

https://dspace.org/

Fractures and bone mass in urban South African children of different ethnic backgrounds

Thandrayen, Kebashni

2014-08-25
http://hdl.handle.net/10539/15246

Downloaded from a DSpace repository. https://dspace.org/

Fractures and bone mass in urban South African children of different ethnic backgrounds

KEBASHNI THANDRAYEN

A thesis submitted to the Faculty of Health Sciences,

University of the Witwatersrand

For the degree of Doctor of Philosophy

Student No: 9401091M

Human Research Ethics Committee Clearance number: M071132

DECLARATION

I, Kebashni Thandrayen declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy in the branch of Paediatrics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

Signature …….

……day of ……..., 2014

DEDICATION

I dedicate this thesis to my son, Aryan Pillay, with all my love and nurturing as a motivational inspiration in his life and his future.

THESIS MATERIAL

Original articles

The following original articles resulted from the research conducted for the PhD:

1. **Thandrayen K**, Norris SA, Pettifor JM. Fracture rates in urban South African children of different ethnic origins: the Birth to Twenty cohort. Osteoporos Int. 2009 Jan;20(1):47-52.

   Student's contribution to the paper: Design of the study, data management including cleaning and analysis, writing of the manuscript.

2. **Thandrayen K**, Norris SA, Micklesfield LK, Pettifor JM. Heterogeneity of fracture pathogenesis in urban South African children: the Birth to Twenty cohort. J Bone Miner Res. 2011 Dec;26(12):2834-42.

   Student's contribution to the paper: Design of the study, data management including cleaning and analysis, writing of the manuscript.

3. **Thandrayen K**, Norris SA, Micklesfield LK, Pettifor JM. Fracture patterns and bone mass in South African adolescent-mother pairs: the Birth to Twenty Cohort. Osteoporos Int. 2013 Aug 14. [Epub ahead of print].

   Student's contribution to the paper: Design of the study, data capturing, data management including cleaning and analysis, writing of the manuscript.

Conference proceedings

1. Childhood fracture rates amongst black, white, mixed ancestry and Indian South Africans: the Birth to Twenty cohort. **Thandrayen K**, Norris SA, Pettifor JM. Poster presentation at the Fourth International Conference on Children's Bone Health, 21st - 24th June 2007, Montreal Canada.

2. Fracture rates in urban South African children of different ethnic origins: the Birth to Twenty cohort. **Thandrayen K**, Norris SA, Pettifor JM. Oral presentation at the 13th NOFSA Congress, 12-15th April 2008, Cape Town

3. Fracture rates in urban South African children of different ethnic origins: the Birth to Twenty cohort. **Thandrayen K**, Norris SA, Pettifor JM. Oral presentation at the Faculty of Health Sciences Research Day, 20 August 2008, University of the Witwatersrand, South Africa.

4. Heterogeneity of fracture pathogenesis in urban South African children: the Birth to Twenty cohort. **Thandrayen K**, Norris SA, Pettifor JM. Poster presentation at the Fifth International Conference on Children's Bone Health, 23rd -26th June 2009, Cambridge, United Kingdom.

5. Heterogeneity of fracture pathogenesis in urban South African children: the Birth to Twenty cohort. **Thandrayen K**, Norris SA, Micklesfield LK, Pettifor JM. Oral presentation at the 14th NOFSA Congress, 12-13th April 2010, Durban.

6. Association of BMI with fracture risk and bone mass in urban South African children: The Birth to Twenty cohort. **Thandrayen K**, Norris SA, Pettifor JM. Oral presentation at the 15th NOFSA Congress, 19-22nd April 2012, Cape Town

7. Fractures and bone mass in children. **Thandrayen K**, Norris SA, Pettifor JM. Oral presentation at the 15th NOFSA Congress, 19-22nd April 2012, Cape Town.

8. Association of BMI with fracture risk and bone mass in urban South African children: The Birth to Twenty cohort. **Thandrayen K**, Norris SA, Pettifor JM. Oral presentation at the Faculty of Health Sciences Research Day, 19 September 2012, University of the Witwatersrand, South Africa.

9. Fracture patterns and bone in South African adolescent-mother pairs: The Birth to Twenty Cohort. **Thandrayen K**, Norris SA, Micklesfield LK, Pettifor JM. Oral presentation at the 6th International Conference on Children's Bone Health, 22nd -25th June 2013, Rotterdam, Netherlands.

Awards

1. Sanofi Aventis travel award from the Society for Endocrinology, Metabolism and Diabetes of South Africa for the best original paper in the field of osteoporosis received in 2009 for the paper "Fracture rates in urban South African children of different ethnic origins: the Birth to Twenty cohort. **Thandrayen K**, Norris SA, Pettifor JM. Osteoporos Int. 2009 Jan;20(1):47-52"

2. Faculty Research prize, the most prestigious prize awarded by the Faculty of Health Sciences in 2012 for the paper: "Heterogeneity of fracture pathogenesis in urban South African children: the Birth to Twenty cohort. **Thandrayen K**, Norris SA, Micklesfield LK, Pettifor JM. J Bone Miner Res. 2011 Dec; 26(12):2834-42".

3. New Investigator Award on the occasion of the 6th International Conference on Children's Bone Health, 22nd-25th June 2013, Rotterdam, Netherlands for best oral abstract "Fracture patterns and bone mass in South African adolescent-mother pairs: the Birth to Twenty Cohort".

Research Grants

1. Faculty Research Committee Individual Research grant (2008,2009)

ABSTRACT

Introduction:

Fracture rates in childhood are as high as those in the elderly. Recent research has been undertaken to understand the reasons for this, but there is little information available on ethnic differences in childhood fracture rates.

Aims:

1) To determine the incidence or rates of fractures, the common sites of fractures, the causes of fractures and grades of trauma causing fractures in urban South African children of different ethnic groups from birth until 17/18 years of age.

2) To investigate the association between fracture prevalence, bone mass and physical activity in South African children.

3) To assess associations of fracture prevalence and bone mass in adolescents with maternal fracture history and bone mass and sibling fracture history.

Design:

Using the Birth to Twenty longitudinal cohort of children, we obtained retrospective information on fractures and their sites from birth to 14.9 years of age on 2031 participants. The ethnic breakdown of the children was black (B) 78%, white (W) 9%, mixed ancestry (MA) 10.5% and Indian (I) 1.5%.

Using the Bone Health cohort of the Birth to Twenty longitudinal study, we retrospectively obtained information of lifetime fractures until age 14.9 years in 533 subjects. Bone mass (measured by DXA), anthropometric data, physical activity scores and skeletal maturity were obtained at age 10 and 15 years. Comparisons were made between those who did and did not fracture within the same sex and ethnic groups.

The third component of the thesis utilized data from 1389 adolescent-biological mother pairs of the Birth to Twenty (Bt20) longitudinal study. Questionnaires were completed on adolescent fractures until 17/18 years of age and on sibling fractures. Biological mothers completed questionnaires on their own fractures prior to the age of 18 years. Anthropometric and bone mass data on adolescent-biological mother pairs were collected.

Results:

Twenty two percent of children had sustained a fracture one or more times during the first 15 years of life (males 27.5% and females 16.3%; $p<0.001$). The percentage of children fracturing differed between the ethnic groups (W 41.5%, B 19%, MA 21%, I 30%; $p<0.001$). Of the children reporting fractures, 20% sustained multiple fractures. The most common site of fracture was the upper limb (57%).

In the second component of the thesis, white males who fractured were found to be significantly taller (10 years $p < 0.05$), more physically active (15 years $p < 0.01$) and had higher lean body mass (10 years $p=0.001$; 15 years $p<0.05$) than those who did not fracture; while white females, who fractured, were fatter (10 and 15 years $p< 0.05$), than their non-fracturing peers. White males who fractured had greater BA (bone area) and BMC (bone mineral content) at most sites at 10 and 15 years; BA and BMC were no different between

fracturing and non-fracturing children in the other ethnic groups. No anthropometric or bone mass differences were found between black children with or without fractures.

The third component of the thesis showed that an adolescent's risk of lifetime fracture decreased with increasing maternal lumbar spine (LS) BMC (24% reduction in fracture risk for every unit increase in maternal LS BMC Z-score) and increased if they were white, male or had a sibling with a history of fracture. Adolescent height, weight, male gender, maternal BA and BMC, and white ethnicity were positive predictors of adolescent bone mass. White adolescents and their mothers had a higher fracture prevalence (adolescents: 42%, mothers: 31%) compared to the black (adolescents: 20%, mothers: 6%) and mixed ancestry (adolescents: 20%, mothers: 16%) groups.

Conclusion:

More than twice as many South African white children fracture compared to black and mixed ancestry children. This is the first study to show ethnic differences in fracture rates among children; a pattern that is similar to that found in South African postmenopausal women. The factor associated with fractures in white boys appears to be participation in sports activities, while in white girls obesity appears to play a role. We were unable to find any factors that could explain fractures in black children. Unlike the findings of some other studies, fractures in these children were not associated with lower bone mass or reduced skeletal size.

Maternal bone mass also appears to play a role in determining fracture incidence in children, as the mother's bone mass has a significant inverse association with their off-springs' fracture risk throughout childhood and adolescence. Furthermore, there is a strong familial component in fracture risk among South African adolescents and their siblings, as evidenced by the

increased risk of fracture in siblings of index children who have fractured during childhood and adolescence.

Differences in fracture rates and bone mass between families and individuals of different ethnic origins may be due to differing lifestyles and/or genetic backgrounds.

ACKNOWLEDGEMENTS

I would like to extend a very heartfelt thank you to my brilliant mentor and supervisor Professor John Pettifor for his endless support, encouragement, supervision and motivation on the drafts of this PhD, publications and presentations.

I am gratefully thankful to Professor Shane Norris for his excellent supervision on the drafts of this PhD and publications that have arisen from this thesis.

I thank Dr Lisa Micklesfield for her tremendous input and support into the publications that have arisen from this thesis.

I also would like to acknowledge the advice that I have received from Prof Elena Libhaber in the statistical analyses for this thesis and to Harry Mainwaring for his assistance in the retrieval of certain aspects of data.

I am very grateful to all the participants and their families in this study; and the entire DPHRU team which includes interviewers, technicians, clerical workers, research scientists, nurses and receptionists. Special thanks to Thabile Sibiya, Elize Tsoeu and Elizabeth Wolff for all their help and support.

Finally, I would like to thank my family and friends, without your support, encouragement and love this would not have been possible.

TABLE OF CONTENTS

	Page
Declaration	ii
Dedication	iii
Thesis material	iv
Original articles	iv
Conference proceedings	v
Awards	vi
Research grants	vii
Abstract	viii
Acknowledgements	xii
Table of contents	xiii
List of tables	xvii
List of figures	xxi
List of abbreviations	xxiv
Preface	xxvii
Chapter 1: Literature review	**1**
1.1 Epidemiology of fractures in childhood	1
1.2 Bone compartments and the various types of bone density	7
1.3 Bone mass in children	8
I. Dual energy x-ray absorptiometry	10

II. Peripheral quantitative computed tomography 15

1.4 Factors associated with childhood fractures and the association of fractures with bone mass 18

1.4.1 Low bone mass 19

1.4.2 Heritability/genetics 21

1.4.3 Maternal and early life influences 23

1.4.4. Nutrition 27

1.4.5 Obesity 30

1.4.6 Puberty 34

1.4.7 Exercise 40

1.4.8 Vitamin D status and its seasonal variation 48

1.4.9 Socioeconomic status 50

1.5. Ethnic differences in fractures and bone mass in children 53

1.7 Summary of the literature review 56

1.7 Gaps in the literature 61

Chapter 2: Study methods **63**

Aims 63

Objectives 63

Study hypotheses 64

Study population 64

Study subjects 67

Methods 68

Statistical analyses 72

Chapter 3: Fracture patterns in urban South African children of different ethnic origins **75**

Results 76

Discussion 87

Summary of major findings 92

Chapter 4: Heterogeneity of fracture pathogenesis in urban South African children **93**

Results 94

Discussion 113

Summary of major findings 119

Chapter 5: Fracture patterns and bone mass in South African adolescent-mother pairs **120**

Results 121

Discussion 136

Summary of major findings 142

Chapter 6: Summary and Conclusion **143**

Summary 143

Aim of the thesis 143

Summary of the objectives, hypotheses and key findings 144

Strengths of the thesis 145

Limitations of the thesis 149

Future research 150

Implications of the study findings 152

Conclusion 154

References 156

Appendices

Appendix A (Ethics clearance certificate)

Appendix B (Year 15 adolescent fracture questionnaire)

Appendix C (Year 17/18 adolescent fracture questionnaire)

Appendix D (Sibling fracture questionnaire)

Appendix E (Biological mother fracture questionnaire)

Appendix F (Fracture verification questionnaire)

Appendix G (PDF of manuscript: Fracture rates in urban South African children of different ethnic origins: the Birth to Twenty cohort)

Appendix H (PDF of manuscript: Heterogeneity of fracture pathogenesis in urban South African children: the Birth to Twenty cohort)

Appendix I (PDF of manuscript: Fracture patterns and bone mass in South African adolescent-mother pairs: the Birth to Twenty cohort)

LIST OF TABLES

		Page
Table 1.1	Fracture prevalence in children and adolescents in different countries	4
Table 1.2	Overview of epidemiological studies describing fractures in children and adolescents	5
Table 1.3	Comparison of studies on obesity versus injury risk in children	30
Table 1.4	Odds ratios of fractures in obese, overweight and increasing weight/BMI children	33
Table 2.1	Grades of trauma causing fractures	68
Table 3.1	The number of children who sustained fractures over the first 15 years of life according to ethnicity and sex in the Birth to Twenty Cohort	77
Table 3.2	Fracture sites by sex	80
Table 3.3	Fracture sites according to the side of fracture (left or right)	81
Table 3.4	Grades of trauma causing fractures by ethnicity and sex until 15 years of age	83
Table 3.5	Sport-related activities associated with fractures by ethnicity and sex until 15 years of age	84
Table 4.1	Fracture rates over the first 15 years of life in the Bone Health Cohort	94

Table 4.2	Predictors of fracture risk at age 15 years in black and white children	96
Table 4.3	Anthropometric and body composition measurements at 10 and 15 years of age of black males and females with and without a history of fractures at 15 years of age	97
Table 4.4	Anthropometric and body composition measurements at 10 and 15 years of age of white males and females with and without a history of fractures at 15 years of age	99
Table 4.5.1	Unadjusted bone area and bone mineral content measurements in white males at 10 and 15 years of age with and without a history of fractures at age 15 years	101
Table 4.5.2	Unadjusted bone area and bone mineral content measurements in white females at 10 and 15 years of age with and without a history of fractures at age 15 years	102
Table 4.5.3	Unadjusted bone area and bone mineral content measurements in black males at 10 and 15 years of age with and without a history of fractures at age 15 years	103
Table 4.5.4	Unadjusted bone area and bone mineral content measurements in black females at 10 and 15 years of age with and without a history of fractures at age 15 years	104
Table 4.6	Bone area and bone mineral content Z scores (adjusted for height and weight) at 10 years of age with and without a history of fractures at age 15 years	105

Table 4.7	Bone area and bone mineral content Z scores (adjusted for height and weight) at 15 years of age with and without a history of fractures at age 15 years	106
Table 4.8	Total physical activity Z scores at 10 and 15 years in children with and without a history of fractures at age 15 years compared to non-fracturing black females	108
Table 4.9	Percentage of obese and overweight children at ages 10 and 15 years in the Bone Health Cohort	109
Table 4.10	The proportions of children with overweight or obesity at 10 and 15 years in those that have or have not fractured at age 15 years.	110
Table 4.11.1	Bone area and bone mineral content Z scores (adjusted for height and weight) at 10 and 15 years of age comparing obese with non-obese females	111
Table 4.11.2	Bone area and bone mineral content Z scores (adjusted for height and weight) at 10 and 15 years of age comparing obese with non-obese males	112
Table 5.1	Comparisons of age, anthropometric data and bone mass measurements between biological mothers who did complete fracture questionnaires and those who did not.	121
Table 5.2	Anthropometric and bone mass measurements of year 17/18 adolescents	124
Table 5.3	Anthropometric and bone mass measurements of mothers	126

Table 5.4	The number and percentage of 17/18 year old adolescents, their mothers and siblings with a history of fractures	128
Table 5.5	Regression models describing the relationship between predictors and adolescent bone area and bone mineral content	131
Table 5.6	Odds ratio for fractures in year 17/18 adolescents	133
Table 5.7	Adjusted odds ratios for fractures in 17/18 year old adolescents	135
Table 6.1	Summary of the objectives, hypotheses and key findings	144

LIST OF FIGURES

		Page
Figure 1.1	Age-specific incidences of limb fractures in males (filled circles) and females (open circles) from southern Sweden.	1
Figure 1.2	Definitions of the various types of mineral density.	7
Figure 1.3	Areal BMD measurements are influenced by bone size, with larger bones of similar volumetric BMD having higher areal BMD values.	11
Figure 1.4	pQCT slices at the 4% and 20% distal radius and various bone measurements that can be obtained.	16
Figure 1.5	Definitions of geometric properties of bone.	17
Figure 1.6	Forest plot for fixed-effect meta-analysis of the association between BMD and fractures in children.	20
Figure 1.7	Interaction of genetic and non-genetic factors on bone mass.	21
Figure 1.8	Forest plot of studies assessing the association between birthweight (kg) and BMC of the lumbar spine in adulthood.	24
Figure 1.9	Forest plot of studies assessing the association between birthweight (kg) and BMC of the hip in adulthood.	25
Figure 1.10	Size-corrected BMD (BMDsc) for males and females by biological age.	36

Figure 1.11	Comparison of ages of peak BMC velocity and peak BA velocity for (A) boys and (B) girls.	37
Figure 1.12	Schematic description of the effect of mechanical stimuli of the skeleton through structural adaptation of bone in the maintenance of physiological homoeostasis by employing the mineral reservoir embedded in the bone structure.	41
Figure 1.13	Proposed relationships between social position in pregnancy and skeletal growth, fat mass, and bone mass in childhood	52
Figure 3.1	Fracture rates per year by age and ethnicity	78
Figure 3.2	Fractures per year by age and sex.	79
Figure 3.3	Fracture rates over 15 years between ethnic groups at the different fracture sites.	82
Figure 3.4	Number of fractures at the different sites between ages 15 and 18 years	85
Figure 3.5	Grades of trauma causing fractures in males and females between ages 15 and 18 years	86
Figure 4.1	Fracture incidence rates per annum at the different fracture sites in white and black children	95

Figure 5.1	Flow diagram describing the attrition of study participants from birth until 17/18 year of age including the number of adolescent-biological mother pairs and their siblings with fracture and bone mass data	122
Figure 5.2	Percentage of fractures at the different sites in year 17/18 adolescents, their siblings and biological mothers.	129
Figure 5.3	Grades of trauma causing fractures in year 17/18 adolescents, siblings and biological mothers.	130

LIST OF ABBREVIATIONS

Abbreviation/Term	Definition
ALSPAC	Avon longitudinal study of parents and children
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
B	Black
BA	Bone area (cm^2)
BAZ	Body mass index for age Z score
BMAD	Bone mineral apparent density (g/cm^3)
BMC	Bone mineral content (g)
BMD, aBMD	Bone mineral density (g/cm^2), areal bone mineral density (g/cm^2),
vBMD	Volumetric bone mineral density
BMDCS	Bone mineral density in childhood study
BMI	Body mass index
Bt20	Birth to Twenty
CD	Cortical density
cm	Centimetre
COX2	Cyclooxygenase 2
CSMI	Cross-sectional moment of inertia
CT	Computed tomography
CV	Coefficient of variation
DOHaD	Developmental origins of Health and Disease
DONALD	Dortmund Nutrition and Anthropometric Longitudinal Design Study

Abbreviation/Term	Definition
DXA	Dual energy X-ray absorptiometry
FN	Femoral neck
g	Grams
GH	Growth hormone
GOOD	Gothenburg osteoporosis and obesity determinants study
H	Hip
HN	Hip neck
HAZ	Height for age Z score
I	Indian
IGF-1	Insulin-like growth factor 1
ISCD	International Society of Clinical Densitometry
LRP	Low-density lipoprotein receptor-related protein
LS	Lumbar spine
m	Metres
MA	Mixed ancestry
MET	Metabolic equivalent
mg	Milligrams
MVPA	Moderate-vigorous physical activity
N	Total number
n	Number
ND	Normal cortical density
25(OH)D	25 hydroxyvitamin D

Abbreviation/Term	Definition
PA	Physical activity
PBM	Peak bone mass
PGE2	Prostaglandin E2
PHV	Peak height velocity
pQCT	peripheral quantitative computed tomography
pSSI	Polar strength-strain index
PTH	Parathyroid hormone
R	Radius
SD	Standard deviation
SEM	Standard error of the mean
SES	Socioeconomic status
SMS	Sexual Maturation Score
TB, TBLH	Total body, total body less head
US	United States
USA	United States of America
W	White
WB, WBLH	Whole body, whole body less head
WHO	World Health Organisation
Wnt	Wingless integration site
Yrs	Years
Z-score	A statistical measurement of a score's relationship to the mean in a group of scores.

PREFACE

South Africa is a country of diverse culture and ethnicity. It is a multifaceted nation with a variety of social and environmental influences. Certain areas are poverty stricken with many people remain unemployed whilst other areas are thriving and prosperous. All these factors play a fundamental role in the development and growth of South African children.

Childhood illnesses, injuries and related problems such as fractures form part of the health burden that health workers and parents face. An understanding of the epidemiology and mechanisms related to fractures and bone mass differences in the various ethnic groups in urban South African children and their families may help to identify the risk factors and thus decrease the incidence of childhood fractures in South Africa and optimize their bone mass and bone health from an early age.

After reviewing the literature, I noted that there were several gaps in the literature and that there were very few studies on ethnic differences in fracture rates and bone mass in children and to the best of my knowledge there is no literature on this field in South African children.

This thesis is based on data obtained from a longitudinal cohort of children (the Birth to Twenty (Bt20) cohort), living in the Greater Johannesburg metropolitan area and who have been studied since their births in 1990. Data have been obtained from the whole cohort, from

more detailed studies of a sub-cohort (the Bone Health sub-cohort) nested within the Bt20 cohort, and from their parents and siblings.

This thesis aims to answer the following questions in a series of published manuscripts which have been collated in the chapters on the results and discussions of the research:

1. What are the rates and site-distribution of fractures, and the activity-related risk factors for fractures in urban South African children of different ethnic backgrounds?

2. What are the associations between fracture prevalence, bone mass, body composition, and physical activity in urban South African children?

3. What are the differences in bone mass and fracture patterns between families of different ethnic backgrounds in South Africa?

4. What are the associations, if any, between bone mass and fracture history of mothers and those of their adolescent children?

The thesis has been divided into 6 chapters. Chapter 1 describes the relevant background literature. Chapter 2 describes the aims, objectives, methods and statistical analyses performed in this study. Thereafter chapters 3, 4 and 5 are designed to answer the questions outlined above. Each of these chapters is based on an individual published manuscript (see appendices F-H) and includes the results, discussion and limitations of the findings. The three chapters cover the following areas:

1. Chapter 3: Fracture patterns in urban South African children of different ethnic origins (answers question 1 above)

2. Chapter 4: Heterogeneity of fracture pathogenesis in urban South African children (answers question 2 above)
3. Chapter 5: Fracture patterns and bone mass in South-African adolescent-mother pairs (answers question 3 and 4 above).

Chapter 6 concludes the thesis by highlighting the salient findings of this study and recommending future studies in this field.

CHAPTER 1

Literature review

This chapter describes the epidemiology of fractures in childhood, how bone mass is measured and assessed in children, the risk factors for fractures and the association of bone mass and fractures in relation to these risk factors and finally, the ethnic differences in bone mass and fractures in children. The chapter concludes with a summary of the literature review and finally, a brief overview on the gaps in the literature.

1.1 Epidemiology of fractures in childhood

Fracture rates in childhood are as high as those in the elderly (Figure 1.1) (1).

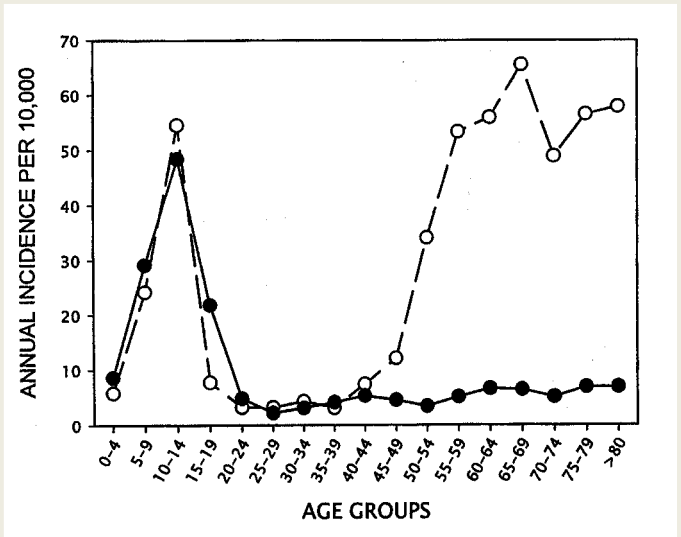


Figure 1.1 Age-specific incidences of limb fractures in males (filled circles) and females (open circles) from southern Sweden (Source: Heaney et al. Osteoporos. Int. 2000; 11:985).

Several epidemiological studies have suggested a site-and sex-specific distribution of lifetime fracture incidence with peaks at both puberty and old age(2-5). A population-based British cohort study showed that the peak annual incidence of fractures during childhood (boys, 3%; girls, 1.5%) was only surpassed at 85 years of age among women but never among men(6).

In developed countries, injury is responsible for most childhood mortality and morbidity(7) and fractures are the most common injury of childhood requiring hospitalization(8) and thus represent a considerable public health burden.

A study on childhood injury epidemiology by Landin defined different levels of trauma in Swedish children based on the analysis of 8682 fractures that were sustained between 1950 and 1979(9). A classification method was derived based on descriptions of the events that surrounded these injuries in Landin's study and key features included height of fall, type of activity engaged in and the use of equipment. These features were utilized to classify fractures as occurring after slight, moderate or severe injury and this classification is described in more detail below (9):

Slight: Injuries from standing on the same level or falling from a height less than 0.5 metres above the ground. Sport injuries of low energy type included skating, skateboard, skiing, wrestling, judo, karate and playground scuffles.

Moderate: Falling from a height of between 0.5-3 metres or trauma from falling from a bunk-bed, falling downstairs, from a bicycle, swing or slides.

Severe: Falling from heights greater than 3 metres. All traffic accidents and being hit by a heavy moving object.

Fractures in childhood are often thought to generally occur after high levels of trauma but research is indicating that fractures in childhood may be associated with underlying

skeletal fragility(10). Landin reported that during the 30 year observation period in Sweden, the annual incidence of fractures caused by slight trauma increased three times ($p<0.001$) and the more severe types of trauma increased only slightly but also significantly ($p<0.001$) (9). The Avon Longitudinal study of Parents and Children (ALSPAC) in the United Kingdom followed 6204 children (mean age of 9.8 years) for 2 years between 2001 and 2003 and concluded that fracture risk in childhood is related to underlying skeletal fragility, even at relatively high trauma levels, although greater skeletal fragility is seen in children who fracture because of slight trauma(11).

Falls are a leading cause of childhood injury(8;12-14). Falls from chairs or beds or into furniture, on stairs, and from being dropped by another person were proportionally highest in the youngest age groups (<2 years of age) (8;14;15). Falls from playground equipment, during sports and from being pushed and shoved by another person were more common in the older age groups (5-12 years of age) (8;14;15). The most common injuries sustained from falls were fractures of the upper limb(8;15). Falls from playground equipment commonly results in fractures(16;17) and more than half of those fracturing sustain a fracture to the upper limb(17). One of the first epidemiological studies confirmed that grass is not a good protective surface beneath play equipment and a child is more likely to have a head injury or fracture when falling on grass compared with sand(17). Keays et al concluded that children who fell off a swing, a slide or jungle gym at home compared to those in public settings, had greater odds of suffering a fracture or severe injury that required follow-up or hospital admission(18).

Participation in sports constitutes a significant portion of injury related emergency department visits among paediatric patients(19). Fractures of the upper limb were the more common sports related injuries in children and occurred mainly in boys during early to mid puberty(13;19;20), and of white race or ethnicity(19).

Over one-third of boys and girls sustain at least one fracture before 17 years of age but the type of fractures varies with age(2;6). All studies have found a high incidence of fracture during childhood and adolescence, with 27-40% of girls and 42-61.4% of boys sustaining at least one fracture during growth(2;6;9;21-23) (Table 1.1).

Table 1.1 Fracture prevalence in children and adolescents in different countries

Country	**Study period**	**Percentage of children and adolescents fracturing**		
		Total N	**Males**	**Females**
Sweden(9)	1950-1979	41553 (In 1979)*	42%	27%
United Kingdom(6)	1988-1999	136753	± 33%	± 33%
New Zealand(23)	1972-1990	1037 (In 1972)*	43%	37%
Poland(22)	2003	1246	36%	25%
Scotland(2)	2000	108987	61%	39%

*The year when the sample size was calculated

Hedstrom et al(24) summarised the findings from their study in Table 1.2 and these authors also included the fracture incidences from other epidemiological studies across geographic regions together with the years of the studies and showed that the sites of fracture and mechanism of injuries were consistent between the different regions and over the years.

Table 1.2 Overview of epidemiological studies describing fractures in children and adolescents

First author	Age group	Study period	Location	Annual incidence per 10^4	Most common fracture site	Most common mechanism of injury
Landin (9)	0-16	1950-1979	Sweden	212	Distal forearm 23%	Falls
Cooper (6)	0-17	1988-1998	Great Britain	133	Forearm 30%	Not available
Kopjar (25)	0-12	1992-1995	Norway	128	Distal radius 27%	Falls 71%
Tiderius (26)	0-16	1993-1994	Sweden	193	Distal forearm 26%	Falls on ground level 40%
Lyons[a] (27)	0-14	1996	Scandinavia	156-178	Forearm 20%	Falls
Lyons[b] (21)	0-14	1996-1996	Wales	361	Forearm 36%	Falls
Brudvik (28)	0-15	1998-1998	Norway	245	Distal forearm 27%	Not available
Rennie (2)	0-15	2000-2000	Scotland	202	Distal forearm 33%	Falls < 1m 37%
Hedstrom(24)	0-19	1993-2007	Sweden	201	Distal forearm 26%	Falls < 0.5m 24%

The peak incidence of fractures in girls occurs between 11-12 years and in boys at approximately 14 years of age(6;9;23). This period corresponds to the age of peak height velocity (PHV) in both genders and precedes by nearly one year the time of peak bone mineral content (BMC) velocity(29). Faulkner and colleagues provide data which support the hypothesis that there is a period of relative bone weakness resulting from dissociation between bone accrual and bone expansion around the time of peak linear growth in both boys and girls when most fractures occur(30). Rizzoli et al reported that the peak age of fracture occurrence in boys and girls is close to the age at which dissociation between height gain and volumetric BMC is most pronounced(31). The findings are supported by Kindblom who found that age at PHV was a negative independent predictor of both cortical and trabecular volumetric bone

mineral density (BMD) and of total body and radius areal BMD; and age at PHV was associated with previous fractures in a logistic regression analysis(32).

Not only do children frequently experience a single fracture in their lifetime but they also are at risk of multiple fractures. The percentage of boys experiencing multiple fractures is higher than in girls(22;23). A first fracture is associated with an increased risk of multiple fractures during growth(33). Moreover, children experiencing their first fracture before 4 years of age are at greater risk of further fractures occurring before 13 years of age(34). A number of reports have documented lower BMD or BMC at several sites of the skeleton among children with fractures compared to controls(35-37). The most common site of fracture in both sexes is the distal forearm(2;6;9;21;22).

Fractures in childhood are not uncommon and are more common in boys than girls. A low bone mass together with other related factors such as the pubertal growth spurt and environmental and genetic factors are important predisposing factors that will be further discussed.

1.2 Bone compartments and the various types of bone density

In order to understand how bone mass is assessed and measured in children, it is important to know the basics of bone composition and mineral density.

The composite tissue of bone is made up of an organic collagen matrix and an inorganic mineral hydroxyapatite. The arrangements of these composites determine two types of bone tissue; namely trabecular and cortical bone tissue. The trabecular bone tissue is found mainly in the vertebrae and ends of long bones while cortical bone is found in the shafts of long bones.

The mass, volume and type of bone tissue is important to determine when measuring bone density. The biological organization of bone consists of three levels: material bone density ($BMD_{material}$), compartment bone density ($BMD_{compartment}$) and total bone density (BMD_{total}) (Figure 1.2)(38). These three levels must be considered when interpreting bone density.

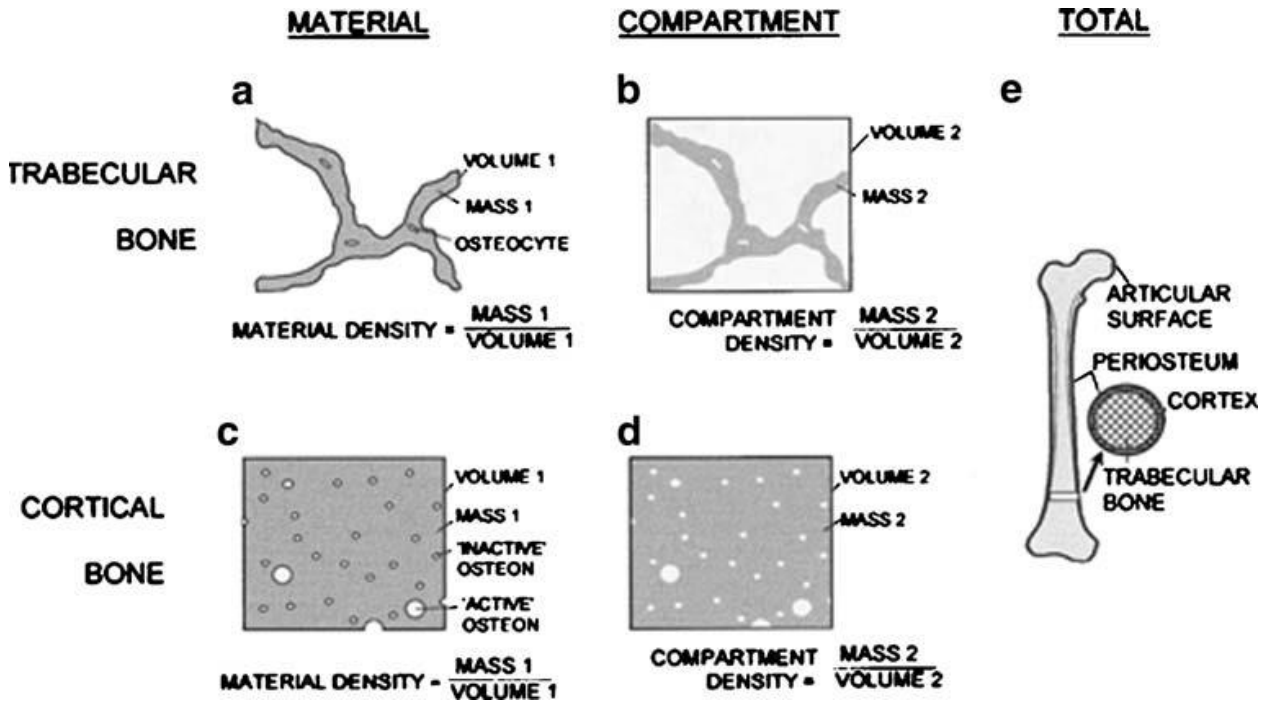


Figure 1.2 Definitions of the various types of mineral density. $BMD_{material}$ (a and c) in trabecular and cortical bone. The mass of mineral (in grey) determining $BMD_{material}$ and $BMD_{compartment}$ is identical (mass 1=mass 2), but the volume (encircled by black lines) differs (volume 2>volume 1). Therefore, $BMD_{material}$ is higher than $BMD_{compartment}$. (E) BMD_{total} is defined as the mass of mineral divided by the volume enclosed by the periosteal envelope. This definition can be applied to the entire bone, part of the bone (e.g., the distal or proximal end), or a section through the bone, as shown. (Source: Rauch et al. JBMR 2001;16:597-604)

The endocortical surface of the bone separates its trabecular and cortical compartments. The trabecular compartment is found within the space of the endocortical surface and the cortical compartment is the space between the endocortical and periosteal surface (Figure 1.2). The cortical compartment has less non-bone tissue compared to the trabecular compartment. Both trabecular and cortical compartments together with their relative volumes are utilized to determine BMD_{total}. As bone grows in childhood, the relative volumes of each compartment change; resulting in changes in BMD_{total}. As an example, cortical bone in the femoral shaft at birth constitutes 92% of the total cross-sectional area while by 6 months of age it has changed to 30% (39).

Techniques that measure bone mass in children may quantitate bone mass of the whole bone or of a bone compartment. Further they may measure cortical or trabecular bone mass or a combination of the two. The techniques used to measure bone mass in children in relation to risk factors for low bone mass and fracture risk will be discussed in further detail in the sections to follow.

1.3 Bone mass in children

Approximately 90% of adult bone mass is gained in the first two decades of life, and many experts believe that optimizing bone mineral accrual early in life may prevent childhood fractures, increase peak bone mass in early adulthood and possibly delay the development of osteoporosis later in life(40).

Rapid bone growth occurs during childhood. During longitudinal growth, prechondrocytes in the growth plates at the proximal and distal ends of bones differentiate into columns of proliferative and then hypertrophic chondrocytes, and cartilage is eventually

replaced with bone in the adjacent metaphyses(40). In addition, an increase in bone size occurs through bone modeling and remodeling(40). Modeling during childhood allows individual bones to grow in width by the formation of new bone on the outer or periosteal surface, while resorption occurs on the inside, or endosteal surface, of the bone(40). The degree of modeling is determined in part by genetics, but also by the response to loading that occurs with strains on bone from physical activity and gains in body weight during growth(40). According to Wolff's law, bones will ultimately achieve a shape and size that best fits their function(41). Remodeling occurs throughout life and although it does not change the shape of bone it is important for bone maintenance and repairing of bone damage and it prevents the accumulation of too much old bone that can become brittle(40). Resorption of the surface of trabecular bone is important for supplying needed calcium and phosphorus during periods of acute mineral need(40).

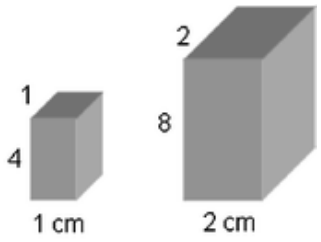
The bone changes and different processes involved in bone growth will have different influences on the skeleton and may influence fracture risk during childhood. During rapid growth bone size increases and higher remodeling rates may lead to lower cortical volumetric BMD.

The measurement of bone mass in children has a number of challenges, as bone mass is very dependent on bone size which changes rapidly during childhood and particularly during the pubertal growth spurt during adolescence. However the use of dual energy X-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT) has revolutionized the measurement of bone mass and structure in children. The challenges related to paediatric bone mass measurements will be discussed further, paying particular attention to the two main methods being utilized to assess bone parameters in children; namely dual energy X-ray absorptiometry (DXA) and peripheral quantitative computed tomography.

I. Dual energy X-ray Absorptiometry

DXA has been used since the early 1990s in children after the development of paediatric software to measure bone density. It is the most widely available and commonly employed densitometry method for assessing bone health in adults and children(40;42). Bone mineral measurements by DXA rely on the attenuation (absorption) of energy that occurs as the x-ray beam scans across the region of interest(42;43). Two energy settings are used to optimize the separation of mineralized and soft tissue components in the area analyzed(42). The low-energy photons are attenuated by the soft tissue surrounding the bone, whereas the high-energy photons are attenuated by bone and soft tissue(42). A detector located above the X-ray tube measures the exiting photons from the site scanned and a computer subtracts the low-energy values from the high-energy measurements(42). Pixel by pixel attenuation values are converted to areal bone mineral density (BMD) by comparison with a bone mineral phantom(42). Bone area is calculated by summing the pixels within the bone edges, as defined by software algorithms(42). BMC is calculated by multiplying mean areal BMD by the projected bone area(42).

DXA measures bone in two- rather than three-dimensions therefore it is difficult to interpret BMD changes during childhood(40). A larger bone size may artificially inflate areal BMD measurements as shown in Figure 1.3 (44).



Volumetric BMD (g/cm³)	1.0	1.0
Projected Area (cm²)	4.0	16.0
Volume (cm³)	4.0	32.0
BMC (g)	4.0	32.0
BMD (g/cm²)	1.0	2.0

Figure 1.3 Areal BMD measurements are influenced by bone size, with larger bones of similar volumetric BMD having higher areal BMD values. (Source: Carter et al. JBMR. 7(2):137-145).

