

Nonlinear growth generates age changes in the moments of the frequency distribution: the example of height in puberty

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SUMMARY

Higher moments of the frequency distribution of child height and weight change with age, particularly during puberty, though why is not known. Our aims were to confirm that height skewness and kurtosis change with age during puberty, to devise a model to explain why, and to test the model by analyzing the data longitudinally. Heights of 3245 Christ's Hospital School boys born during 1927–1956 were measured twice termly from 9 to 20 years ($n = 129\,508$). Treating the data as independent, the mean, standard deviation (SD), skewness, and kurtosis were calculated in 40 age groups and plotted as functions of age t . The data were also analyzed longitudinally using the nonlinear random-effects growth model $H(t) = h(t - \varepsilon) + \alpha$, with $H(t)$ the cross-sectional data, $h(t)$ the individual mean curve, and ε and α subject-specific random effects reflecting variability in age and height at peak height velocity (PHV). Mean height increased monotonically with age, while the SD, skewness, and kurtosis changed cyclically with, respectively, 1, 2, and 3 turning points. Surprisingly, their age curves corresponded closely in shape to the first, second, and third derivatives of the mean height curve. The growth model expanded as a Taylor series in ε predicted such a pattern, and the longitudinal analysis showed that adjusting for age at PHV on a multiplicative scale largely removed the trends in the higher moments. A nonlinear growth process where subjects grow at different rates, such as in puberty, generates cyclical changes in the higher moments of the frequency distribution.

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1. INTRODUCTION

The construction of growth references for height or weight involves modeling the frequency distribution as a function of age, using techniques such as the λ - μ - σ (LMS) method (Cole and Green, 1992) or generalized additive modeling of location, scale, and shape (GAMLSS) (Rigby and Stasinopoulos, 2005). The mean and standard deviation (SD) change with age, and skewness and kurtosis may also be present. Height skewness is hard to detect unless the sample size is very large, and for this reason most national height references (Cole *and others*, 1998; Fredriks *and others*, 2000; Tanner *and others*, 1966) though not all (Kuczmarski *and others*, 2000) treat height as normally distributed throughout childhood and puberty. Weight has a clear skew distribution but kurtosis is hard to see, and the LMS method makes the blanket assumption that kurtosis is absent.

Puberty is a time when these distributional changes are most marked. The mean cross-sectional height curve is steeper in puberty than before or after, reflecting the greater mean annual height increment, and the SD is increased due to the variation in growth tempo. The distribution also becomes transiently skew, as Henry Bowditch (1891) showed over 100 years ago. Franz Boas (1892a,b) provided a mathematical explanation for this, but “couched in obscure prose and almost impenetrable algebra” (Tanner, 1981), it has been little cited.

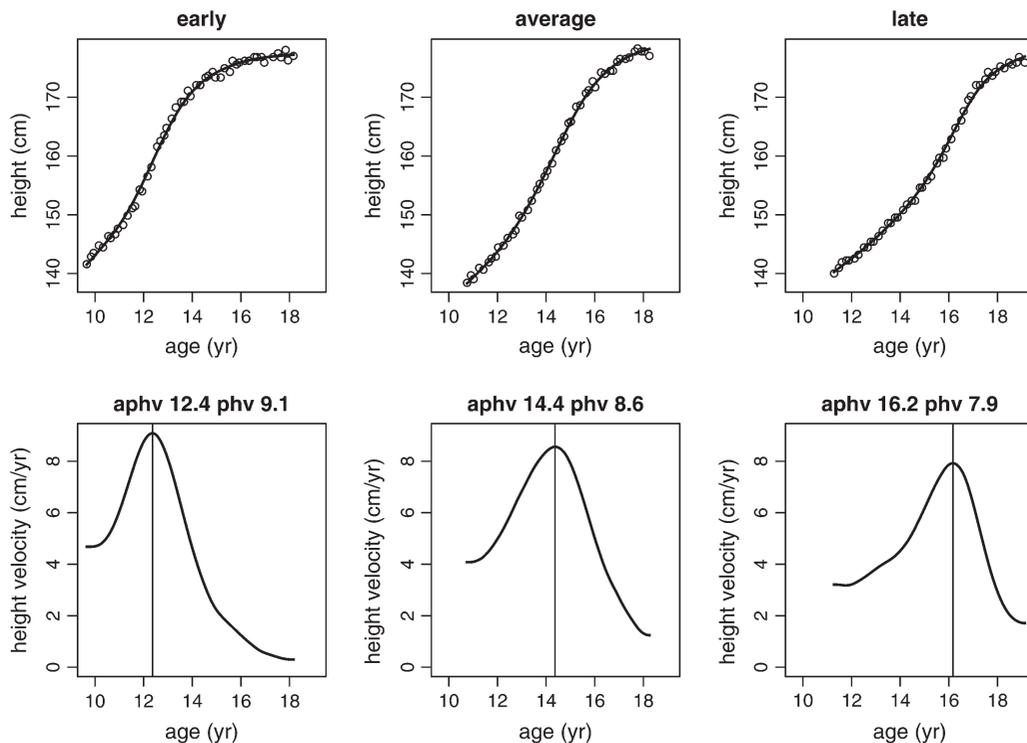


Fig. 1. Serial heights for 3 typical boys with early, average, and late age at PHV, chosen to be similar in adult height. Each boy’s data are summarized by a cubic smoothing spline curve whose derivative provides the velocity curve. Age at PHV is shown by a vertical line. PHV and age at PHV are inversely correlated.

