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Determinants of Relative Skeletal Maturity in South African Children

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Abstract

The variation of skeletal maturity about chronological age is a sensitive indicator of population health. Age appropriate or advanced skeletal maturity is a reflection of adequate environmental and social conditions, whereas delayed maturation suggests inadequate conditions for optimal development. There remains a paucity of data, however, to indicate which specific biological and environmental factors are associated with advancement or delay in skeletal maturity. The present study utilises longitudinal data from the South African Birth to Twenty (Bt20) study to indentify predictors of relative skeletal maturity (RSM) in early adolescence.

A total of 244 black South African children (n=131 male) were included in this analysis. Skeletal maturity at age 9/10 years was assessed using the Tanner and Whitehouse III RUS technique. Longitudinal data on growth, socio-economic position and pubertal development were entered into sex-specific multivariable general linear regression models with relative skeletal maturity (skeletal age-chronological age) as the outcome.

At 9/10 years of age males showed an average of 0.66 years delay in skeletal maturation relative to chronological age. Females showed an average of 1.00 year delay relative to chronological age. In males, being taller at 2 years ($p<0.01$) and heavier at 2 years ($p<0.01$) predicted less delay in RSM at age 9/10 years, independent of current size and body composition. In females, both height at 2 years and conditional weight at 2 years predicted less delay in RSM at 9/10 years ($p<0.05$) but this effect was mediated by current body composition. Having greater lean mass at 9/10 years was associated with less delayed RSM in females ($p<0.01$) as was pubertal status at the time of skeletal maturity assessment ($p<0.01$).

This study identifies several predictors of skeletal maturation at 9/10 years, indicating a role for early life exposures in determining the rate of skeletal maturation during childhood independently of current stature.

Keywords

Skeletal maturity, bone age, South Africa

Abbreviations

Bt20	Birth to Twenty
RSM	Relative Skeletal Maturity

Introduction

One of the core requirements in evaluating the growth, development, health, and wellbeing of children is the ability to sensitively control for their maturational status. Skeletal maturity or ‘bone age’ may be used alongside measures of dental and sexual development as a key indicator of biological maturity. The assessment of skeletal maturity is based upon the predictable, ordered appearance of primary and secondary centres of ossification and upon the process of fusion of the epiphyses of long bones. Normal variation in maturation means that chronological age and bone age may differ by ± two years: for instance a 12 year-old may have a bone age between 10 and 14 years. In a well nourished setting with little constraint on development, being advanced or delayed by more than two years in skeletal maturity relative to reference values is often as a result of underlying endocrine pathology. In a constrained environment the margins of normal variation may be wider. Accordingly, the variation of skeletal maturity about chronological age, within the normal limits, is a sensitive indicator of population health. Age appropriate or advanced skeletal maturity is a reflection of adequate environmental and social conditions, whereas delayed maturation suggests inadequate conditions for optimal development. Comparisons of skeletal maturity between samples of populations can therefore reveal degrees of environmental disadvantage [1-4] while longitudinal observations of maturational markers within a population demonstrate the plasticity of humans in response to environmental change [5]. However, the exposure of healthy children to radiographic assessment has been approached with caution in recent years resulting in few contemporary studies of skeletal maturation and there remains a paucity of data to indicate which biological and environmental factors predict advancement or delay in skeletal maturity and at what stage of development they exert their influence on maturation.

The present study utilises longitudinal data from the South African Birth to Twenty (Bt20) study to investigate which growth and environmental factors are associated with skeletal age deviation in early adolescence.

Material and Methods

The process of recruitment into the cohort, which occurred in 1990, and the characteristics of the children and their parents from the urban conurbation of Johannesburg-Soweto have been described in detail by Richter et al. [6,7]. Data relating to growth, nutrition, pubertal development, socio-economic status, risk behaviours and cognitive development were collected yearly until age 20. At nine years of age, a sub-sample of the original Bt20 cohort was enrolled into a bone health study to investigate factors affecting the acquisition of peak bone mass. In addition to the standard measurements, whole body duel X-ray absorptiometry (DXA) scans and hand-wrist radiographs were obtained at yearly intervals on the 683 children in this sub-study from age 9 years onwards.

