

Metacarpal Growth During Adolescence in a Longitudinal South African Cohort

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ABSTRACT

To monitor the drift of the periosteal and endocortical surfaces during metacarpal growth longitudinally, radiogrammetry was carried out on hand-wrist X-rays of 572 children from the Birth to Twenty Bone Health Cohort annually from ages 9 to 21 years. This is the largest collection of longitudinal X-rays in African children. The second metacarpal bone length, bone width, and medullary width were measured using digital vernier calipers on a total of 4730 X-rays. Superimposition by Translation and Rotation (SITAR) was used to obtain age at peak metacarpal length velocity (PLV). Bone width and medullary width were modeled using SITAR against both chronological age and age from PLV. In black and white females, tempo and velocity of metacarpal length growth was synchronized. Black males, however, attained PLV 7 months later than white males ($p < 0.0001$). Compared to white males, black males had a longer second metacarpal ($p < 0.05$), and greater bone width size ($p < 0.02$), tempo ($p < 0.0009$), and velocity ($p < 0.0001$). Medullary width growth velocity in black participants peaked 2 years prior to attainment of PLV and exceeded that of their white peers ($p < 0.0001$) in whom it peaked 6 to 12 months post-PLV attainment. Black adolescents therefore had wider bones with relatively thinner cortices and wider medullary cavities than their white peers. Ethnic and sex differences also occurred in the timing of medullary width contraction that accompanied expansion in bone width and cortical thickness. In black males, medullary width contraction commenced approximately 3 years later than in black females, whereas in white males this occurred a year later than in white females. The ethnic and sex differences in bone acquisition reported in this study may differentially affect bone mass in later life. © 2017 American Society for Bone and Mineral Research.

KEY WORDS: RADIOGRAMMETRY; SECOND METACARPAL; BONE ACCRUAL; PUBERTY; ETHNICITY

Introduction

Bone mass accrual during childhood and adolescence is key to an individual's predisposition to skeletal fragility in later life.^(1–3) Some 40% of bone mass is acquired during adolescence, making the pubertal phase an opportune time to influence bone mass accrual and future fracture risk.^(2–4) Minimal differences in bone mass exist between the sexes in the prepubertal period.⁽⁵⁾ Divergence arises during puberty when bone growth is influenced by sex hormones.^(5,6) Estrogen limits periosteal bone expansion⁽⁷⁾ but promotes endocortical contraction^(8,9) while androgens stimulate periosteal bone apposition,⁽¹⁰⁾ resulting in males having wider bones, greater cortical thickness, and wider medullary cavities than females.^(11–14)

Radiogrammetry of the metacarpal bones can be used to monitor the movement of the periosteal and endocortical surfaces with growth,^(15–20) thereby providing insight into the acquisition of bone architecture and the attainment of peak bone growth velocity. In US children, greater periosteal bone expansion has been reported in males compared to females.^(6,11) Additionally, females experience bone apposition

at the endocortical interface with subsequent medullary contraction and this occurs approximately 4 years earlier than in males.^(6,11)

Metacarpal bone dimensions vary in different population groups.^(6,21,22) Dequeker⁽²²⁾ reported greater metacarpal cortical area adjusted for bone width in US white and black adults compared to a European white and a Nigerian black population, whereas a metacarpal radiogrammetry study of 14-year-old South African (SA) children conducted over 40 years ago found that black children had narrower cortical thickness compared to white children.⁽²¹⁾

Most studies on metacarpal growth have been undertaken in developed countries,^(6,11,23–25) and there is a paucity of longitudinal radiogrammetry data through adolescence.^(6,24,25) The aim of this longitudinal study was to describe the growth in metacarpal dimensions in healthy black and white South Africans through puberty and adolescence into young adulthood. We hypothesized, first, that puberty has a differential sex effect on the periosteal and endocortical bone surfaces, and second, that black SA children have wider bones with thinner cortices compared to their white peers.

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Subjects and Methods

Participants and protocol

The participants of this Bone Health Cohort (BHC) study consisted of 563 children enrolled specifically from the large Birth to Twenty (Bt20) cohort to investigate factors relating to the acquisition of bone mass during puberty and adolescence. The Bt20 is a longitudinal birth cohort of 3273 singleton children born between April and June 1990 in the greater Johannesburg–Soweto metropolitan area, South Africa. The recruitment protocols for the cohort have been described previously by Richter and colleagues.⁽²⁶⁾ Ethnic classification was based on the race classification used in South Africa for demographic and restitution purposes. Ethnic classification was self-reported by the parents and only those children with both parents belonging to the same ethnic group were included in this study. Because of the small number of white children in the Bt20 cohort (being representative of the ethnic demographics in the region), an additional 120 white children born in the same period were recruited into the BHC at 9 years of age from schools in other areas. They were born during the cohort enrolment dates and their birth weight, socioeconomic status, maternal age, and education were similar to those of the initial white participants of the BHC.⁽²⁷⁾ Participation in the BHC was offered to the entire Bt20 cohort; however, our exclusion criteria included children suffering from chronic illnesses such as epilepsy and asthma because of possible effects of drug therapy on bone development and density. Informed assent from adolescent participants and consent from parents were obtained for inclusion in this study. Ethical clearance was obtained from the University of the Witwatersrand Committee for Research on Human Subjects. Annual measurements, taken at approximately the same time every year, included weight, height, and hand-wrist X-rays.

Anthropometric measurements

Weight and height of participants were measured while participants wore light clothing and no shoes. Weight was measured to the nearest 100 g using a digital scale (Dismed, Miami, FL, USA) and height to the nearest millimeter using a stadiometer (Holtain, Crymch, UK). Quality control annual training and monitoring ensured a coefficient of variation between measurers of less than 2%.

Puberty

All children were assessed by Tanner staging at each visit.⁽²⁸⁾ The ages of onset of puberty in this cohort have been published.⁽²⁹⁾ Because of the asynchrony between the tempo and velocity of growth relative to sexual maturity,⁽³⁰⁾ we used age at peak metacarpal length velocity (PLV) as an indicator of pubertal development. We found no differences between our unpublished data on age at peak height velocity (PHV) and age at PLV. In females, age at PHV corresponds to Tanner stage 3 and in males to Tanner stage 4.⁽³¹⁾ The use of age at PLV allowed us to align females and males on a common biological maturity indicator.

