Received: 26 January 2023 | Accepted: 2 January 2024

DOI: 10.1002/ppul.26861

ORIGINAL ARTICLE

WILEY

BMI increase during early childhood in boys with cystic fibrosis and early adrenarche

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Funding information
None

Abstract

Background: Increase in body mass index (BMI) in early childhood (1–6 years) was found to be a contributing factor for impaired final height in boys with Cystic Fibrosis (CF). Early adrenarche (before age 9 years in boys) may contribute to an impaired final height by triggering an early acceleration of bone age resulting in a compromised growth spurt during puberty. We aimed to analyze the timing of adrenarche in boys with CF and to associate BMI increase in early childhood to timing of adrenarche.

Methods: Boys with CF, aged 8–9 years, visiting the CF expertize center Utrecht were included. Since 2018, anthropomorphic, pubertal and endocrine data were collected. Early adrenarche in boys was defined as a dehydroepiandrosterone sulfate (DHEAS) ≥ 1 µmol/L before the age of 9 years.

Results: Thirteen boys (mean age 8.55 ± 0.27 years) were enrolled. The median (IQR) DHEAS-level was 1.3 µmol/L (0.71–2.40). Eight boys (61.5%) had an early rise in DHEAS-levels ≥ 1 µmol/L. Mean increase in BMI Z-score between 1 and 6 years of age (ΔBMI_{1-6}) was −0.07 ± 0.86. A significant correlation was found between ΔBMI_{1-6} and DHEAS-levels at the age of 8–9 years ($r = 0.624$, $p = 0.040$). In five boys with early rise in DHEAS, accelerated bone age was found (average 1.55 ± 0.96 years).

Conclusion: In this small cohort, 61.5% of boys with CF between 8 and 9 years had an early rise of DHEAS, which was correlated to ΔBMI_{1-6} between 1 and 6 years. Early adrenarche may be caused by ΔBMI_{1-6}.

KEYWORDS

BMI increase, bone age, dehydroepiandrosterone Sulfate, DHEAS, early adrenarche

1 | INTRODUCTION

Good nutritional status is strongly recommended in patients with cystic fibrosis (CF) as it is associated with better pulmonary outcome and survival.[1–6] The European guideline recommends a 120–150% energy intake to maintain good nutritional status.[1] Adequate nutritional status has been defined as a body mass index (BMI) Z-score of 0 for children and adolescents.[1] Increasing energy intake to >100% of daily requirements may result in weight gain and increase in BMI.

It has been reported, that (too) rapid BMI increase in early childhood (between 1 and 6 years of age) may be associated with impaired final height in boys with CF.[7] Impaired final height in boys with CF may have psychological impact, decreased lung volumes and has been associated with shorter survival.[8]

It is not yet clear why boys with CF and rapid BMI increase in early childhood are at risk for impaired final height, though theories have been hypothesized. Rapid BMI increase in early childhood may result in higher insulin levels due to insulin resistance, which subsequently may cause early activation of the adrenal glands.[7,9] In all children, the adrenal glands are activated from early age onwards with the production of primarily dehydroepiandrosterone sulfate (DHEAS). Until age 9 in boys, DHEAS levels are low and not associated with clinical signs of virilization.[10] From age 9 years in boys, DHEAS levels rise ≥ 1 µmol/L and adrenarche starts and clinical signs of virilization can be detected, such as pubic hair, acne or adult-type body-odor.[10] Maturation of the growth plates in long bones is increased by estrogens; conversion of androgens to estrogens occurs in adipose tissue.[9–11] For this reason, radiologically, an accelerated bone age can be found in younger children with exaggerated adrenarche as well as in children with more adipose tissue.

To date, no studies have explored the relation between BMI and (early) adrenarche (before the age of 9 years) in boys with CF. Possibly, the association between BMI increase at the age of 1–6 and impaired final height in boys with CF can be explained by early onset of adrenarche. For this reason, we aimed to explore if early adrenarche is present in boys with CF at the age of 8–9 years. Our secondary aim was to explore the association between significant early BMI change (between age 1–6 years) and early adrenarche in young childhood.

