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ORIGINAL ARTICLE

VARIATIONS IN PHYSICAL GROWTH TRAJECTORIES AMONG CHILDREN AGED 1-15 YEARS IN LOW AND MIDDLE INCOME COUNTRIES: PIECEWISE MODEL APPROACH

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Abstract

Human physical growth consists of different growth phases. These growth phases are characterized by different growth rate changes. Therefore, this study aimed to examine differences in growth rate changes at different growth phases among children in four low- and middle-income countries. Physical height was measured in centimeters for children from infancy to middle adolescence. A total of 3401 males and 3200 females with measured height on five occasions were included in this study. A piecewise linear mixed-effects model was applied to analyze the data. There were significant differences in growth rate changes among children in Ethiopia, India, Peru and Vietnam. Males showed a higher increase in the rate of change during preschool (8.36 cm males and 8.23 cm females) and early adolescence (6.15 cm males and 3.44 cm females), while they showed a lower increase during school-age (5.16 cm males and 5.56 cm females). During school-age, children in Peru and Vietnam had a higher rate of changes (5.73 cm Peru, 5.83 cm Vietnam and 5.56 cm Ethiopia) than children in Ethiopia. However, differences in the rates of change were not significant during preschool and early adolescence among them. Children in India had a lower rate of change in both preschool and school-age, but they had a higher rate of change during early adolescence compared to children in Ethiopia. The study results may help to compare the growth status of children in low- and middle-income countries.

***Keywords**: Covariance structure, Knot point, Mixed-effects model, nonlinear trajectory*

INTRODUCTION

Children's growth trajectories monitoring is an essential part of primary health care in children. For instance, both growing too slowly or too fast may indicate a nutritional or other health problem. Children's growth is a very sensitive indicator of nutrition, illness, and the living conditions of children[1]. Underweight and stunting are related to the lack of growth in children[2]. On the other hand, studying the growth trajectory is important for understanding the key anthropometric indices of growth in children. Children's ability to reach their growth potential might be limited by inadequate nutrition and health[3]. Hence, mean height provides indirect insights about economic conditions which are a direct indicator of health status[4]. In general, studying child growth is widely acknowledged as an important measure of the population's nutritional and health status[2,5-7].

A fundamental incentive to study human growth is to realize the basic biological changes at individual and population levels[8]. Thus, appropriate growth data modeling approach is required to evaluate growth trajectories and investigate factors that influence the trajectory. A longitudinal study provides a more realistic view of growth at both individual and group levels. Several mathematical functions: the parametric, nonparametric and semi-parametric functions, have been proposed to explore the shape of growth trajectories[9-12]. In parametric modeling longitudinal data, the functions determining the relationship between the outcome and explanatory variables are assumed to be known, either linear or nonlinear. However, the main limitation of the parametric modeling approach is that it may be too restrictive for many practical applications and its assumptions are not always satisfied. This limitation has a motivation demand for developing nonparametric models[13]. Nonparametric techniques are very flexible since it makes no assumptions about linearity and nonlinearity forms, except the requirement of some smoothness[14,15].

Human physical growth consists of different phases of growth with different rates of change, such as prenatal, infancy, childhood and adolescence[16]. The growth phases from infancy to adulthood do not follow constant trends because the rates of growth are different for different growth phases. Consistent with this reason, modeling growth changes are quite complex. When the linearity or nonlinearity assumptions do not hold between the outcome and covariates, the parametric modeling approach for growth change may not often provide adequate patterns of growth. Alternatively, a nonparametric model is a flexible approach for studying the growth change when the functional relationship between the outcome and covariate is not specified.

A piecewise regression model is a nonparametric multiphase growth modeling approach that accounts for changes in different phases by allowing for separate growth shapes into different segments. It breaks up the nonlinear growth pattern into separate linear pieces of distinct slops and attempts to account for the observed changes within each phase with simple growth models. The pieces of the growth curve are joined together by knots. The breakpoints or knots are the locations at which the functional form shift from one phase to another[17,18]. A piecewise approach is most useful when there are theoretical reasons to separate the time of growth into different phases and when one is interested in comparing the rate of growth for different phases[17-20]. Therefore, the objective of this study is to examine the mean height difference across four low- and middle-income countries in different growth phases using a piecewise linear mixed-effects modeling approach.

