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RESEARCH PAPER

Pubertal growth in height, sitting height and leg length in achondroplasia

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ABSTRACT
Background: Children with achondroplasia (ACH) appear to lack a pubertal growth spurt in height.
Aim To explore the growth spurt in height and its segments sitting height and leg length, in a large sample of ACH cases using growth curve modelling.
Subjects and methods: Height and sitting height were measured longitudinally in ACH children, and the data were analysed using the SITAR (SuperImposition by Translation and Rotation) growth model, which estimates a mean growth curve and random effects for individuals defining differences in size, pubertal timing and intensity.
Results: Out of 402 ACH children, 85 boys and 75 girls aged 7–20 years had respectively 529 and 454 measurements of height and sitting height, with leg length calculated by difference. SITAR analysis identified peaks in mean height velocity at 13.3 and 11.3 years in boys and girls, with peak velocities of 4.3 and 4.4 cm/year. Mean peak velocity for sitting height was 3.0 cm/year, but leg length showed no peak. The SITAR models explained 92% to 99% of the cross-sectional variance.
Conclusion: ACH children do experience a growth spurt in puberty, but only half that of control children. The spurt is due entirely to sitting height, with no leg length spurt.

Introduction

Achondroplasia (ACH), an autosomal-dominant disorder, is the most common form of inherited disproportionate short stature, with a worldwide birth prevalence, based on meta-analysis, of 4.6 per 100,000 (Spranger 2012; Foreman et al. 2020). It is caused by a gain of function mutation in the type 3 fibroblast growth factor receptor gene (FGFR3) located on chromosome 4p16.3 (Shiang et al. 1994; Bellus et al. 1995). FGFR3 plays an important role in early mammalian skeletal development, especially in post-embryonic linear bone growth with an inhibition predominantly of endochondral ossification (Foldynova-Trantirkova et al. 2012; Qi et al. 2014). Consequently, children with ACH are born with shorter limbs than non-ACH children, and their limb deficit increases throughout childhood (del Pino et al. 2016; del Pino, Ramos Mejía, et al. 2018).

Cross-sectional studies of height growth show that at birth, ACH boys and girls are on average 2.2 and 1.4 SDS respectively below the median of the Argentine national references (Lejarraga et al. 2009; del Pino et al. 2011). During infancy and childhood height falls behind progressively, to a mean of −5 SDS in puberty and −6 SDS in final height for both sexes (Horton et al. 1978; Tachibana et al. 1997; del Pino et al. 2011; Hoover-Fong et al. 2017; Tofts et al. 2017; Merker et al. 2018).

In non-ACH children there is a marked growth spurt in height during puberty, when mean height velocity reaches 8–10 cm/year at its peak (Cole 2020). Analysing the data cross-sectionally, children with ACH appear not to have a pubertal height growth spurt. However, we followed 23 ACH children longitudinally through puberty (8 boys and 15 girls) and observed a growth spurt in height that was similar in shape though half the magnitude of that for non-ACH children (del Pino, Fano, et al. 2018). Sitting height data in 8 girls showed that sitting height accounted for 72% of the peak height velocity, with only 28% due to leg length.

Our previous longitudinal analysis (del Pino, Fano, et al. 2018) used the Preece-Baines model (Preece and Baines 1978), which required complete growth curves for each child and limited the dataset to just 23 of the 342 patients available. To build on the evidence base about pubertal growth in ACH we have reanalysed our height data using the SITAR growth curve model (Cole et al. 2010), which handles incomplete growth curves and increases the sample size. We have also taken the opportunity to analyse sitting height and leg length in the same way, to establish their individual contributions to pubertal height growth.

Subjects and methods

The patients were 402 children with ACH who attended the growth clinic in Garrahan Hospital, Buenos Aires, Argentina,

between 1992 and 2020. ACH was diagnosed on the basis of clinical examination and the X-ray criteria of Spranger (2012). In addition 247 children were subject to molecular testing, and all were heterozygous. The project was approved by the research review committee and the ethics review committee from Garrahan Paediatric Hospital.