The present analysis was undertaken using 244 (n=131 male) 9/10 year olds from the Bone Health sub-study. Children were included on the basis of having complete anthropometric and questionnaire data at birth, two, four and 9/10 years; time points selected to represent early and mid-childhood and early adolescence. White children were under-represented in the original Bone Health sample [6] therefore this analysis includes only black children. There were no significant differences ($p<0.05$) in either growth or socioeconomic characteristics between the children selected for this analysis and the remaining black children in the Bone Health study [8].

Measures

Hand-wrist radiographs for the assessment of skeletal maturity at age 9/10 years were taken and developed by trained radiographers in the Paediatric X-ray department of the Johannesburg Academic Hospital. The left hand was positioned with the X ray beam focussed on the distal end of the third metacarpal. The exposure factor used was 42kV and 12.5 mAs with the distance standardised at 76cm in accordance with the optimal radiograph conditions described by Tanner et al. [9]. Skeletal maturity was assessed using the Tanner and Whitehouse III (TW3) RUS technique which includes the radius, ulna, and the metacarpals of the first, third and fifth phalanx [9]. Radiographs were assessed by a single trained observer (NLH). The standard error of measurement calculated to assess intra-observer reliability was 0.107 and within the acceptable limits of error. Skeletal maturity was not assessed at any time point prior to 9/10 years of age.

Standing height was measured at 2, 4 and 9/10 years of age using a Holtain Stadiometer (Holtain Ltd., UK), length at birth was not recorded in this cohort. Weight at 2, 4 and 9/10 years was measured in light clothing with the participant barefoot, using a digital electric scale (Dismed, USA). A fan-beam densitometer (model QDR 4500A; Hologic Inc, Bedford, MA) was used by a trained technician to obtain DXA scans for the assessment of body composition. Fat mass (kg) and lean tissue mass (kg) were calculated with software version 8.21 (Hologic Inc.) using standardised positioning of the subject and consistent procedures for scan analysis. Bone free lean mass was calculated by subtracting total body bone mineral content from total body lean mass. Indices for fat (FMI) and lean mass (LMI) were created to adjust these measures for concurrent stature using the method proposed by Wells and Cole [10]. Both fat and lean mass were divided by height^2, a power considered appropriate following investigation of the relationships between fat and lean mass and height in this population [10]. To accurately identify those children who are growing more quickly or more slowly within their own environment age- and sex-specific internal Z scores were calculated for measures of height, weight, BMI, fat and lean mass indices. Pubertal status was assessed by a physician at nine and ten years of age using the Tanner staging technique for pubertal assessment [11, 12]. For the purpose of this analysis children were classified as being either pre-pubertal or having entered puberty. The onset of puberty was defined by entry into Tanner stage 2 of either breast/genitalia development or pubic hair development.

Household socio-economic status (SES) was assessed by questionnaires administered to the mother or the primary caregiver. Principal component analysis was used to construct indices for SES at the time of birth and at the end of childhood (year 9/10). Two explanatory variables were created: consumer durables, which included ownership of various household items (car, TV, fridge, washing machine, and telephone) (Eigen value = 1.62-2.50), and sanitation which was a measure of running water and toilet facilities (Eigen value = 1.53 – 1.74). Socioeconomic position was dynamic in this population between the two time points observed, therefore indices at each age could be entered into the same regression analysis (SES variables were all correlated at $r < 0.3$).

All subjects and their parents provided informed consent for inclusion in the Bt20 study. Ethical approval for the study was obtained from the University of the Witwatersrand Committee for Research on Human Subjects.

Statistical Analysis

All statistical analyses were undertaken using the Statistical Package for the Social Sciences (SPSS) version 15.0 (SPSS Inc., Chicago, IL, USA). The outcome of interest for this analysis was relative skeletal maturity (RSM) (RUS skeletal age – chronological age). This measure describes the degree to which a child is advanced or delayed in their skeletal maturation relative to their chronological age, and therefore negates the need to control for chronological age in any model.

A number of anthropometric and socio-economic predictors (shown in Table 2) were identified *a priori* according to published literature and previous associations with skeletal maturity or body composition in the Bone Health cohort. Each explanatory variable was regressed on RSM (table 3). Those variables that were significantly associated with the outcome ($p<0.05$) were retained in the multivariable analysis. Birthweight and current height were also included in the analysis, although non-significant when regressed on RSM, as they have been previously identified to be associated with skeletal maturity in this cohort [13].