The pubertal height growth spurt in individual children is dramatic, the height increment amounting to 30% of adult height in boys (Tanner, 1978). Peak height velocity (PHV) can reach 10 cm/year at a mean age of around 14 years, though the timing of the spurt varies between individuals reflecting differences in their rate of maturation or “tempo of growth” (Tanner, 1962). The population distribution of the growth spurt is summarized by the mean and SD of PHV and age at PHV. Figure 1 illustrates height and height velocity for 3 typical boys with early, average, and late age at PHV; PHV and age at PHV are seen to be inversely correlated (Tanner, 1962).

The variability in age at PHV is usually assumed to operate on an additive scale, yet the underlying variability is in the rate of maturation, implying a multiplicative age scale (Beath, 2007). Which is the more appropriate scale is one of the questions the paper addresses.

Also of interest is the question whether, and how well, cross-sectional data can estimate the parameters of PHV usually estimated from longitudinal data. Margaret Merrell (1931) showed formally that during puberty, the population mean height curve is less steep than the height curve as seen in the average individual, due to differences in growth tempo. This “Merrell bias” in the population curve underestimates PHV and, coupled with an absence of information about variation in the age at PHV, it has led to the view that longitudinal information is essential to quantify the growth spurt.

The motivation for the current study was access to a uniquely large data set of heights in boys from Christ’s Hospital (CH) School followed longitudinally through puberty. The main aims of the study were 3-fold: (i) to quantify changes with age in the first 4 moments of the cross-sectional height distribution, (ii) to develop a mathematical model to explain why age-related changes in the moments are the same shape as derivatives of the mean height curve, and (iii) to reanalyze the data longitudinally to test the assumptions underlying the model.

The aims taken together tell a story, so the statistical methods have been split into 3 parts and are presented with their corresponding results (Sections 3–5).

2. SUBJECTS AND DATA

The school CH was established in the 16th century as a poor school for orphans and beggars, and by the 20th century it accepted boys from a wide variety of social backgrounds. The school has a long tradition of measuring the heights and weights of its pupils. Dr Gerald Edward Friend (1935), an influential figure in the field of childhood nutrition, was the Medical Officer of CH from 1913 to 1946 during which time he recorded meticulously the heights of all the boys, and this practice continued after his retirement. His book (Friend, 1935) included an appendix written by the eminent statistician Major Greenwood to whom he had passed the data for analysis.

The data consist of serial heights in 3245 boys born during 1927–1956 who attended CH during 1936–1969. The boys were measured twice a term between the ages of 9 and 20 years, a mean of 40 heights per boy (median 42, range 1–63) and 129 700 measurements altogether. Other recent papers based on data from the same study have focussed on the 3175 boys who were subsequently traced via the National Health Service Central Register (Sandhu *and others*, 2006a,b). For more information about the data set, see the dedicated CH Study Web site <http://www.epi.bris.ac.uk/chs/>.

3. CROSS-SECTIONAL HEIGHT DISTRIBUTION

3.1 *Methods*

For the initial analysis, the height data were treated as cross-sectional and were sorted and split into 40 age groups of equal size. This used the entire data set to be compatible with the later longitudinal analysis and ensured that on average each group contained just one measurement per boy. In practice, averaged over the central 30 groups, 66% of boys per group had 1 measurement and 17% had 2.

The first 4 moments of height: mean, SD, skewness, and kurtosis were derived for each group and plotted against the group mean age. Defined as in Appendix (see supplementary material available at *Biostatistics* online, <http://www.biostatistics.oxfordjournals.org>), skewness and kurtosis are zero for a normal distribution. The age trends in each moment plot were summarized by a cubic smoothing spline curve with 10 effective degrees of freedom (edf), chosen to give a good fit and a smooth first derivative.

Prior to deriving the moments, height was adjusted for age within each group using linear regression. Throughout, the data have been analyzed both as height and \log_e height. The main analyses use log height, which was closer than height to a normal distribution. However, 2 figures are back-transformed to the height scale.

3.2 Results

The data consisted of 129 700 heights from 3245 boys aged between 9.0 and 20.5 years. A total of 192 heights (0.15%) were excluded as being grossly inconsistent with others for the same boy, leaving 129 508 heights for analysis, an average of 39.9 per boy. The data were sorted by age and split into 40 groups of size 3237 or 3238, with a median age range within each group of 0.19 years.

Figure 2 (top row) shows the first 4 moments of log height for each age group plotted against age, with cubic smoothing spline curves superimposed. The steep slope of the mean curve mid-puberty shows the most rapid growth at that age. The SD curve for log height corresponds to the coefficient of variation (CV) of height and is maximal at about age 14 years. The skewness curve starts and ends at zero, indicating that log height is not skew outside puberty. During puberty, the skewness initially becomes more positive, then switches rapidly to negative skewness and returns to zero postpuberty. The kurtosis curve shows slight (positive) leptokurtosis for most of puberty except for a short period around 14 years when it is clearly platykurtic.