Radiography

Posteroanterior hand-wrist radiographs of the left hand were taken annually from age 9 to 21 years by certified radiographers at the Charlotte Maxeke Academic Hospital in Johannesburg. The left hand was radiographed in all participants irrespective of

hand dominance. The X-ray beam was focused on the distal aspect of the third metacarpal of the left hand. Radiographs were taken using cassettes with single-emulsion film under standard conditions of tube to film distance of 76 cm and exposure at 42 kV and 12 mA/s, and processed in an automatic developer in accordance with the optimal conditions described by Tanner.⁽³²⁾

Radiogrammetry

Second metacarpal dimensions were measured on a total of 4730 hand-wrist X-rays by a single reader (AM). Measurements were carried out using a digital caliper calibrated to 0.01 mm.⁽¹¹⁾ The following parameters were measured in millimeters: total length of bone from proximal to distal end, and outer bone width (D) and inner medullary width (d) at the midshaft of the metacarpal. The cortical thickness was calculated as the difference between the bone width and medullary width (D – d). The geometric relationship between cortical thickness and medullary width was referred to as bone architecture.

Intraobserver reliability

Measurements of 30 randomly selected X-rays were repeated by the same researcher (AM) 1 month after initial measurement and again 16 months later to assess intraobserver reliability and reproducibility. The coefficients of variation for the radiogrammetry measures were as follows: (1) metacarpal length, 0.14%; (2) bone width, 0.80%; and (3) medullary width, 6.20%.

Interobserver reliability

The metacarpal measurements for the 10-year age group were evaluated against measurements performed on the same participants from this cohort in a previous study.⁽³³⁾ The difference between the results of the two studies was less than 3%.

Data analysis

Cross-sectional analyses

Participants were categorized into specific age groups for cross-sectional analyses. For example, individuals ≥ 9 and <10 years were categorized as age group 9.5 years. Data were analyzed cross-sectionally using Stata Version 14 (Stata Corporation, Inc., College Station, TX, USA) and SPSS Version 23 (IBM Corp., Armonk, NY, USA). No imputation of missing data was undertaken. Normality of the data was established. A one-way ANOVA was performed on data to determine between-group variation. Sex and ethnic group differences were ascertained using a Bonferroni multiple comparisons test (alpha level 0.05, degrees of freedom = 3). To determine ethnic and sex differences in bone measures with height as a covariate, an analysis of covariance (ANCOVA) with a Bonferroni multiple comparisons test (alpha level 0.05, degrees of freedom = 3) was performed. Mean annual differences for unadjusted bone measures were determined using a repeated measures ANOVA followed by a pairwise comparison of marginal linear predictions for unbalanced data. A value of $p < 0.05$ was considered to be statistically significant.

Longitudinal analyses

Superimposition by Translation and Rotation

Data were modeled using Superimposition by Translation and Rotation (SITAR) in R (Version 3.2.2; R Foundation for Statistical

Computing, Vienna, Austria; <https://www.r-project.org/>).⁽³⁴⁾ SITAR is a shape invariant model with a single fitted curve that summarizes individual growth patterns with three parameters: size, tempo, and velocity.⁽³⁴⁾ Individual curves are modeled and matched to the mean curve by shifting vertically (to represent differences in individual size), or horizontally for differences in tempo (timing) of growth. Individual differences in velocity cause a stretching or shrinking of the age scale, resulting in an increase or decrease of the slope.⁽³⁴⁾

Joint models were fitted for metacarpal length, bone width, and medullary width data. These first combined the sexes by ethnic group, and second, the black and white participants by sex group. This allowed for group differences by sex or ethnicity to be tested. Distance curves for the bone dimensions of metacarpal length, bone width, and medullary width plotted against chronological age were produced. The SITAR model used was

$$E(y_{it}) = \alpha_i + h\left(\frac{t - \beta_i}{e^{-\gamma_i}}\right) \quad (1)$$

where y_{it} is the bone dimension of the i th participant at age t ; α_i (size parameter), β_i (tempo parameter), and γ_i (velocity parameter) are random effects for participant i ; $h(\cdot)$ is a fitted cubic spline curve with degrees of freedom to minimize the Bayesian Information Criterion.⁽³⁵⁾

To assess sex and ethnic differences in metacarpal growth standardized on a biological maturity indicator, bone measures were plotted against age from PLV. Age from PLV for each bone measure was calculated by subtracting chronological age at measurement from the age at PLV. Growth distance curves for bone width and medullary width were modeled against age from PLV.

Results

Participant recruitment and range in number of observations are presented in Fig. 1. Of the 683 participants recruited into the BHC, 111 participants elected to exit the study because of either time constraints or challenges with transportation. The 572 participants included in these analyses comprised 183 (32%) black females, 93 (16%) white females, 207 (36%) black males, and 89 (16%) white males. Attrition of participants and missing data waves during the study were due to the circular migration of individuals.⁽³⁶⁾ Participant characteristics at first measurement have been published.⁽³⁷⁾

Metacarpal length

The individual curves for metacarpal length growth of female and male individuals of both ethnic groups are presented in Fig. 2A and B, respectively. PLV was attained at similar ages in black (11.7 ± 0.65 years) and white (12.0 ± 0.82 years) females (Fig. 2A; Table 1). White males attained PLV significantly earlier than their black peers (13.4 ± 0.64 years versus 14.0 ± 0.89 years; $p < 0.0001$) (Fig. 2B; Table 1). The tempo of the metacarpal growth spurt in black males lagged white males by 7 months (Fig. 2B; Table 1). In males, metacarpal length growth velocity was greater in white compared to black participants ($p < 0.002$). In both ethnic groups, the metacarpal growth spurt occurred significantly earlier in females with black females attaining PLV 2.6 years earlier than their male peers, and white females

attaining PLV 1.5 years earlier than white males (Table 2). The timing of PLV was synchronized with that of PHV (our unpublished data). Significant ethnic differences were observed in metacarpal length in both sexes. Adolescent black children had on average 1 mm longer second metacarpals than white children ($p < 0.05$) (Table 1). These ethnic differences were accentuated after adjusting data for height (Supporting Tables 1 and 2). The second metacarpal of black and white adolescent males was longer than that of their female counterparts ($p < 0.0001$) (Supporting Fig. 1; Table 2).

