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A Study of the Relationship between Childhood Body Size and Adult Blood Pressure, Cardiovascular Structure and Function

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A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science, at Virginia Commonwealth University.

by

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Abstract

A STUDY OF THE RELATIONSHIP BETWEEN CHILDHOOD BODY SIZE AND ADULT BLOOD PRESSURE, CARDIOVASCLAR STRUCTURE AND FUNCTION

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A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science, Virginia Commonwealth University at Virginia Commonwealth University.

Virginia Commonwealth University, 2014.

Director: Roy T. Sabo, Assistant Professor, Department of Biostatistics.

BACKGROUND: Little is known of the effects of obesity, body size and body composition, and blood pressure (BP) in childhood on hypertension (HBP) and cardiac structure and function in adulthood due to the lack of long-term serial data on these parameters from childhood into adulthood. In the present study, we are poised to analyze these serial data from the Fels Longitudinal Study (FLS) to evaluate the extent to which body size during childhood determines HBP and cardiac structure and function in the same individuals in adulthood through mathematical modeling.

METHODS: The data were from 412 males and 403 females in the FLS. Stature and BMI parameters were estimated using the Preeze-Baines model and the third degree polynomial model to describe the timing, velocity and duration of these measure from 2 to 25 years of age. The biological parameters were related to adult BP and echocardiographic (Echo-) measurements using Generalized Linear Models (GLM).

RESULTS: The parameters of stature and BMI were compared between male and female to their overall goodness of fit and their capabilities to quantify the timing, rate of increase, and duration of the growth events. For stature parameters, the age at onset and peak velocity was earlier for girls; but the peak velocity was greater in boys; the velocity at onset was about the same for boys and girls; and stature at onset, peak velocity and adult was greater for boys. For BMI parameters, boys tended to have larger BMI values than girls, but the rates of change in BMI were almost the same; there was no sex difference in the timing of BMI rebound, but there was for the age of the peak velocity of BMI and maximum BMI, both of which were earlier in girls than in boys.

CONCLUSIONS: Changes in childhood stature and BMI parameters were related to adult BP and Echo-measurements more so in females than males. Also the relationship of the adult BP measurements with corresponding childhood biological parameters was stronger than the relationship for adult Echo-measurements.

CHAPTER I

INTRODUCTION

1.1. Background

Promoting catch-up growth in children has health benefits, but recent research evidence suggests that accelerated child weight gain may increase adult hypertension and cardiac disease risk. Hypertension (HBP), one of the most important risk factors for cardiovascular diseases (CVD),[1] is one of the leading cause of death all around the world.[2] In western populations, 30% of total mortality attributable to CVD could be prevented if blood pressure (BP) could be reduced by 10 mmHg.[3] In eastern populations, like China, people with HBP are five times more likely to experience a stroke than those with normal BP.[4] Although extensively studied, the etiology of HBP cannot be fully explained by genetic factors and adulthood risk factors such as age, body mass index (BMI), physical activity, and cigarette smoking.[3,5] It has been suggested the development of overweight in childhood is highly related to obesity in adulthood,[6] where it is associated with an increased risk of HBP and cardiac disease. Prevention should therefore occur in childhood when it is most likely to be effective for preventing adult obesity. And the relationship between childhood body growth and the adult BP, cardiovascular structure and function should be investigated

Body growth influences BP and cardiac development. The close relation between body size and cardiac development during childhood and adolescence is the hallmark of this influence.[7] From previous studies, little is known of the effects of obesity, body size and body composition, and BP in childhood on HBP and cardiac structure and function in adulthood. This

paucity of information is due to the lack of long-term serial data on these parameters from childhood into adulthood.[8] However, we have echocardiographic (Echo-) measurements of cardiac structure and function in adult participants in the Fels Longitudinal Study (FLS) whose body size, body composition, and BP were measured periodically from birth into adulthood.[9] We are now poised to analyze these serial data to evaluate the extent of which body size during childhood determine HBP and cardiac structure and function in the same individuals in adulthood.

The analysis of longitudinal body growth data requires specific methodological approaches. One of the main goals of longitudinal growth studies is to establish individual growth patterns and to estimate biological parameters, such as the timing and intensity of the adolescent growth spurt, for example.[10] These features are providing us with information about the shape of the growth curve, rather than telling us what size is attained at a particular age.[10,11] A basic technique to establish the continuous growth process from a set of discrete measurements of size in function of age is provided by curve fitting through mathematical modeling.[11] Various models have been proposed to achieve this goal. They can mainly be subdivided into nonstructural and structural models.[12] In this study, two commonly used models were used to describe the analysis of human body growth data of childhood stature and childhood BMI, emphasizing on their applicability to the relationship between adult BP and Echo-measurements.

We used measurements of stature and BMI from the childhood body size measurements as the study subject to examine the patterns of change in childhood body growth. Figure 1.1 below showed the analysis approach and the process design.

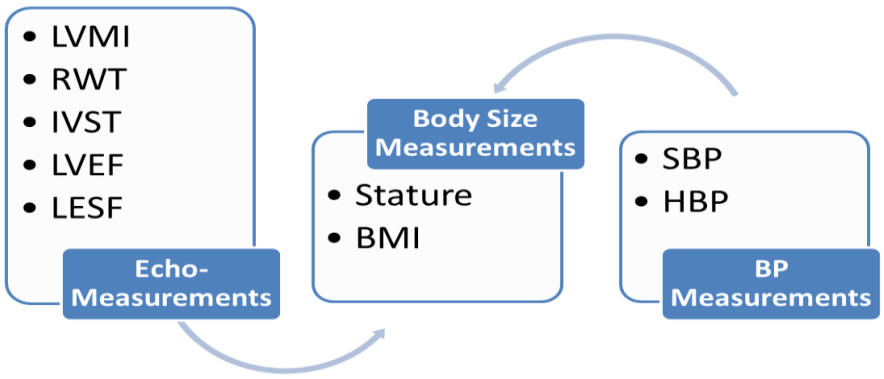

Fig.1.1 Analysis Approach and Process Design

The general procedure of this study mainly included three steps: data cleaning, model fitting and results summarizing. First the data was cleaned and managed based on the selection criteria of participants from FLS longitudinal dataset to obtain the proposed study sample. Then childhood stature and BMI were fitted into the mathematical model to yield biological parameters for the statistical analysis which were then used as representative values of the childhood growth to trajectory. Finally, from the SAS output of the results, the effects of childhood stature and BMI parameters to adult BP, cardiovascular structure and function were discussed and concluded.

The results of the proposed modeling from the FLS longitudinal dataset provided a basis for the early identification of children who are at high risk for developing HBP and abnormalities of cardiac structure and function in adulthood. The proposed analyses may also lead to the development of strategies to interrupt the pathophysiologic processes by which childhood obesity engenders HBP and abnormal cardiac structure and function in adulthood.

1.2. Objective of Study

The overall objective of this study was to evaluate the relationship between childhood body size (including stature and BMI) and adult BP, cardiovascular structure and function. Two specific objectives of this study were:

I. Analyze the biological parameters of childhood body size measurements (Stature, BMI) that quantify the timing, duration, and magnitude of growth derived from the estimated coefficients in the fitted mathematical models

II. Identify the level of body size (Stature, BMI) during childhood in relation to adulthood BP including SBP and HBP, cardiovascular structure and function including left ventricular mass indexed for height$^{2.7}$ (LVMI), interventricular septal thickness (IVST), relative wall thickness (RWT), left ventricular ejection fraction (LVEF) and left ventricular shortening fraction (LVSF) in the same individuals as adults

1.3. Organization of Thesis

This thesis had four chapters with appendix. Chapter I presented a brief background and objectives of the study. Chapter II described the study sample and the mathematical model for childhood biological parameters as well as the statistical analysis. Chapter III summarized the results of biological parameters yielded from the model and examined the effect of childhood stature and BMI parameters to adult BP, cardiovascular and function. Finally, Chapter IV summarized the conclusions of the study and provided recommendations for future research. In addition, the appendix presented the modeling derivative process and the SAS programming.

CHAPTER II

MATERIAL AND METHODS

2.1. Study Sample

2.1.1. Fels Longitudinal Study

The Fels Longitudinal Study (FLS) was initiated in 1929 at the Fels Institute in Yellow Sprints, OH, by Samuel Fels and Arthur Morgan, President of Antioch College. The FLS is the world`s largest and oldest longitudinal observational study of human growth and body composition.[13] Since 1977 the FLS has been housed at Wright State University in Dayton, OH.

A total of 2,567 infants have been enrolled at birth in annual cohorts of 25-35 up to the present time. Pregnant women are recruited by local newspaper advertisements in southwestern Ohio. The oldest participants are now 82 years old.[13, 14] Childhood measurements made from birth through 7 years include weight, height, skinfold thicknesses, arm, head and waist circumferences and BP. At the time of each examination, information is obtained on diet, physical activity, and family economic, educational, and health history. These data are recorded during scheduled examinations at birth, 1, 3, 6, 9, and 12 months and then every 6 months to 18 years, and biennially thereafter. Beginning in 1976, body composition, fasting plasma lipids and lipoproteins, and lifestyle variables such as cigarette smoking, and physical activity as well as family health history are included in the study for participants annually from 8 years to 18 years and biennially thereafter. Blood samples are drawn annually and stored at -80 degrees C. for future analyses.[14, 15]The echocardiographic data to determine cardiac structure and function are collected from 1999 to 2010 on 750 participants in the FLS who are older than 19 years.[14, 15]

Approximately 8% have been lost to follow-up, but their body composition data at last visit do not differ from those who remain in the FLS. And the data of the lost participants are

used where appropriate. Reliability in the FLS is excellent, and reliability coefficients for most of the variables are well above 90%.[15] Currently, 68% of the FLS participants still live in southwestern Ohio.[15] To maintain the integrity of the FLS, participants are reimbursed for expenses incurred when returning to Ohio for their scheduled examinations.