2 | METHODS

2.1 | Study population and design

An observational cohort study was performed from September 2018 until June 2022. In this period, all boys between 8 and 9 years of age visiting the Wilhelmina Children's Hospital, Utrecht, The Netherlands, for annual CF check-up were included. Diagnosis of CF had been made based on clinical presentation or with newborn screening and additional sweat-chloride tests with genetic confirmation of the CFTR-mutations. Additional information on pulmonary function (predicted percentage of the forced expiratory volume in 1 s (FEV1%pred) and CF related comorbidities were obtained as disease severity markers.

Children were excluded from this study if no biochemical assessment of adrenal function (blood test) was available and if they were or had been on oral steroids in the 6 weeks before DHEAS-measurement. All patients and their parents had given their informed consent to use regular care data for research purposes.

2.2 | Physical examination and BMI-assessment

Height was measured to an accuracy of 0.1 cm. Body weight was measured using digital scales. BMI was calculated by dividing the patient's weight in kilograms by their height in meters squared. Standard deviation score (Z-score) values for body height, weight and BMI were determined according to the World Health Organization (WHO) growth data.[12] Information on growth measurements (height-, weight-, and BMI Z-scores) during early childhood (between 1 and 6 years of age) was obtained from the patient medical records. Pubertal stages had been assessed according to the Tanner stages by a pediatric endocrinologist.

Early BMI-increase was defined as the change between BMI Z-score at 1 years of age and the BMI Z-score at 6 years of age (ΔBMI_{1-6}), in accordance with our earlier study.[7] The change in height and weight Z-scores between 1 and 6 years was also calculated. Underweight, overweight and obesity at the age of 1 years were classified, according to the WHO growth data (BMI Z-score < −2.0, BMI Z-score ≥ 2.0 and BMI Z-score ≥ 3.0, respectively).[12] Underweight, overweight and obesity at measurement of DHEAS (between 8 and 9 years) were classified according to the international BMI cutoff points of Cole et al.[13,14]

2.3 | DHEAS-measurements and assessment of early adrenarche

Blood samples were taken between 8.00 and 8.30 AM to determine serum DHEAS-levels. DHEAS was measured on the Atellica® analyzer (Siemens Health care). Inter- and intra assay coefficient of variations are 3.5–6.0% and 1.6–2.5% respectively. Limit of Quantitation is 0.12 µmol/L.

The biochemical start of adrenarche was chosen to define early adrenarche, as clinical signs are not always present when adrenarche starts. DHEAS-levels starts to rise ≥ 1 µmol/L from the age of 9 years in boys. Therefore, early adrenarche was defined as present when the DHEAS-levels were ≥1 µmol/L before the age of 9 years.[10]

2.4 | Bone age

An X-ray of the left hand was taken of the children to assess bone age. These were recorded by a pediatric endocrinologist according to the assessment method of Greulich and Pyle.

2.5 | Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics. Independent *T* tests were used testing continuous variables. To investigate if early adrenarche was related to ΔBMI_{1-6} univariate linear regression analysis was performed. Pearson's R was used to test for correlation between both variables. In case of non-normality nonparametric tests were used (Mann–Whitney *U*-test).

Statistical analyses were performed using the Statistical Package for the Social Sciences Computer Software (SPSS Inc. Version 26.0.0.01; IBM). A $p < 0.05$ was considered statistically significant.

TABLE 1 Patient characteristics of the study population at time of DHEAS-measurement.