Exclusion criteria were the presence of any other chronic disease or co-morbidity that could affect growth, and surgical leg lengthening or spinal arthrodesis. A total of 32 children were excluded for these reasons, due to Sturge-Weber (1), renal failure and blindness (1), surgical leg lengthening (18) or spinal arthrodesis (12).

Baseline information on sex and date of birth was collected from perinatal records provided by the parents. Height and sitting height were then recorded at each visit, and leg length was calculated as the difference between height and sitting height. All measurements were taken by the same trained observer (PA) with standardised anthropometric techniques (Lejarraga et al. 1975). More details about the methods can be found in del Pino, Fano, et al. (2018). Some of the anthropometry was used to construct growth references for ACH (del Pino et al. 2011).

Statistical analysis

The data were first cleaned by plotting them as individual growth curves and identifying and removing 14 outliers. They were then analysed using the SITAR growth curve model with a separate model for each of the three measurements in the two sexes. SITAR (SuperImposition by Translation And Rotation) (Cole et al. 2010) is a nonlinear mixed effects model which summarises the data for a group of children as a mean curve and a set of random effects for each child which define how their growth curve differs from the mean curve. So the mean curve is transformed to match individual curves, a process which involves three simple transformations that do not affect the curve shape. First the mean curve is moved up or down, reflecting the child being taller or shorter than average (this is called the *size* random effect); second the curve is shifted left or right, depending on the individual's age at peak height velocity being early or late (*timing*), and third the curve is rotated in a particular way to make it steeper or shallower (*intensity*) – this reflects the individual's peak height velocity being respectively lower or higher. The mean curve corresponds to the growth pattern of a child whose height, peak height velocity and age at peak height velocity are all average.

The mean curve is fitted as a cubic B-spline curve with knots at the quantiles of the age distribution, and the number of knots is chosen to minimise the Bayesian Information Criterion. The goodness of fit of the model is measured by first fitting a simpler model with the mean curve but no random effects, and then fitting the full model. The goodness of fit is expressed as the percentage reduction in residual variance due to adding the random effects. The mean curve is differentiated to obtain the estimated mean velocity curve.

The full SITAR model includes a random effect for timing, which requires the age at peak velocity to vary across individuals. When the peak is poorly characterised the model can fail to converge, in which case the timing random effect has to be omitted from the model.

Results

Overall there were data for height, sitting height and leg length in 160 children, 75 girls and 85 boys, on 983 distinct measurement occasions. Measurements before age 7 or after age 20 were excluded, as were those for individuals with fewer than two measurements. Table 1 summarises the data by sex, including the ranges of measurement age by case. The boys had more data, reflecting their longer growth period: a median of 6 measurements over a median of 5.5 years, as against 5 measurements over 3.7 years for the girls.

Height

Figure 1 shows the individual height growth curves (left) by sex, with boys above and girls below, colour-coded by case. The curves vary by mean height, and also by their timing of puberty. SITAR models with 5 degrees of freedom were fitted to the two sexes, and the superimposed height curves on the right show the effect of the SITAR adjustment. Each curve has been adjusted for the individual's mean height and puberty timing in the following way: low curves are shifted upwards and high curves are shifted downwards, based on their estimated size random effects; similarly curves with early timing are shifted right and those with late timing are shifted left, and those that are relatively steep, i.e. where the growth spurt is short and of high intensity, are made shallower, and the shallower curves are made steeper. Note that this adjustment process does not alter the shapes of the curves. The net result is that all the curves, after adjustment, are superimposed on each other, as shown on the right of the figure (dashed lines) – they all fall in a narrow band.

Table 2 summarises the fitted SITAR models, and shows that *inter alia* the adjustment process explains 98.4% and

Table 1. Summary statistics for 160 ACH cases aged 7–20 years by sex.