2.1.2. Measurement Protocols

2.1.2.1. Measurements

The data of the present study were available, in part, from the FLS. A summary of the variables and a glossary appeared in Table.1 below. The column on the right described the variables listed in the column on the left.

Table.2.1 Measurements pertinent to the proposed study sample

Body Size	Stature, BMI
Blood Pressure	SBP, DBP
Echocardiography	LVMI, RWT, IVST, LVEF,

The body size measurements were taken following recommendations in the Anthropometric Standardization Reference Manual.[16] Weight was measured to 0.1 kg using a SECA scale. Stature was measured to 0.1 cm using a Holtain stadio-meter. BMI values were calculated from weight and stature measurements collected from FLS between 1929 and 1996. Birth weight data were collected from birth hospital records. All the measurements were taken twice, with a third measurement taken if the difference between the first two exceeds established tolerance (0.3 kg for weight and 0.5 cm for height), and the average values were used for analysis.[15, 16]

Systolic blood pressures (SBP) and diastolic blood pressures (DBP) were measured with a standard mercury sphygmomanometer every six months from ages two through 18 years and

every two year thereafter.[15] SBP and fourth and fifth phase DBP were measured by trained observers with the participant seated. After 1974 a rigorously standardized protocol similar to that used in the Multiple Risk Factors Intervention Trial (MRFIT, 1974) was followed.[17] Three measurements were taken for BP at a single examination, and the average of the second and third readings was used for data analysis.

The echocardiographic (Echo-) measurements were performed by a certified sonographer under the supervision of Dr. Stephen Daniels, using an ATL Philips Medical System HDI 5000 ultrasound imaging system. Two-dimensional and two-dimensional directed M-mode echocardiographic images were recorded, and measurements were made on three or more cardiac cycles according to the recommendations of the American Society of Echocardiography.[17] LVM was calculated using the ASE formula: $LVM = 0.8(1.04\ ([LVIDd + PWTd + IVSTd]^3 - [LVIDd]^3)) + 0.6g$, where LVIDd is LV internal dimension at end diastole, PWTd is posterior wall thickness at end diastole, and IVSTd is interventricular septal wall thickness at end diastole. Left ventricular mid-wall shortening fraction (LVSF) was calculated as: LVSF = (LVEDd – LVESd) / LVEDd, where LVEDd is the end diastolic left ventricular dimension and LVESd is the end-systolic left ventricular dimension. Left ventricular structure was calculated from M-mode measurements of LVEDd, IVST, and PWT. Relative wall thickness (RWT) was calculated as: RWT = 2(PWT) / (LVEDd). Ejection fraction (EF) was calculated as: EF = 100% × SV / EDV, where stroke volume (SV) was calculated as: SV = End Diastolic Volume (EDV) – End Systolic Volume (ESV). Linear measurements from M-mode and 2D images have proven to be reproducible with low intra- and inter-observer variability.[17]

2.1.2.2. Selection Criteria

The longitudinal analyses used data from multiple examinations over time for each individual. The analyses included the periods of time ranging from 2 to 25 years of age as childhood, and the periods of time larger than 35 years of age as adulthood. The selection criteria for the proposed study sample were stated that: i) participants who have at least 10 serial body size visits between 2 and 25 years of age; ii) participants without unreasonable biological parameters (Age<0, Stature<0 or BMI<0) yield from the mathematical modeling; iii) for the same individuals as adults, who have Echo-measurements and blood pressure measurements after 35 years of age. The data flow diagram of progress through the study for each stage was presented as in Figure 2.1 below.

Among the total 2567 participants of 1199 males and 1368 females, there were 815 participants of 412 males and 403 males accessed for the eligibility of at least 10 serial body size visits between 2 and 25 years of age. Through the mathematical modeling fitting, 756 participants (male=378, female=378) without unreasonable stature biological parameters were included; and 648 participants (male=328, female=321) without unreasonable BMI biological parameters were included. For the analysis stage of stature measurements, 399 participants were kept for the same individuals at adulthood who have BP measurements and 292 participants were kept for the same individuals at adulthood who have Echo-measurements. In another hand, to analyze the BMI measurements, 360 and 258 were included for the individuals at adulthood who have BP and Echo- measurements.

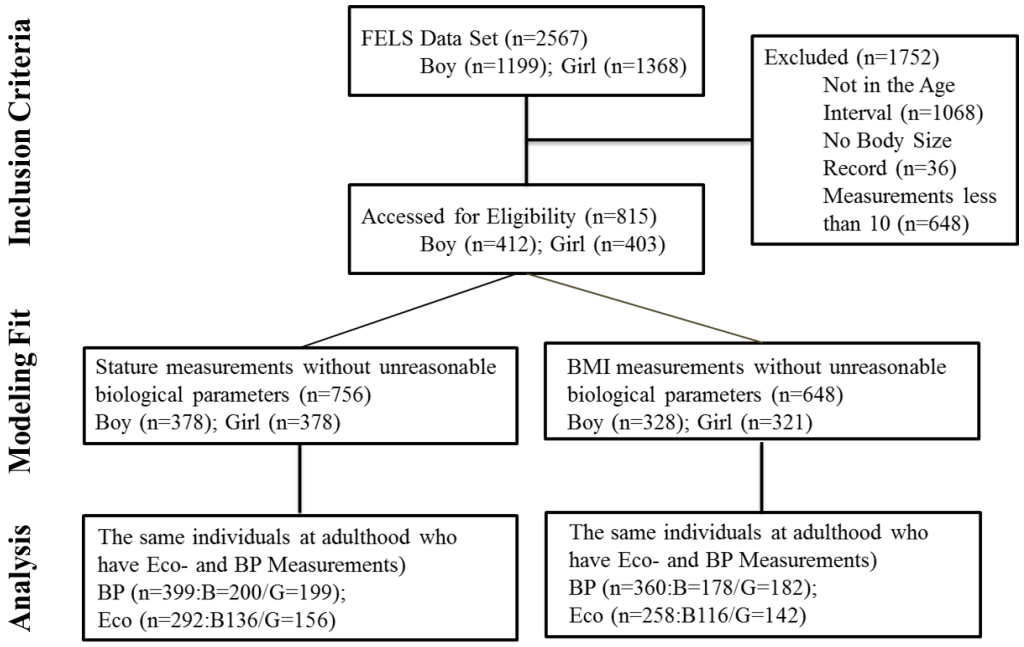

Fig.2.1 Data Flow Diagram of Progress through the Study for Each Stage

2.2. Mathematical Modeling

Fitting a growth model to serial data basically consists of describing and summarizing the growth process with a limited number of new variables which characterize the growth pattern.[18] and which have the same meaning for all individuals. These parameters then allow direct and easy comparison between individuals or between groups of individuals and provide a basis for analysis of the growth process in place of the original data.[19] Moreover it is sometimes possible to attribute to these parameters a biological interpretation.[20]

The success of the mathematical model fitting techniques depends on several factors, such as the nature of the growth variable, the precision of the data, the frequency and age range of the observations studied, the ability of the model to describe a part of the whole of the human growth process, and the flexibility of the model cope with all variations in human growth patterns. Several mathematical models have been proposed to achieve these goals. In the present

study, we choose two families of mathematical models to fit the individual serial data: Preece-Baines (PB) models for the stature measurements and third degree polynomial models for the BMI measurements. [19, 20]

2.2.1. Preece-Baines Model

The PB models originated from a logistic function as the solutions of the following differential equations:

$$\frac{ds}{dt} = (s_1 - s)(s - s_0) \quad (2.1)$$

$$\frac{dh}{dt} = s(t)(h_1 - h_\theta) \quad (2.2)$$

This model has five parameters to be estimated, one of which is adult size (h_1). The parameters s_1 and s_0 were growth rate constants, defining pre-pubertal and pubertal velocity respectively. Parameter θ is defined to locate the adolescent growth spurt along the time axis and h_θ is the size at age θ. The underlying concept of PB was that the rate of growth is proportional to the difference between stature at a particular age and age at maturity. In the present analyses, stature at 25 years was used as adult size, although small increases are common after this age.[18] The derivation of stature parameters from the PB models are found in Appendix A.

