before starting ETI therapy and at follow-up visits at 12 and 24 mo. The visits included anthropometric evaluation, blood withdrawal for quantification of fat-soluble vitamin concentrations and INR, and steatocrit test to assess fat absorption.

Weight and height were recorded at each visit, and BMI was calculated as weight (kg) divided by height (m^2) and expressed as SDS using national growth reference data [16]. For individuals over 20 y old, SDS values were derived from reference standards for age 20. WHO cutoffs were used to classify underweight, normal weight, overweight, and obesity [17]. Considering the increased risk of undernutrition, pwCF are recommended higher BMI targets specific to sex and age: BMI SDS $\geq$0 (50th percentile) for those under 20 y, and for older adults, BMI $>$22 kg/m^2 for females and $>$23 kg/m^2 for males [18]. Accordingly, the percentage of participants achieving the CF-specific BMI target was also calculated.

Plasma concentrations of vitamins A and E were measured using isocratic HPLC/UV (Agilent Technologies 1200 series) with a commercial kit (Eureka Lab Division) and interpreted according to the reference ranges of IRCCS Ca' Granda Ospedale Maggiore Policlinico: 0.2 to 0.7 mg/L for vitamin A and 5.0 to 20.0 mg/L for vitamin E. Serum vitamin D levels were assessed using a chemiluminescent immunoassay (LIAISON 25 OH Vitamin D TOTAL assay; Liaison XL, DiaSorin Inc.) and evaluated based on ESPEN–ESPGHAN–ECFS guidelines (optimal: 30–50 μg/L; deficiency: $<$20 μg/L) [18]. Intra- and interassay coefficients of variation for these methods are provided in the Supplementary materials. As blood level of vitamin K is an unreliable indicator of total body store, the INR was used as surrogate marker for vitamin K status [19].

Fat absorption was assessed using steatocrit test, a semi-quantitative method that measures the centrifugable fraction of fecal fat. Stool samples were collected over three consecutive days preceding follow-up visits, and the average value was calculated. Assessments were conducted at baseline and after 24 mo of ETI therapy.

During follow-up, the dosage of PERT, expressed as lipase units per kilogram of body weight (lipase units/kg), was adjusted as needed. The prescription of CF-specific multivitamin supplementation was recorded at each follow-up visit.

Sample size

A minimum of 80 patients were required to achieve 90% power to detect a hypothesized difference of 0.25 SDS in BMI at the 24-mo study visit. Further details on the sample size calculation are provided in the Supplementary materials.

Data analysis

Baseline characteristics were summarized using absolute frequencies (%) for categorical variables and medians (25th; 75th percentiles) for continuous variables. Changes from baseline in study outcomes were estimated using generalized estimating equations (GEE), with study visit (baseline, 12 mo, and 24 mo) as the predictor and an unstructured working correlation structure. These models account for the correlation between repeated measures taken at different time points on the same subject. Robust standard errors were used to calculate 95% CI. The statistical significance of the model coefficients was evaluated using Wald's test. Steatocrit values, due to their skewed distribution, were log-transformed prior to GEE analysis.

Subgroup analysis was performed for the primary outcome based on age group (pediatric vs. adult, i.e., $<$18 vs. $\geq$18 y) and baseline nutritional status, defined by whether participants achieved the CF-specific BMI target.

All statistical tests were two-sided, with a significance level of 0.05.

Results

The study included 84 pwCF (61.9% males), with a median age of 19.9 y (range: 12–32 y). Pancreatic insufficiency was present in 75 patients (89.3%), who were prescribed a median dose of PERT of

Table 1
Patient characteristics

Characteristic	*N* = 84
Sex	
Females	32 (38.1%)
Males	52 (61.9%)
Age at ETI initiation	19.9 (16.3; 23.8)
Pancreatic insufficiency	75 (89.3%)
PERT (lipase units/kg)	5780 (4037; 7966)
Unknown	9
Steatocrit (%)*	4.0 (3.0; 5.0)
Steatocrit ≥10%*	8 (11.8%)
BMI (SDS)	−0.31 (−1.11; 0.20)
BMI category	
Underweight	6 (7.1%)
Normal weight	74 (88.1%)
Overweight	3 (3.6%)
Obesity	1 (1.2%)
CF-specific BMI target achieved	18 (21.4%)
Vit. A plasma level (mg/L)	0.4 (0.3, 0.6)
25-OH Vit. D serum level (μg/L)	25.8 (21.2; 32.3)
Vit. E plasma level (mg/L)	9.4 (6.6; 11.3)
INR	1.0 (1.0; 1.1)
Vit. A supplementation (IU/day/kg)	317 (245; 368)
Vit. D supplementation (IU/day/kg)	39.4 (30.2; 81.8)
Vit. E supplementation (IU/day/kg)	8.8 (6.7; 10.3)
Vit. K supplementation (IU/day/kg)	24.9 (21.5; 28.7)

BMI, body mass index; CF, cystic fibrosis; ETI, elexacaftor/tezacaftor/ivacaftor; INR, international normalized ratio; PERT, pancreatic enzyme replacement therapy.
Data are frequencies (%) or medians (25th; 75th percentile).
*Steatocrit available in 68 subjects.

