



## Original article

## The relationship between energy intake and body-growth in children with cystic fibrosis

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## SUMMARY

**Background & aims:** Body-growth, expressed as weight- and height gain, is a strong predictor of morbidity and mortality in patients with cystic fibrosis (CF). Whether current historically based recommendations on a high-energy diet are sufficient for optimal growth is questionable. We therefore assessed the longitudinal relation between body-growth and routine energy intake in paediatric CF patients.

**Methods:** Included were patients with CF, aged 2–10 years of whom we obtained 969 measurements of weight and height along with dietary records, and 786 coefficient of fat absorption measurements (CFA). We described body-growth, energy intake, macronutrient intake and the long-term effect of energy intake and coefficient of fat absorption on body-growth during the 8-year follow-up period.

**Results:** Enrolled were 191 children with CF who had a compromised growth when compared to healthy children. The dietary intake was  $\geq 110\%$  estimated average requirement (EAR) in 47% of the measurements (457/969) and did not (fully) achieve the recommended high-energy level (110–200% EAR). Further, the intake expressed as EAR decreased with increasing age. Cross-sectionally, boys and girls with higher caloric intakes had higher weight-for-age (WFA). The caloric intake explained 18 and 6% of the variation. Further, boys with higher caloric intakes had also higher height-for-age-adjusted-for-target-height (HFA/TH) or BMI. The caloric intake explained 6 or 7% of the variation. Longitudinally, caloric intake was associated with both WFA in boys and girls, and with BMI in boys. Each 100 calories increased intake would result in a 0.01 (girls)–0.02 increase in z-score WFA and 0.03 increase in z-score BMI. We found no significant association between CFA and WFA, HFA/TH or BMI. The contribution of protein, fat and carbohydrates was not associated with WFA, nor with HFA/TH or BMI.

**Conclusion:** Even at this relatively early age, a compromised growth in children with CF was found when compared to healthy children. The energy intake was below 110% EAR in 47% of the measurements, and appeared to be insufficient to prevent suboptimal body-growth over the 8-years of follow-up.

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**Abbreviations:** CF, cystic fibrosis; WFA, weight-for-age; TH, target height; HFA/TH, height-for-age-adjusted-for-target-height; CFA, coefficient of fat absorption; EAR, estimated average requirement; FEV<sub>1</sub>% pred, forced expiratory volume in one second expressed as % predicted.

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## 1. Introduction

Cystic fibrosis (CF) is a genetic disorder characterized by progressive pulmonary dysfunctioning. Most patients have pancreatic insufficiency resulting in nutrient malabsorption. In patients with CF, lung disease and body-growth are tightly intertwined [1], and both are strong predictors of morbidity and mortality [2,3]. Therefore, monitoring body-growth has become a key objective in CF-care. For this purpose, international CF-guidelines included recommendations on a high-energy diet, with recommended intakes between 110% and 200% of the gender- and age-specific

estimated average requirement (EAR) [4,5]. These recommendations were derived from the outcomes of the large Boston – Toronto comparative study [2] from the eighties. As both the medical and the nutritional care for patients with CF have dramatically improved over the last decades [6,7], it is questionable whether these historically based recommendations are still applicable. To date, very few details of the actual relation between routine dietary intake and the nutritional status are known. Previous studies were rather small [8], encompassed small age ranges [8,9], were limited by a cross-sectional design [8] and/or were mainly conducted in the context of interventions [10]. We set out to study the long-term effect of energy intake on body-growth in paediatric CF patients, aged 2–10 years.

## 2. Methods

### 2.1. Study population

This retrospective study included Dutch children (born between 1988 and 2012) with proven CF and proven pancreatic insufficiency who received medical care at the CF-centre of the University Medical Centre Utrecht. The diagnose CF was confirmed by a positive sweat test and/or the presence of 2 CF-mutations, as well as clinical signs of CF and/or a positive family history. Each patient attending the clinic routinely received advices on optimising their dietary intake. This study included children aged 2–10 years, who had at least two completed 3-day dietary food records along with a weight and height measurements, and who were receiving pancreatic enzyme replacement therapy. Excluded were children on systemic steroids because of the side effects such as an increased appetite, weight gain and height-growth [11,12].