The peaked shape of the SD curve is reminiscent of height velocity during the same period (see Figure 1). Cross-sectional log height “velocity” is obtained by differentiating the cubic spline fitted to the

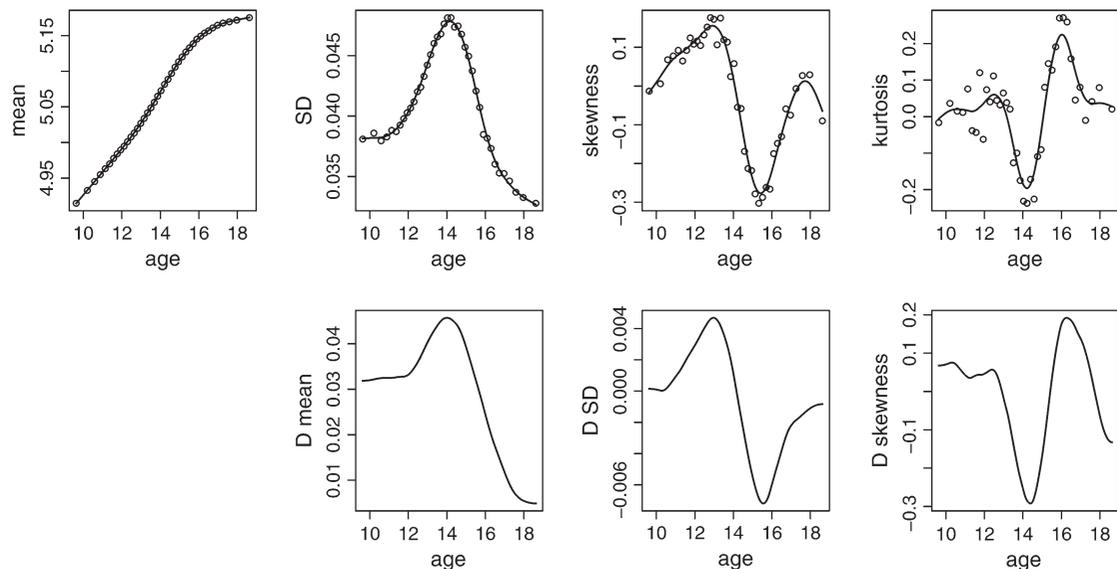


Fig. 2. The upper row shows the first 4 moments of log height, in 40 age groups, plotted against age, with cubic smoothing spline curves superimposed. The lower row gives the first derivatives with respect to age of the moment curves above them and to the left, showing their similarity to the next higher moment curve. See text for details.

mean log height curve, shown in Figure 2 below and to the right of the mean curve and labeled “D mean,” where D indicates the derivative. Also shown in the second row of Figure 2 are the first derivatives of the SD curve and the skewness curve, similarly labeled.

The first derivative of the mean curve is indeed similar in shape to the SD curve above it, with both peaking at 14 years, but surprisingly the same is true of the other 2 derivative curves as well. The D SD curve shows the same rise, steep fall then rise as the skewness curve, and the D skewness curve has the same dip at 14 years as the kurtosis curve.

With suitable differentiation, the relationships between the moments can be summarized as follows:

$$\begin{aligned} \text{SD} &\sim \text{D mean}, \\ \text{Skewness} &\sim \text{D SD} \sim \text{D}^2 \text{ mean}, \\ \text{Kurtosis} &\sim \text{D skewness} \sim \text{D}^2 \text{ SD} \sim \text{D}^3 \text{ mean}, \end{aligned}$$

where \sim means “has the same shape as” and D^2 and D^3 indicate second and third derivatives. Thus, the SD, skewness, and kurtosis curves correspond in shape to the first, second, and third derivatives, respectively, of the mean curve.

Section 4 shows that the explanation for this lies in the tempo-shifted pattern of pubertal growth.

4. GENERALIZED GROWTH PROCESS

4.1 Methods

Generalized growth process. Consider a boy whose age and height at PHV are average for the population and whose longitudinal height measurements are summarized by the smooth curve $h(t)$ plotted against age t . This is the growth tempo-adjusted individual mean curve (Tanner *and others*, 1966) with age at PHV μ_t , where mean PHV μ_v is given by $h'(\mu_t)$. The form of $h'(t)$ is assumed to be the same for all boys but with its timing varying according to the boy’s tempo of growth as expressed by his age at PHV. This forms the basis for a simple generalized growth process

$$H(t) = h(t - \varepsilon) + \alpha, \quad (4.1)$$

where ε and α are subject-specific random variables with mean 0, variances σ_ε^2 and σ_α^2 , and correlation ρ , indicating the boy’s offset in age and height relative to the mean at PHV. Population samples from the growth process $H(t)$ are then height by age as observed cross-sectionally (with the distribution seen in Figure 2), and the mean of $H(t)$ is the population mean curve. It is in effect a nonlinear random-effects model with ε and α as random effects and $h(t)$ a nonparametric smooth curve.

The form of (4.1) implies that growth tempo operates on an additive age scale, with ε measured in units of years. However, a multiplicative scale is equally plausible, with rate of maturation from birth inversely proportional to age at PHV, in which case growth tempo ε is additive on the log age scale. The 2 alternatives correspond to t in (4.1) being age and log age, respectively. Equally (4.1) is assumed to apply to height or log height. The following algebra applies generally to linear or log age and height scales.

The aims here are (i) to show that the moments of $H(t)$ depend on the derivatives of $h(t)$, (ii) to compare the means and slopes of $H(t)$ and $h(t)$ at PHV so as to confirm the Merrell (1931) bias, and (iii) to use the moments of $H(t)$ to estimate μ_t .

