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Original Article

# Body mass index and nutritional intake following Elexacaftor/Tezacaftor/Ivacaftor modulator therapy in adults with cystic fibrosis

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## ABSTRACT

**Background:** Elexacaftor/Tezacaftor/Ivacaftor (ETI) modulator therapy is often associated with increased body mass index (BMI) in people with cystic fibrosis (CF). This is thought to reflect improved clinical stability and increased appetite and nutritional intake. We explored the change in BMI and nutritional intake following ETI modulator therapy in adults with CF.

**Methods:** Dietary intake, measured with myfood24®, and BMI were collected from adults with CF at baseline and follow-up as part of an observational study. Changes in BMI and nutritional intake in participants who commenced ETI therapy between time points were assessed. To contextualize findings, we also assessed changes in BMI and nutritional intake between study points in a group on no modulators.

**Results:** In the pre and post ETI therapy group ( $n = 40$ ), BMI significantly increased from 23.0 kg/m<sup>2</sup> (IQR 21.4, 25.3) at baseline to 24.6 kg/m<sup>2</sup> (IQR 23.0, 26.7) at follow-up ( $p < 0.001$ ), with a median of 68 weeks between time points (range 20–94 weeks) and median duration of ETI therapy was 23 weeks (range 7–72 weeks). There was a significant decrease in energy intake from 2551 kcal/day (IQR 2107, 3115) to 2153 kcal/day (IQR 1648, 2606),  $p < 0.001$ . In the no modulator group ( $n = 10$ ), BMI and energy intake did not significantly change between time points ( $p > 0.05$ ), a median of 28 weeks apart (range 20–76 weeks).

**Conclusions:** These findings tentatively suggest that the increase in BMI with ETI therapy may not simply be attributable to an increase in oral intake. Further exploration into the underlying aetiology of weight gain with ETI therapy is needed.

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## 1. Introduction

Cystic fibrosis (CF) is a life-limiting autosomal recessive disease [1]. It is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene which encodes the CFTR protein, an

anion channel expressed throughout the body [1]. Aberrant production and function of CFTR protein in the lungs leads to dehydrated airways, viscous mucus, recurrent infections and inflammation [1]. The CFTR protein is also expressed in the gastrointestinal (GI) tract resulting in exocrine pancreatic insufficiency (PI), inflammation, dysmotility, dysbiosis and GI symptoms [2].

The combination of PI, gut dysfunction, pulmonary infections and inflammation increases nutritional losses and energy requirements, further hampered by anorexia, nausea, vomiting and

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psychosocial factors [3]. Early intervention with high-energy, high-fat diets, and supplementary enteral nutrition (EN) and oral nutritional supplements (ONS) when required, has improved survival [3,4]. These, in conjunction with improved clinical care, have also increased the prevalence of individuals with overweight and obese status [5].

The introduction of the highly effective CFTR modulators Elexacaftor/Tezacaftor/Ivacaftor (ETI) has further accentuated weight increases [6]. Although the precise aetiology is unclear, it is presumed to be a result of improved appetite and nutritional intake and greater clinical stability [6–8]. However, no study has directly investigated this to date. Therefore, our primary aim was to assess body mass index (BMI) and nutritional intake before and after commencing ETI therapy in adults with CF (awCF). As there is little evidence on temporal stability of these parameters prior to CFTR modulators, we assess BMI and nutritional intake in participants where data were collected just prior to ETI therapy becoming more widely available.

## 2. Methods

### 2.1. Study design

Igloo-CF was a prospective observational cohort study conducted across four UK CF Care Centres (Leeds, Royal Papworth, Birmingham and Manchester). PI adults ( $\geq 18$  years old) with two CF causing mutations, able to provide informed consent were eligible. Exclusion criteria comprised lung transplant recipients, prognosis  $< 6$  months, pregnant or had another significant gastrointestinal pathology. This study comprised a subset of participants who had completed ( $\geq 3$  days) a food diary at both time points, and who had either commenced ETI therapy during the study (pre and post ETI group) or had not yet started therapy as they completed the study prior to its wider availability (pre-ETI group). Voluntary informed consent was received from all participants by the clinical research team and a favourable ethical opinion was received from London Bromley Research Ethics Committee (Reference 18/LO/2241).

