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WILEY PEDIATRIC PULMONOLOGY

Rapid early increase in BMI is associated with impaired longitudinal growth in children with cystic fibrosis

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Abstract

Background: We aimed to assess whether final height in children with cystic fibrosis (CF) is affected by body mass index (BMI), BMI increase, pulmonary function, and cystic fibrosis-related diabetes (CFRD).

Study design: A longitudinal, retrospective study was performed in a cohort of 57 patients with CF (30 boys, 27 girls) born between 1997 and 2001. Height and weight were recorded annually from ages 0.5 to 10 years and biannually up to the age of 18. Measurements were converted to height-for-age-adjusted-for-target-height (HFA-TH) and BMI-for-age *z*-scores. Analyses were performed using the independent *t* tests and the Pearson's correlation.

Results: For both boys and girls, HFA-TH and BMI-for-age *z*-scores were significantly lower in the first year of life, these scores increased rapidly until the age of 11 and 8 years, respectively. In boys, HFA-TH *z*-scores declined during puberty, with subsequently significantly impaired final height (z-score, −0.56, n = 30, standard deviation [SD] = 0.81, $P = 0.001$). In girls, HFA-TH *z*-scores briefly declined after the age of 8 years, but then increased to a z-score of −0.21 (n = 27, SD = 0.87) at age 18, which is not significantly lower than the national average ($P = 0.22$). Pulmonary function and the presence of CFRD were not associated with final height. However, rapid BMI increase between ages 1 and 6 was negatively associated with final height in boys (n = 29, $r = -0.420$; $P = 0.023$) and girls (n = 25, $r = -0.466$; $P = 0.019$).

Conclusions: In boys and girls, early BMI increase was associated with impaired final height. We suggest that early childhood serves as a "window" in which nutritional variations may program subsequent growth. Further refinement of nutritional strategies could be needed.

KEYWORDS

cystic fibrosis-related diabetes, FEV1, final height, pulmonary function, weight

Abbreviations: BMI, body-mass index; CF, cystic fibrosis; CFRD, cystic fibrosis-related diabetes; FEV1%pred, predicted percentage of forced expiratory volume in 1 second; FH, final height; HFA, height for age; HFA-TH, height-for-age-adjusted-for-target-height; PHV, peak height velocity; TH, target height.

1 | INTRODUCTION

Cystic fibrosis (CF) is the most common autosomal recessive disorder in Caucasians, with a birth prevalence of 1 in 4750 live births in the Netherlands between 1974 and 1994.[1] This potentially life-threatening condition is caused by mutations in the cystic fibrosis transmembrane conductance regulator gene (CFTR-gene), encoding for an anion channel in epithelial membranes. Consequently, pathological changes take place in organs that express CFTR. This multiorgan involvement is reflected by the variety of symptoms, including chronic airway disease with impaired pulmonary function, pancreatic insufficiency, diabetes mellitus, and hepatic cirrhosis.[2]

In the follow-up of patients with CF, height and weight parameters are of particular interest, as these seem to be closely related to health status and pulmonary outcomes.[3–5]

In addition, short stature in patients with CF has been associated with reduced life expectancy.[6] This might indicate a role for optimizing linear growth for optimal health status and optimal pulmonary growth.

As has been seen in patients born in the late 70s and early 80s, linear growth and subsequent final adult height are compromised in children with CF.[7–9] This failure of growth is primarily attributed to reduced food absorption and increased energy losses due to chronic inflammation and severe pulmonary disease.[10] During the past decades, major progress has been made in the treatment and nutritional management of CF, with high caloric diet as a key component of nutritional care.[11] Nevertheless, more recent studies still suggest that impaired growth continues to be seen in patients with CF, particularly during puberty, although results on final height and pubertal spurt are conflicting.[5,12–14] However, most of these studies report cross-sectional data,[7,9,12] which is a suboptimal method for assessing linear growth. Only few studies had a longitudinal design and provided data collected throughout the entire period of childhood.[5,13]

In this study, aimed to address the current research gap, we examined whether longitudinal growth from the age of 0.5 until 18 years was impaired in a cohort of Dutch children with CF who were born between 1997 and 2001. We also evaluated whether body mass index (BMI), BMI increase between ages 1 and 6, pulmonary function, and cystic fibrosis-related diabetes (CFRD) were associated with linear growth.

