Racial differences in the growth of the axial and appendicular skeleton and bone mass in 11 year old South African children

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Declaration

I Howard Lukhanyo Nyati declare that this dissertation is my own work. It is being submitted for the degree of Master of Science in Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University

Signed:______________________________on this______30th____day of___October____2013

Dedication

Thank you to the Lord for all the strength and inspiration. To my mother, siblings and partner, for patience and support. To my dearest children, Lifa & Sinesipho, the source of my motivation. This work is dedicated to all the children and parents of Birth to Twenty, without whom this research would not be possible; you are true heroes.

Publication and Presentations Arising from this Study

Publications

i. Nyati HL, Norris SA, Cameron N, and Pettifor JM. 2006. Effect of Ethnicity and Sex on the Growth of the Axial and Appendicular Skeleton of Children Living in a Developing Country. American Journal of Physical Anthropology 130: 135-141

ii. Nyati HL, Pettifor JM and Norris SA. 2013. The Impact of Intrauterine and Early Life Growth on Skeletal Dimensions and Proportions in Late Childhood. Osteoporosis International (**under review**)

- All the authors contributed to conceptual development of both manuscripts
- Nyati HL contributed to data analyses and writing of both manuscripts
- Pettifor JM and Norris SA contributed to critical evaluation and guidance for both manuscripts

Presentations

i. Nyati HL. (2005). The Impact of Intrauterine and Early Life Growth on Skeletal Dimensions and Proportions in Late Childhood. NOFSA/SEMDSA Congress Sandton, South Africa; oral presentation:

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iii. Nyati HL. (2003) Effect of Ethnicity and Sex on the Growth of the Axial and Appendicular Skeleton of Children Living in a Developing Country. NOFSA/SEMDSA Congress, Drakensberg, South Africa; oral presentation

Abstract

Introduction Ethnic differences in bone growth and proportions have previously been investigated in relation to bone fragility. Differential growth in the axial and appendicular skeletons has been suggested to predispose to differential susceptibility to fracture. The developmental origins of bone size and osteoporosis have also been investigated. However, the impact of foetal programming on body proportions and limb lengths in unknown.

Objectives The aim of this study was to investigate the presence of ethnic and sex differences in axial and appendicular growth. Additionally, it was to investigate the impact of early life factors on skeletal dimensions and proportions in childhood

Methods Anthropometric measurements of stature, weight, sitting height and limb lengths were taken on 368 black and white, male and female 9 year old children. DXA scans of the distal ulna; distal radius; hip and lumbar spine were also obtained. The same measurements were obtained for 197 of the black children who had birthweight and weight and length data at 1 year. For the first part of the analyses, Analyses of Covariance were performed to assess differences in limb lengths adjusted for differences in stature. Multiple regression analyses were used to assess significant predictors of site-specific bone mass. Comparisons were made after adjustment for weight, weight and stature and weight and regional segment lengths. For the second part of the analyses, Analyses of Covariance were performed to assess differences in stature and regional segment lengths at different tertiles of birthweight, and weight and height at 1 year. Stepwise multiple regressions were performed with early life growth patterns to assess significant predictors of stature and regional segment lengths at 10 years.

Results Black children had longer limbs but shorter trunks than white children. Regional segment length were a more significant predictor of site-specific bone mass than stature. In black boys birthweight had positive but weak associations with stature and regional segment length while in girls the association were marginal. In contrast, weight and height at 1yr had strong associations with stature and regional segment lengths.

Conclusion There is a differential effect of ethnicity and sex on the growth of the axial and appendicular skeletons, and regional segment length is a better predictor of site-specific bone mass than stature. Early life growth has a long-term influence on stature, as well as on regional segment lengths but marginal effect on body proportions.

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Preface

Observations of population differences in body proportions and differential growth may be traced as far back as comments made by Isabella Leitch in 1951 relating to the cephalo-caudal gradient in growth, and possibly beyond. In recent decades there has been growing interest in the association of body proportions with disease and use of anomalous proportions as marker of disease. Linear limb growth measurements and skeletal proportions have been found to be a useful tool in assessing growth in circumstances where physical deformities may make it difficult to take regular anthropometric measurements. In particular there has been growing interest in the association of leg length with chronic diseases of lifestyle. Poor growth in specifically the lower limb and not the trunk has been associated with type 2 diabetes, hypertension and cardiovascular diseases. The association with osteoporosis has not yet been established. Understanding the antecedents of disease and poor health can add value in combating disease and improving quality of life

Longitudinal studies of human growth and development present an opportunity for non-invasive and cost-effective observations of these antecedent factors and the impact of a changing environment on the manifestation of disease. In 1987 James Tanner wrote about “growth as a mirror of the condition of society”. In a developing country like South Africa where large sections of the population do not display optimal growth, understanding the patterns of growth in axial and appendicular dimensions is critical. Understanding the unique factors that may be operational and their impact on growth may improve assessment of impact of growth on health and vice versa. The current study is the first to investigate body proportions in the South African context. This work presents the partial analysis of the longitudinal data collected from birth in 1990 from a sample of children forming part of the Birth to Twenty cohort. The results are from cross-sectional analyses of data at two points in the study period, ages 9 and 10 years.

The dissertation is divided into four main chapters, the literature review (chapter 1), two original articles, one published (chapter 2) and the other under review (chapter 3), as well as the concluding discussion and remarks (chapter 4). The overall aim of the study was to establish patterns axial and appendicular growth in South African children and how these may relate to bone mass differences. The relationship of axial and appendicular dimensions with early life growth was also explored. The results of this study will add valuable knowledge to the existing body of knowledge and provide critical insight into population differences in skeletal proportions and their implications in a developing country.

Chapter 1 Literature Review

"The differential tempo of growth of size and mass of a region and the differing tempo of growth of one region relative to another, predispose to region specific deficits in bone size, mass and density which in turn contribute to differing types of fractures in old age"

(Bass et al 1999)

The growing years present a window of opportunity for intervention efforts to stimulate positive outcomes for bone health. Understanding factors that predispose to a larger or smaller skeleton, wider or narrower diaphyses, thick or fragile cortices, longer or shorter long bones, can provide insight to direct such interventions. Bone exhibits high plasticity, altering shape in response to short and long-term mechanical and biochemical stimuli. Changes in cross-sectional properties of bone in response to mechanical loading are widely observed (Ruff 2002). A number of factors work independently or in concert to promote or suppress the growth of individuals and concomitantly the shape and strength of bones. Physiological factors mediated by nutrition and the external environment work together to produce the optimum growth trajectory.

Within any homogeneous population group, inter-individual variations in bone characteristics (geometry, thickness and width), body size (tall or short) and body shape (endomorph, mesomorph or ectomorph) can be observed. However, similar patterns in the ratio of the axial to the appendicular skeleton point to a common genetic imprint leading to a population specific body phenotype. Ethnic and sex differences in limb lengths are observed in utero suggesting that these patterns are laid down early in life. Distinct morphological patterns along ethnic lines bear the hallmark of environmental adaptation. Ecological and climatic factors have resulted in the genetic selection of population specific phenotypes appropriately adapted to varying ecological conditions and functions. Adaptation strategies such as reduction of body surface area through changes in body mass and variation in the size of the extremities are widely observed among modern humans and animal models. Factors that influence bone cross-sectional properties can be monitored and manipulated in short-to-long term observations to optimise health benefits. However, factors that influence linear bone growth and allometry are less dependent on individual habits and thus more difficult to observe and control. A number of studies have shown an association between human body shape and climate in past and present populations suggesting thermoregulation as one of the reasons for the observed differences (Roberts 1978; Trinkaus 1981; Ruff 1991, 1994; Ruff & Walker 1993; Holliday 1997). Functional reasons showing the impact of behavioural use of the limbs on diaphyseal structure have also been suggested (Schaffler et al 1985; Ruff 1987; Bikvenicius 1993; Demes & Jungers 1993; Runestad 1997)

Physiological and morphological responses to the external environment are suggested to follow Bergmann's and Allen's ecological rules. The Bergmann rule states that, ''within a polytypic warm-blooded species, the body size of the subspecies usually increases with decreasing mean temperature of its habitat'' (Bergmann, 1847). Allen's rule states that, ''in warm-blooded species, the relative size of exposed portions of the body decreases with decrease of mean temperature'' (Allen, 1877). Thus it is suggested that in order to conserve energy, individuals from colder regions are heavier and have shorter relative limb lengths resulting in a decreased ratio of surface area to body mass (Katzmarzyk and Leonard, 1998). In a reanalysis of published data from 1953, Katzmarzyk and Leonard (1998) found a negative correlation between relative sitting height and mean annual temperature albeit the relationships are tempered by secular changes.

Unlike bone cross-sectional properties which exhibit response to short-term changes in mechanical forces, linear skeletal dimensions cannot be manipulated to offer maximum health benefits. Notwithstanding, factors such as nutrition optimise the expression of the individual and population's full growth potential. Given that allometric growth differences seem to be expressed along geographical, socio-economic and ethnic lines, understanding how the allometric growth differences are physically expressed has important methodological implications. The first is that it demonstrates the limitations of a general application of absolute size in mathematical models that assess the relationship between body size and health for varied populations. Allbrook (1961) showed that the relatively long limb-to-trunk lengths of East Africans result in severe overestimation of stature when applying equations for predicting stature from long bone lengths developed in European samples. Secondly, it could pave the way for future investigations into physiological factors which regulate the expression of allometric growth and body phenotype.

i. Population Variations in Body Phenotype

There is considerable variation in body size and shape among modern human populations. According to Ruff (2002), geographically, populations differ by as much as 50%, 25% and 10% in weight, width (bi-iliac breadth) and stature respectively. A number of studies have been carried out to describe population difference in body proportions. Inter-population and inter-sex variations in body proportions underscored by inherent differences in skeletal growth have been widely observed (Tanner et al., 1976; Malina et al., 1987; Pathmanathan and Prakash, 1994; Yun et al., 1995; Gilsanz et al., 1997; Gilsanz et al., 1998; Seeman, 1998). A number of factors including race, ethnicity, sex, age, socioeconomic status, geography and nutritional status contribute to these differences. Table 1 shows a list of comparative and single population studies assessing population differences and changes in body proportions during the growing years. Although the concept of race as a biological trait is disputed, differences in body phenotype seem to project a steep racial and ethnic gradient. Two main body shapes, dolichomorphic (leg dominant) and brachymorphic (trunk dominant) based on the relative length of the legs to the trunk have been described (figure 1).

Holliday and Hilton (2010) describe a neighbour-joining tree (a diagrammatic representation of relationships between groups) analysis displaying population relationships according to body shape. According to Holliday and Hilton (2010) the tree has two main branches—a long and linear body build branch that includes the Egyptians, Sub-Saharan Africans (except for the Pygmies), and African-Americans and a second, less linear body form branch that includes the Inuit, Europeans, Euro-Americans, Puebloans, Nubians, and Pygmies. As shown in figure 1, there is a general trend towards trunk dominance among Caucasians and towards lower limb dominance among Africanoids. Limb dominance among black populations has also been shown in relation to the proportion between body stature and arm-span. Steele and Chenier (1990) found that among blacks arm-span exceeded body height by an average of 8.7 cm compared to a difference of 3.3cm in whites. These results support previous findings by Steele and Mattox (1987) who found a difference of 8.3cm and 1.8cm in blacks and whites respectively.

Table 1-1: Sample of studies evaluating body proportions and allometric growth

Authors	Title	Sample	Key findings	Publication
Cheng et al (1996)	Anthropometric measurements and body proportions among Chinese children	Population: Chinese Age: 4 – 16; Sex: M & F	• Ratio of standing height to arm span remained constant between 4 to 16 years • Ratio of sitting height to leg length decreased from 1.4 to 1.14 in boys and 1.36 to 1.18 in girls between ages of 4 to 16 years	Clin Orthop
Dasgupta and Das (1997)	A cross-sectional study of trunk and limb segments of the Bengali boys of Calcutta	Population: Indian Age: 7 – 16; Sex: M	• Leg length velocity greater than sitting height velocity up to age 13yrs. • Age at maximum increase: leg length < arm length < sitting height	Ann Hum Biol
Holliday and Hilton (2010)	Body Proportions of Circumpolar Peoples as Evidenced From Skeletal Data: Ipiutak and Tigara (Point Hope) Versus Kodiak Island Inuit	Population: Skeletal samples from Point Hope Inuit, European and European- derived, African and African-	• Brachial & Crural Indices: African >Europeans>Inuit • Limb:trunk indices show apparent clinal distribution	Am J Phys Anthropol

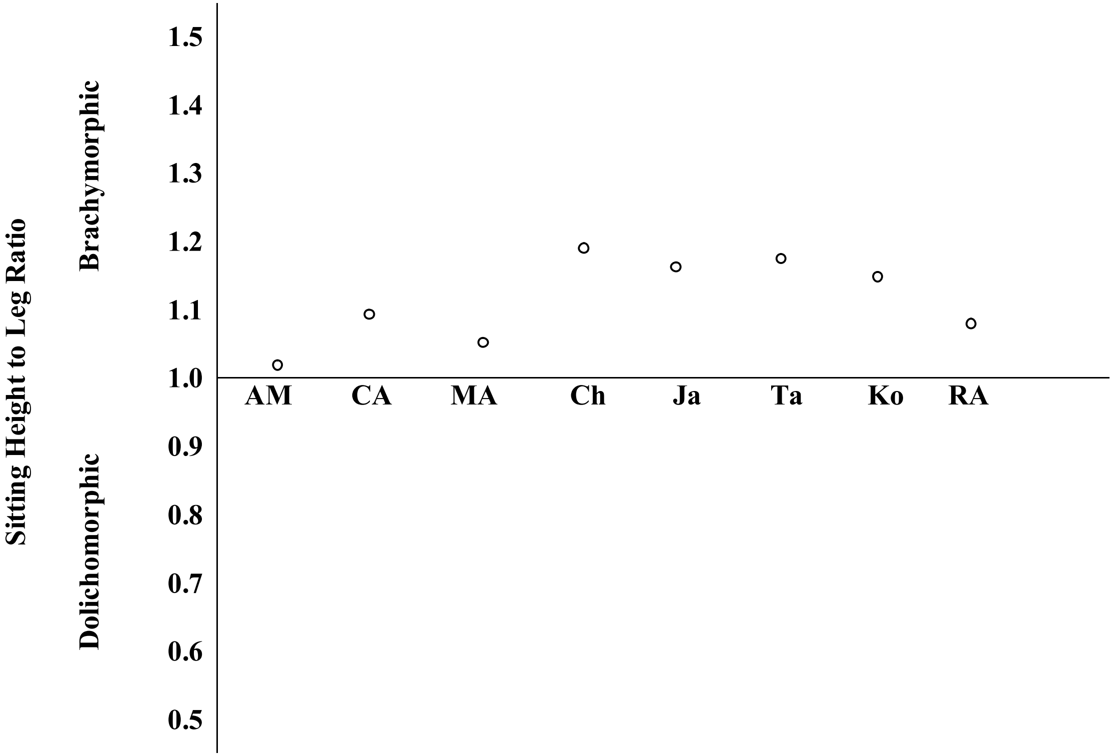
Authors	Title	Sample	Key findings	Publication
		derived, and Native American skeletons (including Koniag Inuit from Kodiak Island, Alaska)	• Bi-iliac breadth indices: Circumpolar>Euro>Africans • 35% of the total variance is due to shape	
Kagawa et al (2009)	Ethnic differences in body composition and anthropometric characteristics in Australian Caucasian and urban Indigenous children	Population: Indigenous Australian; Caucasian Australian Age: 9 – 15; Sex: M & F	• Stature: Indigenous = Caucasian • Forearm lengths: Indigenous > Caucasian • Frame size (girls):Indigenous > Caucasian • Relative arm length: Indigenous > Caucasian • Relative leg length: Indigenous = Caucasian	Br J Nut;
Malina et al (1987)	Relative lower extremity length in Mexican Americans and in American black and white youth	Population: Mexican American, African American, White American Age: 9 – 17; Sex: M & F	• Sitting height: African American = Mexican American < Caucasian American • Relative Sitting Height: Mexican American = Caucasian American	Am J Phys Anthropol