Bone width

Black and white females had similar bone widths with no differences in tempo and velocity of growth (Fig. 3A; Table 1). Black males had significantly greater bone width size ($p < 0.02$), growth tempo ($p < 0.0009$), and velocity ($p < 0.0001$) than their white peers (Fig. 3B; Table 1). Bone width in both black and white adolescent males was approximately 1 mm greater than their respective female peers ($p < 0.0001$) (Table 2). Growth velocity in males also exceeded that of females in both ethnic groups ($p < 0.0001$) (Supporting Fig. 2; Table 2). Peak velocity in bone width was attained at approximately similar ages relative to age at PLV in both sexes and ethnic groups (Supporting Fig. 3). The increase in bone width was greatest during the pubertal growth spurt and continued until a later age in males compared to females (Fig. 3; Supporting Tables 1, 3, and 4).

Medullary width

Adolescent black individuals of both sexes had larger medullary cavities than their white peers ($p < 0.0001$) (Fig. 4A, B; Table 1). Peak growth velocity in medullary width in black participants occurred approximately 2 years prior to PLV, whereas in white participants, this occurred 6 to 12 months post-PLV (Supporting Fig. 5). Significant sex differences in medullary width size occurred in both ethnic groups, with males having greater medullary cavities than their female peers ($p < 0.0001$) (Supporting Fig. 4; Table 2). Growth velocity of medullary width was significantly greater in black ($p < 0.0001$) and white ($p < 0.03$) males relative to their female peers (Table 2). In both ethnic groups, when assessed against the age of PLV, the timing of peak medullary width growth was similar between females and males (Supporting Fig. 5).

In all participants, there was an initial increase in medullary width followed by a decrease (Supporting Tables 1, 3, and 4). Although annual changes in medullary width were not always significant, when the maximum medullary width attained (black and white females, 13.5 years; black males, 16.5 years; white males, 14.5 years) was compared to that at the last time of measure (20.5 years), the decrease was significant in both sexes and ethnic groups (Table 3).

Cortical thickness

In all participants, cortical thickness increased through adolescence (Supporting Tables 1, 3, and 4). Ethnic differences were evident, with white participants having thicker cortices than their black peers, although in females this difference was only until 16.5 years (Supporting Table 1). Significant annual increases in cortical thickness occurred for 2 years longer in males compared to their female peers (Supporting Tables 3 and 4). Sex differences with males having thicker cortices than their female peers were more marked in white compared to black participants (Supporting Table 1).

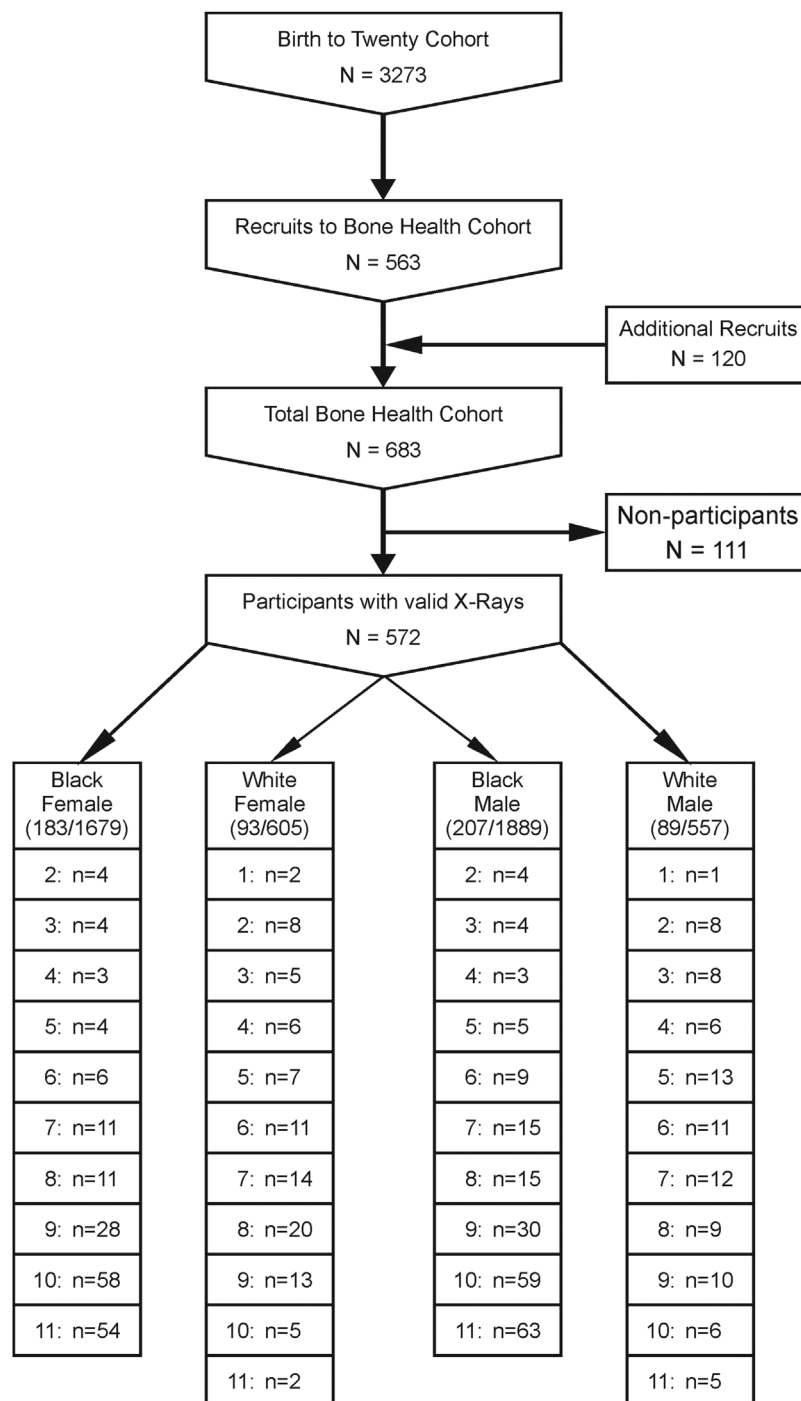


Fig. 1. Participant recruitment (N) and the number of participants (n) with their respective number of observations.