2.2.2. Third Degree Polynomial Model

Serial values for BMI from 2 to 18 years had been fitted by a log third degree polynomial model and summarized into a few biological interpretable parameters in 1991.[19] The model can be expressed as

$$lnY = \hat{\beta}_0 + \hat{\beta}_1 x + \hat{\beta}_2 x^2 + \hat{\beta}_3 x^3 \quad (2.3)$$

In 2000, individual serial data for BMI from 2 to 25 years of age have been summarized by a third degree polynomial model.[19] The developed model can be expressed as

$$Y = \hat{\beta}_0 + \hat{\beta}_1 x + \hat{\beta}_2 x^2 + \hat{\beta}_3 x^3 \quad (2.4)$$

Where Y was BMI at age x, β_0, β_1, β_2, β_3 were parameters. Biological parameters describing the patterns of growth can be derived from the parameters in the model. There was a general trend in the BMI patterns for the group. After approximately 2 years of age BMI decreased and reached a minimum about 5 years, then increased to reach a maximum at about 20 to 22 years of age. Three sets of BMI parameters, representing three "critical periods", were developed from the fitted data for each individual. The parameters for age at rebound, BMI minimum (BMI_{min}) and age at BMI minimum (Age_{min}) represented the changes during the early childhood period. The pubescent periods was represented by the maximum velocity of BMI (V_{max}), BMI at maximum velocity (BMI_{Vmax}) and age at maximum velocity of BMI (Age_{Vmax}). The post-pubescent period was represented by BMI maximum (BMI_{max}) and age at BMI maximum (Age_{max}). The derivation of BMI parameters from the third degree polynomial models could be found in Appendix B.

2.2.3. Biological Parameters

Based on the derivation to the PB models and the third degree polynomial models, the corresponding biological parameters were obtained and summarized in Table 2.2 below. Note that the study subject, mathematical model, number of parameters and age interval were indicated in the table for comparison; and all biological parameters of the two families of models were listed in order to fit the serial of individual data in FLS through SAS programming.

Table.2.2 Biological parameters derivatives for Preece-Baines model and third degree polynomial model

Preece-Baines Model		**Three Degree Polynomial Model**	
Study Subject	Stature	Study Subject	BMI
Mathematical Model	$\frac{ds}{dt} = (s_1 - s)(s - s_0), \frac{dh}{dt} = s(t)(h_1 - h)$	Mathematical Model	$BMI = \beta_0 + \beta_1 Age + \beta_2 Age^2 + \beta_3 Age^3$
Parameters	h_1, h_θ, s_1, s_0, θ	Parameters	BMI, Age, β_0, β_1, β_2, β_3
Age Interval	2 - Adult	Age Interval	2 - Adult
Rate of Growth	$s^* = \frac{(s_1 + s_0) \pm \sqrt{(s_1 + s_0)^2 - 8 s_1 s_0}}{4}$	Age $_{min\ /\ max}$	$A_{min/max} = \frac{-\hat{\beta}_2 \pm \sqrt{\hat{\beta}_2^2 - 3\hat{\beta}_1\hat{\beta}_3}}{3\hat{\beta}_3}$
Age at PV / Onset	$t^* = \theta + \frac{1}{s_1 - s_0} ln\left(\frac{s^* - s_0}{s_1 - s^*}\right)$	Age $_{Vmax}$	$A_{Vmax} = -\frac{\beta_2}{3\beta_3}$
Velocity at PV / Onset	$v = \frac{dh}{dt} = s^*(h_1 - h)$	BMI $_{min\ /\ max\ /\ Vmax}$	$BMI = \beta_0 + \beta_1 Age + \beta_2 Age^2 + \beta_3 Age^3$
Stature at PV / Onset	$h = h_1 - (h_1 - h_\theta)\frac{2}{\exp[s_0(t^* - \theta)] + \exp[s_1(t^* - \theta)]}$	V_{max}	$V_{max} = \beta_1 + 2\beta_2 A_{Vmax} + 3\beta_3 A_{Vmax}^2$

2.3. Statistical Analyses

The fitting of PB models for stature was performed using the SAS nonlinear least squares procedure in which Marquard`s (1963) iterative procedure was employed to estimate the parameters. The individual childhood BMI parameters describing the pattern of changes in BMI were derived from third degree polynomial model using the SAS PROC REG regression. When considering the criteria for a good fit, there was a need to achieve a good fit in both a statistical sense and with respect to what was biologically meaningful. The statistical measure of goodness

of fit was the root mean square error, noted by RMSE. In the present analysis, a model was considered to fit well to the data for stature if the RMSE<1.5.[20]

The BP measurements and Echo-measurements for the adult participants were related to their corresponding childhood body size measurements (stature, BMI) using a generalized linear model (GLM) analysis. If the biological parameters of childhood body size measurements on different occasions yield a significant p-value (<0.05), then the mean and covariance structure are sufficient to describe the process of change in adult BP and cardiac structure and function over time. In particular, these biological parameters can be used to address whether the body size measurements in childhood presage hypertension or abnormal cardiac structure and function in adulthood. All these analyses were processed through SAS PROC GENMOD by sex. Interactions between these biological covariates of childhood body size measurements and the related adult ages were examined also.

CHAPTER III

RESULTS

3.1. Measures of Goodness of Fit

The RMSEs were compared between boys and girls for height parameters and BMI parameters yielded from the models to access their global goodness of fit. As we discussed in Chapter II, a model is considered to fit well to the data for stature if the RMSE < 1.5. Table 3.1 presented the summary statistics of RMSE for two models.

Table.3.1 Summary statistics of root mean square error (RMSE)

	No.	Mean	SD	Min	Max
Height Parameters					
Boys	378	0.65	0.20	0.22	1.30
Girls	378	0.55	0.15	0.23	1.10
BMI Parameters					
Boys	328	0.58	0.25	0.16	1.45
Girls	321	0.66	0.26	0.23	1.49

By considering the RMSEs, 34 boys and 25 girls were excluded from subsequent analyses for height parameters, and 84 boys and 82 girls were excluded for BMI parameters. In boys, the mean RMSE for height parameters was 0.65 cm and the standard deviation was about 0.2 cm; and the mean RMSE for BMI parameters was 0.58 kg/m^2 and the standard deviation was 0.25 kg/m^2. In girls, the corresponding mean RMSE for height parameters was 0.55 cm and the standard deviation was 0.15 cm; and the mean RMSE for BMI parameters was 0.66 kg/m^2 and the standard deviation was 0.26 kg/m^2. Generally speaking, the height parameters and the BMI parameters both yielded good fits. When comparing the global goodness of fit measures, girls yielded better fits than boys from PB model; in contrast, boys yielded a little bit better fit from third degree polynomial.

With the PB model, adult size (h_1) can be estimated from the data; RMSE were larger when adult size was estimated than when adult size was provided, however.[18] Consequently, with the PB model, fitted curves that utilized the observed adult size were used for further analyses. Since PB model involved a few parameters, sometimes the iterative procedure did not converge, or converged but yielded parameter estimates dependent on the initial values. Hence, in our study, the initial values were taken from Preece MA and Baines MJ (1978) who analyzed a similar dataset. However, with the third degree polynomial model, we did not need initial values to derive the BMI parameters.

3.2. Summary of Statistics

3.2.1. Stature Parameters

3.2.1.1. Patterns of Change in Stature

The families of PB models generally simulated the shape of the individual growth curve of stature. PB model was one of the best parametric models to describe patterns of change in stature from 2 year to adult: it only had five parameters; but sometimes it was considered oversimplified and yielded overall bad fits. In addition, the PB models did not model the Mid-growth spurt (MGS) of human growth, whereas some other growth model accommodated the potential existence of MGS. Figure 3.1 illustrated the observed and predicted stature, velocity curve for participant #782 as detected by PB Model. The age at peak velocity for the participant is 9.32 years and 13.64 years at onset

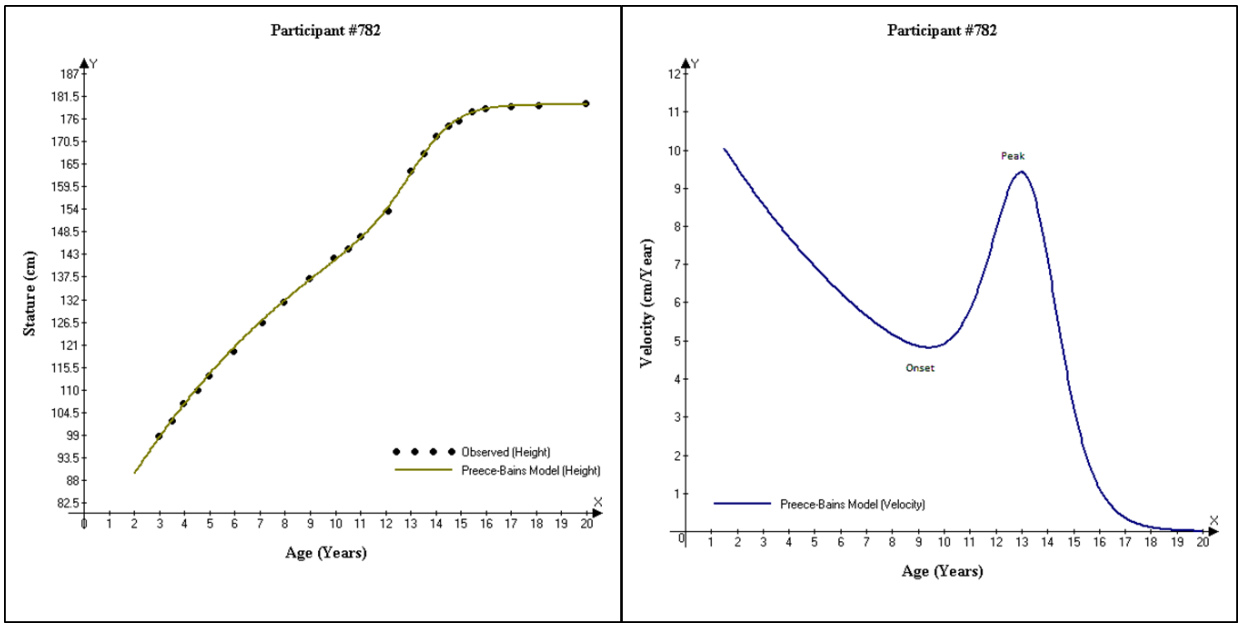

Fig.3.1 Observed and predicted statures, velocity from Preece-Baines Model from 2 to 25 years

3.2.1.2. Comparison between Boys and Girls

The growth patterns of boys and girls were summarized based on the results from PB model. As well the t test procedure was processed through SAS PROC TTEST for the height parameters to test the differences of means between boys and girls. In 378 boys and 378 girls, the summary of biological parameters were presented in Table 3.2 below.