This is illustrated in studies that show that areal BMD increases with age, but volumetric BMD remains relatively constant(45;46). This has been confirmed in girls in whom computed tomography showed vBMD at the lumbar spine to be constant during childhood until the time of puberty when there is an increase between Tanner's stages two and three(47). This increase probably reflects an increase in trabecular bone volume rather than an actual increase in tissue volumetric BMD. The age-related increase in trabecular density is the result of increased thickness of existing trabeculae(48). Before puberty, there is no difference in trabecular density in boys and girls of either Caucasian or African American origin(47). At puberty, trabecular density increases, but within a race there is no sex difference in trabecular thickness(48). Mathematical methods have been proposed to adjust the two-dimensional "areal BMD" measured by DXA to more closely reflect volumetric BMD(49;50). These methods include the calculation of bone mineral apparent density for the spine and femoral neck, which divides BMC by the projected bone area to the power of 1.5 for spine(44) and 2.0 for the

femoral neck(51), or by applying formulae of the femoral neck measurements that assume a cylinder shape(52). Inclusion of bone and body size parameters in a regression approach (size-adjusted bone mineral content), or expressing BMC-for-bone area or BMC-for-height also have been suggested for correcting for the influence of size on areal BMD measures(50). When utilizing bone mass measurements it is important to consider these bone size-related problems, and to understand the differences in the measurements of bone size, bone mass, and bone density measurements and apply the use of these measurements appropriately(40).

Regional measurement at the spine is most often used to assess bone mass in children whereas total body scans are often used for body composition measurements including total body BMC(40;42). The head is a large contribution to total bone mass in the paediatric patient and whether or not BMC or BMD of the head should be included has been an issue in paediatric bone measurements(53). The official recommendation by the International Society for Clinical Densitometry (ISCD) is that the head should be excluded from the whole body measurements(54) .

In the absence of data to define a fracture threshold in children, the ISCD Pediatric Position Development Conference advise the following(54). Firstly, the diagnosis of osteoporosis in children and adolescents should not be made on the basis of densitometric criteria alone. Rather, the diagnosis requires the presence of both a clinically significant fracture history, and low bone mass.

A clinically significant fracture history is one or more of the following: a long bone fracture of the lower extremities; a vertebral compression fracture; and two or more long bone fractures of the upper extremities. And, low bone mass is defined as a DXA BMC or areal BMD Z-score that is less than or equal to -2.0, adjusted for age, sex, and body size, as appropriate.

While these guidelines represent an important first step in the classification of bone health in children, the utility of this approach is not yet proven and the appropriate adjustments for body size have not been established(42).

DXA measurements obtained on 1554 US children, age 6 to 16 years enrolled in the multicentre study "Bone Mineral Density in Childhood Study" (BMDCS) together with supplementary data obtained at other centers have been used to provide reference data for ages 3 to 21 years on the Hologic, Inc. scanners(42;55). Reference data for whole body bone and body composition for children ages 8 through 20 years are also available for Hologic systems based on data collected in the National Health and Nutrition Examination Survey between 1999 and 2004(42;56). Zemel et al. recently published sex- and race- reference curves for lateral distal femoral BMD based on Hologic Discovery/Delphi scans in 821 healthy children, ages 5 to 18 years(57). The new lateral distal femur Z-scores were strongly and significantly associated with weight, body mass index, and spine and whole body BMD Z-scores(42). The authors concluded that the comparability of lateral density femur measurements to other BMD assessment sites supports this alternative site in children with disabilities, who cannot have the lumbar spine scanned because of difficulties in the positioning the child appropriately, and who are particularly prone to low trauma fractures of long bones, and for whom traditional DXA measurement sites are not feasible(42).

Although DXA has been used mainly in research studies in infants, there is limited reference DXA data available. However, Kalkwarf et al recently reported lumbar spine data in 307 healthy infants and toddlers (63 black), ages 1 to 36 months using software developed by Hologic, Inc. to analyze lumbar spine DXA scans in children less than 36 months of age(58). BMC and BMD increased with age, but BMD less so than BMC. Similar ethnic increases were observed relative to weight and length with no sex differences in BMC or BMD when

statistically adjusting for age, length and weight. The study provided age-specific values for aBMD of healthy infants and toddlers that can be used to evaluate bone health and the authors concluded that future studies are needed to identify the age when sex and race differences in aBMD occur. Thus, there was no apparent need to develop race specific reference data for infants and toddlers, if the data obtained were adjusted for differences in body size(42).

Given the ongoing research and studies performed on pediatric DXA measurements and accumulation of pediatric reference data, DXA users may need to contact their manufacturer to determine the reference data source installed on a given machine, and to identify additional relevant databases that maybe more pertinent to their study population(42). For example, longitudinal studies in different countries with varying ethnic groups and genetic backgrounds may publish data in the future based on reference values from within these populations.

In situations where chronic diseases cause children to become stunted or malnourished, it may be more appropriate to determine whether areal BMD or BMC results are appropriate for their body size by comparing the measurements with those of children of similar height or weight(40).

Advantages and disadvantages of DXA

The advantages of using DXA over other possible techniques include those of cost and ease of accessibility. It is child friendly due to the high-speed of the scan (less than 3 minutes of the lumbar spine) which varies depending on type of scan. It also has a low radiation exposure of less than 13μSv(40). It is very useful for longitudinal assessment of bone mass measurements due to its high reproducibility however care should be taken in interpreting longitudinal measures of BMC and areal BMD due to potential size and age effects on these measurements that needs adjusting.

The major disadvantages of using DXA include its inability to separate cortical from trabecular bone and to assess bone geometry, although it does measure projectional BA. In addition, the influence of bone size on areal BMD measurements could pose as a significant disadvantage as mentioned earlier. When performing DXA scans in infants and toddlers it may be difficult to prevent or minimize movement artifacts. Generally, infants need to be fed and wrapped to avoid these movement artifacts.

II. Peripheral quantitative computed tomography (pQCT)

pQCT is a type of computed tomography used to measure volumetric BMD in the peripheral skeleton(40). The first commercial pQCT scanners were available for use in Germany by the early 1990s(40). By the mid-to-late 1990s, the technology was being used to investigate geometric and biomechanical properties of bone(40;59;60). Also at that stage, pQCT had the ability to separate trabecular bone compartments from cortical bone compartments but was being assessed for accuracy and precision(61;62). From the late 1990s onwards, pQCT was used to correlate muscle and bone strength(63) as well as obtain measurements in children(49) and thereafter establish reference data (64).

Dedicated pQCT scanners were developed to measure trabecular, cortical and total volumetric BMD, cortical dimensions, and fat and muscle cross-sectional area of the radius and tibia (Stratec Medizintechnik, Pforzheim, Germany) (42). These scanners are smaller, portable, less expensive and result in substantially less radiation exposure than conventional QCT(42). A scout view is performed to localize the endplate and growth plate (if not yet fused) of the tibia or radius, a reference line is placed relative to the endplate or growth plate, and scan sites are selected as a percentage of bone length(42). Individual 2 mm thick

tomographic slices are taken at these selected sites. The metaphyseal regions are rich in trabecular bone and the shafts are essentially entirely cortical bone(42). Figure1.4 shows slices at the 4% and 20% sites of the distal radius and the various bone measurements that can be obtained from cortical bone and trabecular bone(40).

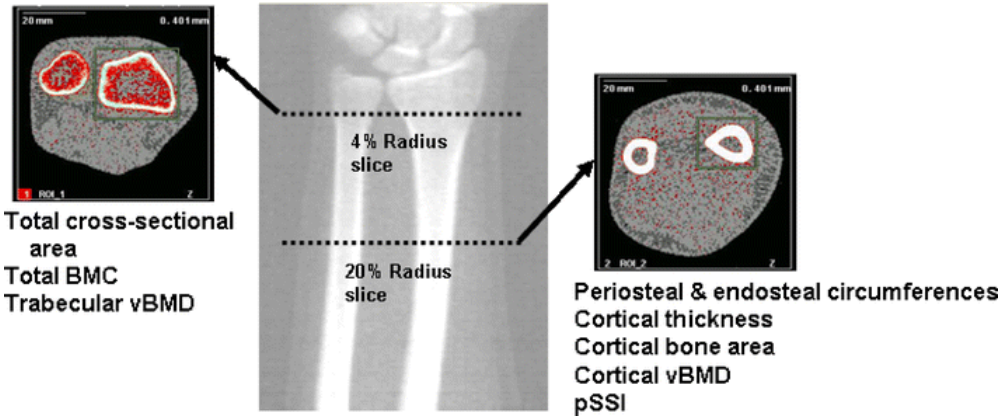


Figure 1.4 pQCT slices at the 4% and 20% distal radius and various bone measurements that can be obtained (Source: Binkley et al. Rev Endocr Metab Disord. 2008 Jun;9(2):95-106).

The two types of bone tissue respond differently to stimuli such as pubertal changes, mechanical forces, and disease-related stresses, so the benefit of separating the two is extremely advantageous in bone research(40). Since the majority of childhood fractures occur in the long bones, there is good rationale for obtaining measures of bone structure and volumetric BMD at these sites(42). Scanning time ranges from 2 to 3 minutes in smaller children to 4 to 5 minutes in adults(42).

Total cross-sectional bone area, cortical bone area, periosteal and endosteal circumferences, and cortical thickness are measures of bone size and geometric properties of bone that are obtained using pQCT. Bone strength index and polar strength-strain index (pSSI) which are surrogate measures of bone strength, and cross-sectional moment of inertia (CSMI)

are all calculated from the geometric and the material measures obtained using pQCT techniques (Figure 1.5)(40).

$$CSMI = \Sigma (r^2 \times a)$$

$$\text{Section modulus} = \frac{\Sigma (r^2 \times a)}{r_{max}}$$

$$pSSI = \frac{\Sigma (r^2 \times a) \times CD/ND}{r_{max}}$$

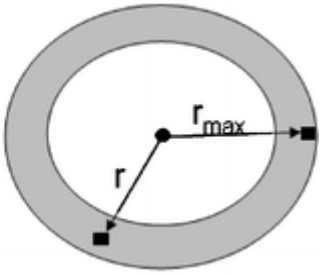


Figure 1.5 Definitions of geometric properties of bone. A schematic view of a cross-section of cortical bone is shown. r is the distance from the center of gravity to a voxel, r_{max} is the distance from the center of gravity to the voxel of maximum distance, a is the area (mm^2) of a voxel, CD is the measured volumetric cortical density, and ND is the maximum normal cortical density under physiologic conditions (1,200 mg/cm^3). Determination of bone strength is based on the calculation of the cross-sectional moment of inertia (CSMI); in this case the center of gravity or polar moment of inertia is used. The section modulus, which is directly proportional to maximum stress in bone, is calculated by dividing the CSMI by the maximum voxel distance from the center of gravity. The polar strength-strain index (pSSI) takes into account the material properties by multiplying the section modulus by the quotient of CD and ND. (Source: Binkley et al. Rev Endocr Metab Disord. 2008 Jun;9(2):95-106)

In healthy children investigations using pQCT have investigated the effects of activity, bone loading, diet, pubertal stage and hormonal status on bone (61-67). Reference ranges for pQCT variables from healthy children have been established for bone growth patterns that can be used as a comparison when studying the bone status of children in disease states (53, 59, 60).

Advantages and disadvantages of pQCT

pQCT is a superior tool over DXA in obtaining some bone measurements as it reports true volumetric BMD in grams/cm^3 , differentiates cortical from trabecular bone tissue, measures bone size and estimates geometric properties of bone. There is minimal radiation exposure, estimated to be 0.22 µSv for a CT slice of the forearm and 0.8 µSv for a scout view scan of the forearm according to the manufacturer of the XCT 2000 (Orthometrix, Inc., White Plains, New York, USA) and ranges from 0.72 µSv in the distal tibia to 1.43 µSv in the distal femur (58).

The disadvantages are that pQCT underestimates cortical volumetric BMD when the cortical shell thickness is small (<2mm)(65) and longitudinal measurements are difficult due to variations in longitudinal bone growth(40). Another disadvantage of pQCT is that it does not measure important fracture sites (spine and hip) directly.

1.4 Factors associated with childhood fractures and the association of fractures with bone mass

There is emerging evidence that fractures in childhood are related to underlying predisposing factors(10;11;37;66). An understanding of the many related risk factors for fractures is important for deciding rational strategies to optimize bone health during childhood. Factors considered to influence childhood fracture risk include calcium and milk intake(67;68), consumption of carbonated beverages(37), exercise or sports participation(11), body composition (fat and lean mass)(69;70), times spent in front of the computer/television(71), smoking(66), BMC and/or BMD(10) and genetics(22). In addition, an understanding of the roles of these factors in fracture pathogenesis and their inter-relation with bone mass is very important in understanding the pathophysiology of fracture occurrence.

The following factors affecting fracture risk and bone mass (listed below) will be discussed in further detail:

I. Low bone mass

II. Heritability/genetics

III. Maternal and early life influences

IV. Nutrition

V. Obesity

VI. Puberty

VII. Exercise

VIII. Vitamin D status and its seasonal variation

IX. Socioeconomic status

1.4.1 Low bone mass

A number of studies have found bone mass to be linked to fracture incidence (36;72) while Cook et al has not(73). Fractures in children are generally thought to reflect the fact that falls and other injuries are common during childhood(74) but there is evidence to suggest that fracture risk is inversely related to BMC and/or BMD and directly related to underlying skeletal fragility(10). Results of a meta-analysis on the association between low bone density and fractures in children(10) showed that the combined standardized mean difference (calculated by the difference in means divided by the pooled standard deviation of

participants' outcomes across the whole trial) in mean bone mass between children with fractures and controls was -0.32 (95% confidence interval [CI]: -0.43 to -0.21; *P* <0.001) (Figure 1.6).

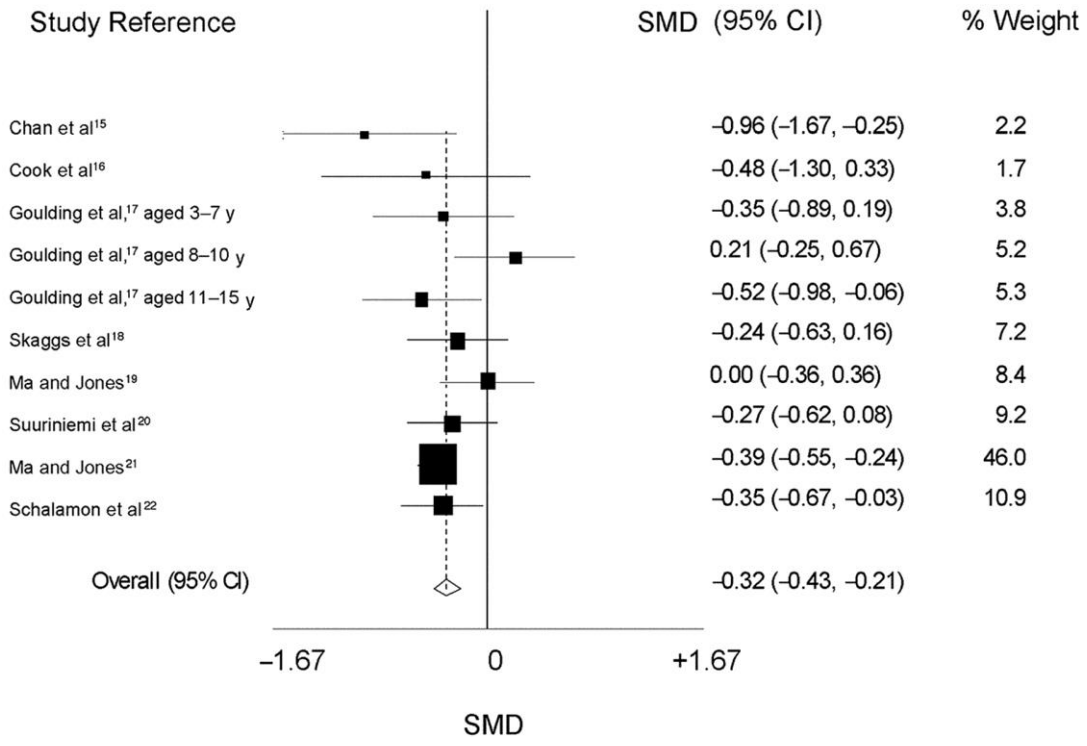


Figure 1.6 Forest plot for fixed-effect meta-analysis of the association between BMD and fractures in children. (Source: Clark et al. Pediatrics 2006;117(2):e291-7)

A number of researchers have found that children with wrist and forearm fractures have a bone mineral density up to 8% lower than children without such fractures(35;36;75). A 5% increase in total body BMD and BMD of the hip or lumbar spine could decrease the relative risk of fracture in childhood by about 17% and 9%, respectively(75). Those with recurrent fractures had similar bone size and mass in both the lumbar spine and total body to those who only fractured once(35;37). In a prospective cohort study of bone mass and fracture risk in

childhood, a strong inverse association was observed between fracture risk and size-adjusted total body less head BMC and estimated humeral vBMD (76).

Peak bone mass is mostly determined by bone size rather than by vBMD, which varies little in normal adults or by variations in micro-architecture. All of these processes are controlled by complex and selective genetic, hormonal, nutritional and other environmental factors, which tightly interact (Figure 1.7)(31)

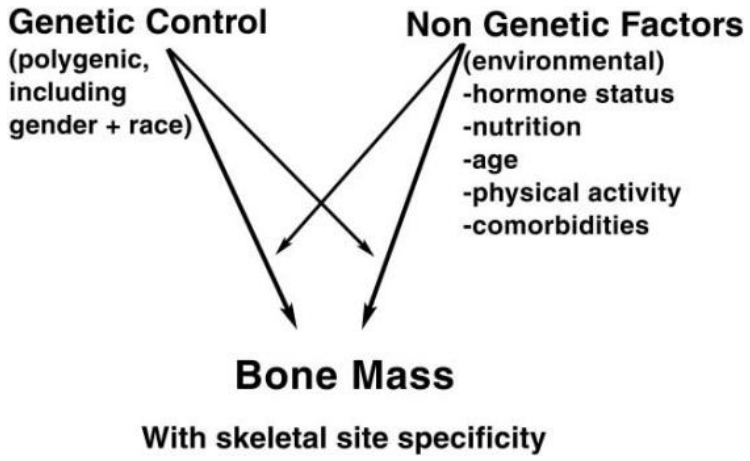


Figure 1.7 Interaction of genetic and non-genetic factors on bone mass (Source: Rizzoli et al. J Mol.Endocrinol. 2001; 26(2):79-94)

1.4.2 Heritability/Genetics

Genetics and heritability plays a major role in bone health. Numerous candidate gene studies have identified several polymorphisms that are associated with BMD, bone loss in adults and osteoporosis(77). Various vitamin D receptor alleles have been shown to be associated with an increased risk of fracture in osteoporotic individuals(78). The COLIA1 gene, encoding the αI chain of type I collagen is another important functional candidate for the pathogenesis of osteoporosis(79). The other important candidates genes are the oestrogen

receptor α (ESR1) that is important for the regulation of bone mass(80) and transforming growth factor β-1 that has been associated with BMD and/or osteoporotic fractures in various studies(81;82). Genetic studies in adults tend to be complicated by environmental covariates. Thus associations between genotypes and bone mass should be easier to detect during childhood, when genetic regulation of bone is at its peak and environmental influences have had limited time to exert their effects(83). May et al(84) have provided the first glimpse into the genetic factors regulating the elevated bone mass of prepubertal South African black children. Both the *ESR1* and *TNFRSF11B* (osteoprotegerin) genes were candidate genes found to influence bone mass(84) and more so at the femoral neck site at which bone mass differences appear to be greatest between black and white South Africans(85;86).

Heritability (87;88) and lifestyle factors (89) of both mother during pregnancy and child influence the accrual of peak bone mass and impact the risk of osteoporosis in later adulthood. Heritability has been estimated to contribute to more than 40% of the variance in adult BMD (1;90). Gains in bone mineral accretion during childhood via interventions such as increased physical activity and nutrient supplementation may only be transient, thus promoting the hypothesis that bone is ultimately governed by a homeostatic system which tends to return towards a yet-to-be defined set point(91). Whether this set point is genetically predetermined needs to be further investigated. The Birth to Twenty cohort has shown that heritability of BA and BMC, by maternal descent is approximately 30% in South African pre/early pubertal black and white children, despite ethnic differences in both body and bone size, as well as in lifestyles (92). This will be discussed in more detail later in the chapter.

Evidence for the role that heritability plays in fracture prevalence is provided by a cross-sectional study on Polish adolescents, which revealed that 52% of adolescents with

multiple fractures reported at least one fracture in a first degree relative whereas 39% of those with a single fracture and 29% of those with no fractures reported fractures in a first degree relative(22).

Genetic and environmental factors and not bone mass on its' own may be attributable to the increased incidence in fractures. The interplay between environmental and genetic factors is still not well understood.

1.4.3 Maternal and early life influences

It is beneficial to identify maternal and early life influences on later BMD, which may assist in the identification of interventions to optimise bone health and reduce fracture risk in childhood and thereafter. There is growing evidence that BMD and thus fracture or osteoporosis risk can be modulated during intrauterine and infant life(93).

Barker's hypothesis or fetal origins hypothesis was first developed in the 1980s from epidemiological studies of birth and death records that revealed a high geographic correlation between rates of infant mortality and certain classes of later adult deaths as well as an association between birth weight and rates of adult death from ischaemic heart disease(94). The Developmental Origins of Health and Disease (DOHaD) hypothesis thereafter evolved from Barker's hypothesis suggesting that nutritional imbalance during critical windows in early life can permanently influence or "programme" long-term development and disease in later life(95). A large population-based mother-offspring cohort study recruited from the Southampton Women's Survey demonstrated that the growth velocity in the late phase of pregnancy appears to predict bone mass at birth more strongly than does growth in the early phase(96). In contrast, bone mass at 4 years, appears to be predicted more strongly by growth

in early than in late pregnancy(96). Ongoing research has shown that growth in infancy and possibly later in childhood is crucial and studies have linked placental weight, birth length and birth weight to later osteoporosis risk(97-99). Higher weight at birth was associated with higher BMC of both the spine and hip in adult men and women at ages 18-80 years across a range of settings (Figure 1.8 and 1.9) and these associations were stronger in women at the lumbar spine site(98).

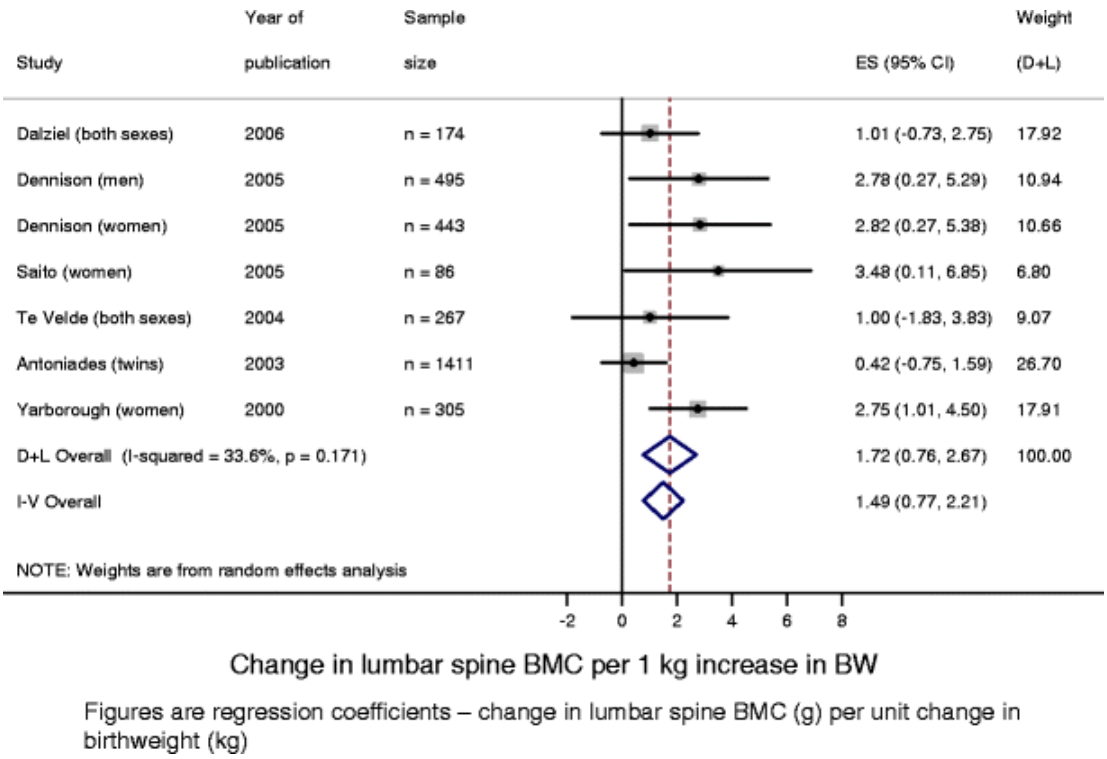


Figure 1.8 Forest plot of studies assessing the association between birthweight (kg) and BMC of the lumbar spine in adulthood (Source: Baird J et al. Osteoporos Int (2011) 22:1323-1334)

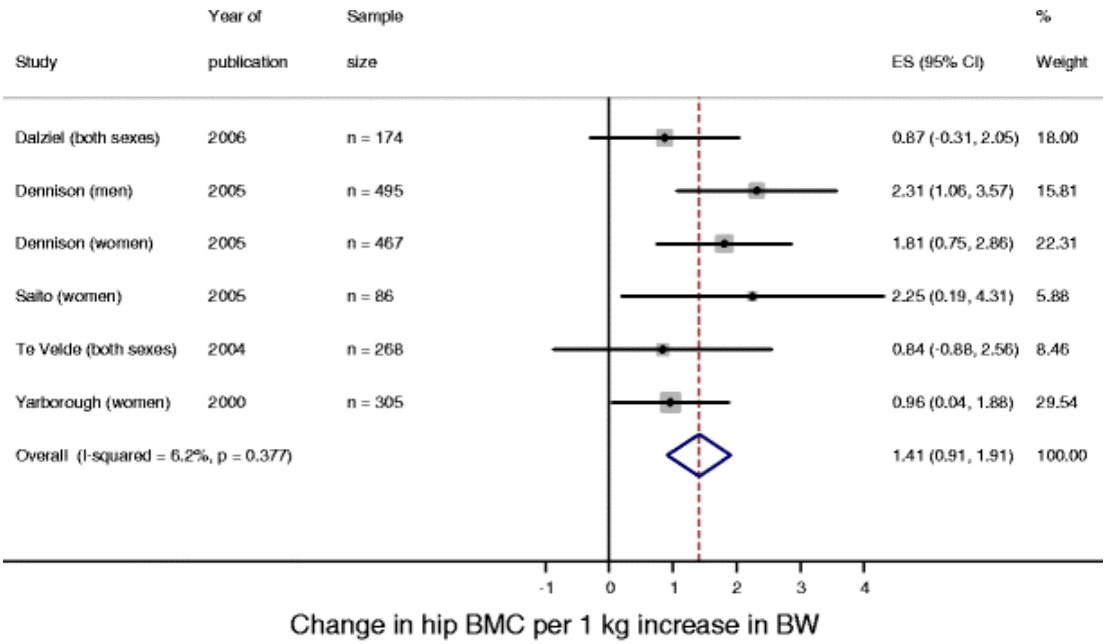


Figure 1.9 Forest plot of studies assessing the association between birthweight (kg) and BMC of the hip in adulthood (Source: Baird J et al. Osteoporos Int (2011) 22:1323-1334)

The pooled estimates suggested an increase in birthweight of 1 kg is associated with a lumbar spine BMC increase of 1.49 g (95% CI 0.77, 2.21) (Figure 1.8) and an increase in hip BMC of 1.41g (95% CI 0.91, 1.91) (Figure 1.9).

The reasons for the stronger association seen in women was postulated by the authors to be due to maternal constraints being greater in boys in utero because they grow more rapidly than girls and so are at greater risk of becoming undernourished if maternal diet is compromised (98;100).

A more recent systematic review and meta-analysis on life-course evidence of birth weight effects on bone mass highlighted that higher birth weights result in a better bone health later in life and this effect was seen in both the BMC and BMD of children suggesting that there could be bone mass programming(101). Two British cohort studies showed that growth

in early life or higher birth weight together with gaining weight and height faster in the prepubertal and postpubertal period were associated with greater bone size and strength in later life (late middle age and postmenopausal period)(102;103).

Despite studies showing that higher birth weights are associated with better bone health in later life, there is contradictory evidence on maternal and early life factors and fracture risk in later life. Children who were born with above average length(37;104) and who were heavy and tall throughout growth, had an increased risk of fracturing during childhood and adolescence(37). Increasing maternal age has been associated with increased fracture risk whilst pre-pregnancy BMI(104) and breastfeeding were not(37). Cohort studies have yielded conflicting results regarding the association between vitamin D status in pregnancy and its influences on offspring bone mass. Recently, in the large prospective ALSPAC study there was no strong evidence that maternal 25(OH)D concentrations during pregnancy are related to childhood BMC(105) but the Western Australian Pregnancy cohort (Raine) study examined their off-spring at skeletal maturity and found that mothers that were vitamin D deficient had offspring with lower peak bone mass(106). However, none of these studies have investigated the influence of maternal diet and vitamin D status during pregnancy on subsequent off-spring fracture risk. There is contradictory evidence regarding maternal smoking and childhood fracture risk(37;104) but daily cigarette smoking in adolescents was associated with a 43% increase fracture risk(37).

A single study reported that tall maternal height, low rate of childhood growth and babies born short were determinants of later hip fracture risk(107). Variables that were positively associated with neonatal bone mass included birthweight and maternal triceps skinfold thickness at 28 weeks, whilst maternal smoking and energy intake at 18 weeks' gestation were negatively associated with neonatal BMC at the spine and whole body(108).

In accordance with the hypothesis of developmental origins of diseases and the evidence outlined above from the literature, bone mass and fractures in childhood and adolescence seem to be partially programmed in early life but careful consideration should be taken when interpreting bone mass measurements in childhood. Many of the differences in bone mass are related to differences in growth and bone measurements must be adjusted for body size. This also may partially explain why there is contradictory evidence in the literature on early life influences, such as weight and height, affecting bone mass and fracture risk in later life.

1.4.4 Nutrition

An adequate nutritional intake is a very important determinant for bone health for all ages(109). Nutrients involved in the production of bone matrix include proteins, vitamins C, D and K and minerals zinc, copper and manganese. Cellular activities and mineral deposition of bone are dependent on phosphorus. The skeleton serves as a very large nutrient reserve for calcium and phosphorus, and the size of that reserve is dependent in part on the daily balance between absorbed intake and excretory losses of these two minerals(1). Adequate quantities of phosphorus (in the form of phosphate) must be present in the diet to mineralise and to maintain the skeleton. Inadequate phosphorus intake is an uncommon cause for poor acquisition of peak bone mass in healthy children.

Calcium is a threshold nutrient and is stored as bone tissue, the mass of which is regulated by mechanical loading and limited but not controlled by diet. The body cannot store a dietary surplus of calcium. Bone accumulation at calcium intakes above the threshold is maximal and further increases in calcium intake produce no increase in calcium retention; and

below the threshold, retained calcium is not sufficient to allow children and adolescents to reach their genetically predetermined peak bone mass. Hence bone mass varies with calcium intake(1). Low calcium intakes are often not thought to have immediate consequences but have in some studies been shown to be associated with increased fracture risk even in the young(36). In other studies no association between dietary intake of calcium and risk of fractures has been found(71;110).

Retrospective studies generally show that low consumption of milk during childhood and adolescence is associated with higher risk of fracture later in life(67). Children with recurrent fractures were noted to have a low milk intake and higher consumption of carbonated drinks(37). Low milk intake and the caffeine and sodium content of some carbonated drinks could increase bone remodeling secondary to inadequate intake and increased losses of calcium(37). Low intake of milk might also result in reduced bone formation due to lack of anabolic factors such as insulin-like growth factor-1(IGF-1) (37). Milk avoiders were shown to have smaller skeletons, significantly lower bone area and bone mineral content, and lower vBMD values than did the fracture-free control children of the same sex and age drawn from the same community(68).

Furthermore, maternal smoking during pregnancy and not being breastfed were the factors that in combination with low milk intake and increased intake of carbonated drinks were found to be predictive of sustaining recurrent fractures during childhood(37). Smoking by adolescents raised their risk of fracturing substantially and is postulated to be due to an associated reduction in bone density(66).

Protein supply from foods is required to optimise bone formation and amino acids are required for the synthesis of intracellular and extracellular bone proteins and nitrogen containing compounds(111). Protein intake has been shown to influence calcium-phosphate

economy and bone metabolism(111). Dietary proteins stimulate the formation of IGF-1 from hepatic cells, which are the main source of circulating growth factor(111). By stimulating IGF-I, food proteins can also exert a favourable impact on bone mineral economy by a dual renal action by enhancing intestinal calcium absorption and an associated increased calciuria (111). However, the increased urinary calcium excretion which can be associated with a high protein diet does not necessarily result in negative skeletal calcium balance that would reflect bone loss(112). Another effect of dietary proteins on mineral metabolism could include an inhibitory activity of L–amino acids on calcium sensing receptors, leading to a decrease in PTH secretion(113). Amino acid-sensing receptors have a positive effect on arginine(114) which in turn has a stimulatory effect on the production of both IGF-I and collagen synthesis(115) and impacts positively on bone acquisition.

Malnutrition, with consequent inadequate supplies of energy and protein during growth, can severely impair bone development(116). An inadequate protein supply appears to play a central role in the pathogenesis of the delayed skeletal growth and reduced bone mass that is observed in undernourished children(111). During childhood and adolescence, a relative deficiency in IGF-I or a resistance to its action due to an inadequate supply in protein(117) may result in a reduction in skeletal longitudinal growth, and impaired width or cross-sectional bone development(111).

Overall good nutrition and healthy dietary patterns are likely to be as important as or more important to bone health and growing bones than adequacy of individual nutrients alone. Constituents of the whole diet enhance or inhibit nutrient absorption, influence their excretion, or influence bone turnover. The whole diet also determines the acid-base balance which is thought to influence excretion of calcium and other minerals. Diets rich in dairy products, protein and fruits and vegetables and low in salt are considered bone healthy diets(118). It is

important to maintain a bone healthy diet to maximize peak bone mass and to reduce the risk of fractures in both childhood and adulthood.

1.4.5 Obesity

Obesity in children is associated with unhealthy nutrition, inactivity and low physical fitness, that may contribute to increased risk of fractures(71). Complications of fractures are amplified in terms of increased surgical times, increased risk of wound infections, and increased time to ambulation in obese subjects(119).

The marked increase in the prevalence of paediatric obesity combined with recent evidence suggesting that excessive fat accumulation may be associated with increased fractures in childhood indicates a need to understand the interplay between body composition components such as fat and lean mass and bone mineral content(120). A comparison of studies on obesity in children versus injury risk is shown below in Table 1.3. The data which were provided by Kessler et al(121) highlights that increased musculoskeletal risks of being overweight and not just being obese, beginning in childhood, which increase the risk of childhood lower extremity fractures.

Table 1.3 Comparison of studies on obesity versus injury risk in children

Study	Study type	Methods	Number of subjects	Main findings
Pomerantz et al., 2010(122)	Retrospective	Chart review at one hospital of patients 3-14 years with traumatic injury seen in the emergency department	23349	Obese children significantly more likely to have lower extremity than upper extremity injury than nonobese
Rana et al., 2009(119)	Retrospective	Single hospital chart review of all admitted paediatric trauma patients	1314	Obese children had a higher incidence of extremity fractures

Taylor et al., 2006(123)	Prospective	Chart review and questionnaire of patients enrolled in clinical studies at the NIH	355	Overweight children reported more fractures and impaired mobility
Zonfrillo et al., 2008(124)	Prospective case-control study	Case-control study of children with acute ankle trauma in single paediatric emergency department	180 cases plus 180 control subjects	Multivariate logistic regression showed significant association between ankle injury and overweight
Kessler et al., 2013 (121)	Retrospective, cross-sectional	Population-based, cross-sectional study of children 2-19 years	913178	Multivariate logistic regression analysis showed overweight, obese, and extremely obese children have a progressively increasing risk for lower extremity fracture as weight increases

There are conflicting results from studies investigating the influence of body fat on bone mineral content among various populations. Vincente-Rodriguez found that weight mediated by lean mass has a beneficial effect on BMC (69), while Hrafnkelsson et al found that fat mass has more effect on increasing total BA than lean body mass and that lean body mass has more effect than fat mass on increasing both BMC and BMD in children between 7-9 years of age(125). Goulding et al reported a detrimental effect of weight on BMC, which is possibly mediated by fat infiltration within bone compartments(70).

Reduced bone mass is a predictor of fracture in children(10) but contradictory results are being reported on skeletal mass in overweight or obese children, who as a group are at increased risk of fracturing. Some studies indicate that overweight children have higher bone mineral content whereas other studies conclude that obesity is associated with a lower bone mineral content. Since most studies have found a normal or increased bone mineral content in obese children(126;127), the main conclusion is that obese children have decreased bone mass

relative to their bone size and body weight(10;128). It is believed that the increased bone mineral density in obese adolescents may not be sufficient to overcome significantly greater forces that are generated when an overweight child falls(128;129). Davidson et al reported that obese and non-obese children had a similar risk of forearm fracture during the first peak maximal force, when the hand makes first contact with the ground, at all tested fall heights and surface stiffnesses (129). The first peak force is not likely therefore to be the main contributor to the differences in fracture risk that are observed clinically between obese and non-obese children. Obese children were shown to be at much greater risk of fracture during the second peak force, when the body weight is transmitted through the arm thus the second peak force is likely to be the main contributor to the observed difference in fracture risk between obese and non-obese children(129).

Obesity and high body weight have been identified as risk factors for fractures and recurrent fractures(37;66;72). Many studies have shown a greater prevalence of overweight and obese subjects among girls with upper limb fractures and in particular with forearm or wrist fractures(36;71). Goulding et al(72) performed a four year follow-up study of fractured and fracture-free girls and demonstrated that previous fractures, age, total body BMD and weight were significant factors predicting the risk of a new fracture. The same group(35) also showed that high BMI tripled the fractured risk (O.R. 3.47, 95% CI 1.69-7.09) in boys who sustained forearm fractures. Valerio et al(71) found a greater prevalence of overweight or obesity in both girls and boys sustaining lower limb fracture. The association between BMI and increased odds of fractures in children is shown in Table 1.4.

Table 1.4 Odds ratios of fractures in obese, overweight and increasing weight/BMI children.

Obese			
Study	**Fractures**	**Odds ratio**	**95% Confidence interval**
Kessler et al(121)	Foot	1.23	1.12-1.35
Kessler et al(121)	Ankle, knee and leg	1.28	1.15-1.42
Overweight			
Kessler et al(121)	Foot	1.14	1.04-1.24
Kessler et al(121)	Ankle, knee and leg	1.27	1.16-1.39
Taylor et al(123)	All fractures	4.54	1.6-13.2
Zonfrillo et al(124)	Ankle	3.26	1.86-5.72
Increasing weight or BMI			
Goulding et al(72)	All fractures (girls)	1.49	1.06-2.08
Goulding et al(72)	Distal radius/ulna (girls)	1.72	1.11-2.68
Goulding et al(35)	Distal forearm (boys)	3.47	1.69-7.09
Jones et al(66)	All fractures except wrist	1.20	1.05-1.36

Obesity/overweight impacts negatively on bone mass by reducing physical activity which limits the anabolic stimuli to bone and results in a mechanical disadvantage during a fall as balance and co-ordination are not as well developed in less active individuals(37;130). Poor balance, unstable postural sway, altered kinetic characteristics of locomotion in overweight children is additional risk factors for fractures(130;131). Lower fall heights and

softer impact surfaces were found not to reduce the relative risk of fracture between obese and non-obese children(129).

Lifestyle behaviours have also been associated with fracture risk in children(37;132-134). Screen time with TV viewing as the most relevant proxy for sedentary lifestyle, has consistently been found associated with childhood obesity(135). Valerio et al(71) found that TV viewing of greater than two hours per day was more prevalent in overweight or obese children with fractures compared to overweight or obese children without fractures. Higher inactivity seems to characterise overweight children reporting fractures(71).

Environmental modifications such as safer playground surfaces and equipment are unlikely to decrease the risk of arm fracture in obese children to the same levels experienced by non-obese children. The best option available for obese children to decrease their fracture risk is to adapt a healthier lifestyle by exercising and eating healthy to attain a healthy body weight.