Discussion

This study presents unique longitudinal data on metacarpal bone development in an urban SA population spanning 12 years through puberty and adolescence and into young adulthood, a period during which significant physiological changes are experienced. The results of our study using radiogrammetry to measure metacarpal dimensions revealed distinctly different ethnic and sex patterns of bone growth compared to previous

studies,^(6,11) as well as ethnic differences in size and cross-sectional architecture of adolescent bone.

Ethnic differences in bone length were accentuated when data were adjusted for height with black individuals of both sexes having longer metacarpals than their white peers at all ages. A previous study of this cohort also reported longer forearm and leg lengths relative to stature in black children compared to their white counterparts at 9 years of age.⁽³⁸⁾ In US children, a similar pattern of ethnic differences in

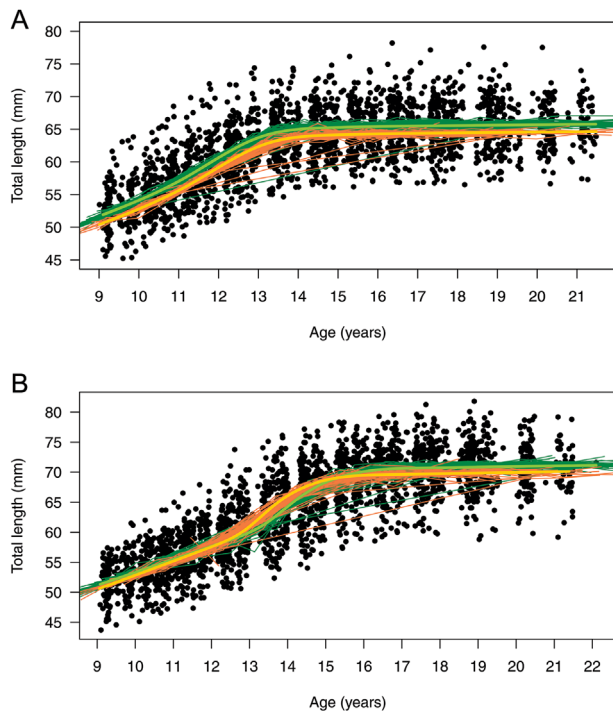


Fig. 2. Scatterplot of metacarpal length against chronological age, and individual curves adjusted for tempo and velocity, with the mean adjusted curve, for metacarpal length growth by ethnicity, in females (A) and males (B). Black participants, green color; white participants, orange color.

metacarpal lengths were reported in black and white children, although their data were not adjusted for height.⁽³⁹⁾ In contrast to SA black children, who are on average 5 to 6 cm shorter than their white peers (Nyati, unpublished data), prepubertal US black children had taller stature compared to their white peers.^(40–42) Ethnic differences in the US were attributed to US black individuals being more efficient than their white peers in absorbing and preserving calcium, particularly during adolescence.^(43,44) Calcium intake was not measured in our study; however, lower calcium intakes have been reported in black compared to white SA children.⁽⁴⁵⁾ Although low calcium intake may influence bone growth, it does not account for the longer metacarpals in black individuals in this study.

Ethnic differences in metacarpal width were reported in a SA study undertaken in 1971 in which 14-year-old urban black males had significantly narrower metacarpals than white males.⁽²¹⁾ Our data do not support this finding. Comparing the results of the present study with those reported in 1971, the average metacarpal widths for our 14-year-old black and white males are 13.5% and 4.8% greater, respectively, while for black and white females they are 7% and 4.7% greater, respectively. These differences likely reflect secular changes in bone growth and the age of PHV in urban SA children, particularly in black individuals. Improved socioeconomic conditions and nutrition may have contributed to the secular trend in black children. The delay in age of PLV in black males has been suggested to be due to them being more sensitive to adverse environmental conditions.⁽⁴⁶⁾

Table 1. Summary of SITAR Analyses of Ethnic Differences in the Size, Tempo, and Velocity of Metacarpal Length, Bone Width, and Medullary Width Growth During Adolescence as Measured Against Chronological Age

	Metacarpal length				Bone width				Medullary width			
	Females		Males		Females		Males		Females		Males	
	Mean ± SE	p	Mean ± SE	p	Mean ± SE	p	Mean ± SE	p	Mean ± SE	p	Mean ± SE	p
Participants/observations (n)	258/2099		275/2271		258/2099		275/2271		258/2099		275/2271	
Degrees of freedom	5		5		5		6		8		5	
Residual SD (mm)	0.51		0.66		0.10		0.11		0.19		0.25	
Tempo-velocity correlation	-0.36		-0.47		-0.60		-0.01		-0.62		-0.01	
Variance explained (%)	98.1		97.1		97.8		98.0		94.6		92.9	
Metacarpal length												
Size (mm)	Females		Males		Females		Males		Females		Males	
	Mean ± SE	p	Mean ± SE	p	Mean ± SE	p	Mean ± SE	p	Mean ± SE	p	Mean ± SE	p
	-1.04 ± 0.48	0.03	-1.10 ± 0.51	0.03	-0.13 ± 0.08	0.13	-0.24 ± 0.1	0.02	-0.40 ± 0.1	0.0001	-0.70 ± 0.12	0.0001
Tempo (years)	Females		Males		Females		Males		Females		Males	
	Mean ± SE	p	Mean ± SE	p	Mean ± SE	p	Mean ± SE	p	Mean ± SE	p	Mean ± SE	p
	0.15 ± 0.13	0.27	-0.58 ± 0.13	0.0001	0.24 ± 0.19	0.23	-0.5 ± 0.15	0.0009	-0.72 ± 0.27	0.008	-1.74 ± 0.29	0.0001
Velocity (mm/year)	Females		Males		Females		Males		Females		Males	
	Mean ± SE	p	Mean ± SE	p	Mean ± SE	p	Mean ± SE	p	Mean ± SE	p	Mean ± SE	p
	-0.01 ± 0.03	0.66	0.09 ± 0.03	0.002	0.02 ± 0.04	0.69	0.19 ± 0.05	0.0001	0.06 ± 0.05	0.18	0.03 ± 0.04	0.4

Data are for white relative to black females and males.