### 2.2. Data collection

Data were collected between April 2019 and June 2021. The study had two time points, baseline and follow-up, originally scheduled six months apart. The study paused March to December 2020 owing to the Covid-19 pandemic at which time a number of participants had completed the study. The pause resulted in a  $> 6$  month gap between time points for those partway through data collection. During this time ETI therapy became more widely available in the UK. This impactful clinical development was incorporated into the observational study with data being collected  $\geq 3$  months after commencing ETI therapy. Covid necessitated a more pragmatic approach to data collection.

For all participants, clinical and sociodemographic data were collected from medical records and the UK CF registry, a minimum of two weeks post-intravenous (IV) antibiotics. This included presence of a feeding tube, IV antibiotic usage, percentage predicted forced expiratory volume in one second (ppFEV<sub>1</sub>), weight (kg) and height (m) to calculate BMI (kg/m<sup>2</sup>). For weight and ppFEV<sub>1</sub> measurements, when available, the most recent clinical value was recorded. Lung function was measured in accordance with standard clinical procedures. While spirometry machines varied between sites, all ppFEV<sub>1</sub> values were calculated with the Global Lung Function Initiative reference system [9]. Clinic weights were measured on scales accurate to 0.01 kg and height with a stadiometer accurate to 0.1 cm. When this was not possible, due to the pandemic, home measured weight and ppFEV<sub>1</sub> values

were employed, which for weight were cross-checked against recent clinical weight history and UK CF Registry, which revealed no implausible home-recorded weight values. Participant's rate of lung function decline was calculated at baseline from previous best ppFEV<sub>1</sub> values and compared against national average figures [10].

#### 2.2.1. Dietary data

Participants recorded all food, fluid and any ONS or EN for four days, on the website myfood24®. An online approach was chosen to mitigate biases arising from an interview approach [11]. Two participants completed paper food diaries which were entered into the website by the research dietitian. Participants were encouraged to complete their food diary shortly after their clinic visit (when weight was measured). If there was a delay, participants were advised to only input their dietary data if there was no significant change in intake since then. Three weekdays and one weekend day was selected to account for variations in intake and as four days correlates with a seven day record, but has a higher completion rate [12,13]. The website, myfood24®, is a validated platform to capture dietary intake, containing branded and unbranded food products, photos of portion sizes and a UK-specific nutritional database [14,15].

#### 2.3. Data analysis

Nutrient intake outputs were generated from myfood24®. The research dietitian was unblinded, but was not their clinical dietitian and results were not fed back to participants or the clinical team. In line with previous Diet and Nutrition Survey methods, only those with completed food diaries ( $\geq 3$  days) at both time points were included [16]. Manual data cleaning was conducted [16]. Daily average nutritional intake at each time point was calculated for each participant. Percentage contribution of macronutrients to total energy intake were generated employing Atwater factors [17]. Both raw and energy-adjusted fibre values (g/1000 kcal) are presented using the Association of Official Analytical Chemists fibre values. Data on ONS and EN consumption were extracted from food diaries. The number of food diaries recorded post-national lockdown (commencing 26/03/2020) were counted. As data were non-normally distributed, median and interquartile range [IQR] are presented.

The primary outcomes were change in BMI, energy and energy-adjusted macronutrient intake in the pre and post ETI therapy group, tested with the Wilcoxon-signed rank test. In the pre and post ETI group, secondary outcomes comprised, firstly, exploratory within group analysis of changes in these same parameters by starting CFTR modulator status (none or double therapy, comprising either Ivacaftor/Tezacaftor or Lumacaftor/Ivacaftor), tested with the Wilcoxon-signed rank test. Secondly, differences in percentage change in BMI and energy intake between time points between the sexes were investigated with the Wilcoxon-rank sum test. Thirdly, the association between duration of ETI therapy and percentage change of both BMI and energy intake was investigated with Spearman's Rank correlation. Descriptive statistics were used to describe contribution of ONS and EN to energy intake.

In the pre-ETI group, changes in BMI, energy and energy-adjusted macronutrient intake between time points were investigated using the Wilcoxon-signed rank test. For both groups, the Wilcoxon-signed rank test was employed to assess changes in ppFEV<sub>1</sub> and days of IV antibiotics, to provide contextual data. To control for multiple testing, the Benjamini-Hochberg procedure was applied separately in the pre and post ETI group for the primary outcome and according to starting CFTR modulator status and for the pre-ETI group [18]. This was selected over more stringent approaches as the study was exploratory [18].

