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Original Research

Adiposity rebound and height velocity in patients with congenital adrenal hyperplasia

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Abstract

Objective **Adiposity rebound is the first rise in BMI that occurs after the initial decrease during infancy. Early adiposity rebound, before age 5, is a risk factor for later obesity and metabolic problems. We investigated adiposity rebound in children with Congenital Adrenal Hyperplasia due to 21-hydroxylase deficiency (CAH).**

Design **Longitudinal observational registry study.**

Methods **Height, weight, and BMI from patients younger than 20 years in the I-CAH Registry was described by non-linear mixed-effects models. Covariates of glucocorticoid dose, mineralocorticoid dose, 17-Hydroxyprogesterone were assessed on growth and bone age.**

Results **A total of 10 261 visits within 573 patients (43.6% male) showed significant variation in age at latest peak height velocity [8.4 years (SD = 3.0) in boys; 9.0 years (SD = 1.6) in girls]. Peak height velocity was more blunted in boys [7.7 cm/year (SD = 1.4)] than girls [7.4 cm/year (SD = 1.3)] in comparison to normative values. Adiposity rebound occurred earlier than age 5 years in 82% of the cohort, mean age 3.7 years (SD = 1.3) in boys and 3.9 years (SD = 0.9) in girls. Girls prescribed higher doses of glucocorticoid were associated with heavier weight in adolescence and earlier adiposity rebound. Bone age was increasingly advanced in those prescribed higher doses in both sexes.**

Conclusions **There is a large variation in the timing of adiposity rebound and SITAR-estimated latest peak height velocity in children with CAH. In addition to identifying individuals with CAH who may be at risk of adverse cardiometabolic outcomes these metrics may serve as early surrogate outcomes in future research investigating early-life treatment strategies.**

Keywords adiposity rebound, congenital adrenal hyperplasia, glucocorticoids, statistical modelling, superImposition by translation and rotation, growth

Significance statement

We used non-linear regression modelling to quantify growth in a large group of children with congenital adrenal hyperplasia. We found large variability in their age at adiposity rebound, occurring early before age 5 years in over 80% of the cohort. The latest peak height velocity was significantly blunted and earlier compared to healthy patient studies, at mean age 8.4 years (SD 3.0) in boys and 9.0 years (SD 1.6) in girls. Multivariate modelling showed girls prescribed higher doses of glucocorticoids associated with significantly higher BMI in adolescence and earlier adiposity rebound. Adiposity rebound can be considered as an early surrogate outcome measure for future studies into early-life treatment strategies.

Background

Congenital Adrenal Hyperplasia (CAH) is the most common form of inherited adrenal insufficiency, affecting approximately 1 in 15 000 individuals. In over 90% of cases, it is due to 21-hydroxylase deficiency (21OHD) causing impaired conversion of 17-hydroxyprogesterone (17OHP) to 11-deoxycortisol, resulting in a deficiency of cortisol, and sex hormone excess. Patients require lifelong glucocorticoid replacement and, in most cases, mineralocorticoid replacement. International consensus guidance recommends a hydrocortisone daily equivalent dose of 10-15 mg/m^2 per day.[1,2]

In healthy children, body mass index (BMI) increases after birth before falling after approximately 1 year, then increasing in early childhood after approximately age six. Adiposity rebound is the last nadir in BMI in early childhood, that corresponds to a decline in fat mass in relation to height. This follows a different trajectory between sexes and is frequently reported at an earlier age in girls than boys, although some studies find no difference in timing with sex. Earlier adiposity rebound in otherwise healthy children is associated with obesity in later life and cardiometabolic diseases in adulthood.[3,4]

Children with CAH have an earlier adiposity peak and rebound compared to healthy children. Precise estimates differ between studies, from as early as 1.7 years in a UK study to 3.8 years in a study of 194 children from the USA.[5-7] The reasons for the early timing of adiposity rebound in CAH are poorly understood and the factors influencing this difference in body composition remain elusive. Multicentre studies have also shown increased prevalence of adverse cardiometabolic markers in adolescents with CAH.[8,9] A better understanding of the factors that contribute to the early adiposity rebound observed in children with CAH and whether this increases the likelihood of later obesity will help to improve monitoring and treatment strategies, ultimately leading to better health outcomes.

Latest peak height velocity has been shown to be blunted in 21OHD, although there are differing estimates about magnitude and timing,[10-12] and studies are yet to quantify this using SuperImposition by Translation And Rotation modelling (SITAR), an effective statistical strategy to model growth in childhood.[13,14] Bone age is known to be inappropriately advanced in this condition, although findings as to how this varies with dose are conflicting.[1,10,15]

The International Congenital Adrenal Hyperplasia (CAH) Registry provides rich longitudinal data in children with CAH due to 21OHD.[16] We set out to use advanced statistical modelling to quantify growth in children with CAH, and assess associations between growth, doses of glucocorticoid replacement and levels of disease control.

Methods

This retrospective cohort study included children and young people under 20 years of age diagnosed with 21OHD and consented for data sharing with the I-CAH Registry. Ethical approval for the registry has been approved by the West of Scotland research ethics committee (24/WS/0059), and was conducted according to the Declaration of Helsinki. Data were extracted on 25/01/2024 and pre-processed, with subsequent clarification of outliers by liaison with contributing centres, to correct data entry errors.

Missing data

Missing data were accommodated using a combined approach of spline interpolation between longitudinal points for height, weight, and bone age and last observation carried forward or next observation carried backward for dosing (Methods[17]).

Statistical analysis

Summary and reference values

Statistical analysis was performed in *R*.[18] Continuous variables were summarised with median and interquartile range. Standard deviation scores (SDS) were derived by comparing to World Health Organization (WHO) reference standards for growth.[19-21]

Treatment dose and disease control

Glucocorticoid doses were converted to hydrocortisone equivalent (hydrocortisone(mg) = prednisolone(mg) × 4, other ratios in Table S1[17]) and summed to total daily dose. Biomarkers 17OHP and androstenedione were measured in local laboratories with different assays, converted to standard units of nmol/L (Table S1[17]) and natural log transformed to better approximate normality.