Table 2. Summary of SITAR Analyses of Sex Differences in the Size, Tempo, and Velocity of Metacarpal Length, Bone Width, and Medullary Width Growth During Adolescence as Measured Against Chronological Age

	Metacarpal length		Bone width		Medullary width	
	Black	White	Black	White	Black	White
Participants/observations (n)	390/3568	182/1162	370/3349	163/1022	370/3349	163/1022
Degrees of freedom	6	4	6	4	6	5
Residual SD (mm)	0.61	0.63	0.10	0.13	0.05	0.22
Tempo-velocity correlation	-0.28	-0.62	0.01	0.21	0.39	-0.01
Variance explained (%)	98.0	97.9	98.6	97.0	94.7	92.8

	Metacarpal length		Bone width		Medullary width	
	Black	White	Black	White	Black	White
Size (mm)	5.42 ± 0.38	5.38 ± 0.53	1.07 ± 0.07	0.99 ± 0.10	0.16 ± 0.02	0.48 ± 0.16
Tempo (years)	2.61 ± 0.10	1.53 ± 0.17	3.00 ± 0.11	2.51 ± 0.20	0.15 ± 0.01	0.06 ± 0.02
Velocity (mm/year)	0.13 ± 0.02	0.24 ± 0.04	0.26 ± 0.04	0.32 ± 0.06	0.22 ± 0.03	0.12 ± 0.05
	<i>p</i>	<i>p</i>	<i>p</i>	<i>p</i>	<i>p</i>	<i>p</i>
	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
	0.0001	0.0001	0.0001	0.0001	0.0001	0.03

Data are for males relative to females in black and white participants.

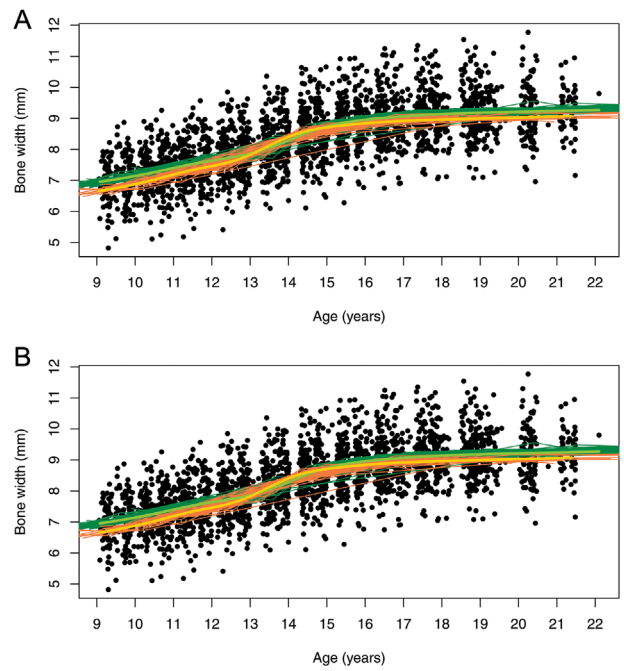


Fig. 3. Scatterplot of bone width against chronological age, and individual curves adjusted for tempo and velocity, with the mean adjusted curve, for bone width growth by ethnicity, in female (A) and male (B) participants. Black participants, green color; white participants, orange color.

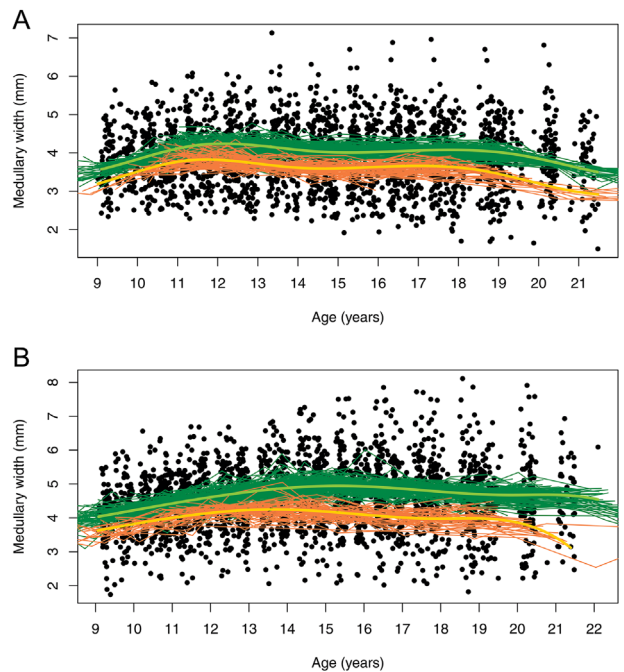


Fig. 4. Scatterplot of medullary width against chronological age, and individual curves adjusted for tempo and velocity, with the mean adjusted curve, for medullary width growth by ethnicity, in female (A) and male (B) participants. Black participants, green color; white participants, orange color.

Table 3. Differences in Bone Width, Cortical Thickness, and Medullary Width Between the Age at First Measurement and Age at Maximal Medullary Width, and Between the Age at Maximal Medullary Width and Age at Last Measurement

Group	Age range (years) ^a	Bone width (mm) (mean ± SE)	<i>p</i>	Medullary width (mm) (mean ± SE)	<i>p</i>	Cortical thickness (mm) (mean ± SE)	<i>p</i>
BF	9.5–13.5	1.09 ± 0.02	0.0001	0.30 ± 0.03	0.0001	0.79 ± 0.03	0.0001
	13.5–20.5	0.29 ± 0.02	0.0001	–0.23 ± 0.03	0.0001	0.52 ± 0.03	0.0001
WF	9.5–13.5	1.03 ± 0.05	0.0001	–0.10 ± 0.07	0.16	1.12 ± 0.08	0.0001
	13.5–20.5	0.35 ± 0.06	0.0001	–0.19 ± 0.08	0.02	0.54 ± 0.09	0.0001
BM	9.5–16.5	1.97 ± 0.03	0.0001	0.64 ± 0.04	0.0001	1.33 ± 0.04	0.0001
	16.5–20.5	0.23 ± 0.03	0.0001	–0.20 ± 0.04	0.0001	0.43 ± 0.04	0.0001
WM	9.5–14.5	1.69 ± 0.06	0.0001	0.38 ± 0.08	0.0001	1.31 ± 0.09	0.0001
	14.5–20.5	0.54 ± 0.07	0.0001	–0.38 ± 0.09	0.0001	0.91 ± 0.10	0.0001

BF = black female; WF = white female; BM = black male; WM = white male.