Table.3.2 Derived height parameters from PB model for boys and girls aged 2 to 25 years

	Boy (n=378)		Girl (n=378)		T Test Procedure			
Height Parameters	**Mean**	**Std Dev**	**Mean**	**Std Dev**	**Diff(1-2)**	**DF**	**t Value**	**Pr > |t|**
Adult Stature (cm)	179.42	7.74	165.05	6.33	14.37	754	27.93	<.0001
Onset								
Age (y)	9.76	1.08	8.16	1.15	1.60	754	19.69	<.0001
Stature (cm)	137.68	7.11	127.65	7.85	10.03	754	18.42	<.0001
Velocity (cm/y)	4.98	0.61	5.44	0.75	-0.45	754	-9.13	<.0001
Peak Velocity								
Age (y)	13.44	1.24	11.32	1.12	2.12	754	24.65	<.0001
Stature (cm)	161.15	7.08	147.61	6.50	13.54	754	27.41	<.0001
Velocity (cm/y)	8.58	1.44	7.58	0.97	1.01	754	11.23	<.0001

Based on the t test and corresponding P value on the right side of the table, all of the differences were considered to be extremely statistically significant. From the left side of the table, we can obtain the information that the age at onset and peak velocity was earlier for girls (8.16±1.15 years and 11.32±1.12 years) than for boys (9.76±1.08 years and 13.44±1.24 years). The peak velocity was greater in boys (8.58±1.44 cm/yr) than in girls (7.58±0.97 cm/yr). The velocity at onset was about the same for boys and girls. The stature at onset, peak velocity and adult was greater for boys (137.68±7.11 cm, 161.15±7.08 cm and 179.42±7.74 cm) than for girls (127.65±7.85 cm, 147.61±6.50 cm and 165.05.42±6.33 cm).

3.2.2. BMI Parameters

3.2.2.1. Patterns of Change in BMI

The families of third degree polynomial models generally simulated the shape of the individual patterns of change in BMI. Three sets of BMI parameters, representing three "critical periods" from 2 to 25 years, were developed from the fitted data including BMI rebound, Pubescence, Post-Pubescence. An example of the measured and fitted BMI values by age from a randomly selected participant #782 was illustrated in Figure 3.2 for the observed and predicted individual patterns of change in BMI with biological parameters from 2 to 25 years.

The BMI decreased at about 2.0 years of age and reached a minimum at 5.4 years of age, then increased, and reached a maximum at 24.2 years of age. The age at maximum velocity was 14.8 years.

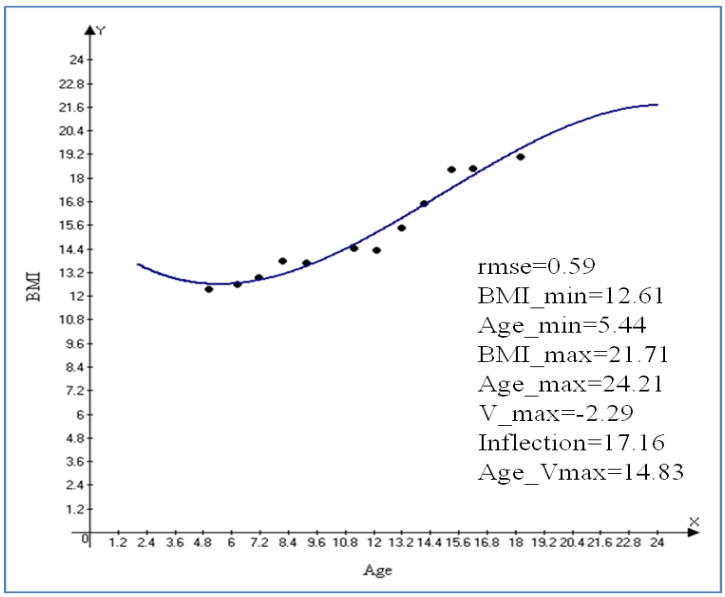

Fig.3.2 Observed and predicted individual patterns of change in BMI with biological parameters from 2 to 25 years

3.2.2.2. Comparison between Boys and Girls

The growth patterns of boys and girls were compared based on the results from third degree polynomial model. Also the t test procedure was processed through SAS PROC TTEST for the BMI parameters to test the differences of means between boys and girls. In 328 boys and 321 girls, the biological parameters of BMI were summarized in Table 3.3 below.

Table.3.3 Derived BMI parameters from third degree polynomial model for boys and girls aged 2 to 25 years

	Boy (n=328)		Girl (n=321)		T Test Procedure			
BMI Parameters	**Mean**	**Std Dev**	**Mean**	**Std Dev**	**Diff(1-2)**	**DF**	**t Value**	**Pr > |t|**
BMI rebound								
Age_min (y)	5.89	2.28	5.97	3.70	-0.13	647	-0.59	0.55
BMI_min (kg/m^2)	15.30	1.48	15.05	1.75	0.21	647	1.86	0.06
Pubescence								
Age_Vmax (y)	13.66	2.82	13.08	2.48	0.54	647	2.62	0.009
BMI_Vmax (kg/m^2)	19.60	2.91	18.99	2.34	0.52	647	2.70	0.007
V_max (kg/m^2/y)	2.76	1.66	2.97	2.32	0.14	647	1.04	0.29
Post-Pubescence								
Age_max (y)	21.44	5.49	20.19	3.93	1.21	647	3.21	0.001
BMI_max (kg/m^2)	23.89	5.08	22.94	3.99	0.83	647	2.44	0.01

Based on the t test and corresponding P value on the right side of the table, most of the differences were considered to be statistically significant except the differences for Age_min and BMI_min in BMI rebound, and V_max in pubescence. Therefore we can summarize the present data on the left side, the average BMI_min for boys at the BMI rebound was 15.30 kg/m^2 at an average Age_min of 5.89 years of age; the corresponding mean values for girls were 15.05 kg/m^2 at 5.97 years of age, which was considered to be no significant difference with boys. After the BMI rebound, BMI values increased. The rage of this increase was not different between boys and girls; as well, the Age_Vmax occurred for girls at age 13.08 years, which was almost the same for boys at age 13.66 years; furthermore, the BMI_Vmax value was higher in boys than in girls. BMI values reach their maximum in each sex during the post-pubertal period. Girls had their Age_max at an earlier age than boys by about 1.25 years, but BMI_max was larger in boys than in girls. BMI values and their time of occurrence during the BMI rebound, pubescence, and post-pubescence reflect the sex difference in the growth of boys and girls.

3.3. Data Summary from GLM Analyses

3.3.1. Stature related to BP and Echo-measurements

The height parameters were related to adult BP measurements and Echo- measurement using a generalized linear model (GLM) analysis with adjustment for the covariate effects of adult age. In order to compare the effects of biological parameters for males and females, we presented the information from SAS output separately (Table 3.4 and Table 3.5) instead of considering gender as a covariate.

From Table 3.4, we can see that, for males, the height parameters in childhood were strongly related to adult BP measurements; however there was no significant relationship

between the height parameters and Echo-measurements. Among the significant relationship to BP measurements, adult height showed negative relationship to both SBP and DBP; age at onset gave a positive relationship to SBP but a negative relationship to DBP, which indicated that males with earlier age at onset of growth curve at childhood would have a smaller SBP but larger DBP at adulthood; height at peak velocity had a negative relationship to SBP; peak velocity and onset velocity showed an opposite relationship with respect to SBP and DBP.