Moments and derivatives. The moments of $H(t)$ are expressed in terms of $h(t)$ and its derivatives by expanding (4.1) as a Taylor series (see Appendix, supplementary material available at *Biostatistics* online

<http://www.biostatistics.oxfordjournals.org>). The leading terms of the first 4 moments are given by

$$\begin{aligned}\mu_H(t) &\approx h(t) + \frac{1}{2}h''(t)\sigma_t^2, \\ \sqrt{\sigma_H(t)^2 - \sigma_h^2} &\approx h'(t)\sigma_t\sqrt{1 - 2\rho\sigma_h/h'(t)\sigma_t}, \\ \text{Skewness}\{H(t)\} &\approx 3h''(t)\sigma_t^2\frac{\delta_H(t)^2}{\sigma_H(t)}, \\ \text{Kurtosis}\{H(t)\} &\approx 2h'''(t)\sigma_t^3\frac{\delta_H(t)[3 + 2\delta_H(t)^2]}{\sigma_H(t)} + 3h''(t)^2\sigma_t^4\frac{[1 + 4\delta_H(t)^2]}{\sigma_H(t)^2},\end{aligned}\tag{4.2}$$

where $\mu_H(t)$ and $\sigma_H(t)$ are the mean and SD of $H(t)$; $h'(t)$, $h''(t)$, and $h'''(t)$ are the first (velocity), second (acceleration), and third derivatives of $h(t)$, and $\delta_H(t) = (h'(t)\sigma_t - \rho\sigma_h)/\sigma_H(t)$. The SD is arranged to show the excess variance due to $h(t)$. The second terms for the mean and kurtosis are small (and zero when $t = \mu_t$), and the square root term for the SD is close to unity, so to first order, for $m = 1, \dots, 4$, the m th moment of $H(t)$ is proportional to $h^{(m-1)}(t)\sigma_t^{m-1}$. Thus, variation in growth tempo (i.e. $\sigma_t^2 > 0$) alters the higher moments of the underlying distribution of $h(t)$ in a way that depends on the form of $h(t)$.

Population and individual mean curves at PHV. Differentiating $\mu_H(t)$ in (4.2) twice gives

$$\begin{aligned}\mu'_H(t) &\approx h'(t) + \frac{1}{2}h'''(t)\sigma_t^2, \\ \mu''_H(t) &\approx h''(t) + \frac{1}{2}h''''(t)\sigma_t^2.\end{aligned}\tag{4.3}$$

The mean age at PHV μ_t is defined as the age when height velocity $h'(t)$ is at a peak, so by definition $h''(\mu_t) = 0$ and $h'''(\mu_t) < 0$. Furthermore, if $h'(t)$ is assumed to be symmetric about μ_t then $h''''(\mu_t) \approx 0$. Then, from (4.2) and (4.3), at $t = \mu_t$,

$$\begin{aligned}\mu_H(\mu_t) &\approx h(\mu_t), \\ \mu'_H(\mu_t) - h'(\mu_t) &\approx \frac{1}{2}h'''(\mu_t)\sigma_t^2 < 0, \\ \mu''_H(\mu_t) &\approx 0.\end{aligned}\tag{4.4}$$

This proves that $\mu'_H(t)$ peaks at $t = \mu_t$. In words, at the mean age at PHV, population mean height and individual mean height are equal (4.4) and the slopes of both curves are maximal, but for $\sigma_t^2 > 0$ the population mean curve is shallower in slope than the individual mean curve (4.4). This confirms and generalizes Merrell's (1931) bias.

Estimates of age at PHV. From (4.2), $\sigma_H(t)$ peaks when $h'(t)$ is maximal at $t = \mu_t$, while the kurtosis and D skewness curves are approximately proportional to $h'''(t)$ which is minimal at $t = \mu_t$. Thus, the 4 moment curves of $H(t)$ each provide an independent estimate of μ_t —the ages when (i) the mean curve is steepest (positive), (ii) the SD curve is maximal, (iii) the skewness curve is steepest (negative), and (iv) the kurtosis curve is minimal.

4.2 Results

Estimates of μ_t were obtained by identifying the relevant turning points in the cubic spline curves for the moments in Figure 2 (D mean, SD, D skewness, and kurtosis). They are summarized in Table 1, for height and log height separately, and are consistently between 14.0 and 14.4 years.

Table 1. Estimates of μ_t the mean age at PHV (years) based on age-related moments of the cross-sectional distributions of height and log height

Moment curve	Derivative	Turning point	Height	Log height
Mean	1	Maximum	14.1	14.0
SD	0	Maximum	14.4	14.2
Skewness	1	Minimum	14.4	14.4
Kurtosis	0	Minimum	14.4	14.2

5. LONGITUDINAL HEIGHT GROWTH

5.1 Methods

Nonlinear mixed-effects model. The data were reanalyzed longitudinally i) to see if growth tempo operates on an additive or multiplicative age scale, ii) to compare the individual and population mean curves, and iii) to test the assumptions underlying the generalized growth process.

The nonlinear mixed-effects model (4.1), along with an implied within-subject residual term, was fitted using the `nlme` function in R (Beath, 2007; Pinheiro and Bates, 2000) with $h(t)$ estimated as a fixed-effect regression spline with 11 degrees of freedom (df). To compare the additive and multiplicative age effects, (4.1) was fitted separately for $t = \text{age}$ and $t = \log \text{age}$.