Authors	Title	Sample	Key findings	Publication
			• Legs: African American > Caucasian American & Mexican American	
Pathmanathan and Prakash (1994)	Growth of sitting height, sub-ischial leg length and weight in well-off Northern Indian children	Population: Indian Age: 6 – 16; Sex: M & F	• Sitting height shorter than British standards • Leg length longer than British standards until age 12 yrs in girls & 14 yrs in boys after which it is equal	
Ruff (2003)	Ontogenetic adaptation to bipedalism: age changes in femoral to humeral length and strength proportions in humans, with a comparison to baboons	Population: White American Age: 6months – 17; Sex: M & F	• Human femoral/humeral diaphyseal strength proportions develop after 1 year of age • Rapid increase in Femoral/humeral strength between 1 & 3 years • Femoral strength shows constant relationship to body size (body mass·bone length) after 5 years • Humeral strength shows decline relative to body size • Femoral/humeral length proportions	J Hum Evol

Authors	Title	Sample	Key findings	Publication
			increase slightly throughout growth • Growth trajectories in length & strength proportions largely independent • Strength proportions more responsive to actual changes in mechanical loading	
Tanner et al (1982)	Increase in length of leg relative to trunk in Japanese children and adults from 1957 to 1977: comparisons with British and with Japanese Americans	Population: British & Japanese Age: children & adults; Sex: M & F	• Between 1957 & 1977 age at peak velocity in height; sitting height & leg length decreased • Adult height increased by 4.3cm in boys & 2.7cm in girls	Ann Hum Biol
Yu-Cheng et al (2004)	The comparisons of anthropometric characteristics among four peoples in East Asia	Population: Chinese, Japanese, Korean & Taiwanese Age: adults 18+; Sex: M & F	• Taiwanese: wide shoulder & narrower hip • Chinese: narrow torso with medium-length limbs. • Japanese: wider torso with shorter limbs	Appl Ergon

Authors	Title	Sample	Key findings	Publication
			• Korean: moderate among the four groups, with longer upper limbs	
Yun et al., 1995	Correlations among height, length and arm span in growing Korean children	Population: Chinese Age: 4 – 16; Sex: M & F	• Upper-to-lower segment ratio decreased from childhood to near puberty but trend was reversed • Arm span minus stature changed from 0.1 to -0.8 cm in boys and -0.1 to -0.4 cm in girls	Ann Hum Biol

Figure 1-1: Comparison of relative sitting height (crude values) among different populations. African American[57] (AM); Caucasian American[57] (CA); Mexican American[57] (MA); Chinese[110] (Ch); Japanese[110] (Ja); Taiwanese[110] (Ta); Korean[110] (Ko); Rural Amazonians[104] (RA)



The apparent trend of differences in body shape along ethnic lines has been supported by observations made in several studies such as those comparing African Americans vs. Caucasian American & Mexican American children (Hamill et al., 1973; Malina et al., 1987); Indian vs. British children (Pathmanathan and Prakash 1994); Japanese vs. British & American Japanese (Tanner et al., 1976); Indigenous Australians vs. Caucasian Australians (Kagawa et al., 2009); as well as Inuit vs. Africans and Europeans (Holliday and Hilton 2010). Non-invasive methods have also been applied to assess ethnic differences in living children (Gilsanz et al., 1998 and Seeman 1998) as well as skeletal samples (Arnold et al 1966; Garn et al 1972; Jantz & Jantz 1999; Trotter & Peterson 1970; and Holliday and Hilton 2010). Even among populations living within a common geographic region, studies have shown significant morphological differences reflecting ethnic differences. Yu-Cheng et al. (2004) observed significant differences in body shape among Chinese, Japanese, Korean and Taiwanese adults. Belonging to the Mongolian race these groups are also highly associated historically. Sexual dimorphism in body stature and body proportions is also established (Gilsanz et al., 1997 and Seeman 2001). Thus optimum bone size is not only an outcome of a conducive growth environment and lifestyle but also a product of design.

ii. Heterogeneous Growth Physiology & Asymmetry

Over and above inter-population differences in body proportions, allometric differences in skeletal segment growth have been observed among individuals of the same population. The human body exhibits a heterogeneous growth pattern with different body segments showing different growth rates at different stages of the growth period. Allometric growth differences have been observed between populations (discussed above); between limbs and limb segments of the same individual; between different stages of the lifecycle of the same individual and between individuals of the same populations.

During the complete span of the human growth lifecycle, body proportions have been shown to vary considerably. From birth to maturity, the contribution to stature by the legs changed from an average of 40% to an average of 52% (Yun et al., 1995). The complex patterns of human growth are suggested to be an ecological adaptation influenced by the unique human growth life cycle. The physical features of the child, including a small body with relatively large head, relatively short extremities in proportion to stature, and a lack of secondary sexual characteristics also influence behaviour in children (Bogin 1988, 1990). The onset of puberty also introduces a transition in the growth rates of the legs relative to the trunk. During the childhood and the pubertal growth phases, both of which are unique features of the human life cycle, dominance of either the legs or the trunk has been observed (Cheng et al., 1996; Dasgupta and Das 1997; and Bradney et al., 2000).

Another area of interest in allometric growth is looking at the growth rates of the limbs and limb segments of the same individual. The presence of a disto-proximal gradient in limb growth is well established (Buschang 1982; Cameron et al 1982). In large part, a greater absolute size of the proximal segments of limbs has been observed (Maresh 1955; Anderson et al 1978) At any given time during growth the more distal segments of the limb are closer to final size and therefore appear more mature (Tanner 1962, 1978). These findings suggest a disto-proximal gradient or pattern in growth. Buschang (1982) found that diaphyseal lengths of long bones maintain positive allometry with stature. In addition to the limb segment differences, differences between limbs have also been observed. At any given time, the upper limb is relatively more mature than the lower limb and these differences in absolute size are established earlier in development and maintained throughout (Buschang 1982). A mechanism of reduction in velocity over time is suggested for the divergent pattern in intra- and inter-limb variations implying that the segments start off at similar points and rate but diverge at a later stage. However, the regulatory mechanism for this phenomenon is unclear. Albeit, this is clear evidence that the body is not a homogeneous growth unit with differential patterns between the axial and appendicular skeletons and segments of the same skeletal unit.

The influence of stature on allometric growth differences between individuals of the same population has also been observed. Yun et al (1995) observed that taller children of the same age group had greater ratios of leg length to height, leg length to arm-span, and arm-span to height than shorter children of both sexes. On the contrary a faster growth of leg length was observed in shorter children than in taller children until the onset of puberty, after which the reverse was observed. These results indicate the possible influence of nutrition and environmental stresses in the expression of body proportions.

iii. Impact on Bone Fragility

The consideration of body phenotype in evaluating the impact of growth on health provides additional insight into complex biological associations of size and health outcomes. Norgan (1998) states that, "the largest differences between ethnic groups, when all are growing up in good environments, are those of shape rather than size." The possible contribution of differential bone growth to observed population differences in bone fragility demands a greater understanding of the relationship between allometric growth and bone geometric properties. The differences in bone loss patterns between population groups can be explained in part by factors influencing differential bone gain during childhood and adolescence.

The amount of bone accumulated early in life determines fracture differences observed in later life (Bachrach 1993; Heaney & Matkovic 1995; Kelly et al 1993; Matkovic & Ilich 1993; Seeman et al 1993 and Riggs & Melton 1987). It is suggested that studies of skeletal growth may provide critical insight into the pathogenesis of bone fragility in old age (Bass et al 1999). Bonjour et al (1991) and Einhom (1992) suggest that changes in bone size during childhood growth have important mechanical implications with respect to loading capacity of the skeleton. Thus, there is an increasing drive that prevention efforts of osteoporosis should focus on building stronger bones, through the promotion of continuous physical activity and adequate nutrition in childhood and adolescence (McVeigh et al 2004). Understanding patterns of growth and variations between population groups could help explain differences in osteoporosis prevalence and the incidence of fragility fractures

Internationally, the prevalence of osteoporosis and the incidence of fractures have been shown to be significantly lower in blacks than in whites and in men than women (Bachrach 1993; Bonjour et al 1995; Cummings et al 1995; Kelly et al 1993 and Luckey et al 1996). This disparity has largely been attributed to population differences in adult bone mass (Gilsanz et al 1993 and Sabatier et al 1996). According to Gilsanz et al (1998), race has a significant and differential effect on the density and size of bones in the axial and appendicular skeleton. Studies in South Africa confirm a higher frequency of fractures and prevalence of osteoporosis in the white than in the black population (Bloom & Pogrund 1982; Schnitzler 1993 and Solomon 1979). Postmenopausal and senile osteoporosis is a disease responsible for considerable morbidity and mortality among white women in South Africa (Patel et al 1993). Earlier studies have shown marked racial differences in fracture rates with femoral neck fracture approximately 17 times lower and spine fractures prevalence about 5.6 times lower in South African blacks than in whites. These figures are reported to have remained fairly consistent as demonstrated by the figures of femoral fracture rates among South African urban blacks (Schnitzler, 1993)

This is in conflict with earlier observations that black South Africans have slightly lower bone density measured by radiogrammetry and reach peak bone mass about 15 years later compared to whites (Solomon, 1979). On the contrary, Daniels et al (1995) demonstrated later using advanced technology of Dual Energy X-ray Absorptiometry (DXA) that there were no significant ethnic differences in bone mineral density (BMD) at the radius and the spine, whereas BMD at the hip was greater in black than white adult South African women. Patel et al (1992) also showed no significant differences in BMC at the distal third of the radius between black and white children aged 6 – 20 years, attending private schools in Johannesburg, South Africa. This is in spite of the predominance of factors considered to lead to lower bone mass such as a lower consumption of calcium containing foods in black communities (Patel et al 1993).

In light of these findings, Luckey et al (1996) and Schnitzler (1993) suggested that the lower bone density of whites than blacks observed in several studies may alone not be a sufficient basis for fragility fractures. In addition, gender differences are also attributed to differences in bone size as well as the earlier onset of bone loss in women than men (Solomon, 1979). According to Schnitzler (1993), gender differences in bone fragility may be a combination of several factors: a larger male skeleton, greater cortical bone density after age 60 years as well as a greater bone turnover, which would replace fatigue damaged bone. Boys have greater bone width at the distal third of the radius than girls in prepubertal, peri-pubertal and post-pubertal children (Patel et al 1992; Pettifor and Moodley 1997). Exploring these factors in relation to bone fragility between blacks and whites may help to elucidate the mechanism for the ethnic differences in osteoporosis prevalence and incidence of fracture. Schnitzler (1993) further stated that there is a higher bone turnover in African blacks than in whites. However, studies that assess skeletal differences between South Africa blacks and whites are limited. Furthermore, studies that assess bone mass differences in relation to allometric growth during childhood growth through puberty and adolescence have not been done in the South African context.

Given the ethnic differences in body phenotype described above and the impact of differential growth on bone fragility a need exists to assess these trends in the South African population. In South Africa where nutritional differences and population differences in physical growth are evident, the lack of differences in peak bone mass at all sites except the hip is unclear. Whether the lack of differences in BMD, in spite of differences in osteoporosis prevalence between South African adult populations, is a consequence of similarities in bone size or cortical thickness is not clearly understood. An accurate understanding of factors influencing skeletal development during the childhood and adolescent growth period is pivotal in establishing an understanding of osteoporosis in adulthood. Peak bone mass is directly/indirectly influenced by the genetic, environmental and lifestyle factors which influence physical growth and maturation of individuals.

iv. Study Objectives and Hypothesis

The differences in bone loss patterns between population groups can be explained in part or wholly by factors influencing differential bone gain during childhood and adolescence. However there are few studies that have examined these differences in bone mass during the period of bone growth and mineral accretion (Patel et al 1992). Particularly in South Africa there is a paucity of studies investigating childhood factors which influence adult bone strength. Thus, the main objective of this study is to investigate whether:

i) There are ethnic differences in the growth of the axial and appendicular skeleton in South Africa

ii) There are sex differences in the growth of the axial and appendicular skeleton in South Africa

iii) These differences, if they exist, have any impact on the expression of ethnic and sex differences in bone mass

iv) There is evidence of pre- and postnatal programming of childhood axial and appendicular dimension and body proportions

Based on these objectives, the study will test the two hypotheses that:

Hypothesis I

H_o: There are no ethnic and sex differences in the growth of the axial and appendicular skeletons in South African children compared to the alternative that;

H_A: There are ethnic and sex differences

Hypothesis II

H_o: that size at birth and infancy does not have long term effects on skeletal dimensions in later life compared to the alternative that;

H_A: Size at birth and in infancy has a long term effect on skeletal dimensions

Chapter 2 Differential bone growth in South African children

Manuscript published as: Nyati HL, Norris SA, Cameron N, and Pettifor JM. 2006. Effect of Ethnicity and Sex on the Growth of the Axial and Appendicular Skeleton of Children Living in a Developing Country. American Journal of Physical Anthropology 130: 135-141

i. Abstract

Bones in the axial and appendicular skeletons exhibit heterogeneous growth patterns between different ethnic and sex groups. However, the influence of this differential growth on the expression of bone mineral content is not yet established. The aim of the present study was to investigate (i) whether there are ethnic and sex differences in axial and appendicular dimensions of South African children (ii) and whether regional segment length is a better predictor of bone mass than stature. Anthropometric measurements of stature, weight, sitting height and limb lengths were taken on 368 black and white, male and female 9 year old children. DXA scans of the distal ulna; distal radius; hip and lumbar spine were also obtained. Analyses of Covariance were performed to assess differences in limb lengths adjusted for differences in stature. Multiple regression analyses were used to assess significant predictors of site-specific bone mass. Stature adjusted means of limb lengths show that black boys have longer legs and humeri but shorter trunks than white boys. In addition, black children have longer forearms than white children and girls have longer thighs than boys. The regression analysis demonstrated that site-specific bone mass was more strongly associated with regional segment length than stature, but this had little

effect on the overall pattern of ethnic and sex differences. In conclusion, there is a differential effect of ethnicity and sex on the growth of the axial and appendicular skeletons and regional segment length is a better predictor of site-specific bone mass than stature.

ii. Introduction

Regional segment lengths such as sitting height and the limb lengths are used as a measure of bone length and growth in the axial and appendicular skeletons. Variations in growth and size of regional bones with respect to sex and ethnicity have been explored to explain the differences of bone fragility and fracture. The differential growth of one region in relation to another and differences in size and mass of bones in the same region are suggested to predispose to differential susceptibility to bone fracture (Bass et al., 1999). Several authors (Gilsanz et al., 1998; Bass et al., 1999; Riggs et al., 1999; Bradney et al., 2000) have noted that there is a greater growth of leg length than trunk length prepubertally, while the opposite occurs during puberty. Legs and arms reach their final size earlier than the trunk (Dasgupta and Das, 1997).