Table.3.4 Significant relationship of childhood stature parameters to adult BP and Echo-measurements for male

	h_AT	t_PV	t_TO	h_PV	h_TO	v_PV	v_TO
BP							
SBP	**-1.19**[a]	3.75	**7.08**[a]	**-0.88**[a]	-0.58	**11.29**[a]	**-12.10**[a]
DBP	**-2.43**[a]	2.99	**-13.54**[a]	0.28	-0.70	**-5.85**[a]	**19.24**[a]
Echo-							
LVMI	0.28	0.80	1.50	0.26	1.07	-0.34	6.72
IVST	0.01	0.05	0.08	0.01	0.01	-0.02	-0.05
RWT	0.002	0.01	0.01	0.001	0.002	-0.01	0.01
LVSF	-0.0003	0.03	0.01	-0.001	-0.003	-0.004	-0.04
LVEF	0.006	0.006	0.006	0.003	0.002	-0.02	0.04

[a] indicated a significant relationship at $p < 0.05$
Otherwise indicated non-significant relationship at $p < 0.05$

Table.3.5 Significant relationship of childhood stature parameters to adult BP and Echo-measurements for female

	h_AT	t_PV	t_TO	h_PV	h_TO	v_PV	v_TO
BP							
SBP	**-0.87**[a]	-1.52	**-3.62**[a]	**-0.85**[a]	**-0.60**[a]	0.77	3.13
DBP	**-2.89**[a]	5.30	**-12.30**[a]	**-6.88**[a]	**-5.21**[a]	7.31	5.77
Echo-							
LVMI	0.17	-3.35	-.288	-0.16	-0.32	2.69	4.78
IVST	**0.03**[a]	**-0.28**[a]	-0.16	0.02	-0.01	0.06	0.11
RWT	0.005	**-0.04**[a]	**-0.04**[a]	-0.002	-0.003	0.01	0.05
LVSF	0.004	**-0.03**[a]	**-0.03**[a]	0.001	-0.001	**0.04**[a]	**0.07**[a]
LVEF	0.006	-0.03	-0.02	0.006	0.005	0.01	0.08

[a] indicated a significant relationship at $p < 0.05$
Otherwise indicated non-significant relationship at $p < 0.05$

Compare to the fit for males, females had an obvious better results. The height parameters in childhood were also strongly related to adult BP measurements; as well there was significant relationship between the height parameters and Echo-measurements.

From Table 3.5, we can see that all the significant relationships for females between childhood stature parameters and adult BP measurements were negative. But the growth velocity for females did not yield significant relationship to BP measurements. This information indicated that females with earlier age at onset of growth curve or a smaller height at onset, peak velocity at childhood would have a larger SBP and DBP at adulthood.

For the relationship to Echo-measurements, adult height, peak velocity and onset velocity had positive significant relationship, which indicated that adult height would enhance females interventricular septal thickness and a bigger peak velocity and onset velocity at childhood growth would lead to larger left ventricular shortening fraction. Alternatively, age at peak velocity and age at onset had negative significant relationship to IVST, RWT and LVSF. We can conclude that females with earlier age at onset and peak velocity in childhood would have thicker interventricular septal and relative wall thickness, and larger left ventricular shortening fraction.

3.3.2. BMI related to BP and Echo-measurements

The BMI parameters from 2 to 25 years of age were also related to adult BP measurements and Echo- measurement. Adult ages were again included as the covariate effects by using generalized linear model (GLM) analysis. Table 3.6 and Table 3.7 collected and summarized the significant relationship of childhood BMI parameters to adult BP and Echo-measurements from SAS output for males and females.

From the preliminary results for males, we can see that the association between BMI parameters in childhood and adult BP and Echo-measurements were not strong, as few biological parameters of BMI yielded significant relationship. BMI maximum and inflection (BMI value at maximum velocity) had a positive relationship to DBP, and maximum velocity of BMI had a negative relationship to DBP. For Echo-measurements, a smaller maximum BMI value for male at childhood would have a bigger left ventricular ejection fraction at adult. But maximum velocity of BMI yielded an opposite relationship to LVEF at adult.

Table.3.6 Significant relationship of childhood BMI parameters to adult BP and Echo-measurements for male

	Age_min	BMI_min	Age_max	BMI_max	Age_Vmax	I_max	V_max
BP							
SBP	0.25	-4.60	-0.61	-0.98	-0.05	-1.87	5.75
DBP	2.94	-3.43	-0.69	**3.86**[a]	-0.24	**6.55**[a]	**-14.58**[a]
Echo							
LVMI	1.51	1.48	-1.68	-1.30	-2.24	-1.48	5.17
IVST	-0.02	0.08	-0.03	-0.01	-0.05	-0.01	0.03
RWT	-0.01	-0.003	-0.01	-0.003	-0.02	-0.005	0.01
LVSF	0.01	-0.02	0.003	-0.005	0.008	-0.01	0.02
LVEF	0.07	-0.03	0.003	**-0.35**[a]	0.005	-0.03	**0.10**[a]

[a] indicated a significant relationship at $p < 0.05$
Otherwise indicated non-significant relationship at $p < 0.05$

Table.3.7 Significant relationship of childhood BMI parameters to adult BP and Echo-measurements for female

	Age_min	BMI_min	Age_max	BMI_max	Age_Vmax	I_max	V_max
BP							
SBP	-0.72	**5.78**[a]	0.65	**1.93**[a]	0.24	**2.32**[a]	-1.62
DBP	**6.30**[a]	**-10.11**[a]	**5.90**[a]	**-6.19**[a]	**14.93**[a]	-8.59[a]	**5.19**[a]
Echo							
LVMI	-2.84	-2.69	-0.90	-1.62	-2.17	-2.34	0.13
IVST	**-0.09**[a]	**0.12**[a]	-0.08	-0.02	0.04	-0.01	0.05
RWT	-0.01	-0.01	-0.002	-0.005	-0.01	-0.01	0.01
LVSF	-0.004	0.001	0.006	0.01	0.006	0.02	-0.01
LVEF	**-0.03**[a]	0.02	-0.01	0.002	**-0.02**[a]	0.01	0.03

[a] indicated a significant relationship at $p < 0.05$
Otherwise indicated non-significant relationship at $p < 0.05$

The association between BMI parameters at childhood and BP, Echo-measurements for female provided a much better results. BMI parameters in childhood were strongly related to both adult BP measurements and Echo-measurements.

From the information of Table 3.7, we can see that the childhood BMI parameters for female were highly related to adult BP measurements. Minimum BMI, maximum BMI and the inflection had positive relationship to SBP and negative relationship to DBP. In addition, we can summarize that an earlier age at minimum BMI, maximum BMI and the inflection would lead to smaller DBP. For the relationship to Echo-measurements, minimum BMI had a positive relationship to IVST. And age at minimum BMI had a negative relationship to IVST and LVEF, which indicated that an earlier age at minimum BMI would have a thicker interventricular septal and larger left ventricular ejection fraction.

CHAPTER IV

DISCUSSION

4.1. Conclusion and Implications

Through appropriate mathematical modeling, the present study was undertaken to increase our understanding of the lifetime changes in human BP and Echo-measurements and how these changes are affected by changes in childhood body size measurements (stature and BMI). We applied the PB model and third degree polynomial model in fitting human early stature growth and childhood BMI respectively. The two families of mathematical functions were fitted to serial measures of childhood body size measurements (stature and BMI) on the participants enrolled in Fels Longitudinal Study. The biological parameters that describe the timing, magnitude, and duration of the growth spurt were derived from the fitted models for each participant. Also the parameters of stature and BMI were compared between male and female to their overall goodness of fit and their capabilities to quantify the timing, rate of increase, and duration of the growth events. The collected BP measurements and Echo-measurements for the adult participants were then related to their corresponding biological parameters of childhood body size measurements (stature, BMI) using generalized linear model (GLM) analysis. The findings present the relationship of the timing and duration of childhood body size development from 2 to 25 years of age with adult BP and cardiac status.

We arrived at several conclusions from the present analyses, we arrived at several conclusions. For stature parameters, the age at onset and peak velocity was earlier for girls; but the peak velocity was greater in boys; the velocity at onset was about the same for boys and girls; and the stature at onset, peak velocity and adult was greater for boys. For BMI parameters, boys tended to have larger BMI values than girls, but the rates of change in BMI were almost the

same; there was no sex difference in the timing of BMI rebound, but there was for the age of the peak velocity of BMI and maximum BMI, both of which were earlier in girls than in boys.

Preliminary results from GLM analyses showed that the childhood body size parameters in both sexes of timing, rate of increase and duration were related to adulthood BP and Echo-measurement in the same individual. We found that the relationship of the adult BP measurements with corresponding childhood biological parameters were stronger than the relationship for adult Echo-measurements. Also the relationship of the adult BP and Echo-measurements with corresponding childhood biological parameters for females were stronger than the relationship for males. The causes of these relationships are numerous, though there may be a genetic component. The potential of the effects needed to be taken into account when applying the present results in clinical or public health assessments.

4.2. Limitation and Future Work

Although the present study and analyses linked the development of body size measurements in childhood to BP and Echo-measurements in adulthood, there were still some limitation for the corresponding research and preliminary results.

First of all, the mathematical models for describing individual human growth patterns (stature and BMI) have interesting features, but at the same time they also have their own limitations. The choice of one approach above another mainly depends on the nature of the longitudinal data at hand (age range, frequency and interval of measurements, type of variable, etc.) and on the kind of problems to be solved (description or interpretation of growth pattern, making inferences about population growth, estimating effects of covariates, etc.)