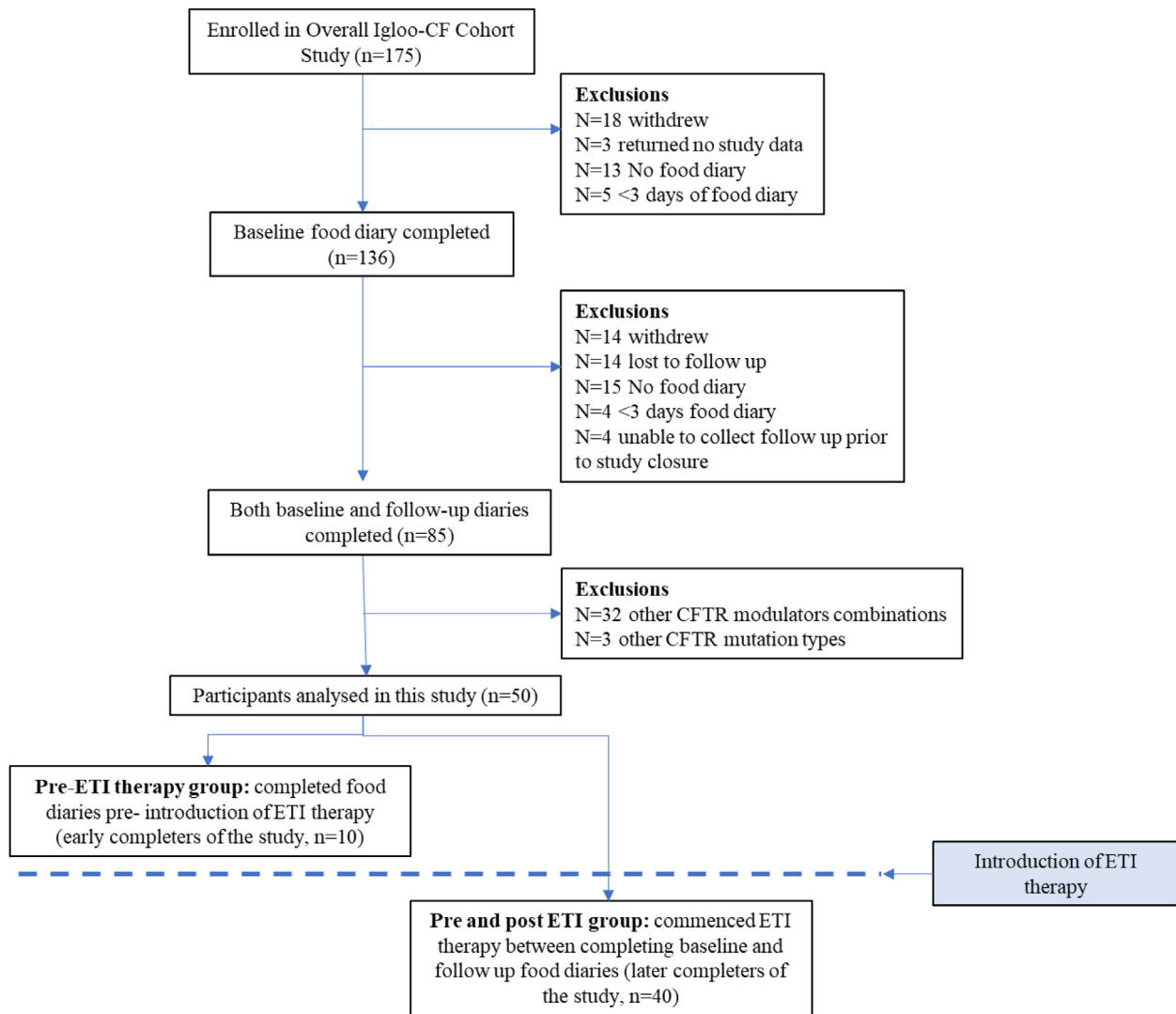


Fig. 1. Recruitment and data collection flow chart for this sub-study from the overall Igloo-CF cohort study.

Differences in baseline clinical and demographic characteristics between the two groups were tested employing Fisher's exact test. To explore the potential influence of non-response bias, differences in BMI and ppFEV<sub>1</sub> between those included in analysis and those with incomplete food diaries but otherwise eligible were tested with the Wilcoxon rank-sum test for both groups. A p-value <0.05 was regarded as statistically significant, unless stated otherwise. Data were analysed in Stata® 17 MP [19].