Ethnic and sex variations in axial and appendicular growth have been noted in children (Malina et al., 1987; Pathmanathan and Prakash, 1994; Gilsanz et al., 1997). During puberty, the contribution towards total gain in stature is mainly in the legs for girls while it is shared equally between the legs and the trunk for boys (Cheng et al., 1996). According to Seeman (2001), the differences in peak height between males and females can be attributed mainly to differences in leg length rather than trunk length as sitting height is similar between these groups. Similarly, Gilsanz et al. (1997) found no sex differences in vertebral heights of the first three lumbar vertebrae but found differences in cross sectional area. The difference in height between adult men and women is linked to the delayed epiphyseal fusion in men relative to women (Seeman, 1998), and is related to differences in the timing and span of the pubertal growth spurt in males and females. There is paucity of data describing axial and appendicular growth trends in males and females matched for stature, age and pubertal development.

On the contrary, ethnic differences in axial and appendicular growth are well documented (Tanner et al., 1976; Malina et al., 1987; Yun et al., 1995; Gilsanz et al., 1998; Seeman, 1998). African-American children have longer legs than both Mexican-American and Caucasian-American children while the latter have longer trunks than both African-American and Mexican-American children (Malina et al., 1987). In another study, prepubertal Indian children were found to have longer legs but shorter trunks than British children giving them parity in stature. However, during puberty there was greater growth in the trunk of British children while leg length reached parity with that of Indian children making British children taller than their Indian peers (Pathmanathan and Prakash, 1994).

The influence of the axial and appendicular variations in growth on the relationship between bone size and mass has not been clearly established. Previous reports have shown an association between BMC and both bone and body size (Bolotin and Sievänen, 2001). Thus, part of the differences observed in areal BMD between different ethnic and sex groups may be due to differences in bone size as a result of variations in growth. Hence, in view of ethnic and sex differences in axial and appendicular skeletal growth shown in other studies, coupled with the possible ineffectiveness of stature and/or weight to fully control for differences in bone size, the inclusion of regional segment length in regression models of bone mass might help to explain ethnic and sex differences in bone mass. Thus, the aims of this study were to test whether there are differences in axial and appendicular skeletal dimensions between prepubertal South African black and white children as these studies have not been conducted in this country where nutritional differences might influence the pattern of growth. Secondly, they were to determine whether these differences, if found, might influence the expression of bone mass differences between the two ethnic and sex groups.

iii. Participants and Methods

This was a cross-sectional study of children recruited from the Birth to Twenty birth cohort, a longitudinal study of child health and development, which has followed the development of 3273 children in the Greater Johannesburg area, South Africa since their birth in 1990 (Yach et al., 1991; Richter et al., 1995; Richter et al., 2004). A random sample of children (n = 429) stratified by ethnic group (black and white), sex and socioeconomic status, who were participating in the Birth to Twenty cohort were enrolled into a longitudinal study assessing factors influencing bone mass during childhood and adolescence (Bone Health Study).

In the first year of the Bone Health Study, 388 (90.4%) of the cohort was seen however, complete data for the current analyses were available for 368 (85.8%) children. Subjects were all healthy and age 9 years at the time of testing. Children who had asthma, were on medication or suffering from any condition likely to affect bone metabolism were excluded from the study. The sample was composed of 38 white males, 35 white females, 157 black males, and 139 black females. Cross-checks were performed to ensure that there were no significant differences between the Birth to Twenty and the Bone Health cohorts for key demographic variables (residential area at birth, maternal age at birth, gravidity, gestational age, and birthweight).

There were no available anthropometric data for the Birth to Twenty cohort at age 9 years however tests at 8 years of age, one year before the commencement of the Bone Health Study, show no significant differences in available anthropometric variables (height and weight) between the Bone Health and the Birth to Twenty cohorts. All participants and their guardians provided written informed consent and ethical approval was obtained from the University of the Witwatersrand Committee for Research on Human Subjects.

Stretch stature and sitting height were measured without shoes to the nearest 0.1cm using a Holtain Stadiometer (U.K.). Weight was measured on an electronic scale to the nearest 0.1kg. Limb lengths (shoulder-elbow, elbow-wrist, thigh and calf) were also measured to the nearest 0.1cm using a Holtain sliding caliper according to the method of Lohman et al. (1991). All limb length measurements were taken on the left side of the body. Shoulder-elbow length was measured from the lateral edge of the acromion process to the posterior surface of the olecranon process, while elbow- wrist length was measured from the posterior surface of the olecranon process to the distal palpable point of the styloid process of the radius. Thigh length was measured from the inguinal crease below the anterior-superior iliac spine to the proximal edge of the patella. Calf length was measured from the proximal edge of the medial border of the tibia to the distal edge of the medial malleolus. Sub-ischial length was calculated as the difference between stature and sitting height. The coefficients of variation for stature and sitting height were 1% and 1.5% respectively. For limb lengths, the coefficients of variation were as follows; ulna length 1.2%, humerus length 2.8%, calf length 1.3% and thigh length 4.3%.

Skeletal maturity was assessed by a single radiologist using the TWII (20) bone age scoring method of Tanner et al. (1983). All radiographs of the wrists and hands were taken by trained radiographers using cassettes with single emulsion film at an exposure of 42kV, 12 MAS and a distance of 76cm. The standard error of measurement of 0.23 for this study was calculated from a test-retest experiment of 20 subjects (Cameron, 1984). According to TWII (20) method the acceptable reliability (SEM) is ±0.5 to ±0.6 years (Tanner et al., 1983).

Site specific bone mass measurements of the distal radius and ulna, total hip and the first four lumbar vertebrae were obtained by dual energy x-ray densitometry using the QDR 4500 (Hologic Inc., Waltham MA, USA). Scans where appropriate were performed on the left side of the body. A standardized positioning procedure was followed and a spine phantom was scanned daily for quality control. The coefficient of variation for this study was calculated from a 4 times test-retest experiment of 10 subjects (Bonnick and Lewis, 2002). The intra-observer coefficient of variation in our study was less than 1%.

All data are presented as means ± standard deviation, unless otherwise stated. All statistics were performed using SPSS v11.0 for windows. Assumptions for normality and homogeneity were examined and found to be satisfactory. Analyses of Variance (ANOVA) were performed for all anthropometric measurements and multiple comparisons were used to identify where detected differences lie. In addition, Analyses of Covariance (ANCOVA) were performed controlling for differences in stature to determine ethnic and sex differences in body segment lengths. To determine significant predictors of BA, BMC and BMD stepwise multiple regression analyses were performed.

iv. Results

The physical characteristics of the children are summarized in table 1; all children were prepubertal. White children of both sexes were significantly taller than black children. Similarly sitting height was significantly greater in white children than black children of both sexes ($p<0.001$). However, sub-ischial, humeral, ulna and calf lengths were similar between the ethnic and sex groups. Black girls had longer thighs than black boys ($p<0.01$), and a similar non-significant trend was noted between white girls and boys. White boys were also heavier than black boys ($p<0.01$) but no sex difference was observed.

Table 2-1: Physical characteristics of the cohort

	White boys	White girls	Black boys	Black girls
N	38	35	157	139
Chronological Age (years)	9.51 (0.3)[†]	9.54 (0.3)	9.54 (0.3)	9.52 (0.3)
Bone Age (years)	9.26 (0.9)	9.29 (1.1)	9.44 (0.9)	9.39 (0.9)
Stature (cm)	137.5 (6.0)^{a***}	136.3 (6.8)^{b*}	132.9 (5.6)	133.0 (5.8)
Sitting ht (cm)	73.9 (3.2)^{a***}	72.5 (4.1)^{b**}	70.1 (2.8)	70.3 (3.4)
Sub-ischial length (cm)	63.6 (3.4)	63.8 (3.7)	62.8 (3.5)	62.7 (3.3)
Weight (kg)	32.8 (7.7)^{a**}	30.4 (6.7)	29.2 (4.6)	29.7 (6.4)
Humerus length (cm)	24.1 (2.0)	24.1 (2.3)	24.2 (2.2)	24.2 (2.3)
Ulna length (cm)	20.4 (1.6)	20.2 (1.4)	20.3 (1.3)	20.4 (1.4)
Thigh length (cm)	33.5 (3.3)	35.1 (3.9)	33.2 (3.2)^{2**}	34.5 (3.0)
Calf length (cm)	34.0 (3.6)	33.7 (3.1)	33.8 (2.6)	34.1 (2.9)

^{a}white boys vs black boys; ^{b}white girls vs black girls;

^{1}white boys vs white girls; ^{2}black boys vs black girls;

*p<0.05, **p<0.01, ***p<0.001;

[†] mean (±SD)

Table 2-2: Stature adjusted means of limb lengths

	White boys	White girls	Black boys	Black girls
Sitting ht (cm)	72.1 (0.3)$^{\dagger\ a***1*}$	71.3 (0.3)	70.5 (0.1)	70.7 (0.1)
Sub-ischial length (cm)	61.7 (0.3)^{a***1*}	62.5 (0.3)	63.2 (0.1)	63.1 (0.1)
Humerus length (cm)	23.3 (0.3)^{a**}	23.6 (0.3)^{b*}	24.4 (0.2)	24.4 (0.2)
Ulna length (cm)	19.9 (0.2)^{a**}	19.8 (0.2)^{b**}	20.5 (0.1)	20.6 (0.1)
Thigh length (cm)	32.5 (0.5)^{1**}	34.5 (0.5)	33.4 (0.2)^{2***}	34.7 (0.2)
Calf length (cm)	32.9 (0.4)^{a**}	32.9 (0.4)^{b**}	34.0 (0.2)	34.3 (0.2)

^{a}white boys vs black boys; ^{b}white girls vs black girls;

^{1}white boys vs white girls; ^{2}black boys vs black girls;

*p<0.05, **p<0.01, ***p<0.001;

†mean (±SEM)

Body segment lengths after adjusting for differences in stature demonstrated significant ethnic and sex differences (table 2). Sitting height remained significantly greater in white boys than black boys but the female differences disappeared, while sub-ischial length was now less in white than black boys. Sitting height was also greater in boys than girls in white children while sub-ischial length was greater in girls than boys. Humeral, ulna and calf lengths were greater in black children than white children of both sexes. Girls had significantly longer thighs than boys in both ethnic groups.

Table 2-3: Ethnic and sex differences in body segment ratios

	White boys	White girls	Black boys	Black girls
Sitting Ht/Sub-Ischial L	1.16(0.007)$^{\dagger\ a***}$	1.14(0.011)	1.12(0.004)	1.12(0.005)
Humerus L/Ulna L	1.18(0.014)	1.20(0.017)	1.19(0.009)	1.19(0.009)
Humerus L/Sitting Ht	0.327(0.004)^{a**}	0.333(0.005)	0.345(0.002)	0.345(0.003)
Ulna L/Sitting Ht	0.276(0.002)^{a***}	0.279(0.003)^{b**}	0.290(0.001)	0.291(0.001)
Thigh L/Calf L	1.00(0.024)	1.05(0.026)	0.99(0.010)	1.02(0.009)

^{a}white boys vs black boys; ^{b}white girls vs black girls;

^{1}white boys vs white girls; ^{2}black boys vs black girls;

*p<0.05, **p<0.01, ***p<0.001;

†mean (±SEM)

In keeping with the stature adjusted observations for sitting height, the sitting height-to-sub-ischial length ratio (table 3) was greater in white boys than black boys. A comparison of segment ratios for the upper and lower limbs, i.e. humerus/ulna and thigh/calf respectively, showed no significant ethnic or sex differences. However, there were significant differences in the upper limb-to-upper body segment ratios with black boys having a greater humeral length/sitting height ratio than white boys and black children of both sexes having greater ulna length/sitting height ratio than white children.