1.4.6 Puberty

The pubertal growth spurt can be defined as a 2 to 3 year period of rapid increase in height and weight that is related to the change in activity of the hypothalamus with a gradual increase in the secretion of pulses of gonadotrophin-releasing hormone(69). An increase in gonadotrophin secretion stimulates gonadal growth and pulsatile secretion of luteinizing hormone, and secondary sexual characteristics appear as the concentration of sex steroids rise (136).

Boys have a longer prepubertal period of growth(137), as their pubertal growth spurt occurs 1 to 2 years later than in girls(45), contributing to the characteristic sex differences in

skeleton proportions of longer lower extremities in adolescent and adult males than females (137). Bone mineral content increases linearly, with no sex differences until the onset of the pubertal growth spurt (138), when BMC accretion rates diverge. Besides the longer and more marked period of increased growth velocity in boys, BMC in boys continues to increase through late adolescence(138), while in girls, BMC barely increases after the onset of puberty(138). Specifically, sex differences in bone size and strength are established in puberty as a result of the minimal endocortical contraction during puberty in males compared with females and the higher endocortical contraction and inhibition of periosteal apposition in females after the pubertal growth spurt(45). As a result, while volumetric bone density remains constant during growth and similar in both sexes (139;140), BMC is around 20% higher in males compared with females at the age of 16 to 17 years, simply because their bones are bigger(141). Thus, sex differences in bone strength are the result of the differences in shape and geometry(141).

Puberty is not only a period of rapid longitudinal growth and accrual of bone mass, but also the period associated with the highest incidence of fractures during childhood and adolescence(142). The physiological mechanisms for this high rate of fracture during growth is not clear; however, there has been speculation that one of the factors may be the result of a dissociation of bone expansion and bone mineralization during peak growth in adolescence(30;143).

Faulkner et al found a decrease in bone mass relative to bone size before the age at PHV (11.9 years in girls and 13.6 years in boys) followed by a rebound after the age of PHV (Figure 1.10) (30).

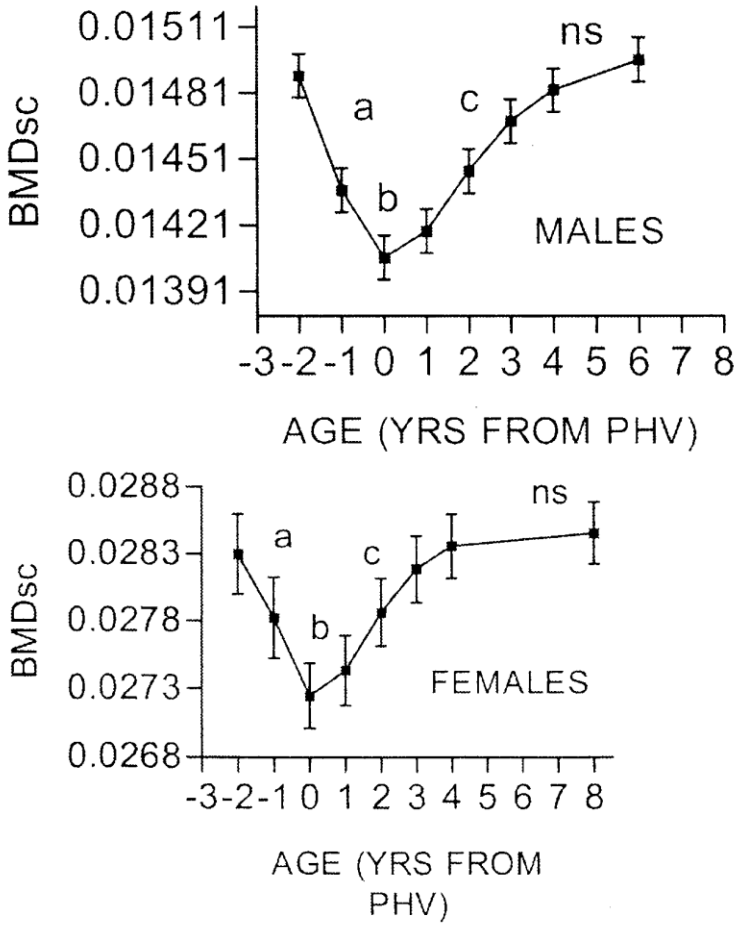


Figure 1.10 Size-corrected BMD (BMDsc) for males and females by biological age. Units for BMDsc are g/cm $^{3.11}$ for boys and g/cm $^{2.94}$ for girls (n = 32 for boys and 27 for girls). ^{a} Significant difference in BMDsc from peak height velocity (PHV) to -2 to -1 years before PHV; ^{b} significant difference in BMDsc from PHV to -1 years before PHV, ^{c} significant difference in BMDsc from PHV to +3 and +4 years from PHV; ^{ns}no difference between +4 years from PHV and young adult value. All values are significant at $p < 0.05$. (Source: Faulkner et al. JBMR 2006; 21(12):1864-1879)

The age of peak BA velocity significantly preceded the age of peak BMC velocity in both boys and girls ($p < 0.05$). In boys, peak BA occurred at 13.69 ± 0.96 years and peak BMC occurred at 14.14 ± 1.05 years; in girls, peak BA occurred at 12.19 ± 0.89 years and peak BMC occurred at 12.67 ± 0.99 years (Figure 1.11) (30).

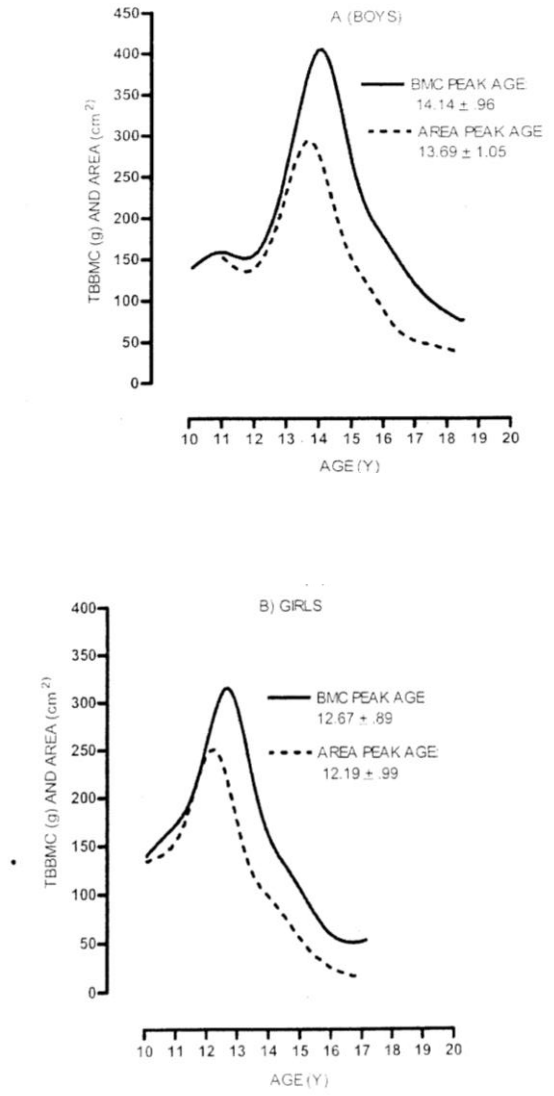


Figure 1.11 Comparison of ages of peak BMC velocity and peak BA velocity for (A) boys and (B) girls. (Source: Faulkner et al. JBMR 2006; 21(12):1864-1879)

In postmenopausal women, a later age at menarche (after 15 years of age) is associated with lower aBMD at several skeletal sites, including forearm, spine, and proximal femur(144-149) and is also associated with increased risk of forearm, vertebral, and hip fractures in the postmenopausal period(150-153). Menarcheal age together with differences in the duration and/or intensity of oestrogen exposure during growth are commonly accepted to play a significant role in the attainment of peak bone mass and structure(154-156). However, this somewhat intuitive explanation, the peak bone mass being related to the timing of menarche and duration of oestrogen exposure has recently been challenged by considering that both pubertal timing and peak bone mass are traits under the strong influence of heritable factors(157). Chevalley et al, hypothesized that both menarcheal age and bone mineral mass acquisition may be predetermined, and that the low bone mass apparently associated with later menarcheal age could already be detectable before the onset of pubertal maturation(158). To test this hypothesis, these authors followed up healthy subjects in Geneva from a mean age of 7.9 to 20.4 years and found that the difference in peak bone mass in girls with earlier than later menarche is generated before and not during pubertal maturation. In the Gothenburg Osteoporosis and Obesity Determinants (GOOD) study on young adult Swedish males between 18 to 20 years of age, the age at peak height velocity was a clear predictor of previous upper limb fractures(32). After adjustment for radius aBMD, age at peak height velocity no longer predicted previous fractures, indicating that reduced BMD in boys with late puberty might be of importance for the mechanical strength of the skeleton already present before peak bone mass is achieved (32).

The peak incidence of fractures occurs in girls between 11-12 years and in boys between 13-14 years of age(6;9;23). This period corresponds to the age of peak height velocity (PHV) in both genders and precedes by nearly one year the time of peak bone mineral

accrual(29). Other authors have found that growth in size precedes increases in bone mass(159), and peak velocity in BMC occurs six months later than PHV(160) and peak calcium accrual(161). Bone turnover and remodeling are dramatically increased during growth, and markers of bone turnover peak in boys around aged 14 years and in girls around aged 12(162); during this time of high turnover there is relatively more undermineralized bone than at times of low turnover(38). It has also been speculated that a temporary increase in cortical porosity may occur through remodeling to provide calcium required for the rapidly growing metaphyses of the long bones during the adolescent growth spurt(163). It has been reported that the timing of peak total body BMC and menarche is coincident(164), and that there are site-specific differences in the tempo and pattern of skeletal development during the growing years(159).

Sabatier et al(165) reported a gain of 30% in spine BMD in girls between Tanner I and menarche and a more important increase of 23.6% in spine BMC between ages 12 and 13. Arabi et al(166) found the difference in lumbar spine BMD to be 43% between pre- and post-pubertal boys and 66% between pre- and post-pubertal girls and in both genders, BMC increased significantly with increments in pubertal stages at the total body less head site . This difference was lower at the cortical sites, indicating that the effect of sex steroids may be more pronounced on trabecular bone (166). Thus, the growth patterns at sites that have relatively more cortical bone (tibial shaft) may be different than at sites with relatively greater trabecular bone (distal radius or lumbar spine) which may in part reflect the different fracture incidence between cortical and trabecular sites(30). In the study by Cooper et al.(6), the fracture incidence of girls at the distal radius was about five times greater than at the tibial and fibular sites. In a cohort of 125 girls followed over a period of 8.5 years, prepubertal BMC at the radial diaphysis was an independent predictor of the relative risk of incidental fractures(167).

There were also deficits in bone mass gain at the spine and trochanter in those girls that fractured from the same cohort, supporting the hypothesis that a delay in bone widening during rapid longitudinal growth may be a major mechanism of childhood fracture(167). The girls with fractures also had lower bone mass at the radius, trochanter, and spine when reaching pubertal maturity indicating that the increased fracture risk was predetermined very early in life and remained unabated until the end of the skeletal development period(167).

Although studies have linked pubertal timing with peak bone mass; other studies have suggested that peak bone mass and fracture risk may be predetermined under the influence of genetic factors.

1.4.7 Exercise

The structural functions of bone are determined primarily by adaptation mechanisms to its loading environment and genetic factors(168;168). During exercise there is a combination of different loading forces (such as axial compression, bending, shearing and twisting) applied on bone, resulting in different effects on the structure of bone(168). Loading increases periosteal deposition and slows endosteal resorption or causes endosteal deposition depending upon the skeletal location(168). Mechanical properties are improved in response to loading, mostly through increases in periosteal deposition and particularly in children and adolescents(169;170).

Exercise influences the skeleton by three main mechanisms: a direct impact on bone that is translated into biological signals by mechanoreceptors; and indirect impact by improving muscle mass and strength that secondarily stimulates these mechanoreceptors; and

an indirect impact by inducing changes in hormone levels such as calciotrophic hormones, leptin and local factors (Figure 1.12) (168).

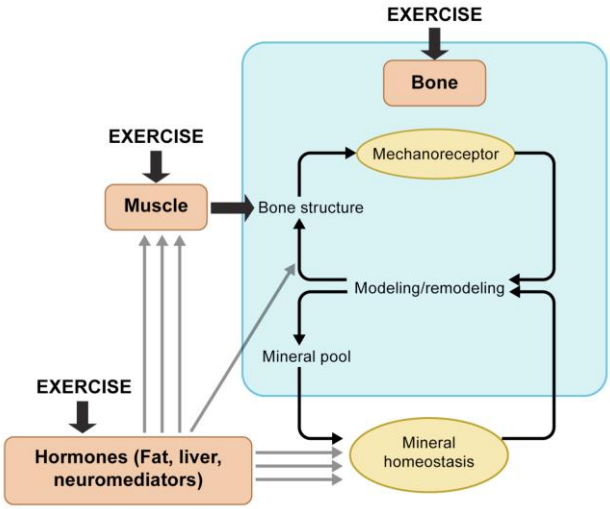


Figure 1.12 Schematic description of the effect of mechanical stimuli of the skeleton through structural adaptation of bone in the maintenance of physiological homoeostasis by employing the mineral reservoir embedded in the bone structure. During exercise load is transmitted to the skeleton through direct stimulation of bone mechanosensor and by indirect stimulation through dynamic muscle activity. Hormones from fat and liver modulate loading by affecting bone and muscle growth as well as muscle performances, and act indirectly through potential changes in the mineral reservoir. Recent data also underscore a paracrine role of muscle factors on bone adaptation in response to loading as well as the importance of neurons' capacity to change their function, chemical profile, or structure in response to mechanical stimuli, improving skeletal modeling/remodeling responses. (Source: Sievanen H. J Musculoskelet Neuronal Interact. 2005 Jul-Sep;5(3):255-61)

The mechanoreceptor, muscle and hormonal inter-relationship between bone and exercise is summarized and described below:

I. Mechanoreceptor-Bone-Exercise relationship:

Bonnet and Ferrari(168) have described the effects of direct mechanical stimuli on bone that have resulted from three main observations:

Firstly, bone adaptive responses require dynamic rather than static mechanical stimuli. Although bone formation increases with the degree of bone deformation after a certain threshold level has been reached for deformation, the bone formation response plateaus.

Secondly, extending the duration of skeletal loading does not yield proportional increases in bone mass as it does with the frequency of exercise. As loading duration is increased, the bone formation response tends to fade as the osteocytes and/or osteoblasts sensing the signals become desensitized. As a corollary, adaptive bone responses are improved with brief, intermittent exercise.

Thirdly, the orientation and magnitude of stress on the skeleton during exercise must differ from the usual pattern of bone loading in order to produce a maximal stimulus on bone formation.

Osteocytes seem to be the most appropriate cells to sense the magnitude and direction of mechanical strain. They are thought not to respond directly to mechanical strains but rather to extracellular fluid waves in the osteocystic lucanae and canalicular system generated by the loading stimuli(171). Mechanoreceptors present on osteocyte dendrites in turn generate small changes in electrical charges, activate calcium channels, and/or stimulate the release of molecular mediators such as prostaglandin through the activation of cyclooxygenase-2 (COX-

2) and nitric oxide(172). The actions of these mechanoreceptors and molecular mediators further communicate the mechanical signal to osteoblasts at the periosteum, and to osteoblasts and osteoclasts intracortically that act at endocortical surfaces(172). Another possibility is that osteocytes, mesenchymal stem cells and/or osteoblast lining cells sense strain at their plasma membranes through stretch-activated ion channels that permit calcium flux, potentially initiating other intracellular responses (173).

These biochemical signals have three primary functions: activation of transcriptional mechanisms regulating bone modeling/remodeling, and propagation of mechanical information to other osteocytes through paracrine effects and transmission of other chemical signals by gap junctions(174;175). There are many mechanotransduction mechanisms activated in response to exercise and the convergence of these pathways results in the activation of select transcription factors such as β-catenin implicated in the Wingless-related integration site/Low-density lipoprotein receptor-related protein (Wnt/LRP) pathway, the most important pathway both in osteoblasts and osteocytes playing a major role in mediating mechanical loading(168).

II. Muscle-Bone-Exercise relationship:

The strong association between muscle mass/strength and bone anabolism and catabolism during growth, development and even during ageing highlights the important interaction of these two systems to optimise mobility and functioning(176). Lean mass is equivalent to muscle mass in the extremities (177) and a surrogate measure of muscle force (178). Despite lean mass development being a good predictor for BMC and areal density accrual during growth in children, it has been suggested that loading-related factors such as

increased physical activity and sport could have a greater influence on bone development than just the enhancement of muscle mass. The muscle-bone relationship during growth could presumably be explained by the mechanostat theory (178;179), as bigger muscles exert higher tensile forces on the bones to which they attach(69). Muscle contraction can activate bone mechanoreceptors (figure 1.10) particularly in the periosteum where tendons are attached(168). In fact, 70% of the tension exerted on bone depends on muscle contraction, which is therefore more important than body weight itself as a mechanical stimulus (180) . There is a 22-42% increase in areal BMD per unit of lean mass in physically active boys compared to age, height and body mass-matched sedentary controls(181;182). The lean (muscle)-bone association may arise because mechanical loading is exerted by exercise in active boys to increase both muscle and bone development(69). Therefore, exercise could drive the direct osteogenic effect and following the mechanostat theory, an indirect osteogenic effect by increasing muscle size and strength and hence tensions generated on bones(69).

III. Hormonal-Bone-Exercise relationship:

An acute bout of exercise can increase concentrations of anabolic hormones, such as growth hormone (GH) or IGF-1, and follicle stimulating hormone/ luteinising hormone /oestrogen, across a wide age range(183). Exercise modifies the flow of GH secreted by the pituitary gland and thus the liver production of IGF-1. The stressing effects of exercise on serum glucose levels (hypoglycaemia) cause a rise in the amplitude and frequency of GH/IGF-1 production (184;185). The activation of mechanoreceptors during exercise causes IGF-1 to be secreted by bone and muscle cells (186) and furthermore IGF-I expression is increased in osteocytes and bone-lining cells within six hours of mechanical loading(187). Conversely, the

low bone formation associated with immobilisation is due in part to resistance to the effects of IGF-1 on bone formation(188). Maximal exercise independently increases parathyroid hormone (PTH) levels of sex, age and training status(189-191) and is also thought to regulate adipokines (such as leptin), and enterokines (such as ghrelin) (192;193). It was reported recently that variations in the circulating level of calciotropic hormones (PTH, vitamin D metabolites, and calcitonin) related to physical activity may modulate the bone tissue response to exercise (194) and that intermittent release of PTH during exercise is a systemic mediator of the anabolic actions on bone tissue(195). Evidence has shown that the administration of PTH before mechanical stimulation significantly increases the osteogenic response (196-198). This could be mediated by a PTH-stimulated production of prostaglandin-E2 (PGE2) (199), and an increase in the activation of intracellular calcium, an important second messenger in the mechanicotransduction cascade (196).

Exercise can effectively improve bone mass, structure and strength, provided it is administered early in life, and with sufficient loading intensity and frequency(168;200;201). Tensile, compressive, shear, bending, and torsion stresses applied during exercise and sport, have an osteogenic potential by eliciting mechanostat-related mechanisms during growth.

Physical Activity Guidelines for children and adolescents recommend that young people should accumulate at least 60 minutes (up to several hours) of moderate-to-vigorous physical activity (MVPA) per day and at least 3 days per week this should include activities to improve bone health and muscle strength(202). A positive association was shown between total hip BMC and the time spent (minutes/day) in vigorous and total physical activity in Swiss boys aged 6-13 years(203) whilst another study of boys and girls aged 11 years in the

United Kingdom showed a positive association between lower limb BMD and the time spent (minutes/day) in MVPA(201). A more recent study in Portugal found a region specific bone response to vigorous physical activity in pre-and early pubertal girls and boys with the more active girls having greater BMD in the trochanter and inter-trochanteric region and more active boys having greater BMD in all sub-regions of the proximal femur(204).

Studies have shown that the most effective period during which to observe a larger increase of bone mineral mass with exercise is during adolescence, especially during the prepubertal years (205;206). A controlled 9-month high-impact exercise training trial found that in premenarcheal girls high-impact exercise had a clearly positive effect on the BMC of the lumbar spine and femoral neck whereas no training effect was seen in postmenarcheal girls however this study did not answer whether this bone benefit is retained once the training stimulus ceases (207). Sports participation during growth increases the peak bone mineral density in weight loaded bones of the active subjects by 10-20% compared with non-physically active counterparts (208). Sport participation acts synergistically with the growth-related bone mass accumulation during the pubertal period leading to higher bone mass during this period (209;210). Physical activity should include activities that generate high ground-reaction forces, such as jumping, skipping and running and should last at least 7 to 20 months, to increase bone mass by about 2% in weight-bearing sites such as the femoral neck and spine (23). Soccer is an intense, weight-bearing intermittent sport and the forces generated while rapidly changing direction, stopping and landing, as well as during jumping and kicking may confer excellent osteogenic properties to soccer, especially in weight-bearing sites(211). Male soccer players showed 10-20% higher BMD than controls in the lower limb(212;213). Soccer participation was positively associated with improved physical fitness and increased BMD in the lower limb, lumbar spine and whole-body, as well as with higher leg muscle strength,

indicating that the muscle-skeletal structures respond positively to the weight-bearing and impact-loading imposed by soccer practice(214). However, girls practicing gymnastics exhibit higher BMD and bone diameter at the midshaft tibia and femur compared to girls playing football(200).

It has been reported that more than half of the BMC gain (+3.5% after 7 months of exercise versus controls) induced by jumping in pre-pubertal boys and girls was lost over 8 years (215), that is even before these subjects reached peak bone mass. To understand this phenomenon, the 'Achilles tendon of the exercise effect', it should be kept in mind that 80% of peak bone mass is genetically determined (216;217). Hence an initially greater bone mass (just after the intervention) may subsequently be remodeled to ultimately reach its genetically determined target(168).

Despite the positive effects of physical activity on bone mass reported above, sports participation and physical activity increases fracture prevalence during childhood(22;37). Studies on the epidemiology of childhood fractures suggest that 36%(21) to 52%(218) of fractures are related to sporting activities, many of which may involve vigorous physical activity, suggesting that exposure to injuries is an important determinant of childhood fracture risk(110). Among children from the ALSPAC at age 9.9 years, an estimated vBMD or bone size relative to body size in the highest tertile and daily or more episodes of vigorous physical activity resulted in tripling of fracture risk(110). Physical activity with a small chance of injury probably increases bone mass and may reduce fracture risk(132), whereas vigorous physical activity or contact sports participation probably also increases bone mass, but because of increased numbers of injuries, also increases fracture risk(110). Detter et al study showed that a general, moderately intense, school-based exercise intervention program in prepubertal children with 5 years' duration improved bone mass and in girls also skeletal architecture

without increasing fracture risk(219). Thus moderate physical activity rather than vigorous physical activity ought to be introduced to younger children with less detrimental effects.

Studies from Tasmania have shown that time spent in front of the computer or videos or playing on a computer was associated with increased upper limb fractures in both boys and girls(132;220). A strong correlation between time spent daily in front of the computer and multiple fractures was also noted by Konstantynowicz et al(22). This association between fractures and time spent watching television was not replicated in the ALSPAC study and the authors postulated that the reasons for this discrepancy in results were due to a smaller sample size in the Tasmanian study and the use of time spent watching TV as a proxy for less physical activity(110). Furthermore, a meta-analysis suggests that the relationship between TV viewing and physical activity in children is negative but small, and watching television may replace other sedentary activities such as reading rather than replacing physical activity(221).

Males generally are more actively involved in sport and team games, thus are more exposed to physical injury and fractures(13;19). Higher levels of physical activity were noted in males than females, with males having a higher prevalence of multiple fractures(22).

1.4.8 Seasonal variation and vitamin D status

Fracture incidence might be expected to show seasonal variation since work and leisure activities, climate and other factors vary throughout the year(222). Two studies have shown that upper limb fractures occur predominantly in the summer months(222;223), when better weather encourages an increase in outdoor activities whilst another study suggested that lower limb fracture admissions occur more in summer than in other seasons(224). Not only does fracture incidence vary with seasonal but so does vitamin D status in childhood which

may impact on underlying bone mass. Vitamin D plays a major role in bone metabolism and mineralization. Concentrations of serum 25-hydroxyvitamin D (25(OH)D) above 50nmol/L are considered to be normal but there is debate about the level of this threshold(225) and the optimal level for bone health maybe above 50nmol/L. Overt vitamin D deficiency leads to rickets and subclinical deficiency may result in lower peak bone mass being attained as assessed by DXA which could in turn contribute to increased fracture risk in childhood and older life. Despite adequate sunshine in certain regions of the world and fortification of food and dairy products with vitamin D in many countries, vitamin D deficiency has resurfaced in developing and developed countries. The major worldwide problems leading to vitamin D deficiency are lack of sun-exposure, breastfeeding without supplementation, individuals with increased melanin pigmentation; use of sunscreens and religious/social practices that limit adequate sun exposure. An association between both lower bone mineral density and vitamin D deficiency and increased risk of fracture has been shown in African American children together with a dose-dependent relationship between forearm fracture risk and 25(OH)D levels(226). There is no other direct evidence describing the association of vitamin D deficiency and fractures in childhood. In a systematic review and meta-analysis study, wherein the mean baseline serum 25(OH)D level of the children was low (<35nmol/l), there were statistically significant effects on total body bone mineral content and lumbar spine bone mineral density after vitamin D supplementation however when data was analysed together regardless of the mean baseline serum 25(OH)D; there were no statistically significant effects on total body BMC, hip and forearm BMD(227).

Targeting children and adolescents with low vitamin D status could result in clinically important improvements in bone density and peak bone mass and thus reduce fracture risk in both childhood and adulthood.

1.4.9 Socio-economic status (SES)

Social deprivation has been shown to be an important factor in childhood and adolescent injury(228;229). Children from lower socio-economic backgrounds tend to live in higher population density neighbourhoods with more traffic and fewer playgrounds, and perhaps reduced use of safety measures at home and in play(230). The risk of childhood injuries is intensified by the presence of social conditions associated with poverty such as single parenthood, teenage parents, and lower levels of parental education, large family size, lack of affordable day-care, and drug and alcohol abuse. Lower SES is an independent and significant predictor of risk in fractures of the hand and upper limb in adolescent males and in fractures of the upper limb and distal radius in adolescent females(231). Court-Brown and Brydone(232) examined the relationship between tibial diaphyseal fractures and social deprivation and found that the most affluent patients tended to sustain their fractures in sporting activities and the most deprived from assault or direct blow injuries and this finding was also noted in children residing in Wales(229). However not all studies have supported the association; a prospective cohort study conducted in Brazil found that socio-economic indicators such as family income and maternal schooling were not associated with the incidence of fractures(104). A similar finding was reported from a study performed in Alberta between April 1995 and March 1996, which found that fractures were not associated with SES(230).

Several different types of environmental exposures have previously been found to be associated with peak bone mass acquisition in childhood, such as nutrition and weight-bearing

physical activity(1). Social status may influence bone mass acquisition in childhood because nutrition and physical activity both show social gradients(233).

Data from the ALSPAC cohort in the United Kingdom showed that social position is directly related to bone mineral content of adolescents meaning that social position is positively associated with BMC and the higher BMC may reduce their risk of fracture(76). Similarly in a lower middle income country, a study found that in girls from lower socio-economic status in India, later onset of puberty and menarche together with lower calcium and protein intake were important contributors to lower bone mass in these underprivileged girls(234). After adjusting BMC for confounders such as lean mass, calcium levels or intake and physical activity, the Helena study on Spanish adolescents showed that SES assessed by the Family Affluence Scale, parental education and occupation is not related with BMC in adolescents(235).

Clark et al described the two opposing influences of social position in pregnancy on bone mass acquisition in childhood(233). Firstly, a higher socioeconomic status during pregnancy tended to increase bone mass and skeletal area in childhood due to the positive effects of longitudinal growth and secondly, children born to mothers of lower socioeconomic status were shorter but their BA and BMC seemed to be preserved as a consequence of their greater fat mass(233). These proposed apposing effects of social position in pregnancy are schematically shown in Figure 1.13 (233).

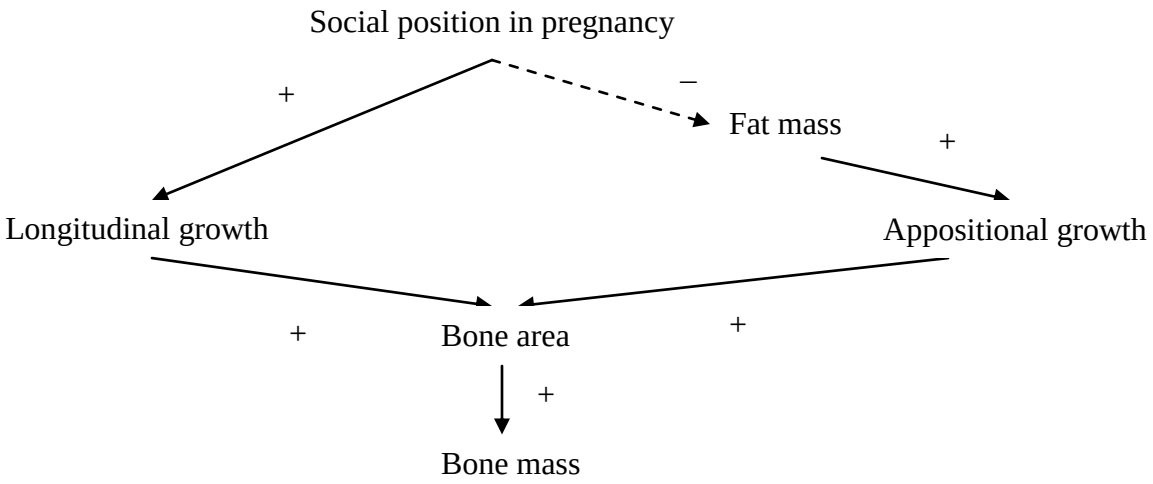


Figure 1.13 Proposed relationships between social position in pregnancy and skeletal growth, fat mass, and bone mass in childhood (solid arrows, positive associations; dashed arrow, negative association). (Source: Clark et al. JBMR 2005; 20:2082-2089.)

The appositional growth of bone is the process by which bone increases in diameter. Bone area is an indirect measure of appositional growth, and the preservation of bone mass and bone area in children of lower SES reflects a positive effect of fat mass on periosteal bone formation. Furthermore, this positive effect of fat mass on preservation of bone mass and bone area may not apply to skeletal fragility and fracture risk. A higher bone mass might be expected to increase skeletal strength and reduce fracture risk more effectively when this occurs in the context of increased appositional rather than longitudinal growth, because of the strong relationship between subperiosteal expansion and bending strength(233;236). Findings from the ALSPAC study suggest that social status may be inversely related to skeletal strength in childhood but previous epidemiological studies in the United Kingdom have reported either no relationship between fractures and social status in children or that fractures are more common in children from poorer backgrounds(228;229;233;237).

Finally, the above findings probably indicate that socioeconomic differences in childhood fracture rates may be unrelated to underlying skeletal strength but more likely due to differences in risk of injury with more affluent populations sustaining fractures from sporting activities and the less affluent from violence, assault and less adult supervision during recreational activities or play. The most recent study in Washington, DC strongly suggested that African-American race, lower education and large families were the more important factors associated with increased risk for childhood fractures(237).

1.5 Ethnic differences in fractures and bone mass in childhood

Adult studies have documented ethnic differences in bone mass and fracture risk(238;239). African American adults fracture less and have greater aBMD than Caucasian adults(238), and similarly South African black women have greater hip bone mass(85;86) and fracture less compared to South African white women(240).

Studies in the USA have shown that bone mineral density of the mid-radius, lumbar spine, trochanter and femoral neck are greater in African-American children than white children(241). Data from the Birth to Twenty cohort has previously shown that South African black children at various ages have greater BMD than their white peers at lumbar spine, proximal femur, femoral neck, midradius and whole body(242-245). Recently, Micklesfield et al have reported that South African black children, despite having a lower body weight than white children at age 13 years, have greater diaphyseal bone strength, as measured by pQCT(246). In the United States, black children have greater estimated bone strength, exhibit higher bone formation and lower bone resorption markers, and have lower 25(OH)D and higher PTH concentrations than white children(247). The greater pSSI in blacks results from

greater cortical bone density and larger cross-sectional areas and perimeters compared to whites. This findings together with those from a similar study (247;248), suggest that racial divergence in the structure and strength of the skeleton precedes puberty and these findings are consistent with bone mineral density measures by DXA(249;250).

The racial difference in BMC and aBMD, though not apparent in infancy(251), emerges by early childhood and persists through adolescence and young adulthood(241;251;252). Hui et al concluded that black children do not differentially gain bone faster than whites during the accelerated bone growth phase in puberty(250). It remains to be determined whether the racial divergence in total bone mineral accrual starts in early childhood(250). Genetic or environmental factors leading to such divergence also need to be explored(250).

The role of lifestyle factors such as physical activity in determining bone mass differences between South African ethnic groups has been investigated by McVeigh et al who only showed an association between physical activity and BMC and BMD, in South African white children at 9 years of age in the Birth to Twenty cohort(245). Increased physical activity has an association with bone mass in the White South African children but not in the black South African children because the latter, it is suggested, did not reach a high enough "threshold" of activity to induce an osteogenic stimulus(245;253). The reported lower physical activity levels in black South African children(245) were thought to be related to the lack of organized sports in schools attended mainly by black subjects and the poorer socio-economic status of the black families(254). Despite the higher physical activity in white children, black children still had a higher hip, mid-radial and lumbar spine (girls only) bone mass and similar values to their white peers at other sites(245;253).

In South African children differences in bone mass and geometry, and physical activity, between the ethnic groups may be contributing risk factors to fractures in the different ethnic groups that need to be investigated. Studies in the United Kingdom conclude that white children have significantly higher fracture rates than other non-white ethnic groups that included mainly blacks and Indians but the reasons as to why have not been elucidated (11;255). A prospective study on the ALSPAC cohort reported an inverse association between fractures and bone mass in children of different ethnic backgrounds but the sample numbers in non-white groups were too small to compare with the white group(76). A recent prospective multicentre study provided strong evidence that ethnicity is a major determinant of fracture risk in healthy children residing in the United States(256). Not only did they find a much higher fracture rate in non-Hispanic white children compared with children of other ancestry, they also reported that fractures occurred predominantly during physical activities such as sports and was more common in boys and during adolescence. Lastly, in general, these study findings were that of an inverse relationship between DXA bone measures and fracture risk but paradoxically, higher DXA values were associated with higher fracture risk in white males(256).

A differential effect of ethnicity on fracture risk has been well documented ever since it was noted more than 50 years ago that fracture rates are lower in the elderly blacks of both South African and American origin(238;240;257). This finding is not confined to the elderly but is also present in childhood and adolescence when bone acquisition, physical activity and the risk for trauma is greatest(256).

1.6 Summary of the literature review

a. Epidemiology of fractures in childhood

Fracture rates in childhood are as high as those in the elderly. Over one-third of boys and girls sustain at least one fracture before 17 years of age. Fractures of the upper limb are the more common sports related injuries in children and occurred mainly in boys during early to mid puberty and of white ethnicity. Boys tend to experience more multiple fractures than girls. A first fracture is associated with an increased risk of multiple fractures during growth.

b. Bone compartments and the various types of bone density

The composite tissue of bone is made up of an organic collagen matrix and an inorganic mineral hydroxyapatite. The biological organization of bone consists of three levels: material bone density ($BMD_{material}$), compartment bone density ($BMD_{compartment}$) and total bone density (BMD_{total}).The two types of bone tissue are namely trabecular and cortical bone tissue. Both trabecular and cortical compartments together with their relative volumes are utilized to determine BMD_{total}. As bone grows in childhood, the relative volumes of each compartment change; resulting in changes in $BMD_{total.}$ Techniques that measure bone mass in children may quantitate bone mass of the whole bone or of a bone compartment. Further they may measure cortical or trabecular bone mass or a combination of the two. The trabecular bone tissue is found mainly in the vertebrae and ends of long bones while cortical bone is found in the shafts of long bones.

c. Bone mass in children

The two main methods being utilized to assess bone parameters in children are DXA and pQCT. DXA measures bone in two- rather than three-dimensions therefore it is difficult to interpret BMD changes during childhood using DXA because of the continual change in volumetric size of bone during growth, whereas pQCT is a type of computed tomography used to measure volumetric BMD in the peripheral skeleton as well as bone strength and structure.

Rapid bone growth occurs during childhood and bone modeling causes an increase in bone size. Modeling is the process of changing the shape of bone in response to growth and changes in weight bearing and muscular stresses. Bones grow in width by the formation of new bone on the outer or periosteal surface, while resorption occurs on the inside, or endosteal surface, of the bone. Genetics, strains on bone from physical activity and loading, and gains in body weight during growth determines the degree and amount of modeling.

Optimizing bone mineral accrual early in life may prevent childhood fractures and possibly delay the development of osteoporosis later in life. This has to be further investigated in randomized control trials.

d. Factors associated with childhood fractures and their association with bone mass

An understanding of the many related risk factors for fractures is important for deciding rational strategies for optimizing bone health during childhood.

i. Low bone mass

A number of studies have linked bone mass to fracture while others have not. Some studies have found that children who sustain one or more fractures have a lower bone mass throughout the skeleton than those who remain fracture-free.

ii. Heritability

Gains in bone mineral accretion during childhood via interventions such as increased physical activity and nutrient supplementation may only be transient, thus promoting the hypothesis that bone is ultimately governed by a homeostatic system which tends to return towards a yet-to-be defined set point.

Heritability has been estimated to contribute to more than 40% of the variance in adult BMD. Heritability of BA and BMC, by maternal descent is approximately 30% in South African pre/early pubertal black and white children, despite ethnic differences in both body and bone size, as well as in lifestyles.

iii. Maternal and early life influences

There is growing evidence that BMD and thus fracture or osteoporosis risk can be modulated during intrauterine and infant life.

Higher birth weight is a determinant of a better bone health later in life and this effect is seen in both BMC and BMD of children. This finding is supported by a greater bone size and bone strength in late middle age and the postmenopausal period. These results suggest that there could be bone mass programming in early life.

There is contradictory evidence on maternal and early life factors and fracture risk in later life. Children who were born with above average length and who were heavy and tall throughout growth had an increased risk of fracturing during childhood and adolescence.

In accordance with the hypothesis of developmental origins of diseases and the evidence from the literature, bone mass and fractures in childhood and adolescence seem to be partially programmed in early life.

iv. Nutrition

Retrospective studies generally show that low consumption of milk during childhood and adolescence is associated with higher risk of fracture later in life. An inadequate protein supply appears to play a central role in the pathogenesis of the delayed skeletal growth and reduced bone mass that is observed in undernourished children.

Longitudinal prospective studies are needed to determine the importance to maintain a bone healthy diet to maximize peak bone mass and to reduce the risk of fractures in both childhood and adulthood.

v. Obesity

Contradictory results are being reported on skeletal mass in overweight or obese children. Some studies indicate that overweight children have higher BMC whereas others conclude that obesity is associated with a lower bone mineral content. Since most studies found a normal or increased bone mineral content in obese children, the main conclusion is that obese children have decreased bone mass and bone area relative to their body weight.

Obesity and high body weight have been identified as risk factors for fractures and recurrent fractures.

vi. Puberty

Puberty is not only a period of rapid longitudinal growth and accrual of bone mass, but also a period of high incidence of fractures. The pathophysiology for this high rate of fracture during growth is not clear; however, it has been suggested that one of the mechanisms may be the dissociation of bone expansion and bone mineralization during peak growth at adolescence.

vii. Exercise

Studies have shown that the most effective period during which to observe a larger increase of bone mineral mass with exercise is during childhood and adolescence, especially during the prepubertal years.

Studies on the epidemiology of childhood fractures suggest that 36% to 52% of fractures are related to sporting activities, many of which may involve vigorous physical activity, suggesting that exposure to injuries is an important determinant of childhood fracture risk.

viii. Seasonal variation and vitamin D status

There is not much evidence showing an association between vitamin D deficiency (other than in frank rickets) and fracture risk. Two studies have shown that upper limb fractures occur predominantly in the summer months when better weather encourages an increase in outdoor activities whilst another study suggested that lower limb fracture admissions occur in summer than in other seasons.