To compare the population and individual mean curves, $\mu_H(t)$ was also estimated as a cubic regression spline with 11 df fitted to the data treated cross-sectionally. The spline curves for $h(t)$ and $\mu_H(t)$ were then back-transformed to give curves of height versus age; these in turn were differentiated, and estimates of mean PHV and mean age at PHV recorded. The key assumption of the growth process (4.1) is that adjusting for growth tempo makes the distribution around the individual mean curve $h(t)$ normal with variance σ_h^2 at all ages. This follows from (4.2), where if $\sigma_i^2 = 0$ then all the age-varying terms vanish. To adjust for growth tempo, maturational age T was derived such that for child i on occasion j , $T_{ij} = t_{ij} - \varepsilon_i$ (additive) or $T_{ij} = t_{ij} \exp(-\varepsilon_i)$ (multiplicative). The distribution of log height was then investigated by maturational age group based on T and summarized as before with cubic smoothing splines of 10 edf.

5.2 Results

Model (4.1) for log height with $t = \log \text{age}$ provided a dramatically better fit to the data than with $t = \text{age}$. The within-subject residual SD was 0.0073 for the multiplicative model as against 0.0079 for the additive model, that is, an 8% reduction. Except where stated the following results are for the multiplicative model.

Figure 3 illustrates the estimated subject-specific random effects, with intercept α (as $\exp(\alpha)$) plotted against offset ε (as $\exp(\varepsilon)$) for 3245 boys. The correlation ρ between α and ε was 0.39, showing that boys who were older at PHV were also taller at PHV. The SD of α was $\sigma_h = 0.039$, lower than the mean SD of log height by age in Figure 2. The SD of ε was $\sigma_t = 0.073$ log years, while for the additive model (4.1) the SD was 1.1 years.

Figure 4 compares the cross-sectional (dotted) and longitudinal (solid) spline curves $\mu_H(t)$ and $h(t)$ (left) and their first derivatives (right). Their ages at PHV μ_t were both about 14.3 years, but PHV μ_v for the cross-sectional curve (7.4 cm/year) was appreciably less than for the longitudinal curve (9.1 cm/year). Based on log height and log age, PHV was 0.65 units cross-sectionally as against 0.80 units longitudinally.

The generalized growth process predicts the moments of $H(t)$ to be approximately proportional to $h(t)$ and its derivatives (4.2). The upper row of Figure 5 shows $h(t)$ and its derivatives, while the lower row shows the predicted $H(t)$ moment curves based on $h(t)$ (4.2). The upper and lower curves are very

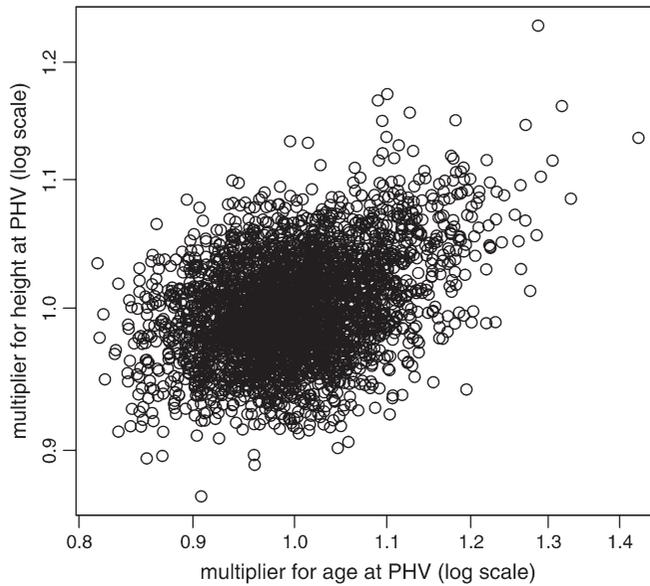


Fig. 3. Plot of subject height offset (multiplier relative to mean height at PHV) versus subject age offset (multiplier relative to mean age at PHV) (both on log scales) for 3245 subjects, the fitted random effects in the nonlinear mixed-effects model (4.1).

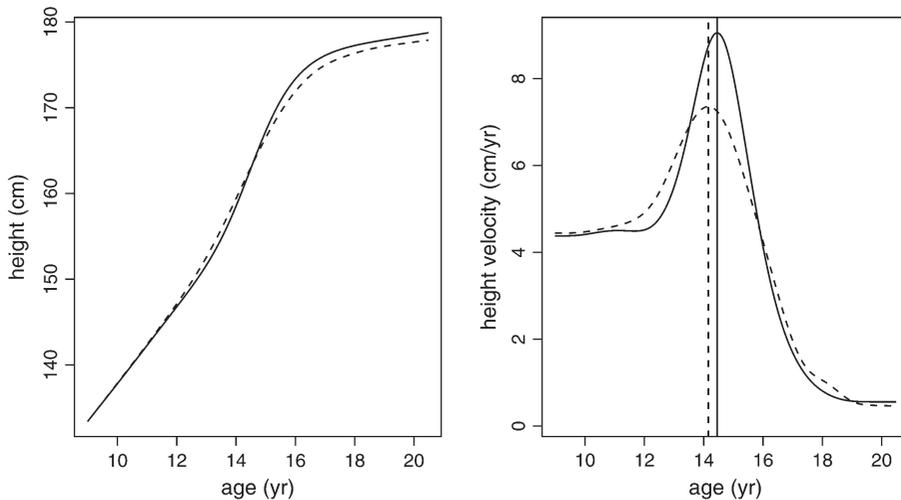


Fig. 4. Comparison of mean curves (left) for the population ($\mu_H(t)$, dotted line) and individual ($h(t)$, solid line). The corresponding velocity curves are shown (right) with mean ages at PHV indicated by vertical lines.

similar in shape, both to each other and to the upper curves in Figure 2, justifying the statement that the derivatives define the moments. However, Figure 5 predicts a wider range of moments than observed in Figure 2 for the SD and particularly the kurtosis.