Yearly, weight and height were measured during routine clinical care visit, and dietary data were collected through 3-day dietary food records in clinical stable patients. Thus, the study's database contained data regarding the clinical parameters, dietary intake and demographics of all children who received medical care for CF at the University Medical Centre Utrecht. All parents or guardians of the children provided written informed consent for the storage and analysis of the data. The study was performed in accordance with the guidelines of the medical ethics board of the University Medical Centre Utrecht.

### 2.2. Weight and height assessment

Weight was measured in patients in their underwear, to the nearest 0.1 kg using a digital weight balance, and height was measured to the nearest 0.5 cm using a stadiometer (Holtain, Crymich, UK). Weight and height were compared to reference values by using *z*-scores, as calculated by specialized software of the Dutch Growth Foundation (Growth Analyser 4 RCT, 2010, Dutch Growth Foundation). Further, as height is a heritable trait depending on the height of the biological parents, it is important to take this genetic potential of the child into account when monitoring height-growth. Therefore, height measurements were adjusted for genetic potential by calculating *z*-scores height-for-age-adjusted-for-target height (HFA/TH) [13]. For this purpose, the target height (TH) was calculated using the measured heights of the patient's biological parents. Target height was calculated by using the following formulas: target height for boys (cm) = 44.5 + 0.376 × father height (cm) + 0.4111 × mother height (cm), target height for girls (cm) = 47.1 + 0.334 × father height (cm) + 0.364 × mother height (cm). *z*-Score target height was calculated using the formulas: *z*-score TH boys = (TH – 183.8)/7.1. *z*-Score TH girls = (TH – 170.7)/6.3. HFA/TH was calculated according the Dutch Consensus Guideline by subtracting *z*-score for

TH from HFA [14]. These formulas for calculating the TH and the HFA/TH are based on a nationwide Dutch growth study [15], and adjusted for genetic potential in children with parents with great differences in parental height [16].

### 2.3. Dietary intake assessment

Yearly, patients were asked to complete a three-day record of their food and beverage intake, consisting of two consecutive weekdays and one weekend-day whenever possible. All food and beverages consumed were recorded in portion sizes or weights. Where weights were not specified, portion size weights were obtained from reference data [17]. The dietary intake was calculated for each assessment according to a standardized approach using the Dutch food composition table (2010) established by the Dutch Nutrition Centre [18].

The nutritional composition, expressed as mean daily caloric intake along with the contribution of protein, fat and carbohydrate was calculated for each assessment.

### 2.4. Clinical measurements

A fat balance study was performed to measure the fat excretion in faeces and to calculate the coefficient of fat absorption (CFA). A 3-day dietary intake assessment was obtained to calculate the mean dietary fat intake of these three days. Further a home-based 72-h stool collection was obtained. The stool collection started on day 2 of the dietary intake assessment and ending 1 day after dietary recording (day 4). The Van de Kamer method for quantitative faecal fat determination was applied to determine the mean faecal fat content of this 3-day collection. The CFA was then calculated from the mean dietary fat intake and the mean daily faecal fat output, and expressed as a percentage.

Pulmonary function was assessed as FEV<sub>1</sub> and expressed as the percentage of the predicted value for a given height, age and sex (FEV<sub>1</sub>% pred.) [19]. For each child, the highest FEV<sub>1</sub>% pred. measured in the preceding calendar year was used (beginning at 6 years of age).

The patients were subdivided into 5 classes based on their CF-transmembrane-conductance-regulator-mutation. Patients who were either homozygous or compound heterozygous for a class I, class II or class III mutation were then classified as severe, and patients who carried at least 1 class IV or class V mutation were classified as mild [20]. Children with missing data regarding their mutation were classified as unknown.

### 2.5. Statistics

All analyses were performed separately by gender. Descriptive statistics of weight, height, WFA, HFA/TH, BMI, energy, protein, fat and carbohydrate intake, CFA and FEV<sub>1</sub>% pred. at baseline were calculated. Subsequently, descriptive statistics of WFA, HFA/TH, BMI and caloric intake throughout the age years were examined. The caloric intake is both expressed as estimated average requirement (EAR) and as absolute caloric intake as the EAR is set for age cohorts comprising four years, meaning that children of different ages share the same caloric recommendation.