Table 2-4: Regression models for (a) BMC, (b) BMD and (c) BA at the 4 regional sites (distal ulna, distal radius, hip and lumbar spine)

(a)

		Standardized Coefficient β	t	p	R-square
Ulna BMC (gm)	Ulna length (cm)	0.579	12.881	< 0.001	0.46
	Weight (kg)	0.210	4.536	< 0.001	
	Thigh length (cm)	-0.119	-2.833	0.005	
Radius BMC (gm)	Ulna length (cm)	0.487	11.158	< 0.001	0.50
	Weight (kg)	0.228	4.007	< 0.001	
	Sitting height (cm)	0.153	2.722	0.007	
	Thigh length (cm)	-0.088	-2.158	0.032	
Hip BMC (gm)	Stature (cm)	0.451	7.926	< 0.001	0.39
	Weight (kg)	0.277	5.079	< 0.001	
	Thigh length (cm)	-0.105	-2.264	0.024	
Spine BMC (gm)	Sitting Ht (cm)	0.534	8.907	< 0.001	0.40
	Weight (kg)	0.127	2.117	0.035	

(b)

		Standardized Coefficient β	t	p	R-square
Ulna BMD (gm/cm^2)	Ulna length (cm)	0.228	4.286	< 0.001	0.06
	Thigh length (cm)	-0.155	-2.925	0.004	
Radius BMD (gm/cm^2)	Weight (kg)	0.292	4.943	< 0.001	0.14
	Ulna length (cm)	0.244	3.766	< 0.001	
	Calf length (cm)	-0.212	-3.538	< 0.001	
	Thigh length (cm)	-0.126	-2.358	0.019	
Hip BMD (gm/cm^2)	Weight (kg)	0.287	5.284	< 0.001	0.07
	Thigh length (cm)	-0.153	-2.824	0.005	
Spine BMD (gm/cm^2)	Weight (kg)	0.265	3.713	< 0.001	0.15
	Sitting Ht (cm)	0.146	2.051	0.041	

(c)

		Standardized Coefficient β	t	p	R-square
Ulna BA (cm^2)	Ulna length (cm)	0.590	13.762	< 0.001	0.61
	Weight (kg)	0.221	5.801	< 0.001	
	Calf length (cm)	0.093	2.323	0.021	
Radius BA (cm^2)	Ulna length (cm)	0.486	10.993	< 0.001	0.55
	Stature (cm)	0.294	5.547	< 0.001	
	Weight (kg)	0.113	2.362	0.019	
	Thigh length (cm)	-0.091	-2.291	0.023	
Hip BA (cm^2)	Stature (cm)	0.723	14.389	< 0.001	0.56
	Weight (kg)	0.114	2.430	0.016	
	Ulna length (cm)	-0.095	-2.175	0.030	
Spine BA (cm^2)	Stature (cm)	0.456	6.014	< 0.001	0.52
	Sitting Ht (cm)	0.290	3.829	< 0.001	

Table 4 shows the significant predictors of BMC, BA and BMD in multiple regression models at the different sites. Bone mineral content at all sites with the exception of the hip, was predicted better by regional segment length than stature. Weight was also a strong predictor at all sites. At the hip, thigh length had a weak but significant negative correlation with BMC. Regional segment length was a strong predictor of site-specific BMD at all sites except the hip, where weight was the only positive predictor. Weight was also a strong predictor of BMD at the radius and spine. Calf length had weak but significant negative correlations with BMD at the radius, while thigh length had weak but significant negative correlations with ulna, radial and hip BMD. Sitting height was a strong predictor of BMD at the spine.

Regional segment length was also a strong predictor of site-specific BA at all sites except the hip. Weight was a strong predictor at the ulna, radius and hip but not at the spine. Thigh and ulna lengths had weak but negative correlations with BA at the radius and hip respectively while calf length had a weak but positive correlation with BA at the ulna. Stature and weight were strong predictors of BA at the hip while stature and sitting height were strong predictors at the spine.

To assess whether adjusting for either regional segment length or stature altered the finding of sex and ethnic differences/similarities in bone mass at different sites, a comparison was made after adjusting the bone mass variables for weight, weight and stature, or weight and regional segment length. Adjusting the bone mass variables for differences in stature or regional segment length, did not change the relationships at most sites. Regional segment length adjustments had a similar effect as adjusting for weight alone, between black and white boys at some sites (table 5a). After adjusting for weight alone or weight and regional segment length there were no significant differences in ulna and radial BA and hip BMC while after adjusting for stature significant differences were introduced. Similarly, adjusting the variables for differences in regional segment length rather than stature in girls, produced results very similar to those obtained when the variables were adjusted for weight alone at the radius and hip for BA as well as hip for BMC (table 5b). However, at the ulna adjusting for weight and stature had a similar effect as adjusting or weight alone, for BMD and BA. Whereas adjusting for weight alone and adjusting for weight and stature showed significant differences between black and white girls in BMD and BA at the ulna, after adjusting for regional segment length the differences disappeared. At the spine for BMC and BA, adjusting for stature and regional segment length both had a different effect compared to adjusting for weight alone.

Comparisons between white boys and girls showed no significant changes after adjusting for stature and regional segment length except for BA at the radius (table 5c). Adjusting for stature had a similar effect as adjusting for weight only with no significant differences in radial BA between white boys and girls. However, after adjusting for regional segment length there were significant differences in radial BA between white boys and girls. Comparisons of bone mass variables between black boys and girls were not altered at any site by adjusting for stature or regional segment length (table 5d).

Table 2-5: An assessment of changes in significant-differences/similarities in bone mass after adjusting for stature/body height (BH) or regional segment length (RSL) on weight (Wt) adjusted regional bone mass

(a) white boys v/s black boys

Region	Variable	Wt	Wt & BH	Wt & RSL
Ulna	BMC	n.s.	n.s.	n.s.
	BMD	n.s.	n.s.	n.s.
	BA	n.s.	$p < 0.05$ (B>W)	n.s.
Radius	BMC	n.s.	n.s.	n.s.
	BMD	n.s.	n.s.	n.s.
	BA	n.s.	$p < 0.001$ (B>W)	n.s.
Hip	BMC	n.s.	$p < 0.01$ (B>W)	n.s.
	BMD	$p < 0.001$ (B>W)	$p < 0.001$ (B>W)	$p < 0.001$ (B>W)
	BA	n.s.	n.s.	n.s.
Spine	BMC	n.s.	n.s.	n.s.
	BMD	n.s.	n.s.	n.s.
	BA	n.s.	n.s.	n.s.

n.s. = not significant

B = black; W= white

(b) white girls v/s black girls

Region	Variable	Wt	Wt & BH	Wt & RSL
Ulna	BMC	$p < 0.01$ (B>W)	$p < 0.001$ (B>W)	$p < 0.05$ (B>W)
	BMD	$p < 0.05$ (B>W)	$p < 0.05$ (B>W)	n.s.
	BA	$p < 0.05$ (B>W)	$p < 0.001$ (B>W)	n.s.
Radius	BMC	n.s.	n.s.	n.s.
	BMD	n.s.	n.s.	n.s.
	BA	n.s.	$p < 0.001$ (B>W)	n.s.
Hip	BMC	n.s.	$p < 0.05$ (B>W)	n.s.
	BMD	$p < 0.001$ (B>W)	$p < 0.001$ (B>W)	$p < 0.001$ (B>W)
	BA	$p < 0.01$ (W>B)	n.s.	$p < 0.01$ (W>B)
Spine	BMC	n.s.	$p < 0.01$ (B>W)	$p < 0.001$ (B>W)
	BMD	$p < 0.01$ (B>W)	$p < 0.01$ (B>W)	$p < 0.01$ (B>W)
	BA	n.s.	$p < 0.05$ (B>W)	$p < 0.01$ (B>W)

n.s. = not significant

B = black; W= white

(c) white boys v/s white girls

Region	Variable	Wt	Wt & BH	Wt & RSL
Ulna	BMC	$p< 0.001$ (b>g)	$p< 0.001$ (b>g)	$p< 0.001$ (b>g)
	BMD	$p< 0.01$ (b>g)	$p< 0.01$ (b>g)	$p< 0.01$ (b>g)
	BA	$p< 0.05$ (b>g)	$p< 0.05$ (b>g)	$p< 0.01$ (b>g)
Radius	BMC	$p< 0.05$ (b>g)	$p< 0.01$ (b>g)	$p< 0.01$ (b>g)
	BMD	n.s.	n.s.	n.s.
	BA	n.s.	n.s.	$p< 0.05$ (b>g)
Hip	BMC	$p< 0.05$ (b>g)	$p< 0.05$ (b>g)	$p< 0.05$ (b>g)
	BMD	$p< 0.001$ (b>g)	$p< 0.001$ (b>g)	$p< 0.001$ (b>g)
	BA	n.s.	n.s.	n.s.
Spine	BMC	$P< 0.05$ (b>g)	$p< 0.05$ (b>g)	$p< 0.05$ (b>g))
	BMD	n.s.	n.s.	n.s.
	BA	$p< 0.01$ (b>g)	$p< 0.001$ (b>g)	$p< 0.01$ (b>g)

n.s. = not significant

b = boys; g = girls

(d) black boys v/s black girls

Region	Variable	Wt	Wt & BH	Wt & RSL
Ulna	BMC	p< 0.001 (b>g)	p< 0.001 (b>g)	p< 0.001 (b>g)
	BMD	p< 0.001 (b>g)	p< 0.001 (b>g)	p< 0.001 (b>g)
	BA	p< 0.01 (b>g)	p< 0.01 (b>g)	p< 0.01 (b>g)
Radius	BMC	p< 0.001 (b>g)	p< 0.001 (b>g)	p< 0.001 (b>g)
	BMD	p< 0.001 (b>g)	p< 0.001 (b>g)	p< 0.001 (b>g)
	BA	p< 0.001 (b>g)	p< 0.001 (b>g)	p< 0.001 (b>g)
Hip	BMC	p< 0.001 (b>g)	p< 0.001 (b>g)	p< 0.001 (b>g)
	BMD	p< 0.001 (b>g)	p< 0.001(b>g)	p< 0.001 (b>g)
	BA	n.s.	n.s.	n.s.
Spine	BMC	n.s.	n.s.	n.s.
	BMD	n.s.	n.s.	n.s.
	BA	p< 0.01 (b>g)	p< 0.001 (b>g)	p< 0.001 (b>g)

n.s. = not significant

b = boys; g = girls

v. Discussion

Most studies reporting ethnic and sex comparisons in axial and appendicular dimensions and bone health have been conducted in developed countries. The present study is unique in that it was conducted in a developing country where the growth of black children has been shown to deviate from international norms (Cameron et al., 1992). Hence, one might expect that bone mass and skeletal growth patterns could deviate from those found in developed countries. Skeletal maturation, as assessed by bone age, is similar between black and white prepubertal children regardless of sex. In contrast, comparisons among people of African and Caucasian descent have shown advanced skeletal development in black children (Tobias, 1958; Garn et al., 1972; Ontell et al., 1996; Mora et al., 2001; Russell et al., 2001). In addition, there was a strong concordance between bone age and chronological age in our sample, an observation that is similar to that made by Cameron et al. (2003).

White prepubertal children are taller than their black peers. In spite of ethnic differences in stature and sitting height, sub-ischial length is similar among the groups. Thus, the differences in stature between black and white South African prepubertal children are a result of differences in the upper body segment. These observations might reflect the influence of different socio-economic and nutritional conditions under which the children are reared. However, similar ethnic differences in axial and appendicular growth have also been demonstrated in communities studied in developed countries suggesting that the differences are not only due to environmental factors but also to genetic differences. A comparison of African-American and Caucasian-American children found that African-American children have longer legs but shorter trunks than white children (Malina et al., 1987). This is in agreement with observations made by Jantz and Jantz (1999) who showed in adult skeletons that black males and females have longer ulnas, radii and tibias than white males and females while the humerii were longer in whites than in blacks.

Differences in axial and appendicular growth in South African children may be concealed by the differing growth rates in black and white children. Hence, adjusting limb lengths for differences in stature have helped to reveal ethnic differences in body proportions. In keeping with observations in American children, stature adjusted limb lengths and body segment ratios show differences between black and white South African children. The results demonstrate ethnic differences in trunk length, sub-ischial length, ulna length, humeral length, thigh length and calf length. In addition, the ratios show that black children have longer arms in relation to their upper body than white children. However, the ratios of proximal to distal segment lengths of the upper and lower limbs are similar between black and white children. After adjustment, black boys have longer legs but shorter trunks than white boys, a pattern similar to that described in prepubertal American children. Thus in black children there is a greater contribution to stature from the lower body segment whereas in whites the contribution is more truncal. These findings thus indicate a predisposition in growth towards the appendicular skeleton in blacks and towards the axial skeleton in whites prepubertally. Thus, each region of the body has an independent but significant contribution towards the total size of an individual. Hence, a complete expression of ethnic differences in size needs to consider differences in segment lengths.

Leg growth is more susceptible to environmental and physiological changes than other regions (Tanner et al., 1982; Malina et al., 1987) hence the ethnic differences in final stature of adults in developing countries as well as sex differences observed in most studies. Females are shorter because of relatively shorter legs than males (Seeman, 2001). In the current study, sex differences are demonstrated in thigh length. The absolute values of thigh length show that black girls have longer thighs than black boys and the differences remained after adjusting for stature. The differences in leg growth between males and females may be an indication of physiological changes due to an earlier commencement of puberty in girls than boys, however in the present study all the children were clinically prepubertal. Prepubertally, there is a predominance of growth in legs compared to trunk while the reverse occurs during puberty. Sexual dimorphism in timing and sequence of lower limb growth has been shown by growth spurts of foot, tibia and sub-ischial lengths. Hands and feet reach peak velocity earlier than forearms and tibias, while the humerus and thigh might exhibit growth spurts between these two regions (Cameron et al., 1982). Thus, the greater thigh length for girls may indicate a peak in the ratio of legs-to-trunk growth rate for girls on the brink of puberty.

In keeping with these observations, the present study has shown that regional segment length is a better predictor of site-specific bone mass than stature at all sites except the hip. Therefore, in the expression of site-specific bone mass, the use of stature to adjust for size may not fully account for some of the differences in bone mass, which could be due to the regional differences in size. Body size adjustment is intended to compare size independent values of bone mass. Consequently, a number of techniques have been developed to achieve this objective. Prentice et al. (1994) for example, suggest an incorporation of bone area/width along with height and weight in the regression models of BMC. However, Neville et al. (2002) stated that there is still uncertainty about the best approach to adjust for the effect of size, and suggested a multiplicative allometric model with the inclusion of other confounding variables while seeking a parsimonious solution. According to Prentice et al. (1994), the relationship between bone size and bone mass is subject to several factors such as the population group, skeletal site, body size, instrumentation and scanning conditions. Thus, using stature as a universal adjustment for bone mass may be an inappropriate method for some population groups therefore, as many contributing factors as possible need to be taken into account in order to construct an appropriate model for the expression of BMC. The ethnic and sex variations in axial and appendicular growth along with the stronger relationship of regional segment length with site-specific bone mass warrant the inclusion of regional segment length in future investigations of an appropriate model for bone mass expression.

Given this strong relationship between regional segment length and site-specific bone mass, using regional segment length to adjust for size may be more effective in attenuating the effect of size on bone mass than body stature. However, when comparing changes in significant differences/similarities when using adjustments for weight alone, weight and regional segment length, and weight and body stature on ethnic differences in bone mass, the changes were marginal. This suggests that there are more critical factors, which contribute to the relationship between bone mass and size. Prentice et al. (1994) observed that the relationship between bone area and BMC is not a straightforward linear relationship. In addition, there is a greater variation in the measurement of limb lengths than stature making limb length less reliable to measure size. The weak but negative correlation of thigh length with hip BMC, BMD and BA further indicates the complexity of this relationship.