In addition, nearly all of the proposed FLS participants are non-Hispanic Caucasians from southwestern Ohio who have been involved with the FLS since birth. They do not comprise a nationally representative sample. Therefore, findings in the FLS population may not be applicable to other races or ethnicities. Although the FLS cohort is restricted in terms of race and ethnicity, information about the specific aims proposed for this study is lacking in all racial and ethnic groups, Analysis of this extensive longitudinal data set in conjunction with echocardiographic studies may elucidate biologic relationships that apply to all races and ethnicities.

As the future work of this research and related studies, we have the following recommendations and suggestions. First we can consider including the childhood body size measurements other than stature and BMI into the study, for example, identifying the levels of BP and body composition measurements in childhood to study the association to adulthood measurements. Also, for the next step work, we can conduct the knowledge of abnormal BP and Echo-measurements to build the relationship. At last, we need to consider the inclusion of more covariates into this study, like physical activity level, alcohol and cigarette use and birth weight etc. It is probable that the accuracy of the prediction of the effect in the present study could be improved by incorporating these factors.

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APPENDIX A

Derivation of A Family of Descriptive Mathematical Functions for Preece-Baines Model

The Preece-Baines (PB) model, which includes five parameters, originates from a logistic function as the solutions of the following differential equations (In this study, γ=1):

$$\frac{ds}{dt} = \gamma(s_1 - s)(s - s_0) \tag{A.1}$$

$$\frac{dh}{dt} = s(t)(h_1 - h) \tag{A.2}$$

Where

s(t) = behavior of the rate of growth;

s_1, s_0 = rate constants;

γ = age center ;

h = the stature at age t;

h_1 = the adult size (stature at 18 years);

Then we derive the PB model. From equation A.1, we have that

$$\frac{1}{(s_1 - s)(s - s_0)} ds = \gamma dt \overset{*NOTE1}{\Leftrightarrow} (\frac{1}{s_1 - s} + \frac{1}{s - s_0})(\frac{1}{s_1 - s_0})ds = \gamma dt$$

Note that:

$$\frac{1}{(s_1 - s)(s - s_0)} = \frac{s_1 - s_0}{(s_1 - s)(s - s_0)} \frac{1}{s_1 - s_0} = \frac{(s_1 - s) + (s - s_0)}{(s_1 - s)(s - s_0)} \frac{1}{s_1 - s_0}$$
$$= [\frac{s_1 - s}{(s_1 - s)(s - s_0)} + \frac{s - s_0}{(s_1 - s)(s - s_0)}] \frac{1}{s_1 - s_0} = (\frac{1}{s - s_0} + \frac{1}{s_1 - s}) \frac{1}{s_1 - s_0}$$

Integrate of t for both side of the equation above, and then we have that

$$\frac{1}{s_1 - s_0}\int(\frac{1}{s_1 - s} + \frac{1}{s - s_0})ds = \gamma\int dt$$

$$\Rightarrow \frac{1}{s_1 - s_0}[-\ln(s_1 - s) + \ln(s - s_0)] = \gamma t + c \Rightarrow \frac{1}{s_1 - s_0}\ln(\frac{s - s_0}{s_1 - s}) = \gamma t + c$$

Solving the differential equation for t=θ and s= $(s_1+s_0)/2$, then we can solve for the constant c

$$\frac{1}{s_1 - s_0}\ln(\frac{(s_1 + s_0)/2 - s_0}{s_1 - (s_1 + s_0)/2}) = \gamma\theta + c \Rightarrow c = \frac{1}{s_1 - s_0}\ln(1) - \gamma\theta = -\gamma\theta$$

Therefore we have the result that

$$\gamma t - r\theta = \frac{1}{s_1 - s_0}\ln(\frac{s - s_0}{s_1 - s}) \tag{A.3}$$

And then we simplify the equation to represent s

$$s = \frac{s_1 e^{\gamma(t-\theta)s_1} + s_0 e^{\gamma(t-\theta)s_0}}{e^{\gamma(t-\theta)s_1} + e^{\gamma(t-\theta)s_0}} \tag{A.4}$$

From equation A.2 and A.4, we have that

$$\frac{1}{h_1 - h}dh = s(t)dt \Leftrightarrow \frac{1}{h_1 - h}dh = \frac{s_1 e^{\gamma(t-\theta)s_1} + s_0 e^{\gamma(t-\theta)s_0}}{e^{\gamma(t-\theta)s_1} + e^{\gamma(t-\theta)s_0}}dt$$

$$\Leftrightarrow \frac{1}{h_1 - h}dh = \frac{s_1}{1 + e^{\gamma(t-\theta)(s_0 - s_1)}}dt + \frac{s_0}{1 + e^{\gamma(t-\theta)(s_1 - s_0)}}dt$$

Integrate of t for both side of the equation above, and then we have that

$$\int\frac{1}{h_1 - h}dh = s_1\int\frac{1}{1 + e^{\gamma(t-\theta)(s_0 - s_1)}}dt + s_0\int\frac{1}{1 + e^{\gamma(t-\theta)(s_1 - s_0)}}dt$$

$$\overset{*NOTE\,2}{\Rightarrow} c - \ln(h_1 - h) = (s_1 + s_0)t + \frac{1}{\gamma(s_1 - s_0)}\ln[\frac{(1 + e^{-\gamma(t-\theta)(s_1 - s_0)})^{s_1}}{(1 + e^{\gamma(t-\theta)(s_1 - s_0)})^{s_0}}]$$

$$\overset{*NOTE\,3}{\Rightarrow} c - \ln(h_1 - h) = (s_1 + s_0)t + \frac{1}{\gamma(s_1 - s_0)}\{\ln[1 + e^{\gamma(t-\theta)(s_1 - s_0)}]^{(s_1 - s_0)} + \ln[e^{-s_1\gamma(t-\theta)(s_1 - s_0)}]\}$$

$$\Rightarrow c - \ln(h_1 - h) = s_0 t + s_1\theta + \ln[1 + e^{\gamma(t-\theta)(s_1 - s_0)}]^{1/\gamma}$$

Note that:

$$\int \frac{1}{1+e^x}dx = \int (\frac{1+e^x}{1+e^x} - \frac{e^x}{1+e^x})dx = \int (1 - \frac{e^x}{1+e^x})dx = \int dx - \int \frac{e^x}{1+e^x}dx = x - \ln(1+e^x)$$

Note that:

$$\ln \frac{(1+e^{-x})^a}{(1+e^x)^b} = \ln[(1+\frac{1}{e^x})^a (1+e^x)^{-b}] = \ln[(\frac{1+e^x}{e^x})^a (1+e^x)^{-b}]$$
$$= \ln[e^{-ax}(1+e^x)^{a-b}] = \ln(1+e^x)^{a-b} + \ln e^{-ax} = (a-b)\ln(1+e^x) - ax$$

Solving the differential equation for t=θ and $h_t=h_\theta$, then we can solve for the constant c

$$c - \ln(h_1 - h_\theta) = s_0\theta + s_1\theta + \ln[1+e^{\gamma(\theta-\theta)(s_1-s_0)}]^{1/\gamma}$$
$$\Rightarrow c = \ln(h_1 - h_\theta) + (s_0+s_1)\theta + \ln 2^{1/\gamma}$$

Substituting c into the equation above, then

$$c - \ln(h_1 - h) = s_0 t + s_1\theta + \ln[1+e^{\gamma(t-\theta)(s_1-s_0)}]^{1/\gamma}$$
$$\Leftrightarrow \ln(h_1 - h_\theta) + (s_0+s_1)\theta + \ln 2^{1/\gamma} - \ln(h_1 - h) = s_0 t + s_1\theta + \ln[1+e^{\gamma(t-\theta)(s_1-s_0)}]^{1/\gamma}$$
$$\Leftrightarrow \ln(h_1 - h) - \ln(h_1 - h_\theta) = \ln 2^{1/\gamma} - \ln[1+e^{\gamma(t-\theta)(s_1-s_0)}]^{1/\gamma} - s_0(t-\theta)$$
$$\Leftrightarrow \ln(h_1 - h) - \ln(h_1 - h_\theta) = \ln 2^{1/\gamma} - \ln[1+e^{\gamma(t-\theta)(s_1-s_0)}]^{1/\gamma} - \ln[e^{\gamma s_0(t-\theta)}]^{1/\gamma}$$
$$\Leftrightarrow \ln(\frac{h_1 - h}{h_1 - h_\theta}) = \ln 2^{1/\gamma} - \ln[e^{\gamma s_0(t-\theta)} + e^{\gamma s_1(t-\theta)}]^{1/\gamma}$$
$$\Leftrightarrow \frac{h_1 - h}{h_1 - h_\theta} = \frac{2^{1/\gamma}}{[e^{\gamma s_0(t-\theta)} + e^{\gamma s_1(t-\theta)}]^{1/\gamma}}$$

Therefore we have the result that

$$h = h_1 - (h_1 - h_\theta)\frac{2^{1/\gamma}}{[e^{\gamma s_0(t-\theta)} + e^{\gamma s_1(t-\theta)}]^{1/\gamma}} \quad \text{(A.5)}$$

The acceleration curve is the derivative of equation A.2

$$\frac{d^2h}{dt^2} = \frac{ds(t)}{dt}(h_1 - h) + s(t)(\frac{-dh}{dt}) \quad \text{(A.6)}$$