5780 lipase units/kg of body weight (25th; 75th percentile: 4037; 7966).

In most patients (88.1%) BMI values were within the recommended range for a healthy population (i.e., between −2 and 0.85 SDS for children and 18.5−24.9 kg/m^2 for adults). Six individuals (7.1%) were classified as underweight, while 4 (4.8%) were overweight or obese. However, only 18 patients (21.4%) met the BMI nutritional targets recommended for pwCF. The characteristics of this population are summarized in Table 1. All patients were prescribed daily supplementation of fat-soluble vitamins. However, 10 subjects reported not taking vitamin A and E supplementation, and 4 reported not taking vitamin D supplementation.

Table 2 and Figure 1 report the marginal mean estimate of the changes from baseline in nutritional outcomes. After 12 mo of ETI therapy, weight increased by an average of 3.7 kg (95% CI: 2.9, 4.4), with a corresponding increase in BMI of 0.36 SDS (95% CI: 0.27, 0.45). This increase was sustained at 24 mo, with an average weight gain of 4.7 kg (95% CI: 3.5, 6.0) and a BMI increase of 0.40 SDS (95% CI: 0.27, 0.53). At the 24-mo follow-up visit, 7 patients (8.3%) were classified as overweight, and 2 patients (2.4%) as obese.

BMI gains were more pronounced in pediatric patients compared with adults. At 24 mo, mean BMI changes were 0.60 SDS (95% CI: 0.44, 0.76) in pediatric patients and 0.28 SDS (95% CI: 0.12, 0.45) in adults (p-value for time-by-age interaction <0.001). BMI increased on average by 0.49 SDS (95% CI: 0.36, 0.62) in patients below the BMI target, whereas no significant change was observed in those who had already achieved the BMI target at baseline (mean change: 0.08; 95% CI: −0.23, 0.38) (P-value for time-by-BMI target interaction < 0.001).

The units of lipase per kg of body weight did not change significantly throughout the observation period. At the 24-mo follow-up visit, steatocrit values significantly increased from a mean value of 4.4% (95% CI: 3.8, 5.1) to 9.0% (95% CI: 8.3, 9.8).

At the 12-mo follow-up visit, mean plasma vitamin A increased by 0.11 mg/L (95% CI: 0.05, 0.17), while 25-OH vitamin D and vitamin E levels did not change significantly, and INR decreased by 0.02 units (95% CI: −0.03, −0.01). By the 24-mo follow-up, vitamin A had returned to approximately baseline levels, 25-OH vitamin D remained unchanged from baseline, vitamin E significantly decreased by 1.29 mg/L (95% CI: −2.22, −0.36), and INR decreased by 0.07 units (95% CI: −0.08, −0.06).

The assessment of individual study outcome profiles throughout the treatment period revealed a significant degree of between-subject heterogeneity (Fig. 2).

At baseline, 10 subjects (11.9%) had plasma vitamin A levels indicative of deficiency (<0.2 mg/L), 5 individuals (6.0%) had plasma vitamin E levels below the deficiency threshold (<5 mg/L). Vitamin D below the insufficiency threshold of 30 μg/L was observed in 56 subjects (66.6%), with 17 individuals (20.2%) having vitamin D levels below the deficiency threshold (<20 μg/L) (Table 3). The frequency of fat-soluble vitamin deficiency decreased after 12 mo of ETI therapy. However, by the 24-mo follow-up, deficiency rates returned approximately to baseline values

Table 2
Mean changes from baseline in nutritional outcomes in pwCF receiving ETI therapy

Study outcomes	Study visit	Number of measurements	Mean change from baseline (95% CI)	*P*-value
Weight (kg)	12 mo	84	3.66 (2.88; 4.44)	<0.001
	24 mo	84	4.72 (3.47; 5.97)	<0.001
BMI	12 mo	84	1.07 (0.83; 1.31)	<0.001
	24 mo	84	1.30 (0.94; 1.66)	<0.001
BMI (SDS)	12 mo	84	0.36 (0.27; 0.45)	<0.001
	24 mo	84	0.40 (0.27; 0.53)	<0.001
PERT (lipase units/kg)	12 mo	74	−65 (−389; 258)	0.693
	24 mo	75	0.2 (−457.6; 457.9)	0.999
Vit. A plasma level (mg/L)	12 mo	81	0.11 (0.05; 0.17)	<0.001
	24 mo	84	−0.05 (−0.1; 0)	0.065
25-OH Vit. D serum level (μg/L)	12 mo	84	2.16 (−0.66; 4.98)	0.13
	24 mo	84	−0.70 (−3.54; 2.14)	0.63
Vit. E plasma level (mg/L)	12 mo	81	0.31 (−0.63; 1.25)	0.52
	24 mo	84	−1.29 (−2.22; −0.36)	0.007
INR	12 mo	83	−0.02 (−0.03; −0.01)	0.012
	24 mo	80	−0.07 (−0.08; −0.06)	<0.001
Log steatocrit (%)*	24 mo	74	0.72 (0.56; 0.88)	<0.001