Longitudinal modelling of growth

Weight, height, and BMI were modelled on the natural log of age in each sex separately using SuperImposition by Translation and Rotation (SITAR).[22] This is a mixed effects model that fits an average b-spline curve through the data applying random effects that are allowed to vary in three dimensions for each individual participant: Size, a translation on the *y* axis; timing, a translation on the *x* axis; and intensity, horizontal stretching or compression of the curve equivalent to a rotation in the anteroposterior plane of the graph. These 3 adjustments allow for the estimation of a growth pattern that is of a similar shape in all children, but comprises a sample of children who vary in stature, experience growth "spurts" at variable times in childhood, and have a variable velocity of growth during such growth spurts. SITAR describes an overall "average" pattern of growth along with a robust estimation of the variability of growth across the sample population. Alternatives, including the Lambda–Mu-Sigma model, cannot estimate the variability in the timing of growth between participants.[14]

The flexibility of a SITAR curve increases with pre-defined degrees of freedom. Due to the complexity of the parameters of model estimation, curves were fit to children with adequate data points between specific age ranges, with optimum degrees of freedom defined by minimizing the Bayesian information criterion (BIC).[23] Age and BMI at adiposity rebound, and age and speed of latest peak height velocity were extracted from models transformed onto the absolute scale. Comparison of mean growth metrics was made to data from studies of healthy children using two-sided *t*-tests. Height and weight for each participant at age 18 was extracted from SITAR models and compared against adiposity rebound and height velocity metrics for each participant by linear regression.

Covariate modelling

To assess the impact of dose and disease control on growth in this cohort, the covariates of dose of hydrocortisone, dose of fludrocortisone, level of 17OHP and level of androstenedione were assessed. As SITAR cannot estimate covariates during model fitting, the modelling was simplified to a cubic spline with a two-level participant level random intercept nested within treatment centre. Each covariate was interacted with each element of the cubic spline basis function, optimum degrees of freedom defined by lowest BIC. This simplified modelling strategy did not require restriction on participant data by age or number of data points, but did require all covariates to be available at each clinic visit for data from that visit to be included. Both glucocorticoid and mineralocorticoid doses were included in the model, but models were tested with a combination of both 17OHP and androstenedione or each biomarker individually to define the most efficient model. Clinically meaningful values of covariates defined by expert consensus were inserted into models to describe model trajectories, confidence intervals calculated by bootstrapping across 500 replications (Methods[17]).

Bone age

Bone age advancement was calculated by bone age minus chronological age. Bone age was calculated locally and thus methodology differed between centres. Due to reduced frequency of this measurement, a basic cubic model was used to estimate the change in bone age advancement on age.[24] The model was fit with similar covariates as growth models, and then reassessed using just dose of glucocorticoid replacement as a single interacted covariate to maximize the number of visits available for modelling.

Results

Biometrics and biomarkers

This observational registry study included 746 children with 21OHD (43.6% male) from 22 countries treated in 47 different centres, 573 children having sufficient data for modelling of height and 457 for modelling of adiposity rebound (Figure S1[17]). Overall, 11 460 visits were distributed with median 11 visits (Q1:6 to Q3:21) within each participant, 10 261 visits contributing to height modelling and 6901 to adiposity rebound modelling. Visits occurred between 23/1/2003 and 17/1/2024, 6388/11 460 (56%) occurring in 2017 or beyond. There was a greater proportion of visits at younger ages, with median age at visit 5.1 years (Q1:1.9 to Q3:9.2) (Table 1). Attrition meant only 206/573 (36%) of participants had data available beyond the age of 12 years for height modelling.

Glucocorticoid treatment was most commonly with hydrocortisone (84.9% of visits, Table S2[17]), 83.5% of visits with fludrocortisone prescribed. Of 1430/11 460 (12.5%) visits with a recorded biomarker available, 17OHP recorded in 1888/11 460 (16.5%) visits (median 29.8 nmol/L Q1:4.2 to Q3:112.0), androstenedione recorded in 1786/11 460 (15.6%) visits (median 1.7 nmol/L Q1: .2 to Q3: 4.4), with 1430/11 460 (12.5%) visits having both biomarkers available for analysis. Height SDS at visits was median −0.1 (Q1: −1.1 to Q3:0.9) and BMI SDS median 0.7 (Q1:−0.2 to Q3:1.5).

Growth modelling and adiposity rebound

There was significant variation in age at latest peak height velocity occurring at mean 8.4 years (between participant SD = 3.0) in boys and 9.0 years (SD = 1.6) in girls (Figure 1). Derived latest peak

Table 1 Summary statistics.

	Total	Male	Female
Number of patients (*n*)	746	325	421
Number of visits (*n*)	11 460	5690	5770
Number of countries (*n*)	22	20	22
Number of centres (*n*)	47	40	47
Number of visits per patient	11	14	10
Median (Q1 to Q3)	(6 to 21)	(8 to 24)	(6 to 18)
Number of years visits spanned within patients	6.5	7.7	5.5
Median (Q1 to Q3)	(2.9 to 10.7)	(3.6 to 11.3)	(2.4 to 10.0)
Age of patient at youngest visit (years)	0.3	0.2	0.3
Median (Q1 to Q3)	(0.1 to 3.4)	(0.1 to 2.9)	(0.1 to 3.7)
Age of patient at most recent visit (years)	9.3	10.0	8.8
Median (Q1 to Q3)	(5.6 to 13.6)	(6.4 to 13.6)	(5.0 to 13.5)
Number of visits with height available	11 251	5600	5651
(% interpolated)[a]	(4.1)	(3.9)	(4.3)
Height SDS at visit	−0.1	0.0	−0.2
(Median (Q1 to Q3)	(−1.1 to 0.9)	(−1.0 to 1.0)	(−1.1 to 0.7)
BMI SDS at visit	0.7	0.8	0.6
(Median (Q1 to Q3)	(−0.2 to 1.5)	(−0.1 to 1.5)	(−0.3 to 1.5)
Number of visits with bone age available	3803	2116	1687
(% interpolated)[a]	(62.4)	(64.5)	(59.8)
Bone age advancement at visit	0.9	0.9	0.9
(Median (Q1 to Q3)	(−0.3 to 2.5)	(−0.4 to 2.8)	(−0.2 to 2.2)
Visits with hydrocortisone equivalent dose available (*n*) (% carried to interpolate)	*n* = 10 088 (46.0%)	*n* = 5129 (47.7%)	*n* = 4959 (44.2%)
Dose of hydrocortisone equivalent at visit per BSA (mg/m^2/day) (median (Q1 to Q3)[b]	13.8 (9.7 to 16.1)	14.1 (10.0 to 16.4)	13.5 (9.5 to 15.7)
Visits with fludrocortisone dose available (*n*)	*n* = 10 804	*n* = 5381	*n* = 5423
(% carried to interpolate)	(1.7%)	(1.3%)	(2.2%)
Dose of fludrocortisone per day (micrograms)	123.5	128.8	118.3
(Median (Q1 to Q3)	(50 to 200)	(50 to 200)	(50 to 150)
17-OH progesterone (nmol/L)	29.8 [*n* = 1888]	29.0 [*n* = 1041]	30.3 [*n* = 847]
(Median [*n*] (Q1 to Q3)	(4.2 to 112.0)	(4.5 to 99.9)	(3.9 to 128.3)
Androstenedione (nmol/L)	1.7 [*n* = 1786]	1.4 [*n* = 987]	2.0 [*n* = 799]
(median [*n*] (Q1 to Q3)	(0.2 to 4.4)	(0.0 to 3.5)	(0.3 to 5.6)