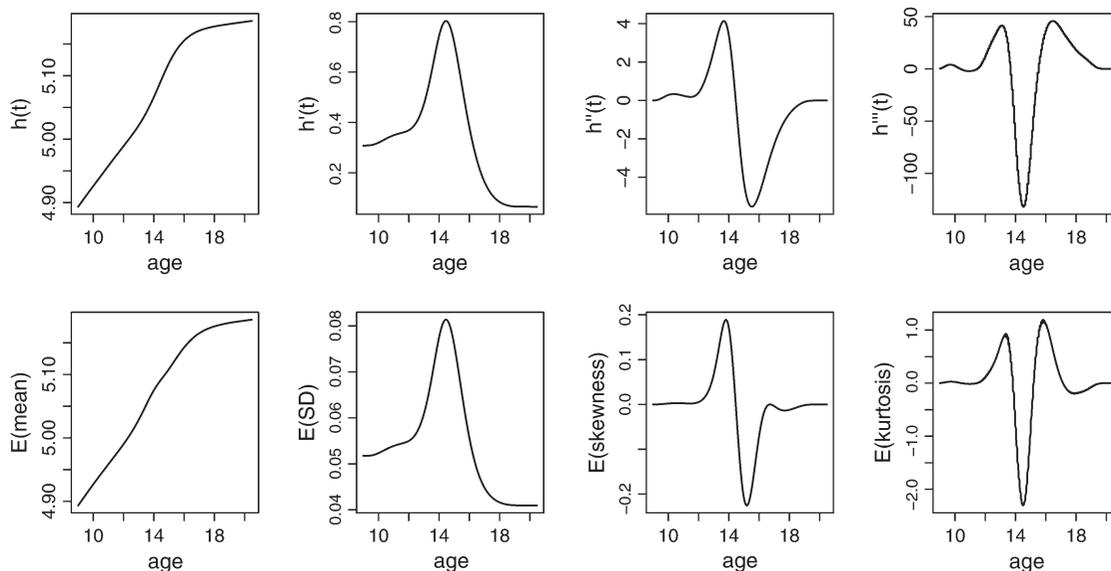


Fig. 5. The upper row shows the fitted individual mean curve $h(t)$ and its first 3 derivatives, while the lower row gives the moments of $H(t)$ predicted as functions of the upper row from (4.2).

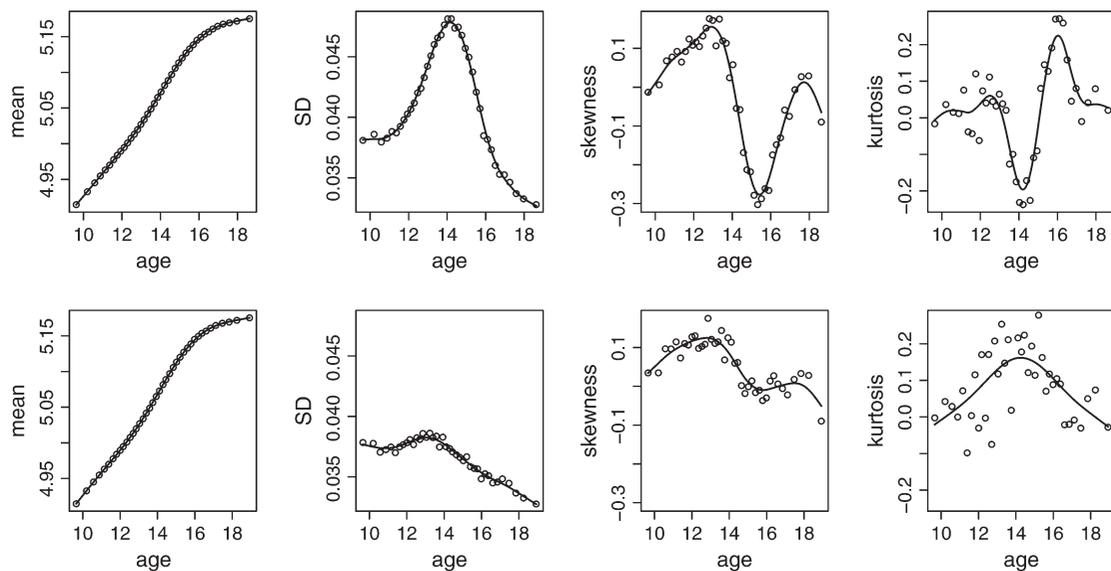


Fig. 6. The upper row shows the first 4 moments of log height by chronological age, as in Figure 2. The lower row shows the same moments in 40 maturational age groups, using the same scales. The distribution changes far less with maturational age than with chronological age.

The distributions of $H(t)$ and $h(t)$ are compared in Figure 6. The first 4 moments of log height are shown grouped by chronological age t (top row, copied from Figure 2) and by maturational age T (bottom row), using the same axis scales. Grouped by T , the 3 higher moments are strikingly more constant across age than the corresponding curves by t . This confirms that the age trends in the higher moments of $H(t)$

seen in Figure 2 are generated by the variability in age at PHV and that adjusting for growth tempo on a multiplicative scale removes the trends and shows the underlying homoscedastic normal distribution about $h(t)$.