METHODS

Data Source

Longitudinal height data of children were obtained from the Young Lives cohort study carried out in Ethiopia, India, Peru and Vietnam from 2002 to 2016. The Young Lives is a 15-year longitudinal study of the changing nature of childhood poverty designed to collect information on children growing up in four low- and middle-income countries. The Young Lives study employed multistage sampling techniques with the first stage involving a selection of sentinel locations from each country. Sentinel site monitoring is a public health concept that entails a purposive sampling of a small number of settings that are thought to reflect a specific population or area, and then being studied uniformly at relatively wide ranges. Following that, 20 sentinel sites were selected at non-random in each study country. Following the selection of 20 sentinel sites, households with children in the appropriate age ranges were chosen at random. This technique, which was implemented in 2002, resulted in the selection of 2,000 infants (ages 6 to 18 months) at random and considered as a younger cohort. Simultaneously, 1,000 older children (aged 7 to 8 years) were chosen at random in the same sites and considered as older cohort[21,22]. Details regarding sampling and participant recruitment have been discussed in previously published work[22,23]. The qualitative and quantitative survey data were gathered in five rounds. The first survey round was carried out in 2002 when children were on average one year of age (younger cohort) and eight years of age (older cohort), the second survey was carried out in 2006, the third was in 2009, the fourth was in 2013 and the fifth was carried out in 2016[21]. The anthropometric data, height (cm) and weight (kg), were collected as quantitative data. From a younger cohort, a total of 3401 males and 3200 females with measured height five times from ages 1 to 15 years were included in this study. Data were analyzed using SAS 9.4 statistical software. The Young Lives data are publicly available and can be accessed from http://www.younglives.org.uk/.

Statistical Analysis

A piecewise linear mixed-effects model was applied to analyze the data. In this model, the mean response is modeled as a combination of fixed and random effects (mixed-effects). A linear mixed-effects model has the following general form[24]:

$$\boldsymbol{y} = \boldsymbol{X}\beta + \boldsymbol{Z}\boldsymbol{b} + \varepsilon \quad (1)$$

where **y** is a vector of a response variable, **X** and **Z** are matrices for fixed and random effects, respectively, β is the vector of fixed effects parameters, **b** is the vector of random effects and ε is error terms. The random errors and random effects are independent of each other and $\boldsymbol{b} \sim N(\boldsymbol{0}, \boldsymbol{D}), \varepsilon \sim N(\boldsymbol{0}, \boldsymbol{R})$. In the longitudinal correlated responses, a mixed-effect model allows the analysis of between- and within-individual variations. In this case, the variance-covariance matrix of random effects measures the between-individual variations and the variance-covariance matrix of random error measures the within-individual variations.

The model given in equation (1) is a single-phase model which used to model the response variable as a linear function of the covariate. However, the functional relationship between the response and covariate is not always linear[7,25]. A difficult problem with a single-phase model is when the growth data is hypothesized to have multiple phases. In such cases, a piecewise approach offers an alternative to model the growth changes in different phases through a series of linear pieces connected at breakpoints. It accommodates several nonlinear patterns that cannot be estimated by a conventional polynomial and allows distinct linear function by separating growth patterns into before and after breakpoints[26]. The choice of location and number of breakpoints can be estimated from the data[27]. A multiphase piecewise model has the following forms[18]:

$$\boldsymbol{f}(\boldsymbol{t}; \boldsymbol{\beta}, \boldsymbol{k}) = \begin{cases} f_1(t; \beta_1), & t \le k_1 \\ f_2(t; \beta_2), & k_1 < t \le k_2 \\ \vdots & \\ f_s(t; \beta_s), & t > k_s \end{cases} \quad (2)$$