n = number; Q1 = quartile 1; Q3 = quartile 3; SDS = standard deviation score; BSA = body surface area.
[a]Missing data for growth and bone age was interpolated between visits using splines, but not extrapolated beyond first or last available data point for each individual patient.
[b]Hydrocortisone equivalent calculated by multiplying preparations by the following factors: prednisolone/prednisone ×4; dexamethasone ×27; cortisone acetate ×.8; methylprednisolone ×5 (Table S1 for all conversion factors[17]). 84.9% of visits prescribed hydrocortisone (Table S2 for proportions of preparations prescribed[17]). Missing data for dose was carried forward or backward within clinically plausible limits set by age (Methods 1[17]).

height velocity was 7.7 cm/year (SD = 1.4) in boys and 7.4 cm/year in girls (SD = 1.3), significantly earlier and lower than that derived from healthy children in the UK Avon Longitudinal Study of Parents and Children [10.6 cm/year at 13.5 years in boys; 7.7 cm/year at 11.7 years in girls (2-sided *t*-tests, $P < .05$)].[13] Optimum SITAR fit was 5 and 6 degrees of freedom for height and weight respectively, $R^2_{marginal}$ 0.91 to 0.99 (Table 2, Table S3[17]).

BMI modelled directly by SITAR estimated adiposity rebound in boys at mean of 3.7 years (SD:1.3) and 3.9 years in girls (SD:0.9), with 80.4% of males and 82.8% of females occurring early before age 5. This was also earlier than the age calculated in a recent large healthy participant cohort of 5.1 years (SD:1.3) in both boys and girls (2-sided *t*-tests, $P < 0.05$)).[25] A sensitivity analysis showed these metrics did not change significantly when interpolated data was not used in the calculations (Table S4, Figure S2). Residual plots showed individual patient estimates were not biased towards the amount or timing of data contributing to the SITAR models (Figure S3).

Earlier adiposity rebound and greater BMI at adiposity rebound was associated with heavier SITAR predicted weight at 18 years in both sexes ($P < 0.05$). Age at adiposity rebound was not associated with predicted height at 18 years ($P > 0.05$), but earlier age at peak height velocity was associated with shorter height at 18 years ($P < 0.05$, Table S5, Figure S4[17]).

Covariate modelling

Optimum model fit with covariates was obtained by using 17OHP alone, in comparison to androstenedione alone or both markers

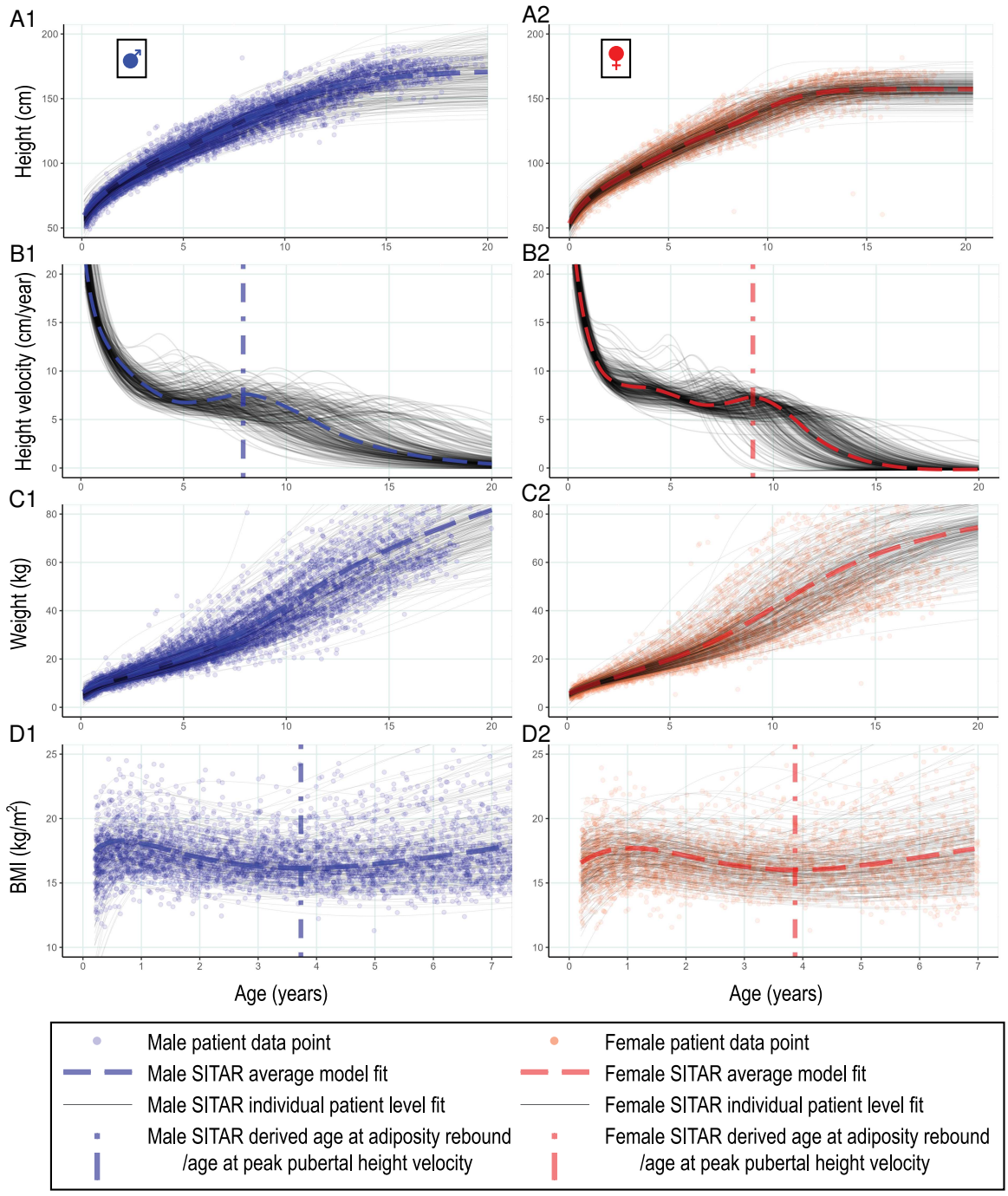

Figure 1 SITAR models to quantify height, weight and BMI. Legend: Prefix A = height; B = height velocity; C = weight; D = BMI. Suffix 1 = male; 2 = female. SITAR: SuperImposition by Translation And Rotation.

