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Mixed Effects Analysis of Height Growth in Ethiopian Children Aged 1-12 Years: A Cohort Study

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ABSTRACT

Modelling physical growth is a key component to examine and identify defining characteristics in the growth process. The goal of this study was to model and capture known features of height growth in Ethiopian children aged 1–12 years. Height measurements of 1760 children followed from 1 to 12 years at Young Lives Ethiopia, a younger cohort, used in the study. The mixed effects method was used to estimate the rate of change within and between subjects over time and to identify defining covariates. Adult height and rate of change over time were individual-specific resulting individual-level growth differences. There was a negative relationship between individual-specific adult height and rate of change over time. The decelerated rate of change was observed from childhood to the onset of puberty in both sexes. Boys were taller than girls between the ages of 3 and 7 years. Mother's educational status, access to quality drinking water, age, and sex had a significant effect on height growth. Children who had a decelerated rate of growth change during the childhood period become taller later in life. Adult height could be determined by an individual-specific rate of change over time.

INTRODUCTION

Growth is a continuous and dynamic process influenced by different unknown factors. Modelling this dynamic process to understand, estimate, and capture the defining characteristics such as initial level, rates of change, periods of acceleration and deceleration when the process enters and leaves different developmental phases (Grimm *et al*., 2011; Howa *et al*., 2016). A common practice of child growth is to measure the increase in body mass, to control and modify the external conditions that affect growth gain (Oliveira *et al*., 2000; Gómez *et al*., 2008; Aggrey, 2009).

There have been different modeling approaches applied to the growth measurement to identify defining characteristics in growth process. An example is the construction of the curve-fitting models that relate age with height and estimate age at which an individual attain maximum growing by associating features in various growth phases (Laird, 1965; Grossman *et al*., 1985; Grossman and Koops, 1988; Galeano-Vasco *et al*., 2014). Studying growth in one phase may have an important influence or

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association with subsequent phases since individual growth is monitored as a sentinel indicator of overall well-being (Tanner, 1981; Gold stein *et al*., 2002; Richard *et al*., 2014).

Many growth modelling approaches are used to obtain descriptions of change in growth processes accounting individual specific effects observed over time, average change, between-individual differences in change and to identify determinants factors (Grimm *et al*., 2011). However, modelling growth trajectory is difficult process due to the model parameters that could not be possible to elaborate from biological perspectives (Aggrey, 2002; Aggrey, 2009; Galeano-Vasco *et al*., 2014). Many scholars have been used cross-sectional data to model features in growth process. Despite of cost effectiveness and easy access to data, cross-sectional centiles for example, only offer a cross-sectional coverage, and hence the growth path of an individual monitored longitudinally in time is unknown since these types of modelling do not describe the dynamic aspect of growth process over time (Grajeda *et al*., 2016).

The mixed effects modeling approaches are among the commonly used methods to capture growth process. This modelling approach is capable of incorporating subject specific rate of change over time and difference across the subjects in the linear predictor expression form (Bates *et al*., 2015). Mixed effects models have been applied to the longitudinal data in different settings (Devidian and Giltinan, 1995; Pan and Goldstein, 1998; Grimm *et al*., 2011; Richard *et al*., 2014; Chirwa*et al*., 2014). In this approach, mixed effects refer to the population mean of the parameter and random effects that indicate the differences between the mean value of the parameter and the adjusted value for each subject (Littell *et al*., 2000; Wang and Zuidhof, 2004). The mixed effects methods quantify variability between and within individuals letting a flexible covariance structure (Pinheiro and Bates, 1995; Aggrey, 2009) to accommodate time dependent and time independent covariates within individual residual terms (Pan and Goldstein, 1998). Many studies have been used the mixed effects models in linear and nonlinear approaches (Pan and Goldstein, 1998; Craig and Schinckel, 2001; Schinckel *et al.*, 2005; Aggrey, 2009; Grimm *et al*., 2011). However, both modelling approaches have not been applied to the longitudinally collected data from low income countries' settings. Thus, the primary objective of this study was to model height growth in Ethiopian children aged 1-12 years and to identify determinant factors using mixed effects modelling approaches in linear and nonlinear forms.