A limiting factor in this study is the small number of white compared to black participants. However, this is attributed to the enrolment protocol within Birth to Twenty which aimed to select a cohort which is demographically representative of the population within the Johannesburg-Soweto area. Consequently, black participants made up the greatest proportion of the study.

vi. Conclusions

There are clear ethnic and sex differences in the growth of axial and appendicular skeletons in South African prepubertal black and white children. The effect of this differential growth on the expression of bone mass is demonstrated by the better correlation of site-specific bone mass with regional segment length than stature. However the effect of these differences and the strong relationship of regional segment length to site-specific bone mass have little effect on the expression of ethnic and sex differences in bone mass. Despite marked socio-economic and thus nutritional differences between South African black and white prepubertal children, the patterns of axial and appendicular growth are similar to those reported between African-American and white children in the USA, suggesting that the patterns are genetically determined rather than due to environmental factors.

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Chapter 3 Early life programming of skeletal dimensions in South African children

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i. Abstract

The influence of intrauterine programming on childhood growth and morbidity in later life has been established. There are suggestions that programming might also influence bone accretion thus the risk of osteoporosis in later life. However, the influence of intrauterine programming on differential growth of the axial and the appendicular skeletons, which might predispose to a differential susceptibility to fracture, has not been investigated. The aim of this study was to investigate the effects of intrauterine and early childhood growth on body proportions in a cohort of 10-year-old South African children. Anthropometric measurements of stature, weight and regional segment lengths (sitting height, and sub-ischial, humeral, forearm, thigh and calf lengths) as well as pubertal development and bone age were obtained at age 10 years. Analyses of Covariance were performed to assess differences in stature and regional segment lengths at different tertiles of birthweight, and weight and height at 1 year. Stepwise multiple regressions were performed with early life growth patterns to assess significant predictors of stature and regional segment lengths at 10 years. Birthweight had a positive but weak association with stature and regional segment length in boys while in girls the association was only significant for sitting height. However, both weight and height at 1yr had strong associations with stature and regional segment lengths. Early life growth was a poor predictor of body proportions at 10 years. In conclusion, early life growth has a long-term influence on stature, as well as regional segment lengths but the relationship with body proportions was only significant for weight at 1 year.

ii. Introduction

There is increasing evidence to suggest that intrauterine and early life programming of bone growth contributes to the risk of osteoporosis and bone fracture in adulthood. Albeit that the bone growth trajectory is laid down early in gestation, genetic influences on adult bone size and bone mass may be modified by nutritional status in early life (Davies et al., 2005). A number of epidemiological studies have revealed an association between birthweight, weight at 1 year and bone mass parameters in adulthood. These studies have largely formed the body of evidence on which the programming of osteoporosis is based. Dennison et al, (2001) showed significant associations between weight at 1 year and lumbar spine and femoral neck BMC in adults. However these associations were attenuated by adjustment for adult weight and bone area. In a comprehensive review, Cooper et al, (2005) highlight studies which have shown a statistically significant relationship between weight at 1 year and BMC at the spine and hip in adult men and women.

Undernutrition during intrauterine life results in slow skeletal development and in a reduction of the peak skeletal proportions attained following the completion of growth (Cooper et al, 2000). In turn, bone mass in adulthood is largely influenced by peak bone mass attained during skeletal growth and the subsequent rate of bone loss (Baird et al., 2011). Thus the interplay between intrauterine life and the size, shape and geometry of bone laid down during critical periods of growth has long-term implications for the manifestation of bone fragility in adulthood.

Ethnic differences in bone fragility are already established in childhood as indicated by significantly different fracture rates among black and white South African children. Biological and social factors are suggested to be responsible for the higher facture rates in South African white children compared to black children (Thandrayen et al., 2009), despite the smaller body size of the latter. Unknown factors, possibly an outcome of differential growth leading to different body phenotypes, seem to offer an advantageous skeletal design to black children. We have previously shown a preponderance towards appendicular growth among blacks compared to axial growth in whites (Nyati et al., 2006). Even within the limbs, there is evidence of population differences in relation to distal vs. proximal segment dominance (Jantz and Jantz 1999; Holliday and Ruff 2001). These ethnic differences in limb growth are already established in utero (Mastrobattista et al., 2004).

Over and above ethnicity, a number of factors at birth are suggested to lead to differences in bone fragility. Male sex, birth length, and maternal age at delivery were positively associated with the risk of fractures in a Brazilian birth cohort (Hallal et al., 2009). Thus a combination of factors at birth coupled with environmental factors during growth may explain the disparity in the susceptibility to fracture between different ethnic groups and communities consequent on the different patterns of growth of the axial and appendicular skeletons in the ethnic groups (Gilsanz et al., 1998; Bass et al., 1999; Riggs et al., 1999; Bradney et al., 2000).

It is unclear how much body phenotype and consequently skeletal proportions are influenced by environmental factors prevailing during the intrauterine and early childhood periods. Given the possible interaction of biological and environmental factors with intrauterine bone growth and skeletal size in adulthood, an investigation into the influence of intrauterine programming on axial and appendicular dimensions is warranted. Thus, the aim of this study was to investigate the influence of birth and early childhood anthropometry on axial and appendicular skeletal dimensions and body proportions in 10-year-old South African children.

iii. Participants and Methods

This was a study of children recruited from the Birth to Twenty birth cohort, a longitudinal study of child health and development, which has followed the development of 3273 children in the Greater Johannesburg area, South Africa since their birth in 1990 (Yach et al., 1991; Richter et al., 1995; Richter et al., 2004). At age 9 years, a sub-sample of children (n = 429) stratified by ethnic group (black and white), sex and socioeconomic status, who were participating in the Birth to Twenty cohort were enrolled into a longitudinal sub-study assessing factors influencing bone mass during childhood and adolescence (Bone Health Study). Data for the current analyses were available for 197 black children (106 boys & 91 girls) participating in the Bone Health cohort who had complete antenatal and childhood data. Subjects were all healthy and aged 10 years at the time of testing. Children, who had asthma, were on medication or suffering from any condition likely to affect bone metabolism were excluded from the study. Cross-checks were performed to ensure that there were no significant differences between the Birth to Twenty and the Bone Health cohorts for key demographic variables (residential area at birth, maternal age at birth, gravidity, gestational age, and birthweight). All participants and their guardians provided written informed assent and consent respectively and ethical approval was obtained from the University of the Witwatersrand Committee for Research on Human Subjects.

Birthweight was obtained from health records, and weight and length at 1 year were measured by trained fieldworkers. Stretch stature and sitting height at 10 years of age were measured without shoes to the nearest 0.1cm using a Holtain Stadiometer (U.K.). Weight was measured on an electronic scale to the nearest 0.1kg. Limb lengths (humeral, fore-arm, thigh and calf) were also measured to the nearest 0.1cm using a Holtain sliding caliper according to the methods of Lohman et al. (1991). All limb length measurements were taken on the left side of the body. Humeral length was measured from the lateral edge of the acromion process to the inferior surface of the olecranon process, while fore-arm length was measured from the posterior surface of the olecranon process to the distal palpable point of the styloid process of the radius. Thigh length was measured from the inguinal crease below the anterior-superior iliac spine to the proximal edge of the patella. Calf length was measured from the proximal edge of the medial border of the tibia to the distal edge of the medial malleolus. Sub-ischial length was calculated as the difference between stature and sitting height. The coefficients of variation for stature and sitting height were 1% and 1.5% respectively. For limb lengths, the coefficients of variation were as follows; fore-arm length 1.2%, humeral length 2.8%, calf length 1.3% and thigh length 4.3%. Skeletal maturity was assessed by a single radiologist using the TWII (20) bone age scoring method of Tanner et al. (1983). All radiographs of the wrists and hands were taken by trained radiographers using cassettes with single emulsion film at an exposure of 42kV, 12 MAS and a distance of 76cm. The standard error of measurement of 0.23 for this study was calculated from a test-retest experiment of 20 subjects (Cameron, 1984). According to TWII (20) method the acceptable reliability (SEM) is ±0.5 to ±0.6 years (Tanner et al., 1983). Metacarpal indices of the second metacarpal were measured using a digital caliper by placing the x-rays horizontally on a light box. The length was measured from the apex of the proximal notch to the tip of the metacarpal head. The outer and inner cortical diameters were measured at the midpoint of the metacarpal. Pubertal development was assessed using Tanner Staging Techniques self assessment for breasts/genitals and pubic hair (Norris and Richter, 2005). Children with a score of 2 or higher for either breasts/genitals and/or pubic hair were classified as pubertal.

Two sided t-test, Analyses of Variance (ANOVA) and Analyses of Covariance (ANCOVA) after adjustment for confounding variables were used to test for statistical significance. Adjustments for multiple comparisons were made by using the Bonferroni method of adjustment for statistical significance where significant differences were detected. The influence of potential independent variables was examined using multiple regressions. Binomial proportion tests were performed to assess significant differences in proportions of pre-pubertal to pubertal boys and girls. All data are presented as means ± standard deviation, unless otherwise stated. All statistics were performed using SPSS v11.0 for windows. Assumptions for normality and homogeneity were examined and found to be satisfactory.

iv. Results

The physical characteristics of the children are summarized in table 1. All children were aged 10 years and there were no sex differences in bone age or chronological age. There were no significant sex differences in height; however girls had longer sitting heights, thighs and metacarpals than boys. Boys had greater birthweight, weight at 1 year and length at 1 year than girls while the gestational ages of the two sexes was similar at birth.

Binomial proportion tests showed that a significantly higher proportion of girls (62.6%) had reached onset of puberty compared to boys (49%; $p < 0.01$). Comparisons were made between pre-pubertal and pubertal children within each sex group (data not shown). The onset of pubertal development had a significant influence on stature and regional segment lengths in girls while in boys the differences were marginal. In girls, significant differences were demonstrated in stature, sub-ischial length, forearm length, calf length as well as metacarpal length while in boys differences were only found in the thigh-to-lower body proportion.

Table 3-1: Descriptive characteristics of the cohort

	Boys	**Girls**	**P-value**
N	106	91	
Chronological age (yr)	10.5 (0.3) [1]	10.5 (0.3)	0.80
Bone age (yr)	10.5 (1.2)	10.9 (1.4)	0.07
Stature (cm)	137.7 (6.1)	139.2 (6.2)	0.09
Sitting height (cm)	71.3 (3.0)	72.5 (3.7)	**0.01**
Sub-ischial length (cm)	66.4 (3.9)	66.7 (3.3)	0.56
Forearm length (cm)	22.1 (1.3)	22.3 (1.3)	0.15
Humerus length (cm)	27.8 (1.5)	28.2 (1.5)	0.10
Thigh length (cm)	33.5 (2.2)	34.3 (2.1)	**0.01**
Calf length (cm)	32.5 (1.9)	32.7 (1.7)	0.43
Metacarpal length (mm)	54.6 (3.2)	55.8 (3.9)	**0.00**
Gestation (wks)	38.0 (1.6)	37.9 (2.0)	0.58
Birthweight (kg)	3.2 (0.5)	3.0 (0.5)	**0.03**
Weight at 1year (kg)	9.6 (1.4)	9.1 (1.4)	**0.01**
Length at 1year (cm)	74.3 (3.2)	72.5 (3.1)	**0.00**

[1] **Mean (± SD)**

The effect of early life growth on axial and appendicular growth parameters at 10 years of age was investigated by stratifying the data into tertiles of birthweight, and weight and length at 1 year. Analyses of Co-Variance (ANCOVA) after adjustments for pubertal development were performed and significant differences were identified using the Bonferroni test (table 2 - 4).

In general, the relationships between early life growth parameters and the various anthropometric measurements at 10 years of age were less strong in girls than boys. Birthweight had positive associations with stature ($p < 0.01$), sitting height, sub-ischial length, humerus length and forearm length ($p < 0.05$) in boys (table 2a & b). There were no significant associations in girls. Despite there being an inverse trend between birthweight tertile and lower body:upper body proportions in girls, the relationship did not reach significance ($p=0.07$).

In boys, weight at 1 year had strong and significant associations ($p < 0.01$) with stature, metacarpal length and all segment lengths (table 3). There was no relationship between lower body:upper body proportions and weight at 1 year in boys. In girls, significant associations were demonstrated with stature, sitting height, forearm lengths ($p < 0.001$) as well as humerus and metacarpal length ($p < 0.05$). The lower body:upper body proportion had a significant but negative association with weight at 1 year in girls ($p < 0.05$ & 0.001).