combined (lower BIC). There were reduced visits available with covariates for modelling (1785/11 460 (15.6%) visits), leading to an optimum model fit achieved with lower degrees of freedom of 3, unable to model latest peak height velocity within this smaller sub section of the population. Incorporating the covariates of hydrocortisone, fludrocortisone and 17OHP improved the proportion of variance explained by the models. The $R^2_{marginal}$ increased by 2.3% in boys and 1.3% in girls for height, and by 6.7% in boys and 4.8% in girls for weight (full model parameters in Tables S6-S7[17]).

Regression modelling assesses the association of variability of continuous variables, rather than artificially dichotomizing the data into groups.[24] Non-linear interactions are illustrated by bootstrapping clinically meaningful values decided by expert consensus into each model to derive representations of participants taking a dose of 8 mg/m^2/day as low dose versus a high dose of 18 mg/m^2/day, and a consistent level of 17OHP of 10 nmol/L to demonstrate good control versus a consistent level of 17OHP of 38 nmol/L to demonstrate poor control (Figure 2). Doses were selected to compare the lowest recommended

Table 2 SITAR model derived metrics of growth.

	Male patients			Female patients		
Age at latest peak height velocity (years)	8.4			9.0		
Mean (SD)	(3.0)			(1.6)		
Latest peak height velocity (cm/year)	7.7			7.4		
Mean (SD)	(1.4)			(1.3)		
Age at adiposity rebound	3.7			3.9		
Mean (SD)	(1.3)			(0.9)		
BMI at adiposity rebound	16.2			16.0		
Mean (SD)	(1.5)			(1.5)		
SITAR outcome variable	**Height (cm)**	**Weight (kg)**	**BMI (kg/m^2)**	**Height (cm)**	**Weight (kg)**	**BMI (kg/m^2)**
Number of patients used to fit SITAR model	266	267	219	307	309	238
Number of data points used to fit SITAR model	5196	5224	3030	5065	5101	2871
SITAR predicted value at age 18	166.9	74.8	27.1	157.2	68.9	28.0
Mean (SD)	(14.2)	(17.0)	(6.0)	(7.2)	(9.7)	(4.5)
WHO z-score of SITAR predicted value at age 18	−1.2	—	1.3	−0.9	—	1.6
Mean (SD)[a]	(1.9)		(1.3)	(1.1)		(1.0)
SITAR degrees of freedom	5	6	3	5	6	3
Restricted age range of patients to fit SITAR (years)	0.2 to 20.0	0.2 to 20.0	0.2 to 7.0	0.2 to 20.0	0.2 to 20.0	0.2 to 7.0
Root mean square error	1.50	1.50	0.77	2.60	2.10	0.91
Marginal R^2	0.74	0.92	0.12	0.91	0.90	0.07
Conditional R^2	0.99	0.99	0.84	0.99	0.91	0.80

SD = Standard deviation, variability defined by between patient random effects. SITAR: SuperImposition by Translation And Rotation. Optimum degrees of freedom defined by lowest Bayesian Information Criterion. Patients' included in models if they had 6 or more measures of the necessary biometric.
[a]WHO do not provide reference standards for weight for age beyond 10 years.

physiological replacement dose in adrenal insufficiency[26] against a plausible high value. A dose of 17 mg/m^2/day has been shown to suppress growth in CAH,[27] and the 80th centile of dose across this cohort was 17.5 mg/m^2/day (Figure S5), thus an illustrative upper dose of 18 mg/m^2/day was selected by consensus.

Larger doses of glucocorticoid replacement were associated with greater weight gain in girls. This achieved a statistically significant difference after the age of 10 where girls on higher doses with poor disease control had greater weight and BMI (Table 3, Figure 3). In girls, adiposity rebound occurred 24.0 months earlier (95% CI 3.6 to 55.9) in patients with higher doses and worse disease control compared to those with lower doses and better disease control. However, this difference in adiposity rebound was not robust to all sensitivity analyses. There was no significant difference in timing with boys (7.2 months earlier, 95% CI −1.2 to 40.6).

Care must be taken when interpreting these covariate models. Alternative example values inserted are demonstrated in Table S8, Figure S6.[17] These show similar trajectories, as does a sensitivity analysis when modelling was carried out without interpolated or carried values (Table S9, Figure S7). However, sensitivity analysis did change whether metrics of growth had a statistically significant difference between example comparisons. The most robust finding was an increase in weight and BMI in girls on higher doses in early adolescence, consistent across all permutations of sensitivity analysis.

Bone age advancement

Across the cohort bone age advancement peaked at age 10.4 (95% CI 8.3 to 17.0, $n_{participants} = 204$) years in boys and 8.7 (95% CI 7.4 to 10.9, $n_{participants} = 240$) years in girls with mean advancement of 2.1 (95% CI 1.7 to 2.6) and 1.2 (.9 to 1.6) years, respectively (Table S10, Figure S8[17]). Covariate modelling with all doses and levels of disease control did not show statistical significance, impacted by reduced visits ($n_{participants} = 144$, $n_{visits} = 572$) with those covariates available for modelling. However, the more parsimonious cubic model incorporating dose of hydrocortisone equivalent alone ($n_{participants} = 415$, $n_{visits} = 3540$) showed children prescribed higher doses within this data had greater bone age advancement between the ages of 2.5 to 11.4 years in boys and 3.0 to 10.8 years in girls. This difference peaked at 1.2 (0.8 to 1.8) and 0.6 (0.3 to 1.0) years more advanced for those modelled on 18 mg/m^2/day compared to 8 mg/m^2/day in boys and girls, respectively (Figure 4). Results were similar when restricted to models trained only on bone age estimated by the Greulich and Pyle method (81% of measurements) (Table S11, Figure S9).