MATERIALS AND METHODS

The study design and source of data

Data on growth measurement gathered over time by Young Lives Ethiopia, a younger cohort, was used in this study. Young Lives is an international collaborative research project supported and coordinated by a team based at Oxford University, UK. The cohort has been studying the lives of children in Ethiopia aiming to reduce childhood poverty. This project built up lives of 3,000 children living in 20 sites across Addis Ababa (the capital) and four other regions (Amhara, Oromia, Former Southern Nations Nationalities and Peoples (SNNPs), and Tigrai). The Young Lives Ethiopia cohorts have been aimed to follow children in two age groups: a younger cohort following of 2,000 children who were 0.5 to 1.5 years old and an older cohort following 1,000 children aged 7.5 to 8.4 years at the baseline (first round) in 2002. The rest three rounds of surveys were carried out in 2006, 2009, and 2013, respectively, for both cohorts. Details of the cohort studies have been referred via the official website of the project (www.younglivesethiopia.org). Based on the inclusion criteria, a total of 1760 children were included in the study. Height growth measurements observed from each subject in four survey rounds were used as outcome variable (see Figure 1). Age and other socio-economic, demographic and health related covariates were included in the study.

Statistical Methods

Two modeling approaches were used in the data analysis as described in the next section. The linear mixed effects modeling approach was used to identify determinant factors associated with height growth difference between and within subjects. The nonlinear mixed effects modeling approach was used to capture growth trajectories and to estimate relationship between rate of change over time and maximum (adult) height.

Linear Mixed Effects Models

Linear mixed models (LMMs) may be expressed in different but equivalent forms. It is common to express such a model in hierarchical form, or just as a mixed model, including additional random-effect terms and associating variance and covariance components (John and Sanford, 2015). When the levels that we observed represent a random sample from the set of all possible values, the random effects can be incorporated in the model (Bates, 2010). This approach decomposes the outcome of an observations as fixed effect (population mean) and random effect (subject specific change over time), and it account for the correlation structure of variations among subjects.

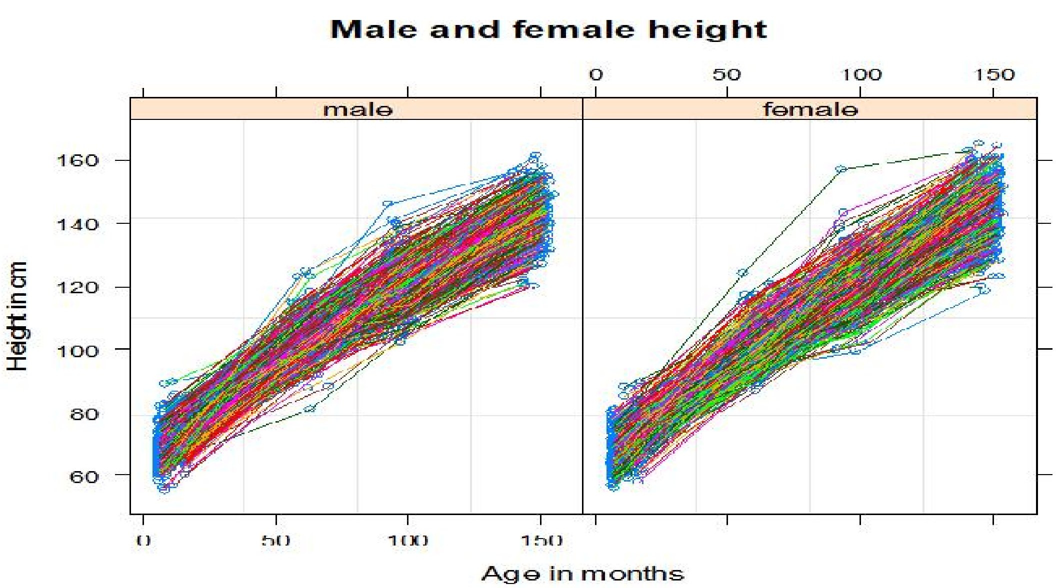

Figure 1: Individual height growth measurements plotted on measurement time by sex (male: left and females right).