	All (*n* = 13)
Age, yrs (mean ± SD)	8.55 ± 0.27
Homozygous ΔF508 (*n*, [%])	6 (46.2)
CFRD (*n*, [%])	2 (15.4)
CFLD (*n*, [%])	1 (7.7)
Height Z-score (median, IQR)	0.37 (−0.0003 to 1.77)
Weight Z-score (median, IQR)	−0.14 (−0.46 to 1.38)
BMI Z-score (median, IQR)	−0.03 (−0.86 to 1.16)
ΔBMI Z-score between 1−6 years (mean ± SD)	−0.07 ± 0.87 (*n* = 11)
FEV1%pred (mean ± SD)	89.2 ± 19.9
FEV1%pred < 70 (*n*, (%))	2 (15.4)

Abbreviations: BMI, body mass index; CFRD, Cystic fibrosis related diabetes; CFRLD, Cystic fibrosis related liver disease; IQR, interquartile range; FEV1%pred, predicted percentage of the forced expiratory volume in 1 s; Yrs, years; Z-score, standard deviation score.

TABLE 2 Bone age and DHEAS-measurements in boys with CF age 8–9 years.

Boys with CF	*N*	
Age (yrs) (mean ± SD)	13	8.55 ± 0.27 years
Bone-age[a] (yrs) (median, IQR)	11	8.30 (7.00–10.0)
ΔBone-age[a] versus chronological age (yrs) (mean ± SD)	11	0.22 ± 1.43
DHEAS-levels (μmol/L) (median, (IQR), [full range])	13	1.30 (0.71–2.40), (0.30–6.30)
DHEAS-levels ≥ 1 μmol/L (*n*, %)	13	8 (61.5%)

Abbreviations: DHEAS, dehydroepiandrosterone sulfate; IQR, interquartile range; SD, standard deviation; Yrs, years.

[a]Bone age was assessed in 11 of 13 boys, with a mean chronological age of 8.51 ± 0.28

3 | RESULTS

3.1 | Study population

Thirteen boys were enrolled in this study, with a mean age of 8.55 ± 0.27 years at time of the DHEAS measurement. An overview of the patient characteristics is presented in Table 1. Two (15.4%) boys had CF related diabetes (CFRD). Two boys (15.4%) had a FEV1% pred below 70%.

At time of evaluation, all boys were normal weight. Precocious puberty was absent in our cohort.

3.2 | Anthropometric and BMI changes between age 1 and 6

Of two boys, not all retrospective anthropometric measurements were available. From the 11 boys who had anthropometric measurements at age 1, none of the boys were underweight or overweight. At age 6, one boy (9.1%) was overweight and 10 boys (90.1%) were normal weight. The mean change in BMI Z-score between age 1 and age 6 was −0.07 ± 0.86 (*n* = 11). The mean change in weight Z-scores between age 1 and 6 was 0.20 ± 0.82 (*n* = 11) and the mean change in height Z-scores between 1 and 6 years of age was 0.40 ± 0.94.

3.3 | DHEAS measurements

The median (IQR) DHEAS-level between 8 and 9 years old was 1.30 μmol/L (0.71–2.40). Eight boys (61.5%) had an early rise in DHEAS-level of ≥1 μmol/L before the age of 9 years (Table 2). The ΔBMI_{1-6} was significantly higher in boys with DHEAS-levels ≥ 1 μmol/L than in boys with DHEAS-levels < 1 μmol/L (0.38 ± 0.54 vs. −0.87 ± 0.73 respectively, $p = 0.01$).

3.4 | Bone age

Bone age could be assessed in 11 boys. In 5 (45.5%) boys, all with DHEAS levels > 1 μmol/L, the bone age was accelerated (mean [SD] accelerated bone age of +1.55 ± 0.96) (Table 2). In 6 boys without DHEAS ≥ 1 μmol/L, bone age was not accelerated (mean [SD] decelerated bone age of −0.88 ± 0.38). No significant difference was seen in median height Z-scores between boys with or without accelerated bone age at time of DHEAS measurement (Table 3).