where $f(t; \beta)$ represents different functions in different growth phases and k is the breakpoints. By fitting a simple model for each piece, we may detect differences in the rates of change in different growth phases. To examine the growth differences between individuals, random effects associated with different time intervals should be included in the model. The height growth is modeled as a linear function of time with different growth parameters (the intercept and slopes). Consequently, a piecewise linear mixed-effects model that allowed subject-level random effects for each parameter can be expressed as:

$$y_{ij} = \begin{cases} \beta_{0i} + \beta_{1i}t + \varepsilon, \ t \le k_1 \\ \beta_{0i} + \beta_{1i}k_1 + \beta_{2i}(t - k_1) + \varepsilon, \ k_1 < t \le k_2 \\ \vdots \\ \beta_{0i} + \beta_{1i}k_1 + \beta_{2i}(k_2 - k_1) + \cdots + \beta_{si}(t - k_s) + \varepsilon, \ t > k_s \end{cases} \quad (3)$$

where y_{ij} is the i^{th} individual height at j^{th} measurement occasion, $\beta_{0i}, \dots, \beta_{si}$ are the i^{th} subject-specific intercept and the growth rates or slopes for s^{th} growth phases. After specifying a model at the individual level for the time before and after each breakpoint, the individual parameters can be expressed as $\beta_{0i} = \beta_0 + b_{0i}$, $\beta_{1i} = \beta_1 + b_{1i}$,… , $\beta_{si} = \beta_s + b_{si}$. The values $\beta_0, \dots, \beta_s$ are parameters of fixed effects and $b_{0i}, \dots, b_{si}$ are random effects associated with the intercept and slopes for the corresponding group parameters.

RESULTS

Exploratory Data Analysis

Exploratory data analysis is the initial step in the model-building process to visualize the nature and structure of the data. Plotting the response profiles against an explanatory variable provides the visualized patterns of the data[28] and it can visually investigate the trends of growth over time and provide indication where the locations of knot points appear. For instance, the locally weighted scatterplot smoothing (LOESS) is the nonparametric smoothing technique used to show the trends of mean response over time and estimate where the place of breakpoints will appear[29]. Therefore, we performed exploratory data analysis at first to look for unusual aspects in the data, to depict the hypothesis under investigation, and to verify the data's validity for modeling. The visual information displayed in Figure 1 shows that individuals' variation is smaller in early childhood than in early adolescence. This trend of increasing spread over time could be described in terms of the difference in the rate of growth. To illustrate the general pattern in growth over time and to identify the functional form of the pattern, the mean profile plot against the time points was displayed in Figure 2. The mean profile plot exhibits an increase in height from age 1 to age 5, but from age 5 to age 12 and after age 12 the changes relatively show some decrement with different rates. The combination of these segments makes the trajectories nonlinear. From these figures, it is clear that the height growth exhibited different patterns in a different time interval. Visually, however, it is difficult to distinguish the degree of differences in the changes of growth. A multiphase mixed-effects model is a suitable approach for such growth changes to describe the extent of the differences in the change of growth in different growth phases.