Whether targeting children and adolescents with low serum vitamin D concentrations would result in clinically important improvements in bone density and peak bone mass, thus

reducing future fracture risk in both childhood and adulthood is questionable. This question warrants further investigations and research.

ix. Socio-economic status (SES)

Socioeconomic differences in childhood fracture rates may be unrelated to underlying skeletal strength but more likely due to differences in risk of injury with more affluent populations sustaining fractures from sporting activities and the less affluent from violence, assault and less adult supervision during recreational activities or play.

e. Ethnic differences in fractures and bone mass in childhood

A differential effect of ethnicity on fracture risk in adults has been well documented ever since it was noted more than 50 years ago that fracture rates are lower in the elderly black subjects both in North America and South Africa. This finding is not confined to the elderly but is also present in childhood and adolescence when bone acquisition, physical activity and the risk for trauma is greatest.

In South African children differences in bone mass and geometry, and confounding factors such as differences in physical activity, between the ethnic groups may be contributing risk factors to fractures that need to be further investigated.

1.8 Gaps in the literature

More research needs to be undertaken to investigate and understand how bone mass develops during childhood and adolescence and the relationship between fracture risk and bone mass prior to young adulthood. The studies which will be presented in this thesis will

provide an improved understanding of childhood fractures and the physiopathology of low bone mass and will help to establish preventative strategies to lessen the burden of childhood fractures. There has also been emerging research on ethnic differences in bone mass and fractures in children but the data is limited in terms of the ethnic disparities between the association of fractures, related risk factors, heritability and bone mass in children. The pattern and incidence of childhood fracture rates amongst the various South African ethnic groups have not been investigated previously. Further, the contribution of bone mass and physical activity to ethnic differences in fracture risk, and the familial relationship between first degree relatives with regard to fracture and bone mass patterns amongst children of different ethnic groups have not been studied. Few studies have been conducted utilizing pQCT in children to determine whether a relationship exists between bone size, bone geometry and bone strength and fracture risk. There is also a need for studies to determine if assessing trabecular volumetric BMD could enhance fracture prediction during growth in healthy and chronically ill children.

Lastly, if this study confirms that there are ethnic differences in fracture rates in South African children, further studies using different techniques such as pQCT, will be required to teaze out the underlying physiological mechanisms for these ethnic differences.

CHAPTER 2

This chapter describes the aims, objectives and the hypotheses of this study based on the gaps in the literature that were highlighted in chapter 1. The study population, methods utilized and the statistical analyses performed in the study are explained in detail in this chapter.

Aims

To investigate the epidemiology (number and pattern of fractures) and risk factors for fractures in children and their siblings of black, white, mixed ancestry and Indian ethnic origins in Johannesburg, South Africa; and to determine the association between fractures and bone mass in these children and their biological mothers.

Objectives

1. To determine the incidence or rates of fractures, their common sites of occurrence, their causes and the grades of trauma associated with fractures in urban South African children of different ethnic groups from birth until 17/18 years of age.
2. To investigate the associations between fracture prevalence for the first 15 years of life and bone mass, body composition and physical activity at ages 10 and 15 years in these children.
3. To assess the fracture patterns and bone mass of South African adolescent-biological mother pairs.

4. To determine if a familial association exists between first degree relatives (biological mothers and siblings) and the cohort children of different ethnic groups with regard to the prevalence of fractures.

Study hypotheses

1. South African black children fracture less than white children; an ethnic pattern that is seen in the post-menopausal South African population.
2. All ethnic groups have a similar pattern of age and sex related distribution of fractures.
3. There is a strong association between mothers' and their adolescents' bone mass measurements.
4. Maternal bone mass is associated with fracture prevalence in their adolescent offspring; and a history of fractures in the mother or other siblings is associated with a history of fractures in the adolescent.

Study population

The study is based on data obtained from a longitudinal cohort of children (the Birth to Twenty cohort) who have been living in the Greater Johannesburg metropolitan area since their births in 1990. More detailed information was also obtained from the sub-cohort (the Bone Health sub-cohort) from the age of 9 years for the purpose of this study. The demographics and origins of these cohorts are described in more detail below.

The Birth to Twenty cohort and the Bone Health sub-cohort:

The longitudinal Birth to Twenty study (Bt20) is based on a cohort of urban children, which included all singleton neonates delivered within the public sector hospitals within Johannesburg and Soweto between April 23 and June 8 1990 and who were still resident in the greater Johannesburg area six months after delivery, with the aim of tracking their growth, health, well-being and educational progress. 3273 singleton neonates were enrolled. The total cohort is demographically representative of long-term resident families living in Johannesburg-Soweto. However, the cohort under represents white children due to white families frequently utilizing private practitioners and facilities for maternity services and thus not being enrolled. The Bone Health study is a sub-cohort nested within Bt20 and was constituted when the children were 9 years of age in 1999 to investigate in more detail factors influencing bone mass accretion during puberty and adolescence. The Bone Health study was a random sample of 682 children, stratified by ethnic group (black and white), gender, and socioeconomic status. The Bt20 and Bone Health cohort were cross-checked to ensure that there were no significant differences between the samples for key demographic variables such as residential area at birth, maternal age at birth, gravidity, gestational age, and birth weight. To compensate for the under-representation of white children in this sub-cohort, a supplementary sample of 120 white children born during the same period in 1990 were recruited at the age of 10 years into the Bone Health sub-study. These additional children were the same age as those of the original cohort and were selected from schools in the greater Johannesburg metropolitan area. They were asked to volunteer to participate in the study. There were no differences in birth weight, maternal age and education, and socioeconomic status between the supplementary children and the original white participants of the cohort.

Children who had chronic diseases such as rheumatoid arthritis, epilepsy and asthma were excluded from the data analyses, as the use of certain medications and immobility are risk factors for low bone mass and may increase the incidence of fractures.

Of the 3273 children in the cohort initially, contact had been maintained with more than 70% at the age of 16 years. A cohort profile describing the study sample, research objectives and attrition has been documented by Richter et al.(258). The child's ethnic classification was defined by the race classification currently in use in South Africa for demographic and restitution purposes. Although the South African government currently classifies race into black (ethnic Africans), white (Europeans, Jews and Middle Easterners), mixed ancestry (mixed race) and Indian (Asian), only children for whom both parents were classified as either white, black, mixed ancestry or Indian were included in this study. Participants were born prior to the HIV epidemic in South Africa and thus were unlikely to suffer from HIV. The reported child mortality in the original Birth to Twenty cohort of some 3200 participants by age 10 years was 28 participants and this number had increased to 40 by age 15 years. This mortality rate also did not include children that demised in the first 6 months of age as one of the mandatory selection criteria was that the baby and mother had to remain in the area until the child was 6 months old. The cause of death was mainly accident/trauma related. Thus the bone mass demographics were unlikely to be affected by chronic illnesses or death.

All subjects provided assent and their parents provided written, informed consent; ethical approval having been obtained from the University of Witwatersrand Committee for Research on Human Subjects (ethics clearance number: M071132 (appendix A)).

Study subjects

The Birth to Twenty cohort was used to determine fracture incidence in children. Fracture histories from 2031 children were analyzed to meet the first objective of this thesis to document fracture incidence and patterns in children up to 14.9 years of age. The ethnic breakdown of this study sample was predominantly black (B) (1600 [78%]), with the remainder of the cohort being made up of white (W) (188 [9%]), mixed ancestry (MA) (213 [10.5%]) and Indian (I) (30 [1.5%]).

Information on fractures between 15 and 17/18 years of age was also obtained from 1813 children so as to provide data on fracture incidence and patterns in adolescents beyond 14.9 years of age. The number of study participants at 17/18 years was lower than at 15 years due to a poorer follow-up at 17/18 years as these adolescents were older and less committed.

The Bone Health cohort (533 children) was used to assess the relationship between fracture and bone mass, body composition and physical activity (objective 2 of the thesis) which is discussed in more details below.

Data from 1389 adolescent-biological mother pairs from the Birth to Twenty (Bt20) longitudinal study of child health and development were utilized to meet objectives 3 (to assess the fracture patterns and bone mass of South African adolescent-biological mother pairs) and 4 (to determine if a familial association exists between first degree relatives and the cohort children of different ethnic groups with regard to the prevalence of fractures) of this thesis. The relatively small number of mother-child dyads was as a result of the mothers' bone mass measurements being performed when the adolescents were aged 13 years. During the time period between birth to 13 years, a number of mothers had either demised or were no longer staying with the adolescent. The children in such situations were generally cared for by grandmothers.

Methods

Fracture questionnaires:

A fracture questionnaire (appendix B) was completed by each adolescent at age 15 years and verified for completeness and accuracy by the parent or primary caregiver of the child. The questionnaire included information on previous fractures, their sites with the aid of a skeletal diagram, the causes and age at fracture. The methodology used for year 15 fracture data collection was able to confirm the age, site and cause of previous fractures that had been recorded at year 13 (fracture questionnaire not included) and also collected information on new fractures occurring between 13 and 14.9 years. The grading of severity of trauma causing fractures was classified into slight (grade 1), moderate (grade 2) or severe (grade 3) (Table 2.1). The definitions were slightly modified from Landin (9) and Manias et al (37) to be appropriate for local conditions as skiing and other similar snow/ice related activities are generally not available in South Africa and to simplify the classification all sport injuries were classified as grade 2 trauma.

Table 2.1 Grades of trauma causing fractures

Grade 1 (Slight)	• Falling to the ground from standing on the same level • Falling from less than 0.5 metres (falling from stools, chairs and beds)
Grade 2 (Moderate)	• Falling from between 0.5 – 3 metres • Falling down stairs, from a bicycle, roller blades, skateboard or swing • Playground scuffles • Sport injuries
Grade 3 (Severe)	• Falling from a height > 3 metres (falls from windows or roofs) • Motor vehicle or pedestrian accidents • Injuries caused by heavy moving or falling objects (e.g. bricks or stones)

A second fracture questionnaire (appendix C) was completed by each adolescent with the help of his/her parent or caregiver at 17/18 years of age. At age 17/18 years, the fracture questionnaire included information on fractures since their previous questionnaire.

Mothers/caregivers also completed a questionnaire on fractures occurring since birth in the adolescent's sibling/s (appendix D). Biological mothers completed questionnaires on their own fractures prior to the age of 18 years (appendix E).

Due to the retrospective nature of the fracture data collection, the fractures could not be verified by radiographs. Six months to a year after completing fracture questionnaires at age 17/18 years, verification of fracture data was done telephonically by randomly sampling 51(9%) participants with a history of fractures. Initially 56 participants with a history of fracture were randomly selected for telephonic verification of fractures. This was 10% of the total number of reported fractures, however only 51 participants could be contacted. The questionnaire (appendix F) used to verify the fractures included information on the side, site and cause of the last sustained fracture together with information on how, where and by whom the diagnosis of the fracture was confirmed, whether radiographs were performed, what treatment was offered and if any records were available.

Anthropometric measurements, skeletal maturity and DXA-derived parameters of children at 10 and 15 years enrolled in the Bone Health cohort:

Anthropometric measurements, skeletal maturity and bone mass data has been obtained annually from the age of 9 years when the participants of the Bone Health cohort were first enrolled. Data at age 10 years (pre- or early puberty) and 15 years (mid- or late puberty) were used for the present studies. Height was measured to the nearest millimetre using a stadiometer (Holtain, Crosswell, UK). Weight was measured to the last 100g using a

digital scale (Dismed, Halfway House, South Africa) with participants wearing light clothing and no shoes. Skeletal maturity was assessed by a trained expert by scoring bone age from hand radiographs using the Tanner-Whitehouse bone-specific scoring technique (TWIII 20)(259).

Total body less head bone area (TBLH BA), total body less head bone mineral content (TBLH BMC), whole body composition (fat mass and lean mass) and site-specific measurements of bone area (BA) and BMC at the radius (R), hip (H), hip neck (HN) and lumbar spine (LS) were performed using an Hologic QDR 4500A dual-energy X-ray absorptiometer (DXA) according to standard procedures (software version 11.2, Hologic, USA). The data were analysed with the software supplied by the manufacturer, version 11.2. A lumbar spine phantom was scanned daily to determine the machine's measurement precision, expressed as the coefficient of variation (CV) which for BA and BMC were 0.47% and 0.78% respectively. All measurements were performed and analysed by the same person.

Assessment of physical activity levels from the Bone health cohort:

Questionnaires quantifying total physical activity (PA) for the previous 12 months were administered at ages 10 and 15 years via interview. These questionnaires were modified from studies by Pate et al (260) and Gordon-Larsen et al(261) to be appropriate for South African children. Results have been previously published on the Bone Health cohort at 9, 10 and 13 years of age utilising these modified physical activity questionnaires(245). The intensity, frequency and duration of all physical activities (physical education, extra-mural school and club sport, informal physical activity, and active commuting to and from school) and sedentary activities were recorded. Formal activities included sporting activities at school and club level while informal activities included play activities at home or in the

neighbourhood outside of school. Physical activity was scored in minutes per week multiplied by metabolic equivalents (MET, one MET is defined as the energy expenditure for sitting quietly, which for the average adult is approximately 3.5 ml of oxygen/kg body weight/min) according to the classification of Ainsworth et al.(262), to obtain a measure of physical activity related energy expenditure (METmins/wk). The total, formal and informal physical activity scores where thereafter converted to Z scores by utilizing the physical activity scores of the largest non-fracture group (black females) as the reference data for comparison between those who did and did not sustain a fracture.

Anthropometric measurements and DXA-derived parameters on adolescent-biological mother pairs from the Birth to Twenty cohort:

Anthropometric measurements and bone mass (total body including head and lumbar spine) data on the Bt20 subjects at the age of 17/18 years were obtained. Biological mothers' anthropometric data and bone mass measurements had been collected over 2 years when the adolescents were on average 13 years of age. Height was measured to the nearest millimetre using a stadiometer (Holtain, Crosswell, UK). Weight was measured to the last 100g using a digital scale (Dismed, Halfway House, South Africa) with participants wearing light clothing and no shoes. Tanner staging of pubertal development was assessed by the adolescents privately using a protocol based on Tanner's Sexual Maturation Scale (SMS)(263). This protocol, which had been previously validated for black South Africans(264), consists of drawings of the five Tanner stages of secondary sexual characteristics (breast development in females and genital development for males and pubic hair in both sexes), ranging from stage 1 (pre-pubertal), through to stage 5 (post-pubertal) and written descriptions of the different Tanner stages. The subjects were asked to look at the various drawings and corresponding

written descriptions and mark off that which closely resembled their stage of development.

Total body (TB) including head and lumbar spine (LS) BA and BMC were measured in both the adolescents and biological mothers using Hologic QDR 4500A dual-energy X-ray absorptiometer (DXA) according to standard procedures using the same software version for both the adolescents and biological mothers (software version 11.2, Hologic, MA, USA).

Statistical analyses

Fracture incidence:

Data were initially analyzed using Statistica statistical software version 7.0 (StatSoft, USA) and thereafter using version 10.0. Fracture rates were calculated as the number of subjects with new fractures or the total number of new fractures divided by total person-time of observation. Categorical data were summarized as numbers and percentages. Comparisons were made between those who had and had not fractured within ethnic groups and between ethnic groups using chi-square or Fisher-exact analysis. A p-value of <0.05 was considered to be statistically significant. Because of the small number of subjects in the Indian ethnic group, statistical analyses generally did not include this group.

Statistical analyses for data obtained from children at ages 10 and 15 years from the Bone Health cohort:

Individual anthropometric Z-scores (height for age Z score (HAZ) and BMI for age Z score (BAZ)) were calculated using the WHO Anthroplus software (http://www.who.int/growthref/tools/en/).

Using logistic regression analyses, ethnicity and sex were found to be important factors predicting fracture risk in the entire cohort, therefore analyses were performed for each sex and ethnic group separately. Data were summarized as means (standard deviations) or medians (interquartile range), depending on the distribution of the data. Comparisons were made between those who had and had not fractured within the same sex and ethnic group using chi-square analysis. A *p*-value of <0.05 was considered to be statistically significant. The largest non-fracturing group (black females) were used as the control or reference group to compare with other groups for whole body composition, bone mass measurements and physical activity scores. Individual whole body composition measurements were compared with the control group (non-fracturing black females) by calculating Z-scores, by subtracting the control mean from the participant's specific measurement and dividing by the control standard deviation (SD). Bone mass, height and weight variables were log transformed to adjust for skewed data, following which BA and BMC were adjusted for height and weight of the whole cohort using multiple regression analyses. Thereafter, Z scores for BA and BMC of each of the sexes and ethnic groups were derived using the non-fracturing black females as the control group. Unadjusted physical activity Z scores were derived using the same control group.

Statistical analyses for data obtained on adolescent-biological mother pairs from the Birth to Twenty cohort:

Data were analyzed using SAS (version 9.3) package. In the descriptive analysis of the adolescent-biological mother pair characteristics, baseline data were summarized as means (standard deviations). ANOVA was used to test for differences in age and anthropometric measurements and ANCOVA, adjusting for height and weight, was used to test for differences

in bone mass (BMC and BA) measurements between ethnic groups. Bonferonni correction was used for post hoc comparisons of individual groups. Categorical data were summarized as numbers and percentages. Comparisons were made between those who had and had not fractured using chi-square or Fisher's exact analysis. A *p* value of <0.05 was considered to be statistically significant. Ethnicity was dummy coded in all regression models, with whites as the reference group. The pubertal stages of the adolescents were divided into early puberty (Tanner stages 1-3) and late puberty (Tanner stages 4-5) for use in the regression models. Multiple forward selection and backward elimination stepwise regression analyses examined the independent contributions of various factors to adolescent TB and LS BA and BMC, and a significance value of 0.15 was used for both inclusion and exclusion. Logistic regression analyses were performed to determine the factors influencing fracture risk in the adolescents before and after adjusting for confounding variables. The maternal bone mass measurements used in the logistic regressions were converted to Z-scores using the entire cohort of mothers as the reference group

The next three chapters of the thesis describe the results of the three major studies using the objectives, methods and statistical analyses described above. Chapter 3 describes the fracture incidences and patterns in children up to 17/18 years of age, while chapter 4 assesses the relationship between fracture and bone mass, body composition and physical activity (objective 2) and chapter 5 describes the fracture patterns and bone mass of South African adolescent-biological mother pairs and determines if a familial relationship exists between first degree relatives (biological mothers and siblings) and the cohort children of different ethnic groups with regard to the prevalence of fractures (objectives 3 and 4).

CHAPTER 3

Fracture patterns in urban South African children of different ethnic origins

This chapter describes the fracture incidence and patterns in children up to 17/18 years of age. The results are provided and discussions pertaining to these findings are outlined together with the limitations.

Most of the findings and discussion in this chapter have been published in the following publication (appendix G):

Thandrayen K, Norris SA, Pettifor JM. Fracture rates in urban South African children of different ethnic origins: the Birth to Twenty cohort. Osteoporos Int. 2009 Jan;20(1):47-52.

Results

Fracture prevalence and rates from birth until 15 years of age:

Of the 3273 subjects originally enrolled in the Birth to Twenty cohort, fracture data were available on 2031 subjects at age 15 years. Nine hundred and eighty six (48.5%) were males and one thousand and forty five (51.5%) were females. Of the 2031 subjects, 441 (22%) children had had one or more fractures during their lifetime. (Table 3.1) The total number of fractures in the entire cohort was 565. White children had the highest proportion with a history of fractures (41.5%), followed by the Indian (30%), mixed ancestry (21%) and black (19%) children. (Table 3.1) There was a significant difference between the ethnic groups in the percentage of children who had fractures over the first 15 years of life ($p<0.001$). A higher percentage of both males and females among white children (47% and 36% respectively) had fractured compared to those in the black (25% and 14% respectively) and mixed ancestry (26% and 15% respectively) groups. (Table 3.1)

Table 3.1 The number of children who sustained fractures over the first 15 years of life according to ethnicity and sex in the Birth to Twenty Cohort

Ethnicity	All children	Number of children with fractures			
		Total children with fractures		Males	Females
	n	n	%	%	%
White	188	78	41.5*	47[a,b]	36[c,d]
Indian	30	9	30	43	19
Mixed ancestry	213	44	21	26	15
Black	1600	310	19	25	14
Total	2031	441	22	27.5	16.3

*p<0.001 between white and other ethnic groups, [a]p<0.001 between white and black males, [b]p<0.004 between white and mixed ancestry males, [c]p<0.001 between white and black females, [d]p<0.001 between white and mixed ancestry females

The overall fracture rate over the first 15 years of life was 18.5/1000 children/annum. The fracture rate over this period was three times greater in the white group than in the black and mixed ancestry groups (W 46.5 [95% CI 30.4-58.3] ; B 15.4 [95% CI 9.8-20.1]; MA 15.6 [95% CI 7.7-23.5] /1000 children/annum, p<0.001). The fracture rate in Indians over the first 15 years of life was 28.9 [95% CI 4.9-52.9] but not significantly different from the other ethnic groups, probably because of the small number of subjects.

The age distribution and peak rates of fractures were similar between the black and mixed ancestry ethnic groups but the fracture rates were consistently higher in the white

population in each age group (Figure 3.1). The Indian group was not included in the table due to the small numbers.

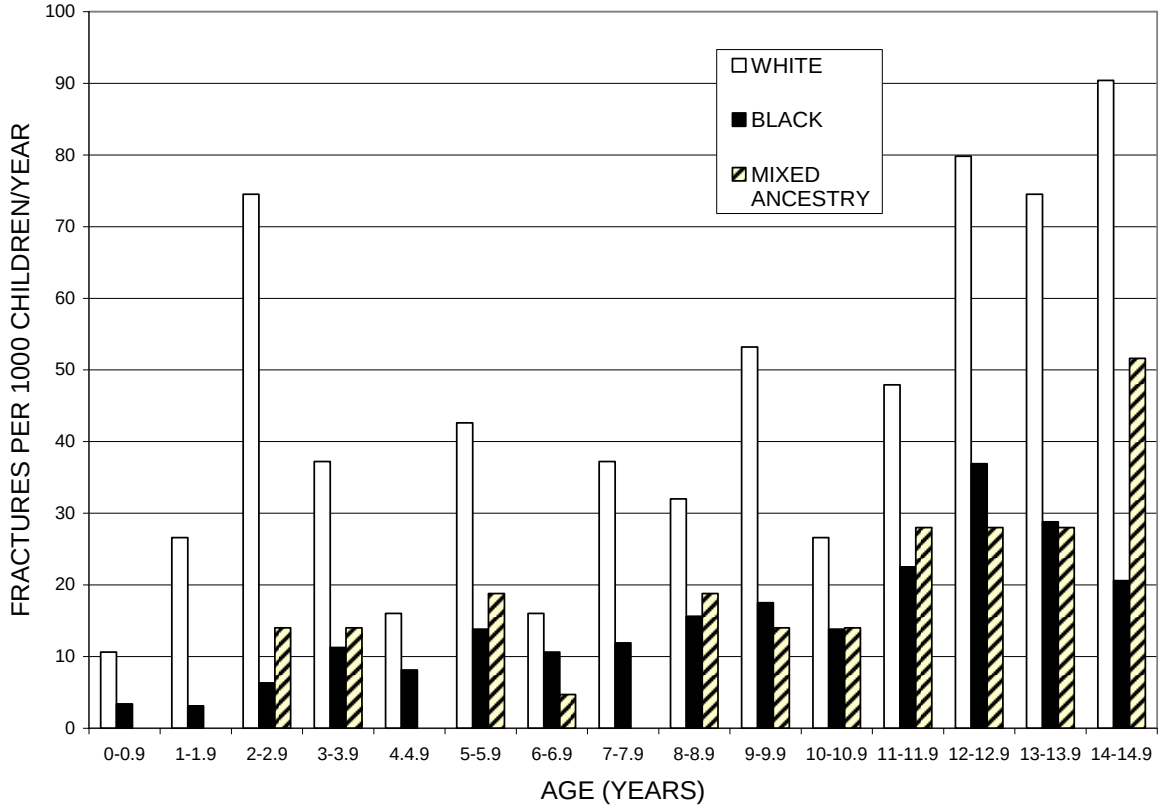


Figure 3.1 Fracture rates per year by age and ethnicity

First fractures were more common in the white group than in the black and mixed ancestry groups (W 31.2 [95% CI 19-41.6]; B 12.9 [95% CI 8.7-16.4]; MA 13.8 [95% CI 6.9-20.6] /1000 children/annum; $p<0.001$ and I 17.8 [95% CI 0.9-34.7]).

Sex differences in fracture rates:

More boys than girls sustained fractures (27.5% vs 16.3%; $p<0.001$) throughout all age groups except in the first year of life. (Figure 3.2)

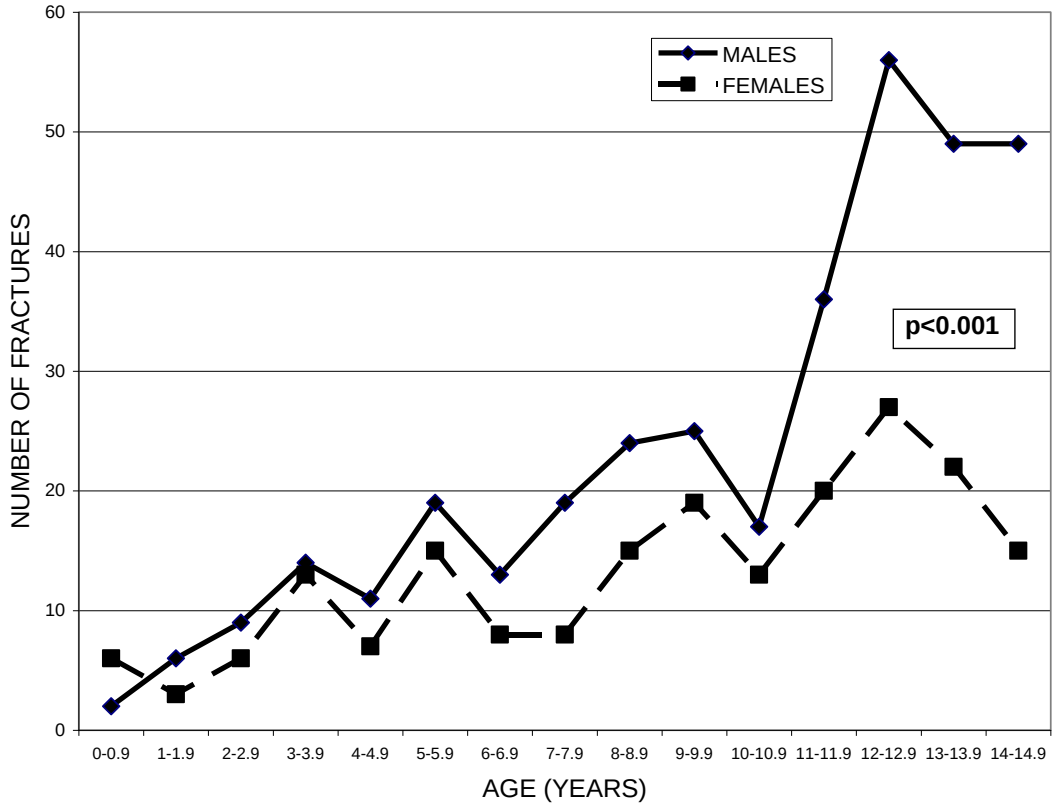


Figure 3.2 Fractures per year by age and sex. The number of males and females in the study were similar.

Of all fractures, 64% occurred in males. The peak age of fractures was between 11-14.9 years for the sexes combined. The peak fracture rate for girls occurred between 11-13.9 years of age during which period 10% of those who fractured, fractured and between 11-14.9 years of age for boys when 19% fractured. The fracture rate from 11-14.9 years of age in white males was almost three times higher than in black males (101.1 [95% CI 59.9-142.4] vs 37.3 [95% CI 19.5-55.2] /1000 children/annum, $p<0.001$) and double that of the mixed ancestry group (49.5 [95% CI 10-89] /1000 children/annum, $p<0.002$). The fracture rate from 11-13.9 years of age in white females was three times greater than in black (60.6 [95% CI 17.1-104.1] vs 17 [95% CI 9-25.1] /1000 children/annum; $p<0.001$) and mixed ancestry

females (18.7 [95% CI -4.6-41.9] /1000 children/annum; p<0.003). The Indian group was excluded due to the small numbers.

Single and multiple fractures:

Of the 441 children who reported having had a fracture, 80% (352) had sustained a single fracture while 20% (89) had fractured on more than one occasion. More boys than girls sustained two or more fractures (23% (63) vs 15% (26) of those fracturing; p<0.001). The maximum number of fractures sustained by any individual was five.

There were no significant differences between the sites of fractures when comparing males and females (Table 3.2)

Table 3.2 Fracture sites by sex

Fracture site	**Total n (%)**	**Males n (%)**	**Females n (%)**
Upper limb	320 (57)	206 (64)	114 (36)
Lower limb	126 (22)	71 (56)	55 (44)
Hand	54 (10)	40 (74)	14 (26)
Foot	26 (5)	15 (58)	11 (42)
Shoulder	25 (4)	17 (68)	8 (32)
Other/ non-specified	14 (2)	11 (79)	3 (21)
Total	565 (100)	360 (64)	205 (36)

With all fractures combined, there were an almost equal number of fractures occurring in the left and right sides and at most sites except at the sites of the upper limbs and foot. Upper limb fractures occurred more frequently on the left side and foot fractures occurred more frequently on the right side. Of the upper limb fractures, 31% (96) were of the left wrist or lower arm and 23% (72) were of the right wrist or lower arm ($p<0.05$).

Table 3.3 Fracture sites according to the side of fracture (left or right)

Fracture site	**Total n (%)**	**Left side n(%)**	**Right side n(%)**
Upper limb	311 (55)	166* (53)	145 (47)
Lower limb	115 (20)	56 (49)	59 (51)
Hand	52 (9)	21 (40)	31 (60)
Foot	20 (3.5)	5 (25)	15* (75)
Shoulder	19 (3.5)	9 (47)	10 (53)
Other/ non-specified	4 (1)	1 (25)	3 (75)
Both sides/ Do not recall	44 (8)	-	-
Total	565 (100)	258 (46)	263 (46.5)

*$p<0.05$

The fracture rate at each site was highest in white children ($p<0.025$) (Figure 3.3). Fracture rates at the different sites were similar in the black and mixed ancestry groups, but lower than in white and Indian children.

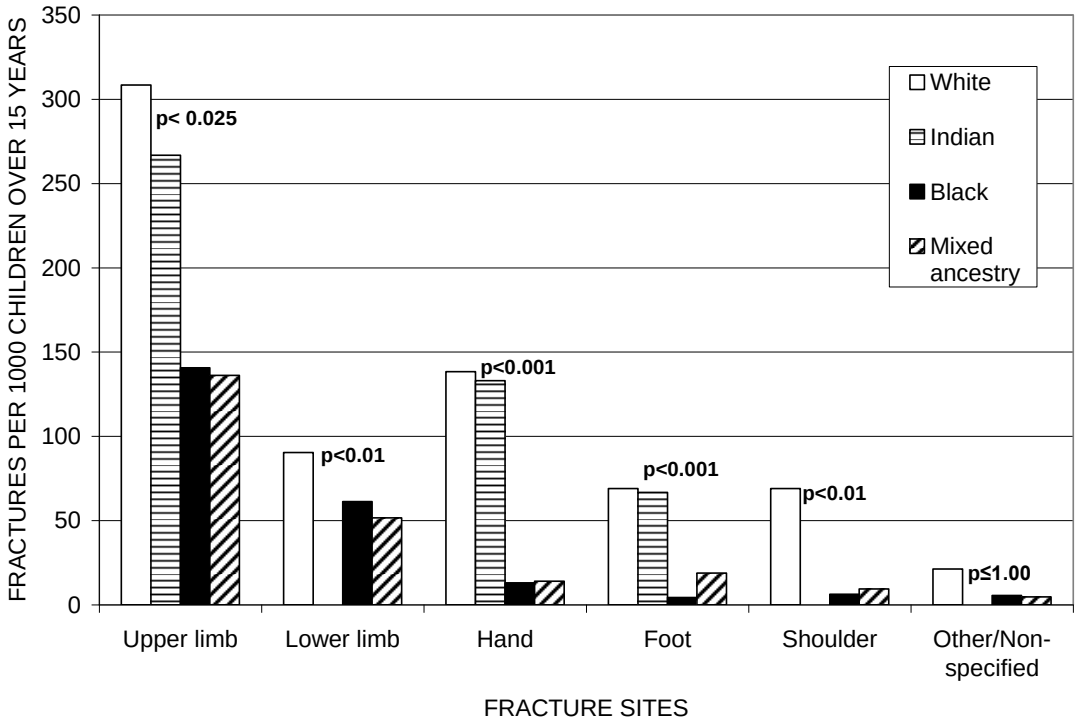


Figure 3.3 Fracture rates over 15 years between ethnic groups at the different fracture sites. The p values indicate significant differences between fracture rates of the white children and those of the black and mixed ancestry children.

Grades of trauma causing fractures:

Most fractures occurred as a consequence of grade 2 trauma within all ethnic groups. There was a statistically significant difference in the grades of trauma causing fractures between the white and black children ($p < 0.025$), with whites generally fracturing at more severe levels of trauma. (Table 3.4)

Table 3.4 Grades of trauma causing fractures by ethnicity and sex until 15 years of age

Grades of trauma causing fractures	Fractures occurring in individuals according to grades of trauma							
	Black*		White		Mixed Ancestry		Indian	
	Males** n (%)	Females n (%)	Males n (%)	Females n (%)	Males n (%)	Females n (%)	Males n (%)	Females n (%)
Grade 1	61 (25)	41 (32)	10 (13.5)	9 (16)	9 (26)	7 (44)	1 (10)	3 (75)
Grade 2	151 (62)	70 (55)	56 (76)	38 (67)	21(62)	7 (44)	7 (70)	1 (25)
Grade 3	28 (12)	16(12.5)	7 (9.5)	9 (16)	3 (6)	2 (12)	2 (20)	0 (0)
Do not recall	2 (1)	1 (0.5)	1 (1)	1 (1)	1 (3)	0 (0)	0 (0)	0 (0)

Note: The Indian group was excluded from the Fisher exact or Chi-square statistical analyses due to small number of subjects
* $p < 0.025$ Fractures in blacks associated with lower grades of trauma than in whites
** $p < 0.035$ Fractures in black males associated with lower grades of trauma than in white males

Sport-related activities resulting in fractures

Thirty one percent (110) of the incidents resulting in fractures in males were associated with sport-related activities whilst in females only 17% (35) of fractures were related to sport-related activities ($p<0.001$). A greater percentage of whites sustained fractures due to sport-related activities compared to blacks and mixed ancestry groups. Black males sustained more fractures due to sport-related activities compared to black females and, within groups of similar gender, a greater percentage of both white males and females had sustained fractures due to sport-related activities compared to the mixed ancestry and black ethnic groups.

Table 3.5 Sport-related activities associated with fractures by ethnicity and sex until 15 years of age

Ethnicity	All fractures	Number of children with sport-related activities causing fractures	Percentage of children with sport-related activities causing fractures	
			Males	Females
	n	n	%	%
White	131	50*	45** †	30†
Indian	14	5	50	0
Mixed ancestry	50	6	18	0
Black	370	84	27**	14
Total	565	145	31*	17

*p<0.001 between white and blacks, between whites and mixed ancestry and between males and females
**p<0.01 between black males and females, between white males and black males
† p<0.05 between white males and mixed ancestry males; between white females and mixed ancestry females and between white females and black females

Fractures between 15 and 17/18 years of age:

At 17/18 years of age, a total of 1813 fracture questionnaires were completed. Of the 1813 subjects, 22% (399) reported a history of sustaining at least one fracture from birth till 17/18 years of age (after adding the number of fractures that occurred until 14.9 years to those that occurred between 15 -17/18 years of age). This percent is similar to that reported at age 15 years on fractures from birth till 14.9 years of age. Between the ages of 15-18 years, 59 subjects reported a history of sustaining a fracture; three individuals reporting multiple fractures thus bringing the total number of fractures to 62.

Of the 59 subjects who reported fractures, 41 (69.5%) were males and 18 (31.5%) were females (p=0.001).

Whites had a higher prevalence of fractures [9% (10/106)] between 15 and 18 years of life than black [3% (44/1520)], mixed ancestry [2% (4/174)] and Indian groups [1/13(8%)]; (W>B, $p<0.001$ and W >MA, $p<0.05$). Further data analyses were not performed on the different ethnic and sex groups due to the small number of fractures in each group.

An almost equal number of fractures occurred on the left (31/62) and right (28/62) sides of the body and 3 incidents of fractures involved both the left and right sides of the body.

There were almost equal numbers of upper limb (34%) and lower limb (35.5%) fractures and of hand (14.5%) and foot (11%) fractures (Figure 3.4).

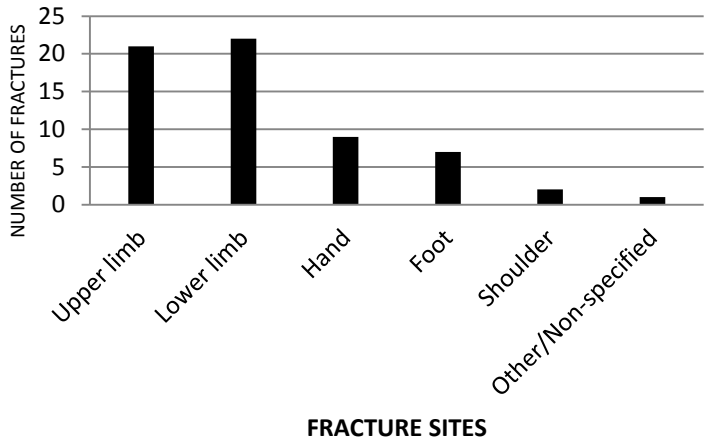


Figure 3.4 Number of fractures at the different sites between ages 15 and 18 years

As in the younger age group (<15 years of age), most fractures occurred as a consequence of grade 2 trauma in the males between ages 15 and 18 years (Figure 3.5) however there were no significant differences in grades of trauma between males and females.

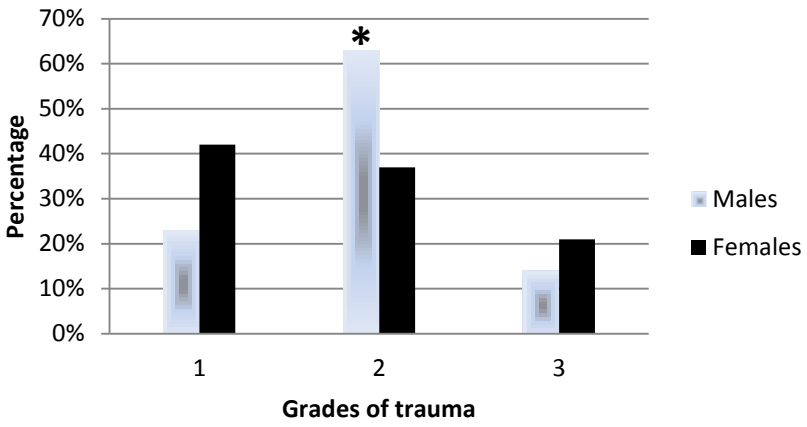


Figure 3.5 Grades of trauma causing fractures in males and females between ages 15 and 18 years. *p<0.001 between grades 1 and 2 and; between grades 2 and 3 in males.

Verification of fracture data

To assess data quality, fractures were verified telephonically some 6 to 12 months after completing the initial questionnaire in 51 (9%) of the original 565 reported fractures in the Bt20 cohort. Forty eight (94%) confirmed having had one or more fractures. Of the remaining three, 2 had initially reported strains as fractures as telephonically they reported that there were no fractures noted by the attending health care worker after radiographs were taken and one had reported no history of fractures in the initial questionnaire and on the subsequent questionnaire had incorrectly reported a fracture. On enquiring about more detail pertaining to the last fracture, 58% (28) of the individuals or caregivers had 100% recall of the event including the age, site, side and trauma resulting in the fracture. Thirty seven percent had partial recall for the event as recorded in the initial questionnaire and in four percent the recollection did not correlate with that reported in the previously completed questionnaires. Of the reported fractures, 46 (96%) were said to have been diagnosed by a doctor and one by a nursing sister and one was self-diagnosed. Of the last reported fracture, eighty nine percent

(42/48) had confirmed that they had had a radiograph performed, three did not and two could not remember and one fracture was self-diagnosed. Of the last reported fractures, sixty two percent (29) had had plaster of Paris applied, 15% had had a bandage applied, 11% had had an operation, 6% a splint or brace applied and the remaining 6% had had a sling applied or were advised to rest.

Discussion

This study shows that fracture rates in children in South Africa vary across the different ethnic groups, with the proportion of children reporting fractures in the white ethnic group being almost double that of the black and mixed ancestry groups. As far as I have been able to ascertain this study of children's fractures, which was published in 2009, was the first study to report ethnic comparisons in the world. Numerous studies from developed countries have reported on the incidence of childhood fractures in defined populations(2;6;9;22;27;229) and in longitudinal cohort studies(23), but none had reported on ethnic differences in childhood fracture patterns. The pattern of lower fracture incidence in black than white children is similar to that noted for femoral neck fractures in adults in South Africa(240).