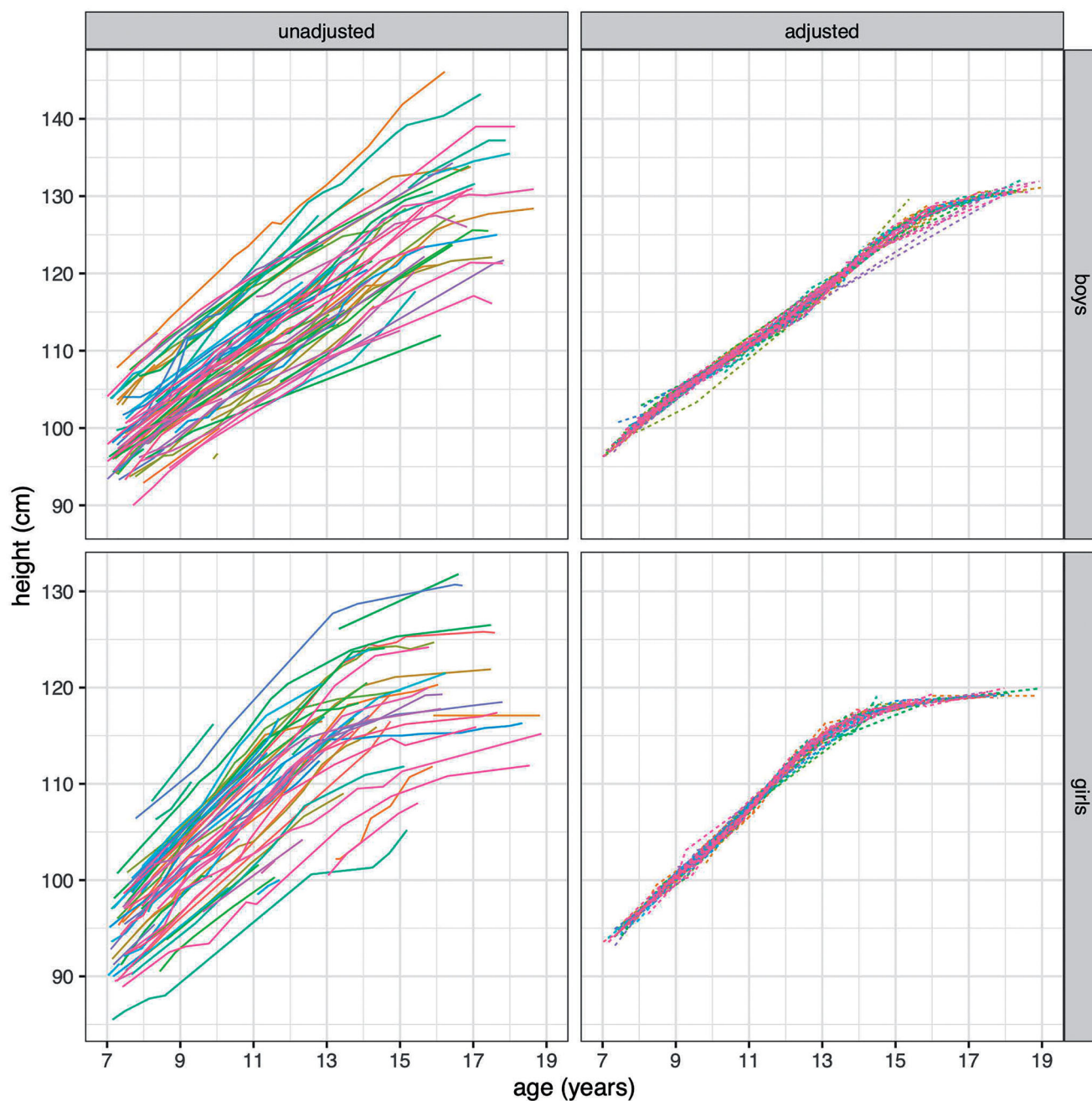|	Boys	Girls
N of cases	85	75
N of measurements	529	454
n of measurements per child (median, IQR*)	6 (3–8)	5 (3–8)
Age at first measurement (median, IQR)	7.6 (7.3–8.9)	7.6 (7.4–8.4)
Age at last measurement (median, IQR)	13.6 (11.4–16.2)	12.9 (10.8–15.8)
Time in study (median, IQR)	5.5 (2.2–7.8)	3.7 (1.7–7.3)

*interquartile range.