Discussion

We have used advanced statistical modelling on multicentre registry data from children with CAH to quantify the blunted latest peak of height velocity and early adiposity rebound seen in this condition, as well as significant variability in those metrics between individuals. We have shown associations with increased weight gain, higher BMI and advanced bone age in those prescribed higher doses of glucocorticoids.

The blunting of latest peak height velocity was more marked in boys than girls. While one previous study of 598 individuals with CAH noted an earlier growth spurt but reported no reduction in

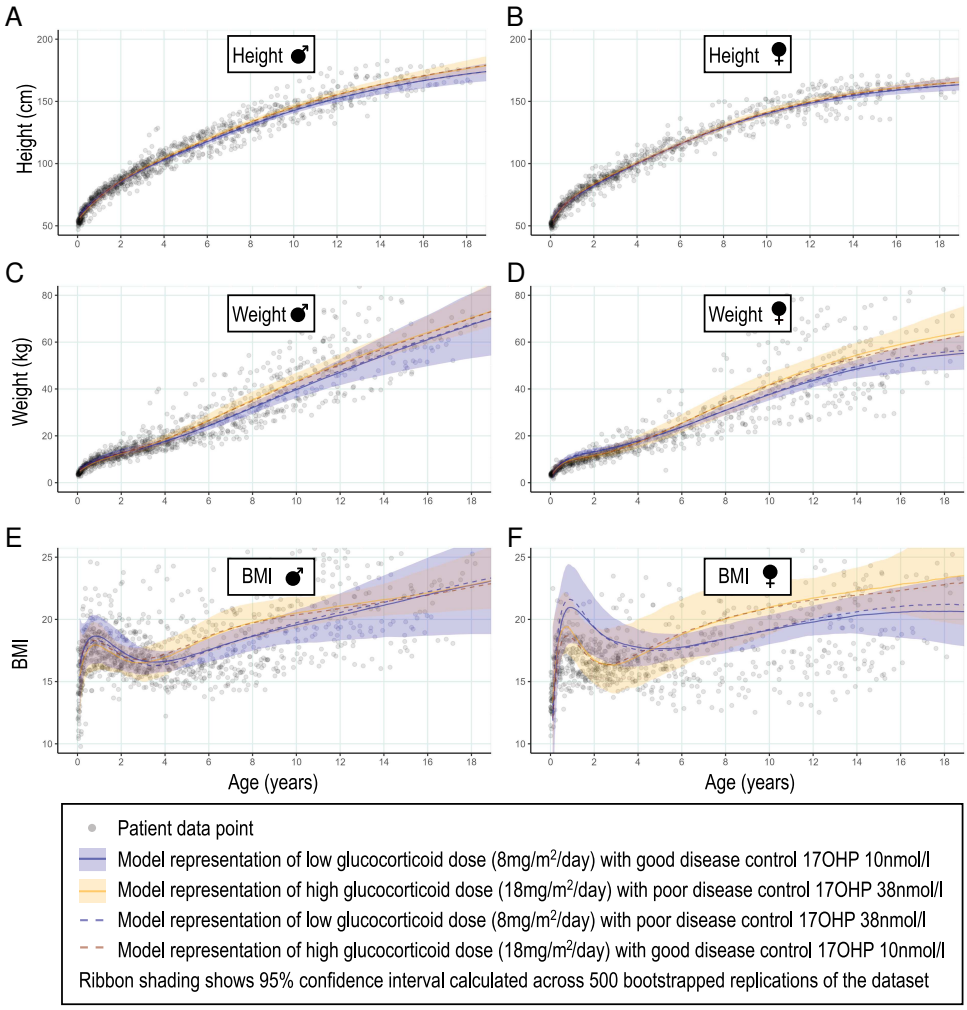

Figure 2 Covariate models representations of different glucocorticoid doses and levels of 17-hydroxyprogesterone. Legend: A = male height; B = female height; C = male weight; D = female weight. E = male BMI; F = female BMI. Figures show trajectories of growth for modelled values contained within Table 3. Alternative example values applied to models is found in Figure S3.[17]

height velocity,[28] the majority of studies assessing height velocity in CAH have found blunting.[10-12] None of these studies have employed SITAR, a method more appropriate to assess between participant variability.[22] The large standard deviation we have found in magnitude-of and age-at latest peak height velocity highlights the importance of modelling repeated measures appropriately to reduce the risk of aggregation bias,[14] and is likely to explain why we have estimated the mean peak height velocity of 7-8 cm/year in CAH slightly higher than others. Other powerful techniques including the quadratic-exponent-pubertal-stop technique (QEPS) may provide more detailed insights into growth in this disease in the future.[29] This method requires more data points per patient and was unable to converge with these data.

Mean age at adiposity rebound estimated by SITAR modelling was similar between sexes in this cohort, in over four-fifths of the cohort occurring before 5 years of age, a much higher proportion than the 40% of healthy children reported in a recent meta-analysis.[30] Early adiposity rebound has been associated with adverse metabolic profiles including higher glucose and insulin resistance in healthy children at age 7, as well as increased risk of overweight and obesity in adolescence and adulthood.[4,9,25,31,32] Our results highlight this association with later obesity is also the case in CAH. We must consider the possibility of a confounding obesogenic environment or metabolome causing the change in both metrics, but it may be possible that this early shift in adiposity reflects metabolic changes that lead to later obesity. Whether directly causal or simply an associated risk factor, early adiposity rebound can highlight children that are at greater risk of obesity later in life, and can be used as an early outcome metric when researching different early treatment strategies.