### 3. Results

#### 3.1. Demographic and clinical characteristics

Of the 175 participants enrolled in the overarching study, 40 were included in the pre and post ETI group and 10 in the pre-ETI group. The reasons for exclusion from analysis are detailed in Fig. 1. There was no statistically significant difference in BMI and ppFEV<sub>1</sub> at baseline or follow-up in those with complete and incomplete food records in either group, Table S1. Clinical and demographic characteristics are presented in Table 1; there was no statistically significant difference in these key characteristics between the two groups, including genotype (Table S2). In the pre-ETI group, baseline and follow-up were a median of 28 weeks (range 20 to 76 weeks) apart. For the pre- and post ETI group,

follow-up periods were more variable owing to covid-19, being a median of 68 weeks apart (range 20 – 94 weeks). Participants were taking ETI therapy for a median of 23 weeks (range 7 to 72 weeks) prior to follow-up. In this group, 15 (38%) were on double therapy, of which 11 (73%) were prescribed it early under the compassionate use programme, and remaining 25 (63%) participants were on no CFTR modulator at baseline.

#### 3.2. Nutrition: pre and post ETI therapy

In the pre and post ETI group, median BMI increased significantly between time points, from 23.03 kg/m<sup>2</sup> (IQR 21.43, 25.26) to 24.58 kg/m<sup>2</sup> (IQR 22.96, 26.74),  $z = -4.059$ ,  $P < 0.001$ , Table 2, Fig. 2. In contrast, energy intake significantly decreased, from 2551 kcal/day (IQR 2107, 3315) at baseline to 2153 Kcal/day (IQR 1648, 2606) at follow-up ( $z = 4.436$ ,  $p < 0.001$ ), Table 2, Fig. 2. The contribution of macronutrients to total energy intake did not significantly change between time points ( $p > 0.05$ ), Table 2. At follow-up, median fibre intake was 15 g (IQR 11, 18), Table 2.

Exploratory subgroup analysis according to baseline CFTR modulator status was undertaken. Descriptively, at baseline, those on double therapy had a lower median BMI and higher energy intake than those on no modulator at baseline (Table S3). At follow-up, BMI increased and energy intake decreased in both groups; how-

**Table 1a**

Clinical and demographic characteristics of pancreatic insufficient adult participants with cystic fibrosis from the Igloo-CF cohort study who completed food records and commenced elxacaftor/tezacaftor/ivacaftor (ETI) modulator therapy between study time points (pre and post ETI group,  $n = 40$ ).

Pre and post ETI group ( $N = 40$ )	
CF Care centre	
Leeds	21 (60%)
Royal Papworth	11 (28%)
Manchester	2 (5%)
Birmingham	3 (8%)
Sex	
Female	19 (48%)
Male	21 (53%)
Age Category	
18–28 years old	9 (23%)
29–39 years old	18 (45%)
40–50 years old	11 (28%)
51+ years	2 (5%)
CFRD	
Yes	15 (38%)
No	25 (63%)
CFRLD <sup>b</sup>	12 (30%)
[of whom liver cirrhosis]	[3, 25%]
CFTR genotype	
F508del/F508del	31 (78%)
F508del/other	9 (23%)
Chronic <i>Pseudomonas aeruginosa</i> growth	
Yes	28 (70%)
No	12 (30%)
Chronic Burkholderia Cepacia Complex growth	
Yes	4 (10%)
No	36 (90%)
Rate of Lung Function Decline <sup>a</sup>	
Slow	21 (53%)
Fast	19 (48%)
Enteral Feeding Tube in situ	
Yes	4 (10%)
Enteral feeding recording in food diary	
Yes	2 (5%)
Oral nutritional supplements recorded in food diary	
Yes	9 (22%)
Corticosteroid use <sup>c</sup>	
Yes	4 (10%)
No	36 (90%)
Number of Food diaries completed after national lockdown	
Baseline	0 (0%)
Follow-up	39 (98%)
Weight measured in clinic n (%)	
Baseline	40 (100%)
Follow-up	26 (65%)
Median number of days between weight measurement and commencing food diary (range)	
Baseline	7 (0 – 81)
Follow-up	8 (–60 – 70)

**Table 1b**

Clinical and demographic characteristics of pancreatic insufficient adult participants with cystic fibrosis from the Igloo-CF cohort study who completed food records who were not on a CFTR modulator at either time point (pre-ETI Group,  $n = 10$ ).