Figure 1. Height growth curves for 160 ACH cases, unadjusted (left, solid lines) and SITAR adjusted (right, dotted lines), with boys above and girls below. The adjustment causes the individual curves to be superimposed, explaining 98.4% and 99.0% of the variance in the unadjusted curves for boys and girls respectively.

Table 2. Results for SITAR models fitted to the three measurements by sex.

	Boys			Girls		
	Height	Sitting height	Leg length*	Height	Sitting height	Leg length*
Spline curve degrees of freedom	5	3	3	5	3	3
% of variance explained	98.4	94.4	93.0	99.0	95.4	92.4
Residual standard deviation (cm)	0.70	0.81	0.93	0.51	0.69	0.87
Size standard deviation (cm)	6.4	5.0	3.5	4.8	3.7	3.1
Timing standard deviation (years)	1.2	1.9	–	1.0	1.4	–
Intensity standard deviation (%)	15	15	30	16	18	20
Age at peak height velocity (years)	13.3	12.8	–	11.3	11.9	10.4**
Peak velocity (cm/year)	4.3	2.9	–	4.4	3.0	1.6**
Predicted value at 19 years (cm)	131.0	84.1	45.6	120.0	80.2	39.7

*timing random effect omitted, **not a true peak – see Figure 4.

99.0% of the variance in the unadjusted height curves, with residual standard deviations of 0.7 and 0.5 cm for boys and girls respectively.

The adjusted curves in Figure 1 are averaged to provide mean curves by sex. Figure 2 shows the fitted mean height curves (left) and mean height velocity curves (right) for ACH boys (above) and girls (below). Predicted height at age 19 is 131 cm for the boys and 120 cm for the girls, so as adults the boys are 11 cm taller than the girls (Table 2).

Figure 2 also illustrates the pubertal height growth spurt, seen as a peak on the velocity curve. The ages at peak height velocity are marked by vertical dashed lines, 13.3 years for boys and 11.3 years for girls, 2.0 years apart, with peak height velocities of respectively 4.3 and 4.4 cm/year (Table 2). The standard deviation of age at peak velocity

is 1.2 years for boys and 1.0 years for girls, based on the timing random effects in Table 2.

Sitting height and leg length

Table 2 also summarises the SITAR models for sitting height and leg length by sex. The model spline curves had 3 degrees of freedom as against 5 for height, indicating a simpler curve shape. The models for leg length both failed to converge, so they were refitted omitting the timing random effect.