BMI, body mass index; ETI, elexacaftor/tezacaftor/ivacaftor; INR, international normalized ratio; PERT, pancreatic enzyme replacement therapy; pwCF, people with cystic fibrosis.
*Steartocrit values were log transformed to account for their skewed distribution.

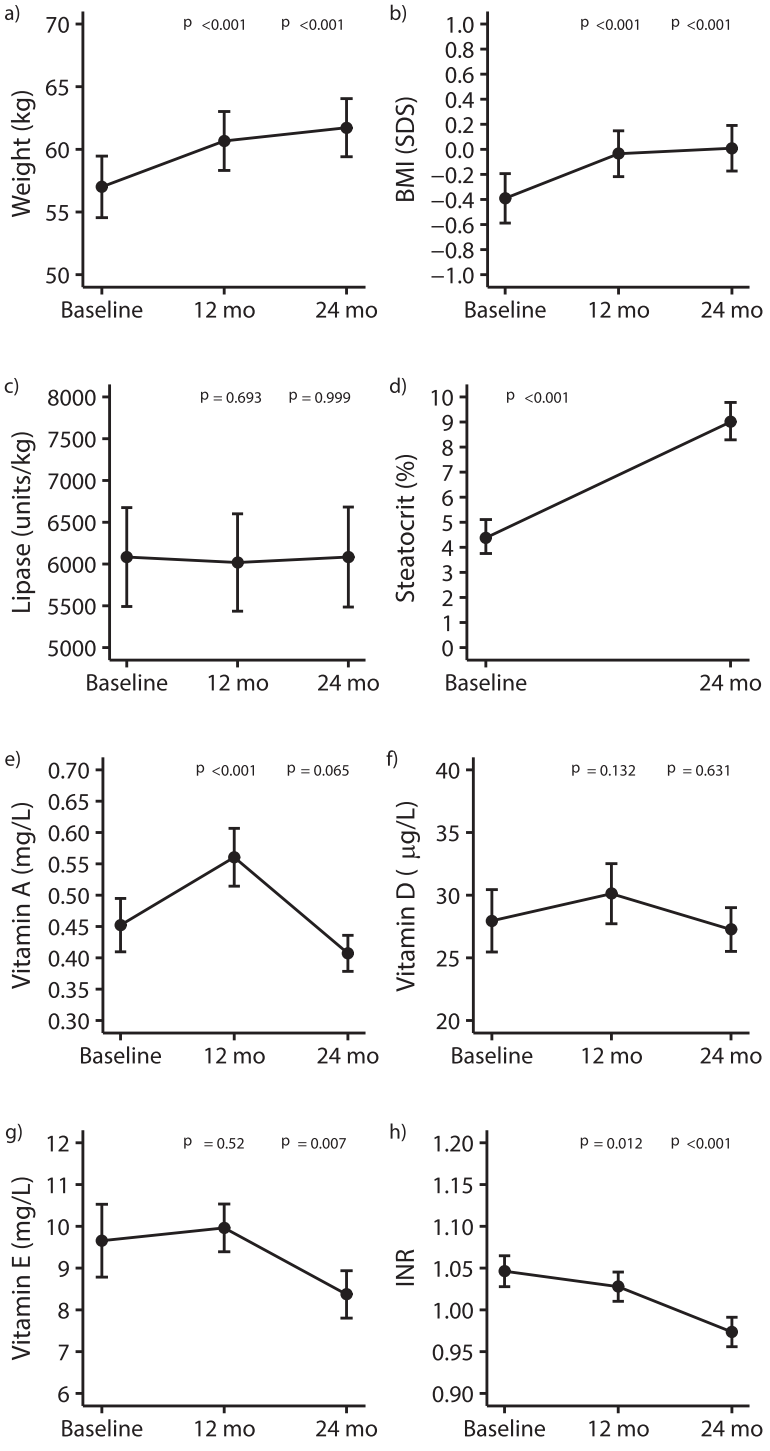

Fig. 1. Nutritional outcomes in pwCF receiving ETI therapy. Error bars indicate 95% confidence intervals of estimated marginal means. Statistical tests compare follow-up visits with baseline.