2 | MATERIALS AND METHODS

2.1 | Study population

This longitudinal retrospective study was performed in Dutch children with CF who were born between 1997 and 2001. Each child received medical care in the University Medical Center Utrecht. The diagnosis CF was confirmed for each child by means of a positive sweat test and/or the presence of two CF mutations as well as clinical signs of CF. None of these children had been diagnosed through newborn screening (NBS), as this method was not introduced in the Netherlands until 2011.

Height and weight were measured during routine clinical visits at least yearly from the moment of CF diagnosis until the age of 18 (27 measurements per patient). Missing data were extracted from patient records, if possible. All parents or guardians of the children included in the study gave their informed consent for the storage and use of these data for scientific purposes.

Patients were excluded if there were missing data on height or if they had not yet reached final height (defined as an increase in height lower than 0.2 cm in the past 6 months) at the termination of the study. Patients were also excluded if more than 5 out of 27 weight measurements per patient were missing. Finally, patients were excluded if they suffered from other non-CF-related morbidities that could cause significant growth impairment.

2.2 | Height and weight measurements

For patients up to the age of two, height was measured with a measuring table in a horizontal Frankfurt plane. In older patients, height was measured with a Harpenden stadiometer to the nearest 0.1 cm. Weight was measured with a digital scale to the nearest 0.1 kg.

Height parameters and BMI parameters were converted to *z*-scores for height-for-age and BMI-for-age to compare them with reference values for Dutch children.[15] Since predicted final height is highly genetically determined, the heights of both biological parents were taken into account. Individual target height (TH) was calculated with the following formulas, based on a nationwide Dutch growth study[16]: TH (boys) = 44.5 × 0.376 x height father (cm) + 0.441 x height mother (cm); TH (girls) = 47.1 × 0.334 x height father (cm) + 0.364 x height mother (cm). Subsequently, *z*-scores for target height were calculated on the basis of Dutch standards for final height.[15] Finally, a z-score for height-for-age-adjusted-for-target-height (HFA-TH) was computed by subtracting the z-score for TH from the z-score for HFA, as proposed by the *Dutch Consensus Guideline*.[17]

Further, to assess the effect of a change in BMI during early childhood, a new variable was computed by subtracting *z*-scores for BMI at age 1 from *z*-scores for BMI at age 6.

2.3 | Clinical measurements

Patients were subdivided based on cystic fibrosis transmembrane regulator (CFTR) gene mutations. Patients who carried at least one class IV or class V were classified as mild; patients carrying only class I, II, and III mutations were classified as severe. Pulmonary function was measured by means of spirometry and expressed as the percentage of predicted forced expiratory volume in 1 second (FEV1%pred).

Diagnosis of CFRD was established when fasting plasma glucose levels intermittently exceeded 126 mg/dL (7.0 mmol/L) or 2-hour postprandial plasma glucose levels intermittently exceeded 200 mg/dL (11.1 mmol/L) during 72 hours of continuous glucose monitoring.

TABLE 1 Characteristics of study population

		Gender	
		Boys (N = 30)	Girls (N = 27)
Caucasian (%)		100	100
Median age of diagnosis, y*		0.30 (0.43)	0.50 (2.70)
Genotype (%)*	Severe	93.3	96.3
	Mild	3.3	3.7
	Unknown	3.3	…
Homozygous F508del (%)*		56.7	55.6
CFRD diagnosis <18 years (%)*		23.3	40.7
Mean HFA-TH *z*-score 0.5 years*		−0.96 (1.23)	−0.64 (1.15)
Mean HFA-TH *z*-score 10 years*		−0.33 (0.86)	−0.35 (1.04)
Mean HFA-TH *z*-score 18 years*		−0.56 (0.81)	−0.21 (0.87)

Abbreviations: CFRD, cystic fibrosis-related diabetes; HFA-TH, height-for-age-adjusted-for-target-height.
Means are expressed with standard deviation (SD), medians with interquartile range (IQR).
*None of above values were significantly different between boys and girls at $P < 0.05$ based on χ^2 and independent groups *t* test.