The risk of osteoporotic fractures in the elderly is related to gender and ethnicity. The National Osteoporosis Risk Assessment (NORA) longitudinal observational study of osteoporosis among postmenopausal women in primary care practices in the USA compared white, Asian, Hispanic and Native American women in terms of osteoporosis risk and showed that these ethnic groups are more at risk for osteoporosis than African-American women(265).

Similarly African-American women have a lower fracture risk than white women at every level of bone mineral density and this relationship is largely explained by environmental and genetic factors that need to be further investigated(238).

In our Bt20 cohort, 22% of children overall reported fractures, however 41.5% of white children suffered one or more fractures; this latter figure being comparable to that found in the Dunedin Multidisciplinary Health and Development study whose participants were predominantly Caucasian(23). The proportion of white boys and girls reporting fractures in the present study is also similar to that reported by Landin where by the age of 16 years, 42% of boys and 27% of girls from Sweden had suffered a fracture(9), however the figures are somewhat higher than those reported from a cross-sectional study in Poland, in which 30% of 1246 respondents had fractured by the age of 16 to 20 years(22). A more recent study conducted in Sweden reported a 34% cumulative risk of sustaining a fracture before 17 years, of which 61% of all fracture events occurred in boys(24). In the Bt20 study, the fracture rate in white children was three-fold that found in the black and mixed ancestry groups and more males than females sustained multiple fractures, the latter finding being in keeping with other population based studies(2;6;9;21-23).

A recent study conducted between 2010 and 2011 in Norway reported an annual fracture incidence of 180.1 per 10,000 children(266). Swedish studies have reported a slightly higher fracture incidence of 212 fractures per 10,000 children between 1950 and 1979(9) and of 213 to 240 per 10,000 children between 1998 and 2007 (24). Raustorp and Ludvigsson(267) showed an increase in daily physical activity in Swedish children between 2000 and 2006 and concluded that the change in activity levels was due to an increased awareness of the importance of physical activity. Hedstrom et al(24) postulated that this increase in fracture incidence between 1998 and 2007 is partly explained by increased physical activity levels.

The reasons for the increased fracture rate in boys may be due to the fact that males are more involved in contact and high impact team sports than girls and tend to spend more time outdoors playing(22). Landin reported a fivefold increase in fracture rates caused by sports between 1950 and 1979 in Sweden and between the ages of 10 and 15 years, the incidence of sports-related injuries doubled in girls and more than tripled in boys(9). The Swedish Sports Council reported a 5% increase in participation in organised sports among teenagers between 1998 and 2005, and that children became more involved in organised sports at a younger age(24). The fact that more males sustained multiple fractures supports the evidence for sport or rougher playground scuffles playing a role in the increased fracture rate in males. There was a significant difference in the grading of trauma associated with fractures between white and black children suggesting that sport and physical activity play roles in the increased rate of fractures in the white group. Further analyses show that more males sustained a fracture due to sport-related activities than females and a higher percentage of whites sustained sport-related fractures compared to the black and mixed ancestry groups. Simon et al have also reported that sport related injuries occurred mainly in white boys during early to mid-puberty(19). Other studies support these findings and indicate that sport and play activities contribute to most of the paediatric fracture events(24;268;269). Play activities dominated as the activity resulting in fracture during the first decade of life whilst sport-related fractures were predominant in teenagers(24;268).

Data from the Bt20 longitudinal study indicate that there are lower physical activity levels in black than white children(245) which is probably related to the lack of organized sporting activities in schools attended mainly by black subjects and the poorer socio-economic status of the black families(254). McVeigh et al. also reported that white males at age 9 and 10

years in the Bt20 longitudinal study had the highest physical activity levels of all the ethnic and gender groups and that those white male children falling into the highest quartile of activity exhibited bone mass benefits at the whole body, total hip and lumbar spine sites(253). Despite the higher physical activity levels in white male than other children, black children still had a higher hip, mid-radial and lumbar spine (girls only) bone mass and similar values to their white peers at other sites(245;253). These findings support the hypothesis of a genetic protection against low bone mass and fracture in blacks. Fractures on average were reported to have occurred at a higher energy level in white children. This finding is unlikely to have been due to different interpretations of the questions by the various ethnic groups as a single researcher classified the degree of trauma resulting in fractures according to the answers given as to how the fractures happened. Further, a single interviewer helped with the questionnaires to eliminate the problem with language and interpretation of questions.

Upper limb or radial fractures have been consistently reported to be the most common site of fracture in both sexes(2;6;9;21;23;24;266). My study confirms these findings in all the ethnic groups. The most common site was recorded as being the lower arm or wrist (29.7%) which has a similar prevalence to a Norwegian study (31.1% of fractures occurred at the distal radius)(266) and to a British study (almost 30% at the radius/ulna) (6). A similar percentage (53%) of upper limb fractures occurred in the non-dominant arm in both the Bt20 study and the Norwegian study(266). The 1950-1979 Swedish study by Landin(9) found no significant side preponderance for most fractures but a significant preponderance for left-sided fractures with a ratio of 1.3/1 ($p<0.001$) at the humerus, distal forearm and carpal-metacarpal sites and a right-sided preponderance for ankle fractures of 0.8/1 ($p<0.05$) which is similar to the Bt20 study and to that of a study in Mumbai, India(270). It has been suggested that when the right

upper extremity is in use, the left assumes the protective role during injury(271) and that the less mature neuromuscular coordination of the non-dominant extremity may also be responsible for the slight increase in left sided preponderance (272).

Peak age of fractures for both males and females found in the Bt20 study correlates with stages of pubertal growth and peak height velocities which are compatible with other studies(6;9;22-24;266). The differences in peak age between males and females reflect differences in the timing of maximal growth velocities and the relative decrease in bone mineral density, which is due to bone expansion associated with growth and insufficient mineralisation coinciding with the pubertal growth spurt and the peak incidence of fractures(30).

Seasonal variations in fracture rates have been observed in some studies with more fractures occurring in the spring and summer months(24;222;266). We did not assess seasonal variation in the Bt20 cohort, as we felt that the retrospective nature of the study would introduce considerable error.

Limitations of the study include the fact that the results for Indian children are unreliable due to very small number of subjects included in the cohort. Recall bias might be another limitation as the diagnosis of all fractures was based on recall by the subject and the parent or caregiver and was not confirmed with radiological assessments, however this was probably not a major factor in the study as at all ages the findings were consistent between the ethnic groups. The methodology used for year 15 fracture data collection was able to confirm the age, site and cause of previous fractures that had been recorded at year 13 and also collected information on new fractures occurring between 13 and 15 years. In addition, all

questionnaires had a skeletal diagram attached to confirm the site of fracture and the information was verified for accuracy and completeness by the parent or primary caregiver. The chances of a fracture not being diagnosed in the different ethnic groups are unlikely to have differed despite having access to different levels of health care as health care in the public sector is free for all children. Both public and private health facilities in urban areas would perform routine radiological assessments to confirm fractures. Further limitations are that there are currently no comparative analyses of potential fracture-associated risk factors, dietary intake of calcium or vitamin D and measurements of calcium homeostasis and vitamin D status between the ethnic groups.

Summary of major findings

Four hundred and forty one (22%) children had sustained a fracture one or more times during their lifetime (males 27.5% and females 16.3%; $p<0.001$). The percentage of fractures differed between the ethnic groups (W 41.5%, B 19%, MA 21%, I 30%; $p<0.001$).

This is the first study to show ethnic differences in fracture rates among children. Greater sports participation in Whites and genetic protective factors in Blacks may be contributing factors.

CHAPTER 4

Heterogeneity of fracture pathogenesis in urban South African children

This chapter describes and discusses the results of my investigations into the associations between fracture prevalence for the first 15 years of life and bone mass, body composition and physical activity at ages 10 and 15 years in these children.

Most of the findings and discussion in this chapter have been published in the following manuscript (appendix H):

Thandrayen K, Norris SA, Micklesfield LK, Pettifor JM. Heterogeneity of fracture pathogenesis in urban South African children: the Birth to Twenty cohort. J Bone Miner Res. 2011 Dec;26(12):2834-42.

Results

Fracture patterns in the Bone Health sub-cohort:

Of the 533 subjects in the Bone Health cohort at 15 years of age, 186 (35%) were white (W) and 347 (65%) black (B). The total number of children who sustained fractures over the first 15 years of life was 130 (24%). In this cohort, the proportion of white children who reported a fracture in the first 15 years of life was 41.5% (n=78) compared to 15% (n=52) in black children ($p<0.001$). The overall fracture rate in the Bone Health cohort for the first 15 years of life was 23 (95% CI 15.1-30.9) per 1000 children per annum.

Sex differences in fractures:

In the Bone Health cohort, the proportions of white males (WM) and females (WF), who had fractured, were significantly higher than for black males (BM) and females (BF), respectively (WM 47% vs BM 37%; $p<0.001$ and WF 18% vs BF 11%; $p< 0.001$) (Table 4.1).

Table 4.1 Fracture rates over the first 15 years of life in the Bone Health Cohort

Ethnic group	Fracture rate per 1000 children per annum	95% Confidence intervals
White males	52.4[a]	28.3-76.5
Black males	14.4	7.6-21.3
White females	37.1[b]	24.6-49.5
Black females	8.4	4.1-12.7

[a] $p < 0.01$ between white and black males [b] $p < 0.001$ between white and black females

Sites of fractures:

The fracture incidence rates for all sites (in the Bone Health cohort) except the lower limb were significantly higher in the white population (Figure 4.1). The commonest site of fracture was the upper limb (48%).

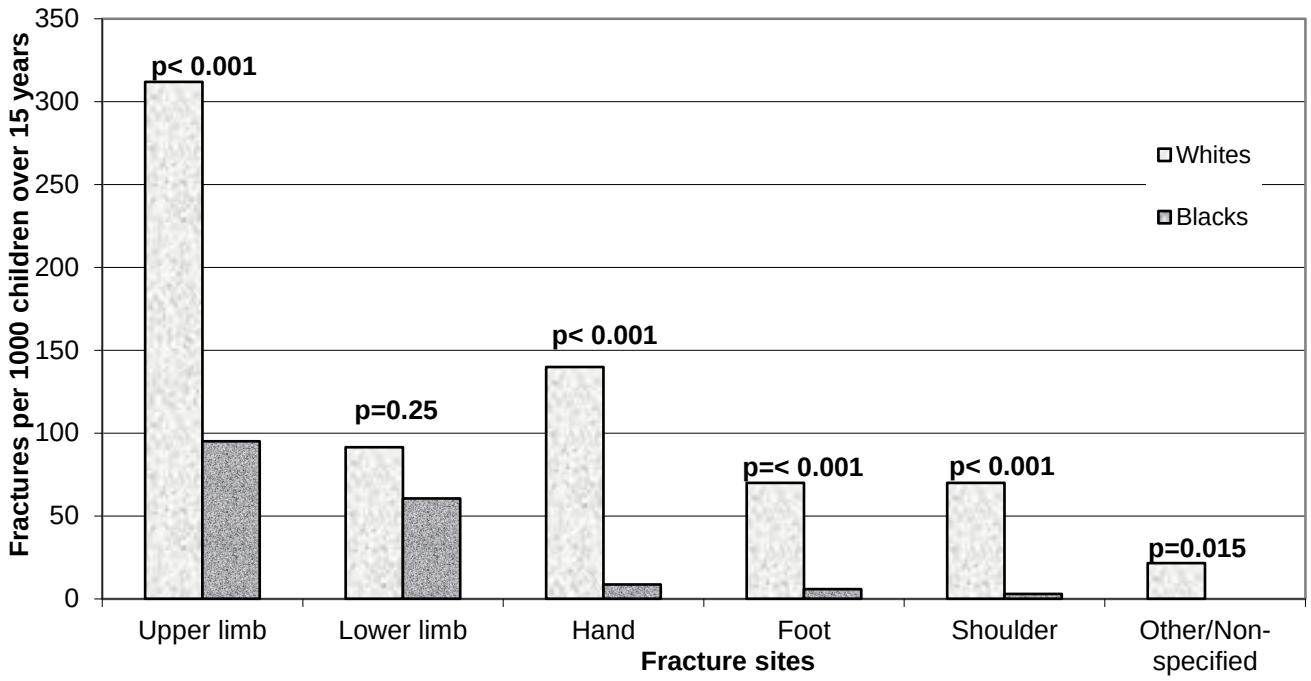


Figure 4.1 Fracture incidence rates per annum at the different fracture sites in white and black children

Anthropometric and whole body composition characteristics at 10 and 15 years of age:

Ethnicity ($p<0.001$) and sex ($p = 0.024$) were shown by logistic regression to be important predictors of fracture risk in the entire cohort (Table 4.2), thus further analyses were performed within the same sex and ethnic groups.

Table 4.2 Predictors of fracture risk at age 15 years in black and white children

Fractures **n = 533**	**Adjusted** **odds ratio**	**95%** **confidence interval**
Whites	4.24 *	2.79-6.45
Males	1.62 **	1.06-2.47

*p<0.001 **p=0.024

Black children:

Complete anthropometric and whole body composition measurements were available on 304 of the 347 black children with fracture data at mean age of 10.5 years and on 332 of the 347 children at mean age of 15.5 years. Of the black children with incomplete data at 10 and 15 years of age, 7 of 43 (16%) and 2 of the 15 (13%) respectively had reported a fracture (proportions very similar to those with complete data, suggesting no selection bias in those used in the analyses).

There were no statistically significant differences in anthropometry or body composition measurements at either age 10 or age 15 years between black children of the same sex with and without a history of fractures at age 15 years (Table 4.3). Using non-fracturing black females as the reference group, black males with and without fractures at both 10 years and 15 years had a lower fat mass ($p<0.001$) and at 15years had a greater lean mass ($p<0.001$) (Table 4.3).

Table 4.3 Anthropometric and body composition measurements at 10 and 15 years of age of black males and females with and without a history of fractures at 15 years of age

	Black females at 10 years		Black females at 15 years		Black males at 10 years		Black males at 15 years	
	Without fractures (n=128)	**With fractures (n=16)**	**Without fractures (n=140)**	**With fractures (n=17)**	**Without fractures (n=131)**	**With fractures (n=29)**	**Without fractures (n=142)**	**With fractures (n=33)**
Chronological age (yrs)	10.5 (0.26)	10.5 (0.28)	15.6 (0.24)	15.5 (0.25)	10.6 (0.27)	10.5 (0.28)	15.6 (0.26)	15.5 (0.28)
Bone age (yrs)	9.9 (1.10)	9.8 (0.88)	14.7 (0.62)	14.7 (0.50)	9.9 (0.70)	9.9 (0.76)	14.8 (1.30)	14.73 (1.16)
HAZ* Score	-0.41 (0.95)	-0.67 (0.65)	-0.48 (0.89)	-0.52 (0.99)	-0.52 (0.90)	-0.41 (1.04)	-0.13 (0.97)	0.04 (1.01)
BAZ* score	0.16 (1.21)	-0.28 (0.91)	0.60 (1.10)	0.16 (0.94)	0.07 (1.12)	-0.11 (0.94)	0.02 (1.13)	-0.14 (1.05)
Lean mass Z score†	0.00 (1.00)	-0.46 (0.43)	0.00 (1.00)	-0.37 (0.48)	0.02 (0.80)	-0.08 (0.72)	1.51[1] (1.35)	1.38[1] (1.16)
Fat mass Z score†	0.00 (1.00)	-0.33 (0.53)	0.00 (1.00)	-0.29 (0.49)	-0.52[1] (0.82)	-0.61[1] (0.48)	-1.06[1] (0.93)	-1.09[1] (0.79)

Data presented as mean (SD). There were no significant differences within the same sex and age groups; HAZ - height age Z-score; BAZ - BMI age Z score;
*Computed using WHO Anthroplus software
† The Z score of lean and fat masses of each ethnic and sex group was derived from the values obtained from the black non-fracturing females.
[1]$p<0.001$ significant differences in lean and fat mass Z scores comparing non-fracturing black females to other ethnic and sex groups

White children:

Complete anthropometric and whole body composition measurements were available from 101 of the 186 white children with fracture data at a mean age of 10.6 years and from 116 of the 186 white children at a mean age of 15.7 years. The major reason for the lack of complete data at the two time points was an unwillingness of parents or children to take time off from school for the DXA and radiological studies. Thirty four of the 85 white children (40%) at age 10 years and 34 of the 70 (48.5%) at age 15 years with incomplete data had reported a fracture (proportions very similar to those with complete data, suggesting no selection bias in those used in the analyses).

Comparing children of the same sex with and without fractures, white males who had fractured in the first 15 years of life were significantly taller ($p<0.01$) and had a higher lean body mass ($p=0.01$) at the age of 10 years, and at age 15 years ($p<0.001$) compared to their non-fracturing peers (Table 4.4). White males at 15 years with fractures had a slightly greater bone age compared to those without fractures ($p=0.05$) but Tanner staging for genital assessment and pubic hair was not significantly different between the two groups. White females who had fractured similarly had a higher lean body mass at age 15 ($p < 0.05$) but also had a higher BMI at age 10 ($p=0.05$) and 15 years ($p<0.05$) compared to the white females who had not fractured (Table 4.4).

Comparing body mass variables of the different ethnic and sex groups with those of non-fracturing black females, white males at ages 10 and 15 years and white females at 15 years had a greater lean mass (Table 4.4).

Table 4.4 Anthropometric and body composition measurements at 10 and 15 years of age of white males and females with and without a history of fractures at 15 years of age

	White females at 10 years		White females at 15 years		White males at 10 years		White males at 15 years	
	Without fractures (n=28)	**With fractures (n=20)**	**Without fractures (n=44)**	**With fractures (n=19)**	**Without fractures (n=29)**	**With fractures (n=24)**	**Without fractures (n=30)**	**With fractures (n=23)**
Chronological age (yrs)	10.6 (0.27)	10.6(0.27)	15.7(0.28)	15.7 (0.26)	10.6 (0.22)	10.7 (0.25)	15.7 (0.24)	15.7 (0.25)
Bone age (yrs)	10.0 (1.24)	10.2(1.26)	14.6(0.71)	14.8 (0.48)	10.1 (0.66)	10.2 (0.72)	**15.3[a] (1.06)**	**15.8 (0.86)**
HAZ Score*	0.17 (1.16)	0.20(1.17)	0.51(1.03)	0.25(1.01)	**-0.08 [b] (1.15)**	**0.88 (1.11)**	0.43 (1.11)	0.90 (1.08)
BAZ score*	**-0.12 [a] (1.06)**	**0.52(1.11)**	**0.13 [a](0.94)**	**0.73(1.07)**	0.01 (0.86)	0.29 (1.06)	0.02 (0.76)	0.49 (1.02)
Lean mass Z score†	0.34 (1.04)	0.63[2](1.15)	**0.51 [a1](0.96)**	**1.18[3] (1.30)**	**0.36[b1] (0.83)**	**1.12[3](0.77)**	**2.78 [c3] (1.60)**	**4.05[3] (1.51)**
Fat mass Z score†	-0.14[1] (0.77)	0.27[3](0.90)	-0.27(0.71)	0.15(1.17)	-0.53[2] (0.50)	-0.28 (0.66)	-1.09[3] (0.78)	0.87[3] (0.75)

Data presented as mean (SD); significant differences within the same sex and age groups [a] $p \leq 0.05$, [b] $p < 0.01$, [c] $p < 0.001$; HAZ - Height age Z score; BAZ - BMI age Z score; *Computed using WHO Anthroplus software

† The Z score of lean and fat masses of each ethnic and sex groups was derived by comparing values with those of the black non-fracturing females.

[1] $p < 0.05$, [2] $p < 0.01$, [3] $p < 0.001$ significant differences in lean and fat mass Z scores comparing non-fracturing black females to other ethnic and sex groups.

Associations between fractures, bone mass characteristics and physical activity:

Unadjusted BA and BMC at 10 and 15 years were compared within the same sex and ethnic group between those who did and did not report a fracture during the first 15 years of life (Tables 4.5.1 - 4.5.4).

White males who reported a previous fracture/s during the first 15 years of life had greater BA and BMC at age 10 years (BA at all sites and BMC at the TBLH, R (except 1/3 radius), HN and LS sites (Table 4.5.1)), and at 15 years (BA greater at the TBLH, total hip and LS, and BMC higher at TBLH, R (except 1/3 radius), total hip, HN and LS at 15 years (Table 4.5.1)).

There were no significant differences in either BA or BMC (unadjusted) at age 10 or 15 years in black or white females or in black males between those who did or did not fracture at age 10 and 15 years (Tables 4.5.2 – 4.5.4).

Table 4.5.1 Unadjusted bone area and bone mineral content measurements in white males at 10 and 15 years of age with and without a history of fractures at age 15 years

White males				
Bone mass measurements	**10 years**		**15 years**	
	Without fractures (n = 29)	**With fractures (n = 24)**	**Without fractures (n = 30)**	**With fractures (n = 23)**
TBLH BA	**1050 [b] (142)**	**1171 (137)**	**1857 [b] (197)**	**1989 (188)**
R 1/3 BA	**2.38 [a] (0.17)**	**2.41 (0.19)**	2.81 (0.43)	2.90 (0.27)
R Mid BA	**4.27 [b] (0.79)**	**4.88 (0.70)**	8.58 (1.61)	9.32 (1.47)
R Ultra Distal BA	**2.62 [b] (0.28)**	**2.82 (0.24)**	3.89 (0.39)	4.11 (0.44)
R Total BA	**9.17 [b] (1.18)**	**10.11 (0.99)**	15.28 (2.25)	15.60 (3.67)
H BA	**21.57 [a] (2.90)**	**23.27 (2.29)**	**39.27 [b] (4.10)**	**42.15 (3.71)**
HN BA	**4.26 [a] (0.36)**	**4.43 (0.30)**	5.44 (0.37)	5.50 (0.38)
LS BA	**45.23 [b] (5.01)**	**48.54 (4.69)**	**62.53 [a] (6.96)**	**66.35 (5.98)**
TBLH BMC	**745 [a] (131)**	**847 (130)**	**1840 [b] (324)**	**2064 (363)**
R 1/3 BMC	1.13 (0.13)	1.18 (0.10)	1.89 (0.31)	1.99 (0.29)
R Mid BMC	**1.77 [b] (0.36)**	**2.02 (0.34)**	**4.52 [a] (1.01)**	**5.19 (1.05)**
R Ultra Distal BMC	**0.75 [b] (0.10)**	**0.84 (0.10)**	**1.51 [b] (0.29)**	**1.72 (0.37)**
R Total BMC	**3.66 [a] (0.57)**	**4.05 (0.52)**	7.93 (1.48)	8.52 (2.42)
H BMC	15.68 (2.93)	17.09 (2.37)	**38.65 [b] (7.39)**	**44.05 (8.75)**
HN BMC	**2.95 [a] (0.42)**	**3.19 (0.37)**	**4.83 [a] (0.67)**	**5.29 (0.89)**
LS BMC	**25.84 [a] (4.51)**	**29.03 (4.04)**	**57.44 [a] (13.17)**	**62.68 (10.11)**

Bone area= BA; bone mineral content=BMC; total body less head=TBLH; R=radius; H=total hip; HN=Hip neck; lumbar spine=LS. Significant differences within the same sex and age group: [a] $p<0.05$, [b] $p<0.01$.

Table 4.5.2 Unadjusted bone area and bone mineral content measurements in white females at 10 and 15 years of age with and without a history of fractures at age 15 years

White females				
Bone mass measurements	**10 years**		**15 years**	
	Without fractures (n = 28)	**With fractures (n = 20)**	**Without fractures (n = 45)**	**With fractures (n = 19)**
TBLH BA	1116 (191)	1128 (184)	1693 (156)	1725 (169)
R 1/3 BA	2.20 (0.23)	2.23 (0.19)	2.59 (0.25)	2.54 (0.17)
R Mid BA	4.39 (0.83)	4.48 (0.84)	6.99 (1.11)	7.28 (1.05)
R Ultra Distal BA	2.64 (0.25)	2.57 (0.30)	3.46 (0.39)	3.50 (0.32)
R Total BA	9.20 (1.26)	9.28 (1.22)	12.94 (1.62)	13.32 (1.39)
H BA	23.31 (3.37)	23.98 (3.57)	31.08 (3.72)	32.88 (4.12)
HN BA	4.20 (0.29)	4.24 (0.30)	4.85 (0.38)	4.90 (0.36)
LS BA	45.10 (4.69)	43.55 (3.95)	56.96 (5.27)	55.19 (4.47)
TBLH BMC	798 (197)	800 (161)	1569 (229)	1614 (219)
R 1/3 BMC	1.08 (0.16)	1.07 (0.13)	1.62 (0.21)	1.65 (0.13)
R Mid BMC	1.75 (0.40)	1.83 (0.38)	3.72 (0.70)	3.98 (0.67)
R Ultra Distal BMC	0.74 (0.11)	0.74 (0.10)	1.31 (0.23)	1.38 (0.19)
R Total BMC	3.56 (0.63)	3.64 (0.57)	6.65 (1.06)	7.01 (0.92
H BMC	15.75 (3.94)	16.26 (3.25)	28.29 (5.11)	29.73 (5.55)
HN BMC	2.74 (0.54)	2.80 (0.32)	3.96 (0.56)	4.11 (0.65)
LS BMC	26.58 (6.11)	25.41 (4.67)	52.08 (9.18)	51.38 (9.02)

Bone area= BA; bone mineral content=BMC; total body less head=TBLH; R=radius; H=total hip; HN=Hip neck; lumbar spine=LS.

Table 4.5.3 Unadjusted bone area and bone mineral content measurements in black males at 10 and 15 years of age with and without a history of fractures at age 15 years

Black males				
Bone mass measurements	**10 years**		**15 years**	
	Without fractures (n = 131)	**With fractures (n = 29)**	**Without fractures (n = 145)**	**With fractures (n = 33)**
TBLH BA	1015 (138)	986 (133)	1714 (195)	1701 (191)
R 1/3 BA	2.30 (0.21)	2.35 (0.24)	2.77 (0.28)	2.84 (0.36)
R Mid BA	4.47 (0.82)	4.55 (0.78)	8.42 (1.42)	8.83 (1.64)
R Ultra Distal BA	2.57 (0.28)	2.65 (0.27)	3.68 (0.40)	3.83 (0.43)
R Total BA	9.34 (1.19)	9.55 (1.18)	14.8 (2.21)	15.51 (2.37)
H BA	20.38 (2.33)	20.23 (2.64)	35.03 (4.63)	35.04 (5.11)
HN BA	4.13 (0.31)	4.18 (0.30)	5.16 (0.38)	5.21 (0.51)
LS BA	42.63 (4.10)	43.99 (5.14)	56.72 (6.56)	57.80 (8.70)
TBLH BMC	722 (126)	688 (131)	1614 (290)	1565 (297)
R 1/3 BMC	1.09 (0.12)	1.07 (0.16)	1.73 (0.21)	1.71 (0.26)
R Mid BMC	1.76 (0.34)	1.72 (0.38)	4.10 (0.90)	4.13 (1.02)
R Ultra Distal BMC	0.76 (0.12)	0.75 (0.16)	1.34 (0.28)	1.33 (0.35)
R Total BMC	3.61 (0.53)	3.54 (0.66)	7.13 (1.48)	7.17 (1.62)
H BMC	15.67 (2.50)	14.61 (2.67)	34.05 (7.46)	31.99 (6.63)
HN BMC	3.09 (0.37)	2.98 (0.42)	4.55 (0.77)	4.37 (0.79)
LS BMC	23.45 (3.59)	23.59 (4.49)	45.70 (9.84)	45.25 (11.38)

Bone area= BA; bone mineral content=BMC; total body less head=TBLH; R=radius; H=total hip; HN=Hip neck; lumbar spine=LS.

Table 4.5.4 Unadjusted bone area and bone mineral content measurements in black females at 10 and 15 years of age with and without a history of fractures at age 15 years

Black females				
Bone mass measurements	**10 years**		**15 years**	
	Without fractures (n = 128)	**With fractures (n = 16)**	**Without fractures (n = 140)**	**With fractures (n = 19)**
TBLH BA	1051 (173)	1002 (96)	1620 (157)	1594 (108)
R 1/3 BA	2.18 (0.21)	2.16 (0.19)	2.52 (0.23)	2.51 (0.25)
R Mid BA	4.37 (0.88)	4.28 (0.67)	7.03 (1.04)	7.04 (1.31)
R Ultra Distal BA	2.54 (0.27)	2.59 (0.23)	3.40 (0.37)	3.40 (0.37)
R Total BA	9.10 (1.27)	9.03 (0.97)	12.88 (1.76)	12.44 (1.82)
H BA	20.69 (2.62)	20.29 (2.34)	28.29 (2.93)	28.75 (2.79)
HN BA	4.06 (0.31)	4.01 (0.26)	4.68 (0.35)	4.64 (0.35)
LS BA	43.18 (4.44)	41.95 (3.53)	53.58 (4.99)	52.31 (4.58)
TBLH BMC	744 (170)	689 (101)	1485 (227)	1427 (174)
R 1/3 BMC	1.04 (0.15)	1.00 (0.15)	1.57 (0.19)	1.56 (0.22)
R Mid BMC	1.69 (0.43)	1.59 (0.32)	3.61 (0.68)	3.45 (0.68)
R Ultra Distal BMC	0.69 (0.12)	0.67 (0.09)	1.30 (0.21)	1.18 (0.18)
R Total BMC	3.43 (0.66)	3.26 (0.80)	6.44 (1.14)	6.18 (1.03)
H BMC	14.61 (3.11)	13.95 (2.40)	25.94 (4.44)	25.62 (3.22)
HN BMC	2.78 (0.43)	2.72 (0.29)	4.03 (0.58)	3.96 (0.46)
LS BMC	25.56 (5.37)	23.47 (4.12)	49.16 (7.99)	45.93 (5.91)

Bone area= BA; bone mineral content=BMC; total body less head=TBLH; R=radius; H=total hip; HN=Hip neck; lumbar spine=LS.

TBLH BA and TBLH BMC Z scores adjusted for height and weight at 10 and 15 years of age were compared between the non-fracturing black female controls and the other sex and ethnic groups; and within the same sex and ethnic groups for those who did and did not report a fracture during the first 15 years of life (Tables 4.6 and 4.7).

Table 4.6 Bone area and bone mineral content Z scores (adjusted for height and weight) at 10 years of age with and without a history of fractures at age 15 years

Bone mass measurements (Z scores)	Females at 10 years				Males at 10 years			
	Blacks		Whites		Blacks		Whites	
	Without fractures (n = 128)	With fractures (n = 16)	Without fractures (n = 28)	With fractures (n = 19)	Without fractures (n = 130)	With fractures (n = 29)	Without fractures (n = 29)	With fractures (n = 24)
TBLH BA	0.00 (1.00)	-0.36 (0.52)	0.32 (1.01)	0.59[1] (1.14)	-0.30[2] (0.88)	-0.33 (0.72	**0.11[b] (0.93)**	**0.78[3] (0.79)**
R 1/3 BA	0.00 (1.00)	-0.33 (0.53)	0.45[1] (1.07)	0.63[2] (1.19)	-0.31[2] (0.92)	-0.30 (0.84)	**0.21[b] (1.02)**	**0.95[3] (0.90)**
R Mid BA	0.00 (1.00)	-0.30 (0.55)	0.54[2] (1.11)	0.65[2] (1.21)	-0.32[1] (0.94)	-0.28 (0.92)	**0.27[b] (1.06)**	**1.05[3] (0.97)**
R Ultra Distal BA	0.00 (1.00)	-0.28 (0.57)	0.59[2] (1.13)	0.66[2] (1.22)	-0.32[1] (0.96)	-0.26 (0.98)	**0.31[b] (1.09)**	**1.11[3] (1.02)**
R Total BA	0.00 (1.00)	-0.30 (0.55)	0.54[2] (1.11)	0.65[2] (1.21)	-0.32[1] (0.94)	-0.28 (0.93)	**0.27[b] (1.06)**	**1.05[3] (0.97)**
H BA	0.00 (1.00)	-0.26 (0.59)	0.63[2] (1.15)	0.66[2] (1.22)	-0.31[1] (0.97)	-0.25 (1.01)	**0.33[b] (1.11)**	**1.15[3] (1.06)**
HN BA	0.00 (1.00)	-0.31 (0.54)	0.50[1] (1.10)	0.65[2] (1.20)	-0.32[2] (0.93)	-0.29 (0.89)	**0.24[b] (1.04)**	**1.01[3] (0.94)**
LS BA	0.00 (1.00)	-0.21 (0.64)	0.69[2] (1.16)	0.66[2] (1.21)	-0.30[1] (1.00)	-0.21 (1.09)	**0.39[b] (1.13)**	**1.22[3] (1.13)**
TBLH BMC	0.00 (1.00)	-0.36 (0.53)	0.31 (1.00)	0.58[1] (1.14)	-0.30[2] (0.87)	-0.33 (0.71)	**0.10[b] (0.92)**	**0.76[3] (0.78)**
R 1/3 BMC	0.00 (1.00)	-0.35 (0.52)	0.38 (1.04)	0.61[2] (1.17)	-0.31[2] (0.89)	-0.32 (0.77)	**0.15[b] (0.96)**	**0.85[3] (0.83)**
R Mid BMC	0.00 (1.00)	-0.33 (0.53)	0.45[1] (1.08)	0.63[2] (1.19)	-0.31[2] (0.92)	-0.31 (0.84)	**0.20[b] (1.02)**	**0.95[3] (0.89)**
R Ultra Distal BMC	0.00 (1.00)	-0.36 (0.53)	0.29 (1.00)	0.57[1] (1.13)	-0.30[2] (0.87)	-0.33 (0.70)	**0.09[a] (0.91)**	**0.75[3] (0.78)**
R Total BMC	0.00 (1.00)	-0.34 (0.53)	0.41[1] (1.06)	0.62[2] (1.18)	-0.31[2] (0.90)	-0.31 (0.81)	**0.18[b] (0.99)**	**0.90[3] (0.86)**
H BMC	0.00 (1.00)	-0.33 (0.53)	0.45[1] (1.07)	0.63[2] (1.19)	-0.31[2] (0.91)	-0.30 (0.83)	**0.20[b] (1.01)**	**0.94[3] (0.89)**
HN BMC	0.00 (1.00)	-0.37 (0.53)	0.26 (0.99)	0.56[1] (1.12)	-0.29[2] (0.86)	-0.34 (0.68)	**0.07[a] (0.89)**	**0.70[3] (0.76)**
LS BMC	0.00 (1.00)	-0.31 (0.54)	0.50[1] (1.10)	0.64[2] (1.21)	-0.32[2] (0.93)	-0.30 (0.88)	**0.24[b] (1.04)**	**1.00[3] (0.93)**

Bone area= BA; bone mineral content=BMC; total body less head=TBLH; R=radius; H=total hip; HN=Hip neck; lumbar spine=LS. Data presented as mean (SD); significant differences within the same sex and age group [a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$. Significant differences between white males with and without fractures are bolded.

[1] $p<0.05$, [2] $p< 0.01$, [3] $p<0.001$ significant differences in BA and BMC Z scores comparing non-fracturing black females to fracturing and non-fracturing white males, white females, and black males

Table 4.7 Bone area and bone mineral content Z scores (adjusted for height and weight) at 15 years of age with and without a history of fractures at age 15 years

Bone mass measurements (Z scores)	Females at 15 years				Males at 15 years			
	Blacks		Whites[1]		Blacks[2]		Whites[3]	
	Without fractures (n = 147)	With fractures (n = 19)	Without fractures (n = 45)	With fractures (n = 20)	Without fractures (n = 146)	With fractures (n = 33)	Without fractures (n = 30)	With fractures (n = 25)
TBLH BA	0.00 (1.00)	-0.20 (0.65)	0.60 (0.92)	0.90 (1.23)	0.64 (1.13)	0.72 (0.94)	**1.61** [b] **(1.13)**	**2.43 (1.01)**
R 1/3 BA	0.00 (1.00)	-0.01 (1.02)	1.03 (1.02)	1.05 (1.25	1.19 (1.19)	1.38 (1.25)	**2.33** [b] **(1.23)**	**3.12 (1.21)**
R Mid BA	0.00 (1.00)	-0.04 (0.98)	0.99 (1.01)	1.05 (1.26)	1.14 (1.19)	1.31 (1.22)	**2.27** [b] **(1.23)**	**3.08 (1.19)**
R Ultra Distal BA	0.00 (1.00)	-0.08 (0.90)	0.92 (1.00)	1.03 (1.26)	1.04 (1.19)	1.20 (1.16)	**2.16** [b] **(1.22)**	**2.98 (1.16)**
R Total BA	0.00 (1.00)	-0.04 (0.97)	0.99 (1.01)	1.05 (1.26)	1.13 (1.19)	1.30 (1.22)	**2.26** [b] **(1.23)**	**3.07 (1.19)**
H BA	0.00 (1.00)	0.04 (1.10)	1.10 (1.03)	1.05 (1.23)	1.29 (1.19)	1.49 (1.30)	**2.41** [a] **(1.22)**	**3.16 (1.23)**
HN BA	0.00 (1.00)	-0.04 (0.97)	0.99 (1.01)	1.05 (1.26)	1.13 (1.19)	1.31 (1.22)	**2.26** [b] **(1.23)**	**3.07 (1.19)**
LS BA	0.00 (1.00)	0.02 (1.07)	1.08 (1.03)	1.05 (1.24)	1.26 (1.19)	1.46 (1.29)	**2.39** [a] **(1.22)**	**3.15 (1.23)**
TBLH BMC	0.00 (1.00)	-0.21 (0.61)	0.55 (0.91)	0.87 (1.22)	0.58 (1.12)	0.65 (0.91)	**1.52** [b] **(1.11)**	**2.33 (0.99)**
R 1/3 BMC	0.00 (1.00)	-0.12 (0.81)	0.81 (0.97)	0.99 (1.26)	0.91 (1.17)	1.03 (1.09)	**1.99** [b] **(1.20)**	**2.82 (1.11)**
R Mid BMC	0.00 (1.00)	-0.16 (0.74)	0.72 (0.95)	0.96 (1.25)	0.80 (1.16)	0.91 (1.03)	**1.84** [b] **(1.17)**	**2.67 (1.07)**
R Ultra Distal BMC	0.00 (1.00)	-0.27 (0.52)	0.35 (0.86)	0.74 (1.18)	0.33 (1.07)	0.35 (0.80)	**1.13** [b] **(1.03)**	**1.89 (0.90)**
R Total BMC	0.00 (1.00)	-0.18 (0.69)	0.66 (0.93)	0.93 (1.24)	0.72 (1.14)	0.81 (0.98)	**1.72** [b] **(1.15)**	**2.54 (1.04)**
H BMC	0.00 (1.00)	-0.11 (0.85)	0.85 (0.98)	1.01 (1.26)	0.96 (1.18)	1.10 (1.11)	**2.06** [b] **(1.20)**	**2.89 (1.13)**
HN BMC	0.00 (1.00)	-0.22 (0.61)	0.55 (0.91)	0.87 (1.22)	0.57 (1.11)	0.64 (0.91)	**1.51** [b] **(1.11)**	**2.32 (0.99)**
LS BMC	0.00 (1.00)	-0.23 (0.58)	0.50 (0.89)	0.84 (1.21)	0.51 (1.10)	0.57 (0.88)	**1.42** [b] **(1.10)**	**2.21 (0.96)**

Bone area= BA; bone mineral content=BMC; total body less head=TBLH; R=radius; H=total hip; HN=Hip neck; lumbar spine=LS. Data presented as mean (SD); significant differences within the same sex and age group [a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$

[1] $p<0.05$ for all BA and BMC Z scores between non-fracturing black females and white females with and without fractures

[2] $p< 0.01$ for all BA and BMC Z scores between non-fracturing black females and black males with and without fractures except for the RA ultra distal BMC Z score in black males with fractures

[3] $p<0.001$ for all BA and BMC Z scores between non-fracturing black females and white males with and without fractures

Comparing the same ethnic and sex groups with and without fractures, white males who reported a previous fracture/s during the first 15 years of life had greater BA and BMC at all sites at ages 10 years (table 4.6), and 15 years (table 4.7) than their non-fracturing peers. There were no significant differences in either BA or BMC at age 10 or 15 years in black or white females or in black males at age 10 and 15 years between those who did or did not fracture (tables 4.6 and 4.7).

Comparing bone mass variables (adjusted for differences in height and weight) of the different ethnic and sex groups with those of non-fracturing black females, white males with fractures and white females with and without fractures at 10 years had greater BA and BMC at most sites and black males without fracture had lower BA and BMC at all sites (table 4.6). The number of black females with fractures was too small to make a meaningful comparison. At 15 years, all groups of white males and females and black males had greater BA and BMC compared to the non-fracturing black female controls (table 4.7).