(Table 3). High levels of vitamin A were observed in 9.5%, 16.0%, and 2.4% of subjects at baseline, 12 mo, and 24 mo, respectively. Two patients had high levels of vitamin E and 5 had high levels of vitamin D at baseline, while no subjects had vitamin D or E levels exceeding the reference values at the 24 mo of follow-up. INR was elevated above the recommended levels in 21.2%, 14.3%, and 6.2% of individuals at baseline, 12 mo, and 24 mo of follow-up. During the observation period, initial dosages of vitamin A was reduced in 9 patients, vitamin D in 12 patients, vitamin E in 9 patients and vitamin K in 8 patients.

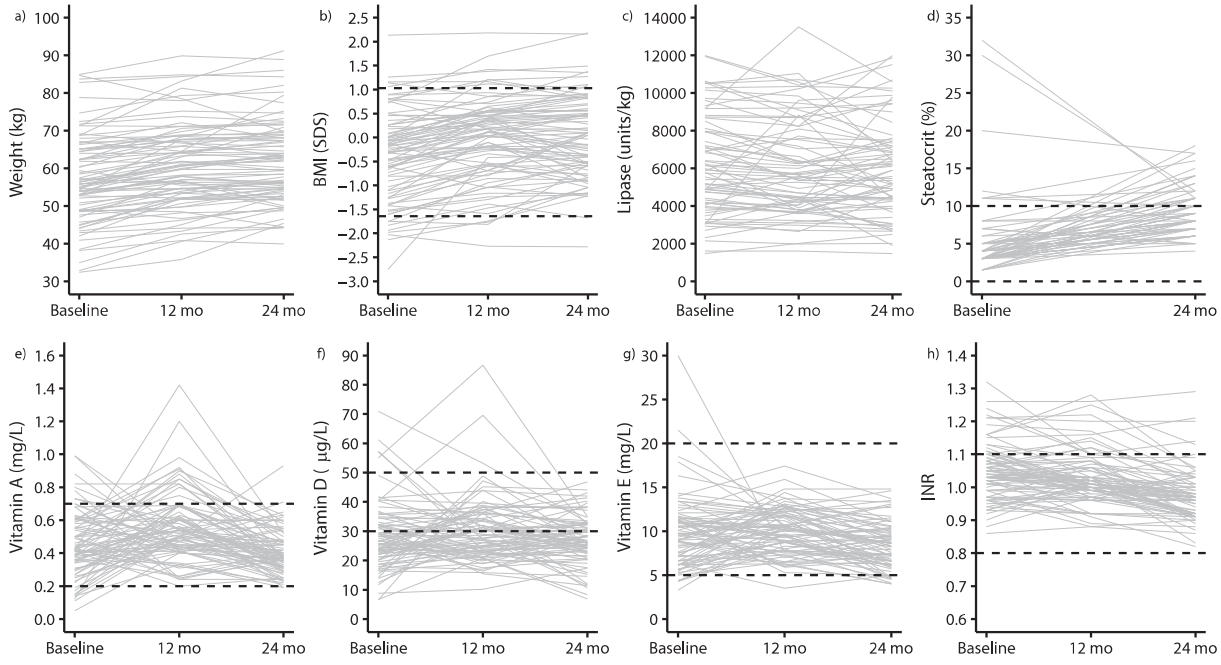

Fig. 2. Individual changes in nutritional outcomes in pwCF receiving ETI therapy. Dashed lines define the reference values.

Discussion

The study found sustained improvements in BMI in children and adults with CF over a 24-mo period of ETI therapy. Changes in fat-soluble vitamins showed heterogeneous results. Vitamin A levels increased after 12 mo, but reduced to pre-treatment level at 24 mo. Vitamin D levels remained unchanged, while vitamin E and INR levels decreased. Some patients showed supra-therapeutic levels of vitamins A and D during treatment, but no clinical consequences were observed.

Table 3
Distribution of pwCF in nutritional outcome categories over 24 mo of ETI therapy

Outcome	Categories	Baseline	12 mo	24 mo
BMI	Underweight	6 (7.1)	5 (6.0)	2 (2.4)
	Normal weight	74 (88.1)	72 (85.7)	73 (86.9)
	Overweight	3 (3.6)	6 (7.1)	7 (8.3)
	Obese	1 (1.2)	1 (1.2)	2 (2.4)
	BMI nutritional goal met	18 (21.4)	37 (44.0)	37 (44.0)
Vitamin A	Deficiency	10 (11.9)	0	2 (2.4)
	Normal	66 (78.6)	68 (84.0)	80 (95.2)
	High	8 (9.5)	13 (16.0)	2 (2.4)
Vitamin D	Deficiency	17 (20.2)	9 (10.7)	12 (14.3)
	Insufficiency	39 (46.4)	35 (41.7)	42 (50.0)
	Normal	23 (27.4)	37 (44.0)	30 (35.7)
	High	5 (6.0)	3 (3.6)	0
Vitamin E	Deficiency	5 (6.0)	1 (1.2)	9 (10.7)
	Normal	77 (91.7)	80 (98.8)	75 (89.3)
	High	2 (2.4)	0	0
INR	Low	0	0	0
	Normal	67 (79.8)	72 (86.7)	75 (93.8)
	High	17 (20.2)	11 (13.3)	5 (6.2)
Steatocrit	<10%	60 (88.2)	.	43 (58.1)
	≥10%	8 (11.8)	.	31 (41.9)