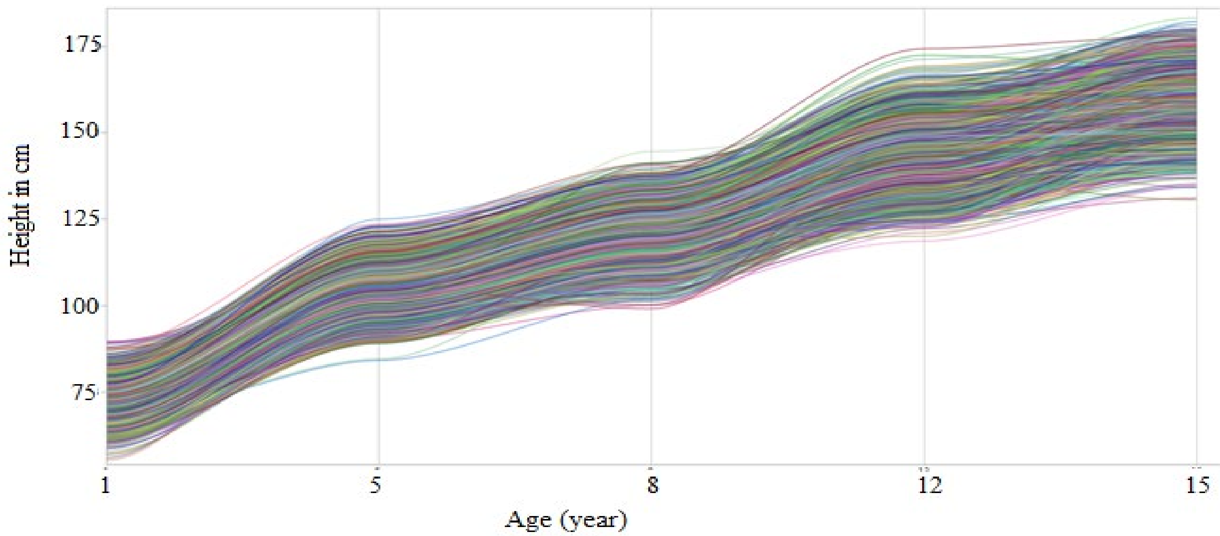

Figure 1. Individual response profile plot of physical height

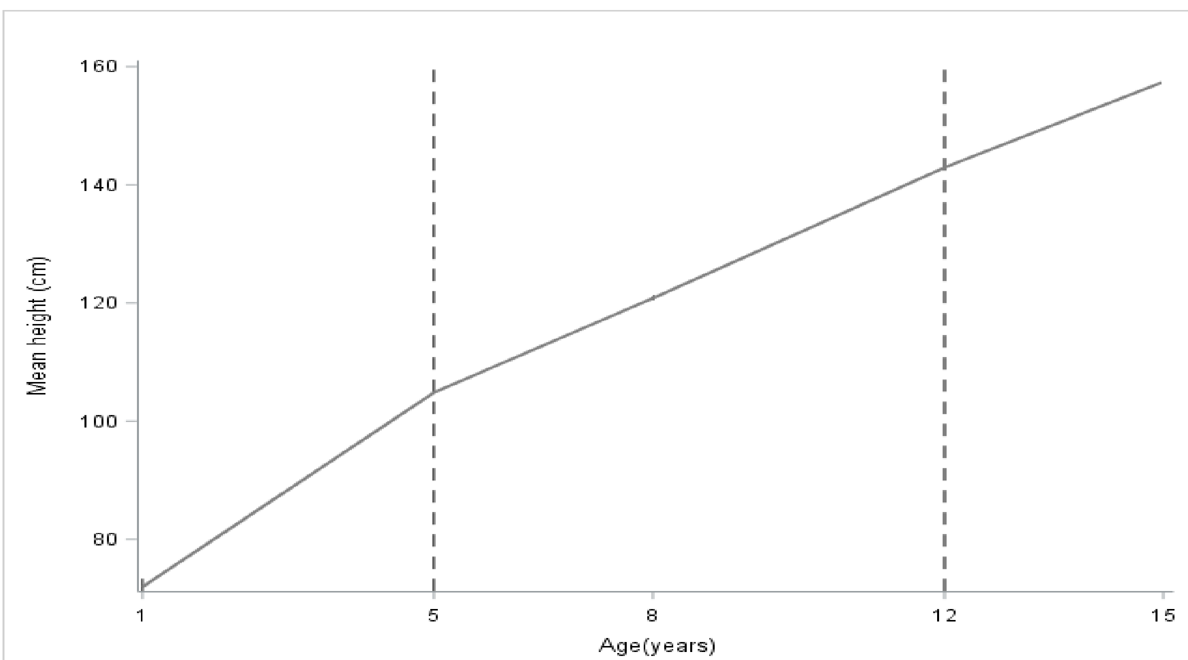

Figure 2. Profile plot of growth change in mean height over time in a different time interval