Model description

LMMs used in this study have only two-levels, across and within individual variations. For y_{ij} is height measurements of ith subject taken on jth measurement occasion, where j = 4; i = 1,2,…,n. The extended form of linear model with random components is described as follows:

$$y_{ij} = \ {}_1x_{1ij} + ... + \ {}_p x_{pij} + b_{1i}z_{1ij} + ... + b_{iq}z_{qij} + \pounds_{ij}$$

The matrix form of this model is equivalent and considerably simpler to write as:

$$Y_{ij} = \ {}_0 + X_{ij} \quad + Z_i b_i + \pounds_{ij},$$

where Y_{ij} is the $n_i \times 1$ vector of response observations in the i^{th} subject at j^{th} measurement occasion, X_{ij} is the $n_i \times p$ model matrix of fixed-effect regressors, is the $p \times 1$ vector of fixed-effect coefficients which is invariant across groups, Z_i is the $n_i \times q$ matrix of regressors for the random effects of observations in subject i, b_i is the $q \times 1$ vector of random effects for group i, potentially different in different groups and $\pounds_{ij}$ *is* the $n_i \times 1$ vector of errors for j^{th} measurement in i^{th} subject.

Model assumptions

The linear mixed effects analysis was performed with some assumptions: random effects are different across the subject and normally distributed with mean zero and variance co-variance structure, covariates are uncorrelated with each other (no multicollinearity), time variant covariates are a subset of the time invariant covariates, error terms are assumed to have a multivariate normal distribution and within subject measurement errors are auto correlated.

Under certain conditions, physical growth does not follow linear pattern over time. Modeling growth spurts using linear form of models could lead us into wrong conclusion and may have weak prediction power. Thus, the nonlinear models are alternative ways of modeling growth spurts. This modelling approach uses mixed or fixed effects form based on the objectives of underlying study.

Non-Linear Mixed Effects Models

Nonlinear mixed effects models refer to the population mean of the parameter and random effects that indicates the differences between the mean value of the parameter and the adjusted value for each individual growth over time (Wang and Zuidhof, 2004).The nonlinear mixed effects growth curve models used in this study are Logistic and Gompertz which are most commonly used growth curve models due to their mathematical tractability with biologically meaningful parameters.

Logistic Model (Nelder, 1961)

$$y_{ij} = \frac{{}_1 + b_{1i}}{1 + (\ {}_2 + b_{2i}) \exp(-(\ {}_3 + b_{3i}) t_{ij})} + \pounds_{ij}$$

Gompertz Model (Winsor, 1932)

$$y_{ij} = (\beta_1 + b_{1i})\exp((\beta_2 + b_{2i})\exp(-(\beta_3 + b_{3i})t_{ij}) + \varepsilon_{ij}$$

where, y_{ij} is height of i^{th} subject at j^{th} measurement occasion, t_{ij} is age of i^{th} subject at j^{th} measurement time, β_1 is asymptotic or maximum height (adult height), β_2 is scaling parameter and β_3 is growth rate (between subjects); b_{1i} is random effects for β_1, b_{2i} is random effects for β_{2i}, b_{3i} is random effect for β_{3i} and ε_{ij} is error term.

$$b_{ik} \sim N(0, \Sigma_k), \qquad \varepsilon_{ij} \sim N(0, \sigma^2) \text{ for } k = 1,2,3,$$

$$\Sigma_k = \begin{bmatrix} \Sigma_{b11} & \Sigma_{b12} & \Sigma_{b13} \\ \Sigma_{b21} & \Sigma_{b22} & \Sigma_{b23} \\ \Sigma_{b31} & \Sigma_{b32} & \Sigma_{b33} \end{bmatrix}$$

Since our sample data is repeated measurements taken on the same subject, the expression for the within-subject variance-covariance matrix can be formed in the following way:

$R_i = \sigma^2 \Gamma_i I_{n_i}$, I_{n_i} = An identity matrix ($n_i \times n_i$), Γ_i = Correlation structures and σ^2 = Residual variance of the model.

Methods of parameter estimation

Maximum likelihood estimation method was implemented to estimate underlying model parameters using R-package "lme4" and "nlme". Statistical test was done at 5% level of significance. Further details of mixed effects model parameter estimation has been described by Lindstrom and Bates (1990), Lindstrom and Bates (1995), Davidian and Giltinan (1995) and, Sedigheh and Debasis (2012).