BMI, body mass index; ETI, elexacaftor/tezacaftor/ivacaftor; pwCF, people with cystic fibrosis.
Missing values: vitamin A (3 subjects, 12 mo), vitamin E (3 subjects 12 mo), INR (1 subject, 12 mo; 4 subjects 24 mo), steatocrit (16 subjects baseline; 10 subjects, 24 mo).
Data are frequency (%).

The increase in BMI following ETI therapy was first reported in clinical trials over 24 wk [4,20,21], and later confirmed in a 144-wk interim analysis of an extension study [22]. Reported improvements ranged from 1 to 1.8 kg/m^2, corresponding to an increase of approximately 0.3 SDS. Our estimates through 24 mo were consistent, with a mean increase of +1.3 kg/m^2 (+0.40 SDS), further supporting the long-term, sustained increase in BMI during ETI treatment. Notably, patients with optimal nutritional status at baseline did not experience a further increase in BMI. By 24 mo, approximately 10% of participants were overweight or obese, supporting concerns about the increase in overweight prevalence in this population [23].

Previous studies have reported fat-soluble vitamin deficiency in patients receiving ETI. Hergenroeder et al. found sub-therapeutic levels of fat-soluble vitamins A, D and E in 15.8%, 52.2%, and 17.2% of patients, with supra-therapeutic levels in 5.7% for vitamin A and 9.6% of vitamin E [15]. Our results confirm these findings in a different cohort treated for 24 mo.

The observed increase in vitamin A levels has been attributed to enhanced intestinal absorption and reduction in systemic inflammation. Vitamin A has anti-inflammatory and antioxidant properties, and its metabolic demand rise under conditions of inflammation and oxidative stress [24]. In contrast, no similar increase was observed for vitamin E. This may relate to its less efficient absorption via chylomicrons. Unlike vitamin A, vitamin E is not stored in the liver, making it more sensitive to lipid malabsorption. Vitamin D levels did not change, likely due to factors beyond intake, including sun exposure and genetics [25].

Before treatment initiation, 20% of patients showed prolonged prothrombin time, consistent with findings in patients naïve to CFTR modulators [26]. After 24 mo, this proportion decreased to 6%, suggesting improved vitamin K status. This may partly reflect shifts in gut microbiota composition towards that observed in healthy subjects [27]. However, INR is a nonspecific indicator of vitamin K deficiency and has limited sensitivity. In fact,

prothrombin time becomes abnormal only after an approximately reduction of 50% in prothrombin levels [28].

After 12 mo of ETI, 16% of patients had supra-therapeutic vitamin A levels, and 3.6% had elevated vitamin D levels. These elevated levels were not associated with any clinical evidence of hypervitaminosis. Nevertheless, cases of intracranial hypertension and papilledema during ETI have been described [29–31], not always linked to concomitant hypervitaminosis A. Vitamin A supplementation therefore requires close monitoring, as highlighted even before the introduction of ETI therapy (26,27). Vitamin D toxicity, accompanied by severe hypercalcemia, acute kidney injury, and electrocardiogram changes, was rarely reported in CF and typically resulted from accidental errors in the magistral preparation of liposoluble vitamin supplements by local pharmacists [32]. None of the participants in our study reached toxic levels of vitamin D (i.e., >150 μg/L).

By 24 mo, vitamin A had returned to baseline levels, vitamin D remained unchanged, and vitamin E levels declined. Considering the increase in vitamin levels observed after 1 y of therapy and sustained improvement in nutritional status, we can only hypothesize that these findings resulted from reduced adherence to PERT and vitamin supplementation. After the first year of ETI, patients may have achieved significant clinical improvement, leading to self-discontinuation of standard CF therapy, including vitamin supplements. Adherence to vitamin supplement prescription was suboptimal even before the introduction of CFTR modulators, and may have worsened with ETI [33,34].