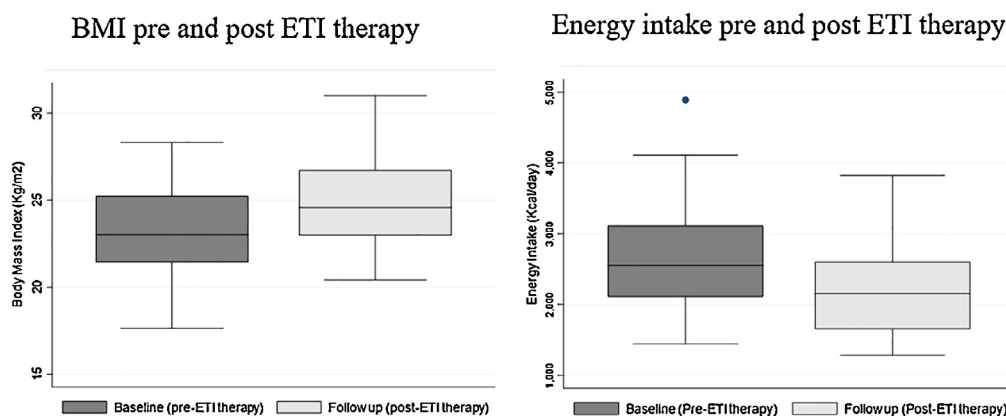
Pre-ETI therapy group ( $n = 10$ )	
CF Care centre	
Leeds	9 (90%)
Royal Papworth	1 (10%)
Manchester	0 (0%)
Birmingham	0 (0%)
Sex	
Female	5 (50%)
Male	5 (50%)
Age Category	
18–28 years old	1 (10%)
29–39 years old	3 (30%)
40–50 years old	3 (30%)
51+ years	3 (30%)

(continued on next page)

**Table 1b** (continued)

Pre-ETI therapy group (n = 10)	
CFRD	
Yes	5 (50%)
No	5 (50%)
CFRLD <sup>b</sup>	2 (20%) <sup>b</sup>
[of whom liver cirrhosis]	[0, 0%]
CFTR genotype	
F508del/F508del	5 (50%)
F508del/other	5 (50%)
Chronic <i>Pseudomonas aeruginosa</i> growth	
Yes	6 (60%)
No	4 (40%)
Chronic <i>Burkholderia Cepacia</i> Complex growth	
Yes	2 (20%)
No	8 (80%)
Rate of Lung Function Decline <sup>a</sup>	
Slow	2 (20%)
Fast	8 (80%)
Enteral Feeding Tube in situ	
Yes	0 (0%)
No	10 (100%)
Enteral feeding recording in food diary	0 (0%)
Oral nutritional supplements recorded in food diary	3 (30%)
Corticosteroid use	
Yes	0 (0%)
No	10 (100%)
Number of Food diaries completed after national lockdown	
Baseline	0 (0%)
Follow-up	1 (10%)
Weight measured in clinic n (%)	
Baseline	10 (100%)
Follow-up	10 (100%)
Median number of days between weight measurement and commencing food diary (range)	
Baseline	1 (0 – 25)
Follow-up	11 (2 – 59)

a) Calculated based on published values by age and sex categories for pancreatic insufficient adults with cystic fibrosis [10]; b) one participant excluded from this figure as had a liver transplant; c) all four participants taking low dose corticosteroids (5–10 mg/day) at baseline and one participant stopped this medication by follow-up; cystic fibrosis (CF); cystic fibrosis related diabetes (CFRD); cystic fibrosis related liver disease (CFRLD); cystic fibrosis transmembrane conductance regulator (CFTR); Elexacaftor/Tezacaftor/Ivacaftor (ETI).



**Fig. 2.** Boxplot of energy intake and body mass index at baseline (pre-ETI therapy) and at follow-up (post commencing ETI therapy) in 40 adults with cystic fibrosis part of the Igloo-CF observation cohort study.