2.4 | Statistics

Statistical analyses were performed using the Statistical Package for the Social Sciences Computer Software (SPSS Inc. version 21; IBM, Chicago, IL). All analyses were performed for boys and girls separately.

Continuous variables were tested using one sample and independent *t* tests, after being tested for normality using the Shapiro-Wilk test. Furthermore, a Pearson's correlation test was used to evaluate the possible correlation between continuous variables. The Pearson χ^2 test was used to compare categorical variables.

A $P < 0.05$ was considered the threshold for statistical significance.

3 | RESULTS

3.1 | Clinical characteristics

Of the 71 patients in the CF database born between 1997 and 2001, 57 patients (30 boys, 27 girls) were eligible for inclusion. In total, 14 patients were excluded: 10 because of insufficient measurements, 1 because of relevant comorbidity, and 3 because they had not yet reached final height at the termination of inclusion.

Table 1 shows the clinical characteristics of the included patients. Median age of diagnosis was 0.30 years (interquartile range [IQR] = 0.43) for boys and 0.50 years (IQR = 2.70) for girls. Before diagnosis, height was already decreased. Only two patients' genotypes were classified as mild.

3.2 | HFA-TH

Figure 1 shows the longitudinal registration of growth in both boys and girls with CF, expressed as *z*-scores with a 95% confidence interval.

In boys, mean *z*-scores for HFA-TH were significantly lower than the national average at all ages (Figure 1), with the exception of *z*-scores at ages 10 to 11 and 14 years. At age 0.5, height was already substantially impaired. Subsequently, height in boys with CF gradually increased to a maximum mean HFA-TH z-score of −0.31 at age 11. From this age onwards, *z*-scores for HFA-TH were found to be impaired again, only interrupted by a slight increase in *z*-scores between 12.5 and 14 years. Final height in boys, defined as mean HFA-TH z-score at age 18, was −0.56 compared to Dutch reference values (n = 30; $P = 0.001$), which corresponds with −4 cm.

In girls with CF, mean *z*-scores for HFA-TH were also lower than the national average, and only reached the threshold for statistical significance at ages 0.5 to 3 and ages 11 to 12. Similar to what was found for boys, *z*-scores initially showed an upward trend, but declined from the age of 8. Then, at age 11, female linear growth seemed to catch-up again, with increasing *z*-scores for HFA-TH to a maximum of −0.09 at age 14.5. Final height in girls was −0.2, which