Results of fitted piecewise linear mixed-effects model

The response variable height was measured five times at age of 1, 5, 8, 12, and 15 years for each child. Before analyzing the data, the number and location of breakpoints should be determined. One possibility in which the number of breakpoints can be determined is to start the analyses with a maximum number of breakpoints and step by step decreasing the number of knots until a best-fitting or smooth curve is attained[30,31]. The placement of breakpoints was performed from the data by fitting piecewise models using a nonlinear least square method[32]. As a result, a model with two-knot points at 4.95 and 12.17 years provided best-fitting. With this specification, three growth phases are being modeled. The time interval from age 1 to 4.95 years was considered as phase one represents a preschool period, from age 4.95 to 12.17 years was considered as phase two represents a school-age period and from age 12.17 to 15 was considered as phase three represents an early adolescence period. The fitting performance of the two models, a piecewise ordinary least square and piecewise linear mixed-effects models, were compared for modeling the growth trajectories. The best-fitting model was chosen using values of AIC and BIC information criteria. A piecewise ordinary least square model provides the worst estimates. This indicates that further modeling components are needed to account for the correlated set of observations measured on the same individuals over time. After the random effects were added to the model, the model goodness of fit is highly reduced from 213005 AIC to 193180 AIC values. This could imply a piecewise linear mixed-effects model fits well a longitudinal height data than a piecewise ordinary least square model.

A mixed-effects model is a powerful tool for modeling correlated and clustered data by describing covariance structure in the model. Furthermore, the random effects in the mixed-effects model can be used to identify between-individual variation and within-individual correlation in the data. The different covariance structures were tested and chosen using the likelihood ratio test approaches for the nested model and using the likelihood-based information criteria: AIC, AICC, BIC, and HQIC for the non-nested model. Accordingly, a model with random effects associated with intercept and slopes of all growth phases was tested and compared. The large values of test statistics and small p-values (p = 0.0000) suggest that incorporating all the specified random effects in the model enables to improve the performance of the model. Furthermore, the height measurements within individuals follow a heterogeneous first-order autoregressive covariance structure. Lastly, the effects of gender and country differences on a child's growth were investigated and the results are summarized in Table 1.

The questions answered in this study are 1) Are the patterns of growth in all phases stay the same or change among children in all four countries? and 2) Are the patterns of growth in all phases differ by gender and country? According to the results in Table 1, the estimated mean intercept was 63.70 with mean rates of change of 8.22, 5.56 and 3.44, respectively, during preschool, school-age and early adolescence. The coefficient of intercept represents an estimate of the mean height at baseline, excluding all explanatory variables in the model. The estimated rate of changes for each growth phase gives information about the degree of changes of growth in that phase. The small p-values (p <.0001) of these estimates imply that the rates of change are significantly positive in all growth phases. The results showed that the rates of growth in height decrease as a child's age increases. For instance, faster growth was observed during the period of preschool age with an estimated rate of growth of 8.22 cm/year and the rate of growth reduced to 3.56 cm/year after a school-age. The mean profile plot presented in Figure 2 depicted the same investigation with these results.

To examine the effects of gender and country differences on child growth, gender and country were added as covariates to the model. The effects of the interactions between gender and time before and after each breakpoint exhibit the difference in growth change between males and females in each growth phase. Likewise, the effects of the interactions between country and time before and after each breakpoint show differences in growth

Table 1 Estimates of the fixed effect parameters and covariance of random effects