6. DISCUSSION

The study has shown that the distribution of height changes cyclically during puberty. Figure 2 shows 1, 2, and 3 turning points, respectively, in the age-varying SD, skewness, and kurtosis. The age when mean height increases fastest is also the age when skewness decreases fastest, which is in turn the age when height variability is greatest and kurtosis least. This age of 14.3 years represents in 4 distinct ways the mean age of PHV for the population and is typical of a boys' population measured half a century ago (Tanner, 1978).

The age-related skewness pattern in Figure 2 confirms Boas's (1892a,b) observation that skewness increases when puberty starts. It subsequently falls sharply and then rises again, returning to where it started. The kurtosis pattern in Figure 2 has not previously been reported. Yet, the Tanner-Whitehouse (Tanner *and others*, 1966), British 1990 (Freeman *and others*, 1995) and Dutch 1997 (Fredriks *and others*, 2000) references all failed to detect skewness or kurtosis and treated height as normally distributed. By contrast, the US Centers of Disease Control 2000 reference (Kuczmarski *and others*, 2000) did adjust for skewness, but the age-related changes were complex and showed nothing of the cyclical pattern in puberty seen here. This demonstrates the very large sample sizes needed to detect skewness in height, which probably relates to its small variability (Pan and Cole, 2004) ($\log SD < 0.05$ in Figure 2, i.e. $CV < 5\%$). The impact of skewness on height centiles is relatively modest, less than 0.5% on the 2nd or 98th centile, and the dip in kurtosis at the age at PHV (Figure 2) is even harder to detect and has a tiny effect on the extreme centiles. This justifies the decision to treat height as normally distributed in growth references.

However, the cyclical change in the height distribution has wider implications. A remarkable feature of the age-related changes in the moments is that each corresponds in shape to the derivative of the previous moment. So the rise and fall in the SD are synchronized with the rise and fall in height velocity and similarly for skewness and SD "velocity" and for kurtosis and skewness "velocity." These observations together show that age-related changes in the variability, skewness, and kurtosis of height are similar to those for height velocity, height acceleration, and the third derivative of height, respectively. Not only does this confirm and generalize Boas's observation that skewness changes, but also predicts that skewness changes in line with height acceleration.

The pattern can be explained mathematically with a simple growth process that treats height growth as a nonlinear function where individuals vary in growth tempo. Fitting this to the longitudinal data as a mixed-effects model shows clearly that growth tempo varies on a multiplicative not an additive age scale, inversely proportional to each child's age at PHV. The finding generalizes in the following way: in any nonlinear process, where individuals "grow" following the same pattern but at different rates, the shape of the underlying individual mean "growth" curve defines time changes in the moments of the cross-sectional distribution.

If, for example, the growth curve had nonzero first and second derivatives but zero higher derivatives, that is, the growth curve was linear or quadratic, then acceleration would be zero and skewness constant. It would not necessarily be zero as the growth process superimposes changes on the underlying distribution, which like height may already be skewed before puberty. So the age changes in height SD, skewness, and kurtosis arise from the complex shape of the mean individual height curve.

The reason why the multiplicative (log) age model fits so much better than the additive model is at least partly because it accounts for the known correlation between PHV and age at PHV seen in Figure 1 (Tanner, 1962). Figure 7 illustrates predicted height and height velocity for individuals whose age at PHV

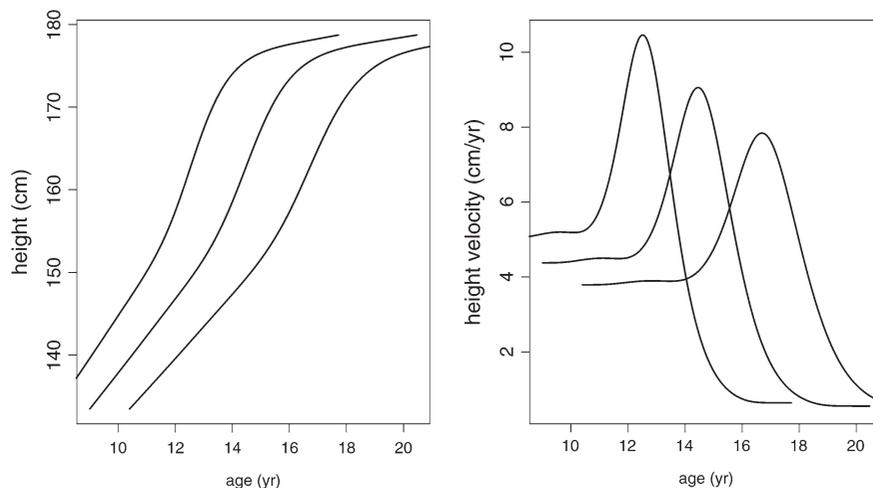


Fig. 7. The effect of a multiplicative scale for age at PHV. Back-transforming the log age scale generates steeper predicted height curves for early maturers, resulting in the known inverse correlation between PHV and age at PHV (Tanner, 1962).

is early, average, and late, that is, $h(t - 2\sigma_t)$, $h(t)$ and $h(t + 2\sigma_t)$. Back-transforming to the age scale has led to a steeper height curve for early maturers compared to late and a corresponding inverse trend in PHV.

The growth process also clarifies the relationship between the population mean curve and the individual mean curve. Merrell (1931) showed in a mathematical tour de force that assuming a logistic growth pattern, the population mean curve is flattened relative to the individual mean curve, due to the time shifts in individual curves. Equation (4.4) shows the same relationship for a smooth growth curve of unspecified shape, where the population mean curve and individual mean curve coincide at the mean age and mean height at PHV, but the population curve is shallower than the individual curve unless σ_t^2 is zero. This generalizes Merrell's finding, as seen in Figure 4 with the present data.