Figure 3 shows the data for sitting height (above) and leg length (below) for boys (left) and girls (right). Each facet contains three separate layers: the grey curves are the unadjusted data, the coloured curves are the SITAR-adjusted
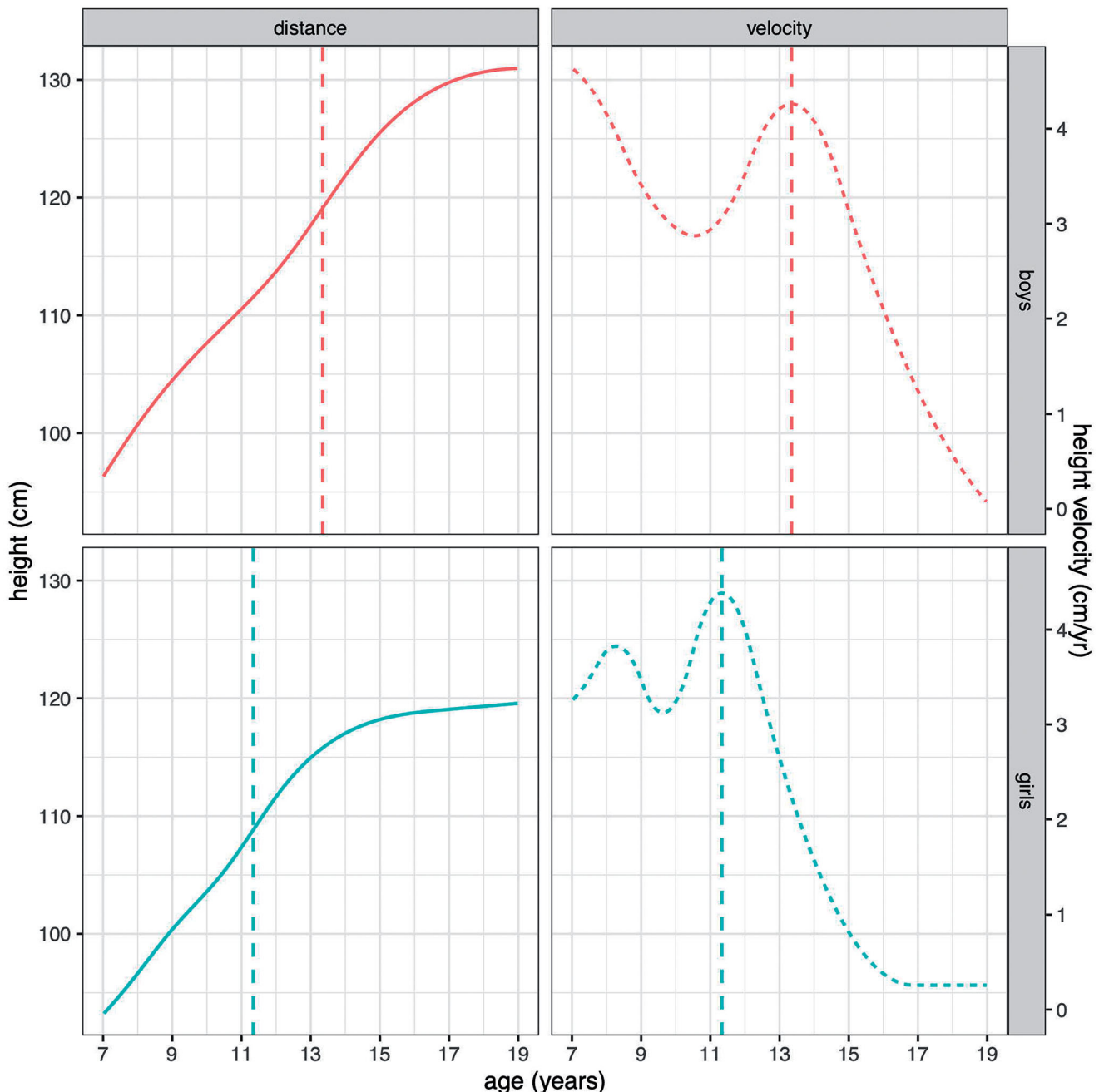