Sex-specific multivariable general linear regression models were built to examine the influences of height, weight and BMI on RSM at 9/10 years of age. Males and females were modelled separately, but with the same group of predictors, in order to identify commonalities or differences between the sexes. Separate models were built for each dimension of growth in order to ascertain the independent effects of weight and height on RSM, and also the effect of weight adjusted for height (BMI). To avoid the statistical issues associated with collinearity between measures at multiple time points within the same individual, conditional weight, height, and BMI variables at 2, 4 and 9/10 years were created to represent each individual's size given their previous size(s) [14]. Conditional measures represent the residuals from sex-specific regressions of weight Z-score (or length/BMI) on weight Z-scores (or length/BMI) at all previous ages. The residuals were standardised to allow comparison of the size of the coefficients at different ages. By design, these conditional variables have no correlation with the variables they are conditional on and can therefore be included in the same regression model without causing issues of collinearity. FMI and LMI were added in a second stage to each model to examine whether potential effects of weight, length or BMI were mediated by differences in body composition.

Results

Mean RSM was -0.66 years (SD=0.57) in males and -1.00 years (SD=0.96) in females, indicating that on average skeletal age was delayed by almost 8 months relative to chronological age in males and by a year relative to chronological age in females. The range of variation in relative skeletal maturity in this sample was greater in females than in males (Table 1).

Table 1 Here

Table 2 gives descriptive statistics associated with the variables identified *a priori* for analysis, comparing those individuals who were delayed in skeletal maturity by more than one year with those who were delayed by less than one year relative to chronological age (mean RSM for the whole sample was -0.99 years) . Those individuals whose skeletal maturity at 9/10 years was less delayed (RSM >-1.0 years) were consistently heavier and taller, with greater BMI, fat mass and lean mass (females only). In females only, those with less delayed skeletal maturation were more likely to have entered puberty (55.4% of those with RSM >-1.0 years vs. 12.3% of those with RSM < -1.0 years, χ^2 = 23.5, p<0.001).

Table 2 Here, Table 3 Here

Tables 4 and 5 present the results of the sex-specific multivariable linear regression models for weight, height, and BMI. In males, conditional weight at 2 years and height at 2 years were significant independent predictors of RSM at 9/10 years of age (p< 0.01) in the weight and height models respectively (Table 4). In both models these associations with RSM were not mediated by the inclusion of body composition variables at 9/10 years. When weight adjusted for height (BMI) was modelled, no significant predictors of RSM at 9/10 years were identified; furthermore the BMI models were not significant. The model that explained the most variance in RSM at age 9/10 years in males incorporated measures of weight throughout childhood and body composition at age 9/10 years. This model explained 19.7% of the variance in RSM.

Table 4 Here

In females, conditional weight at 2 years and height at 2 years were significant independent predictors of RSM at 9/10 years in the weight and height models respectively ($p < 0.05$) (Table 5). These associations were, however, mediated in the second stage of the models (models 1B and 2B) by the introduction of body composition measures at 9/10 years becoming non-significant after the inclusion of FMI and LMI at age 9/10 years. When body composition at 9/10 years was accounted for, conditional weight at 9/10 years ($p < 0.01$), height at 9/10 years ($p < 0.05$) and lean mass index ($p < 0.01$) were all positively and significantly associated with RSM. Pubertal status in females was consistently a significant predictor of RSM at 9/10 years ($p < 0.01$). When weight was adjusted for height in the BMI models pubertal status and lean mass at 9/10 years remained significant predictors of RSM ($p < 0.01$). The model that explained the most variance in RSM at age 9/10 years in females incorporated height throughout childhood as well as body composition at age 9/10 years, explaining 46.6% of the variation in RSM.

Table 5 Here

Discussion

This analysis used multivariable general linear regression modelling to determine which growth and socio-economic characteristics, measured at birth and during childhood, were associated with RSM of black children aged 9/10 years in a South African cohort. We have previously reported that all children in the Bt20 cohort, both black and white, had delayed skeletal maturation compared with international references [15]. The children in the present analysis showed similar skeletal delay. Average RSM in males was -0.66 years (SD 0.57 years) and in females was -1.00 year (SD 0.96 years) indicating a substantial delay in skeletal maturation relative to chronological age.