Whiskers on boxplot denote minimum and maximum values (excluding outliers), dot represents an outlier, the top and bottom of the box indicated the upper and lower quartile of data respectively and the line within the box represents the median value. Baseline and follow-up data collected as part of an observational cohort study, a median of 65 weeks apart (Range 20–94 weeks), at follow-up participants had been taking ETI therapy for a median of 23 weeks (Range 7–72 weeks). BMI - body mass index; ETI - Elexacaftor/Tezacaftor/Ivacaftor.

ever, after correcting for multiple testing, it only reached statistical significance for those on no modulator at baseline, Table S3.

The number of weeks on ETI therapy did not significantly correlate with percentage change of either BMI (Spearman's  $\rho = -0.0446$ ,  $p = 0.7848$ ) or energy intake (Spearman's  $\rho = 0.0691$ ,  $p = 0.6716$ ) between time points. Nutritional intake and BMI pre- and post-ETI therapy were also described by sex, Table S4. There

was no statistically significant difference in percentage change for either energy intake or BMI between the sexes ( $p > 0.05$ , Table S4).

Four (10%) participants in this group had EN tubes at baseline. Of whom, two (5%) recorded supplementary EN in their food diary and two did not, with one being non-adherent and the other intermittently feeding. For the participants who recorded EN, it contributed 1200 kcal/day and 40–49% of total energy intake. There

**Table 2**

Lung function, intravenous antibiotic use, body mass index, energy and macronutrient intake at two time points in pancreatic insufficient adults with cystic fibrosis part of the Igloo-CF cohort study who commenced ETI therapy between study time points (pre and post ETI group,  $n = 40$ ).

	N = 40		Statistical Significance * $p < 0.05$
	Baseline: Pre-ETI therapy	Follow-up: Post-ETI therapy)	
Annual days of IV antibiotics <sup>a</sup>	14 (0, 47)	8 (0, 27)	0.0875
Annual Courses of IV antibiotics <sup>a</sup>	1 (0, 3)	1 (0, 2)	-
ppFEV <sub>1</sub>	46.8 (34.8, 65.8)	56.5 (43.5, 72.6) <sup>c</sup>	<0.0001*
BMI (kg/m <sup>2</sup> )	23.03 (21.43, 25.26)	24.58 (22.96, 26.74)	<0.0001*
%Change BMI		6 (0, 11)	
BMI category			
Underweight (<18.5 kg/m <sup>2</sup> )	3 (8%)	0 (0%)	
Healthy weight (18.5–24.9 kg/m <sup>2</sup> )	26 (65%)	24 (60%)	
Overweight (25–29.9 kg/m <sup>2</sup> )	11 (28%)	15 (38%)	
Obese (≥30 kg/m <sup>2</sup> )	0 (0%)	1 (3%)	
Energy (Kcal)	2551 (2107, 3115)	2153 (1648, 2606)	<0.0001*
%Change Energy		-13 (-25, -5)	
Protein (g)	92 (74, 112)	80 (66, 90)	-
Protein (% Kcal) <sup>b</sup>	15 (13, 17)	15 (13, 17)	0.2214
Fat (g)	103 (78, 127)	80 (65, 111)	-
Fat (% Kcal) <sup>b</sup>	37 (32, 39)	36 (33, 40)	0.9206
Sat. fat (g)	36 (30, 47)	34 (26, 40)	-
Sat. fat (% Kcal) <sup>**</sup>	13 (11, 16)	14 (13, 16)	0.1831
Carbohydrate (g)	292 (237, 359)	233 (197, 298)	-
Carbohydrate (% Kcal) <sup>b</sup>	49 (42, 55)	47 (44, 51)	0.2766
Total sugars (g)	127 (102, 165)	99 (82, 123)	-
Total sugars (% Kcal) <sup>b</sup>	22 (18, 24)	19 (17, 23)	0.2649
Alcohol (g)	0 (0, 5)	0 (0, 5)	-
Alcohol (%Kcal)	0 (0, 1)	0 (0, 2)	0.9026
Fibre (g)	18 (14, 22)	15 (11, 18)	-
Fibre (g/1000 kcal)	7 (5, 9)	7 (6, 9)	0.3074