Effect	Estimate	SE	t-value	p-value	95% CI

Intercept	63.6980	0.0653	975.20	<.0001	63.5699	63.8260
Preschool	8.2187	0.0274	300.55	<.0001	8.1651	8.2723
School-age	5.5619	0.0204	272.98	<.0001	5.5219	5.6018
Early adolescence	3.4391	0.0521	66.04	<.0001	3.3370	3.5412
Gender (reference = female)						
Preschool × gender	0.1396	0.0228	6.13	<.0001	0.0949	0.1842
School-age × gender	-0.4040	0.0178	-22.70	<.0001	-0.4388	-0.3691
(Early adolescence) × gender	2.7062	0.0455	59.53	<.0001	2.6171	2.7953
Country (reference = Ethiopia)						
Preschool × India	-0.1524	0.0325	-4.68	<.0001	-0.2162	-0.0886
Preschool × Peru	-0.0542	0.0327	-1.66	0.0966	-0.1182	0.0097
Preschool × Vietnam	-0.0225	0.0321	-0.70	0.4835	-0.0854	0.0404
School-age × India	-0.1429	0.0254	-5.62	<.0001	-0.1927	-0.0930
School-age × Peru	0.1680	0.0255	6.58	<.0001	0.1180	0.2180
School-age × Vietnam	0.2735	0.0251	10.90	<.0001	0.2244	0.3227
(Early adolescence) × India	0.1572	0.0650	2.42	0.0155	0.0299	0.2845
(Early adolescence) × Peru	-0. 1054	0.0652	-1.62	0.1058	-0.2331	0.0223
(Early adolescence) × Vietnam	0.0258	0.0641	0.40	0.6876	-0.0998	0.1513
Covariance parameter						
σ_{01}	1.5275	0.1143	13.37	<.0001	1.3035	1.7515
σ_{02}	0.1785	0.0767	2.33	0.0200	0.0281	0.3289
σ_{03}	-1.0170	0.1201	-8.47	<.0001	-1.2523	-0.7816
σ_{12}	0.1329	0.0174	7.66	<.0001	0.0989	0.1669
σ_{13}	-0.1780	0.0266	-6.69	<.0001	-0.2301	-0.1259
σ_{23}	0.0221	0.0506	0.44	0.6623	-0.0770	0.1212

changes between the reference group (Ethiopia) and the corresponding countries in each growth phase. The interaction effects between gender and time before and after each breakpoint were significantly associated with child growth. Males had higher mean rates of change during preschool ($\beta_{11} = 0.1396, p < 0.0001$) and during early adolescence ($\beta_{13} = 2.7062, p < 0.0001$), but they had a lower mean rate of change during the school-age ($\beta_{12} = -0.404, p < 0.0001$) compared to females. The estimated mean rates of change related to the effects of time during preschool and school-age with country interaction were significantly negative ($\beta_{21} = -0.1524, p < 0.0001$, $\beta_{22} = -0.1429, p < 0.0001$) for children in India, but it was significantly positive ($\beta_{23} = 0.1572, p = 0.0155$) during early adolescence. These indicate that children in India had a slower growth rate during preschool and school-age and had a faster growth rate in early adolescence compared to children in Ethiopia. The estimated mean rates of change related to the effects of time during school-age for children in Peru ($\beta_{22} = 0.1680, p < 0.0001$) and Vietnam ($\beta_{23} = 0.2735, p < 0.0001$) were significantly positive. These indicate that the mean rates of change for Peruvian and Vietnamese children were 0.1680 and 0.2735, respectively, times higher than Ethiopian children. During preschool and early adolescence, however, there were no significant variations in the rates of change between children in these countries.

There are other important aspects of longitudinal study the between-individual variability analysis. All covariances except σ_{03} and σ_{13} were significantly positive. These positive covariances suggest that children who had a higher mean rate of change before knot points also tended to report a higher mean rate of change following the knot point. For instance, the covariance between random intercept and the slope of preschool age was 1.528, indicating that children who were taller at the beginning of the cohort study also tended to have a higher growth rate during preschool. The significant negative covariance between random intercept and slope of phase three (σ_{03} = -1.017) suggesting that children who were taller at the beginning of the cohort study tended to have a lower rate of change during the school-age. A similar interpretation could be given for the rest significant covariances displayed in Table 1.

DISCUSSION

We found an appropriate preliminary functional form of the growth model based on the descriptive and profile plots. The preliminary mean profile plot revealed that growth change displayed varied patterns in different time intervals with a greater change in early childhood and then relatively show some decrement in the subsequent period. Therefore, we adopted a piecewise model which captures trajectories through a series of linear pieces connected at breakpoints. The Linear piecewise growth rates in different growth phases were compared across countries and gender.