The variables were tested for normality and skewness, and the cross-sectional relations between energy intake and WFA, HFA/TH, and BMI at the initiation of the study were measured using linear regression analysis.

In addition, linear mixed-model regression was used to evaluate the effect of caloric intake on longitudinal changes in WFA, HFA/TH and BMI. This model allows inclusion of variable numbers of measurements per child and irregularly timed and missing

observations. The following covariates were included as fixed effects: age, caloric intake and CFA. A random intercept and random slope for the age of child was included to account for correlations between measurements within children. The mixed-model regression was also applied to evaluate the effect of the composition of protein, fat and carbohydrate intake expressed as En% on longitudinal changes in WFA, HFA/TH and BMI. Statistical analyses were performed using the Statistical Package for the Social Sciences Computer Software (SPSS Inc., version 20, IBM, Chicago, IL). All of the values were considered significant at  $p < 0.05$ .

### 3. Results

#### 3.1. Clinical characteristics

A total of 191 children with proven CF (98% Caucasian, 98 boys) were eligible for inclusion. The mean time between the age at

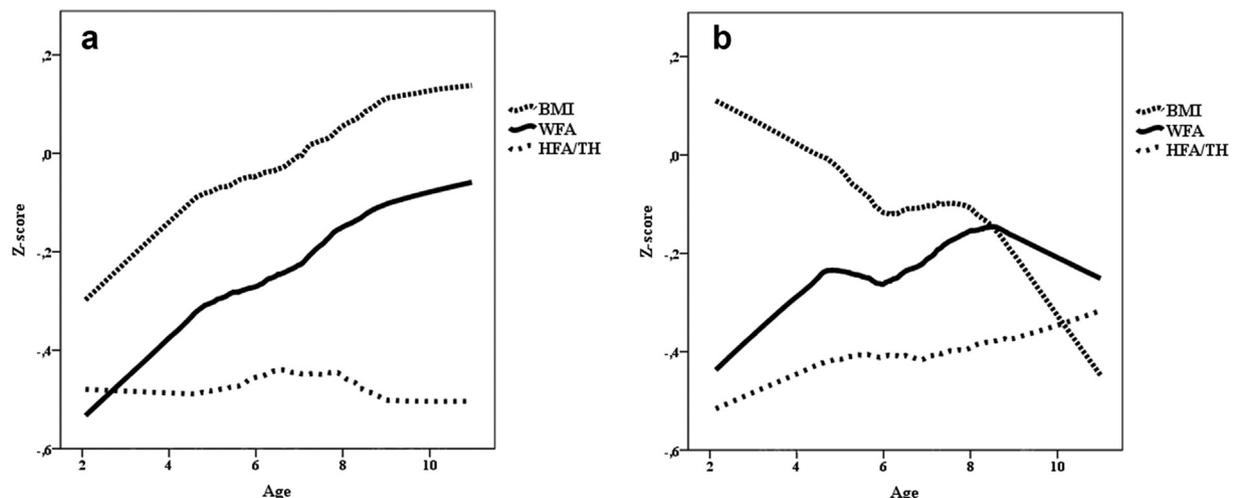
diagnose and the initiation time of the study was  $3.9 \pm 2.1$  years and, after enrolment, the mean follow-up period was  $4.7 \pm 2.3$  years. On average,  $5 \pm 2$  number of measurements of weight, height and dietary intake of, were eligible for inclusion. See Table 1 for baseline characteristics. In these patients, we obtained a total of 969 measurements of weight and height along with dietary records and 786 CFA measurements. At the initiation of the study, we found z-scores WFA, HFA/TH or BMI below zero in 125/191 (65%), 131/188 (70%) and 106/191 (55%) children, and z-scores below  $-1$  in 43/191 (23%), 55/188 (29%) and 31/191 (16%) children respectively. Overall, z-scores of the study sample were significantly lower than that of healthy counterpart throughout the age years, with the exception of z-score BMI for boys (Fig. 1a,b).