Figure 2. Mean height curves (left, solid lines) and height velocity curves (right, dotted lines) for ACH boys (above) and girls (below) fitted by SITAR. The ages at peak height velocity are marked by vertical dashed lines.
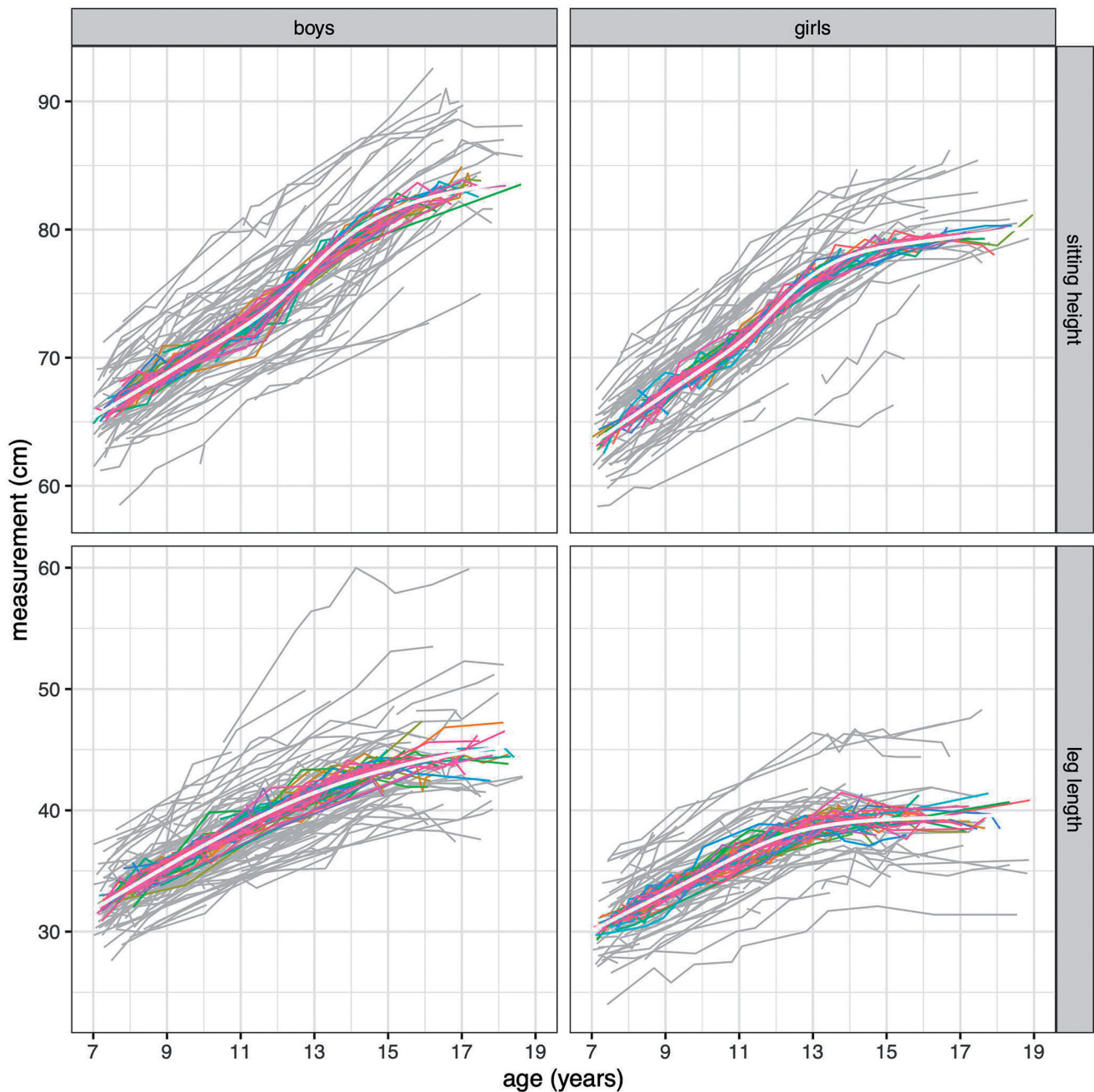
Figure 3. Growth curves of sitting height (above) and leg length (below) for 160 ACH cases, boys (left) and girls (right). Each facet consists of three layers: a) the unadjusted curves (grey); b) the SITAR-adjusted curves (coloured by subject) and c) the mean curve (white). The sitting height curves have a pubertal peak while the leg length curves do not.

data, and the white curve is the fitted mean curve. The coloured curves are clustered around the mean curve indicating a good fit, with between 92% and 95% of variance explained and residual standard deviations of 0.7–0.9 cm (Table 2).