Model adequacy checking

The model assumptions were checked using residual plots versus fitted values, QQ and P-P plots. The goodness of fit was tested based on the Bayesian Information Criteria (BIC) and Akaikie Information Criteria (AIC). However, some scholars argue that many measures of model fit, even the likelihood ratio chi-square, will often appear to reflect relatively poor fit – when a model fits data very closely – that is, if residual variances are quite small (Browne *et al*., 2002).

RESULTS

Descriptive statistics

Descriptive statistics of height measurements taken on each survey visit presented below in Table 1. More height growth variation was observed in girls than in boys after period I. Growth variation became higher in the fourth period for both sexes

Table 1: Summary statistics of height in each measurement periods by sex.

Measurement Period in years	Female					Male				
	N	Min	Max	Mean	Std. D	N	Min	Max	Mean	Std. D
Period I (age 1)	841	56.00	89.50	70.425	5.498	947	55.30	89.50	71.45	5.227
Period II (age 5)	843	86.50	124.00	103.563	5.512	947	80.90	124.90	103.95	5.291
Period III (age 8)	843	99.10	157.00	120.628	6.469	947	102.0	146.00	120.66	6.129
Period IV (age 12)	843	118.2	178.00	142.205	7.880	947	120.0	161.50	139.80	6.628

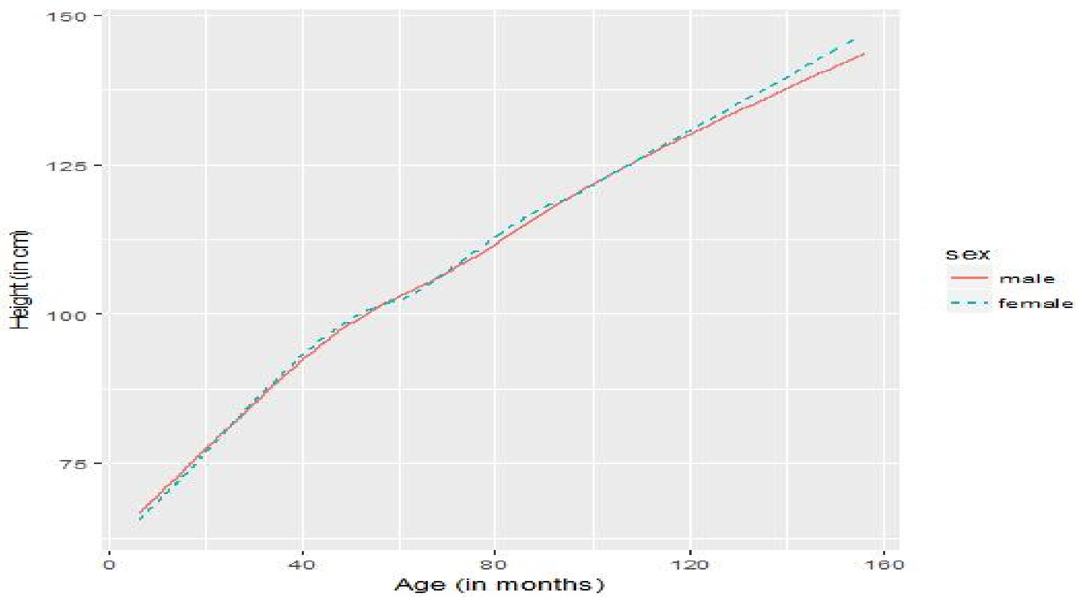

Figure 2: Smooth line curve of height growth over measurement time by sex

Boys and girls had almost the same height between 12-84 months (1-7 years). After 84 months girls become taller than boys (Figure 2). However, the smooth curve plot in Figure 2 doesn't show where the rate of change was accelerated or decelerated. In order to identify where rapid and slow rate of change lies we have used height growth velocity curves presented in Figure 3.

Height growth Velocity

Height growth velocity was calculated to investigate time of accelerated and decelerated growth periods. To assess these curvatures, the following velocity formula used (Grajeda *et al*., 2016):

$$\Delta height \ (t_{ij}) = \frac{height \ (t_{i(j-1)}) - height \ (t_{i(j-1)})}{t_{ij} - t_{i(j-1)}}$$

where ,

$\Delta height(t_{ij})$ = height change for i^{th} individual at j^{th} measurement period.