At baseline, 71 children (37%) had already started with oral supplements ( $n = 56$ , 29%) or enteral tube feeding ( $n = 15$ , 8%), which accounted for  $20 \pm 17$ , and  $36 \pm 30\%$  of total energy intake. The EAR was  $\geq 110$  EAR% in 457/969 (47%) of the measurements (213/497 measurements in boys) (Fig. 2a). The energy intake at

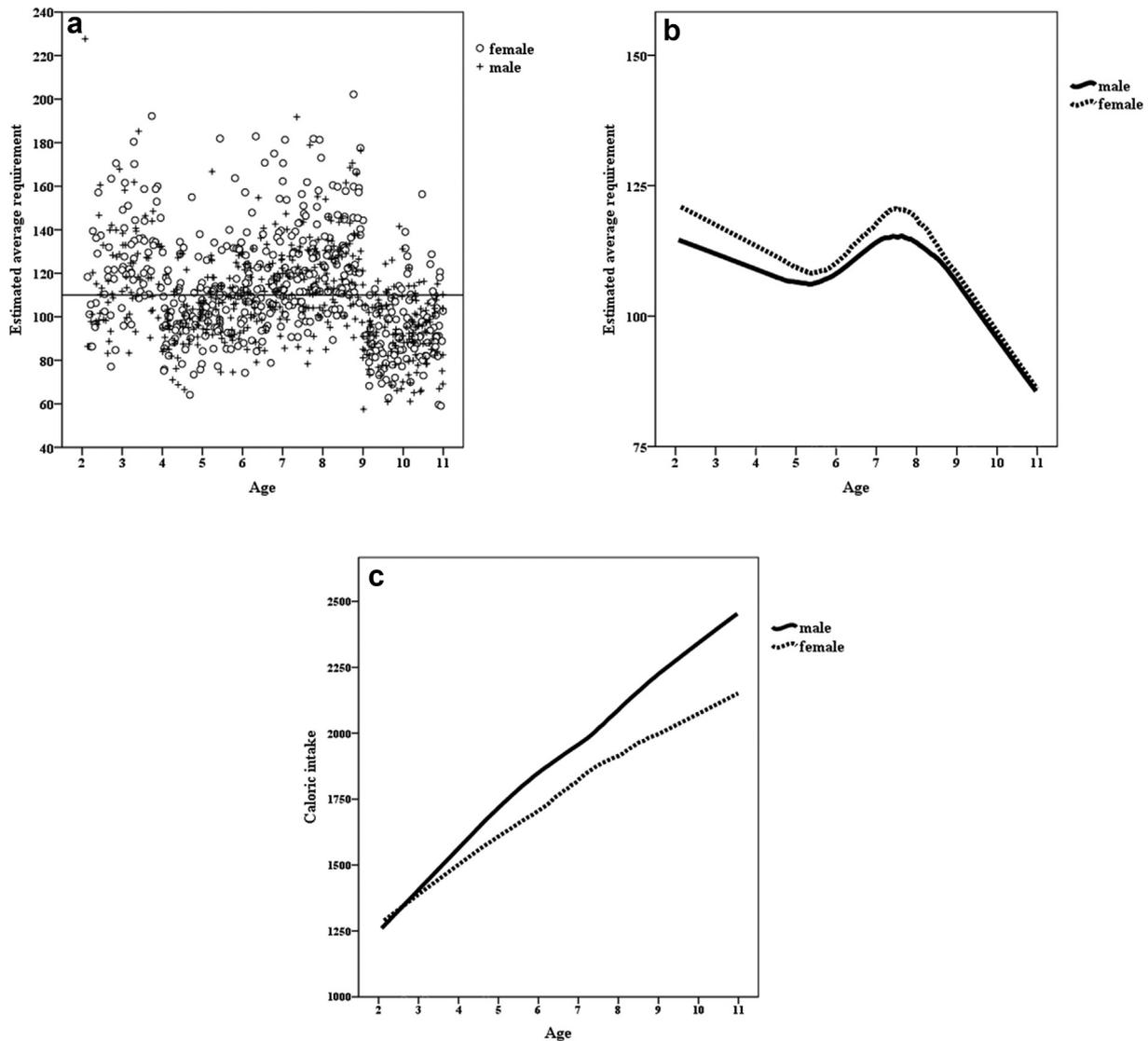
**Table 1**  
Baseline characteristics of 191 patients with cystic fibrosis at the year of inclusion.