Table 2 shows that mean leg length is less variable than mean sitting height, the size effect standard deviations being 20–30% smaller in the two sexes. However mean leg length at age 19 is only about half of mean sitting height, so in percentage terms leg length variability is greater. This is also true for the intensity of growth, where the leg length standard deviation is appreciably larger than for sitting height. Thus growth in leg length is much more variable than growth in sitting height.

Figure 4 contrasts the velocity curves for the three measurements in the two sexes. It also includes the mean velocity curve for sitting height and leg length combined, calculated as the sum of the two velocity curves. The peaks for sitting height in the two sexes are broadly similar in shape to those for height, whereas the leg length curves have no obvious peak. Although there is a vestigial peak on the girls leg length curve at 10.6 years, it is too early in time and too small in magnitude to be viewed as a true peak.

The combined sitting height and leg length curves are similar in shape to the corresponding height curves, with the peaks in velocity differing by only 0.2 cm/year. This provides reassurance that the SITAR models are internally consistent.
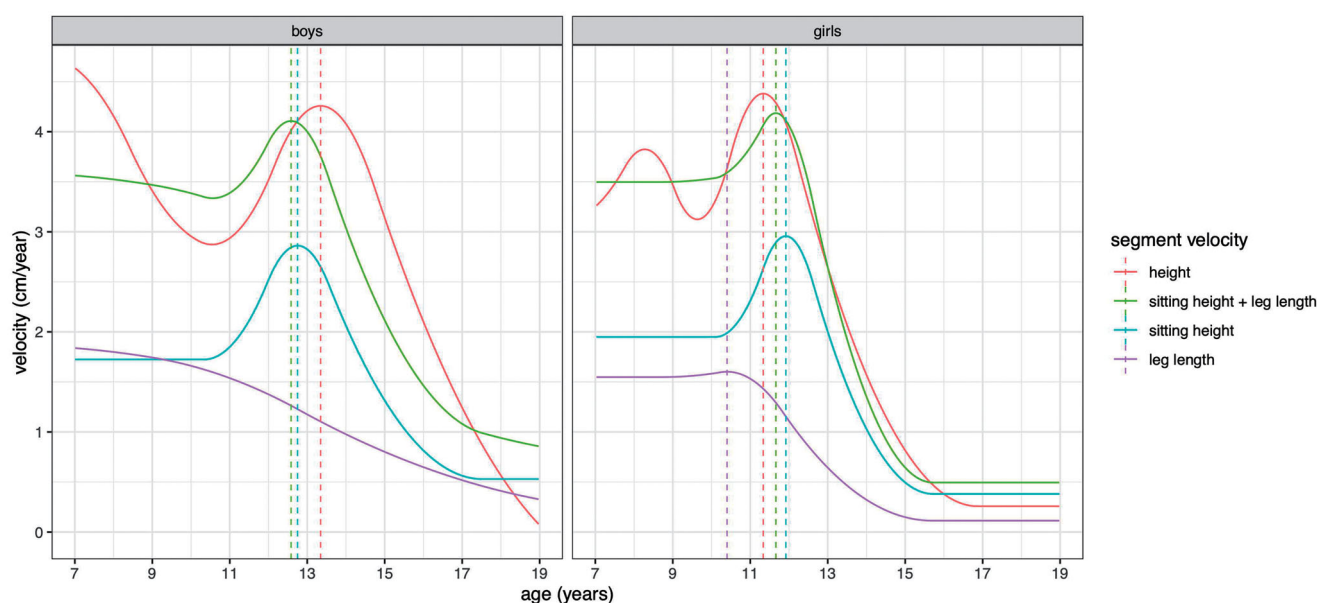
Figure 4. Mean velocity curves for height, sitting height and leg length in boys (left) and girls (right). Also shown is the velocity curve for the sum of sitting height and leg length, which can be compared directly with that for height. The vertical dashed lines show the mean ages at peak velocity. There are obvious peaks in velocity for sitting height but not leg length.