Between 60 to 84 months, boys and girls had shown very similar rate of growth change. After 84 months (7 years) rate of change in girls became accelerated than boys. The growth difference in this time could be due to various factors. Thus, we have used linear mixed effects models to identify factors associated with rate of change for both sexes. On the other hand, nonlinear mixed effects models were used to estimate height at maximum growth and rate of change over time within and between subjects.

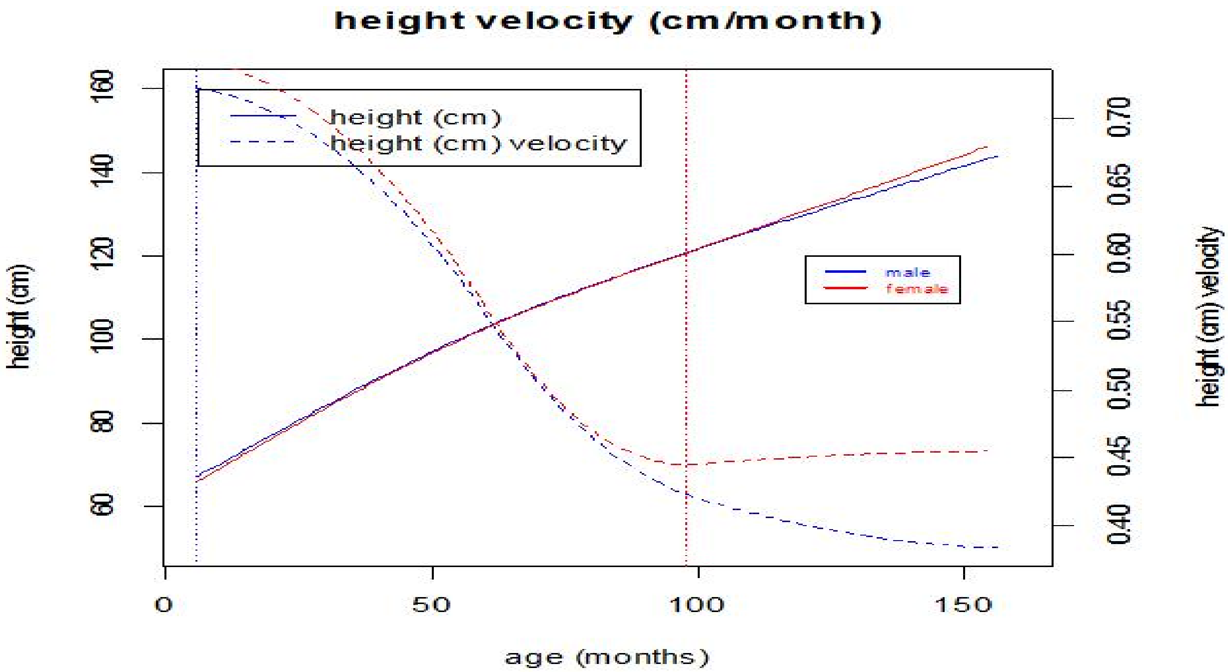

Figure 3: Smooth line and growth velocity curves by sex

Linear fixed and mixed effects models

Table 2 presents the goodness of fit test for the linear models. Linear mixed effects model better fit the data than fixed effects model.

Table 2: Assessing the goodness of fit of linear models

Fit statistics	Linear fixed	Linear mixed
AIC	44485.57	43010.67
Log.Lik	-24546.60	-21446.34

The estimated values of the mixed effects model are presented in Table 3. Within an individual growth variation over time was around 0.03 cm. There was a positive relationship between within-individual rate of change (slope) and height at the baseline (random intercept). This points that a child who was taller at the baseline shown faster growth over time (r = 0.728). There was a positive correlation between two consecutive measurements taken on the same subjects at different measurement occasions (AR (1): π = 0.2) (Table 3).

Table 3: Estimated values of random effects model

Random Components	Estimates		Serial correlation Continuous AR(1)
	St. Dev.	Correlation	
(Intercept)	1.893	(Intr)	π = 0.2
Age in months	0.0299	0.728	
		Residual = 4.664	

Access to quality drinking water, mother's educational status and sex had a significant effect on height growth. Children who had access to quality drinking water were 3.8 cm taller than children who had no access to quality drinking water (Table 4).