In developed country settings African children have been shown consistently to be more advanced in skeletal development than children of European origin as measured by the appearance of ossification centres in the early years of life [16-18]. Comparisons between black children in Africa [19] and black children in the USA [20], however, show US African American children to be more advanced in terms of their skeletal maturity than Africans living in Africa, suggesting that this observation may be as a result of health and nutritional factors rather than ethnicity itself. While there seems to be a genetically determined potential for advanced skeletal maturation in the African population, it can only be exploited under optimal environmental conditions and the post-apartheid conditions experienced by this cohort likely explain the delay in skeletal maturation relative to chronological age reported here.

The fact that growth in early life appears to influence the rate of skeletal maturation in this cohort, with greater attained height and weight at 2 predicting more advanced skeletal maturity, adds further support to an established body of literature reporting the influence of growth in infancy (birth to 2 years) on the timing of maturation. Several studies report, in particular, the relationship between rapid weight gain in infancy and age at menarche in females [21-23]. The results of this analysis suggest that an association between early life growth and the timing of maturation (as measured here by indicators of skeletal maturity) is also evident in males. This study replicates previous findings shown in a combined analysis of children from both the Bt20 Bone Health cohort and the Fels Longidudinal Study (USA) [13]. Rapid weight gain in infancy (an increase in weight-for-age of greater than 0.67 Z scores between birth and 2 years [24]) was associated with greater skeletal maturity at age 9 years in both cohorts, despite their differing environments, with skeletal maturity advanced by the same magnitude in both settings; approximately 2.4 months per standard deviation score increase in weight from 0-2 years [13]. The conditional weight measure used here at 2 years, while not necessarily representing 'clinically significant' rapid infant weight gain, does represent the extent to which a child's rate of growth deviates from the rate predicted based on the individuals birthweight [14]. The finding that greater conditional weight at 2 years is positively associated with RSM at 9/10 years indicates that it is the tempo of growth in the first two years, rather than absolute weight at 2 years, which influences the rate of skeletal maturation. In the absence of skeletal maturity indicators at birth or during infancy, however, we are unable to say whether advanced skeletal maturation predated the greater stature at age 2 in this cohort. Pryor [25] suggested that most variations in the sequence and timing of skeletal maturation are genetically determined, and therefore may be set before birth, something that we are unable to consider in this analysis.

The amount of bone-free lean mass present at 9/10 years was a significant predictor of RSM in females. This finding is consistent with a previous study by Powell et al. [26] where bone-free lean mass had the strongest association with RSM in their cross-sectional study of Australian children. It is unlikely that the association between increased lean mass and advanced skeletal maturation is a causal pathway as the endocrine control of both processes is likely to confound this association. Growth hormone and insulin-like growth factor (IGF-1) are known to increase linear bone growth and maturation and to stimulate increases in lean body mass during childhood, particularly during puberty. Sex steroids, estradiol and testosterone are other potential hormone mediators of the relationship between lean mass and skeletal maturation [27-30].

The fact that the amount of lean mass present at 9/10 years was only significantly associated with skeletal maturation in females is likely to be related to the pubertal status of the females, another significant predictor of RSM in this cohort. Many of the females included in this analysis had entered puberty at the time of skeletal maturity assessment, and those who had entered puberty were less delayed in their skeletal maturation compared to their pre-pubertal peers (mean pre-pubertal RSM = -1.34 years, mean pubertal RSM = -0.31 years, $t=-6.25$, $p<0.01$). In contrast, few males were pubertal at the time of skeletal maturity assessment (20.6%) and those that were pubertal were in early puberty (Tanner stage 2).