3.5 | (Δ)BMI z-score and early adrenarche

In the boys, ΔBMI_{1-6} was significantly associated with DHEAS-levels ($\beta = 1.50$ μmol/L/SD; 95% 0.084–2.922; $p = 0.040$) with a positive correlation ($r = 0.624$, $p = 0.040$, Figure 1). Current BMI and weight Z-score values (at the age of DHEAS measurement) and change in weight and height Z-scores were not associated with DHEAS-levels.

4 | DISCUSSION

In this small observational cohort study, we found early adrenarche in 61.5% of boys with CF with a positive association between the increase in BMI Z-score during early childhood (between ages 1–6 years) and DHEAS-levels at the age of 8–9 years. As may be expected, all boys with early adrenarche (DHEAS-levels ≥ 1 μmol/L) had an accelerated bone age, which was not seen in boys without adrenal activation.

To our knowledge, this is the first study to investigate early adrenarche in relation to BMI change in boys with CF. These results

TABLE 3 Bone-age in relation to DHEAS concentration.

	Boys (n = 11)		
	With accelerated bone-age (n = 5)	Without accelerated bone-age (n = 6)	p Value
Δbone versus chronological age (yrs)*	+1.55 ± 0.96	−0.88 ± 0.38	0.003[a]
DHEAS-level (μmol/L)*	3.56 ± 2.38	1.03 ± 0.56	0.076[a]
Height Z-score (median, [IQR])	1.23 (0.52–2.37)	0.06 (−0.09 to 1.77)	0.14[b]

Abbreviations: DHEAS, dehydroepiandrosterone sulfate; IQR, interquartile range; Yrs, years; Z-score, standard deviation score.

Values are means and standard deviations unless otherwise indicated.