Table 4.8 compares total physical activity Z scores (combining formal and informal activities) at ages 10 and 15 years between children with and without a history of fractures over the first 15 years.

Table 4.8 Total physical activity Z scores at 10 and 15 years in children with and without a history of fractures at age 15 years compared to non-fracturing black females

	Physical activity Z scores															
	10 years								**15 years**							
	Without fractures				**With fractures**				**Without fractures**				**With fractures**			
	n	**Total**	**Formal**	**Informal**	**n**	**Total**	**Formal**	**Informal**	**n**	**Total**	**Formal**	**Informal**	**n**	**Total**	**Formal**	**Informal**
Black females	136	0.0 (-0.6- 0.4)	-0.5 (-0.6- 0.3)	0.0 (-0.7- 0.4)	16	0.2 (-0.4- 0.4)	0.0 (-0.6-0.5)	0.0 (-0.7-0.4)	145	-0.3 (-0.6- 0.1)	-0.4 (-0.4- -0.1)	-0.4 (-0.6- 0.1)	18	-0.2 (-0.6- 0.3)	-0.4 (-0.4- 0.1)	-0.3 (-0.6- -0.1)
White females	28	-0.8 (-1.3 - -0.5)	0.4 (-0.6 – 3.0)	-1.1 (-1.3 – -0.8)	20	-0.8 (-1.2- -0.5)	0.8 (-0.0 – 2.1)	-1.1 (-1.3- -0.8)	38	0.0 (-0.6 – 1.1)	0.8 (-0.1 – 2.5)	-0.5 (-0.6- 0.0)	18	-0.3 (-0.5 – 1.0)	0.2 (-0.2 – 1.7)	-0.4 (-0.6 – 0.3)
Black males	129	0.2 (-0.3- 0.8)	-0.3 (-0.6- 1.7)	0.1 (-0.3 – 0.6)	31	0.2 (-0.2- 1.0)	0.1 (-0.6 -1.1)	0.1 (-0.3- 0.6)	140	0.1 (-0.4- 0.9)	0.01 (-0.4 – 1.1)	-0.1 (-0.5 – 0.3)	32	0.2 (-0.2- 0.9)	0.6 (-0.4- 1.5)	-0.3 (-0.6- 0.5)
White males	23	-0.7 (-1.0 - 0.4)	**0.8 [a] (-0.2-2.2)**	-0.7 (-1.2- -0.1)	20	-0.5 (-0.9- -0.2)	**1.7 (0.5-3.8)**	-0.7 (-1.2- -0.1)	24	**0.0 [a] (-0.5 - 0.6)**	**0.2 [b] (-0.3 - 0.9)**	-0.2 (-0.4 – 0.6)	22	**0.8 (0.0 – 2.1)**	**1.6 (0.6 – 3.8)**	0.0 (-0.4 – 0.4)

Data presented as median (interquartile range); significant differences between those with and without fractures (bolded values) within the same sex and age groups [a] $p<0.05$, [b] $p<0.01$

Each of the physical activity components of the black non-fracturing females was used as the control to create Z scores for the other sex and ethnic groups.

White males who reported a fracture during the first 15 years of life participated in more physical activity at age 10 years (formal only; $p < 0.05$) and at 15 years (total and informal; $p < 0.05$ and $p < 0.01$ respectively) compared to white males with no fracture history. Fracture risk was positively associated with physical activity; at age 15 years for every 1 SD increase in formal physical activity (Z score of METmins/wk) the odds ratio for fracturing was 2.2 (95% CI 1.22-3.97 $p < 0.01$) and for every 1 SD increase in total physical activity (Z score METmins/wk) the odds ratio for fracturing was 1.78 (95% CI 1.06-3.00 $p < 0.05$). There was no significant difference in physical activity at age 10 or 15 years in black or white females or in black males between those who did or did not report a previous fracture.

Associations between body mass index, fracture risk and bone mass

There were no significant differences in the number of obese or overweight children within sex groups between the two ethnic groups at ages 10 and 15 years (table 4.9).

Table 4.9 Percentage of obese and overweight children at ages 10 and 15 years in the Bone Health Cohort

	Obese or overweight at 10 years % (n)	**Obese or overweight at 15 years % (n)**
Black females	21 (30)	32 (50)
White females	28 (13)	27 (17)
Black males	16 (26)	16 (27)
White males	21 (11)	18 (9)

Of the 17 obese/overweight white females, 53% (10) had sustained one or more fractures (Table 4.10). There were no differences in the other obese/overweight ethnic and sex groups when comparing those with and without fractures.

Table 4.10 The proportions of children with overweight or obesity at 10 and 15 years in those that have or have not fractured at age 15 years.

	10 years		**15 years**	
	With fractures n (%)	**Without fractures n (%)**	**With fractures n (%)**	**Without fractures n (%)**
Black females	2/16 (13)	28/128(22)	3/17 (18)	47/139 (34)
White females	8/19 (42)	5/28(18)	**10/19 (53) ***	**7/43 (16)**
Black males	3/29 (10)	23/130 (18)	4/53 (12)	23/140 (16)
White males	7/24 (29)	4/29 (14)	6/22 (27)	3/29 (10)

*$p<0.01$

Bone area and bone mineral content were greater at nearly all sites in obese/overweight children at 10 years compared to their non-obese peers in all ethnic and sex groups (Tables 4.11.1 and 4.11.2). At 15 years of age, TBLH BA was increased in all ethnic and sex groups with obesity/overweight except in the white males compared to their non-obese peers and BMC was increased at all sites in the obese/overweight children except at most sites in the white obese/overweight males compared to their non-obese peers (Tables 4.11.1 and 4.11.2).

Table 4.11.1 Bone area and bone mineral content Z scores (adjusted for height and weight) at 10 and 15 years of age comparing obese with non-obese females

Bone mass measurements (Z scores)	Females at 10 years				Females at 15 years			
	Blacks		Whites		Blacks		Whites	
	Obese (n = 30)	Non-obese (n = 109)	Obese (n = 13)	Non-obese (n = 33)	Obese (n = 50)	Non-obese (n = 106)	Obese (n = 17)	Non-obese (n = 45)
TBLH BA	**1.09 (0.86)** [c]	-0.28 (0.71)	**1.59 (0.75)** [c]	-0.01 (0.81)	**0.56 (0.99)** [c]	-0.29 (0.80)	**1.33 (0.94)** [c]	0.40 (0.89)
R 1/3 BA	**0.91 (0.91)** [c]	-0.23 (0.79)	**1.03 (0.90)** [c]	0.11 (0.90)	0.04 (1.06)	0.01 (0.96)	1.18 (1.06)	0.90 (1.03)
R Mid BA	**0.77 (0.96)** [c]	-0.20 (0.84)	**1.62 (0.99)** [c]	0.18 (0.95)	0.12 (1.06)	-0.03 (0.95)	1.21 (1.05)	0.85 (1.02)
R Ultra Distal BA	**0.66 (0.99)** [c]	-0.17 (0.87)	**1.60 (1.04)** [c]	0.23 (0.99)	0.23 (1.05)	-0.09 (0.93)	1.27 (1.04)	0.76 (1.00)
R Total BA	**0.76 (0.96)** [c]	-0.20 (0.84)	**1.62 (0.99)** [c]	0.19 (0.95)	0.13 (1.06)	-0.04 (0.94)	1.22 (1.05)	0.84 (1.01)
H BA	**0.57 (1.01)** [c]	-0.15 (0.89)	**1.58 (1.08)** [c]	0.27 (1.01)	-0.11 (1.04)	0.09 (0.97)	1.08 (1.06)	1.00 (1.03)
HN BA	**0.83 (0.94)** [c]	-0.22 (0.82)	**1.63 (0.96)** [c]	0.15 (0.93)	0.13 (1.06)	-0.04 (0.95)	1.22 (1.05)	0.84 (1.02)
LS BA	**0.38 (1.06)** [a]	-0.10 (0.92)	**1.50 (1.15)** [c]	0.35 (1.04)	-0.06 (1.05)	0.06 (0.97)	1.11 (1.06)	0.96 (1.03)
TBLH BMC	**1.12 (0.85)** [c]	-0.29 (0.70)	**1.56 (0.74)** [c]	-0.02 (0.79)	**0.63 (0.99)** [c]	-0.31 (0.78)	**1.32 (0.92)** [c]	0.34 (0.87)
R 1/3 BMC	**1.03 (0.88)** [c]	-0.27 (0.75)	**1.61 (0.82)** [c]	0.04 (0.84)	**0.37 (1.04)** [a]	-0.17 (0.89)	**1.31 (1.01)** [b]	0.63 (0.97)
R Mid BMC	**0.91 (0.91)** [c]	-0.24 (0.79)	**1.63 (0.9)** [c]	0.10 (0.89)	**0.47 (1.03)** [b]	-0.22 (0.85)	**1.32 (0.98)** [c]	0.53 (0.94)
R Ultra Distal BMC	**1.13 (0.85)** [c]	-0.29 (0.69)	**1.58 (0.72)** [c]	-0.02 (0.79)	**0.79 (0.93)** [c]	-0.39 (0.69)	**1.27 (0.83)** [c]	0.12 (0.79)
R Total BMC	**0.97 (0.89)** [c]	-0.25 (0.77)	**1.62 (0.86)** [c]	0.07 (0.87)	**0.53 (1.01)** [b]	-0.26 (0.83)	**1.33 (0.96)** [c]	0.46 (0.91)
H BMC	**0.92 (0.91)** [c]	-0.24 (0.79)	**1.63 (0.89)** [c]	0.10 (0.89)	**0.32 (1.05)** [a]	-0.14 (0.90)	**1.29 (1.02)** [a]	0.68 (0.98)
HN BMC	**1.16 (0.84)** [c]	-0.3 (0.68)	**1.56 (0.69)** [c]	-0.05 (0.71)	**0.64 (0.99)** [c]	-0.31 (0.78)	**1.32 (0.91)** [c]	0.34 (0.87)
LS BMC	**0.84 (0.94)** [c]	-0.22 (0.82)	**1.63 (0.95)** [c]	0.15 (0.93)	**0.68 (0.97)** [c]	-0.33 (0.75)	**1.31 (0.89)** [c]	0.28 (0.85)

Bone area= BA; bone mineral content=BMC; total body less head=TBLH; R=radius;H=total hip; HN=Hip neck; lumbar spine=LS. Data presented as mean (SD); significant differences within the same sex and age group [a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$. Each of the bone mass measurements of the black non-fracturing females were used as the control to create Z scores for the other sex and ethnic groups.

Table 4.11.2 Bone area and bone mineral content Z scores (adjusted for height and weight) at 10 and 15 years of age comparing obese with non-obese males.

Bone mass measurements (Z scores)	Males at 10 years				Males at 15 years			
	Blacks		Whites		Blacks		Whites	
	Obese (n = 26)	Non-obese (n = 130)	Obese (n = 11)	Non-obese (n = 41)	Obese (n = 27)	Non-obese (n = 146)	Obese (n = 9)	Non-obese (n = 42)
TBLH BA	**0.59 (1.12)**[b]	-0.48 (0.66)	**1.32 (0.59)**[c]	0.17 (0.86)	**1.47 (1.23)**[c]	0.52 (1.01)	2.46 (1.16)	1.84 (1.12)
R 1/3 BA	**0.37 (1.21)**[c]	-0.45 (0.77)	**1.34 (0.65)**[c]	0.31 (1.01)	1.27 (1.28)	1.23 (1.21)	2.57 (1.23)	2.71 (1.33)
R Mid BA	**0.21 (1.25)**[b]	-0.41 (0.84)	**1.34 (0.69)**[b]	0.41 (1.09)	1.32 (1.29)	1.15 (1.20)	2.59 (1.23)	2.64 (1.32)
R Ultra Distal BA	**0.09 (1.28)**[a]	-0.38 (0.87)	**1.32 (0.71)**[b]	0.47 (1.15)	1.38 (1.29)	1.02 (1.17)	2.61 (1.24)	2.49 (1.30)
R Total BA	**0.20 (1.25)**[b]	-0.41 (0.84)	**1.34 (0.69)**[b]	0.41 (1.10)	1.32 (1.28)	1.14 (1.19)	2.60 (1.23)	2.62 (1.32)
H BA	0.00 (1.28)	-0.36 (0.90)	**1.31 (0.73)**[a]	0.51 (1.19)	1.16 (1.26)	1.36 (1.21)	2.48 (1.20)	2.81 (1.34)
HN BA	**0.28 (1.24)**[c]	-0.42 (0.81)	**1.34 (0.67)**[c]	0.37 (1.06)	1.32 (1.29)	1.14 (1.19)	2.60 (1.23)	2.62 (1.32)
LS BA	-0.19 (1.30)	-0.32 (0.95)	1.24 (0.76)	0.60 (1.25)	1.20 (1.27)	1.32 (1.21)	2.51 (1.21)	2.78 (1.34)
TBLH BMC	**0.62 (1.11)**[c]	-0.48 (0.65)	**1.31 (0.58)**[c]	0.15 (0.84)	**1.46 (1.21)**[c]	0.44 (0.99)	**2.42 (1.13)**[a]	1.73 (1.09)
R 1/3 BMC	**0.51 (1.16)**[c]	-0.47 (0.70)	**1.33 (0.61)**[c]	0.22 (0.92)	**1.43 (1.28)**[b]	0.85 (1.13)	2.60 (1.22)	2.29 (1.25)
R Mid BMC	**0.37 (1.21)**[c]	0.44 (0.77)	**1.35 (0.65)**[c]	0.31 (1.01)	**1.46 (1.26)**[c]	0.71 (1.08)	2.55 (1.20)	2.11 (1.20)
R Ultra Distal BMC	**0.64 (1.15)**[c]	-0.48 (0.64)	**1.31 (0.57)**[c]	0.14 (0.83)	**1.42 (1.14)**[c]	0.14 (0.86)	**2.19 (1.04)**[b]	1.26 (0.94)
R Total BMC	**0.44 (1.19)**[c]	-0.46 (0.74)	**1.34 (0.63)**[c]	0.27 (0.97)	**1.47 (1.24)**[c]	0.61 (1.05)	2.51 (1.18)	1.97 (1.16)
H BMC	**0.38 (1.20)**[c]	-0.45 (0.76)	**1.34 (0.65)**[c]	0.30 (1.00)	**1.42 (1.28)**[a]	0.92 (1.14)	2.61 (1.23)	2.37 (1.27)
HN BMC	**0.68 (1.08)**[c]	-0.48 (0.62)	**1.29 (0.56)**[c]	0.11 (0.79)	**1.46 (1.21)**[c]	0.43 (0.98)	**2.41 (1.13)**[a]	1.72 (1.09)
LS BMC	**0.29 (1.23)**[c]	-0.43 (0.80)	**1.34 (0.67)**[c]	0.36 (1.06)	**1.46 (1.20)**[c]	0.36 (0.95)	**2.36 (1.11)**[a]	1.60 (1.05)

Bone area= BA; bone mineral content=BMC; total body less head=TBLH; R=radius; H=total hip; HN=Hip neck; lumbar spine=LS. Data presented as mean (SD); significant differences within the same sex and age group [a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$. Each of the bone mass measurements of the black non-fracturing females were used as the control to create Z scores for the other sex and ethnic groups.

Discussion

This is the first study to demonstrate heterogeneity in the pathogenesis of fractures in children of different ethnic groups. White males who reported a previous fracture were more physically active at age 10 and 15 years and had greater BA and BMC at the same ages at various sites. Increased physical activity seems to be the key contributory factor in the pathogenesis of fractures in white urban South African males. These differences were not present in white females or in black children, however in white females, fat mass appeared to be a contributory factor, as has been reported in other studies(72;273). No anthropometric or bone mass and size factors were found to be associated with fractures in black children.

The findings of this study support those of Clark et al(110) in a high-income country setting, who described the relationship between physical activity, bone mass and fracture risk in mainly white children (3.1% were of non-white ethnicity) and showed that despite having a higher BMD, daily or more vigorous physical activity increased fracture risk. This South African study is the first one to investigate the relationship between physical activity, bone mass and fracture risk in children of different ethnic origins.

There are both bone dependent and bone-independent factors that contribute to fracture risk in childhood(274). Many studies have investigated the influence of physical activity, socioeconomic status, exposure to sunlight, breastfeeding in early life and maternal smoking during childhood on bone mass (66;166;275;276). Flynn et al. prospectively followed-up 8 year old children for 8 years and concluded that there was an inverse relationship between bone mass at 8 years and upper limb fracture risk at 16 years of age, and that overweight or

obesity at age 8 years was also associated with an increased risk of fracture (277). In the ALSPAC prospective study, an 89% increased risk of fracture per SD decrease in size-adjusted BMC at age 9.9 years was found(76). Despite the inverse relationship observed between fracture risk and bone mass, Clark et al were the first to suggest that the higher bone mass associated with increased physical activity in children does not necessarily compensate for the increased exposure to injuries and higher fracture risk(110). Studies indicate that African-American and Hispanic children have a significantly greater bone strength than Caucasian children, due to greater bone density at the distal trabecular bone regions and greater bone density and area at the cortical sites of the radius and tibia (278); and the authors suggest that the differences in fracture rates reported between different ethnic groups in adulthood may be traced back to these differences in bone strength in childhood. Several studies on the Bt20 cohort have reported greater BMD in black compared to white children at 9 and 10 years of age(242-244) and more recently Micklesfield et al(246) have shown that South African black children have greater bone strength as measured by pQCT however the association between fracture risk and bone strength or geometry in South African children has to be further investigated. It can be postulated that structural differences in bone geometry may provide protection against fractures in black South Africans.

As discussed earlier, there is a significant difference in the grading of trauma associated with fractures between white and black children with white children fracturing at more severe levels of trauma than black children. McVeigh et al(245) have shown in this same cohort that white males with the highest physical activity scores have a greater BMD. Therefore although more physically active white males may have higher BMD, this does not appear to protect them from fracturing.

It has also been previously documented that black children are less physically active than white children (245), but this does not seem to impact negatively on their bone mass as black children have a greater hip bone mass, and black girls a greater lumbar spine bone mass as well, than their white peers(245). Despite South African black children being less active and consuming a diet lower in calcium (whites 703-711mg/day vs blacks 297-331mg/day) than white children(253), this study shows that they fracture less as well. The complexities of bone turnover and geometry have to be further investigated in the different ethnic groups to explain the possible pathogenesis of ethnic differences in fracture rates and bone mass among children.

A higher BMI at 10 and 15 years of age is the only difference between white females with and without a history of fractures. There are no significant differences in any bone mass or anthropometric measurements in black females with and without fractures. The Dortmund Nutritional and Anthropometric Longitudinal Designed (DONALD) study conducted in Germany on healthy children highlighted the inverse association between the accrual of bone mass and subcutaneous adipose tissue in prepubertal females. They further found that pubertal females with relatively high subcutaneous fat area (high ratio fat area/fat mass) were characterized by lower bone strength(273). Our finding of increased adiposity being associated with greater fracture risk in white girls is in keeping with previous studies conducted in Caucasian individuals. Goulding et al(72) found that girls with fractured forearms are often overweight and those with recurrent fractures and high body weight have a substantially higher fracture risk than girls with a history of a single fracture.(36). The reasons why increased adiposity in white South African females is associated with increased fracture risk

needs to be investigated. No previous studies have compared body composition characteristics and fracture risks in black individuals and this is the first study to suggest that there does not appear to be an association between fat mass, or adiposity, and fracture risk in black girls and boys, despite an increasing (but similar) prevalence of overweight or obesity in both black and white females . At age 15 years, 24% of BF were overweight and 8 % were obese; 22% of WF were overweight and 5% were obese; 8% of BM were overweight and 7.5% were obese, and 14% of WM were overweight and 4% were obese.

BA and BMC were increased at nearly all sites in obese/overweight children at 10 years compared to their non-obese peers across all ethnic and sex groups. A similar pattern was found at most sites at age 15 years. The relationship between bone and excess adiposity in children is complex. There are contradictory reports on skeletal mass in overweight or obese children but most studies have found normal or increased BMC in obese children(126;127). A null effect of fat mass on bone mass and density has also been found(279). One of the reasons for the conflicting results may be explained by the variability in fat distribution with possibly different consequences for bone(280). Childhood fractures have been shown to be linked to alterations in metabolic parameters associated with deposition of visceral fat mass, which may be indicative of future skeletal insufficiency(281). The higher incidence of fractures during puberty in obese children compared to their normal-weight peers maybe partly explained by the mismatch of bone strength and mineral accrual to body weight(280;282;283) Furthermore, despite the increased bone mass noted in some obese adolescents it may not be sufficient to overcome the greater forces that are generated when they fall resulting in fractures (128;284).

A recent study during a period of rapid mineral accrual in young girls aged 8-13 years showed that total and android or abdominal adiposity are significant determinants of bone development although their effects may be different(285). Whereas higher total body fat promotes gains in weight-bearing bone strength, at higher levels, android fat may be detrimental to gains in vBMD, particularly at diaphyseal regions of weight bearing bones where cortical bone predominates(285).

These higher levels of central adiposity may counteract the stimulatory effects of whole body fat mass on bone and compromise skeletal adaptations in vBMD and bone structural development(286). Laddu et al(285) suggested that this greater abdominal adiposity may offset the positive effects on cortical bone development at proximal weight-bearing bone sites, possibly by increased inflammation, metabolic abnormalities, or other factors that may affect bone such as advanced glycation end products, thereby resulting in a greater risk of fractures later in life.

Future research to examine the site-specific differences in the effects of fat on bone at both the weight-bearing and non-weight-bearing skeletal sites and also to determine the relationship between total body and regional adiposity on specific skeletal sites in the different ethnic groups and sexes in South African children is essential but also to explain why there were differences in bone measurements and fracture rates in obese and non-obese white females and none noted in the blacks.

There are three potential limitations to this study: firstly, the small number of subjects in the white group, which was influenced by the original sampling method that represented the demographics of racial proportions in urban South Africa. Despite the small number of white children this study was able to document statistically significant differences in bone size and

area and physical activity between the white boys who did and did not fracture. Further, in white girls this study was able to show an association between adiposity and fracture risk.

Secondly, this study has not adjusted for potential modifiers (socio-economic, nutrition and 25-hydroxyvitamin D). Vidulich et al found no effect of nutritional factors on bone mass and stated that the site-specific ethnic differences in bone mass were not the result of poor nutrition or poorer households in South African black children but suggested rather that genetic factors might play a role(242). Poopedi et al found no significant relationship between vitamin D status and BMC in either black and white subjects in the same cohort(287) however an inverse relationship between fat mass and 25-hydroxyvitamin D was found in both black and white children(287). Despite black children having lower levels of 25-hydroxyvitamin D than white children, this does not appear to influence their bone health(287). Similarly, the HELENA study of Spanish adolescents showed no relation between calcium and vitamin D intakes and bone mass(288).

Lastly, the lack of radiological confirmation of fractures might be considered a limitation of this study, the fracture rates for whites and blacks in the whole Bt20 cohort were similar to those reported in this smaller sub-cohort and the previous findings were similar between the ethnic groups at all ages. Furthermore, fracture data that had been previously collected at year 13 and those collected in the current year 15 questionnaires confirmed the previous fracture rates. The use of skeletal diagrams also confirmed the site of fracture and was filled in with the help of the parent or caregiver for accuracy and completeness.

The present study did not explore ethnic differences in bone geometry and volumetric BMD measurements utilizing peripheral quantitative computed tomography, or their relationship to fractures; and it is possible that further insights into the reasons for the ethnic differences in fracture risk may come to light.

Summary of major findings

Of the 533 subjects, 130 (24%) reported a fracture (black (15%), white (41.5%); $p<0.001$). White males who fractured were significantly taller, more physically active and had higher lean body mass, white females, who fractured, were fatter, than their non-fracturing peers. White males who fractured had greater BA and BMC at most sites at 10 and 15 years; BA and BMC were similar in each of the other sex and ethnic groups. No anthropometric or bone mass differences were found in black children with and without fractures.

The factor associated with fractures in white males appears to be participation in sports activities, while in white females obesity appears to play a role. The contributing factors in black males and females need to be elucidated.

CHAPTER 5

Fracture patterns and bone mass in South-African adolescent-mother pairs

This chapter describes and discusses the results of the studies to assess the fracture patterns and bone mass of South African adolescent-biological mother pairs and to determine if a familial relationship exists between first degree relatives (biological mothers and siblings) and the cohort children of different ethnic groups with regard to the prevalence of fractures.

Most of the findings and discussion in this chapter have been published in the following manuscript (appendix I):

Thandrayen K, Norris SA, Micklesfield LK, Pettifor JM. Fracture patterns and bone mass in South African adolescent-mother pairs: The Birth to Twenty Cohort. Osteoporos Int. 2013 Aug 14. [Epub ahead of print]

Results

Of the 3273 neonates originally enrolled in the Bt20 cohort, fracture and bone mass data were available on 1389 adolescents at age 17/18 years. Bone mass measurements were available on nearly all of their biological mothers (TB=1383 and LS=1261), however information on previous fractures was only available on 688 (~50%) of these. There were an almost equal number of biological mothers that completed and those that did not complete fracture questionnaires (B 580 vs 590; W 45 vs 46; MA 63 vs 65). There were no differences in age, anthropometric data or bone mass measurements between those mothers who did complete the fracture questionnaire and those who did not (Table 5.1). Differences in parity were not assessed.

Table 5.1 Comparisons of age, anthropometric data and bone mass measurements between biological mothers who did complete fracture questionnaires and those who did not.

	Biological mothers who completed fracture questionnaires		**Biological mothers who did not complete fracture questionnaires**	
	n	**Measurements**	**n**	**Measurements**
Age (yrs)	688	40.4	701	39.8
Weight (kg)	686	75.9	697	74.6
Height (m)	686	1.59	697	1.59
BMI (kg/m^2)	686	30	697	29.5
TB BA (cm^2)	688	1959	701	1947
TB BMC (g)	688	2213	701	2197
LS BA (cm^2)	678	55.7	587	55.8
LS BMC (g)	678	56.4	587	56.2

Figure 5.1 depicts the attrition of subjects in the cohort from birth until 17/18 years of age. The figure also shows the numbers of fracture questionnaires and bone mass measurements available at age 17/18 on adolescent-biological mother pairs as well as the number of fracture questionnaires on the siblings of the 17/18 year old adolescents.

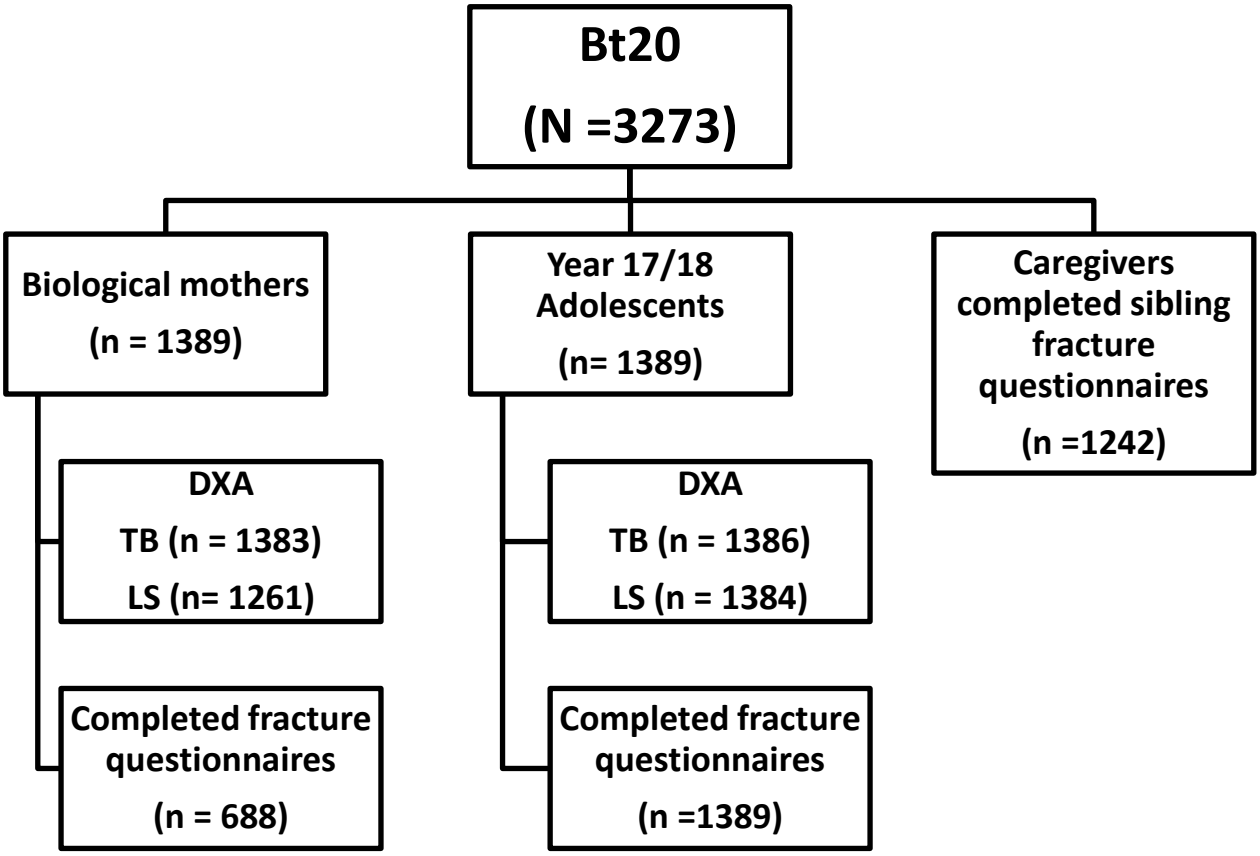


Figure 5.1 Flow diagram describing the attrition of study participants from birth until 17/18 year of age including the number of adolescent-biological mother pairs and their siblings with fracture and bone mass data

Anthropometric and bone mass measurements of adolescent-biological mother pairs:

Of the 1389 adolescent-biological mother pairs with bone mass and anthropometric data, 91 (6.6%) were white (W), 1170 (84.2%) were black (B) and 128 (9.2%) were of mixed

ancestry (MA). The baseline descriptive data of the adolescent-biological mother pairs of the different ethnic groups are shown in Tables 5.2 and 5.3. Mixed ancestry adolescents were on average 4 months older than their black and white peers ($p<0.001$). White adolescent males were heavier, had a greater BMI, were taller, and also had greater unadjusted BA and BMC of the total body and lumbar spine than black and MA adolescent males. White adolescent females were taller and had a greater unadjusted TB and LS BA than the black and MA adolescent females. Black adolescent females were heavier, had a greater BMI and unadjusted TB BA and BMC than the MA adolescent females.

After adjusting for height and weight, white males still had greater TB BA, LS BA and LS BMC than the males of the other ethnic groups. Mixed ancestry adolescent females had significantly lower TB BA than the black and white adolescent females. Adjusted TB BMC was not significantly different between the ethnic groups in either the adolescent males or the females, and adjusted LS BMC was not different between the adolescent female ethnic groups. Pubertal development was similar in the female adolescents of the different ethnic groups, but was less advanced in black adolescent males than in males of the other ethnic groups (Table 5.2).

There were no differences in age or weight between the mothers in the different ethnic groups. White mothers were taller and had a lower BMI and greater TB BA, and LS BA and BMC than their black and mixed ancestry peers. White and black mothers had greater TB BMC than mixed ancestry mothers. After adjusting for height and weight, black mothers had greater TB BA and BMC than mothers in the other two groups, and LS BMC was no longer significantly different between the ethnic groups.

Table 5.2 Anthropometric and bone mass measurements of year 17/18 adolescents

Anthropometric and bone mass measurements	Whites				Blacks				Mixed ancestry				P values	
	Males		Females		Males		Females		Males		Females		Males	Females
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)		
Age (years)	41	17.8 (0.3)	50	17.8 (0.2)	577	17.9 (0.4)	593	17.9 (0.4)	61	18.2 (0.5)	67	18.2 (0.5)	MA>B*, MA>W*	MA>B*, MA>W*
Weight (kg)	41	72.3 (12.4)	50	61.7 (12.9)	577	59.1 (8.9)	590	59.2 (11.9)	61	59.4 (12.6)	67	53.8 (11.7)	W>B*, W>MA*	W>MA**, B>MA**
Height (m)	41	1.78 (0.09)	50	1.66 (0.07)	577	1.71 (0.07)	590	1.60 (0.06)	61	1.71 (0.07)	67	1.60 (0.06)	W>B*, W>MA*	W>B*, W>MA*
BMI (kg/m^2)	41	22.6 (3.1)	50	22.4 (4.1)	577	20.1 (2.6)	590	23.2 (4.5)	61	20.3 (3.8)	67	21.1 (4.2)	W>B*, W>MA***	B>MA*
TB BA (cm^2)	41	2336.2 (225.3)	50	2010.7 (176.8)	577	2086 (180.2)	593	1883 (165.1)	61	2045 (205.3)	67	1781 (157.6)	W>B*, W>MA*	W>B*, W>MA*, B>MA*
Adjusted TB BA (cm^2)‡	41	2087.8 (13.6)	50	2026.8 (11.9)	577	2051.4 (3.8)	590	2008.2 (4.4)	61	2013.4 (10.8)	67	1956.9 (10.6)	W>B***, W>MA*, B>MA***	W>MA*, B>MA*
TB BMC (g)	41	2694.8 (446.5)	50	2144.5 (282.8)	577	2308.9 (344.2)	593	2034.2 (282.9)	61	2310.0 (388.1)	67	1894.5 (268.2)	W>B*, W>MA*	W>MA*, B>MA**
Adjusted TB BMC (g)‡	41	2354.2 (37.2)	50	2158.6 (32.4)	577	2277.5 (10.4)	590	2185.3 (12.0)	61	2280.9 (29.5)	67	2130.9 (28.9)	NS	NS

LS BA (cm^2)	41	68.9 (6.2)	50	57.8 (5.4)	575	62.7 (6.0)	593	54.5 (5.9)	61	61.8 (5.6)	67	53.2 (5.8)	W>B*, W>MA*	W>B**, W>MA*
Adjusted LS BA (cm^2)‡	41	62.8 (0.8)	50	58.8 (0.7)	575	60.7 (0.2)	590	58.8 (0.2)	61	60.0 (0.6)	67	57.8 (0.6)	W>B**, W>MA**	NS
LS BMC (g)	41	71.8 (12.6)	50	56.1 (10.0)	575	58.3 (10.8)	593	53.1 (9.6)	61	59.0 (10.9)	67	50.1 (8.5)	W>B*, W>MA*	W>MA***
Adjusted LS BMC (g)‡	41	62.8 (1.4)	50	56.8 (1.2)	575	56.7 (0.4)	590	58.0 (0.5)	61	57.6 (1.1)	67	56.5 (1.1)	W>B*, W>MA**	NS
Pubertal status	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**		
Stage 1	0	0	0	0	0	0	0	0	0	0	0	0		
Stage 2	0	0	0	0	2	0.4	0	0	0	0	0	0		
Stage 3	1	2.4	5	10	74	13.8	81	14.3	3	7	4	9.3	W>B* MA>B**	NS
Stage 4	14	34.2	22	45	319	59.5	275	48.7	20	46.5	18	41.9		
Stage 5	26	64.4	22	45	141	26.3	209	40.0	20	46.5	21	48.8		

Data are presented as number (n) and percentage (%) or means (SD) and ‡adjusted BA or BMC is adjusted for weight and height and is presented as means (SEM).

Data compared between groups using ANOVA for continuous data and Chi-square or Fisher's exact for categorical data.

P values presented for ethnicity in male and females separately (W = white, B= black, MA = mixed ancestry), * $p < 0.001$; ** $p<0.01$; ***<0.05. NS = not significant.

TB = total body, LS = lumbar spine, BA = bone area, BMC = bone mineral content.

Table 5.3 Anthropometric and bone mass measurements of mothers

Anthropometric and bone mass measurements	Whites		Blacks		Mixed Ancestry		p value
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	
Age (years)	91	39.9 (5.1)	1170	40.0 (7.0)	128	41.1 (6.7)	NS
Weight (kg)	91	72.2 (16.4)	1165	75.7 (16.3)	127	73.8 (16.5)	NS
Height (m)	91	1.65 (0.06)	1165	1.59 (0.06)	127	1.59 (0.07)	W>B*, W>MA*
BMI (kg/m^2)	91	26.5 (6.2)	1165	30.1 (6.2)	127	29.0 (6.4)	W<B*, W<MA**
TB BA (cm^2)	91	2016.5 (149.5)	1170	1953.5 (154.8)	128	1903.9 (171.7)	W>B*, W>MA*,B>MA**
Adjusted TB BA (cm^2)‡	91	1955.5 (8.1)	1165	1986.4 (2.4)	127	1933.7 (6.8)	B>W*,B>MA*,W>MA***
TB BMC (g)	91	2229.5 (276.9)	1170	2 211 (315.6)	128	2139 (336.7)	B>MA***
Adjusted TB BMC (g)‡	91	2149.2 (24.7)	1165	2252.4 (7.4)	127	2181.5 (20.6)	B>W*, B>MA**
LS BA (cm^2)	91	60.6 (5.4)	1067	55.4 (5.8)	107	55 (5.5)	W>B*; W>MA*
Adjusted LS BA (cm^2)‡	91	58.0 (0.5)	1064	57.1 (0.2)	106	55.8 (0.4)	W>MA*, B>MA***
LS BMC (g)	91	61.5 (10.7)	1067	56 (10.8)	107	55.1 (10.7)	W>B*, W>MA*
Adjusted LS BMC (g)‡	91	58.1 (1.0)	1064	58.1 (0.3)	106	56.6 (0.9)	NS

Data are presented as means (SD) and ‡ adjusted BA or BMC is adjusted for weight and height and presented as means (SEM).
Data compared between groups using ANOVA for continuous data.
P values presented for ethnicity (W = white, B= black, MA = mixed ancestry), * $p < 0.001$; ** $p<0.01$; *** $p <0.05$.
NS = not significant. TB = total body, LS = lumbar spine, BA = bone area, BMC = bone mineral content.

Fracture patterns:

Twenty two percent of the adolescents reported a history of having fractured a bone previously. The percentage of white children who reported fractures was double that of the other groups (W: 42% vs. B: 20% and MA: 20%; both $p<0.001$) (Table 5.4). White males had a higher prevalence of fractures than black males ($p<0.001$), and white females had a higher prevalence of fractures than black and mixed ancestry females ($p<0.001$ and $p<0.01$, respectively).

Eighty three percent of the adolescents had siblings. Of the 258 (22%) adolescents (with siblings) with a history of fracture, 58 (23%) of their siblings had fractured (Table 5.4). Of the remaining 900 adolescents (with siblings) without a history of fracture, 126 (14%) of their siblings had fractured (23% vs. 14%; $p<0.01$). Of the 688 biological mothers, who completed the fracture questionnaire, 60 (9%) indicated that they had sustained a fracture before the age of 18 years (white mothers 31%, mixed ancestry 16%, and black mothers (6%) W>B, $p<0.001$; MA>B, $p=0.01$) (Table 5.4). Unlike the pattern of fracture prevalence among the adolescents and their siblings, there was no difference in the prevalence of fractures between the adolescents of mothers who had or did not have a history of fractures.

Table 5.4 The number and percentage of 17/18 year old adolescents, their mothers and siblings with a history of fractures

Ethnic Group	Adolescent males		Adolescent females		Sibling fracture history associated with adolescents who had fractured		Biological mothers	
	n	n (%) with fractures	n	n (%) with fractures	n	n (%) of sibling fractures	n	n (%) with fractures
White	41	18 * (44)	50	20 * † (40)	34	8 (24)	45	14 * (31)
Blacks	577	144 * (25)	593	92 (16)	201	45 (22)	580	36 (6)
Mixed ancestry	61	17 (28)	67	10 (15)	23	5 (22)	63	10 ** (16)
Total	679	175(25.8)	710	122(17.1)	258	58 (22.5)	688	60(8.7)

* $p < 0.001$ between white and black males
between black males and black females
between white and black females
between white and black biological mothers;
** $p = 0.01$ between mixed ancestry and black biological mothers;
† $p < 0.01$ between white and mixed ancestry females

The commonest site of fracture in adolescents, their siblings and biological mothers was the upper limb followed by the lower limb (Figure 5.2).