Apart from their theoretical interest, these moment-derivative relationships have a practical application in the construction of growth references. The LMS method, for example, summarizes growth reference centiles in terms of curves representing the median M , coefficient of variation S , and skewness L by age (Cole and Green, 1992). The S curve is closely similar to the log SD curve, and the L curve, being the Box–Cox power to transform to normality, is essentially the inverse of the skewness curve. As shown here, derivatives of the M curve contain information about the likely shapes of the S and L curves. The M curve is the most precise of the 3 to estimate, being based on the first moment of the distribution, whereas the S curve refers to the second moment and the L curve to the third. This means that a relatively modest sample can be used to estimate the M curve, then the (underpowered) S curve can “borrow strength” from the M velocity curve and similarly for the (even more underpowered) L curve from the M acceleration curve. It could be done by using each derivative of the M curve as a covariate with the GAMLSS package (Rigby and Stasinopoulos, 2005), which extends the LMS method by including covariates and optionally modeling kurtosis as well. It would be a potentially useful way of improving the precision of the S and L curves and/or reducing the required sample size.

In conclusion, a very large sample of heights has shown cyclical changes in the higher moments of the distribution through puberty, the patterns of change corresponding in shape to derivatives of the mean height curve. This relationship is explained by a tempo-adjusted growth process. As Major Greenwood

stated prophetically in his appendix to Friend's (1935) book describing the CH heights, "I think that Dr. Friend has provided material which will be of service to workers for some time to come."

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REFERENCES

- BEATH, K. J. (2007). Infant growth modelling using a shape invariant model with random effects. *Statistics in Medicine* **26**, 2547–2564.
- BOAS, F. (1892a). The growth of children. *Science* **19**, 256–257.
- BOAS, F. (1892b). The growth of children. *Science* **19**, 281–282.
- BOWDITCH, H. P. (1891). The growth of children studied by Galton's percentile grades. *22nd Annual Report of the State Board of Health of Massachusetts*. Boston, MA: Wright and Potter.
- COLE, T. J., FREEMAN, J. V. AND PREECE, M. A. (1998). British 1990 growth reference centiles for weight, height, body mass index and head circumference fitted by maximum penalized likelihood. *Statistics in Medicine* **17**, 407–429.
- COLE, T. J. AND GREEN, P. J. (1992). Smoothing reference centile curves: the LMS method and penalized likelihood. *Statistics in Medicine* **11**, 1305–1319.
- FREDRIKS, A. M., VAN BUUREN, S., BURGMEIJER, R. J., MEULMEESTER, J. F., BEUKER, R. J., BRUGMAN, E., ROEDE, M. J., VERLOOVE-VANHORICK, S. P. AND WIT, J. M. (2000). Continuing positive secular growth change in The Netherlands 1955–1997. *Pediatric Research* **47**, 316–323.
- FREEMAN, J. V., COLE, T. J., CHINN, S., JONES, P. R. M., WHITE, E. M. AND PREECE, M. A. (1995). Cross-sectional stature and weight reference curves for the UK, 1990. *Archives of Disease in Childhood* **73**, 17–24.
- FRIEND, G. E. (1935). *The Schoolboy: A Study of His Nutrition, Physical Development and Health*. Cambridge, UK: Heffer.
- KUCZMARSKI, R. J., OGDEN, C. L., GRUMMER-STRAWN, L. M., FLEGAL, K. M., GUO, S. S., WEI, R., MEI, Z., CURTIN, L. R., ROCHE, A. F. AND JOHNSON, C. L. (2000). *CDC Growth Charts: United States*. Hyattsville, MD: National Center for Health Statistics.
- MERRELL, M. (1931). The relationship of individual growth to average growth. *Human Biology* **3**, 37–70.
- PAN, H. AND COLE, T. J. (2004). A comparison of goodness of fit tests for age-related reference ranges. *Statistics in Medicine* **23**, 1749–1765.
- PINHEIRO, J. C. AND BATES, D. M. (2000). *Mixed-Effects Models in S and S-PLUS*. New York: Springer.

- RIGBY, R. A. AND STASINOPOULOS, D. M. (2005). Generalized additive models for location, scale and shape (with discussion). *Applied Statistics* **54**, 507–544.
- SANDHU, J., BEN-SHLOMO, Y., COLE, T. J., HOLLY, J. AND DAVEY SMITH, G. (2006a). The impact of childhood body mass index on timing of puberty, adult stature and obesity: a follow-up study based on adolescent anthropometry recorded at Christ's Hospital (1936–1964). *International Journal of Obesity* **30**, 14–22.
- SANDHU, J., DAVEY SMITH, G., HOLLY, J., COLE, T. J. AND BEN-SHLOMO, Y. (2006b). Timing of puberty determines serum insulin-like growth factor-1 in late adulthood. *Journal of Clinical Endocrinology and Metabolism* **91**, 3150–3157.
- TANNER, J. M. (1962). *Growth at Adolescence*. Oxford: Blackwell.
- TANNER, J. M. (1978). *Foetus into Man: Physical Growth from Conception to Maturity*. London: Open Books.
- TANNER, J. M. (1981). *A History of the Study of Human Growth*. Cambridge, UK: Cambridge University Press.
- TANNER, J. M., WHITEHOUSE, R. H. AND TAKAISHI, M. (1966). Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965 parts I and II. *Archives of Disease in Childhood* **41**, 454–471, 613–635.

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