^aAge at first measurement (9.5 years); age at maximal medullary width (BF = 13.5 years; WF = 13.5 years; BM = 16.5 years; WM = 14.5 years); age at last measurement (20.5 years).

The rate of bone growth was similar in both sexes prior to the pubertal growth spurt and consistent with those of other studies.^(6,11,24) A divergence in bone length and width between females and males occurred during the pubertal growth spurt in response to the presumed differential expression of sex hormones. Although the sex differences in which males are taller and have longer and wider bones are believed to be the result of the later onset of puberty in males compared to females,^(14,38) we also show significantly greater peak bone length and bone width velocity during puberty in males.

In keeping with the findings of Garn,⁽¹¹⁾ there were no significant sex differences in bone width prior to the onset of the pubertal growth spurt. However, during adolescence the degree of sexual dimorphism was similar in both ethnic groups, and these differences diminished when height was factored in. In contrast, Garn and colleagues⁽⁴⁷⁾ reported less sexual dimorphism in adults of largely African ancestry compared to European subjects when raw data were analyzed.

Our results showed that although sexual dimorphism emerged during the growth spurt, the pattern of bone growth in males was dissimilar to that of some previous metacarpal radiogrammetry studies.^(6,11) In males, the expansion in bone width and cortical thickening during puberty has been attributed primarily to periosteal bone apposition,^(11,13) with endocortical expansion continuing until 16 years in US white boys.⁽⁶⁾ However, in our study, in white males, the endocortical area ceased to expand at an earlier age and was followed by contraction, concurring with the results of Martin and colleagues.⁽²⁴⁾ The relative delay in endocortical contraction in black males may be a consequence of their later entry into puberty and/or related to their different bone architecture.

Previous studies in females reported dimensional changes in cortical thickness due to endocortical apposition and this was attributed to the pubertal rise in estrogen.^(11,24) Our results are consistent with these findings because greater endocortical contraction was observed in black and white adolescent females, and this occurred at similar ages to those previously reported.^(6,11,24) Endocortical bone accrual is more closely associated with insulin-like growth factor-1 (IGF-1) in girls and with testosterone in boys.⁽⁴⁸⁾ It is therefore interesting that, in the present study, endocortical contraction commenced only a year later in white males compared to white females and conflicts with Garn's observations in Ohio whites.⁽¹¹⁾ Longitudinal hormonal assays through adolescence may reveal the

endocrine influence on the endocortical surface. In a recent longitudinal pQCT study of the tibia it was proposed that in females, instead of increased endocortical bone deposition relative to males, there is less endocortical resorption.⁽⁴⁹⁾ The regulation of remodeling at the endocortical interface may therefore be region-specific^(8,11) and/or genetically determined.⁽⁴⁷⁾ Given that in both sexes peak medullary width expansion in black participants occurred at least 2 years prior to attaining PLV compared to white participants, in whom it occurred at least 6 months after attainment of PLV, genetic influences at the endocortical surface may possibly override hormonal influences in bone development.

Distinct relationships of cortical thickness relative to medullary width and bone diameter were evident between black and white adolescents. Black adolescents had wider bones with thinner cortices and wider medullary cavities than white adolescents. These differences may be due to differences in calcium intake between the two ethnic groups.⁽⁴⁵⁾ A study comparing hypocalcemic and normocalcemic rural black SA children reported greater bone width and lower bone mineral density in the hypocalcemic group.⁽⁵⁰⁾ It was suggested that secondary hyperparathyroidism contributed to increased endocortical bone resorption and periosteal bone deposition.⁽⁵⁰⁾ The outward displacement of the cortex from the central axis seen in black participants may therefore be a compensatory mechanism enhancing the bone's resistance to torsional and bending forces.⁽⁵¹⁾ Because the metacarpal is a non-weight bearing bone, the role of mechanical loading in determining bone size is unclear.⁽⁵²⁾ SA black children have smaller muscle cross-sectional area relative to bone size compared to white children and this may elicit a differential response to mechanical forces.⁽⁵³⁾

The initiation and duration of the growth spurt and the attainment of PLV were synchronized between black and white females. In males, ethnic differences were observed whereby the black males' delayed entry into puberty allowed for greater prepubertal appendicular growth⁽³⁸⁾ and the attainment of PLV later than in white males is in keeping with the delayed skeletal maturity reported in the same cohort.⁽⁴⁶⁾ The lag in pubertal development in black males has been proposed to be a consequence of negative early life influences impacting growth.⁽⁴⁶⁾ An earlier onset of puberty is thought to be associated with an accelerated time through puberty;^(46,54) however, in this study the duration of the growth spurt was similar in all groups regardless of the timing of the onset of the growth spurt.

The strengths of this study are its longitudinal nature spanning 12 years and its provision of information on a critical developmental period. Furthermore, it provides data based on ethnicity and sex and aligns these to biological maturity. SITAR has only been used to model stature⁽⁵⁵⁾ and skeletal maturity of short bones;⁽⁴⁶⁾ however, in this study we have shown its applicability in modeling appendicular bone growth. We acknowledge that errors may occur with repeated measures but because we expect repeat measures to vary with age we sought to minimize these errors by using standardized protocols for radiography and radiogrammetry. Although radiogrammetry was performed manually using calipers, precision of the method was validated by interobserver and intraobserver results. A digitized method may have been limiting in that it requires a minimum cortical thickness for recognition by an automated system, a challenge in pediatric populations.⁽⁵⁶⁾ Our study was standardized on the second metacarpal of the left hand irrespective of hand dominance. Previous radiogrammetry studies have shown greater bone width and cortical area of the right second metacarpal compared to the left regardless of hand dominance.^(57,58) Participants who may have experienced a forearm fracture were not excluded because the fracture data on this cohort were obtained retrospectively. We do not, however, believe that this would have significantly impacted the metacarpal dimensions. A limitation of the study was the relatively smaller number of white participants.