	Median (25th–75th percentile)		
	Study sample	Boys ( $n = 98$ )	Girls ( $n = 93$ )
Age (y)	3.9 (2.8–6.3)	4.1 (2.7–6.7)	3.8 (2.8–6.1)
Age at diagnose	0.3 (0.1–1.0) ( $n = 189$ )	0.3 (0.1–0.7) ( $n = 97$ )	0.3 (0.1–1.1) ( $n = 92$ )
Weight (kg)	16.8 (13.8–21.0)	16.8 (13.7–21.5)	16.8 (14.0–20.6)
Height (cm)	103 (93–117)	103 (93–124)	103 (94–114)
WFA	−0.33 (−0.94 to 0.20)	−0.36 (−0.97 to 0.23)	−0.29 (−0.90 to 0.19)
HFA/TH	−0.45 (−1.06 to 0.23) ( $n = 188$ )	−0.53 (−1.11 to 0.25) ( $n = 96$ )	−0.44 (−0.97 to 0.18) ( $n = 92$ )
BMI	−0.10 (−0.74 to 0.60)	−0.07 (−0.81 to 0.47)	−0.12 (−0.67 to 0.68)
Energy (calories)	1582 (1343–1958)	1643 (1370–2095)	1537 (1319–1817)
Energy (% EAR)	115 (100–131)	112 (98–129)	120 (103–135)
Protein (g)	51.0 (40.5–60.3)	50.8 (40.4–63.1)	51.3 (40.7–58.5)
Protein (En%)	12 (11–14)	12.0 (10.6–13.6)	12.8 (11.6–14.0)
Fat (g)	60 (49–78)	62 (50–81)	56 (49–72)
Fat (En%)	35 (31–38)	35 (31–38)	35 (30–39)
Carbohydrate (g)	207 (170–253)	217 (174–275)	198 (165–241)
Carbohydrate (En%)	51 (49–56)	52 (49–56)	51 (47–56)
CFA	89 (82–93) ( $n = 144$ )	89 (82–93) ( $n = 76$ )	89 (83–91) ( $n = 68$ )
PF	96 (87–107) ( $n = 49$ )	95 (88–108) ( $n = 26$ )	96 (81–103) ( $n = 23$ )
Genotype, $n$ (%)			
Severe	179 (94)	92 (94)	87 (94)
Mild	10 (5)	5 (5)	5 (5)
Unknown	2 (1)	1 (1)	1 (1)

WFA: z-score weight-for-age; BMI: z-score body-mass-index; En%: energy % of total energy intake; PF: pulmonary function ( $FEV_1\%$  pred.); HFA/TH: z-score height-for-age-adjusted-for-target-height; EAR: estimated average requirement; CFA: Coefficient of fat absorption.



**Fig. 1.** a. Weight and height measurements, expressed as z-score weight-for-age (WFA), height-for-age-adjusted-for-target-height (HFA/TH) and body-mass-index (BMI) set out against age in years, derived from 491 measurements of 98 boys with CF. b. Weight and height measurements, expressed as z-score weight-for-age (WFA), height-for-age-adjusted-for-target-height (HFA/TH) and body-mass-index (BMI) set out against age in years, derived from 478 measurements of 93 girls with CF.



**Fig. 2.** a. Energy intake, expressed as estimated average requirement per gender set out against age in years, derived from 969 measurements of 191 children with CF (497 measurements in boys). b. Mean energy intake, expressed as estimated average requirement per gender set out against age in years, derived from 969 measurements of 191 patients with CF (98 boys). c. Mean energy intake, expressed as mean caloric intake per gender set out against age in years, derived from 969 measurements of 191 patients with CF (98 boys).

baseline, expressed as %EAR, was in line with the recommendations of international CF-guidelines [4,5], although, the EAR was below 100% in older age groups (Fig. 2b). It was found that the absolute caloric intake increased with age, and boys had a higher caloric intake than girls (Fig. 2c).