Table 3-2: The effect of birthweight on the growth parameters of 10 year old children (a) boys, and (b) girls; results presented as mean (±SEM)

(a)

Variables at age 10 years	Tertile 1	Tertile 2	Tertile 3	P-Value
Birthweight (kg)[1]	2.6 (0.3)	3.2 (0.1)	3.7 (0.3)	
Stature (cm)	135.3[a] (1.0)	137.9 (1.0)	139.9 (1.0)	**0.00**
Sitting height (cm)	70.3[a] (0.5)	71.4 (0.5)	72.2(0.5)	**0.02**
Sub-ischial length (cm)	65.0[a] (0.6)	66.4 (0.6)	67.7 (0.6)	**0.01**
Humerus length (cm)	27.4[a] (0.3)	27.9 (0.3)	28.3 (0.3)	**0.04**
Forearm length (cm)	21.8[a] (0.2)	22.0 (0.2)	22.5 (0.2)	**0.04**
Thigh length (cm)	33.1 (0.4)	33.8 (0.4)	33.7 (0.4)	0.33
Calf length (cm)	32.1 (0.3)	32.6 (0.3)	33.0 (0.3)	0.14
Metacarpal length (mm)	53.7 (0.5)	54.5 (0.5)	55.5 (0.5)	0.07
Lower body-to-upper body (%)	92.5 (0.8)	93.1 (0.8)	93.7 (0.8)	0.55

[1] **Mean (± SD)**

[a] Difference between tertiles 1 and 2

(b)

Variables at age 10 years	**Tertile 1**	**Tertile 2**	**Tertile 3**	**P-Value**
Birthweight (kg)[1]	2.5 (0.4)	3.1 (0.1)	3.5 (0.2)	
Stature (cm)	137.7 (1.1)	140.0 (1.1)	139.9 (1.1)	0.25
Sitting height (cm)	71.2 (0.7)	73.2 (0.7)	73.2 (0.7)	0.05
Sub-ischial length (cm)	66.5 (0.6)	66.9 (0.6)	66.6 (0.6)	0.89
Humerus length (cm)	27.9 (0.3)	28.3 (0.3)	28.5 (0.3)	0.29
Forearm length (cm)	22.1 (0.2)	22.6 (0.2)	22.4 (0.2)	0.33
Thigh length (cm)	34.1 (0.4)	34.6 (0.4)	34.4 (0.4)	0.64
Calf length (cm)	32.5 (0.3)	32.8 (0.3)	32.9 (0.3)	0.70
Metacarpal length (mm)	54.7 (0.7)	56.9 (0.7)	56.1 (0.7)	0.07
Lower body-to-upper body (%)	93.6 (0.8)	91.6 (0.8)	91.0 (0.8)	0.07

[1] **Mean (± SD)**

Table 3-3: The effect of weight at 1 year on the growth parameters of 10 year old children (a) black boys, and (b) black girls; results presented as mean (±SEM)

(a)

Variables at age 10 years	Tertile 1	Tertile 2	Tertile 3	P-Value
Weight at 1 year (kg)[1]	8.2 (0.7)	9.6 (0.3)	11.2 (0.9)	
Stature (cm)	133.7^{ab} (0.9)	138.6 (0.9)	140.9 (0.9)	**0.00**
Sitting height (cm)	69.3^{ab} (0.4)	71.7 (0.4)	73.0 (0.5)	**0.00**
Sub-ischial length (cm)	64.3^{ab} (0.6)	66.9 (0.6)	68.0 (0.6)	**0.00**
Humerus length (cm)	27.0^{ab} (0.2)	28.1 (0.2)	28.5 (0.2)	**0.00**
Forearm length (cm)	21.4^{ab} (0.2)	22.3 (0.2)	22.6 (0.2)	**0.00**
Thigh length (cm)	32.8^{b} (0.4)	33.8 (0.4)	34.1 (0.4)	**0.03**
Calf length (cm)	31.6^{ab} (0.3)	32.7 (0.3)	33.4 (0.3)	**0.00**
Metacarpal length (mm)	53.0^{ab} (0.5)	55.4 (0.5)	55.3 (0.5)	**0.00**
Lower body-to-upper body (%)	92.8 (0.8)	93.3 (0.8)	93.2 (0.8)	0.87

[1] **Mean (± SD)**

[a] **Difference between tertiles 1 and 2**

[b] **Difference between tertiles 1 and 3**

(b)

Variables at age 10 years	**Tertile 1**	**Tertile 2**	**Tertile 3**	**P-Value**
Weight at 1 year (kg)[1]	7.7 (0.5)	9.0 (0.4)	10.7 (0.9)	
Stature (cm)	136.9^{b} (1.1)	138.4^{c} (1.0)	142.1 (1.1)	**0.00**
Sitting height (cm)	70.3^{b} (0.7)	72.3^{c} (0.6)	74.7 (0.6)	**0.00**
Sub-ischial length (cm)	66.6 (0.6)	66.1 (0.5)	67.4 (0.6)	0.27
Humerus length (cm)	27.5^{b} (0.3)	28.2 (0.2)	28.9 (0.3)	**0.01**
Forearm length (cm)	21.8^{b} (0.2)	22.3^{c} (0.2)	23.1 (0.2)	**0.00**
Thigh length (cm)	33.7 (0.4)	34.2 (0.3)	35.0 (0.4)	0.07
Calf length (cm)	32.4 (0.3)	32.5 (0.3)	33.4 (0.3)	0.06
Metacarpal length (mm)	54.9^{b} (0.7)	55.4 (0.6)	57.4 (0.7)	**0.03**
Lower body-to-upper body (%)	94.9^{ab} (0.8)	91.5(0.7)	90.3 (0.8)	**0.00**

[1] Mean (± SD)

[a] Difference between tertiles 1 and 2

[b] Difference between tertiles 1 and 3

[c] Difference between tertiles 2 and 3

Length at 1 year in boys had similar significant associations ($p < 0.01$) as weight at 1 year with stature, sitting height, sub-ischial, humerus, forearm, thigh, calf and metacarpal lengths being influenced (table 4). Lower body:upper body proportions were not associated with the tertiles of length at 1 year in boys or girls. In girls, length at 1 year did not have a significant association with any of the childhood growth parameters except calf length ($p < 0.05$).

Table 3-4: The effect of length at 1 year on the growth parameters of 10 year old children (a) black boys, and (b) black girls; results presented as mean (±SEM)

(a)

Variables at age 10 years	Tertile 1	Tertile 2	Tertile 3	P-Value
Length at 1 year (cm)[1]	70.8 (2.0)	74.5 (0.6)	77.5 (1.6)	
Stature (cm)	133.8[ab] (0.9)	138.9 (1.0)	140.3 (0.9)	**0.00**
Sitting height (cm)	69.5[ab] (0.5)	71.8 (0.5)	72.6 (0.5)	**0.00**
Sub-ischial length (cm)	64.3[ab] (0.6)	67.1 (0.6)	67.7 (0.6)	**0.00**
Humerus length (cm)	27.0[ab] (0.2)	28.0 (0.2)	28.5 (0.2)	**0.00**
Forearm length (cm)	21.5[ab] (0.2)	22.3 (0.2)	22.5 (0.2)	**0.00**
Thigh length (cm)	32.8[b] (0.3)	33.2[c] (0.4)	34.6 (0.3)	**0.00**
Calf length (cm)	31.8[b] (0.3)	32.7 (0.3)	33.2 (0.3)	**0.01**
Metacarpal length (mm)	53.1[b] (0.5)	54.7 (0.5)	55.8 (0.5)	**0.00**
Lower body-to-upper body (%)	92.7 (0.8)	93.5 (0.8)	93.2 (0.8)	0.75

[1] **Mean (± SD)**

[a] **Difference between tertiles 1 and 2**

[b] **Difference between tertiles 1 and 3**

[c] **Difference between tertiles 2 and** 3

(b)

Variables at age 10 years	Tertile 1	Tertile 2	Tertile 3	P-Value
Length at 1 year (cm)[1]	69.2 (1.6)	72.6 (0.5)	75.6 (1.7)	
Stature (cm)	137.6 (1.0)	139.2 (1.2)	140.7 (1.0)	0.12
Sitting height (cm)	71.3 (0.6)	72.7 (0.7)	73.5 (0.6)	0.06
Sub-ischial length (cm)	66.3 (0.6)	66.5 (0.6)	67.2 (0.6)	0.50
Humerus length (cm)	27.8 (0.3)	28.3 (0.3)	28.6 (0.3)	0.13
Forearm length (cm)	22.1 (0.2)	22.3 (0.3)	22.7 (0.2)	0.19
Thigh length (cm)	33.9 (0.4)	34.2 (0.4)	34.8 (0.4)	0.20
Calf length (cm)	32.2[a] (0.3)	32.9 (0.3)	33.2 (0.3)	**0.04**
Metacarpal length (mm)	55.3 (0.7)	55.9 (0.8)	56.5 (0.7)	0.45
Lower body-to-upper body (%)	93.2 (0.8)	91.5 (0.9)	91.5 (0.8)	0.27

[1] Mean (± SD)

[a] Difference between tertiles 1 and 3

Multiple regression analyses (table 5) show that in boys length at 1 year was a significant predictor ($p < 0.01$) of stature, sitting height, and all body segment lengths (except forearm length) while weight at 1 year was a significant predictor for only sitting height ($p < 0.01$). Birthweight was not significant predictor of any of the growth parameters at age 10 years in boys. In girls, neither birthweight nor length at 1 year were significant predictors of anthropometric parameters at 10 years, while weight at 1 year was a significant predictor for humerus and forearm lengths ($p < 0.05$). Early growth variation was also not associated with the limb and body proportions (data not shown).

Table 3-5: Regression analyses of Regional Body Segments; (a) boys, (b) girls

(a)

		Standardized Coefficient β	*t*	*p*	R-square
Stature (cm)	Birthweight	1.07	0.96	0.34	0.34
	Weight at 1	0.45	1.90	0.06	
	Length at 1	0.20	3.92	**<0.001**	
Sitting height (cm)	Birthweight	0.55	0.15	0.88	0.31
	Weight at 1	0.23	2.69	**0.008**	
	Length at 1	0.10	3.11	**0.003**	
Sub-ischial length (cm)	Birthweight	0.73	1.30	0.20	0.25
	Weight at 1	0.31	0.78	0.44	
	Length at 1	0.13	3.43	**<0.001**	
Humerus length (cm)	Birthweight	0.23	0.46	0.65	0.25
	Weight at 1	0.12	0.77	0.45	
	Length at 1	0.05	3.93	**<0.001**	
Forearm length (cm)	Birthweight	0.25	0.79	0.43	0.19
	Weight at 1	0.10	1.99	0.05	
	Length at 1	0.05	1.90	0.06	
Thigh length (cm)	Birthweight	0.42	-0.28	0.78	0.22
	Weight at 1	0.18	0.71	0.48	
	Length at 1	0.08	3.78	**<0.001**	
Calf length (cm)	Birthweight	0.37	-0.50	0.62	0.21
	Weight at 1	0.16	1.99	0.05	
	Length at 1	0.07	2.67	**0.009**	

(b)

		Standardized Coefficient β	*t*	*p*	R-square
Stature (cm)	Birthweight	1.34	0.05	0.96	0.11
	Weight at 1	0.69	1.24	0.22	
	Length at 1	0.30	1.08	0.28	
Sitting height (cm)	Birthweight	0.77	0.91	0.37	0.21
	Weight at 1	0.40	2.32	**0.02**	
	Length at 1	0.17	0.70	0.48	
Sub-ischial length (cm)	Birthweight	0.75	-0.84	0.41	0.03
	Weight at 1	0.39	-0.15	0.88	
	Length at 1	0.17	1.21	0.23	
Humerus length (cm)	Birthweight	0.33	-0.61	0.55	0.11
	Weight at 1	0.17	2.20	**0.03**	
	Length at 1	0.07	0.19	0.85	
Forearm length (cm)	Birthweight	0.29	-1.04	0.23	0.12
	Weight at 1	0.15	2.04	**0.04**	
	Length at 1	0.06	0.56	0.58	
Thigh length (cm)	Birthweight	0.47	-0.27	0.78	0.07
	Weight at 1	0.24	0.80	0.42	
	Length at 1	0.10	1.18	0.24	
Calf length (cm)	Birthweight	0.39	-0.50	0.62	0.07
	Weight at 1	0.20	0.42	0.67	
	Length at 1	0.09	1.53	0.13	

v. Discussion

Sexual dimorphism in neonatal and childhood growth is well established (Gasser et al., 2001; Hindmarsh et al., 2002). As expected, the boys were slightly heavier at birth and heavier and taller than girls at one year. The data also show sex differences in several anthropometric variables and indices at age 10 years. Girls had greater sitting height but similar stature to boys, and greater thigh length but similar sub-ischial length to boys. In addition, girls had longer metacarpals than boys. A relatively higher proportion of girls had reached the onset of puberty compared to boys. Consequently, comparisons between the prepubertal and pubertal groups showed more significant differences among girls compared to marginal differences showed in boys. In girls, we found that in early puberty there was a preponderance of appendicular growth compared to axial growth and in distal versus proximal segments.

The current study has also shown sex difference in the associations between early life factors and late childhood growth. After adjustment for pubertal development, boys exhibited a consistent relationship between early life factors (birthweight, and weight and length at 1 year) and late childhood growth parameters while in girls the relationships were less strong and inconsistent. The impact of pubertal development on modifying the manifestations of these associations is unclear, despite statistical adjustment for its effect. A sex specific and marked postnatal effect has been demonstrated by Dennison et al, (2005) who reported a stronger relationship of weight at 1 year with BMC at the lumbar spine and proximal femur in men than women. The mechanism for this differential association is unclear but is further evidence of the influence of sex and possibly sex hormones on these relationships.

Attention to the possible programming of intermediate health outcomes which may be precursors to chronic disease has been suggested (Cooper et al., 2000). Bone fragility and fracture are mediated by changes in bone size and shape which are essential components of strength. Assessing the impact of programming on these intermediate outcomes could shed some light on the relationship between early life events and later bone mass accrual. Gruss (2007) suggested that the length of lower limbs has significant impact on antero-posterior bending forces on the lower limb during the stance phase of human walking. Individuals with longer limbs were shown to incur greater bending moments along the lower limb during the first half of stance phase (Gruss 2007). Given allometric variations between populations and limb segments, the impact of early life factors on relative skeletal size and body shape needs to be further investigated.

Our results show that poor growth during the intrauterine period alters regional segment lengths in both sexes but has marginal effects on body proportions in girls. Given previous evidence for sub-optimal growth in stature (Nyati et al., 2006), the poor association of early life growth with body proportions at 10 years of age is noteworthy. Relative bone lengths indicate proportionality at the given age but a study of the possible impact of early life factors on allometric growth gradients (timing and peak) may offer more insight. Postnatal factors demonstrate long term effect on segment lengths, and consequently the growth trajectory, highlighting the importance of the external environment in nurturing growth. Environmentally induced phenotypic plasticity resulting in long term morphological changes and allometric growth variations is well established in animal experimentation (Crichigno et al., 2012; Lee et al., 1969). Similarly in humans, positive changes in socio-economic status have a positive effect on the relative leg length of a population (Bogin et al., 2002; Louw and Naidoo, 2001). Thus nurture more than nature has pre-eminence in the determination of body phenotype and proportions.

It is likely that postnatal stresses have a greater influence on growth than conditions prevailing during gestation. Cameron et al (2005) found that 9 year old children who were stunted at 2 years were significantly shorter and lighter than non stunted children demonstrating a strong correlation between sizes in infancy and childhood. Similarly, the relative contribution of weight at 1 year to the variation in proximal femur bone area has been shown to be greater than the relative contribution of birthweight (Dennison et al., 2005). Stein et al (2010) have shown that growth failure in the early infant period (birth to 12 months) is more critical in determining adult stature than growth failure in the later toddler period (12-24 months). They suggest that growth failure, which occurs mainly during gestation and in the first two years of life, has a greater influence on adult dimensions than growth failure in any other period (Stein et al., 2010).