Having previously identified the tempo of skeletal maturation to be responsive to environmental change over time in this setting [15] it was reasonable to predict that measures of socio-economic position, either at birth or at the time of skeletal maturity assessment, might be associated with RSM at the end of childhood. Indeed, several indicators of SES were significantly associated with RSM in univariable general linear regression analyses, resulting in their inclusion in the multivariable models. When included in the multivariable models with measures of stature and body composition, however, none of the socio-economic predictors retained a significant association with the outcome. Many studies have considered the effect of SES on skeletal maturity with inconsistent findings. Those that study relatively homogenous groups find little association [31-33] between SES and skeletal maturity while those that observe the extremes of SES find consistently that experiencing deprivation (nutritional, economic) delays skeletal maturation [2,3]. This sample was a relatively homogenous group of black South African children, living within a defined geographical region, so the finding that no socio-economic predictor was independently associated with RSM may be explained by the lack of variation in socio-economic position within the sample. When children grow in a constrained environment, such as the immediately post-apartheid environment experienced by this cohort, small individual constraints may not be detected sufficiently by the type of analysis used here. It is also possible that the SES acts on skeletal maturation through its influence on childhood growth, something unaccounted for in previous studies of SES and skeletal maturation, but addressed in this analysis. The effect of SES may have been mediated by growth during infancy which was shown to be positively associated with RSM. The fact that a large amount of variation in RSM was unexplained by the models presented here indicates there may also be other dimensions of SES, such as nutritional status, which were not captured by the SES indicators available for this cohort, acting on skeletal maturation.

The strength of this study lies in the use of a longitudinal sample, assessed at several time points during childhood, to identify determinants of RSM. The immediate clinical significance of RSM in late childhood / early adolescence has been reported by Jones and Ma [34], who showed RSM to be positively associated with measures of bone strength and to be negatively associated with upper limb fracture risk. The wider significance of RSM at this age for later health or adult stature remains to be explored and necessitates the follow up of these individuals to the completion of skeletal development, something that is possible in this longitudinal cohort and will be addressed in future analyses.

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Table 1: Characteristics of study sample

	Male (*N*=131) Mean (SD)	Female (*N*=113) Mean (SD)
Age (years)	9.67 (0.45)	9.67 (0.45)
Skeletal Age (years)	9.01 (0.63)	8.67 (1.15)
Relative Skeletal Maturity (years)	-0.66 (0.57)	-1.00 (0.96)
Relative Skeletal Maturity (range in years)	-2.30 to 1.19	-2.84 to 2.47

Table 2: Growth and Socioeconomic characteristics of the sample according to relative skeletal maturity (RSM)

	Male		Female	
	RSM >-1.0 *N*=98	RSM < -1.0 *N*=33	RSM > -1.0 *N*=56	RSM < -1.0 *N*=57
Birthweight (kg) (Mean [SD])	3.2 (0.5)	3.2 (0.5)	3.1 (0.5)	3.0 (0.4)
Gestational Age (weeks) (Mean [SD])	37.9 (1.7)	38.1 (1.4)	37.9 (1.9)	38.1 (1.3)
Maternal Age at Birth (years) (Mean [SD])	25.2 (5.5)*	27.7 (6.6)*	25.5 (5.9)	27.0 (6.7)
Maternal Marital Status at Birth				
Single [a] (%)	69.4	78.8	83.9	82.5
Married / Cohabiting (%)	30.6	21.2	16.1	17.5
Maternal Education at Birth[b]				
< High school (%)	59.2	51.5	50.0	59.6
> High school (%)	40.8	48.5	50.0	40.4
Height at 2 years (cm) (Mean [SD])	84.0 (3.7)**	81.2 (4.4)**	83.8 (3.6)**	81.5 (3.3)**
Weight at 2 years (kg) (Mean [SD])	11.9 (1.8)**	10.8 (1.4)**	12.0 (1.6)**	11.0 (1.3)**
BMI at 2 years (kg/m^2) (Mean [SD])	16.8 (2.1)	16.5 (2.6)	17.1 (2.1)	16.6 (1.8)
Height at 4 years (cm) (Mean [SD])	99.7 (4.2)**	97.4 (3.7)**	99.9 (3.8)**	97.4 (3.6)**
Weight at 4 years (kg) (Mean [SD])	15.8 (2.0)**	14.6 (1.6)**	15.8 (2.2)**	14.6 (1.3)**
BMI at 4 years (kg/m^2) (Mean [SD])	15.9 (1.3)	15.4 (1.3)	15.8 (1.6)	15.4 (1.1)
Height at 9/10 years (cm) (Mean [SD])	134.4 (6.3)*	131.6 (4.9)*	135.6 (6.8)*	132.8 (4.8)*
Weight at 9/10 years (kg) (Mean [SD])	30.6 (6.3)*	27.7 (3.7)*	30.9 (6.3)	28.9 (4.9)
BMI at 9/10 years (kg/m2) (Mean [SD])	16.8 (2.4)	15.9 (1.8)	17.1 (2.0)	16.7 (1.8)
Fat mass at 9/10 years (kg) (Mean [SD])	6.5 (4.1)	6.3 (2.9)	10.1 (5.2)**	7.1 (3.2)**
Lean mass at 9/10 years (kg) (Mean [SD])	19.4 (3.1)**	17.5 (2.1)**	19.0 (3.1)**	16.6 (2.1)**
Pubertal Status at 9/10 years				
Pre-pubertal (%)	77.6	81.8	44.6**	87.7**
Pubertal (%)	22.4	18.2	55.4**	12.3**
Primary Caregivers Marital Status at 9/10 years				
Single [a] (%)	50.0	45.5	55.6	70.9
Married / Cohabiting (%)	50.0	54.5	44.4	29.1
Primary Caregivers Education at 9/10 years [b]				
< High school (%)	67.7	62.5	37.0	43.6
> High school (%)	32.3	37.5	63.0	56.4