The relation between intake and growth parameters was first analysed cross sectionally. A linear regression analysis was used to calculate the association between baseline measurement of WFA, HFA/TH or BMI and energy intake, expressed as absolute caloric intake. In boys, we found that those with a higher caloric intake had also a higher WFA, HFA/TH or BMI (all  $p < 0.05$ ). Each 100 calories increase in intake resulted in a 0.07 increase in WFA, a 0.05 unit increase in both HFA/TH and BMI (Table 2). However, the caloric intake explained no more than 18%, 6% or 7% of variation in WFA, HFA/TH or BMI respectively ( $R^2$  varied between 0.18 (WFA), 0.06 (HFA/TH) and 0.07 (BMI)) (Table 2). In girls, we found that those with a higher caloric intake had only a significant higher WFA ( $p < 0.05$ ). Each 100 calories increase in intake resulted in a 0.06 increase in z-score WFA. However, the caloric intake accounted only for 6% of the variation in WFA ( $R^2 = 0.06$ ). We found no

**Table 2**

Baseline association between energy intake, expressed as caloric intake per 100 calories, and nutritional status, expressed as z-score weight-for-age (WFA), height-for-age-adjusted-for-target-height (HFA/TH) ( $n = 96$ ) and body-mass-index (BMI) of 98 boys with CF.

	B	SE B	$R^2$
WFA			
Constant	-1.65	0.29	
Caloric intake (per 100 calories)	0.07	0.02	0.18*
HFA/TH			
Constant	-1.37	0.38	
Caloric intake (per 100 calories)	0.05	0.02	0.06**
BMI			
Constant	-0.99	0.35	
Caloric intake (per 100 calories)	0.05	0.02	0.07**

\* $p < 0.0001$ ; \*\* $p < 0.005$ .  $R^2$  proportion of variance in nutritional status is predictable from caloric intake.

significant association between HFA/TH or BMI and caloric intake (Table 3).

Longitudinally, in boys, the caloric intake was associated with WFA and BMI but not with HFA/TH (95% CI -0.01–0.01  $p = 0.88$ ).

**Table 3**

Baseline association between energy intake, expressed as caloric intake per 100 calories, and nutritional status, expressed as z-score weight-for-age (WFA), height-for-age-adjusted-for-target-height (HFA/TH) ( $n = 92$ ) and body-mass-index (BMI) of 93 girls with CF.

	<i>B</i>	SE <i>B</i>	<i>R</i> <sup>2</sup>
WFA			
Constant	−1.19	0.37	
Caloric intake (per 100 calories)	0.06	0.02	0.06**
HFA/TH			
Constant	−1.05	0.37	
Caloric intake (per 100 calories)	0.04	0.02	0.03
BMI			
Constant	−0.33	0.41	
Caloric intake (per 100 calories)	0.02	0.03	0.01

\* $p < 0.0001$ ; \*\* $p < 0.005$ .  $R^2$  proportion of variance in nutritional status is predictable from caloric intake.

Each time a boy increased his intake with 100 calories the z-score WFA would increase with 0.02 (95% CI 0.01–0.04), and z-score BMI increased with 0.03 (95% CI 0.01–0.05). In girls, we found that caloric intake was associated with WFA but not with HFA/TH and BMI (95% CI −0.00–0.02,  $p = 0.14$ , and 95% CI −0.01–0.03  $p = 0.18$  respectively). Each time a girl increased her intake with 100 calories, the z-score WFA would increase with 0.01 (95% CI 0.00–0.03). We found no significant associations between CFA and WFA, HFA/TH or BMI. Furthermore, the contribution of protein, fat and carbohydrates, expressed as a percentage of the total energy intake, was not associated with WFA, nor with HFA/TH or BMI (data not shown).

#### 4. Discussion

This study was designed to examine the association between body-growth and energy intake in a large cohort of children with CF, aged 2–10 years.