[a]Independent sample's *T*-test

[b]Mann–Whitney *U*-test

*A statistically significantly difference was seen at the level $p < 0.05$

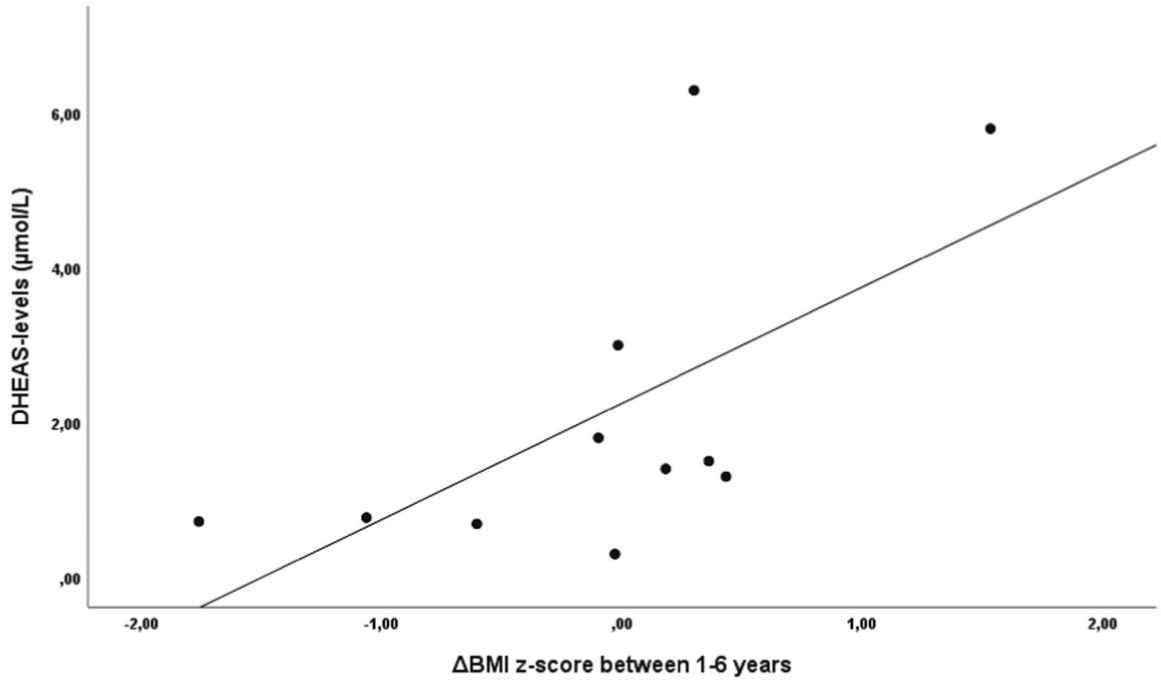

FIGURE 1 DHEAS-levels (μmol/L) plotted against ΔBMI Z-score between 1 and 6 years in boys. ΔBMI Z-score between 1 and 6 years = the change in BMI Z-score at 1 years of age and at 6 years of age. •, indicating a boy with CF with DHEAS-levels and change in BMI z-scores between 1 and 6 years; DHEAS, dehydroepiandrosterone sulfate.

cautiously support our hypothesis that impaired height in boys with CF might be the result of an early adrenal activation due to (too) rapid BMI increase in early childhood, a phenomenon we described in our earlier study,[7] potentially leading to earlier skeletal maturation and closure of epiphyseal growth plates.

In our cohort study, we defined early adrenarche as present when DHEAS-levels ≥ 1 μmol/L before the age of 9 years.[10] It is important to realize that from earlier studies we know that sex and age matched reference values differ among populations. In a Finnish cohort, mean DHEAS-levels were below 1 μmol/L in boys before the age of 9 years,[15] but in a Turkish population, boys showed an earlier rise in DHEAS-levels, with DHEAS-levels ≥ 1 μmol/L from the age of 7 onwards.[16] In both studies, children had healthy mean BMI Z-scores (−0.2 vs. 0.2 in the Finnish study vs. the Turkish study respectively) based on national growth studies.[17,18] We did not note ethnical background of our cohort, but considering the high probability of an overall Dutch population we have chosen 1 μmol/L as cut-off level for presence of activation of the adrenal glands.

Previous research has shown an association between rapid early childhood weight gain and higher androgen levels at age 8 years in healthy children.[19] Similarly, several studies showed that children born small for gestational age (SGA) had higher DHEAS-levels at 8 and 9 years of age than children born appropriate for gestational age (AGA).[20,21] Both studies included children born SGA who had comparable weight or BMI to the control groups at baseline assessment, indicating catch-up growth. Another study showed that children born SGA without catch-up growth had similar DHEAS-levels compared with children born AGA.[22] In our study, we also

reported a positive association between BMI increase and DHEAS-levels. Despite not being able to statistically differentiate between children with or without catch-up growth, (due to our sample size), we have shown that BMI increase in early childhood is related to higher DHEAS-levels. Accordingly to the studies in children born SGA, we hypothesize that the early adrenarche in boys with CF is caused by higher insulin levels due to insulin resistance, as a consequence of rapid early childhood weight gain.[23] Increased insulin levels enhance steroidogenic enzyme activation.[24] This phenomenon is also common in children with obesity, who experience excessive weight gain during a short period.

In addition, higher DHEAS-levels have been described in obese children when compared to healthy controls in several reports.[24–26] Another study reported that children with individually the largest BMI increase showed the highest DHEAS-levels.[27] This supports our hypothesis that early adrenarche could be the consequence of increased insulin resistance due to BMI increase in early childhood.

While we could not find an association between current weight or BMI and DHEAS-levels, some studies did find a relation.[22,25,28] This discrepancy may originate from the differences between the cohorts with regard to age and sample size. Also, weight or BMI was mostly higher in the cohorts describing an association between current weight or BMI and DHEAS-levels.

In our previous study,[7] we found impaired final height in relation to early increase of BMI in boys and not in girls. For this reason we have now studied the boys. The reason for this sex difference is, however, uncertain. In Dutch boys the pubertal growth spurt will start on average at the age of 13 years, whereas girls on average will have their growth spurt at the age of 11 years. One hypothesis is that because of a later start of puberty, boys who undergo early adrenarche, will be exposed for a longer period of time to the effects of DHEAS-levels, and thus have an increased bone age at start of the growth spurt, in comparison to girls. Future studies could evaluate DHEAS levels in girls with CF aged 6–8 in relation to BMI Z-score changes between ages 1 and 6.