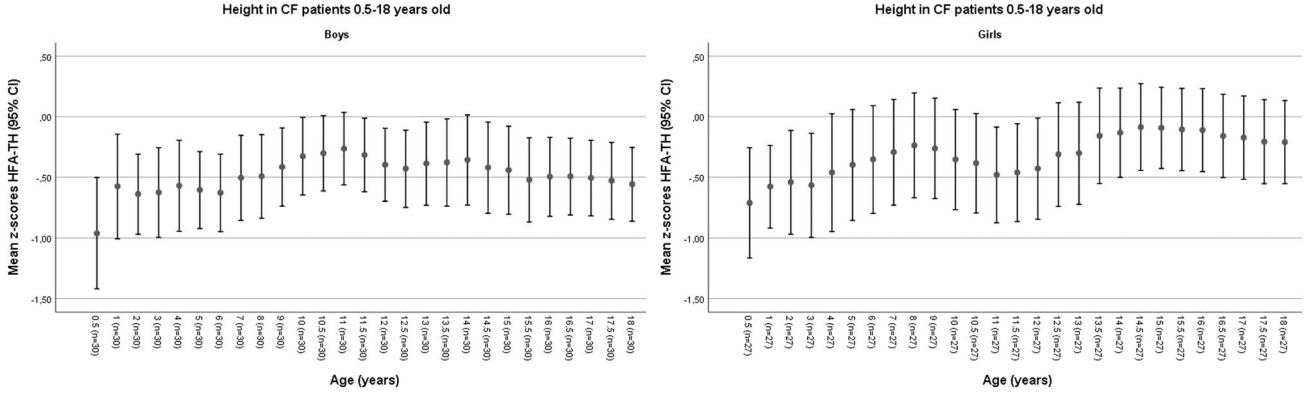

FIGURE 1 Longitudinal registration of *z*-scores for height-for-age-adjusted-for-target-height in 30 boys and 27 girls with CF, compared to Dutch reference values. *Z*-scores are expressed with 95% confidence interval. CF, cystic fibrosis

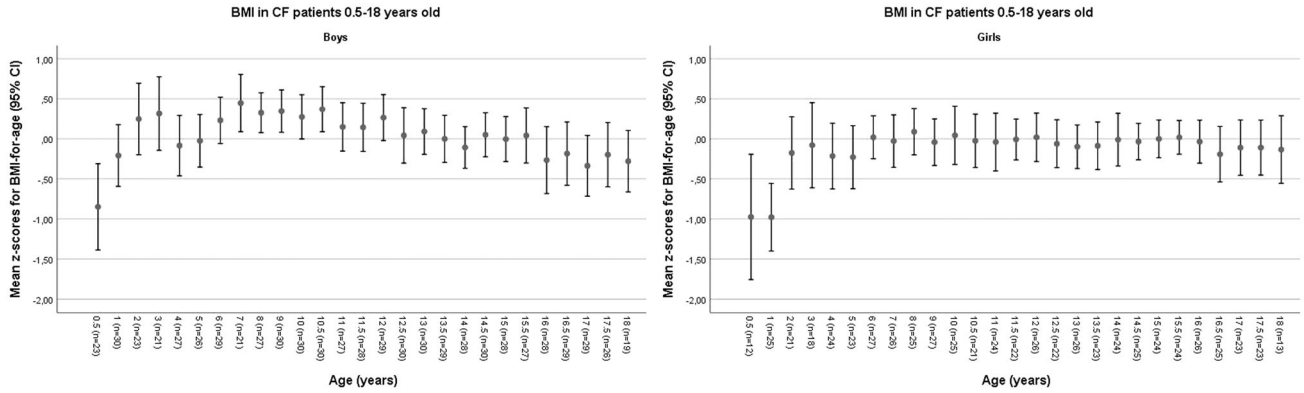

FIGURE 2 Longitudinal registration of *z*-scores for BMI-for-age in patients with CF, compared to Dutch reference values. *Z*-scores are expressed with 95% confidence interval. Skewness of mean BMI-for-age z-scores did not exceed ±0.65, except for the age of 15.5, 16, and 16.5 years old in boys, and for the age of 14, 16.5, and 18 years old in girls. BMI, body mass index; CF, cystic fibrosis

corresponds with −1.4 cm, yet this was not significantly lower than national average (n = 27, *P* = 0.22).

3.3 | BMI-for-age

For both boys and girls, BMI-for-age *z*-scores were impaired in the first year of life, but these rapidly increased to rather normal values for age in early childhood (Figure 2).

Specifically, in male patients, mean *z*-scores for BMI-for-age were only significantly lower than national reference values at age 0.5. At ages 7 through 10.5 years, *z*-scores for BMI-for-age were in fact even higher than the average BMI for the reference population. At higher ages, mean *z*-scores did not significantly differ from mean reference values.

In female patients, BMI-for-age *z*-scores were only significantly below average at ages 0.5 through 1 year.