\*Multiple testing was addressed within each group using Benjamini-Hochberg method to control false discovery rate at the 0.05 level; Data is expressed as median and inter quartile ranges. a) Baseline values refer to 12 months preceding data collection, follow-up values refer to the number of courses and days of IV antibiotics between baseline and follow-up divided by length of time between baseline and follow-up and multiplied by 12 to provide a standardised annual value; b) Macronutrient values converted from percentage of total energy intake into g using Atwater factor of 4 kcal/g for carbohydrates, 4 kcal/g for protein, 9 kcal/g for fat and 7 kcal/g for alcohol [17]; c).  $n = 2$  ppFEV<sub>1</sub> values excluded as measured prior to ETI therapy (with limited spirometry results for them owing the pandemic); CFTR – cystic fibrosis transmembrane conductance regulator; BMI- body mass index; ETI - Elexacaftor/Tezacaftor/Ivacaftor therapy; IV – intravenous; ppFEV<sub>1</sub> - percentage predicted forced expiratory volume in 1 second; Sat. – saturated.

were nine (22%) participants reporting ONS at baseline (one of whom was also receiving EN), which contributed a median of 400 kcal/day (IQR 281, 1017) and 14% (IQR 10, 30%) of their total energy intake. At follow-up, one (3%) participant had a feeding tube, which contributed 400 kcal/day and 15% of their total energy intake. There were seven (18%) participants reported consuming ONS at follow-up, which contributed a median of 494 kcal/day (IQR 165, 600) and 18% (IQR 10, 22) of their total energy intake.

### 3.3. Nutrition: Pre-ETI group

In the pre ETI group, median BMI was 24.9 kg/m<sup>2</sup> (IQR 21.6, 27.6) and 24.6 kg/m<sup>2</sup> (IQR 21.9, 26.9) at baseline and follow-up respectively and energy intake approximately 2400 Kcal/day at both time points. These were not statistically significant different nor was the percentage contribution of macronutrients to total energy intake between time points (Table S5).

## 4. Discussion

While it is known that BMI frequently increases with ETI therapy, it has not previously been investigated whether dietary intake is shifting. We found that BMI increased and energy intake decreased after commencing ETI therapy. Contrastingly, BMI and energy intake were stable in participants whose data were collected just prior to commencing ETI therapy. This provides the first tentative evidence that the increase in BMI with ETI therapy may not be simply the result of increased oral intake but that other mechanisms may be contributing.

Correction of CFTR function results in partial correction of complex cellular perturbations, which may modify metabolism and energy balance. Previous research suggests that ETI therapy can reduce pulmonary exacerbations, gut and systemic inflammation, potentially downregulating energy expenditure [20–22]. Drugs with a higher potency for CFTR correction appear to be associated with a greater weight gain [23]. It could be postulated that weight gain is a positive marker of clinical response to treatment.

We found a median 6% (IQR 0, 11) increase in BMI after ETI therapy, comparable to other studies [6]. To our knowledge, we are the first to investigate nutritional changes. At follow-up, while energy intake decreased, the contribution of macronutrients to total energy intake was relatively similar to baseline. This suggests an overall reduction in intake rather than one macronutrient being greatly altered. At follow-up, fibre intake was half that recommended for the general population of 30 g/day [24]. As life expectancy increases, the lack of dietary fibre may potentially accentuate gut dysbiosis, cardiovascular disease and colorectal cancer risk [24].

Exploratory subgroup analysis of the pre and post ETI group demonstrated that those on double therapy at baseline appeared to have a higher median energy intake but lower BMI than those on no CFTR modulator, probably because they were more clinically unwell. Despite this, BMI increased and energy intake decreased in both subgroups following ETI therapy. However, it did not reach statistical significance after correcting for multiple testing for those on double therapy at baseline, likely owing to the sample size, as results appeared clinically significant. These findings fit with the

wider literature, that clinical improvements have been observed in both these subgroups [25].

Although starting BMI and energy intake appeared to vary between the sexes, we found that both had a similar degree of change after commencing ETI therapy. The number of participants receiving EN were relatively low. Despite no participant being underweight at follow-up, just under a fifth of participants were still receiving ONS. As nutritional status continues to improve, they may be required less. The number of participants with an overweight or obese status increased from 28% at baseline to 41% at follow-up. Nutritional guidelines should now encompass the broader spectrum of nutritional status and greater opportunity to modulate diet to reduce longer-term complications of CF in an ageing population. As we transition, a supportive, non-judgmental approach is imperative because failing to acknowledge the complex relationship between nutritional intake and weight gain could lead individuals to feel misunderstood and blamed [26]. Miss-assuming the causes of weight gain, as simply eating too much, could be detrimental to the therapeutic relationship [27]. Particularly given that post-modulator dietary advice may entail a significant departure from previous clinical advice [3]. Given the growing spectrum of nutritional status in awCF, a person-centred approach to nutrition is essential.