a Single includes separated, divorced and widowed

Independent *t* test (continuous variables) or Chi^2 test (categorical variables)*$P < 0.05$, ** $P < 0.01$

Table 3: Predictors of Relative Skeletal Maturity at age 9/10 years: Significant predictors identified by univariable linear regression

	Male B (SE)	Female B (SE)
Birthweight	0.06 (0.05)	0.15 (0.09)*
Maternal Age at Birth	-0.09 (0.01)*	-0.00 (0.01)
Sanitation at Birth	-0.17 (0.05)**	-0.11 (0.07)
Durables at Birth	0.10 (0.05)*	-0.06 (0.06)
Pubertal Status	0.04 (0.12)	1.03 (0.17)**
Sanitation at 9/10 years	-0.09 (0.03)*	-0.01 (0.13)
Durables at 9/10 years	0.15 (0.05)**	0.02 (0.06)
Conditional weight at 2 years	0.21 (0.05)**	0.27 (0.09)**
Conditional weight at 4 years	0.09 (0.04)*	0.17 (0.08)*
Conditional weight at 9/10 years	0.04 (0.05)	0.17 (0.09)*
Height at 2 years	0.19 (0.05)**	0.09 (0.02)**
Conditional height at 4 years	0.09 (0.04)*	0.15 (0.09)
Fat mass index at 9/10 years	0.03 (0.05)	0.38 (0.08)**
Lean mass index at 9/10 years	0.15 (0.05)**	0.51 (0.08)**

Table 4: Predictors of Relative Skeletal Maturity at age 9/10 years in females: multivariable regression models for weight, height and BMI