Age at adiposity rebound in CAH has been reported even earlier than our analysis, including 1.7 years in 22 children,[6] 3.0 years in 29 children,[33] 3.8 years in 16 children[34] and 3.3 years in 42 children.[5] The largest cohort to date included 515 children and an adiposity rebound of 3.9 years in boys and 3.3 years in girls, although unfortunately this was derived from LMS modelling that did not allow an estimate of between patient variability or quantification of height velocity.[35] The non-linear SITAR modelling and large cohort is a significant strength of our work, allowing us to robustly estimate the variability in adiposity rebound. The SD of 1.3 years in males shows the extent of this variability, highlighting how this metric can differentiate between

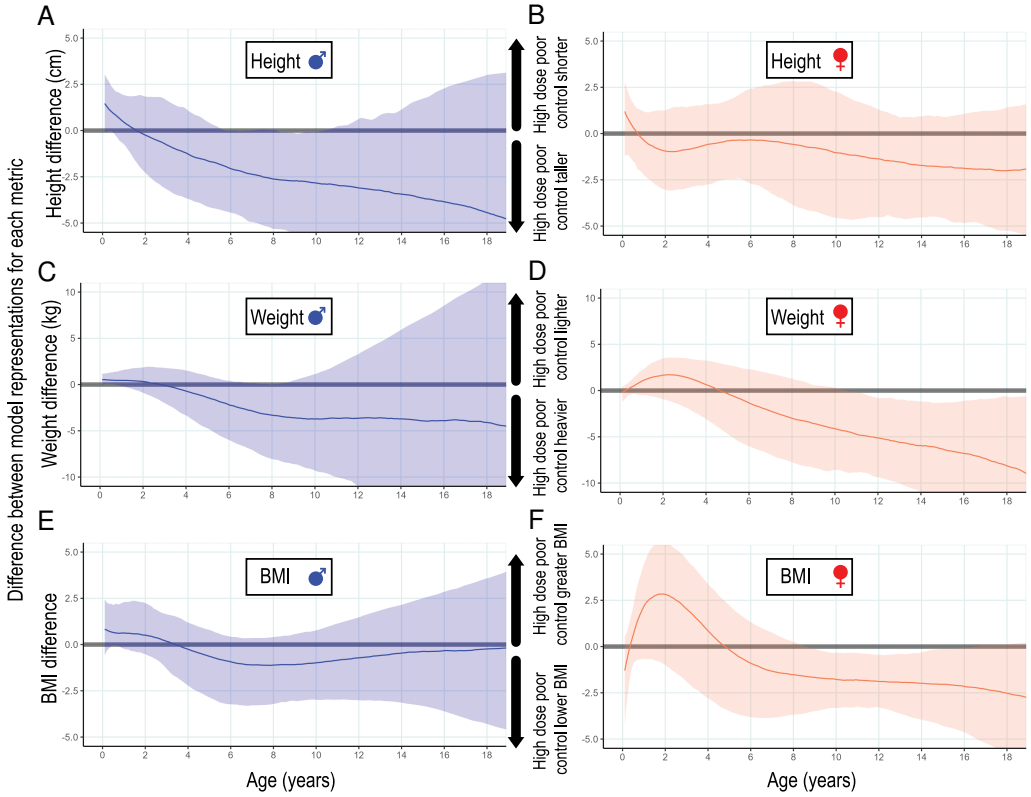

Figure 3 Bootstrapped differences between model representation of patient with low glucocorticoid dose and consistently good disease control versus patient with high glucocorticoid dose and consistently poor disease control. Legend: Model trajectories calculated from multivariate models with the following clinically meaningful values: Low glucocorticoid replacement dose defined as 8 mg/m^2/day hydrocortisone equivalent, high defined as 18 mg/m^2/day; Good disease control defined as 17-OH progesterone consistently 10 nmol/L, poor disease control defined as 38 nmol/L. Differences calculated as a model representation of patients with low dose good control minus a model representation of patients with high dose and poor control. 95% Confidence interval shading produced by calculating difference in metrics across 500 bootstrap replications of the data. A: Male height difference, B: female height difference, C: male weight difference D: female weight difference, E: male BMI difference, F: female BMI difference.

individuals at an early age at greater risk of adverse metabolic outcomes. The estimate of a later adiposity rebound than previous studies may be indicative of improving management of the condition, likely due to improving iterations of international guidance over the last 2 decades.[1]

The multivariate modelling of height and weight showed girls prescribed higher doses and with poorer disease control gained more weight in later childhood and adolescence, driving an increase in BMI. The higher dose and poorer disease control was also associated with earlier adiposity rebound. Trajectories of BMI were similar in boys but not statistically significant, due in part to slightly less data and larger variability. This differs from previous studies that report no association between dose, disease control and adiposity in CAH in much smaller cohorts.[33,34] The multivariate modelling must be interpreted with care, model estimates having wider confidence intervals at later ages, driven by less than a third of patients having any data beyond 12 years of age. However, the SITAR modelling done on a larger proportion of the cohort did show an earlier peak in height velocity was associated with shorter predicted height at age 18. Future work with data from the I-CAH registry will aim to assess a greater number of individuals followed to final height, highlighting the importance of ongoing data collection.

The associations we have shown between growth and glucocorticoid dose highlight the controversy in applying disease specific growth charts for this condition. While patients with CAH have different growth trajectories to healthy patients, growth charts recently published developed from a heterogenous population of patients with CAH must be used with care, as comparisons may be made to data from patients that have had an unreported level of disease control.[35] Clinicians should aim to optimize growth in children with CAH towards normal growth.

Bone age advancement was higher in individuals prescribed higher doses in this cohort. Correlation does not necessarily mean causation, as it is undisputed that underdosing of glucocorticoid replacement in CAH is likely to cause bone age advancement. International guidance since 2002 has helped clinicians target appropriate dosing strategies for children with CAH, recommending regular review and dose adjusted dependent upon clinical need.[1] Individuals deemed to have poor control, as indicated by bone age advancement or biomarkers of disease control, are therefore likely to be prescribed higher doses, indicative of the heterogeneity of treatment effect that we see from glucocorticoid replacement in CAH.