Table 4: Estimated values of different covariates on height growth of children aged 1-12 years based on the linear mixed effects model

Covariates	Categories	β	Std.Error	DF	t-value	p-value
(Intercept)	-	66.97115	2.618180	5067	25.57927	0.0000
Age	-	0.49914	0.007732	5067	64.55163	**0.0000**
Sex	Male (ref.)					
	Female	-1.30927	1.348283	1698	-0.97106	0.3317
Birth order	-	-0.01189	0.042960	1698	-0.27685	0.7819
BCG status	Yes (ref.)					
	No	-0.21590	0.244046	1698	-0.88469	0.3765
Had quality drinking	No (ref.)					
water:	Yes	-3.86616	0.748315	5067	-5.16649	**0.0000**
Household size	-	0.24943	0.132781	5067	1.87850	0.0604
Had ANC visit	No (ref.)					
	Yes	0.20970	0.225077	5067	0.93170	0.3515
Breast feeding duration	Never fed (ref.)					
	fed for 1-3 months	0.48811	2.516145	1698	0.19399	0.8462
	fed for 4-6 months	2.07767	2.539510	1698	0.81814	0.4134
	fed for > 6 months	1.48964	2.419669	1698	0.61564	0.5382
Mother's age at birth	-	-0.00786	0.019595	1698	-0.40107	0.6884
Father's education:	No education ref.					
	Elementary (1-8)	1.70812	0.210840	5067	8.10153	0.0000
	0ther	-1.52816	3.234500	5067	-0.47246	0.6366
Mother's education:	No education ref.					
	Elementary (1-8)	0.83562	0.233946	5067	3.57187	**0.0004**
	>= High school	1.93923	0.290056	5067	6.68570	**0.0000**
Region	Addis Ababa ref.					
	Amhara	-1.60553	1.437172	5067	-1.11714	0.2640
	Oromia	-4.24911	1.382365	5067	-3.07380	0.0021
	SNNP	-1.19146	1.384214	5067	-0.86074	0.3894
	Tigrai	-2.45187	1.403808	5067	-1.74658	0.0808
Area of residence	Urban ref.					
	Rural	-0.72144	0.436144	5067	-1.65413	0.0982
Interaction effects						
Age*sex	Male (ref.)					
	Female	0.02708	0.007462	5067	3.62902	**0.0003**
Quality drinking	A.A (No ref.)					
water*region	Amhara	2.17289	0.919798	5067	2.36236	**0.0182**
	Oromia	6.04705	0.928457	5067	6.51301	**0.0000**
	SNNP	2.99661	0.911643	5067	3.28704	**0.0010**
	Tigrai	2.14791	0.907350	5067	2.36724	**0.0180**
Age*Had quality	(No ref.)					
drinking water	Yes	0.03497	0.008313	5067	4.20725	**0.0000**

Mother's educational status also plays a significant role on height growth of children. Children whose mother had elementary (1-8) and high school plus educational status were 0.84cm and 1.9 cm taller than children whose mother had no formal education, respectively. As age increased by a month, girls' height increased by 0.27 cm compared to boys holding other covariates constant in the model. The interaction effect between age and sex was higher in girls compared to boys. Height in girls increased by 0.035 cm than boys as age increased by one month. On the other hand, access to quality drinking water had a significant effect on height growth of children (Table 4). Children those who had access to quality drinking was had 0.035 cm increased height compared to children those who had no access to quality drinking water.

Nonlinear Models

After identifying the best model fit to the data, the average rate of change over time and maximum (adult height) estimated height for both sexes separately.