Our findings have important clinical implications. First, although most patients achieved normal nutritional status during treatment, some remained below the CF nutritional target, while others gained more weight than desired. This heterogeneity highlights the need for individualized management with nutritional intakes and energy expenditure carefully monitored in patients outside the optimal BMI range. Second, our data indicates that fat-soluble vitamin supplementation remains necessary during ETI therapy. Supplementation has always been a cornerstone of CF nutritional management, and recommendations have not changed in the CFTR modulator era [18]. Although standardized starting and maintenance dosages are provided for all patients, our results suggest that a tailored approach is needed. Dosage should be adjusted for body weight, which is particularly relevant in children. Monitoring is equally important. Current guidelines recommend at least annual testing of vitamin status, with closer monitoring when dosages change [18]. However, the asymptomatic nature of vitamin deficiencies reduces adherence to this recommendation. Finally, proper adjustment of PERT therapy in response to increased food intake and monitoring for steatorrhea ensures effective fat absorption and prevent vitamin deficiency.

The main strengths of the study include the extended observation period and the wide range of nutritional outcomes considered.

However, some limitations should be acknowledged. We did not collected data on patient adherence to therapies, particularly vitamin supplementation. We also did not collect dietary intake information, which prevented us to evaluate the adequacy of caloric and nutrient intake. Lastly, the study was conducted at a single CF center in Italy, which may restrict generalizability.

The introduction of ETI has clearly improved nutritional status of pwCF, reflected in higher BMI values. While this is a positive outcome, it raises new concerns about excessive weight gain and its potential complications [35]. Clinical attention should therefore shift from a high-energy content to a healthy diet with balanced nutrient content. Our observation of increased steatocrit values reinforces the need for dietary optimization and careful management of fat intake, highlighting the importance of effective management of fat intake. Finally, our findings confirm the continued need to monitor fat-soluble vitamin levels and support adherence to supplementation. Healthcare providers should stress the importance of continuing vitamin supplementation, even in the context of general health improvements associated with ETI therapy.

Data statement

Due to confidentiality concerns, the data cannot be made publicly available. However, data may be requested from the corresponding authors upon reasonable request.

Funding

The study was partially funded by 1) Ricerca Corrente 2024 Ministero della Salute, IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, 2) Regione Lombardia Progetto Fibrosi Cistica Cod 18563 Cap 13.01.104.8378 2023, 3) The Italian Ministry of Education and Research—MUR ('Dipartimenti di Eccellenza' Programme 2023–27—Department of Pathophysiology and Transplantation, Università degli Studi di Milano).

Ethical approval

The study received approval from the local ethics committee of our institution (protocol number 594_201). Before enrollment, written informed consent was obtained from all patients or their parents.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Valeria Dacco reports financial support was provided by Ministry of Health. Francesco Blasi reports financial support was provided by Lombardy Region. Gianfranco Alicandro reports financial support was provided by Ministry of Education and Research. Andrea Gramegna reports a relationship with Vertex Pharmaceuticals that includes: consulting or advisory and speaking and lecture fees. Francesco Blasi reports a relationship with Vertex Pharmaceuticals that includes: consulting or advisory and speaking and lecture fees. Valeria Dacco reports a relationship with Vertex Pharmaceuticals that includes: consulting or advisory and speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Gianfranco Alicandro: Writing – original draft, Software, Methodology, Formal analysis, Conceptualization. **Laura Zazzeron:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Valentina Visciola:** Investigation, Data curation. **Anna Bulfamante:** Investigation, Data curation. **Arianna Biffi:** Investigation, Data curation. **Fabiola Corti:** Investigation, Data curation. **Andrea Gramegna:** Writing – review & editing. **Francesco Blasi:** Writing – review & editing, Funding acquisition. **Valeria Daccò:** Writing – original draft, Supervision, Project administration, Funding acquisition.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.nut.2025.112984.