3.4 | Factors associated with height-for-age-adjusted-for-TH

In boys, BMI-for-age was not associated with HFA-TH at the same age. However, we did find a significant negative association between an increase in z-score for BMI-for-age between 1 and 6 years and z-score for final height (n = 29, *r* = −0.420; r^2 = 0.176; *P* = 0.023) (Figure 3). BMI-for-age *z*-scores at ages 1 and 6 themselves were not significantly correlated with final height z-score (age 1: n = 30, *r* = 0.084; *P* = 0.659; age 6: n = 29, *r* = −0.170; *P* = .378) and BMI increase was not significantly associated with HFA-TH z-score at age 10 (n = 29, *r* = − 0.290; *P* = .127).

Figure 4 shows the longitudinal registration of mean FEV1%pred. in both boys and girls with CF. Mean FEV1%pred. in boys declined from 93.55% (n = 12, standard deviation [SD] = 11.04) to 78.30% (n = 29, SD = 20.94) at ages 10 to 18, respectively. No significant correlation was found between FEV1%pred. and final height.

There was no significant difference in mean final height z-score in boys who developed CFRD (n = 7, *M (mean)* = −0.84; SD = 0.87) and those who did not (n = 23, *M* = −0.47; SD = .80; *P* = 0.302).

In girls, an increase in BMI between 1 and 6 years was also negatively associated with final height z-score (n = 25, *r* = −0.466; r^2 = 0.217; *P* = 0.019). Mean FEV1%pred. in girls impaired from 89.80% (n = 11, SD = 13.44) at age 10 to 74.55% (n = 24, SD = 12.42) at age 18. Similar to boys, FEV1%pred. did not correlate at any age with z-score for final height. Likewise, *z*-scores for final height in patients who developed CFRD (n = 11, *M* = −0.12; SD = 1.17) and no

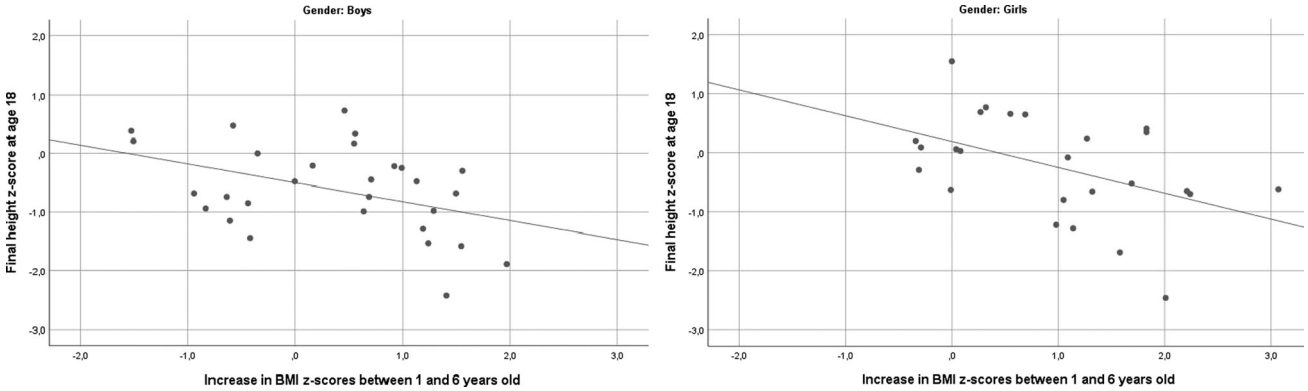

FIGURE 3 Association on final height and increase in BMI *z*-scores between 1 to 6 years old in patients with CF. BMI, body mass index; CF, cystic fibrosis