Bone mass and strength in later life are significantly associated with peak size and possibly shape attained during skeletal growth. Studies have shown that BMC rather than BMD has an association with birthweight (Javaid and Cooper, 2002; Dennison et al 2005) suggesting that the influence of intrauterine and early life programming on bone mass may be directly mediated through bone size. These studies provide indirect evidence that bone growth trajectory and skeletal size are programmed by pre and postnatal factors. The critical stage for long bone growth is the second trimester of gestation during which time accelerated growth is experienced. Undernutrition in this period will lead to slow rates of cell division which translate into pathology and determine disease in later life (Cooper et al, 2000). Sayer and Cooper (2005) have also suggested the role of paternal influences on the establishment of the early growth trajectory while maternal nutrition is suggested to modify foetal nutrient supply and subsequent bone accretion. Fall et al, (1998) also suggest that the association between early life factors and later bone mineral accrual may be a reflection of the programming of the GH/IGF-1 axis. There are strong suggestions that conditions prevailing in utero and the neonatal period produce a permanent effect altering the sensitivity of the body to GH and cortisol thereby influencing skeletal size (Sayer and Cooper, 2005).

Results from the current study provide evidence for programming of skeletal dimensions but less so for programming of body proportions. There are however several limitations which may make interpretation of the current data more difficult. Firstly, the absence of birth length data does not allow us to differentiate intrauterine from early childhood effects on bone growth. Lastly, the cross-sectional nature of the outcomes that were measured does not allow for observation of programming of relative growth gradients, which would provide a better indication of the final outcome of body proportions. Given also the peri-pubertal state of the sample, the physiological complexities presented by the transition could present limitations in the establishment of the relationships.

In conclusion, ethnic and sex differences in axial and appendicular growth are widely reported globally. These differences point to the possible role of genetic factors in determining the differences in skeletal development between children of different sexes and ethnic origins. However, as stated by Davies et al (2005), this influence may be modified by environmental factors, such as undernutrition, in early life. Previously, we have alluded to the presence of chronic undernutrition and its impact on skeletal growth in South African black children (Nyati et al, 2006). In this sample the genetic influence on the skeletal envelope laid out in utero is likely to have been masked by the sub-optimal environmental conditions prevailing peri- and post-natally. This makes it unlikely for children in the cohort to realize the attainment of peak bone growth and thus the current axial and appendicular body proportions might not be a true reflection of those that might be obtained in more ideal environmental circumstances.

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vii. References

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Chapter 4 Concluding Discussion and Remarks

This research set out to establish patterns of axial and appendicular growth in South African children and to explore the influence of early life programming on the skeletal dimensions. With respect to the main objectives outlined in chapter 1 the following key findings were made.

Table 4-1: Summary of the main outcomes of the study

	Objective	Paper	Main Outcomes
1	Ethnic differences in axial & appendicular dimensions	Paper 1	Black children have longer legs and upper limbs but shorter trunks than white children
2	Sex differences in axial & appendicular dimensions	Paper 1	White girls have longer legs but shorter trunks than white boys Black girls have longer thighs than black boys
3	Influence of differential growth on expression of site-specific bone mass	Paper 1	Regional segment lengths are better predictors of site-specific bone mass Adjusting for regional segment length influenced expression of differences in bone mass
4	Programming of axial and appendicular dimension and proportions	Paper 2	Significant relationship between early life factors and childhood dimensions Postnatal factors have greater influence than prenatal factors

Based on these results both null hypotheses are rejected and the alternative hypotheses accepted. These results appear to give credence to the notion raised in chapter 1 that in spite of prevalence of factors which have a negative influence on bone mass among blacks, the skeletal envelope seems to offer a genetic protection to blacks against fracture. An inquiring mind has to ask the fundamental question; why? In seeking to address this question the current chapter gives emphasis to the description of body morphology in South Africa in the context of the global trends. To get closer to answering the question, the debate about the origin of the worldwide variation in body proportions is discussed. The direct implication of these results on studies comparing population differences in bone mass is also highlighted. Other implications of the results and their contribution to the debate about the influence of growth on health are discussed.

i. Body Morphology in South Africa

This study is the first to describe body morphology in South Africa. The influence of ecological factors in moulding body proportions and establishing clear patterns along ethnic lines has already been discussed. In 1987, James Tanner put forward the widely accepted view of “growth as a mirror of conditions in society”. Tropical populations whether in Africa, Australasia or the Americas exhibit the same dolichomorphic body types characterized by linear body shapes with long legs and relatively shorter trunk. On the contrary, populations from colder regions exhibit a brachymorphic body shape with a larger trunk and relatively shorter extremities.

The study also adds a new dimension to known general growth patterns in South Africa. Previous studies have shown that sub-optimal social and economic conditions experienced by South African black children have had a negative impact on growth (Cameron and Kgamphe 1997; Krynauw et al., 1983; Jacobs et al., 1988; Woods et al., 1978; Smit et al., 1967). However, the impact of these conditions on body proportions has, to the best of my knowledge, not been investigated in relation to the black and white populations in this country. A number of studies have looked at linear segment dimensions in both living and skeletal samples (Louw and Naidoo 2001; Steyn and Iscan 1999; Price et al., 1987; Smit et al., 1967). None have looked at relative lengths and allometric growth. Given also the observed growth differences between South African racial/ethnic groups, statistical adjustment for stature to obtain relative limb lengths was a new approach introduced in the current study.

Adjusting for differences in height is imperative in light of the suggested greater susceptibility of the legs to negative environmental influence (Malina et al., 1987). A cephalo-caudal growth gradient which ensures the preservation of the brain and vital organs in periods of limited resources has been observed. In 1951, Leitch noted that "…it would be expected on general principles that children continuously underfed would develop into underdeveloped adults…with normal or near normal size head, moderately retarded trunk and relatively short legs" (p145, Leitch 1951). Thus through the body's energy redistribution mechanisms, leg growth is compromised in favour of more cranial sections of the body.

In support of the this theory, a recent study by Louw and Naidoo (2001) looking at a cohort of mixed-race children in Cape Town showed the impact of improved socio-economic status (SES) on among other variables stature, sitting height and leg length. Albeit not discussed in the paper and significance values not provided, the graphs show increased stature and leg length while sitting height was similar between the high and the low SES groups. A similar study comparing Mayan American children with those living in Guatemala found increased stature and relative leg length among the migrant population (Bogin et al., 2002).

In keeping with trends observed worldwide, body shapes in South Africa are divided between dolichomorphic and brachymorphic phenotypes for black and white children respectively. A differentiation between lower and upper limb dominance for blacks and trunk dominance for whites was observed. Stature-adjusted means of limb lengths show that black boys have longer legs and humerii but shorter trunks than white boys. In addition, black children have longer forearms than white children, and girls have longer thighs than boys. Both distal and proximal segment of the upper limb and the distal segment of the lower limb were relatively longer in black than white children. Notwithstanding the diverse geographic origins of these groups, the perpetuation of these patterns despite long term exposure to a common climate and environment brings in the question of nature versus nurture. In addition, given that notable changes in body proportions were observed by Bogin et al (2002) in the American Mayan population over a few decades shows the high plasticity of the body proportions in relation to environmental changes. Thus it has become of great import to consider the degree of genetic and environmental influences on population variations in body proportions.

ii. Genetic and Environmental Influences

By their very nature human growth & development processes are a product of complex biological phenomena and the relative importance of genetic and environmental factors can be easily confounded. Growth processes are fuelled by an interaction between these factors through their influence on endocrine regulatory processes. “Growth and development phenotypes also are referred to as being complex traits, meaning that genes at a few and perhaps several loci contribute to the variation observed in the trait, as do environmental factors, possibly through interaction with those genes” (Towne et al 2002). The interplay between genetics and the environment has been subject of discussion in relation to body proportions.

Based purely on observed differences between ethnic groups albeit in diverse geographical and ecological environments, the importance of genetics has been suggested. According to Eveleth and Tanner (1990) the ethnic differences in body proportions “are certainly genetic in origin, for better environmental circumstances appear to produce relatively longer, not shorter, legs”. In addition, long-standing observations of racial or ethnic differences in height seem to give credence to the preeminent influence of genetics in the pattern and tempo of growth. Variations in adult stature have been found even among geographically and socio-economically closely-related populations.

Silventoinen et al (2003) found significant differences in mean body height among European countries. Mean height ranged from 177 cm and 163 cm in Italy to 184 cm and 171 cm in Netherlands among men and women respectively. Differences in body shape among Chinese, Japanese, Korean and Taiwanese adults have also been observed (Yu-Cheng et al 2004). A number of studies have sought to establish the existence of a “genetic potential” in absolute growth and body proportions which can be enhanced or subverted by existing environmental conditions. The observed phenotypic differences in body proportions along ethnic and racial lines, despite centuries of migration to varied ecological environments, also seem to lend support to the notion of genetic potential.

To the contrary, the plasticity of height, body proportions and body composition is given as an argument against the existence of a genetic potential (Bogin et al 2001). Differences in relative leg length between children from the same population but varied socio-economic backgrounds have been cited as evidence of a greater environmental influence compared to genetics. In a review by Bogin et al (2001), several studies showing a relationship between growth in stature and legs, and changes in the socio-economic environment have been cited as evidence of the plastic nature of human size. Positive secular change in relative leg length of Japanese children has been previously demonstrated (Tanner et al 1982). Initially attributed to genetic influence, the diminished difference in relative leg length between Japanese and British children due to positive secular change has strengthened the argument of environmental influence (Bogin et al 2001).

In a study of women of low SES living in Chiapas Mexico, Gurri and Dickson (1990) found that 80% of the variance in stature was attributed to socio-economic region while 20% was attributed to ecological region. In a reanalysis of data previously published by Eveleth and Tanner (1990), Bogin et al (2001) evaluated the influence of age, sex, race (based on area of origin), region, world (level of industrialization), SES and SES*world on variations in body proportions. Only 3.6% of the variance was due to race; with a similar contribution by SES. The modest contribution by race to the variance was interpreted to highlight the minimal influence of genes to body proportion differences.

These analyses present strong support for the significant, and in some cases the sole contribution of the environment to population variations in size. Notwithstanding, differences in relative leg length due to varying socio-economic conditions cannot be promoted to understate the contribution of genetics to population variations in body proportions. A number of varied external influences ranging from lifestyle and nutrition to geographical location and climate are grouped together under the banner of environment factors. This collective view may present a bias in the interpretation of the influence of the environment on growth. Lifestyle and socio-economic changes which may have short-term influence may differ in their interaction with genetic influences compared to the physical environment. Recent advances in genetic epidemiology of growth using sophisticated methods and techniques have been applied to investigate the question of genes and growth.

According to Towne et al (2002), the control of genes on growth extends beyond the impact on the heritability of the physical size but also influences the time and tempo of maturation. Population-based association studies or family-based quantitative trait linkage studies are the two basic strategies used to evaluate the involvement of genes in the regulation of growth and development (Towne et al 2002). To this end, quantitative genetic analysis such as family studies within populations can provide a clear indication of heritability of certain traits although the influence of the common environment has to be taken into account.

In a study to “evaluate the extent of the possible genetic effects on the inter-individual variation of a number of body configuration indices amenable to clear functional interpretation” a significantly higher genetic influence was reported (Livshits et al 2002). Two “ethnically different pedigree” samples, Turkmenians (Central Asia) and Chuvasha (Volga riverside, Russian Federation), were studied on 3 traits i.e. integral index of torso volume, an index reflecting a predisposition of body proportions to maintain a balance in a vertical position and an index of skeletal extremities volume. According to Livshits et al (2002), 40 to 75% of the inter-individual variation in the traits after adjustment for age and sex were due to genetic effects. Heritability of physical traits has also been investigated (Silventoinen et al 2003, Ermakov et al 2005). Analyses from twin data from 8 European countries showed high levels of heritability ranging 0.87 to 0.93 for men and 0.68 to 0.84 for women.

Albeit non-quantitative, the effect of heterosis/gene flow in a geographically and socially secluded community was also assessed by comparing growth differences between hybrid and non-hybrid girls (Khongsdiery and Mukherjee 2003). Significant differences in size and the tempo of growth of height and its components, sitting height and sub-ischial length, after adjustment for household income were observed. According to Khongsdiery and Mukherjee (2003), sub-ischial length was similar at many stages of the growth period indicating a lesser susceptibility to heterosis. In addition, all differences were observed above the age of six as children below 5 years of age are more sensitive to environmental factors like nutrition and infections than to genetic factors ((Khongsdiery and Mukherjee 2003).

The genetic and environmental underpinnings of the size and shape resulting from complex biological processes may be difficult to decipher. “The ultimate size and shape that a child attains as an adult is the result of a continuous interaction between genetical and environmental influences during the whole period of growth” (Eveleth and Tanner 1990, p 176). The body shape of South African children after controlling for differences in stature reflects a distinct racial pattern similar to those observed in other parts of the world. On the other hand, significant effects of environmental stresses on growth are clearly defined in the growth differences between white and black children. Whether this supports the genetic argument or is a confirmation of diverse origins of the South African population is a subject of further study. Ostensibly, these differences find expression in ethnic differences in skeletal form and bone architecture which have a significant impact on manifestation of bone fragility in later life.

iii. Body Form and Skeletal Protection

These data indicate a physically disparate appendicular skeletal design, provides better protection against fracture for black children. Marked differences in geometry, histomorphometric analyses and bone strength favouring black children have been observed (Schnitzler et al 2009). This despite the smaller lean mass and muscle cross-sectional area as well as lower physical activity and calcium intake levels among the black children (McVeigh et al, 2004; Vidulich et al, 2006).

A translation of these differences into benefits against fracture risk has been shown (Thandrayen et al 2009). Significant differences in the fracture rates between the black and white ethnic groups were observed with a prevalence of 41.5% for white children, and only 19% for black children.

According to Mickelsfield et al (2011) the skeleton of black children appears to be more resistant to bending and torsional forces. Given the strong association between lean mass and diaphyseal cortical bone area (Mickelsfield et al 2011), the higher geometric parameters and strength in the appendicular skeleton observed in black children appear to be a direct result of limb-dominant body phenotype. Black children were shown to have significantly greater osteoid thickness, endocortical wall thickness and cortical thickness than white children (Schnitzler et al 2009). The polar strength-strain index was 10–20% greater in black children despite thinner cortices and a larger marrow cavity in black children (Mickelsfield et al 2011).