Using equation A.1 and A.2 in equation A.6, we have

$$\frac{d^2h}{dt^2} = \gamma(s_1 - s)(s - s_0)(h_1 - h) - s^2(h_1 - h)$$
$$\Rightarrow \frac{d^2h}{dt^2} = (h_1 - h)[\gamma(s_1 - s)(s - s_0) - s^2]$$
$$\Rightarrow \frac{d^2h}{dt^2} = -(h_1 - h)[(\gamma + 1)s^2 - \gamma(s_1 + s_0)s + \gamma s_1 s_0]$$

Solving $d^2h/dt^2=0$ for s, we have

$$-(h_1 - h)[(\gamma + 1)s^2 - \gamma(s_1 + s_0)s + \gamma s_1 s_0] = 0$$
$$\Leftrightarrow (\gamma + 1)s^2 - \gamma(s_1 + s_0)s + \gamma s_1 s_0 = 0$$

Denoted as s*

$$s^* = \frac{\gamma(s_1 + s_0) \pm \sqrt{\gamma^2(s_1 + s_0)^2 - 4\gamma(\gamma + 1)s_1 s_0}}{2(\gamma + 1)} \quad \text{(A.7)}$$

Replacing s in equation A.3 by s* and solving for t, denoted as t*

$$t^* = \theta + \frac{1}{\gamma(s_1 - s_0)} \ln\left(\frac{s^* - s_0}{s_1 - s^*}\right) \quad \text{(A.8)}$$

For the two solutions, the lower t* is age at onset of the spurt and the higher t* is the age at peak velocity of spurt. The velocity of growth at onset and at peak velocity can be computed from equation A.2, A.4, A.5 and A.8. The statures at onset and at peak velocity are derived from equation A.5. The difference between stature at onset and at peak velocity represents the increment in stature during the spurt. The increment from spurt to adult stature is calculated as the difference between stature at PV and adult stature. The intensity of the spurt is the increment in velocity from onset to peak velocity.

Derived biological parameters of stature from PB model (adult size measured) were summarized and indicated in Table 2.2 in Chapter II. Note that in the present study we take the value of age center γ equal to 1.

APPENDIX B

Derivation of A Family of Descriptive Mathematical Functions for Third Degree Polynomial Model

The third degree polynomial model, which includes four parameters, can be expressed as

$$Y = \hat{\beta}_0 + \hat{\beta}_1 x + \hat{\beta}_2 x^2 + \hat{\beta}_3 x^3 \quad \text{(B.1)}$$

Where Y was BMI at age x, β_0, β_1, β_2, β_3 were parameters.

The derivation of BMI parameters from the third degree polynomial is as follows:

$$A_{min} = \frac{-\hat{\beta}_2 + \sqrt{\hat{\beta}_2^2 - 3\hat{\beta}_1\hat{\beta}_3}}{3\hat{\beta}_3} \quad \text{(B.2)}$$

Where $\hat{\beta}_2^2 - 3\hat{\beta}_1\hat{\beta}_3 \geq 0$, and

$$BMI_{min} = \hat{\beta}_0 + \hat{\beta}_1 A_{min} + \hat{\beta}_2 {A_{min}}^2 + \hat{\beta}_3 {A_{min}}^3$$

(B.3)

Age at maximum velocity is calculated by equating the second derivative of the mathematical function to zero.

$$A_{Vmax} = -\frac{\hat{\beta}_2}{3\hat{\beta}_3} \quad \text{(B.4)}$$

The BMI value at maximum velocity of BMI is calculated as:

$$I_{max} = \hat{\beta}_0 + \hat{\beta}_1 A_{Vmax} + \hat{\beta}_2 {A_{Vmax}}^2 + \hat{\beta}_3 {A_{Vmax}}^3 \quad \text{(B.5)}$$

$$V_{max} = \hat{\beta}_1 + 2\hat{\beta}_2 A_{Vmax} + 3\hat{\beta}_3 A_{Vmax}^2 \quad \text{(B.6)}$$

At last the maximum BMI value and age at maximum BMI are calculated as:

$$A_{max} = \frac{-\hat{\beta}_2 - \sqrt{\hat{\beta}_2^2 - 3\hat{\beta}_1\hat{\beta}_3}}{3\hat{\beta}_3} \quad \text{(B.7)}$$

Where $\hat{\beta}_2^2 - 3\hat{\beta}_1\hat{\beta}_3 \geq 0$, and

$$BMI_{max} = \hat{\beta}_0 + \hat{\beta}_1 A_{max} + \hat{\beta}_2 {A_{max}}^2 + \hat{\beta}_3 {A_{max}}^3 \quad \text{(B.8)}$$

Derived biological parameters of BMI from third degree polynomial model were summarized and indicated in Table 2.2 in Chapter II.