One of the most appealing futures of a piecewise model is the knot points (called breakpoints), which is the age or time when growth shifts from one process to another. Each individual's height was fitted with three straight lines joined at two-knot points. The two-knot points separate the growth trajectories into three growth phases: the preschool phase, school-age phase and early adolescence phase. Two piecewise models, the linear least square and the linear mixed-effects models, were employed to analyze the data. The fitted values of both models are compared and the use of random effects in the mixed-effects model significantly minimizes parameter variability across all estimations and hence improves the estimation efficiency and it provides a good fit for the analyses of growth trajectories. This finding is consistent with that of Grajeda[33] in that a spline mixed-effects model is well suited for modeling the nonlinear growth of children than the ordinary least square approach.

Our overall piecewise growth trajectory study showed that the rate of height growth was highest during preschool then gradually declines in the two consecutive growth phases (i.e., in school-age and early adolescence). The finding is consistent with the previous work done by Howe[30] outlined the application of a linear spline multilevel approach to model childhood growth trajectories in height and weight among five birth cohorts from different geographical regions and economic development. Similarly, Rosenbloom[16] compared the heterogeneity of growth in different growth phases from prenatal to adolescence and reported that infancy is a phase of a rapidly changing rate of growth. In addition, our findings support previous study[34] suggesting that children in low- and middle-income countries experienced fast growth during their first two years of life.

We have also found that the 15-years trajectories of children were significantly associated with gender differences. The estimated mean differences in rates of change between males and females were 0.13, -0.40 and 2.53, respectively, during preschool, school-age and early adolescence. These findings show that males had a larger rate of change during preschool and early adolescence, but they had a lower rate of change at school age than females. Grajeda[33] evaluated the contribution of gender differences in height growth and reported that males were 1.5 cm taller than females.

Another important concentration of this study was to examine the effect of countries on child growth. Our findings show that child growth trajectories differed significantly among the four study countries, possibly indicating the impact of environmental context. For instance, Aizawa[5] examined inequality of opportunity in child growth trajectories in Ethiopia, India, Peru and Vietnam and reported that a significant variation in height trajectory between clusters. Compared to children in Ethiopia, children in India showed a lower increase in the rate of change during preschool and school-age, while they showed a higher increase in the rate of change during early adolescence. In contrast to children in India, children in Peru and Vietnam showed a higher increase in the rate of change during school-age compared to children in Ethiopia. However, there were no significant differences in the rate of change between them during preschool and early adolescence. The growth variations across all four countries could be due to socioeconomic variations between them. Differences in growth across high-, middle-, and low-income countries are caused by the geographical and social patterning of nutritional and health shocks[35]. Children from low-income families are more likely to have a lack of development of human capital throughout their lives[6]. There are certain limitations to our study which mainly emanated from the limitedness of factors and covariates captured in the Young Lives study. However, the model used in this study can be easily extended to many time-invariant and time-varying covariates in future studies.

CONCLUSIONS

In analyzing a relationship between height growth and a child's age at distinct ranges of time, there may be different forms of relationship that occur in different growth phases. In such cases, linear or nonlinear models are not conducive to characterize the trajectories well. A more flexible technique is to model trajectories by separating them into multiple linear phases. A multiphase mixed-effects model is especially well-suited to model growth data that includes such events. A piecewise model in the context of the mixed-effects model is more preferable that allows multiphase models in modeling the trajectories for various ranges of time[30,36]

Monitoring the physical growth of children throughout infancy and early adolescence looks to be critical in allowing children in low- and middle-income countries to realize their maximum growth potential. We have used a piecewise mixed-effects model with two-knot points at age approximately 5 and 12 years and found a difference in growth change before and after these knot points. The growth patterns before and after each knot point differ by gender and country. The results of the study may potentially be useful to compare the growth status of children in low- and middle-income countries. Although we used a continuous response variable in this study, this model can easily be extended to accommodate discrete response variables as well. The findings of this study contribute to a better understanding of the growth change analysis in human physical growth.

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Conflict of Interest
The authors declare no conflict of interest.

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