	Model 1 (Weight)		Model 2 (Height)		Model 3 (BMI)	
	A	B	A	B	A	B
	B (SE)	B (SE)	B (SE)	B (SE)	B (SE)	B (SE)
Maternal Age at Birth	-0.01 (0.01)	-0.00 (0.01)	-0.02 (0.01)	-0.01 (0.01)	-0.01 (0.01)	0.00 (0.01)
Sanitation at Birth	0.03 (0.07)	-0.03 (0.07)	0.01 (0.07)	-0.04 (0.07)	0.04 (0.08)	-0.02 (0.07)
Durables at Birth	-0.10 (0.07)	-0.05 (0.06)	-0.10 (0.07)	-0.06 (0.06)	-0.11 (0.07)	-0.05 (0.06)
Pubertal Status	0.78 (0.19)**	0.52 (0.19)**	0.77 (0.19)**	0.43 (0.19)**	0.90 (0.19)**	0.59 (0.18)**
Sanitation at 9/10 years	-0.10 (0.14)	-0.06 (0.13)	-0.07 (0.14)	-0.03 (0.12)	-0.12 (0.14)	-0.08 (0.13)
Durables at 9/10 years	-0.07 (0.06)	-0.04 (0.05)	-0.07 (0.06)	-0.05 (0.05)	-0.07 (0.06)	-0.04 (0.06)
Birth Weight	0.06 (0.09)	0.07 (0.09)				
Conditional weight at 2 years	0.17 (0.08)*	0.01 (0.09)				
Conditional weight at 4 years	0.10 (0.09)	-0.02 (0.09)				
Conditional weight at 9/10 years	0.10 (0.08)	0.18 (0.08)*				
Height at 2 years			0.22 (0.09)*	0.12 (0.09)		
Conditional height at 4 years			0.08 (0.08)	-0.04 (0.08)		
Conditional height at 9/10 years			0.09(0.09)	0.23 (0.08)**		
BMI at 2 years					0.04 (0.09)	-0.07 (0.09)
Conditional BMI at 4 years					0.10 (0.09)	-0.03 (0.08)
Conditional BMI at 9/10 years					0.08 (0.08)	0.10 (0.08)
Fat mass index at 9/10 years		0.09 (0.10)		0.08 (0.09)		0.11 (0.10)
Lean mass index at 9/10 years		0.41 (0.10)**		0.42 (0.10)**		0.37 (0.09)**
Adjusted R^2	**0.332****	**0.446****	**0.325****	**0.466****	**0.292****	**0.426****

*P <0.05, **P <0.01

(Weight, height, BMI, Fat and Lean mass indices expressed as internal z-scores)

Table 4: Predictors of Relative Skeletal Maturity at age 9/10 years in males: multivariable regression models for weight, height and BMI

	Model 1 (Weight)		**Model 2 (Height)**		**Model 3 (BMI)**	
	A	**B**	**A**	**B**	**A**	**B**
	B (SE)	**B (SE)**	**B (SE)**	**B (SE)**	**B (SE)**	**B (SE)**
Maternal Age at Birth	0.00 (0.01)	0.00 (0.01)	0.00 (0.01)	0.00 (0.01)	0.00 (0.01)	0.00 (0.01)
Sanitation at Birth	0.02 (0.05)	0.03 (0.05)	0.04 (0.05)	0.04 (0.05)	0.03 (0.05)	0.04 (0.05)
Durables at Birth	-0.01 (0.05)	-0.03 (0.05)	-0.02 (0.05)	-0.03 (0.05)	-0.01 (0.05)	-0.02 (0.05)
Pubertal Status	0.01 (013)	-0.03 (0.13)	0.01 (0.13)	-0.02 (0.13)	-0.03 (0.13)	-0.05 (0.13)
Sanitation at 9/10 years	0.03 (0.04)	0.02 (0.04)	0.05 (0.04)	0.05 (0.04)	0.01 (0.05)	0.00 (0.05)
Durables at 9/10 years	0.05 (0.05)	0.04 (0.05)	0.05 (0.05)	0.04 (0.05)	0.06 (0.05)	0.05 (0.05)
Birth Weight	0.07 (0.05)	0.10(0.06)				
Conditional weight at 2 years	0.19 (0.05)**	0.24 (0.06)**				
Conditional weight at 4 years	0.07 (0.05)	0.09 (0.06)				
Conditional weight at 9/10 years	0.01 (0.06)	0.15 (0.11)				
Height at 2 years			0.18 (0.05)**	0.18 (0.05)**		
Conditional height at 4 years			0.09 (0.05)	0.08 (0.05)		
Conditional height at 9/10 years			0.03 (0.06)	0.03 (0.06)		
BMI at 2 years					0.10 (0.05)	0.11 (0.08)
Conditional BMI at 4 years					0.05 (0.06)	0.05 (0.08)
Conditional BMI at 9/10 years					0.02 (0.06)	0.07 (0.17)
Fat mass index at 9/10 years		-0.18 (0.10)		-0.02 (0.06)		-0.04 (0.08)
Lean mass index at 9/10 years		-0.01 (0.07)		0.09 (0.06)		0.05 (0.10)
Adjusted R^2	**0.170***	**0.197***	**0.156***	**0.178***	**0.075**	**0.092**

*P <0.05, **P <0.01

(Weight, height, BMI, Fat and Lean mass indices expressed as internal z-scores)