We found, even at this relatively early age, a compromised growth in children with CF when compared to healthy children. These findings are more or less comparable with results of a study from the UK, including 41 pancreatic insufficient children with CF, 5–12 years of age. Their study sample remained up to 0.5 z-score below the population mean for weight [21].

In addition, we found that the absolute caloric intake increased with increasing age. However when the caloric intake was expressed as EAR, it exceeded the EAR for healthy referents at a younger age, but it stayed below the recommended intake for children with CF. In the older age groups, the intake was even below the EAR for healthy referents. It seems that, despite, the improved medical and nutritional care for patients with CF, the energy intake in our study sample, was insufficient to attain or maintain growth at an optimal rate which is consistent with a previous, relative small study [9].

Both cross sectional and longitudinal evaluation of our study population showed an association between energy intake and particularly WFA, as was also found by others [9]. This implicates that a higher caloric intake especially has an impact on weight (gain). Nevertheless, cross sectionally, the variation explained by caloric intake was restricted by 18% in boys, and 6% in girls. Longitudinally, the magnitude of the association appeared relatively small as each time the caloric intake increased with 100 calories this would result in a 0.01–0.02 increase in z-score WFA. However, if these effects will be repeated, they may cumulate to a clinically significant effect on weight-gain.

Longitudinally, no association between HFA/TH and energy intake was found. Important to note is that this study lacks varia-

tion in HFA/TH as the distribution remained constant over the subsequent age years. Therefore we cannot exclude any association between HFA/TH and dietary intake.

Nutritional support is an integral part of the multidisciplinary care, and each patient attending the clinic routinely received advice on optimising their dietary intake. In this sample, we found a trend toward an increased WFA during subsequent age years, but we cannot exclude that this is the result of augmenting the energy intake as it concerns a retrospective study. The variation in body-growth, explained by caloric intake was restricted. Other factors such as behavioural, social, environmental and inflammation factors, may influence energy intake, energy expenditure and physical activity [22,23]. Information on activity and exercise levels were not recorded in this study and it is possible that those with higher energy intakes also had higher activity levels. Further, in healthy children, increased recreational in-activities such as TV, videos and games, and/or fewer hours of physical activities were associated with a higher BMI [24], but also with body fatness [25]. The latter indicates that weight and BMI measurements do not give an indication of body-tissue composition which is extremely important to know in CF-care as (hidden) fat-free mass depletion, rather than low body-weight, is strongly associated with prognosis [26,27].

Dietary recommendations are based on the EAR which was designed to describe the needs of the population of healthy individuals. The EAR has limited use for evaluating diets of individual patients with CF as these individuals have to compensate for the increased energy needs of infection and the energy cost of breathing. Addition of regular measurements of the body composition which reflects changes due to growth, illness or nutritional rehabilitation, along with evaluations of the dietary intake and measurements of resting energy expenditure might be beneficial, especially for those with a persistently compromised growth. The outcomes of these measurements allow children, who might consistently fail to meet their increased energy needs, to be monitored efficiently, and to address their specific nutritional needs appropriately.

Among the strengths of the analysis are the large sample size and the longitudinal design, which allowed us to study the long-term effect of routine energy intake on body-growth. Several limitations of this study merit to be mentioned. Firstly it is known that keeping food records can be burdensome, leading to alterations of the diet, over- and/or under-reporting and the accuracy might depend on the person who fills in the record. Moreover, portion size weights, obtained from reference data, may not accurately reflect the patients' intake. These limitations might affect the validity. Secondly, the possibilities to generalize the results are reduced by the single centre design as centre variability exists in terms of patient characteristics and therapy.

#### 5. Conclusion

The present study showed that dietary intake was  $\geq 110\%$  EAR in 47% of the measurements, and did not (fully) achieve the recommended level. A positive impact of increasing energy intake on especially WFA was demonstrated. Continuous monitoring of growth and assessment of dietary intake is of great importance in paediatric CF-care.

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## Statement of authorships

JW conceived of the study, contributed to the database construction, carried out the study and data analyses and drafted the manuscript.

GD participated in the design of the study and helped to draft the manuscripts.

CE participated in the design of the study and helped to draft the manuscripts.

RH conceived of the study, participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

## Conflict of interest

None.

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