A lack of association between bone age and glucocorticoid dose has often been shown in other studies.[8,36,37] Karishma et al. found that those with higher doses had lower bone mineral

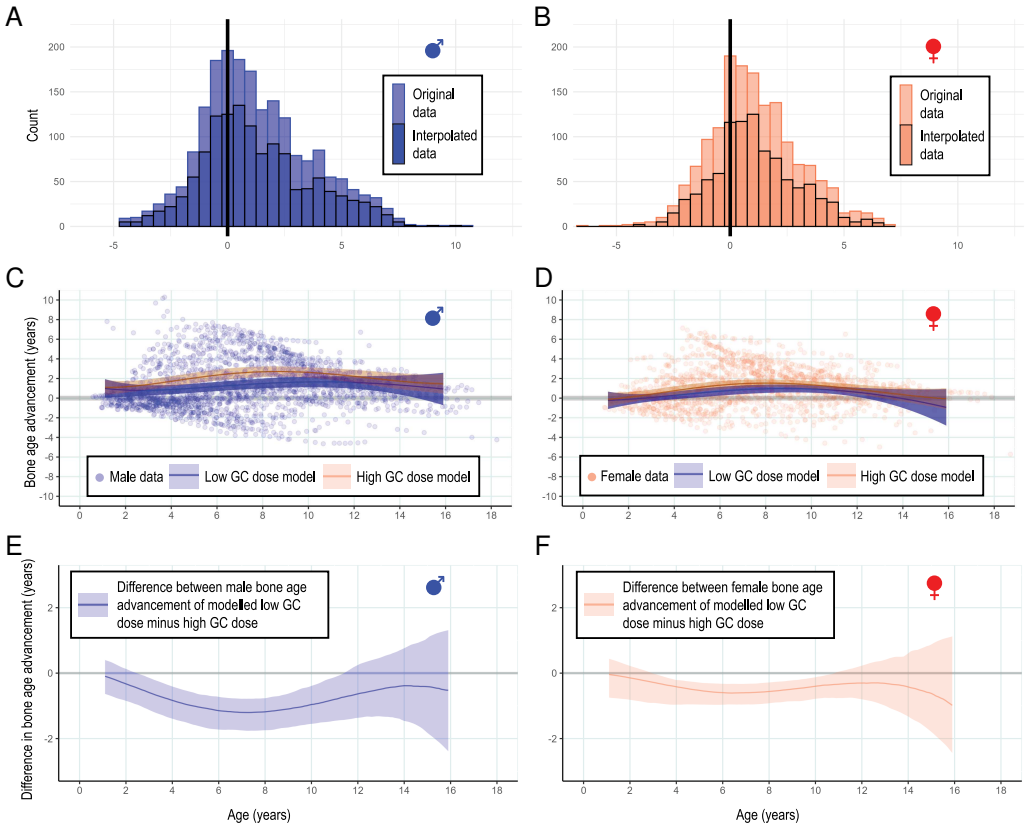

Figure 4 Bone age advancement modelling. Legend: Data available for bone age modelling, displaying parsimonious bone age models with only dose of hydrocortisone equivalent added as a covariate. A, B: bone age data available, showing proportion of values interpolated between measurements, C, D: Bone age advancement (bone age—chronological age) in individuals overlaid with model representations of those prescribed low dose hydrocortisone equivalent (8 mg/m^2/day) versus those prescribed high dose hydrocortisone equivalent (18 mg/m^2/day), E, F: Difference between model representations of bone age advancement in those on high dose subtracted from those on low dose. A, C, E male data and models, B, D, F female data and models.

density, although, those with low bone mineral density were significantly older within their cohort, and their comparison did not account for age.[38] The non-linear relationship between bone age advancement and age we report here, similar to the shape reported by Bretones et al,[10] highlights the importance of accounting for non-linearity. Al-rayess et al. found lower bone age SDS in children on lower doses, driven by the availability of glucocorticoids as suspension rather than tablets.[15] That study design was able to take advantage of differences in available treatment preparations between their groups, inferring that those on tablet preparations were more likely to be receiving greater doses than they required, and thus a reason as to why their data showed the opposite association to that we report here. Our finding in a larger cohort of observational data highlights that bone age is a lagging indicator of previously inadequate disease control.[1]

Limitations of this study include only 15% of visits having adequate data available for multivariate modelling, and the resultant simplification of multivariate models that had fewer degrees of freedom. Multivariate examples assume a consistent dose throughout childhood and adolescence, whereas patients may require higher doses during puberty due to the downregulation of 11β-hydroxysteroid dehydrogenase type 1.[39] SITAR modelling could only be carried out by restricting data to individuals with adequate data points for models to converge. We have not been able to assess timing of replacement doses, clinical pubertal staging, body fat percentage or other measures such as insulin resistance or bone density. However, the number of individuals modelled here provides estimates for adiposity rebound in CAH in the largest cohort to date. Age at diagnosis and ethnicity of patients as well as methods of measurement of biometrics, bone age and biomarkers vary between centres, and thus effect sizes must be interpreted with caution. This centre effect has been controlled for appropriately as a centre level random effect in multivariate modelling but may still have some residual effect on the estimates presented, and caution must be applied before considering that associations will be consistent across different ethnic groups. Significant attrition with age means we must be cautious about the overall trajectories of growth presented. However, the longitudinal non-linear modelling complies with recent state-of-the-art guidance on such analysis.[24]

Age at adiposity rebound was highly variable in this cohort of children with CAH. Early adiposity rebound and early increases in height velocity were associated with detrimental growth trajectories, which are likely to be related to adverse metabolic health outcomes later in life. Age at adiposity rebound could potentially serve as a surrogate marker of long-term health risk when comparing treatment strategies for CAH in future controlled studies.

Table 3 Covariate adjusted multivariate model metrics assessing disease associations with growth.