In conclusion, in SA children distinct ethnic and sex differences in bone acquisition emerge during puberty. The resultant bone morphology and cross-sectional architecture at the end of skeletal maturity differs from previous studies in high-income countries. These dissimilarities in bone accrual during adolescence may differentially influence bone mass in later life.

Disclosures

All authors state that they have no conflicts of interest.

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References

- Hui SL, Slemenda CW, Johnston CC Jr. The contribution of bone loss to postmenopausal osteoporosis. *Osteoporos Int*. 1990;1(1):30–4.
- Matkovic V, Jelic T, Wardlaw GM, et al. Timing of peak bone mass in Caucasian females and its implication for the prevention of osteoporosis. Inference from a cross-sectional model. *J Clin Invest*. 1994;93(2):799–808.
- Ferrari S, Rizzoli R, Slosman D, Bonjour JP. Familial resemblance for bone mineral mass is expressed before puberty. *J Clin Endocrinol Metab*. 1998;83(2):358–61.
- Baxter-Jones AD, Faulkner RA, Forwood MR, Mirwald RL, Bailey DA. Bone mineral accrual from 8 to 30 years of age: an estimation of peak bone mass. *J Bone Miner Res*. 2011;26(8):1729–39.
- Gilsanz V, Kovanlikaya A, Costin G, Roe TF, Sayre J, Kaufman F. Differential effect of gender on the sizes of the bones in the axial and appendicular skeletons. *J Clin Endocrinol Metab*. 1997;82(5):1603–7.
- Frisancho AR, Garn SM, Ascoli W. Subperiosteal and endosteal bone apposition during adolescence. *Hum Biol*. 1970;42(4):639–64.
- Bouillon R, Bex M, Vanderschueren D, Boonen S. Estrogens are essential for male pubertal periosteal bone expansion. *J Clin Endocrinol Metab*. 2004;89(12):6025–9.
- Bass S, Delmas PD, Pearce G, Hendrich E, Tabensky A, Seeman E. The differing tempo of growth in bone size, mass, and density in girls is region-specific. *J Clin Invest*. 1999;104(6):795–804.
- Vandewalle S, Taes Y, Fiers T, et al. Associations of sex steroids with bone maturation, bone mineral density, bone geometry, and body composition: a cross-sectional study in healthy male adolescents. *J Clin Endocrinol Metab*. 2014;99(7):E1272–82.
- Turner RT, Wakley GK, Hannon KS. Differential effects of androgens on cortical bone histomorphometry in gonadectomized male and female rats. *J Orthop Res*. 1990;8(4):612–7.
- Garn SM. The earlier gain and later loss of cortical bone. Springfield, IL: Thomas; 1970. 146 p.
- Schoenau E, Neu CM, Mokov E, Wassmer G, Manz F. Influence of puberty on muscle area and cortical bone area of the forearm in boys and girls. *J Clin Endocrinol Metab*. 2000;85(3):1095–8.
- Seeman E. Clinical review 137: sexual dimorphism in skeletal size, density, and strength. *J Clin Endocrinol Metab*. 2001;86(10):4576–84.
- Iuliano-Burns S, Hopper J, Seeman E. The age of puberty determines sexual dimorphism in bone structure: a male/female co-twin control study. *J Clin Endocrinol Metab*. 2009;94(5):1638–43.
- Barnett E, Nordin BE. The radiological diagnosis of osteoporosis: a new approach. *Clin Radiol*. 1960;11:166–74.
- Garn S, Rohmann C, Wagner B, Sascoli W. Continuing bone growth throughout life: a general phenomenon. *Am J Phys Anthropol*. 1967;26:313–7.
- Exton-Smith AN, Millard PH, Payne PR, Wheeler EF. Pattern of development and loss of bone with age. *Lancet*. 1969;2(7631):1154–7.
- Gatti D, Sartori E, Braga V, Corallo F, Rossini M, Adami S. Radial bending breaking resistance derived by densitometric evaluation predicts femoral neck fracture. *Osteoporos Int*. 2001;12(10):864–9.
- Thodberg HH, van Rijn RR, Tanaka T, Martin DD, Kreiborg S. A paediatric bone index derived by automated radiogrammetry. *Osteoporos Int*. 2010;21(8):1391–400.
- Martin DD, Heckmann C, Neuhof J, Jenni OG, Ranke MB, Binder G. Comparison of radiogrammetrical metacarpal indices in children and reference data from the First Zurich Longitudinal Study. *Pediatr Radiol*. 2012;42(8):982–91.
- Walker AR, Walker BF, Richardson BD. Metacarpal bone dimensions in young and aged South African Bantu consuming a diet low in calcium. *Postgrad Med J*. 1971;47(548):320–5.
- Dequeker J. Quantitative radiology: radiogrammetry of cortical bone. *Br J Radiol*. 1976;49(587):912–20.
- Kimura K. Growth of the second metacarpal according to chronological age and skeletal maturation. *Anat Rec*. 1976;184(2):147–57.
- Martin DD, Heckmann C, Jenni OG, Ranke MB, Binder G, Thodberg HH. Metacarpal thickness, width, length and medullary diameter in children—reference curves from the First Zurich Longitudinal Study. *Osteoporos Int*. 2011;22(5):1525–36.
- Duren D, Seselj M, Froehle AW, Nahhas RW, Sherwood RJ. Skeletal growth and the changing genetic landscape during childhood and adulthood. *Am J Phys Anthropol*. 2013;150:48–57.
- Richter L, Norris S, Pettifor J, Yach D, Cameron N. Cohort profile: Mandela's children: the 1990 Birth to Twenty study in South Africa. *Int J Epidemiol*. 2007;36(3):504–11.
- Thandrayen K, Norris SA, Micklesfield LK, Pettifor JM. Heterogeneity of fracture pathogenesis in urban South African children: the birth to twenty cohort. *J Bone Miner Res*. 2011;26(12):2834–42.