In the present study we report early adrenarche in boys with CF related to BMI increase in early childhood, presumably caused by an overly calorie-rich dietary regimen. Even though overall mean BMI Z-score between 1 and 6 years of age remained stable in our cohort, we found an increase in mean BMI Z-score between 1 and 6 years of age in boys with DHEAS levels ≥ 1 μmol/L and a decrease in mean BMI Z-score in boys with DHEAS levels < 1 μmol/L. The fact that significant early BMI Z-score increase in young boys with CF may result in decreased final height due to early adrenarche should be taken into account when deciding on the feeding regimen in new young boys with CF. While good nutritional status should remain emphasized, recent health care developments for children with CF should be taken into account when recommending for current and future feeding regimens. Newly diagnosed children with CF by the newborn screening program are in better nutritional state than those diagnosed before newborn screening. New promising treatments such as CFTR modulators may be serious game-changers, positively influencing CF outcome, making high caloric feeding redundant in the long run, also by decreasing the resting energy expenditure and therefore the need for high caloric feeding.[29] Of course, CF care providers will need to continue the monitoring of weight gain and nutritional status because there will still remain children who experience poor growth or failure to thrive while they have been diagnosed with CF.[30]

This study has some limitations. First, the study sample was small and thus our results are descriptive and must be confirmed in a larger group of boys with CF. No multivariate analyses could be performed due to the insufficient patient numbers. Second, the time of follow up was short and no patient had reached final height. Although it is assumed in prior research[7] that the early adrenarche with accelerated bone age results in impaired final height, this has not been proven yet in this cohort.

In conclusion, significant BMI Z-score increase in early childhood (between 1 and 6 years) results in (too) early adrenarche in boys with CF. Future research is needed in a larger longitudinal cohort to confirm if early adrenarche is indeed the underlying mechanism for an impaired final height in boys with CF and to study the effects of significant BMI Z-score increase in early childhood in girls with CF. Bearing the recent therapeutic developments in mind, we also recommend future studies to focus on reevaluating the current recommended feeding regimens in children with CF, balancing between ensuring sufficient calorie intake necessary for the underlying disease and avoiding excessive calorie intake and thereby causing a too rapid BMI gain. Monitoring BMI in children with CF is essential, not only for pulmonary outcomes, longitudinal growth and the impact of BMI Z-score increase in early childhood on final height, but also because of the general risk of BMI gain in childhood and obesity on future cardiovascular health.[31] High calorie feeding regimens may need to be reconsidered, especially in early childhood in boys, as it may result in a too rapid BMI gain and potentially resulting in a decreased final height.

AUTHOR CONTRIBUTIONS

Gizem Tamer: Conceptualization; investigation; writing—original draft; methodology; validation; visualization; writing—review and editing; formal analysis; project administration; data curation. **Hubertus Gerardus Maria Arets**: Conceptualization; funding acquisition; writing—original draft; writing—review and editing; methodology; supervision; resources; project administration. **Cornelis Kors van der Ent**: Conceptualization; funding acquisition; writing—original draft; writing—review and editing; methodology; supervision; resources; project administration. **Hanneke Margo van Santen**: Conceptualization; funding acquisition; writing—original draft; writing—review and editing; methodology; supervision; resources; project administration. **Hetty Jacoba van der Kamp**: Conceptualization; funding acquisition; writing—original draft; writing—review and editing; methodology; validation; supervision; resources; project administration.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Tamer G, Arets HGM, van der Ent CK, van Santen HM, van der Kamp HJ. BMI increase during early childhood in boys with cystic fibrosis and early adrenarche. *Pediatr Pulmonol*. 2024;59:991-996. doi:10.1002/ppul.26861