This study had several strengths and limitations. The Covid-19-related study pause led to uneven time frames between participants but also coincided with the wider introduction of ETI in the UK, offering a unique opportunity to capture changes in nutritional intake. We found no significant change in BMI and energy intake in the pre-ETI group. This may suggest that changes detected in the pre and post ETI group are not simply due to factors such as fatigue in recording intake. However, lockdown may have induced nutritional changes. On a population level, a UK-based study found that BMI initially significantly increased and then decreased so that six months later it was no different to pre-pandemic [28]. Evidence in awCF is more limited and studies conflicting. One study in Berlin found that BMI remained stable [29], while an Australian study reported an increased annual trend in BMI, from 0.03 kg/m<sup>2</sup> to 0.30 kg/m<sup>2</sup> pre- and post-pandemic [30]. It appears our findings align more closely with previous literature on ETI therapy than the pandemic.

Reassuringly, we found no statistically significant difference in absolute values for ppFEV<sub>1</sub> or BMI at baseline and follow-up respectively in those with complete and incomplete food diaries. The median ppFEV<sub>1</sub> in our study participants was lower than the UK national average for PI awCF [10]. Our figures pertained to ppFEV<sub>1</sub> at the time of data collection rather than an individual's best ppFEV<sub>1</sub>, and therefore are not directly comparable to UK CF Registry data. Secondly, participants were taking ETI therapy for varying periods and our study was not designed to directly measure clinical response to modulator therapy. Additionally, it could be speculated that this represents a degree of prescribing bias, as individuals with more severe lung disease had earlier access to ETI therapy. We had uneven recruitment between sites, reducing generalisability. There are UK-wide CF nutritional guidelines, standardising nutritional advice between centres, but this may vary between countries as will nutritional intake [3].

Post-covid, a mix of home and clinic weight and ppFEV<sub>1</sub> measures were employed, potentially increasing data variability. A gap between weight measurement and completing the food diary along with participants' perception of their recent weight, could have influenced reported dietary intake. Dietary data were collected at two time points. Therefore, fluctuations between time points were unrecorded and discrete food diaries may not represent usual intake. All dietary assessment methods ensue limitations, which we sought to mitigate with a validated online platform [11,14]. Future studies would benefit from a large sample size, repeated mea-

asures of dietary intake and exploration of differences between the sexes, adjusting for BMI, length of time on ETI therapy and degree of lung disease. Physical activity, diet quality and cardiovascular health should also be measured.

In conclusion, we found that BMI increased and energy intake decreased after commencing ETI therapy. It could be speculated that the weight gain following ETI therapy may not be simply attributable to increased energy intake but may reflect a host of other factors, such as altered energy requirements and metabolic perturbations. This needs further investigation.

### Declaration of Competing Interest

JB: previous paid work for Vertex

DP: speaker/board honoraria from Vertex

HW: Received previous funding from Gilead, which was not directly related to this research project and from Health Education England for simulated placement delivery funding.

LRC, HHJG, LS, LG, LK, VD, MN, AJ, JLW, DS and RAF declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

### CRediT authorship contribution statement

**L.R. Caley:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Visualization, Project administration, Writing – original draft. **H.H. Jarosz-Griffiths:** Writing – review & editing. **L. Smith:** Writing – review & editing. **L. Gale:** Investigation, Writing – review & editing. **J. Barrett:** Investigation, Writing – review & editing. **L. Kinsey:** Investigation, Writing – review & editing. **V. Davey:** Investigation, Writing – review & editing. **M. Nash:** Investigation, Writing – review & editing. **A.M. Jones:** Resources, Writing – review & editing. **J.L. Whitehouse:** Resources, Writing – review & editing. **D. Shimmin:** Writing – review & editing. **R.A. Floto:** Conceptualization, Methodology, Resources, Funding acquisition, Writing – review & editing. **H. White:** Conceptualization, Methodology, Funding acquisition, Supervision, Writing – review & editing. **D.G. Peckham:** Conceptualization, Methodology, Resources, Funding acquisition, Supervision, Project administration, Writing – original draft.

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### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2023.06.010.

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