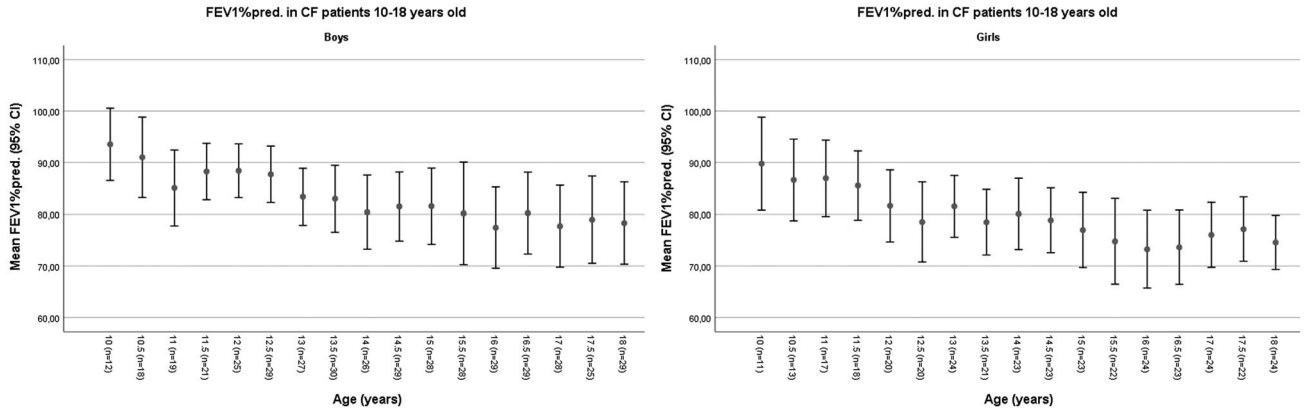

FIGURE 4 Longitudinal registration of FEV1%pred. in patients with CF between 10 and 18 years old. Means are expressed with 95% confidence interval. CF, cystic fibrosis; FEV1%pred, predicted percentage of forced expiratory volume in1 second

CFRD (n = 16, $M = -.27$; SD = .63) were not significantly different ($P = 0.674$).

4 | DISCUSSION

Our study has yielded important new insights into linear growth in children with CF. Firstly, we demonstrated that final height in our cohort did indeed remain significantly impaired in boys born between 1997 and 2001, but not in girls. Still, we have reason to suspect that female final height was also impaired, albeit to a lesser extent. Possibly, the decrease in female final height did not reach the threshold for statistical significance due to the smaller size of our sample.

Secondly, with regard to factors that influence final height, our study revealed that a rapid increase in BMI during early childhood was negatively associated with final height. Since BMI increase was not associated with height at the age of 10, this might imply that rapid weight gain during early childhood contributes to attenuated final height through impairment of growth in puberty.

Finally, we found that mean height was already impaired in the first year of life in boys as well as in girls. In subsequent years, patients with CF in our cohort seemed to catch-up with the average Dutch children. However, in boys this catch-up growth did not persist during puberty: HFA-TH *z*-scores declined after the age of 11, which resulted in impaired final height. Although mean *z*-scores in girls temporarily declined after the age of 8, they showed a remarkable increase after the age of 11. This deviation between the sexes suggests a role for gender-specific causes of differences in growth patterns. This matter will be discussed below.

Our observations on mean final height *z*-scores are generally in line with those reported in previous studies, since all of these acknowledge growth impairment to a certain extent, particularly during puberty.[5,12–14] However, findings with respect to final height are inconsistent. Bournez et al[12] reported that final height in patients with CF was lower compared to healthy counterparts, with an average z-score of −0.73 in boys and lower than −0.50 in girls. This appeared to be due to impaired peak height velocity (PHV) during the pubertal growth spurt. Additionally, both Zhang et al[13] and Assael et al[5] observed attenuated as well as delayed PHV, leading to a lower adult height. In contrast, Aswani et al[14] did not find lower final height in English patients with CF, in spite of impaired and delayed PHV.

In light of these studies, our findings are especially relevant since a majority of earlier investigations based conclusions on patients born before 1990. Furthermore, and in contrast to several previous studies,[5,12,14] we have taken genetic height potential into account by using adjusted height *z*-scores, which has proven to be substantially more accurate.[18] Finally, to the best of our knowledge, we are the first to demonstrate an association between early childhood BMI increase and impaired final height in patients with CF.