However the ages at peak velocity match less well, differing by up to 0.6 years (Table 2), which reflect the uncertainty attached to the estimated ages at peak velocity. Even so the plot makes clear how the velocity peak for height is made up of a peak for sitting height with no contribution from leg length.

Discussion

The results confirm that ACH children experience a height growth spurt in puberty, which confirms our earlier findings on a cohort of 23 cases analysed with the Preece-Baines model 1 (del Pino, Fano, et al. 2018). However the spurt is restricted to sitting height, with leg length contributing very little. The SITAR growth curve model works well in that applied to incomplete growth curves it estimates the timing of peak velocity in individuals, and it proves sensitive enough to detect the height spurt despite its small size.

To put the results in context they can be compared with growth in non-ACH children. According to the growth reference of Lejarraga et al. (2009) Argentinian non-ACH children achieve a mean height at age 19 of 173 and 161 cm in boys and girls, with the boys 12 cm taller. Compared to the heights of 131 and 120 cm in ACH children at the same age, with a similar sex difference of 11 cm, the mean adult height deficit in ACH is 41–42 cm. However the ACH mean height curves are based on sparse data past puberty (see Figure 1) and the predicted heights at age 19 are extrapolated, which adds to their uncertainty.

To assess growth velocity in non-ACH children the Harpenden Growth Study (Tanner et al. 1976) provides a useful reference, the data having recently been reanalysed using SITAR (Cole 2020). The Harpenden study consisted of 248 girls and 371 boys recruited from a children's home in Harpenden England between 1949 and 1969, with regular measurements of height, sitting height and leg length

(by difference) from 7 to 20 years. Mean peak height velocity in Harpenden was 9.3 and 7.7 cm/year by sex as against 4.3 and 4.4 cm/year in the ACH cohort, so that peak height velocity in ACH children is about half that in non-ACH children.

What does the reduced height growth spurt tell us about the nature of growth in ACH children? The mutated *FGFR3* gene severely restricts long bone growth, but despite its modifying the anatomy of the vertebral bodies, it is believed not to affect trunk growth. The height growth spurt is made up of separate spurts for leg length and sitting height, and the Harpenden Growth Study measured both. This allows a more nuanced interpretation of the reduced ACH peak height velocity.

In Harpenden, mean peak velocity in sitting height was 4.9 and 4.1 cm/year by sex, and in leg length 4.6 and 4.0 cm/year. The corresponding values for the ACH children are 2.9 and 3.0 cm/year for sitting height, i.e. about two-thirds of those for Harpenden, but zero for leg length in that there is effectively no peak in leg length velocity. This suggests that sitting height velocity is also reduced in ACH children, which is surprising given that it does not depend on long bone growth.

Novel therapeutic strategies have emerged over the past decade that directly block *FGFR3* activation or regulate signalling pathways controlling chondrocyte proliferation and differentiation (Ornitz and Legeai-Mallet 2017; Savarirayan et al. 2019). These new treatments aim to stimulate linear growth, decrease disproportion, reduce complications and increase final height. To be effective they need to be administered before puberty. Awareness of the magnitude of the pubertal spurt of ACH children should help to evaluate the effectiveness of these new therapies on longitudinal growth at this stage.

A strength of the study is the use of the SITAR model, which again demonstrates its value for exploring pubertal height growth in individuals. A limitation of the study is the

small number of growth curves with data in later puberty (see Figure 1), which makes the estimates of final height more uncertain.

Conclusions

Growth curve analysis of a cohort of 160 ACH children shows that there is a detectable height growth spurt in puberty, but only half that seen in non-ACH children. The spurt is attributable almost entirely to sitting height, with no contribution from leg length, and sitting height velocity is only two-thirds of that for non-ACH children.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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