References

[1] Elborn J. Cystic fibrosis. Lancet 2016;388:2519–31.
[2] Gibson-Corley KN, Meyerholz DK, Engelhardt JF. Pancreatic pathophysiology in cystic fibrosis. J Pathol 2016;238:311–20. https://doi.org/10.1002/path.4634.
[3] Assis DN, Freedman SD. Gastrointestinal disorders in cystic fibrosis. Clin Chest Med 2016;37:109–18. https://doi.org/10.1016/J.CCM.2015.11.004.
[4] Middleton PG, Mall MA, Dřevínek P, Lands LC, McKone EF, Polineni D, et al. Elexacaftor–tezacaftor–ivacaftor for cystic fibrosis with a single Phe508del allele. N Engl J Med 2019;381:1809–19. https://doi.org/10.1056/nejmoa1908639.
[5] Zemanick ET, Taylor-Cousar JL, Davies J, Gibson RL, Mall MA, McKone EF, et al. A phase 3 open-label study of elexacaftor/tezacaftor/ivacaftor in children 6 through 11 years of age with cystic fibrosis and at least one F508del allele. Am J Respir Crit Care Med 2021;203:1522–32. https://doi.org/10.1164/RCCM.202102-0509OC.
[6] Szentpetery S, Fernandez GS, Schechter MS, Jain R, Flume PA, Fink AK. Obesity in cystic fibrosis: prevalence, trends and associated factors data from the US cystic fibrosis foundation patient registry. J Cyst Fibros 2022;21:777–83. https://doi.org/10.1016/J.JCF.2022.03.010.
[7] Gramegna A, Ruscica M, Leonardi G, Macchi C, Fichtner I, Putti G, et al. Cardiometabolic risk factors in adults with cystic fibrosis undergoing elexacaftor/tezacaftor/ivacaftor therapy. J Cyst Fibros 2025;24:53–6. https://doi.org/10.1016/J.JCF.2024.11.009.
[8] Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H, et al. Clinical Practice Guidelines on Growth and Nutrition Subcommittee. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. J Am Diet Assoc 2008;108:832–9. https://doi.org/10.1016/j.jada.2008.02.020.
[9] Wisniewski BL, Aylward SC, Jordan CO, Kopp BT, Paul GR. Hypervitaminosis A with fulminant secondary intracranial hypertension following personalized medicine-based elexacaftor/tezacaftor/ivacaftor initiation in a preadolescent with cystic fibrosis. J Cyst Fibros 2022;21:e217–20. https://doi.org/10.1016/J.JCF.2022.01.010.
[10] Francalanci M, Terlizzi V, Fevola C, Di Rosa G, Pierattini V, Roselli E, et al. Nutritional status and circulating levels of fat-soluble vitamins in cystic fibrosis patients: a cohort study and evaluation of the effect of CFTR modulators. Child 2023;10. https://doi.org/10.3390/CHILDREN10020252.
[11] Wright BA, Ketchen NK, Rasmussen LN, Bartels AR, Singh SB. Impact of elexacaftor/tezacaftor/ivacaftor on vitamin D absorption in cystic fibrosis patients. Pediatr Pulmonol 2022;57:655–7. https://doi.org/10.1002/PPUL.25781.
[12] Carnovale V, Scialò F, Gelzo M, Iacotucci P, Amato F, Zarrilli F, et al. Cystic fibrosis patients with F508del/minimal function genotype: laboratory and nutritional evaluations after one year of elexacaftor/tezacaftor/ivacaftor treatment. J Clin Med 2022;11. https://doi.org/10.3390/JCM11236900.
[13] Schembri L, Warraich S, Bentley S, Carr SB, Balfour-Lynn IM. Impact of elexacaftor/tezacaftor/ivacaftor on fat-soluble vitamin levels in children with cystic fibrosis. J Cyst Fibros 2023;22:843–6. https://doi.org/10.1016/J.JCF.2023.04.019.
[14] Patel T, McBennett K, Sankararaman S, Schindler T, Sundaram K, Minich NM, et al. Impact of elexacaftor/tezacaftor/ivacaftor on lipid and fat-soluble vitamin levels and association with body mass index. Pediatr Pulmonol 2024;59:734–42. https://doi.org/10.1002/PPUL.26823.
[15] Hergenroeder GE, Faino A, Bridges G, Bartlett LE, Cogen JD, Green N, et al. The impact of elexacaftor/tezacaftor/ivacaftor on fat-soluble vitamin levels in people with cystic fibrosis. J Cyst Fibros 2023;22:1048–53. https://doi.org/10.1016/J.JCF.2023.08.002.
[16] Cacciari E, Milani S, Balsamo A, Spada E, Bona G, Cavallo L, et al. Italian cross-sectional growth charts for height, weight and BMI (2 to 20 yr). J Endocrinol Invest 2006;29:581–93. https://doi.org/10.1007/BF03344156.
[17] World Health Organization. BMI-for-age (5–19 years). Growth Ref Data 5-19 Years 2016. https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/bmi-for-age (accessed August 28, 2025).
[18] Wilschanski M, Munck A, Carrion E, Cipolli M, Collins S, Colombo C, et al. ESPEN-ESPGHAN-ECFS guideline on nutrition care for cystic fibrosis. Clin Nutr 2024;43:413–45. https://doi.org/10.1016/J.CLNU.2023.12.017.