The strength observations in South African children are in agreement with those made in the United States (US) where the bone strength index was 47% higher in African American and 32% higher in the Hispanic children compared to Caucasian (Wetzsteon et al 2009). These differences were observed despite a smaller total bone area in the African American children compared to Caucasian children. Unlike in the South African study (Mickelsfield et al 2011), where significant ethnic differences in bone strength were not found at the metaphyseal sites of the radius and tibia, differences were found at both sites in the US study (Wetzsteon et al 2009). Leonard et al (2010) also found greater cortical dimensions and mineral content in black compared to white children. Although conferring significant protection against fracture in black children from such diverse geographical locations (South Africa and USA), the mechanisms for the expression of this strength may differ. Different mechanisms or factors influencing bone mass accretion and subsequent bone loss in black and white SA women have been suggested (Mickelsfield et al 2011)

These differences do not appear to be purely a result of environmental plasticity given the diverse conditions prevailing in South African and in developed countries where similar trends are observed. Mickelsfield et al (2007) compared whole body bone mineral content (WBBMC) differences between South African black, white and mixed-race children and those found in African American and Caucasian American children. In both samples (SA & US) black children had significantly greater WBBMC than white children while SA children of both races had greater WBBMC than US children of both races. Thus there is a clear indication of both genetic and environmental influences on bone mineral accrual.

iv. Influence of Body Morphology on Expression of Differences in BMD

As highlighted in chapter 1 and above, the higher bone strength and lower fractures in blacks than whites is not consistent with comparative measurements of bone mass. Given the wide use of dual x-ray absorptiometry (DXA) in assessing population differences in bone mass, the possible impact of this differential growth on the expression of ethnic and sex difference in BMC, BMD and bone area (BA) has to be explored. The intrinsic size-related artefact in BMD measured by DXA can lead to erroneous interpretation of bone mass (Rauch and Schoenau 2001;

Gafni and Baron 2004; Leonard et al 2004). Using multiple regression analyses, the relationship between absolute size as measured by stature, regional segment lengths and bone mass indicators was evaluated. The results show that regional segment lengths are better predictors of site-specific bone mass than stature. Thus, a significant amount of the variance in bone mass measured by DXA can be explained by differences in regional bone size rather than in stature.

The stronger relationship between bone mass and regional segment lengths indicates a greater sensitivity of regional size to bone mass compared to body stature. This is not unexpected when the population differences in allometric growth and body morphology are taken into account. Thus comparisons based on absolute size could potentially mask or accentuate differences in bone mass considering that individuals with similar stature could possess differing regional dimensions. This likelihood was investigated by exploring the impact using different models of adjustment would have on the expression of bone mass differences. Adjustment for differences in body size in the measurement of bone mass has been suggested given the relationship between BMC and size (Ross et al 1996, Warner et al 1998). However, the influence of population differences in body proportions on the size-related artefact in measurements obtained from DXA has not previously been investigated.

Ethnic and sex differences in BMC, BMD and BA were evaluated after adjustment for weight, weight and body height (stature), and weight and regional segment lengths. The purpose of this analysis was to assess whether adjusting independently for the three combinations of measure of size would result in any alteration in the presence, level and direction of bone mass difference. Significant alterations in the expression of ethnic differences were observed while sex differences in both black and white children were marginally affected by the type of adjustment model. The alterations between stature adjusted and regional segment length adjusted differences in bone mass were observed between black and white children of both sexes and not between boys and girls of the same race. This in itself is a considerable observation that could indicate the important contribution of heterogeneous body shape in expression of bone mass differences. Taking into account the closeness of body proportions between prepubertal girls and boys of the same race, differences would be accentuated or attenuated by a similar degree.

The second observation is that in boys, adjustment for weight only produced similar outcomes as adjusting for weight and regional segment lengths while in girls the two adjustments yielded different results. The meaning of these results is unclear and further investigations are needed to unpack these relationships. Of the total measured indicators of site-specific bone mass, alterations between stature adjusted and regional segment length adjusted differences were observed in three out of twelve in boys. In girls however, substantial alterations were observed in eight out of the twelve indicators, representing two thirds of the measures. The influence of sex hormones and early onset of physiological changes due to pubertal development should be investigated. The results indicate that adjusting for body stature or regional segment lengths can produce different outcomes for the same variable. Differences observed after adjustment for weight and stature disappeared after adjustment for weight and regional segment lengths. Thus absolute size has a tendency to accentuate bone mass differences in this sample. These findings warrant further investigations into new models of adjustment for difference in size when measuring bone mass.

The use of appropriate reference standards for the correct interpretation of DXA output in children has been advocated (Gafni and Baron 2004).). However, several challenges in the interpretation of the data have been identified including the appropriateness of normative data for small- or large-for-age children (Gafni and Baron 2004). Data are limited in addressing interpretation problems related to skeletal size. The influence of allometric growth on this limitation needs to be investigated. Body size, sex and ethnicity were among the critical factors that were identified to lead to erroneous interpretation and misdiagnosis of low bone mass in children (Gafni and Baron 2004).

Abnormally low areal BMD in children with short stature is attributed to smaller bone size despite normal volumetric density. When looking at ethnic differences, the tempo of growth of mass and size of the same region needs to be taken into serious consideration. In our sample, black children demonstrated advanced appendicular skeletal growth and thus are likely to accentuate differences in bone mass. This contention is supported by the results which show that after adjustment for weight and regional segment lengths, some of the differences disappeared. These differences could be directly linked to differences in bone size and not a reflection of differences in bone density. The introduction of peripheral quantitative computed tomography (pQCT) in this sample, albeit not within the scope of the current analysis, can provide critical information on the relationship between bone size and density. Exploring the longitudinal patterns in these relationships will further elucidate the mechanisms of development in bone strength and the impact of size and body morphology. In addition, these analyses were performed on data from growing children. Further investigations are required to establish these trends in adults. Ongoing bone growth and mineral accrual present a complication in the interpretation of DXA (Soyka et al 2000 in Gafni and Baron 2004).

v. Influence of Intrauterine & Postnatal Environment on Body Proportions

An aspect of the environment suggested to play an important role in fashioning childhood growth and possibly body proportions includes factors in operation during the early life growth period. The intrauterine and postnatal growth periods are critical periods for laying the foundation of the growth trajectory and maximizing bone size. Maternal, physiological and nutritional insults during this period have lasting effects on body size (Wingerd and Schoen 1974; Rasmussen and Irgen 2003; Adair 2007; Stein et al 2010) and by extension bone size. Thus understanding the contribution of the environmental influences prevailing in this period on the development of body shape could broaden the understanding of factors regulating skeletal form.

The environmental and genetic influences described above as contributing to the final form and architecture of the skeletal envelope could be moulded by the intrauterine environment. Indirect evidence for this has been provided by the established association between birthweight, weight at 1 year and bone mass in later life (Dennison et al, 2001; Dennison et al., 2005; Baird et al 2011). A substantial proportion of the variance in bone mass within the general population cannot be explained by known genetic and environmental factors. Evidence exists that appears to link the residual variance in bone mass to pre- and post-natal growth (Cooper et al 2006).

Much of the relationship explored between early life growth and childhood or adult skeletal development has focused on bone mass. There is scarcity of studies looking at the influence early life growth factors have on size and skeletal proportions. Intrauterine programming of antecedent factors of osteoporosis such as bone size is critical in establishing the mechanisms for the programming of osteoporosis. The relationship between measures of prenatal and early postnatal growth with height in late childhood and adulthood has previously been described. Birth length and length at 12 months were the strongest predictors of adult height (Stein et al 2010). Similarly, birthweight accounted for 19.4% of the variability in height at 5 years of age and 10.3% at 7.8 years of age (Elia et al 2007). According to Stein et al (2010), these results demonstrate the significant and long-term effect that growth failure prior to age 12 months has on adult stature. In light of these data, the effect of these early life growth parameters on the different components of stature and lengths of long bones is worthy of consideration. Analyses were performed to investigate the influence of the pre- and postnatal growth parameters on body proportions and bone size. Positive associations, albeit inconsistently, were observed between birthweight, weight and length at 1 year with stature, sitting height, sub-ischial length, and limb long bone lengths.

In boys, while birthweight had a significant association with sub-ischial length, a measure of leg length, yet none of its components (thigh and calf lengths) were significantly associated with birthweight. Similarly, the components of the stature were not consistently associated with weight at 1 year in girls despite the positive association of stature. If chance could be ruled out as a possible explanation for these trends, the results could indicate the importance of allometry in the influence early life factors on growth. This notion could be supported by the positive association between weight at 1 year and the lower-to-upper body proportion observed in girls. Although marginal, these associations indicate a possible differential influence of early life factors on regional segment lengths thus possibly influencing body shape. During the early life growth period, the external environment seems to have a greater influence on body proportions than the more protected intrauterine environment. These results are consistent with the observations that body shape (largely affecting leg length) can be altered in adaptation to nutritional deficiency or surplus mentioned previously.

Stronger and more inclusive associations were observed with postnatal growth than birthweight. However as mentioned in chapter 3, the absence of birth length data presents a limitation in the interpretation of these findings. These observations are in keeping with the multiple regression analyses which showed that length at 1 year was a strong predictor of regional segment lengths in boys while no associations were found in girls. Surprisingly, sexual dimorphism in the expression of the relationships was observed. Of the total of nine bone mass variables measured, significant associations with birthweight were observed with five for boys and none for girls. Similarly, length at 1 year had a positive association with only one variable for girls compared to eight for boys while with weight at 1 year more associations were observed in girls with six variables compared to nine in boys. The influence of the earlier onset of puberty among girls is a possible reason for this disparity despite adjustment for its influence. Given the nominal nature of the data (0 for prepubertal and 1 for pubertal), statistical adjustment for pubertal development could be inadequate. However more research is needed to establish the source of these sex differences.

In keeping with Stein et al (2010), these results suggest relatively greater importance of the postnatal growth compared to intrauterine growth as measured by birthweight. This could indicate the degree of influence of the factors which regulate growth at these two periods. Bier (2008) suggests that there are different factors at play in regulating pre- and postnatal growth. Intrinsic and extrinsic factors are involved in shaping the tempo and pattern of growth in utero. However lack of secular change in birthweight despite improvements in nutrition intake appears to suggest a limited influence of the extrinsic factors (Bier 2008). Differences in birthweight are not purely a result of environmental stresses prevailing in utero. Differing degrees of influence in the variation in birthweight have been suggested; 0 to 50% foetal genes, 27 to 50% for maternal factors, and 8 to 43% random environmental factors (Towne et al 2002).

A plausible interpretation of these statements is that genetic influences play a stronger role in intrauterine growth than environmental factors while the opposite in postnatal growth is true. The variable relationship between intrauterine growth and size and shape at birth appears to support this interpretation (Hindmarsh et al., 2002; Milani et al., 2005). Anthropometric measures assessed by ultrasound at 20 and 30 wks of gestation were poor predictors of birthweight, length and head circumference (Hindmarsh et al., 2002). Milani et al, (2005) suggest that neonatal growth indicators such as birthweight, birth length and head circumference can be attributed to differences in growth velocity emerging during early gestation. Thus, the use of birthweight alone as a measure of intrauterine growth may be a weakness of the current study particularly that the measured outcomes are skeletal growth. Length at 1 year was a better predictor of linear growth at 10 years than both weight at 1 year and birthweight.

vi. Concluding Remarks

The study has highlighted differences in body morphology among South African children and the possible implications on expression of bone mass. Black children had longer limbs but shorter trunks than white children. Regional segment length were a significant predictor of site-specific bone mass than stature. In black boys birthweight had positive but weak associations with stature and regional segment length while in girls the association were marginal. In contrast, weight and height at 1yr had strong associations with stature and regional segment lengths. The size, shape and mass of bone obtained at the cessation of bone development is an outcome of the accumulative growth & development processes which can be influenced at various stages of the human growth life cycle. Notwithstanding conflicting evidence obtained through DXA observed in other studies, several aspects of skeletal development on this sample lend support to the notion that the differential growth observed in this study predisposes to differential susceptibility to fracture.

a. Limitations

There were no major limitations to the study save those highlighted in chapters 2 and 3 and further highlighted here. The cross-sectional nature of these analyses also presents a limitation with obtaining a full understanding of the trends and whether longitudinally the similarities with children elsewhere are maintained. There were several limitations relating to sample size which could compromise the interpretation of the data. As highlighted in chapter 2 there was a small number of white compared to black participants attributed to the enrolment protocol within the Birth to Twenty study.

With regards to chapter 3, absence of data for white children was also a limitation. The influence of ethnicity on the relationships between early life factors and childhood growth parameters could not be evaluated. This is critical given the clear ethnic distinction in the growth patterns. The significance of the absence of birth length data was also highlighted in chapter 3.

b. Implications

The data from this research shows that the human body is not a homogeneous growth unit and that various skeletal segments display unique growth patterns which are in turn influenced by sex and ethnicity. Thus each skeletal segment will respond differently to external influences and the responses will vary between ethnic and sex groups. The implications of these observed differences are far-reaching. From an anthropological perspective, standards for estimation of stature from skeletal remains need to consider secular changes in body proportions. With increasing upward social mobility among black South Africans, it is expected that improved socio-economic condition will have an impact on body stature through improvement in leg length. It was shown in this and other studies that growth in the legs is compromised by environmental stresses more than the growth of other segments. Secular changes in the relative leg length will thus mandate a review of existing standards. Even from a public health perspective, the general use of BMI for assessment of body composition may be in question. Previous studies have shown that the leg dominant phenotype is more sensitive to existing methods for working out BMI resulting in overestimation of fatness. Both of the above call into question the use of international standards for assessment of growth among South Africans. From a socio-ecological perspective, the leg dominant phenotype offers a selective advantage in mobility with implication for success in modern-day sports such as athletics.

c. Future research

Albeit presenting only cross-sectional analysis, this study has given insight into existence of differential patterns between population groups and between the different skeletal segments of the same individual. Significant opportunities for further study of these patterns exist. The longitudinal nature of the Birth to Twenty Programme makes it possible to explore these patterns further and evaluate the influence of puberty on axial and appendicular growth. The influence of early life growth on the growth rates of the axial and appendicular skeleton as opposed to proportions at a given age could add further insight into these relationships. In addition future research could address the following areas:

- Physiological control of differential growth – to create a better understanding of the hormonal control of allometric growth and the factors that influence it.
- Given the difference in allometric growth and its implications for clinical, anthropological and forensic application, local growth standards for limb segments may be a necessary
- Modelling the effect of size on ethnic and gender differences in bone mass – research into mathematical models for expression of bone mass to further understand the influence of regional bone size in population difference in site-specific bone mass

- Intra-population variation in body proportions – investigating whether taller children exhibit differing patterns in body proportions and whether socially mobility has any influence on body proportions as highlighted in other studies.

d. Conclusion

In conclusion, the outcomes of this research are:

(i) The axial and appendicular patterns are global thus appearing to support the notion that they are perpetuated by genetics albeit that their origin may be environmental

(ii) There are ethnic & sex differences in skeletal maturation thus leading to differential susceptibility to fracture as partly indicated by different fracture rates between black and white children

(iii) The body does not grow homogeneously and proportions differ, thus current adjustment models for body size may not be adequate in addressing the major methodological basis for establishing population differences in bone mass

Chapter 5 References

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