The mechanism through which rapid infant BMI increase might influence final height has yet to be elucidated. One explanation could be that infancy serves as an early "window" in which nutritional variations may program subsequent growth and development,[19] with an important role for glucose and insulin metabolism. Indeed, in infants, rapid weight gain has been associated with an increased cardiovascular risk in adolescence[20] as well as with insulin resistance at the age of 8 years.[21] This idea is also supported by a study reporting that children who suffered severe early malnutrition are at far greater risk of developing diabetes.[22] In patients with CF, poor early childhood nutritional status was likewise associated with higher risk of disordered glucose metabolism.[23]

We hypothesize that disordered insulin metabolism due to rapid infant BMI gain, as a marker for weight gain, could stimulate the adrenal glands to produce androgens prematurely, as insulin is not only involved in energy metabolism, but is also a stimulator of the steroidogenesis. Indeed, rapid infant weight gain has been associated with higher levels of the androgens androstrenedione and dehydroepiandrosterone sulfate at age 8 years in children without CF.[24] These heightened levels might indicate premature adrenal activation through insulin stimulation,[25] a process which could trigger earlier bone maturation and pubertal development. In a similar way, this mechanism of early exaggerated androgen production may be responsible for the earlier pubertal onset observed in obese children

accompanied by reduced height gain in adolescence.[26] Earlier pubertal onset has also been reported in adopted children, who often experience catch-up weight and height gain in the first years following adoption. Despite this promising catch-up growth, final height was still attenuated in these children due to suboptimal prepubertal and pubertal growth.[27]

Second, disordered glucose metabolism might heighten the risk of developing CFRD. To illustrate, Cheung et al[28] reported that failure to thrive, an initial presenting feature of CF, was almost three times more common in patients who later developed CFRD, although both failure to thrive and CFRD might also be the result of patient-specific disease severity. Still, the development of CFRD seems to negatively influence growth. Height velocity was found to be significantly lower in the 2 years pre-CFRD, but also post-CFRD diagnosis, compared to patients with CF without CFRD.[28] Lower final height in patients with CFRD was also reported by Bizzarri et al.[29] In our cohort, however, we did not find significantly lower final height in patients with CFRD, but boys with CFRD did tend to show a more rapid decline in height *z*-scores during puberty. Nevertheless, these results might not be significant due to the small number of patients with CFRD in our study.

In addition to the effect of early childhood BMI increase, we assume that reduced levels of testosterone affect final height specifically in boys with CF. In male patients with CF, serum levels of testosterone, mainly produced in the testes, have been found to be reduced during puberty.[30] This might contribute to the difference in pubertal growth observed between boys and girls, as boys are largely reliant on testosterone for their pubertal growth spurt, after adipocyte aromatization to oestrogens.[31] In girls, oestrogens are primarily made in higher concentrations. Unfortunately, we were unable to obtain data on pubertal milestones or sex hormone levels to assess pubertal onset, nor did we have sufficient data on bone maturation.

Nevertheless, it must be noted here that since NBS was introduced in the Netherlands in 2011, early detection may prevent failure to thrive in patients with CF as well as the potential subsequent rapid weight gain in early childhood. This means that compromised growth and weight during infancy as reported in our study may now be less likely to be seen. That being said, Vernooij-Van Langen et al[32] showed that weight and height were already below average at the moment of diagnosis through NBS in a Dutch CF population, and that values did not significantly differ from clinically diagnosed patients with CF. This indicates that failure to thrive in newborns could not fully be prevented by NBS and thus remains a matter of concern.

Our study has several limitations. First, our conclusions should be limited to patients with CF with a severe genotype, as these account for more than 90% of included patients. Second, the study's retrospective design did not enable us to consider data on pubertal milestones, sex hormone levels or bone maturation. Finally, our relatively small sample size did not allow for subgroup analysis. A larger sample is needed not only to assess the role of CFRD on linear growth, but also to validate our findings, especially with respect to the association between early childhood BMI increase and final height.

To conclude, our study has demonstrated that final height remains impaired in boys with CF despite major improvements in nutritional and clinical care. Future research should investigate the role of early childhood BMI increase in growth retardation in greater depth and detail: this may yield important new knowledge for the further refinement of future nutritional strategies.

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