[19] Fusaro M, Gallieni M, Rizzo MA, Stucchi A, Delanaye P, Cavalier E, et al. Vitamin K plasma levels determination in human health. Clin Chem Lab Med 2017;55:789–99. https://doi.org/10.1515/CCLM-2016-0783.
[20] Sutharsan S, McKone EF, Downey DG, Duckers J, MacGregor G, Tullis E, et al. Efficacy and safety of elexacaftor plus tezacaftor plus ivacaftor versus tezacaftor plus ivacaftor in people with cystic fibrosis homozygous for F508del-CFTR: a 24-week, multicentre, randomised, double-blind, active-controlled, phase 3b trial. Lancet Respir Med 2022;10:267–77. https://doi.org/10.1016/S2213-2600(21)00454-9.
[21] Zemanick ET, Taylor-Cousar JL, Davies J, Gibson RL, Mall MA, McKone EF, et al. A phase 3 open-label study of elexacaftor/tezacaftor/ivacaftor in children 6 through 11 years of age with cystic fibrosis and at least one F508del allele. Am J Respir Crit Care Med 2021;203:1522–32. https://doi.org/10.1164/RCCM.202102-0509OC.
[22] Daines CL, Tullis E, Costa S, Linnemann RW, Mall MA, McKone EF, et al. VX17-445-105 Study Group. Long-term safety and efficacy of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis and at least one F508del allele: 144-week interim results from a 192-week open-label extension study. Eur Respir J 2023;62(6):2202029. https://doi.org/10.1183/13993003.02029-2022.
[23] Proud D, Duckers J. Weight a minute: exploring the effect on weight and body composition after the initiation of elexacaftor/tezacaftor/ivacaftor in adults with CF. J Cyst Fibros 2023;22:847–50. https://doi.org/10.1016/J.JCF.2023.06.002.
[24] Greer RM, Buntain HM, Lewindon PJ, Wainwright CE, Potter JM, Wong JC, et al. Vitamin A levels in patients with CF are influenced by the inflammatory response. J Cyst Fibros 2004;3:143–9. https://doi.org/10.1016/j.jcf.2004.04.003.
[25] Braun AT, Lai HCJ, Laxova A, Biller JA, Hubertz EK, Zhao Z, et al. Vitamin D status and variable responses to supplements depend in part on genetic factors in adults with cystic fibrosis. J Cyst Fibros 2024;23:754–7. https://doi.org/10.1016/J.JCF.2024.02.005.
[26] Rana M, Wong-See D, Katz T. Fat-soluble vitamin deficiency in children and adolescents with cystic fibrosis. J Clin Pathol 2014. https://doi.org/10.1136/jclinpath-2013-201787.
[27] Marsh R, Dos Santos C, Yule A, Dellschaft NS, Hoad CL, Ng C, et al. Impact of extended elexacaftor/tezacaftor/ivacaftor therapy on the gut microbiome in cystic fibrosis. J Cyst Fibros 2024;23:967–76. https://doi.org/10.1016/J.JCF.2024.05.002.
[28] Suttie JW. Vitamin K and human nutrition. J Am Diet Assoc 1992;92:585–90. https://doi.org/10.1016/S0002-8223(21)00681-7.
[29] Wisniewski BL, Aylward SC, Jordan CO, Kopp BT, Paul GR. Hypervitaminosis A with fulminant secondary intracranial hypertension following personalized medicine-based elexacaftor/tezacaftor/ivacaftor initiation in a preadolescent with cystic fibrosis. J Cyst Fibros 2022;21:e217–20. https://doi.org/10.1016/J.JCF.2022.01.010.
[30] Miller MJ, Foroozan R. Papilledema and hypervitaminosis A after elexacaftor/tezacaftor/ivacaftor for cystic fibrosis. Can J Ophthalmol 2022;57:e6–10. https://doi.org/10.1016/J.JCJO.2021.04.018.
[31] Kam CW, McKinzie CJ, Omecene NE, Peters S, Pettit RS, Poisson MO, et al. Pediatric pulmonology clinical correspondence papilledema in children with cystic fibrosis receiving elexacaftor/tezacaftor/ivacaftor: a multicenter case series. Pediatr Pulmonol 2025;60:27455. https://doi.org/10.1002/ppul.27455.
[32] Planté-Bordeneuve T, Berardis S, Bastin P, Gruson D, Henri L, Gohy S. Vitamin D intoxication in patients with cystic fibrosis: report of a single-center cohort. Sci Rep 2021;11(1):7719. https://doi.org/10.1038/s41598-021-87099-w.
[33] Rouzé H, Viprey M, Allemann S, Dima AL, Caillet P, Denis A, et al. Adherence to long-term therapies in cystic fibrosis: a French cross-sectional study linking prescribing, dispensing, and hospitalization data. Patient Prefer Adherence 2019;13:1497–510. https://doi.org/10.2147/PPA.S211769.
[34] Narayanan S, Mainz JG, Gala S, Tabori H, Grossoehme D. Adherence to therapies in cystic fibrosis: a targeted literature review. Expert Rev Respir Med 2017;11:129–45. https://doi.org/10.1080/17476348.2017.1280399.
[35] Gramegna A, Addy C, Allen L, Bakkeheim E, Brown C, Daniels T, et al. Standards for the care of people with cystic fibrosis (CF); planning for a longer life. J Cyst Fibros 2024;23:375–87. https://doi.org/10.1016/j.jcf.2024.05.007.