28. Tanner JM. Growth at adolescence. Oxford, UK: Blackwell Scientific Publications; 1962.
29. Jones LL, Griffiths PL, Norris SA, Pettifor JM, Cameron N. Is puberty starting earlier in urban South Africa? *Am J Hum Biol.* 2009;21(3):395–7.
30. Sherar LB, Baxter-Jones AD, Mirwald RL. Limitations to the use of secondary sex characteristics for gender comparisons. *Ann Hum Biol.* 2004;31(5):586–93.
31. Abbassi V. Growth and normal puberty. *Pediatrics.* 1998;102(2 Pt 3):507–11.
32. Tanner JM. Assessment of skeletal maturity and prediction of adult height (TW3 method). Philadelphia: W.B. Saunders; 2001.
33. Vidulich L, Norris SA, Cameron N, Pettifor JM. Differences in bone size and bone mass between black and white 10-year-old South African children. *Osteoporos Int.* 2006;17(3):433–40.
34. Cole TJ, Donaldson MD, Ben-Shlomo Y. SITAR—a useful instrument for growth curve analysis. *Int J Epidemiol.* 2010;39(6):1558–66.
35. Schwarz G. Estimating the dimension of a model. *Ann Stat.* 1978;6(2):461–4.
36. Richter LM, Norris SA, De Wet T. Transition from Birth to Ten to Birth to Twenty: the South African cohort reaches 13 years of age. *Paediatr Perinat Epidemiol.* 2004;18(4):290–301.
37. Thandrayen K, Norris SA, Pettifor JM. Fracture rates in urban South African children of different ethnic origins: the Birth to Twenty cohort. *Osteoporos Int.* 2009;20(1):47–52.
38. Nyati LH, Norris SA, Cameron N, Pettifor JM. Effect of ethnicity and sex on the growth of the axial and appendicular skeleton of children living in a developing country. *Am J Phys Anthropol.* 2006;130(1):135–41.
39. Garn SM, Clark DC. Nutrition, growth, development, and maturation: findings from the ten-state nutrition survey of 1968–1970. *Pediatrics.* 1975;56(2):306–19.
40. Garn SM, Sandusky ST, Nagy JM, McCann MB. Advanced skeletal development in low-income Negro children. *J Pediatr.* 1972;80(6):965–9.
41. Garn SM, Clark DC. Problems in the nutritional assessment of black individuals. *Am J Public Health.* 1976;66(3):262–7.
42. Malina RM, Brown KH, Zavaleta AN. Relative lower extremity length in Mexican American and in American Black and White youth. *Am J Phys Anthropol.* 1987;72(1):89–94.
43. Bryant RJ, Wastney ME, Martin BR, et al. Racial differences in bone turnover and calcium metabolism in adolescent females. *J Clin Endocrinol Metab.* 2003;88(3):1043–7.
44. Gutierrez OM, Farwell WR, Kermah D, Taylor EN. Racial differences in the relationship between vitamin D, bone mineral density, and parathyroid hormone in the National Health and Nutrition Examination Survey. *Osteoporos Int.* 2011;22(6):1745–53.
45. McVeigh JA, Norris SA, Pettifor JM. Bone mass accretion rates in pre- and early-pubertal South African black and white children in relation to habitual physical activity and dietary calcium intakes. *Acta Paediatr.* 2007;96(6):874–80.
46. Cole TJ, Rousham EK, Hawley NL, Cameron N, Norris SA, Pettifor JM. Ethnic and sex differences in skeletal maturation among the Birth to Twenty cohort in South Africa. *Arch Dis Child.* 2015;100(2):138–43.
47. Garn SM, Nagy JM, Sandusky ST. Differential sexual dimorphism in bone diameters of subjects of European and African ancestry. *Am J Phys Anthropol.* 1972;37(1):127–9.
48. Kirmani S, Christen D, van Lenthe GH, et al. Bone structure at the distal radius during adolescent growth. *J Bone Miner Res.* 2009;24(6):1033–42.
49. Gabel L, Nettlefold L, Brasher PM, et al. Reexamining the surfaces of bone in boys and girls during adolescent growth: a 12-year mixed longitudinal pQCT study. *J Bone Miner Res.* 2015;30(12):2158–67.
50. Pettifor JM, Moodley GP. Appendicular bone mass in children with a high prevalence of low dietary calcium intakes. *J Bone Miner Res.* 1997;12(11):1824–32.
51. Buxsein ML. Determinants of skeletal fragility. *Best Pract Res Clin Rheumatol.* 2005;19(6):897–911.
52. Pandey N, Bhola S, Goldstone A, et al. Interindividual variation in functionally adapted trait sets is established during postnatal growth and predictable based on bone robustness. *J Bone Miner Res.* 2009;24(12):1969–80.
53. Micklesfield LK, Norris SA, Pettifor JM. Determinants of bone size and strength in 13-year-old South African children: the influence of ethnicity, sex and pubertal maturation. *Bone.* 2011;48(4):777–85.
54. Peto R. The horse-racing effect. *Lancet.* 1981;2(8244):467–8.
55. Prentice A, Dibba B, Sawo Y, Cole TJ. The effect of prepubertal calcium carbonate supplementation on the age of peak height velocity in Gambian adolescents. *Am J Clin Nutr.* 2012;96(5):1042–50.
56. Renz DM, Malich A, Ulrich A, et al. Reference values for digital X-ray radiogrammetry parameters in children and adolescents in comparison to estimates in patients with distal radius fractures. *J Bone Miner Metab.* 2016;34(1):55–64.
57. Plato CC, Wood JL, Norris AH. Bilateral asymmetry in bone measurements of the hand and lateral hand dominance. *Am J Phys Anthropol.* 1980;52(1):27–31.
58. Roy TA, Ruff CB, Plato CC. Hand dominance and bilateral asymmetry in the structure of the second metacarpal. *Am J Phys Anthropol.* 1994;94(2):203–11.