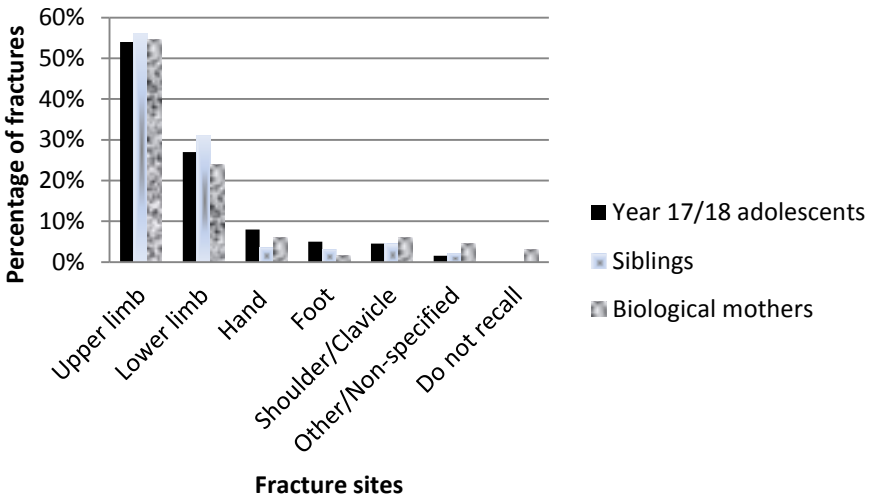


Figure 5.2 Percentage of fractures at the different sites in year 17/18 adolescents, their siblings and biological mothers.

Most fractures occurred as a consequence of grade 2 trauma within the year 17/18 adolescent and sibling groups (Figure 5.3). Fractures in the biological mothers occurred as a consequence of both grade 1 and grade 2 traumas. A greater number of fractures occurred secondary to grade 2 and 3 trauma in the year 17/18 adolescents compared to their biological mothers ($p=0.041$).

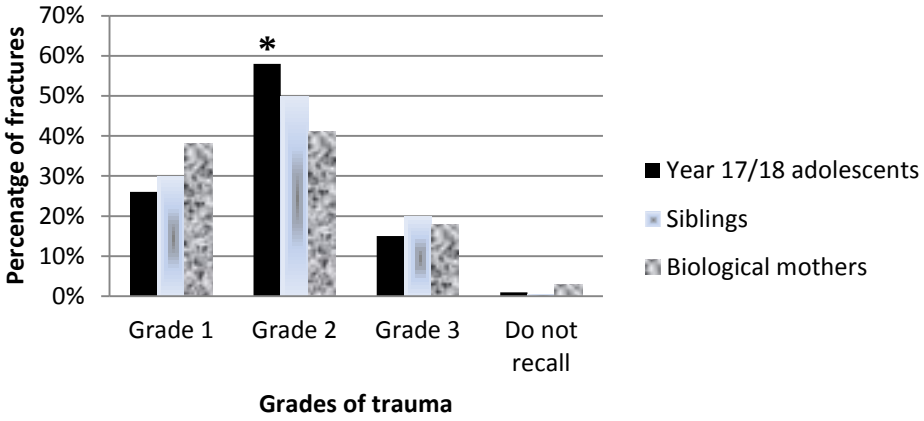


Figure 5.3 Grades of trauma causing fractures in year 17/18 adolescents, siblings and biological mothers. *p<0.05 between year 17/18 adolescents and their biological mothers.

Predictors of BA and BMC in 17-18 year old adolescents

To determine factors that made a significant contribution to adolescent TB and LS BA and BMC, ethnicity, gender, adolescent height, adolescent weight and Tanner stage (subdivided into early (n=170) or late puberty (n=1107)), maternal height, maternal weight, maternal TB and LS BA and BMC were chosen as candidate explanatory variables for the multivariate stepwise regression analyses. The results from the regression models are presented in Table 5.5. Including adolescent height, weight and maternal LS BA and LS and TB BMC resulted in the highest partial R^2 values for the respective adolescent bone variables. Maternal height and weight were negative predictors of adolescent BA and BMC, but contributed minimally to the overall variance. White ethnicity was a positive predictor of adolescent TB BA and BMC and LS BMC and male gender was a positive predictor of TB BA and BMC and LS BA.

Table 5.5 Regression models describing the relationship between predictors and adolescent bone area and bone mineral content

	TB BA (n =1269)			TB BMC (n =1269)			LS BA (n =1169)			LS BMC (n =1169)		
	Parameter estimate	**SE**	**Partial R^2**	**Parameter estimate**	**SE**	**Partial R^2**	**Parameter estimate**	**SE**	**Partial R^2**	**Parameter estimate**	**SE**	**Partial R^2**
Intercept	-525.3	77.3		-672.2	190.5		-27.1	3.9		-28.9	7.4	
Whites	39.21	9.6	**0.002***	62.4	24.9	**0.002*****	Not included			2.2	1.0	**0.003*****
Males	53.9	6.7	**0.006***	115.6	17.4	**0.018***	2.3	0.4	**0.019***	Not included		
Adolescent height (m)	1345.9	42.5	**0.660***	1486.5	110.3	**0.409***	51.7	2.3	**0.580***	47.8	3.0	**0.275***
Adolescent weight (kg)	8.47	0.2	**0.170***	14.0	0.6	**0.170***	Not included			0.25	0.02	**0.051***
Tanner stage (Early=0 Late=1)	Not included			27.3	17.9	0.001	Not included			Not included		
Maternal height (m)	-485.8	66.9	**0.005***	-709.4	132.4	**0.007***	-10.7	3.0	**0.004***	-14.1	5.0	**0.003*****
Maternal weight (kg)	-1.4	0.2	**0.003***	-2.9	0.4	**0.012***	Not included			-0.03	0.02	**0.004****
Maternal bone measurement	0.32	0.03	**0.004***	0.37	0.03	**0.029***	0.29	0.03	**0.021***	0.28	0.03	**0.084***
Total R^2	**0.852***			**0.648***			**0.624***			**0.420***		

Mother's bone measurement corresponds to the respective TB or LS BA or BMC value for each column. All variables left in the model are significant at the 0.15 level. Total body = TB; bone area= BA; bone mineral content=BMC; lumbar spine=LS.
* $p < 0.001$; ** $p<0.01$; *** $p <0.05$.

Factors associated with fractures in 17/18 year old adolescents:

Bivariate logistic regression analyses were initially performed for the whole group to assess if any confounding variables, such as weight, height, ethnicity, gender, pubertal stage, adolescents' and mothers' BA and BMC (TB and LS) and sibling history of fracture or maternal history of fracture were individually associated with adolescent fracture risk (Table 5.6). In these analyses, the adolescents' risk of fracture was higher if a sibling had a history of fracture (OR = 1.6; 95% CI 1.12-2.32; p=0.01) but was not associated with maternal history of fracture (OR = 1.09; 95% CI 0.63-1.86; p=0.762). Neither adolescent weight nor pubertal stage was associated with fracture risk of the entire cohort, however height was positively associated with the risk of fracture (OR = 9.85; 95% CI 2.31-41.83; p<0.01) and males were at greater risk of fracture compared to females (OR = 1.73; 95% CI 1.33-2.24; p<0.001). Adolescent TB BA (OR = 1.0008; 95% CI 1.0002-1.001; p<0.05) and TB BMC (OR = 1.0004; 95%CI 1.000002-1.0007; p<0.05) were both marginally associated with increased fracture risk. Maternal LS BMC (Z score) was inversely associated with fracture risk in their adolescent offspring (OR=0.80; 95% CI 0.7-0.93; p<0.01). White adolescents had a greater risk of fracture than other ethnic groups (OR = 2.82; 95% CI 1.82-4.37; p<0.001).

Table 5.6 Odds ratio for fractures in year 17/18 adolescents

Fractures	**n**	**Odds ratio**	**95% confidence interval**
Whites	1389	**2.82***	1.82-4.37
Males	1389	**1.73***	1.33-2.44
Adolescents height	1386	**9.85 ****	2.31-41.83
Adolescents weight	1386	1.00	0.99-1.02
Maternal height	1383	2.14	0.26-17.71
Maternal weight	1382	0.99	0.99-1.005
Pubertal stages (Early=0, Late=1)	1277	1.53	0.99-2.36
Maternal history of fracture	688	1.09	0.63-1.86
Sibling history of fracture	1144	**1.60****	1.12-2.32
Adolescent TB BA	1389	**1.0008*****	1.0002-1.001
Adolescent TB BMC	1389	**1.0004*****	1.000002-1.0007
Adolescent LS BA	1387	1.02	0.99-1.03
Adolescent LS BMC	1387	1.002	0.99-1.01
Maternal TB BA	1389	0.9995	0.9987-1.0003
Maternal TB BMC	1389	0.9996	0.9992-1.0001
Maternal LS BA	1265	0.982	0.960-1.005
Maternal LS BMC	1265	0.980	0.9677-0.9929
Maternal LS BMC (Z-score)	1265	**0.80****	0.7-0.93

Total body = TB; bone area= BA; bone mineral content=BMC; lumbar spine=LS. *$p < 0.001$; ** $p \leq 0.01$; ***$p < 0.05$.

Multivariate logistic regression analyses were performed on the entire group (n=1099) to determine the risk factors for fractures in the adolescents. Factors which had been found to be significantly associated in simple logistic regression and multiple regression analyses were included in the model, namely, gender, ethnicity, sibling history of fracture, adolescent and maternal heights, adolescent TB BA and BMC and maternal LS BMC. The risk factors for adolescent fracture risk are shown in Table 5.7. White ethnicity and male gender remained significant with a greater risk of adolescent fracture. The adolescent's risk of fracture was 50% greater if a sibling had a history of fracture (OR = 1.5; 95% CI 1.02-2.21; $p<0.05$). Maternal LS BMC was protective against the risk of fracture in the adolescent (24% reduction in fracture risk for every 1 unit increase in maternal BMC Z-score).

Table 5.7 Adjusted odds ratios for fractures in 17/18 year old adolescents

Fractures **n = 1099**	**Adjusted** **odds ratio**	**95%** **confidence interval**
Whites	**3.16** *	1.89-5.32
Males	**1.94** **	1.25-2.99
Adolescent height	0.31	0.01-11.05
Maternal height	3.09	0.12-77.09
Adolescent TB BA	1.00	0.998-1.002
Adolescent TB BMC	1.00	0.999-1.001
Sibling history of fracture	**1.50** ***	1.02-2.21
Maternal LS BMC (Z-score)	**0.76** **	0.63-0.91

Total body = TB; bone area= BA; bone mineral content=BMC; lumbar spine=LS. * $p < 0.001$; ** $p<0.01$; *** $p <0.05$. Odds ratios are adjusted for all variables in this table.

Discussion

To my knowledge this is the first study to describe familial characteristics of fracture patterns in childhood and adolescence and their relationship with bone mass measurements in adolescent-biological mother pairs of different ethnic backgrounds. The main findings of this study were that an adolescent's risk of fracture was decreased if his/her mother had a greater lumbar spine BMC (24% reduction in fracture risk for every SD increase in maternal BMC), but was increased if a sibling had a history of fracture or if the adolescent was white or male. Adolescent height and weight, maternal BA and BMC, males and white ethnicity were positive predictors of adolescent bone mass. Lastly, there was a higher prevalence of fractures in white mothers prior to 18 years of age compared to the other ethnic groups, a pattern similar to that of their adolescent children. However, we were unable to show any association between a maternal history of childhood/adolescent fractures and the prevalence of fractures in their adolescent offspring.

Maternal influences such as height, adiposity and vitamin D status have been postulated to be important in intrauterine programming and in the tracking of skeletal development and body composition from infancy to adulthood(289;290). These maternal influences are beyond the scope of this thesis but it will be important to determine if these factors predict or influence fracture risk and bone mass in adolescents from the different ethnic groups in South Africa.

A study in the early 1990's (291) had shown that South African black girls had a greater appendicular bone width than white girls, and recently, Micklesfield et al(246)

reported that black children have greater diaphyseal bone area and strength compared to whites. Despite these differences, Vidulich et al(92) found that heritability of BMC in black and white children was comparable and similar to that reported for Caucasians in other parts of the world(83;292).

Adolescents from the Bt20 cohort and their biological mothers were assessed at a mean age of 17.9 years and 40.1 years respectively. Estimates of the youngest age at which peak bone mass is achieved at the lumbar spine and proximal femur are at the end of longitudinal growth phase between 15 and 17 years of age(293;294) and it is suggested that about 85-90% of final adult bone mass is acquired by the age of 18 years in girls and 20 years in boys(1). Thus the current study describes fracture prevalence and bone mass in adolescents at an age when they are very close to having achieved peak bone mass, and assesses the influence of their bone mass at this stage of development on their lifetime fracture prevalence and further determines the influence of maternal and sibling fracture prevalence on adolescent fracture risk.

The prevalence of fractures in the Bt20 cohort up to the age of 17/18 years was 26% in males and 17% in females, with white males and females having double the prevalence of fractures compared to the other ethnic groups, a finding similar to that when the adolescents were aged 15 years. South African black children fracture less than white children because it is hypothesized that they might have protective genetic factors against low bone mass and fracture risk, they participate less in formal sport activities and they have lower physical activity scores than their white peers (245;253;295). Studies conducted in other countries have shown a similar prevalence of fractures in children less than 20 years of age to that of the white South African children in the Bt20 study (6;9;22;23). Similarly black or non-white children have a lower prevalence of reported fractures in keeping with South African studies

(76;255), despite some US studies suggesting a higher incidence of fractures in African-American children(296;297). A recent study from the US has however reported that white children have a higher prevalence of fracture at all time points compared to non-whites regardless of sex(256).

In the Bt20 study, the pattern of differences in fracture prevalence between ethnic groups was similar in the biological mothers to that of their adolescent offspring with the white mothers and adolescents reporting the highest prevalence of fractures (White mothers 31% vs Blacks 6% vs MA 16%). It is likely that the actual prevalence is higher than that recorded as the fractures were historic, occurred during childhood, and had no means of verification. However these figures are higher than those reported by an older group of men and women (>50 years of age) participating in the European Prospective Osteoporosis Study (EPOS). They reported a fracture prevalence between the ages of 8 and 18 years of 8.9% in men and 4.5% in women (298). We were unable to show any association between the history of childhood/adolescent fractures in mothers and the prevalence of fractures in their adolescent offspring within each ethnic group (data not shown). The findings support those of Ma and Jones, who did not observe any association between the prevalence of childhood fractures in offspring and maternal fracture history (but the number of participants was small) (274). However, the Bt20 study does show an association within the same family, as the prevalence of sibling fractures was significantly higher in families who had adolescents who had fractured (23%) than in families whose adolescents had not fractured (14%) ($p<0.01$). Similar evidence of fracture association among siblings has been reported from Poland, where more than 50% of adolescents with multiple fractures indicated that at least one family member had sustained a fracture, while only 29% of the adolescents who had no fractures had a family member who had had a fracture(s) (22).

This study was unable to show an association between the risk of childhood fractures and bone mass measurements at 17/18 years of age for the entire group. There are conflicting results concerning the association between childhood fractures and bone mass around the time of peak bone mass attainment. Childhood fracture in men has been associated with low BMD and smaller bone size in young adulthood, but this was not found in women who had fractured during childhood(299). However, another study reported that low BMD in pubertal girls with fractures persists into adulthood(300), but this was not confirmed by Kawalilak et al(301), who showed no significant differences in adjusted BMC between fracture and non-fracture groups at most sites in young adulthood. The EPOS study conducted in over 50 year old adults supports the latter study in that BMD was similar among those who did and did not report sustaining a fracture during childhood (298).

Despite this study reporting no relationship between childhood or adolescent fracture risk and their bone mass, we found that a 1 SD increase in maternal LS BMC reduced the risk of fracture in children by 24%. This novel finding applies across all ethnic groups. Although the positive relationship between mother's bone mass and her offspring's has been researched and documented worldwide (87;216;302;303), the finding that maternal bone mass might influence her offspring's fracture prevalence has not been reported previously. Intuitively, this association should not be surprising as several studies, although not all, have shown that children who had a fracture(s) tend to have reduced BMC and BA compared to their peers who had no fractures (10;35;36;75), and genetic inheritance (maternal and paternal bone mass) plays a large role in determining childhood BMC, BA and peak bone mass. What is surprising is that this study as described in chapter 4 did not find an inverse association between fracture

history prevalence during childhood and adolescence and bone mass at ages 10 and 15 years. In fact, in white males, there was a positive association between fracture risk and bone mass possibly associated with increased contact sport participation. Thus, the association between maternal LS BMC and adolescent fracture risk might be a proxy for structural differences in the adolescents, with low maternal BMC indicating poorer adolescent bone strength rather than differences in bone mass per se.

In addition to predicting adolescent fracture, maternal bone mass was also an independent predictor of adolescent BA and BMC. Twin and family-based studies have indicated that 60-85% of the variance in BMD is genetically determined(87;304). Ferrari et al investigated the familial resemblance for bone mineral mass at the lumbar spine and femoral neck before the pubertal bone growth spurt in healthy Caucasian prepubertal daughters and their mothers and found that familial resemblance was detected particularly at sites of predominantly trabecular bone(216). Furthermore, heritability for all lumbar spine parameters and for femoral neck areal BMD and bone mineral apparent density was close to heritability for height (38%), a trait known to be under strong genetic determination(216). Recent studies in Japan have documented significant correlations of BMD and lifestyles in both pre- and post-menarche daughters and their mothers but there was no correlation between daughters and their grandmothers or mothers and grandmothers (but the number of grandmothers in the study was small) (302;303). All of these studies suggest that bone mass in pre- and post-menarche daughters are related to BMD of their mothers. Joaunney et al(305) found statistically significant relationships between BMD in mother/daughter pairs ($r = 0.236$ $p = 0.018$), mother/son pairs ($r = 0.304$; $p = 0.004$) and all possible parent/children pairs ($r = 0.27$; $p<0.0001$). Similarly Krall and Dawson-Hughes(87) found correlation coefficients of between

0.22 – 0.52 between mothers and daughters and between 0.27 – 0.58 between mothers and sons. In the 2009-2010 Korean National Health and Nutrition Examination survey, parental BMD positively influenced BMD in daughters and sons after adjustment for physique, dietary intakes, and lifestyles: BMD values in the low tertile for both parents doubled the prevalence ratio for a BMD value in the low tertile in adolescents as compared with a low BMD tertile in one parent(306). The prevalence ratio of whole body less head BMD being in the low tertile increased by eight-fold and ten-fold in daughters and sons respectively if both parents were in the low BMD tertile(306). We found similar heritability rates (approximately 30%) by maternal descent in pre- and early pubertal South African children(92) indicating that genetics plays an important role in determining bone mass in black, white and mixed ancestry South African children.

This study has several limitations. As has been noted in previous chapters, the study relies heavily on the self-reporting of historical childhood fractures in adolescents, their siblings and their mothers. Being historical, we could not verify the occurrence of the fracture, its site, or if x-rays confirmed the presence of a fracture. Thus we are dependent on memory of fracture events which is likely to be influenced by the severity of the fracture and the time between completing the questionnaire and the fracture event, which in the case of the mothers was at least 20 to 30 years. Potential differences in literacy between the black and white participants are not relevant as questionnaires were completed with the help of a research assistant. Finally, this study did not include confounding variables such as vitamin D levels, calcium intake, physical activity scores or socioeconomic status, but the relationship between sports activities and fractures has been reported previously in this cohort (295).

Summary of major findings

An adolescent's risk of lifetime fracture decreased with increasing maternal lumbar spine (LS) BMC (24% reduction in fracture risk for every unit increase in maternal LS BMC Z-score) and increased if they were white, male or had a sibling with a history of fracture. White adolescents and their mothers had a higher fracture prevalence compared to the black and mixed ancestry groups.

Maternal bone mass has a significant inverse association with their adolescent off-springs' fracture risk and bone mass. Furthermore, there is a strong familial component in fracture patterns among South African adolescents and their siblings.

CHAPTER 6

This concluding chapter of my thesis summarises the overall aim of the thesis, followed by the key objectives, hypotheses, findings and strengths of the thesis. The contextual relevance of the salient findings and key points pertaining to future research will be outlined followed by the conclusion.

Summary

Aim of the thesis

The main aim of this thesis was to investigate the epidemiology of and risk factors for fractures in urban South African children of different ethnic backgrounds and to determine the association between fractures and bone mass in these children and their biological mothers, a topic which has not been investigated previously.

Summary of objectives, hypotheses and key findings

Table 6.1: Summary of the objectives, hypotheses and key findings

Objectives	Hypotheses	Summary of key findings
1. To determine the incidence or rates of fractures, their common sites of occurrence, their causes and the grades of trauma associated with fractures in urban South African children of different ethnic groups from birth until 17/18 years of age	South African black children fracture less than white children. All ethnic groups have a similar pattern of age and sex related distribution of fractures	Prevalence of fractures in white children is double that of black and mixed ancestry groups. There was a similar pattern of age and sex related distribution of fractures in all ethnic groups. Fractures in white boys were associated with sport related activities, a pattern not found in the black and mixed ancestry groups.
2. To investigate the associations between fracture prevalence at 15 years of age and bone mass, body composition and physical activity at ages 10 and 15 years in these children.		White males who fractured were significantly taller, more physically active, and had higher lean mass. White females who fractured were fatter. White males who fractured had greater BA and BMC adjusted for height and weight. Bone mass and anthropometric measurements in black children did not differ between those with and without a history of fractures.
3. To assess the fracture patterns and bone mass of South African adolescent-biological mother pairs.	Maternal bone mass is associated with fracture prevalence in their adolescent offspring. There is a strong association between mothers' and their adolescents' bone mass measurements.	An adolescent's risk of lifetime fracture decreased with increasing maternal LS BMC and increased if they were white, male, or had a sibling with a history of fracture. Maternal BA and BMC and white ethnicity were positive predictors of adolescent bone mass.

4. To determine if a familial association exists between first degree relatives (biological mothers and siblings) and the cohort children of different ethnic groups with regard to the prevalence of fractures.	A history of fractures in the mother or other siblings is associated with a history of fractures in the adolescent.	White adolescents and their mothers had a higher fracture prevalence compared to the black and mixed ancestry groups. The adolescent's risk of fracture was 50% greater if a sibling had a history of fracture.

Strengths of the thesis

This study comprised both retrospective and prospective longitudinal aspects on a large cohort of urban South African children which is representative of the different ethnic groups in proportion to the population statistics.

The novel findings of this thesis are summarised below and are placed in context with the current world literature or research pertaining to the field of bone mass and fractures in children.

1) I have shown that white children fracture more than children from black and mixed ancestry groups. This is a novel finding, but is in keeping with previously reported differences in hip fracture rates between South African black and white adults. Similarly African-American women have a lower fracture risk than white women at every level of bone mineral density. A recent study from the US has reported that white children have a higher prevalence of fracture at all time points compared to non-whites regardless of sex. Other studies indicate that African-American and Hispanic children in the USA have significantly greater bone strength than Caucasian

children and the differences in fracture rates reported between these different ethnic groups in adulthood may be traced back to these differences in bone strength in childhood.

Our research group has previously shown in the Bt20 cohort, that black children have a higher hip, mid-radial and lumbar spine bone mass and that adult black women have greater hip BMD than their white peers, supporting the hypothesis of a genetic protection against low bone mass and fractures in black children and post-menopausal women. More recently it has been shown that South African black children have greater bone strength as measured by pQCT, however the association between fracture risk and bone strength or geometry in South African children has to be further investigated. It is postulated that structural differences in bone geometry provide protection against fractures in black South Africans.

The proportion of white boys and girls fracturing in the first 15 years of life in this Bt20 study is similar to that reported in Caucasian children in developed countries, such as in Europe and USA. Upper limb or radial fractures were the most common types of fractures in both sexes and in all ethnic groups.

There was a significant difference in the grading of trauma associated with fractures between the white and black South African children with a greater percentage of whites sustaining fractures due to sport related activities compared to the black and mixed ancestry groups. The association of fractures with physical activity has also been reported from developed countries. The lower physical activity levels in black than white South African children are probably related to the lack of organized

sporting activities in schools attended mainly by black subjects and the poorer socio-economic status of black families.

Whether the reported ethnic differences in fracture rates and bone mass are largely explained by environmental or genetic factors is unclear and requires to be further investigated.

2) This is the first study to demonstrate heterogeneity in the pathogenesis of fractures in children of different ethnic backgrounds.

In white males, increased physical activity (formal sport), possibly leading to a greater opportunity for injury, is an associated factor to their increased incidence of fractures despite bone area and mass of those fracturing being greater than those who did not fracture. This however is not a novel finding as a study in a high-income country (United Kingdom) with predominantly white study participants showed that daily or more vigorous physical activity increased fracture risk despite those participating in sporting activities having a higher BMD.

Recently, our research group has shown that black children in the Bt20 cohort have greater bone strength as measured by pQCT, however the association between fracture risk and bone strength or geometry has to be further investigated.

In keeping with other studies worldwide, white females with fractures had a higher BMI than their peers who did not fracture.

An interesting and novel finding was that we were unable to find any associations between physical activity or body composition and fractures in the black children. Though black children are less physically active than white children, this does not seem to impact negatively on their bone mass as has been shown in previous studies

from the Bt20 cohort, nor on their fracture risk. Despite an increasing but similar prevalence of overweight or obesity in both black and white females, there does not appear to be an association between fat mass, adiposity and fracture risk in black girls or boys.

Bone area and BMC were increased at nearly all sites in obese/overweight children at 10 years of age compared to their non-obese peers across all ethnic and sex groups. There are contradictory reports in the literature of the effect of overweight or obesity on skeletal mass in children but most studies have found normal or increased BMC in obese children, although some studies have also shown that obese children with fractures may have narrower bones.

3) To my knowledge, this is the first study to describe familial characteristics of fracture patterns in childhood and adolescence and their relationship with bone mass measurements in adolescent-biological mother pairs of different ethnic backgrounds. There is a strong ethnic component in fracture patterns within South Africa as the prevalence of fractures is higher in white South African families compared to the other ethnic groups. In addition, the prevalence of sibling fractures was significantly higher in families in whom adolescents had fractured than in families whose adolescents had not fractured. Similar evidence of fracture association among siblings has been reported from Poland. However, this thesis was unable to show any association between the history of childhood/adolescent fractures in mothers and the prevalence of fractures in their adolescent offspring within each ethnic group.

Our studies have been unable to show an association between the risk of childhood fractures and bone mass at 17/18 years of age for the entire group. This is not a

surprising finding as there are conflicting results concerning the association between childhood fractures and bone mass around the time of peak bone mass attainment.

Despite the lack of a relationship between childhood or adolescent fracture risk and bone mass, the most important novel finding of this study was that 1 SD increase in maternal LS BMC reduced the risk of fracture in children by 24%. Thus, the association between maternal LS BMC and adolescent fracture risk might be a proxy for structural differences in the adolescents, with low maternal BMC indicating poorer adolescent bone strength rather than differences in bone mass per se.

Maternal bone mass was also an independent predictor of adolescent BA and BMC, a finding previously reported by researchers in many studies, who have found positive correlations between BMD in mother/daughter, mother/son and parent/children pairs.

The findings outlined above leave us with an unanswered question: Does genetics play a major role in determining fracture patterns and bone mass across all ethnic groups?

Limitations of the thesis

A major limitation of this study is the self-reporting of historical childhood fractures in adolescents, their siblings and their mothers. Being historical, I could not verify the occurrence of the fracture, its site, or if x-rays confirmed the presence of a fracture. However, this was probably not a major factor in the study as at all ages of the adolescents the findings were consistent between the ethnic groups. The sites of the reported fractures were confirmed with the aid of a skeletal diagram and completed by the parent or primary caregiver.

Another possible limitation was the small number of subjects in several of the ethnic groups, including the white group in the Bone Health cohort. Despite the small numbers, this

study was able to document statistically significant differences in bone size and area and physical activity between the white boys who did and did not fracture. The Indian children were excluded from most of the analyses of the Bt20 cohort as the numbers were too small to make a meaningful comparison with other ethnic groups.

This study did not include confounding variables such as vitamin D levels, calcium intake or socioeconomic status but ethnic differences investigating the influences of these confounders on this cohort that has been previously reported by colleagues have been incorporated into the discussion.

Future research

Many questions remain unanswered regarding the pathogenesis of fractures in children worldwide. Our multi-ethnic population and the availability of many sophisticated techniques to measure bone mass, structure and strength and possible relevant associated factors provide ideal opportunities to continue the research in South Africa.

My future goals in bone health research are to perform additional prospective studies on the participants from the Bt20 cohort (a multi-ethnic population) focusing on bone health and future risk of fractures during adulthood. This will entail more detailed research looking into the nature, specific levels of trauma or activity and incidents causing fractures and more importantly, differentiating between measures of bone mass and bone structure or strength as underlying predisposing factors for fractures. The current study in this thesis has focused mainly on bone mass measurements in relation to fracture risk rather than focusing on bone structure and strength which needs to be investigated at all stages of bone development (bone growth, peak bone mass and during the post-menopausal period). These new findings might provide insight into why there may or may not be differences in bone mass, structure, strength

and fractures in individuals of different ethnic backgrounds. In addition, genetic, socioeconomic and environmental predisposing factors to fractures in relation to bone mass measurements need to be thoroughly investigated.

With these rapidly changing economical, lifestyle and environmental patterns, I am more inclined to advocate for further bone health research to be performed on the next generation of children to follow on from the Bt20 cohort. Furthermore, research in this younger group would be more structured and eliminate many limitations encountered in the current study.

To strengthen these research studies in our new generation, collaborations with other groups such as ALSPAC in the UK and others in USA so that comparisons can be made with African Americans and whites to our South African ethnic groups; would be mandatory to determine if similar ethnic differences persist worldwide.

These are the more detailed research questions that were not addressed in this thesis and that should be investigated in the future (the methodology of which was briefly outlined above):

1. What are the differences in bone geometry, strength and structure in urban South African children in different ethnic groups with and without fractures and do these differences persist into old age?

2. What are the effects of fat (or body composition) on bone and fracture risk in children of different ethnic backgrounds?

3. Is pQCT a superior tool in determining fracture risk and low bone mass compared to DXA measurements in children?

4. How do gene-environmental interactions affect bone mass and fracture risk in children of different ethnic backgrounds?

5. Which genes are responsible for low bone mass and increased fracture risk in children from different ethnic backgrounds?

6. What are the early life variables and maternal risk factors for fractures in relation to bone mass in urban South Africans of different ethnic backgrounds?

7. Does socioeconomic status affect fracture risk independent of bone mass?

8. Is there an increased risk of osteoporotic fractures during adulthood in children with fractures and if so, what are the predisposing risk factors?

9. Will there be a change in the pattern and incidence of fractures in generations to follow with changing lifestyle and environmental influences?

10. Are there modifiable lifestyle and environmental factors in this cohort and generations to follow with regards to improving bone health?

Implications of the study findings

This thesis has provided new insights into the pathogenesis of fractures and its association with bone mass in children of different ethnic backgrounds. Whether these findings in South African children provide a rationale for interventions to improve bone health remains debatable.

This thesis emphasizes that there are ethnic differences in fracture prevalence and bone mass in children of different ethnic backgrounds. Whether these relate to differences in dietary

patterns (especially calcium and protein intakes) and socio-economic status among the different ethnic groups is unclear. Not only should medical practitioners but all South Africans be made aware that fracture injuries in childhood are not an uncommon occurrence and that black children fracture less compared to other ethnic groups. Fractures during childhood have proven to be a significant health burden that health workers and parents face with nearly 40-50% of white children sustaining at least one fracture during childhood and adolescence. This high incidence of childhood fractures is largely due to increased physical activity in white males. Thus exposure to injuries is an important determinant of fracture risk in healthy children.

In order to decrease the incidence of childhood fractures in South Africa and to optimize their bone mass and bone health from an early age, healthy eating patterns and exercise regimens implemented in the physical education programs of schools and sports clubs may be valuable.

Conclusion

My thesis was based on a cohort of children born in 1990 from the heart of an urban area (Johannesburg) in South Africa. The findings of this thesis are reflective of the current modern day adolescent or youth of South Africa from multiethnic backgrounds with differing socioeconomic circumstances and environmental exposures. Despite the poorer SES circumstances that black children were exposed to, there were important favourable ethnic differences noted in black children with regards to bone mass and fracture risk compared to white children in South Africa.

The salient findings of my thesis are that South African white children fracture more than black, Indian and mixed ancestry children which are consistent with findings in black and white postmenopausal women. Secondly, an adolescent's risk of fracture is decreased if his/her mother had a greater lumbar spine BMC. These findings suggest that blacks may have genetic protective factors against fractures and low bone mass and that greater maternal bone mass decreases fracture risk in children.

Together with Mandela's legacy in fostering racial reconciliation have come changes in lifestyles and environmental influences that may, in combination, alter the effect of genetic protective factors against fractures and low bone mass in blacks. The changing dietary patterns with increasing incidence of obesity in children and adolescents, the differing levels of physical activity and modified lifestyle behaviours may influence fracture patterns and bone health in the future. To maintain greater maternal bone mass that is protective against fracture risk in children, parental influences and behaviours for optimal bone health also need to be addressed hand-in-hand with that of their children. Whether lifestyle and behavioural changes

will positively or negatively influence bone health is questionable and will require ongoing research in this field.

However, in order to decrease the burden of fractures in children and osteoporosis risk in later life, bone healthy diets and modifiable lifestyle behaviours to improve bone health in children and their parents need to be adopted and further research with longitudinal studies must be conducted, in this diverse multi-ethnic cultural country, South Africa.

Reference List

(1) Heaney RP, Abrams S, Dawson-Hughes B, Looker A, Marcus R, Matkovic V, et al. Peak bone mass. *Osteoporos Int* 2000;**11**(12):985-1009.

(2) Rennie L, Court-Brown CM, Mok JY, Beattie TF. The epidemiology of fractures in children. *Injury* 2007 Jul 10;**38**(8):913-22.

(3) Alffram.P.A., Bauer.G.C. Epidemiology of fractures of the forearm. A biomechanical investigation of bone strength. *J Bone Joint Surg Am* 1962 Jan;**44-A**:105-14.

(4) Garraway WM, Stauffer RN, Kurland LT, O'Fallon WM. Limb fractures in a defined population. I. Frequency and distribution. *Mayo Clin Proc* 1979 Nov;**54**(11):701-7.

(5) Court-Brown CM, Rimmer S, Prakash U, McQueen MM. The epidemiology of open long bone fractures. *Injury* 1998 Sep;**29**(7):529-34.

(6) Cooper C, Dennison EM, Leufkens HG, Bishop N, van Staa TP. Epidemiology of childhood fractures in Britain: a study using the general practice research database. *J Bone Miner Res* 2004 Dec;**19**(12):1976-81.

(7) Chiaviello CT, Christoph RA, Bond GR. Stairway-related injuries in children. *Pediatrics* 1994 Nov;**94**(5):679-81.

(8) Kypri K, Chalmers DJ, Langley JD, Wright CS. Child injury morbidity in New Zealand, 1987-1996. *J Paediatr Child Health* 2001 Jun;**37**(3):227-34.

(9) Landin LA. Fracture patterns in children. Analysis of 8,682 fractures with special reference to incidence, etiology and secular changes in a Swedish urban population 1950-1979. *Acta Orthop Scand Suppl* 1983;**202**:1-109.

(10) Clark EM, Tobias JH, Ness AR. Association between bone density and fractures in children: a systematic review and meta-analysis. *Pediatrics* 2006 Feb;**117**(2):e291-e297.

(11) Clark EM, Ness AR, Tobias JH. Bone fragility contributes to the risk of fracture in children, even after moderate and severe trauma. *J Bone Miner Res* 2008 Feb;**23**(2):173-9.

(12) American Academy of Pediatrics: Falls from heights: windows, roofs, and balconies. *Pediatrics* 2001 May;**107**(5):1188-91.

(13) Falvey EC, Eustace J, Whelan B, Molloy MS, Cusack SP, Shanahan F, et al. Sport and recreation-related injuries and fracture occurrence among emergency department attendees: implications for exercise prescription and injury prevention. *Emerg Med J* 2009 Aug;**26**(8):590-5.

(14) Flavin MP, Dostaler SM, Simpson K, Brison RJ, Pickett W. Stages of development and injury patterns in the early years: a population-based analysis. *BMC Public Health* 2006 Jul 18;**6**:187.

(15) Pitone ML, Attia MW. Patterns of injury associated with routine childhood falls. *Pediatr Emerg Care* 2006 Jul;**22**(7):470-4.

(16) Loder RT. The demographics of playground equipment injuries in children. *J Pediatr Surg* 2008 Apr;**43**(4):691-9.

(17) Laforest S, Robitaille Y, Dorval D, Lesage D, Pless B. Severity of fall injuries on sand or grass in playgrounds. *J Epidemiol Community Health* 2000 Jun;**54**(6):475-7.

(18) Keays G, Skinner R. Playground equipment injuries at home versus those in public settings: differences in severity. *Inj Prev* 2012 Apr;**18**(2):138-41.

(19) Simon TD, Bublitz C, Hambidge SJ. Emergency department visits among pediatric patients for sports-related injury: basic epidemiology and impact of race/ethnicity and insurance status. *Pediatr Emerg Care* 2006 May;**22**(5):309-15.

(20) Sytema R, Dekker R, Dijkstra PU, ten Duis HJ, van der Sluis CK. Upper extremity sports injury: risk factors in comparison to lower extremity injury in more than 25 000 cases. *Clin J Sport Med* 2010 Jul;**20**(4):256-63.

(21) Lyons RA, Delahunty AM, Kraus D, Heaven M, McCabe M, Allen H, et al. Children's fractures: a population based study. *Inj Prev* 1999 Jun;**5**(2):129-32.

(22) Konstantynowicz J, Bialokoz-Kalinowska I, Motkowski R, Abramowicz P, Piotrowska-Jastrzebska J, Sienkiewicz J, et al. The characteristics of fractures in Polish adolescents aged 16-20 years. *Osteoporos Int* 2005 Nov;**16**(11):1397-403.

(23) Jones IE, Williams SM, Dow N, Goulding A. How many children remain fracture-free during growth? a longitudinal study of children and adolescents participating in the Dunedin Multidisciplinary Health and Development Study. *Osteoporos Int* 2002 Dec;**13**(12):990-5.

(24) Hedstrom EM, Svensson O, Bergstrom U, Michno P. Epidemiology of fractures in children and adolescents. *Acta Orthop* 2010 Feb;**81**(1):148-53.

(25) Kopjar B, Wickizer TM. Fractures among children: incidence and impact on daily activities. *Inj Prev* 1998 Sep;**4**(3):194-7.

(26) Tiderius CJ, Landin L, Duppe H. Decreasing incidence of fractures in children: an epidemiological analysis of 1,673 fractures in Malmo, Sweden, 1993-1994. *Acta Orthop Scand* 1999 Dec;**70**(6):622-6.

(27) Lyons RA, Sellstrom E, Delahunty AM, Loeb M, Varilo S. Incidence and cause of fractures in European districts. *Arch Dis Child* 2000 Jun;**82**(6):452-5.

(28) Brudvik C, Hove LM. Childhood fractures in Bergen, Norway: identifying high-risk groups and activities. *J Pediatr Orthop* 2003 Sep;**23**(5):629-34.

(29) McKay HA, Bailey DA, Mirwald RL, Davison KS, Faulkner RA. Peak bone mineral accrual and age at menarche in adolescent girls: a 6-year longitudinal study. *J Pediatr* 1998 Nov;**133**(5):682-7.

(30) Faulkner RA, Davison KS, Bailey DA, Mirwald RL, Baxter-Jones AD. Size-corrected BMD decreases during peak linear growth: implications for fracture incidence during adolescence. *J Bone Miner Res* 2006 Dec;**21**(12):1864-70.

(31) Rizzoli R, Bonjour JP, Ferrari SL. Osteoporosis, genetics and hormones. *J Mol Endocrinol* 2001 Apr;**26**(2):79-94.

(32) Kindblom JM, Lorentzon M, Norjavaara E, Hellqvist A, Nilsson S, Mellstrom D, et al. Pubertal timing predicts previous fractures and BMD in young adult men: the GOOD study. *J Bone Miner Res* 2006 May;**21**(5):790-5.

(33) Goulding A, Jones IE, Williams SM, Grant AM, Taylor RW, Manning PJ, et al. First fracture is associated with increased risk of new fractures during growth. *J Pediatr* 2005 Feb;**146**(2):286-8.

(34) Yeh FJ, Grant AM, Williams SM, Goulding A. Children who experience their first fracture at a young age have high rates of fracture. *Osteoporos Int* 2006 Feb;**17**(2):267-72.

(35) Goulding A, Jones IE, Taylor RW, Williams SM, Manning PJ. Bone mineral density and body composition in boys with distal forearm fractures: a dual-energy x-ray absorptiometry study. *J Pediatr* 2001 Oct;**139**(4):509-15.

(36) Goulding A, Cannan R, Williams SM, Gold EJ, Taylor RW, Lewis-Barned NJ. Bone mineral density in girls with forearm fractures. *J Bone Miner Res* 1998 Jan;**13**(1):143-8.