Table 5: Goodness of fit test for nonlinear mixed effects models by sex

Models	Fit statistics	Fixed effects models		Random effects	
		Male	Female	Male	Female
Gompertz	AIC	23759.5	21781.9	4243.28	2902.96
	BIC	23799.2	21798.4	4280.23	2956.96
Logistic	AIC	23784.4	21772.6	4216.93	2921.48

Table 6: Estimated values and fit statistics based on nonlinear mixed effects growth curve models by sex

Female										
Nonlinear mixed models	**Fixed estimate**			**Random components**					**Fit statistics**	
	parameter	**Estimated**	**Std.err**	$r_{b_1b_3}$	$\acute{O}_1$	$\acute{O}_2$	$\acute{O}_{b1b2}$	$r_{b\,sb}$	**AIC**	**BIC**
Gompertz	b1	**179.44**	2.398	-0.889	10.582	0.049	0.374	0.718	2901.48	2934.96
	b2	1.054	0.0108							
	b3	0.0105	0.0003							
	b1	**166.703**	1.716	-0.802	9.750	0.103	0.758	0.752	2922.96	2956.44
Logistic	b2	1.623	0.0215							
	b3	0.0156	0.0003							
	b3	0.0087	0.0003							
Male										
Gompertz	b1	**171.652**	1.3951	-0.879	7.9496	0.039	0.227	0.717	4216.93	4253.88
	b2	0.98945	0.0066							
	b3	0.0111	0.0002							
	b1	**161.340**	1.034	-0.802	7.2219	0.047	0.340	0.995	4243.28	4280.23
Logistic	b2	1.4912	0.0125							
	b3	0.01618	0.0002							

Model comparisons

Incorporating an individual-specific rate of change over time in the nonlinear models had dramatically reduced the estimation error and increased the fitting performance of the model. For instance, when adult height, rate of change and scaling (point of growth change) allow to varying across individuals, the fitting performance of the models had improved (Table 6).

Random effects parameters were selected based on their capability to map with theoretical and physical meanings. When adult height and rate of change vary across individual over time, Logistic models better fitted the data for both sexes. The mean adult height was estimated to be 166.7 cm and 171.6 cm in girls and boys, respectively. Adult height and rate of change had inverse relationship for both sexes (for girls r_{13}, = -0.802; for boys r_{13} = -0.879).

DISCUSSION

This study was aimed to model individual specific growth spurt over time in children aged 1-12 years old. The mixed effects models were applied to the height growth measurements to interpolate growth spurt within and between subjects over time. The effect size of different covariates on height growth was estimated using the linear mixed effects models. Decelerated and accelerated growth periods were identified using growth velocity curves.

The fitting performance of the models increased when adult height and rate of change were allowed to as individual specific. Random effects were partitioned into between (σ) and within (Σ) subject variations. The consistent result by other study (Spyrides *et al*., 2008) reported that considering random effects in the proposed models increase the precision of estimated parameters since parameters vary from individual to individual that might be demanded using margin of errors in the fixed effects model set-up. However, most of the mixed effects models applied to human physical growth data had no clear identification towards random and fixed effects parameters that should be included in the models. Thus, one of the objects of this study was to identify model that best fits height growth in the defined time points when individual specific effects were taken in to account. In addition, this study was concerned to identify mixed effects parameters that best map on theoretical basis having biologically meaningful interpretations. Of course, here the study was concerned to use some notations suggested by Browne and co-authors (Browne *et al*., 2002) to identify those parameters and to select best fit to the data. The authors discussed their arguments that many measures of model fit, even the likelihood ratio chi-square, will often appear to reflect relatively poor fit: when a model fits data very closely, that is, if residual variances are quite small. Therefore, this study had carefully examined and identified that adult height and rate of change over time were individual specific and had random effect on height growth.

The present study found that rapid growth was observed in children between 1 to 3 years followed by decelerated rate of change. Other consistent study reported that children of both sexes grow at approximately the same rate until the adolescent growth spurt (Rogol *et al*., 2000). Adult height and rate of change had inverse relationship for both sexes. The consistent findings reported that the adolescents with a later APHV tended to have a higher height later in life (Chen *et al*., 2022). The interaction effect of age on rate of change in growth was higher in girls compared to boys. This may be due to girls experience adolescence earlier than boys.

CONCLUSIONS

The logistic mixed effects models best fit and captured height growth pattern for both sexes. Boys were taller than females until onset of puberty. The most decelerated rate of growth was observed in early childhood period for both sexes. Mother's educational status, access to quality drinking water, age and sex could be one of the determinant factors of height growth in children aged 1- 12 years. Rate of change at the base line had no a significant effect on adult height. Child whose growth was accelerated during childhood period attains adult height later in life.

Competing interest

Authors have no conflict of interest

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