APPENDIX C

SAS Code for Derivation of Biological Parameters

```
libname fmt "E:\YANGYANG DENG\Thesis\FLS Data Set";
options fmtsearch=(fmt.fmt64);
proc contents data=fmt.vcu0610;run;

/************************** Proposed Study Sample*****************************/
/*All the participants who had Stature, Weight, BMI and Echo-Measurements in Fels Study*/
data Sample_0; set fmt.vcu0610;
keep ptno visit age sex ANstature ANweight BCbmi ANbpsys ANbpd5 ECLVMASS ECIVSD
ECRELWALL ECLVDD ECLVDS Ecfac; run;
proc sort data=Sample_0; by ptno; run;
/*2567 ptnos in the data set; 1199 boys and 1368 girls*/

/*Record the variables*/
data Sample_0; set Sample_0;
Height=ANstature; BMI=BCbmi; SBP=ANbpsys; DBP=ANbpd5;
LVMI=ECLVMASS/((ANstature/100)**2.7); IVST=ECIVSD; RWT=ECRELWALL;
LVSF=(ECLVDD-ECLVDS)/ECLVDD; LVEF=Ecfac/100;
keep ptno visit age sex Height BMI SBP DBP LVMI IVST RWT LVSF LVEF; run;

/*Individual serial Stature and BMI data from ages 2 to 25 years*/
data Sample_1; set Sample_0; if 2<=age<=25; run;
```

```
data Sample_1; set Sample_1; if BMI=. then delete; run;
proc sort data=Sample_1; by ptno; run;
/*1463 ptnos accessed for eligibility; 702 boys and 761 girls*/

/*Ptnos who have at least 10 serial body size visits*/
proc freq data=Sample_1; table ptno/out=counts noprint; run;
data counts; set counts; if count<10 then delete; run;
data Sample_1 counts; merge counts(in=c) Sample_1(in=d); by ptno; if c and d; drop percent;
run;
/*815 ptnos in proposed study sample; 412 boys and 403 girls*/

/*************************** Height Parameters ********************************/
/*Fit the data into the Preece Baines model*/
proc nlin data=Sample_1 method=MARQUARDT maxiter=200 noprint; by ptno;
parms h1=170 ht=155 s0=0.12 s1=1.5 t=13;
            eb0 = exp(s0*(age-t));
     eb1 = exp(s1*(age-t));
model Height = h1-((2*(h1-ht))/(eb0+eb1));
output out=Height parms=h1 ht s0 s1 t p=nlinpred r=nlinresi ess=rsht; run;
/*Consider a Goodness of Fit by RMSE<1.5*/
data Height; set Height; mse=rsht/count; rmse=sqrt(mse); run;
data Height; set Height; if rmse>1.5 then delete; run;
```

```
/*Calculate the biological parameters of Height at Onset and PV*/
data Summary_Height; set Height;
h_AT=h1;
s_PV=(s0+s1)/4+sqrt(((s0+s1)**2)/16-(s1*s0/2));
s_TO=(s0+s1)/4-sqrt(((s0+s1)**2)/16-(s1*s0/2));
t_TO=t+(1/(s1-s0))*log((s_TO-s0)/(s1-s_TO));
t_PV=t+(1/(s1-s0))*log((s_PV-s0)/(s1-s_PV));
h_TO=h1-((2*(h1-ht))/(exp(s0*(t_TO-t))+exp(s1*(t_TO-t))));
h_PV=h1-((2*(h1-ht))/(exp(s0*(t_PV-t))+exp(s1*(t_PV-t))));
v_TO=s_TO*(2*(h1-ht))/(exp(s0*(t_TO-t))+exp(s1*(t_TO-t)));
v_PV=s_PV*(2*(h1-ht))/(exp(s0*(t_PV-t))+exp(s1*(t_PV-t)));
drop h1 ht s0 s1 t mse nlinpred nlinresi rsht; run;

/*Delete the un-reasonable results*/
data Sample_Height; set Summary_Height;
if h_AT<0 or h_AT>200 then delete; if t_PV<0 or t_TO<0 then delete;
if h_PV<0 or h_PV>200 then delete; if h_TO<0 or h_TO>200 then delete;
if v_PV<0 or v_TO<0 then delete; if v_PV>100 or v_TO>100 then delete; run;
proc sort data=Sample_Height; by ptno; run;
/*756 ptnos in study sample with height parameters;378 boys and 378 girls*/

/*Basic statistics of Height parameters*/
data Sample_height_count; set Sample_Height; by ptno; if first.ptno; run;
```

```
proc sort data=Sample_height_count; by sex; run;
proc means data=Sample_height_count; var rmse h_AT s_PV s_TO t_PV t_TO h_PV h_TO
v_PV v_TO; by sex; run;

/*T test on the difference for Hegith parameters between boys and girls*/
proc ttest data=Sample_height_count; class sex; var h_AT t_PV t_TO h_PV h_TO v_PV v_TO;
run;

/********** Height Parameters and Echo-Measurements **********/
/*Ptnos with the same individuals at adulthood who have Echo-Measurements and BP
Measurements*/
data Sample_3; merge Sample_Height(in=c) Sample_0(in=d); by ptno; if c and d; run;
data Sample_3; set Sample_3; if age>=35; run;

/*Study sample for BP measurements*/
data Sample_BP_Height; set Sample_3; if SBP=. and DBP=. then delete; run;
data Sample_BP_Height; set Sample_BP_Height; keep ptno visit age sex Height BMI SBP DBP
h_AT s_PV s_TO t_PV t_TO h_PV h_TO v_PV v_TO; run;
proc sort data=Sample_BP_Height; by sex; run;
/*399 ptnos in BP measurements study sample; 200 boys and 199 girls*/

/*Study sample for Echo-measurements*/
```

```
data Sample_Eco_Height; set Sample_3; if LVMI=. and IVST=. and RWT=. and LVSF=. and
LVEF=. then delete; run;
data Sample_Eco_Height; set Sample_Eco_Height; keep ptno visit age sex Height BMI LVMI
IVST RWT LVSF LVEF h_AT s_PV s_TO t_PV t_TO h_PV h_TO v_PV v_TO; run;
proc sort data=Sample_Eco_Height; by sex; run;
/*292 ptnos in Eco measurements study sample; 136 boys and 156 girls*/


/****************************** GLM Analysis ******************************/
/*GLM for childhood Height parameters in relation to adulthood BP measurements*/
%macro genmod5(para=SBP);
%macro genmod6(var=h_AT);
title "Regression childhood &var parameter to adulthood &para measurements";
proc genmod data=Sample_BP_Height;
by sex;
class ptno;
model &para = &var age &var*age / dist=normal link=identity;
repeated subject=ptno /corr=UN covb corrw;
run;
%mend genmod6;
%genmod6(var=h_AT)
%genmod6(var=t_TO)
%genmod6(var=t_PV)
%genmod6(var=h_TO)
```

```
%genmod6(var=h_PV)

%genmod6(var=v_TO)

%genmod6(var=v_PV)

%mend genmod1;

%genmod5(para=SBP)

%genmod5(para=DBP)


/*GLM for childhood Height parameters in relation to adulthood Echo-measurements*/

%macro genmod7(para=LVMI);

%macro genmod8(var=h_AT);

title "Regression childhood &var parameter to adulthood &para measurements";

proc genmod data=Sample_Eco_Height;

by sex;

class ptno;

model &para = &var age &var*age / dist=normal link=identity;

repeated subject=ptno /corr=UN covb corrw;

run;

%mend genmod8;

%genmod8(var=h_AT)

%genmod8(var=t_TO)

%genmod8(var=t_PV)

%genmod8(var=h_TO)

%genmod8(var=h_PV)
```

```
%genmod8(var=v_TO)

%genmod8(var=v_PV)

%mend genmod7;

%genmod7(para=LVMI)

%genmod7(para=IVST)

%genmod7(para=RWT)

%genmod7(para=LVSF)

%genmod7(para=LVEF)


/*************************** BMI Parameters ********************************/

/*Fit the data into the third degree polnomial model*/

data Sample_1; set Sample_1; age2=age**2; age3=age**3; run;

proc reg data=Sample_1 noprint outest=bmi; by ptno;

model BMI=age age2 age3; run;

data bmi; set bmi; rmse=_rmse_; beta0=intercept; beta1=age; beta2=age2; beta3=age3; run;

data bmi; set bmi; keep ptno rmse beta0 beta1 beta2 beta3; run;

data summary_bmi; merge sample_1 bmi; by ptno; run;

/*Consider a Goodness of Fit by RMSE<1.5*/

data summary_bmi; set summary_bmi; if rmse>1.5 then delete; run;

/*788 ptnos in study sample with bmi parameters;401 boys and 387 girls*/


/*Calculate the biological parameters of BMI*/

data summary_bmi; set summary_bmi;
```

```
age_min=-beta2/(3*beta3)+(sqrt(beta2**2-3*beta1*beta3)/(3*beta3));
BMI_min=beta0+beta1*age_min+beta2*(age_min**2)+beta3*(age_min**3);
age_max=-beta2/(3*beta3)-(sqrt(beta2**2-3*beta1*beta3)/(3*beta3));
BMI_max=beta0+beta1*age_max+beta2*(age_max**2)+beta3*(age_max**3);
age_Vmax=-beta2/(3*beta3);
I_max=beta0+beta1*age_Vmax+beta2*(age_Vmax**2)+beta3*(age_Vmax**3);
V_max=beta1+2*beta2*age_Vmax+3*beta3*(age_max**2);
drop age2 age3 beta0 beta1 beta2 beta3;
run;
proc sort data=summary_bmi; by ptno; run;

/*Delete the un-reasonable results*/
data Sample_bmi; set summary_bmi; if age_min<0 or age_max<0 then delete; if age_min>35 or
age_max>35 then delete; run;
proc sort data=Sample_bmi; by ptno; run;
/*649 ptnos in study sample with bmi parameters;328 boys and 321 girls*/

/*Basic statistics of BMI parameters*/
data Sample_bmi_count; set Sample_bmi; by ptno; if first.ptno; run;
proc sort data=Sample_bmi_count; by sex; run;
proc means data=Sample_bmi_count; var rmse age_min BMI_min age_max BMI_max
age_Vmax I_max V_max; by sex; run;
/*T test on the difference for BMI parameters between boys and girls*/
```

```
proc ttest data=Sample_bmi_count; class sex; var age_min BMI_min age_max BMI_max
age_Vmax I_max V_max; run;

/******************** BMI Parameters and Echo-Measurements **********************/
/*Ptnos with the same individuals at adulthood who have Echo-Measurements and BP
Measurements*/
data Sample_2; merge Sample_bmi(in=c) Sample_0(in=d); by ptno; if c and d; run;
data Sample_2; set Sample_2; if age>=35; run;

/*Study sample for BP measurements*/
data Sample_BP_BMI; set Sample_2; if SBP=. and DBP=. then delete; run;
data Sample_BP_BMI; set Sample_BP_BMI; keep ptno visit age sex Height BMI SBP DBP
age_min BMI_min age_max BMI_max age_Vmax I_max V_max; run;
proc sort data=Sample_BP_BMI; by sex; run;
/*360 ptnos in BP measurements study sample; 178 boys and 182 girls*/

/*Study sample for Echo-measurements*/
data Sample_Eco_BMI; set Sample_2; if LVMI=. and IVST=. and RWT=. and LVSF=. and
LVEF=. then delete; run;
data Sample_Eco_BMI; set Sample_Eco_BMI; keep ptno visit age sex Height BMI LVMI IVST
RWT LVSF LVEF age_min BMI_min age_max BMI_max age_Vmax I_max V_max; run;
proc sort data=Sample_Eco_BMI; by sex; run;
/*258 ptnos in Eco measurements study sample; 116 boys and 142 girls*/
```

```
/****************************** GLM Analysis ******************************/

/*GLM for childhood BMI parameters in relation to adulthood BP measurements*/

%macro genmod1(para=SBP);

%macro genmod2(var=age_min);

title "Regression childhood &var parameter to adulthood &para measurements";

proc genmod data=Sample_BP_BMI;

by sex;

class ptno;

model &para = &var age &var*age / dist=normal link=identity;

repeated subject=ptno /corr=UN covb corrw; run;

%mend genmod2;

%genmod2(var=age_min)

%genmod2(var=BMI_min)

%genmod2(var=age_max)

%genmod2(var=BMI_max)

%genmod2(var=age_Vmax)

%genmod2(var=I_max)

%genmod2(var=V_max)

%mend genmod1;

%genmod1(para=SBP)

%genmod1(para=DBP)


/*GLM for childhood BMI parameters in relation to adulthood Echo-measurements*/
```

```
%macro genmod3(para=LVMI);
%macro genmod4(var=age_min);
title "Regression childhood &var parameter to adulthood &para measurements";
proc genmod data=Sample_Eco_BMI;
by sex;
class ptno;
model &para = &var age &var*age / dist=normal link=identity;
repeated subject=ptno /corr=UN covb corrw;
run;
%mend genmod4;
%genmod4(var=age_min)
%genmod4(var=BMI_min)
%genmod4(var=age_max)
%genmod4(var=BMI_max)
%genmod4(var=age_Vmax)
%genmod4(var=I_max)
%genmod4(var=V_max)
%mend genmod3;
%genmod3(para=LVMI)
%genmod3(para=IVST)
%genmod3(para=RWT)
%genmod3(para=LVSF)
%genmod3(para=LVEF)
```

Vita

Yangyang Deng was born Oct 15, 1984 in Beijing, China. He received his Bachelor of Science from Shandong University in Jinan, Shandong, China in 2007. In addition he received his Master of Science in Mathematics and Master of Science in Engineering from Mississippi State University, Mississippi State in 2010 and 2012.