Sex of patients in underlying model	Male				Female			
Data points with covariates available to train model	982 Visits | 139 patients				803 Visits | 143 patients			
Representation of model	Low dose good control	Low dose poor control	High dose good control	High dose poor control	Low dose good control	Low dose poor control	High dose good control	High dose poor control
Metrics inserted to demonstrate covariate model fit								
Hydrocortisone equivalent (mg/m^2/day)	**8**	**8**	**18**	**18**	**8**	**8**	**18**	**18**
Fludrocortisone dose (micrograms/day)	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
17-OH progesterone (nmol/L)	**10**	**38**	**10**	**38**	**10**	**38**	**10**	**38**
Model derived estimates: (bold type indicates statistically significant difference between those on low dose with good control versus those with high dose and poor control)								
Height at age 8 (cm)	131.0	131.5	133.1	133.6	129.4	129.6	129.8	130.0
(95% CI)	(128.9 to 132.9)	(129.3 to 133.3)	(131.2 to 134.9)	(131.5 to 135.6)	(127.8 to 131.0)	(127.9 to 131.2)	(127.1 to 132.3)	(127.0 to 132.7)
Height SDS at age 8	0.7	0.7	1.0	1.1	0.5	0.5	0.6	0.6
(95% CI)	(0.3 to 1.0)	(0.4 to 1.1)	(0.7 to 1.4)	(0.7 to 1.5)	(0.2 to 0.8)	(0.2 to 0.8)	(0.1 to 1.0)	(0.1 to 1.1)
Weight at age 8 (kg)	32.0	32.3	35.0	35.3	30.9	30.9	33.9	34.0
(95% CI)	(29.3 to 34.1)	(29.7 to 34.7)	(32.2 to 38.4)	(32.3 to 38.9)	(28.9 to 33.1)	(28.8 to 33.0)	(28.8 to 38.9)	(28.8 to 39.0)
Weight SDS at age 8	1.5	1.6	2.0	2.1	1.2	1.2	1.7	1.7
(95% CI)	(1.0 to 1.9)	(1.0 to 2.0)	(1.5 to 2.6)	(1.6 to 2.7)	(0.9 to 1.6)	(0.8 to 1.6)	(0.8 to 2.4)	(0.8 to 2.4)
BMI at age 8 (kg/m^2)	18.6	18.7	19.7	19.8	18.5	18.4	20.1	20.0
(95% CI)	(17.5 to 19.6)	(17.6 to 19.8)	(18.4 to 21.3)	(18.5 to 21.3)	(17.3 to 19.6)	(17.3 to 19.6)	(17.5 to 22.8)	(17.5 to 22.6)
BMI SDS at age 8	1.6	1.6	2.0	2.0	1.3	1.3	1.9	1.8
(95% CI)	(1.0 to 2.0)	(1.1 to 2.0)	(1.5 to 2.6)	(1.5 to 2.6)	(0.8 to 1.7)	(0.8 to 1.7)	(0.9 to 2.6)	(0.9 to 2.5)
Height at age 12 (cm)	152.3	152.5	155.2	155.4	148.5	148.9	149.4	149.8
(95% CI)	(149.2 to 155.1)	(149.6 to 155.1)	(152.5 to 158.2)	(152.9 to 158.6)	(146.6 to 150.5)	(147.1 to 150.8)	(146.6 to 152.2)	(147.2 to 152.6)
Height SDS at age 12	0.5	0.5	0.9	0.9	−0.4	−0.3	−0.3	−0.2
(95% CI)	(0.0 to 0.9)	(0.1 to 0.9)	(0.5 to 1.3)	(0.5 to 1.3)	(−0.7 to −0.1)	(−0.6 to −0.1)	(−0.7 to 0.2)	(−0.6 to 0.2)
Weight at age 12 (kg)	47.1	47.8	50.3	50.9	**43.6**	44.3	48.2	**48.9**
(95% CI)	(41.6 to 52.6)	(42.1 to 53.3)	(46.9 to 53.7)	(47.2 to 54.8)	**(40.7 to 46.7)**	(41.1 to 47.7)	(42.9 to 52.8)	**(44.2 to 53.5)**
BMI at age 12 (kg/m^2)	20.3	20.6	20.9	21.1	**19.8**	20.0	21.6	**21.7**
(95% CI)	(18.3 to 22.1)	(18.5 to 22.3)	(19.7 to 22.0)	(20.0 to 22.1)	**(18.7 to 21.1)**	(18.8 to 21.4)	(19.7 to 23.2)	**(20.1 to 23.3)**
BMI SDS at age 12	1.1	1.2	1.3	1.4	**0.7**	0.8	1.2	**1.3**
(95% CI)	(0.4 to 1.7)	(0.4 to 1.7)	(0.9 to 1.6)	(1.0 to 1.6)	**(0.3 to 1.1)**	(0.3 to 1.2)	(0.7 to 1.6)	**(0.8 to 1.7)**
Age at adiposity rebound	3.6	3.5	2.9	2.9	**4.8**	4.8	2.5	**2.6**
(95% CI)	(2.5 to 4.8)	(2.4 to 4.5)	(1.1 to 3.8)	(0.7 to 3.7)	**(2.6 to 7.3)**	(2.6 to 6.6)	(1.9 to 4.0)	**(1.9 to 4.1)**
BMI at adiposity rebound (kg/m^2)	16.5	16.2	16.6	16.3	17.5	17.3	16.3	16.2
(95% CI)	(15.5 to 17.4)	(15.3 to 17.1)	(15.3 to 17.7)	(14.9 to 17.5)	(16.1 to 18.7)	(16.0 to 18.5)	(14.3 to 19.0)	(14.0 to 19.0)

(*continued*)

Table 3 Continued

Sex of patients in underlying model	Male				Female			
Data points with covariates available to train model	982 Visits | 139 patients				803 Visits | 143 patients			
Representation of model	Low dose good control	Low dose poor control	High dose good control	High dose poor control	Low dose good control	Low dose poor control	High dose good control	High dose poor control
BMI z-score at adiposity rebound (95% CI)	0.8 (−0.1 to 1.5)	0.6 (−0.3 to 1.3)	0.7 (−0.4 to 1.5)	0.5 (−0.8 to 1.4)	1.3 (0.6 to 1.9)	1.2 (0.5 to 1.8)	0.6 (−1.0 to 2.3)	0.6 (−1.1 to 2.2)

CI = Confidence interval. SDS = Standard deviation score (calculated from World Health Organization normative standards, not available for weight above age 12). Doses and level of 17-OH progesterone to define disease control defined by expert consensus, underlying model trained from visits extracted from the International Congenital Adrenal Hyperplasia Registry with all covariates available. Full multilevel spline model estimates reported in Tables S5–S6.[17] Metrics calculated for alternative doses and levels of disease control applied to the same models are in Table S7.[17] Comparisons between low dose good control and high dose poor control made across 500 bootstrapped replications to define statistical significance of the difference between metrics indicated by bold type. Appropriate values within the table under femal patients are now highlighted in bold.

Conclusion

This study quantifies an early adiposity rebound in children with CAH and significantly blunted SITAR-estimated latest peak height velocity, with large variation between participants. Biomarkers of poor disease control and higher prescribed glucocorticoid doses were associated with earlier adiposity rebound and higher BMI in adolescence in girls. Participants of both sexes prescribed higher doses, indicative of more significant disease or possibly poor adherence, were associated with earlier bone age advancement. The timing of adiposity rebound and latest peak height velocity can allow the identification of individuals with CAH who may be at risk of adverse long-term cardiometabolic outcomes, and may be used as early surrogate outcomes in future research investigating early-life treatment strategies.

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Author's contribution

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Supplementary material

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Data availability

All code associated with this analysis can be found at: https://github.com/neilxlawrence/I-CAH_Adiposity_rebound

Requests for access to data must be sought through SDM Registries: https://sdmregistries.org/data-access/

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