(37) Manias K, McCabe D, Bishop N. Fractures and recurrent fractures in children; varying effects of environmental factors as well as bone size and mass. *Bone* 2006 Sep;**39**(3):652-7.

(38) Rauch F, Schoenau E. Changes in bone density during childhood and adolescence: an approach based on bone's biological organization. *J Bone Miner Res* 2001 Apr;**16**(4):597-604.

(39) Trotter M. The density of bones in the young skeleton. *Growth* 1971 Sep;**35**(3):221-31.

(40) Binkley TL, Berry R, Specker BL. Methods for measurement of pediatric bone. *Rev Endocr Metab Disord* 2008 Jun;**9**(2):95-106.

(41) Forwood MR, Turner CH. Skeletal adaptations to mechanical usage: results from tibial loading studies in rats. *Bone* 1995 Oct;**17**(4 Suppl):197S-205S.

(42) Leonard MB, Bachrach LK. Non-invasive techniques for bone mass measurement. In: Glorieux FH, Pettifor JM, Juppner H, editors. Pediatric bone: biology and diseases. 2nd ed. London: Elsevier; 2012. p. 309-42.

(43) Cullum ID, Ell PJ, Ryder JP. X-ray dual-photon absorptiometry: a new method for the measurement of bone density. *Br J Radiol* 1989 Jul;**62**(739):587-92.

(44) Carter DR, Bouxsein ML, Marcus R. New approaches for interpreting projected bone densitometry data. *J Bone Miner Res* 1992 Feb;**7**(2):137-45.

(45) Seeman E. Clinical review 137: Sexual dimorphism in skeletal size, density, and strength. *J Clin Endocrinol Metab* 2001 Oct;**86**(10):4576-84.

(46) Matkovic V, Jelic T, Wardlaw GM, Ilich JZ, Goel PK, Wright JK, et al. Timing of peak bone mass in Caucasian females and its implication for the prevention of osteoporosis. Inference from a cross-sectional model. *J Clin Invest* 1994 Feb;**93**(2):799-808.

(47) Gilsanz V, Roe TF, Mora S, Costin G, Goodman WG. Changes in vertebral bone density in black girls and white girls during childhood and puberty. *N Engl J Med* 1991 Dec 5;**325**(23):1597-600.

(48) Seeman E. Structural basis of growth-related gain and age-related loss of bone strength. *Rheumatology (Oxford)* 2008 Jul;**47 Suppl 4**:iv2-iv8.

(49) Cowell CT, Lu PW, Lloyd-Jones SA, Briody JN, Allen JR, Humphries IR, et al. Volumetric bone mineral density--a potential role in paediatrics. *Acta Paediatr Suppl* 1995 Sep;**411**:12-6, discussion 17.

(50) Prentice A, Parsons TJ, Cole TJ. Uncritical use of bone mineral density in absorptiometry may lead to size-related artifacts in the identification of bone mineral determinants. *Am J Clin Nutr* 1994 Dec;**60**(6):837-42.

(51) Katzman DK, Bachrach LK, Carter DR, Marcus R. Clinical and anthropometric correlates of bone mineral acquisition in healthy adolescent girls. *J Clin Endocrinol Metab* 1991 Dec;**73**(6):1332-9.

(52) Sievanen H, Kannus P, Nieminen V, Heinonen A, Oja P, Vuori I. Estimation of various mechanical characteristics of human bones using dual energy X-ray absorptiometry: methodology and precision. *Bone* 1996 Jan;**18**(1 Suppl):17S-27S.

(53) Courteix D, Lespessailles E, Obert P, Benhamou CL. Skull bone mass deficit in prepubertal highly-trained gymnast girls. *Int J Sports Med* 1999 Jul;**20**(5):328-33.

(54) Rauch F, Plotkin H, DiMeglio L, Engelbert RH, Henderson RC, Munns C, et al. Fracture prediction and the definition of osteoporosis in children and adolescents: the ISCD 2007 Pediatric Official Positions. *J Clin Densitom* 2008 Jan;**11**(1):22-8.

(55) Kalkwarf HJ, Zemel BS, Gilsanz V, Lappe JM, Horlick M, Oberfield S, et al. The bone mineral density in childhood study: bone mineral content and density according to age, sex, and race. *J Clin Endocrinol Metab* 2007 Jun;**92**(6):2087-99.

(56) Kelly TL, Wilson KE, Heymsfield SB. Dual energy X-Ray absorptiometry body composition reference values from NHANES. *PLoS One* 2009 Sep 15;**4**(9):e7038.

(57) Zemel BS, Stallings VA, Leonard MB, Paulhamus DR, Kecskemethy HH, Harcke HT, et al. Revised pediatric reference data for the lateral distal femur measured by Hologic Discovery/Delphi dual-energy X-ray absorptiometry. *J Clin Densitom* 2009 Apr;**12**(2):207-18.

(58) Kalkwarf HJ, Zemel BS, Yolton K, Heubi JE. Bone mineral content and density of the lumbar spine of infants and toddlers: influence of age, sex, race, growth, and human milk feeding. *J Bone Miner Res* 2013 Jan;**28**(1):206-12.

(59) Louis O, Willnecker J, Soykens S, Van den WP, Osteaux M. Cortical thickness assessed by peripheral quantitative computed tomography: accuracy evaluated on radius specimens. *Osteoporos Int* 1995;**5**(6):446-9.

(60) Ferretti JL. Perspectives of pQCT technology associated to biomechanical studies in skeletal research employing rat models. *Bone* 1995 Oct;**17**(4 Suppl):353S-64S.

(61) Grampp S, Lang P, Jergas M, Gluer CC, Mathur A, Engelke K, et al. Assessment of the skeletal status by peripheral quantitative computed tomography of the forearm: short-term precision in vivo and comparison to dual X-ray absorptiometry. *J Bone Miner Res* 1995 Oct;**10**(10):1566-76.

(62) Takada M, Engelke K, Hagiwara S, Grampp S, Genant HK. Accuracy and precision study in vitro for peripheral quantitative computed tomography. *Osteoporos Int* 1996;**6**(3):207-12.

(63) Schoenau E. The development of the skeletal system in children and the influence of muscular strength. *Horm Res* 1998;**49**(1):27-31.

(64) Butz S, Wuster C, Scheidt-Nave C, Gotz M, Ziegler R. Forearm BMD as measured by peripheral quantitative computed tomography (pQCT) in a German reference population. *Osteoporos Int* 1994 Jul;**4**(4):179-84.

(65) Binkley TL, Specker BL. pQCT measurement of bone parameters in young children: validation of technique. *J Clin Densitom* 2000;**3**(1):9-14.

(66) Jones IE, Williams SM, Goulding A. Associations of birth weight and length, childhood size, and smoking with bone fractures during growth: evidence from a birth cohort study. *Am J Epidemiol* 2004 Feb 15;**159**(4):343-50.

(67) Kalkwarf HJ, Khoury JC, Lanphear BP. Milk intake during childhood and adolescence, adult bone density, and osteoporotic fractures in US women. *Am J Clin Nutr* 2003 Jan 1;**77**(1):257-65.

(68) Black RE, Williams SM, Jones IE, Goulding A. Children who avoid drinking cow milk have low dietary calcium intakes and poor bone health. *Am J Clin Nutr* 2002 Sep;**76**(3):675-80.

(69) Vicente-Rodriguez G. How does exercise affect bone development during growth? *Sports Med* 2006;**36**(7):561-9.

(70) Goulding A, Grant AM, Williams SM. Bone and body composition of children and adolescents with repeated forearm fractures. *J Bone Miner Res* 2005 Dec;**20**(12):2090-6.

(71) Valerio G, Galle F, Mancusi C, Di O, V, Guida P, Tramontano A, et al. Prevalence of overweight in children with bone fractures: a case control study. *BMC Pediatr* 2012 Oct 22;**12**:166.

(72) Goulding A, Jones IE, Taylor RW, Manning PJ, Williams SM. More broken bones: a 4-year double cohort study of young girls with and without distal forearm fractures. *J Bone Miner Res* 2000 Oct;**15**(10):2011-8.

(73) Cook SD, Harding AF, Morgan EL, Doucet HJ, Bennett JT, O'Brien M, et al. Association of bone mineral density and pediatric fractures. *J Pediatr Orthop* 1987 Jul;**7**(4):424-7.

(74) Dowd MD, Keenan HT, Bratton SL. Epidemiology and prevention of childhood injuries. *Crit Care Med* 2002 Nov;**30**(11 Suppl):S385-S392.

(75) Ma D, Jones G. The association between bone mineral density, metacarpal morphometry, and upper limb fractures in children: a population-based case-control study. *J Clin Endocrinol Metab* 2003 Apr;**88**(4):1486-91.

(76) Clark EM, Ness AR, Bishop NJ, Tobias JH. Association between bone mass and fractures in children: a prospective cohort study. *J Bone Miner Res* 2006 Sep;**21**(9):1489-95.

(77) Ralston SH. Genetics of osteoporosis. *Proc Nutr Soc* 2007 May;**66**(2):158-65.

(78) Fang Y, van Meurs JB, d'Alesio A, Jhamai M, Zhao H, Rivadeneira F, et al. Promoter and 3'-untranslated-region haplotypes in the vitamin d receptor gene predispose to osteoporotic fracture: the rotterdam study. *Am J Hum Genet* 2005 Nov;**77**(5):807-23.

(79) Stewart TL, Jin H, McGuigan FE, Albagha OM, Garcia-Giralt N, Bassiti A, et al. Haplotypes defined by promoter and intron 1 polymorphisms of the COLIA1 gene regulate bone mineral density in women. *J Clin Endocrinol Metab* 2006 Sep;**91**(9):3575-83.

(80) Ioannidis JP, Ralston SH, Bennett ST, Brandi ML, Grinberg D, Karassa FB, et al. Differential genetic effects of ESR1 gene polymorphisms on osteoporosis outcomes. *JAMA* 2004 Nov 3;**292**(17):2105-14.

(81) Langdahl BL, Knudsen JY, Jensen HK, Gregersen N, Eriksen EF. A sequence variation: 713-8delC in the transforming growth factor-beta 1 gene has higher prevalence in osteoporotic women than in normal women and is associated with very low bone mass in osteoporotic women and increased bone turnover in both osteoporotic and normal women. *Bone* 1997 Mar;**20**(3):289-94.

(82) Yamada Y, Miyauchi A, Takagi Y, Tanaka M, Mizuno M, Harada A. Association of the C-509-->T polymorphism, alone of in combination with the T869-->C polymorphism, of the transforming growth factor-beta1 gene with bone mineral density and genetic susceptibility to osteoporosis in Japanese women. *J Mol Med (Berl)* 2001 Apr;**79**(2-3):149-56.

(83) Duren DL, Sherwood RJ, Choh AC, Czerwinski SA, Cameron Chumlea W, Lee M, et al. Quantitative genetics of cortical bone mass in healthy 10-year-old children from the Fels Longitudinal Study. *Bone* 2007 Feb 1;**40**(2):464-70.

(84) May A, Pettifor JM, Norris SA, Ramsay M, Lombard Z. Genetic factors influencing bone mineral content in a black South African population. *J Bone Miner Metab* 2013 Nov;**31**(6):708-16.

(85) Chantler S, Dickie K, Goedecke JH, Levitt NS, Lambert EV, Evans J, et al. Site-specific differences in bone mineral density in black and white premenopausal South African women. *Osteoporos Int* 2012 Feb;**23**(2):533-42.

(86) Daniels ED, Pettifor JM, Schnitzler CM, Russell SW, Patel DN. Ethnic differences in bone density in female South African nurses. *J Bone Miner Res* 1995 Mar;**10**(3):359-67.

(87) Krall EA, Dawson-Hughes B. Heritable and life-style determinants of bone mineral density. *J Bone Miner Res* 1993 Jan;**8**(1):1-9.

(88) Runyan SM, Stadler DD, Bainbridge CN, Miller SC, Moyer-Mileur LJ. Familial resemblance of bone mineralization, calcium intake, and physical activity in early-adolescent daughters, their mothers, and maternal grandmothers. *J Am Diet Assoc* 2003 Oct;**103**(10):1320-5.

(89) Ondrak KS, Morgan DW. Physical activity, calcium intake and bone health in children and adolescents. *Sports Med* 2007;**37**(7):587-600.

(90) Obermayer-Pietsch B. Genetics of osteoporosis. *Wien Med Wochenschr* 2006 Mar;**156**(5-6):162-7.

(91) Gafni RI, Baron J. Childhood bone mass acquisition and peak bone mass may not be important determinants of bone mass in late adulthood. *Pediatrics* 2007 Mar;**119 Suppl 2**:S131-S136.

(92) Vidulich L, Norris SA, Cameron N, Pettifor JM. Bone mass and bone size in pre- or early pubertal 10-year-old black and white South African children and their parents. *Calcif Tissue Int* 2011 Apr;**88**(4):281-93.

(93) Dennison EM, Cooper C, Cole ZA. Early development and osteoporosis and bone health. *Journal of Developmental Origins of Health and Disease* 2010;**1**(03):142-9.

(94) Wadhwa PD, Buss C, Entringer S, Swanson JM. Developmental origins of health and disease: brief history of the approach and current focus on epigenetic mechanisms. *Semin Reprod Med* 2009 Sep;**27**(5):358-68.

(95) Wood CL, Wood AM, Harker C, Embleton ND. Bone mineral density and osteoporosis after preterm birth: the role of early life factors and nutrition. *Int J Endocrinol* 2013;**2013**:902513.

(96) Harvey NC, Mahon PA, Kim M, Cole ZA, Robinson SM, Javaid K, et al. Intrauterine growth and postnatal skeletal development: findings from the Southampton Women's Survey. *Paediatr Perinat Epidemiol* 2012 Jan;**26**(1):34-44.

(97) Hovi P, Andersson S, Jarvenpaa AL, Eriksson JG, Strang-Karlsson S, Kajantie E, et al. Decreased bone mineral density in adults born with very low birth weight: a cohort study. *PLoS Med* 2009 Aug;**6**(8):e1000135.

(98) Baird J, Kurshid MA, Kim M, Harvey N, Dennison E, Cooper C. Does birthweight predict bone mass in adulthood? A systematic review and meta-analysis. *Osteoporos Int* 2011 May;**22**(5):1323-34.

(99) Harvey NC, Javaid MK, Arden NK, Poole JR, Crozier SR, Robinson SM, et al. Maternal predictors of neonatal bone size and geometry: the Southampton Women's Survey. *J Dev Orig Health Dis* 2010 Feb;**1**(1):35-41.

(100) Eriksson JG, Kajantie E, Osmond C, Thornburg K, Barker DJ. Boys live dangerously in the womb. *Am J Hum Biol* 2010 May;**22**(3):330-5.

(101) Martinez-Mesa J, Restrepo-Mendez MC, Gonzalez DA, Wehrmeister FC, Horta BL, Domingues MR, et al. Life-course evidence of birth weight effects on bone mass: systematic review and meta-analysis. *Osteoporos Int* 2013 Jan;**24**(1):7-18.

(102) Oliver H, Jameson KA, Sayer AA, Cooper C, Dennison EM. Growth in early life predicts bone strength in late adulthood: the Hertfordshire Cohort Study. *Bone* 2007 Sep;**41**(3):400-5.

(103) Kuh D, Wills AK, Shah I, Prentice A, Hardy R, Adams JE, et al. Growth from birth to adulthood and bone phenotype in early old age: a british birth cohort study. *J Bone Miner Res* 2014 Jan;**29**(1):123-33.

(104) Hallal PC, Siqueira FV, Menezes AM, Araujo CL, Norris SA, Victora CG. The role of early life variables on the risk of fractures from birth to early adolescence: a prospective birth cohort study. *Osteoporos Int* 2009 Nov;**20**(11):1873-9.

(105) Lawlor DA, Wills AK, Fraser A, Sayers A, Fraser WD, Tobias JH. Association of maternal vitamin D status during pregnancy with bone-mineral content in offspring: a prospective cohort study. *Lancet* 2013 Jun 22;**381**(9884):2176-83.

(106) Zhu K, Whitehouse AJ, Hart P, Kusel M, Mountain J, Lye S, et al. Maternal Vitamin D Status During Pregnancy and Bone Mass in Offspring at 20 Years of Age: A Prospective Cohort Study. *J Bone Miner Res* 2013 Nov 5;**DOI: 10.1002/jbmr.2138**.

(107) Cooper C, Eriksson JG, Forsen T, Osmond C, Tuomilehto J, Barker DJ. Maternal height, childhood growth and risk of hip fracture in later life: a longitudinal study. *Osteoporos Int* 2001;**12**(8):623-9.

(108) Godfrey K, Walker-Bone K, Robinson S, Taylor P, Shore S, Wheeler T, et al. Neonatal bone mass: influence of parental birthweight, maternal smoking, body composition, and activity during pregnancy. *J Bone Miner Res* 2001 Sep;**16**(9):1694-703.

(109) Lau EM, Lau W. Nutritional assessment of nutrients for bone health. In: Holick MF, Dawson-Hughes B, editors. Nutrition and bone health.Totowa, New Jersey: Humana Press; 2004. p. 105-11.

(110) Clark EM, Ness AR, Tobias JH. Vigorous physical activity increases fracture risk in children irrespective of bone mass: a prospective study of the independent risk factors for fractures in healthy children. *J Bone Miner Res* 2008 Jul;**23**(7):1012-22.

(111) Bonjour JP, Chevalley T, Ferrari S, Rizzoli R. Peak bone mass and its regulation. In: Glorieux FH, Pettifor JM, Juppner H, editors. Pediatric bone: biology and diseases. 2nd ed. London: Elsevier; 2012. p. 189-221.

(112) Kerstetter JE, O'Brien KO, Insogna KL. Dietary protein, calcium metabolism, and skeletal homeostasis revisited. *Am J Clin Nutr* 2003 Sep;**78**(3 Suppl):584S-92S.

(113) Conigrave AD, Mun HC, Delbridge L, Quinn SJ, Wilkinson M, Brown EM. L-amino acids regulate parathyroid hormone secretion. *J Biol Chem* 2004 Sep 10;**279**(37):38151-9.

(114) Conigrave AD, Brown EM, Rizzoli R. Dietary protein and bone health: roles of amino acid-sensing receptors in the control of calcium metabolism and bone homeostasis. *Annu Rev Nutr* 2008;**28**:131-55.

(115) Chevalley T, Rizzoli R, Manen D, Caverzasio J, Bonjour JP. Arginine increases insulin-like growth factor-I production and collagen synthesis in osteoblast-like cells. *Bone* 1998 Aug;**23**(2):103-9.

(116) Garn SM, Rohmann CG, Behar M, Viteri F, Guzman MA. Compact bone deficiency in protein-calorie malnutrition. *Science* 1964 Sep 25;**145**(3639):1444-5.

(117) Bonjour JP, Ammann P, Chevalley T, Rizzoli R. Protein intake and bone growth. *Can J Appl Physiol* 2001;**26 Suppl**:S153-S166.

(118) Weaver CM. The role of nutrition on optimizing peak bone mass. *Asia Pac J Clin Nutr* 2008;**17 Suppl 1**:135-7.

(119) Rana AR, Michalsky MP, Teich S, Groner JI, Caniano DA, Schuster DP. Childhood obesity: a risk factor for injuries observed at a level-1 trauma center. *J Pediatr Surg* 2009 Aug;**44**(8):1601-5.

(120) Casazza K, Thomas O, Dulin-Keita A, Fernandez JR. Adiposity and genetic admixture, but not race/ethnicity, influence bone mineral content in peripubertal children. *J Bone Miner Metab* 2010 Jul;**28**(4):424-32.

(121) Kessler J, Koebnick C, Smith N, Adams A. Childhood obesity is associated with increased risk of most lower extremity fractures. *Clin Orthop Relat Res* 2013 Apr;**471**(4):1199-207.

(122) Pomerantz WJ, Timm NL, Gittelman MA. Injury patterns in obese versus nonobese children presenting to a pediatric emergency department. *Pediatrics* 2010 Apr;**125**(4):681-5.

(123) Taylor ED, Theim KR, Mirch MC, Ghorbani S, Tanofsky-Kraff M, dler-Wailes DC, et al. Orthopedic complications of overweight in children and adolescents. *Pediatrics* 2006 Jun;**117**(6):2167-74.

(124) Zonfrillo MR, Seiden JA, House EM, Shapiro ED, Dubrow R, Baker MD, et al. The association of overweight and ankle injuries in children. *Ambul Pediatr* 2008 Jan;**8**(1):66-9.

(125) Hrafnkelsson H, Sigurdsson G, Magnusson KT, Sigurdsson EL, Johannsson E. Fat mass increase in 7-year-old children: more bone area but lower bone mineral density. *J Bone Miner Metab* 2013 Jul;**31**(4):442-8.

(126) De SJ, Van den BM, Jonckheer MH. Study of lumbar spine bone mineral density in obese children. *Acta Paediatr* 1995 Mar;**84**(3):313-5.

(127) Leonard MB, Shults J, Wilson BA, Tershakovec AM, Zemel BS. Obesity during childhood and adolescence augments bone mass and bone dimensions. *Am J Clin Nutr* 2004 Aug;**80**(2):514-23.

(128) Goulding A, Taylor RW, Jones IE, McAuley KA, Manning PJ, Williams SM. Overweight and obese children have low bone mass and area for their weight. *Int J Obes Relat Metab Disord* 2000 May;**24**(5):627-32.

(129) Davidson PL, Goulding A, Chalmers DJ. Biomechanical analysis of arm fracture in obese boys. *J Paediatr Child Health* 2003 Dec;**39**(9):657-64.

(130) Goulding A, Jones IE, Taylor RW, Piggot JM, Taylor D. Dynamic and static tests of balance and postural sway in boys: effects of previous wrist bone fractures and high adiposity. *Gait Posture* 2003 Apr;**17**(2):136-41.

(131) Nantel J, Brochu M, Prince F. Locomotor strategies in obese and non-obese children. *Obesity (Silver Spring)* 2006 Oct;**14**(10):1789-94.

(132) Ma D, Jones G. Television, computer, and video viewing; physical activity; and upper limb fracture risk in children: a population-based case control study. *J Bone Miner Res* 2003 Nov;**18**(11):1970-7.

(133) Goulding A, Rockell JE, Black RE, Grant AM, Jones IE, Williams SM. Children who avoid drinking cow's milk are at increased risk for prepubertal bone fractures. *J Am Diet Assoc* 2004 Feb;**104**(2):250-3.

(134) Goulding A. Risk factors for fractures in normally active children and adolescents. *Med Sport Sci* 2007;**51**:102-20.

(135) Fulton JE, Wang X, Yore MM, Carlson SA, Galuska DA, Caspersen CJ. Television viewing, computer use, and BMI among U.S. children and adolescents. *J Phys Act Health* 2009;**6 Suppl 1**:S28-S35.

(136) Raine JE, Donaldson MDC, Gregory JW, Van Vliet G. Practical endocrinology and diabetes in children. 3rd ed. Blackwell; 2011.

(137) Cameron N, Tanner JM, Whitehouse RH. A longitudinal analysis of the growth of limb segments in adolescence. *Ann Hum Biol* 1982 May;**9**(3):211-20.

(138) Molgaard C, Thomsen BL, Prentice A, Cole TJ, Michaelsen KF. Whole body bone mineral content in healthy children and adolescents. *Arch Dis Child* 1997 Jan;**76**(1):9-15.

(139) Lu PW, Briody JN, Ogle GD, Morley K, Humphries IR, Allen J, et al. Bone mineral density of total body, spine, and femoral neck in children and young adults: a cross-sectional and longitudinal study. *J Bone Miner Res* 1994 Sep;**9**(9):1451-8.

(140) Schoenau E. The development of the skeletal system in children and the influence of muscular strength. *Horm Res* 1998;**49**(1):27-31.

(141) Schoenau E, Neu CM, Rauch F, Manz F. The development of bone strength at the proximal radius during childhood and adolescence. *J Clin Endocrinol Metab* 2001 Feb;**86**(2):613-8.

(142) Ma D, Jones G. The Association between Bone Mineral Density, Metacarpal Morphometry, and Upper Limb Fractures in Children: A Population-Based Case-Control Study. *J Clin Endocrinol Metab* 2003 Apr 1;**88**(4):1486-91.

(143) Wang Q, Alen M, Nicholson P, Lyytikainen A, Suuriniemi M, Helkala E, et al. Growth patterns at distal radius and tibial shaft in pubertal girls: a 2-year longitudinal study. *J Bone Miner Res* 2005 Jun;**20**(6):954-61.

(144) Rosenthal DI, Mayo-Smith W, Hayes CW, Khurana JS, Biller BM, Neer RM, et al. Age and bone mass in premenopausal women. *J Bone Miner Res* 1989 Aug;**4**(4):533-8.

(145) Ribot C, Pouilles JM, Bonneu M, Tremollieres F. Assessment of the risk of post-menopausal osteoporosis using clinical factors. *Clin Endocrinol (Oxf)* 1992 Mar;**36**(3):225-8.

(146) Fox KM, Magaziner J, Sherwin R, Scott JC, Plato CC, Nevitt M, et al. Reproductive correlates of bone mass in elderly women. Study of Osteoporotic Fractures Research Group. *J Bone Miner Res* 1993 Aug;**8**(8):901-8.

(147) Tuppurainen M, Kroger H, Saarikoski S, Honkanen R, Alhava E. The effect of gynecological risk factors on lumbar and femoral bone mineral density in peri- and postmenopausal women. *Maturitas* 1995 Feb;**21**(2):137-45.

(148) Ito M, Yamada M, Hayashi K, Ohki M, Uetani M, Nakamura T. Relation of early menarche to high bone mineral density. *Calcif Tissue Int* 1995 Jul;**57**(1):11-4.

(149) Varenna M, Binelli L, Zucchi F, Ghiringhelli D, Gallazzi M, Sinigaglia L. Prevalence of osteoporosis by educational level in a cohort of postmenopausal women. *Osteoporos Int* 1999;**9**(3):236-41.

(150) Johnell O, Gullberg B, Kanis JA, Allander E, Elffors L, Dequeker J, et al. Risk factors for hip fracture in European women: the MEDOS Study. Mediterranean Osteoporosis Study. *J Bone Miner Res* 1995 Nov;**10**(11):1802-15.

(151) Melton LJ, III, Khosla S, Atkinson EJ, O'Fallon WM, Riggs BL. Relationship of bone turnover to bone density and fractures. *J Bone Miner Res* 1997 Jul;**12**(7):1083-91.

(152) Silman AJ. Risk factors for Colles' fracture in men and women: results from the European Prospective Osteoporosis Study. *Osteoporos Int* 2003 May;**14**(3):213-8.

(153) Paganini-Hill A, Atchison KA, Gornbein JA, Nattiv A, Service SK, White SC. Menstrual and reproductive factors and fracture risk: the Leisure World Cohort Study. *J Womens Health (Larchmt)* 2005 Nov;**14**(9):808-19.

(154) Armamento-Villareal R, Villareal DT, Avioli LV, Civitelli R. Estrogen status and heredity are major determinants of premenopausal bone mass. *J Clin Invest* 1992 Dec;**90**(6):2464-71.

(155) Galuska DA, Sowers MR. Menstrual history and bone density in young women. *J Womens Health Gend Based Med* 1999 Jun;**8**(5):647-56.

(156) Nguyen TV, Jones G, Sambrook PN, White CP, Kelly PJ, Eisman JA. Effects of estrogen exposure and reproductive factors on bone mineral density and osteoporotic fractures. *J Clin Endocrinol Metab* 1995 Sep;**80**(9):2709-14.

(157) Bonjour JP, Chevalley T. Pubertal timing, peak bone mass and fragility fracture risk. *IBMS BoneKEy* 2007 Feb;**4**(2):30-48.

(158) Chevalley T, Bonjour JP, Ferrari S, Rizzoli R. The influence of pubertal timing on bone mass acquisition: a predetermined trajectory detectable five years before menarche. *J Clin Endocrinol Metab* 2009 Sep;**94**(9):3424-31.

(159) Bass S, Delmas PD, Pearce G, Hendrich E, Tabensky A, Seeman E. The differing tempo of growth in bone size, mass, and density in girls is region-specific. *J Clin Invest* 1999 Sep;**104**(6):795-804.

(160) Iuliano-Burns S, Mirwald RL, Bailey DA. Timing and magnitude of peak height velocity and peak tissue velocities for early, average, and late maturing boys and girls. *Am J Hum Biol* 2001 Jan;**13**(1):1-8.

(161) Fournier PE, Rizzoli R, Slosman DO, Theintz G, Bonjour JP. Asynchrony between the rates of standing height gain and bone mass accumulation during puberty. *Osteoporos Int* 1997;**7**(6):525-32.

(162) Beardsworth LJ, Eyre DR, Dickson IR. Changes with age in the urinary excretion of lysyl- and hydroxylysylpyridinoline, two new markers of bone collagen turnover. *J Bone Miner Res* 1990 Jul;**5**(7):671-6.

(163) Parfitt AM. The two faces of growth: benefits and risks to bone integrity. *Osteoporos Int* 1994 Nov;**4**(6):382-98.

(164) McKay HA, Bailey DA, Mirwald RL, Davison KS, Faulkner RA. Peak bone mineral accrual and age at menarche in adolescent girls: a 6-year longitudinal study. *J Pediatr* 1998 Nov;**133**(5):682-7.

(165) Sabatier JP, Guaydier-Souquieres G, Laroche D, Benmalek A, Fournier L, Guillon-Metz F, et al. Bone mineral acquisition during adolescence and early adulthood: a study in 574 healthy females 10-24 years of age. *Osteoporos Int* 1996;**6**(2):141-8.

(166) Arabi A, Nabulsi M, Maalouf J, Choucair M, Khalife H, Vieth R, et al. Bone mineral density by age, gender, pubertal stages, and socioeconomic status in healthy Lebanese children and adolescents. *Bone* 2004 Nov;**35**(5):1169-79.

(167) Ferrari SL, Chevalley T, Bonjour JP, Rizzoli R. Childhood fractures are associated with decreased bone mass gain during puberty: an early marker of persistent bone fragility? *J Bone Miner Res* 2006 Apr;**21**(4):501-7.

(168) Bonnet N, Ferrari SL. Exercise and the skeleton: How it works and what it really does. *IBMS BoneKEy* 2010 Jul;**7**(7):235-48.

(169) Bass SL. The prepubertal years: a uniquely opportune stage of growth when the skeleton is most responsive to exercise? *Sports Med* 2000 Aug;**30**(2):73-8.

(170) Bass SL, Saxon L, Daly RM, Turner CH, Robling AG, Seeman E, et al. The effect of mechanical loading on the size and shape of bone in pre-, peri-, and postpubertal girls: a study in tennis players. *J Bone Miner Res* 2002 Dec;**17**(12):2274-80.

(171) Turner CH. Bone strength: current concepts. *Ann N Y Acad Sci* 2006 Apr;**1068**:429-46.

(172) Cowin SC, Moss ML. Mechanosensory mechanism in bone. In: Cowin SC, editor. Bone mechanics handbook. 2nd ed. Boca Raton, FL:CRC Press; 2001. p. 29-1-29-17.

(173) Davidson RM, Lingenbrink PA, Norton LA. Continuous mechanical loading alters properties of mechanosensitive channels in G292 osteoblastic cells. *Calcif Tissue Int* 1996 Dec;**59**(6):500-4.

(174) Rubin J, Rubin C, Jacobs CR. Molecular pathways mediating mechanical signaling in bone. *Gene* 2006 Feb 15;**367**:1-16.

(175) Jaalouk DE, Lammerding J. Mechanotransduction gone awry. *Nat Rev Mol Cell Biol* 2009 Jan;**10**(1):63-73.

(176) Rittweger J. Ten years muscle-bone hypothesis: what have we learned so far?--almost a festschrift--. *J Musculoskelet Neuronal Interact* 2008 Apr;**8**(2):174-8.

(177) Kim J, Wang Z, Heymsfield SB, Baumgartner RN, Gallagher D. Total-body skeletal muscle mass: estimation by a new dual-energy X-ray absorptiometry method. *Am J Clin Nutr* 2002 Aug;**76**(2):378-83.

(178) Rauch F, Bailey DA, Baxter-Jones A, Mirwald R, Faulkner R. The 'muscle-bone unit' during the pubertal growth spurt. *Bone* 2004 May;**34**(5):771-5.

(179) Schoenau E, Frost HM. The "muscle-bone unit" in children and adolescents. *Calcif Tissue Int* 2002 May;**70**(5):405-7.

(180) Kohrt WM, Bloomfield SA, Little KD, Nelson ME, Yingling VR. American College of Sports Medicine Position Stand: physical activity and bone health. *Med Sci Sports Exerc* 2004 Nov;**36**(11):1985-96.

(181) Vicente-Rodriguez G, Ara I, Perez-Gomez J, Dorado C, Calbet JA. Muscular development and physical activity as major determinants of femoral bone mass acquisition during growth. *Br J Sports Med* 2005 Sep;**39**(9):611-6.

(182) Vicente-Rodriguez G, Ara I, Perez-Gomez J, Serrano-Sanchez JA, Dorado C, Calbet JA. High femoral bone mineral density accretion in prepubertal soccer players. *Med Sci Sports Exerc* 2004 Oct;**36**(10):1789-95.

(183) Copeland JL, Consitt LA, Tremblay MS. Hormonal responses to endurance and resistance exercise in females aged 19-69 years. *J Gerontol A Biol Sci Med Sci* 2002 Apr;**57**(4):B158-B165.

(184) Nindl BC, Hymer WC, Deaver DR, Kraemer WJ. Growth hormone pulsatility profile characteristics following acute heavy resistance exercise. *J Appl Physiol* 2001 Jul;**91**(1):163-72.

(185) Wideman L, Weltman JY, Hartman ML, Veldhuis JD, Weltman A. Growth hormone release during acute and chronic aerobic and resistance exercise: recent findings. *Sports Med* 2002;**32**(15):987-1004.

(186) Adams GR. Autocrine and/or paracrine insulin-like growth factor-I activity in skeletal muscle. *Clin Orthop Relat Res* 2002 Oct;(403 Suppl):S188-S196.

(187) Lean JM, Jagger CJ, Chambers TJ, Chow JW. Increased insulin-like growth factor I mRNA expression in rat osteocytes in response to mechanical stimulation. *Am J Physiol* 1995 Feb;**268**(2 Pt 1):E318-E327.

(188) Sakata T, Wang Y, Halloran BP, Elalieh HZ, Cao J, Bikle DD. Skeletal unloading induces resistance to insulin-like growth factor-I (IGF-I) by inhibiting activation of the IGF-I signaling pathways. *J Bone Miner Res* 2004 Mar;**19**(3):436-46.

(189) Iwamoto J, Shimamura C, Takeda T, Abe H, Ichimura S, Sato Y, et al. Effects of treadmill exercise on bone mass, bone metabolism, and calciotropic hormones in young growing rats. *J Bone Miner Metab* 2004;**22**(1):26-31.

(190) Maimoun L, Simar D, Caillaud C, Coste O, Barbotte E, Peruchon E, et al. Response of calciotropic hormones and bone turnover to brisk walking according to age and fitness level. *J Sci Med Sport* 2009 Jul;**12**(4):463-7.

(191) Scott JP, Sale C, Greeves JP, Casey A, Dutton J, Fraser WD. The effect of training status on the metabolic response of bone to an acute bout of exhaustive treadmill running. *J Clin Endocrinol Metab* 2010 Aug;**95**(8):3918-25.

(192) Jurimae J, Kums T, Jurimae T. Adipocytokine and ghrelin levels in relation to bone mineral density in physically active older women: longitudinal associations. *Eur J Endocrinol* 2009 Mar;**160**(3):381-5.

(193) Prouteau S, Benhamou L, Courteix D. Relationships between serum leptin and bone markers during stable weight, weight reduction and weight regain in male and female judoists. *Eur J Endocrinol* 2006 Mar;**154**(3):389-95.

(194) Maimoun L, Sultan C. Effect of physical activity on calcium homeostasis and calciotropic hormones: a review. *Calcif Tissue Int* 2009 Oct;**85**(4):277-86.

(195) Rudberg A, Magnusson P, Larsson L, Joborn H. Serum isoforms of bone alkaline phosphatase increase during physical exercise in women. *Calcif Tissue Int* 2000 May;**66**(5):342-7.

(196) Zhang J, Ryder KD, Bethel JA, Ramirez R, Duncan RL. PTH-induced actin depolymerization increases mechanosensitive channel activity to enhance mechanically stimulated Ca2+ signaling in osteoblasts. *J Bone Miner Res* 2006 Nov;**21**(11):1729-37.

(197) Kim CH, Takai E, Zhou H, von SD, Muller R, Dempster DW, et al. Trabecular bone response to mechanical and parathyroid hormone stimulation: the role of mechanical microenvironment. *J Bone Miner Res* 2003 Dec;**18**(12):2116-25.

(198) Sugiyama T, Saxon LK, Zaman G, Moustafa A, Sunters A, Price JS, et al. Mechanical loading enhances the anabolic effects of intermittent parathyroid hormone (1-34) on trabecular and cortical bone in mice. *Bone* 2008 Aug;**43**(2):238-48.

(199) Bakker AD, Joldersma M, Klein-Nulend J, Burger EH. Interactive effects of PTH and mechanical stress on nitric oxide and PGE2 production by primary mouse osteoblastic cells. *Am J Physiol Endocrinol Metab* 2003 Sep;**285**(3):E608-E613.

(200) Pettersson U, Nordstrom P, Alfredson H, Henriksson-Larsen K, Lorentzon R. Effect of high impact activity on bone mass and size in adolescent females: A comparative study between two different types of sports. *Calcif Tissue Int* 2000 Sep;**67**(3):207-14.

(201) Tobias JH, Steer CD, Mattocks CG, Riddoch C, Ness AR. Habitual levels of physical activity influence bone mass in 11-year-old children from the United Kingdom: findings from a large population-based cohort. *J Bone Miner Res* 2007 Jan;**22**(1):101-9.

(202) 2008 Physical activity guidelines for Americans summary. Available from: URL: http://www health gov/paguidelines/guidelines/summary aspx 2013

(203) Kriemler S, Zahner L, Puder JJ, Braun-Fahrlander C, Schindler C, Farpour-Lambert NJ, et al. Weight-bearing bones are more sensitive to physical exercise in boys than in girls during pre- and early puberty: a cross-sectional study. *Osteoporos Int* 2008 Dec;**19**(12):1749-58.

(204) Cardadeiro G, Baptista F, Ornelas R, Janz KF, Sardinha LB. Sex Specific Association of Physical Activity on Proximal Femur BMD in 9 to 10 Year-Old Children. *PLoS One* 2012;**7**(11):e50657.

(205) Kannus P, Haapasalo H, Sankelo M, Sievanen H, Pasanen M, Heinonen A, et al. Effect of starting age of physical activity on bone mass in the dominant arm of tennis and squash players. *Ann Intern Med* 1995 Jul 1;**123**(1):27-31.

(206) Nordstrom P, Pettersson U, Lorentzon R. Type of physical activity, muscle strength, and pubertal stage as determinants of bone mineral density and bone area in adolescent boys. *J Bone Miner Res* 1998 Jul;**13**(7):1141-8.

(207) Heinonen A, Sievanen H, Kannus P, Oja P, Pasanen M, Vuori I. High-impact exercise and bones of growing girls: a 9-month controlled trial. *Osteoporos Int* 2000;**11**(12):1010-7.

(208) Bass S, Pearce G, Bradney M, Hendrich E, Delmas PD, Harding A, et al. Exercise before puberty may confer residual benefits in bone density in adulthood: studies in active prepubertal and retired female gymnasts. *J Bone Miner Res* 1998 Mar;**13**(3):500-7.

(209) Bailey DA, Martin AD, McKay HA, Whiting S, Mirwald R. Calcium accretion in girls and boys during puberty: a longitudinal analysis. *J Bone Miner Res* 2000 Nov;**15**(11):2245-50.

(210) Gustavsson A, Thorsen K, Nordstrom P. A 3-year longitudinal study of the effect of physical activity on the accrual of bone mineral density in healthy adolescent males. *Calcif Tissue Int* 2003 Aug;**73**(2):108-14.

(211) Vicente-Rodriguez G, Jimenez-Ramirez J, Ara I, Serrano-Sanchez JA, Dorado C, Calbet JA. Enhanced bone mass and physical fitness in prepubescent footballers. *Bone* 2003 Nov;**33**(5):853-9.

(212) Wittich A, Mautalen CA, Oliveri MB, Bagur A, Somoza F, Rotemberg E. Professional football (soccer) players have a markedly greater skeletal mineral content, density and size than age- and BMI-matched controls. *Calcif Tissue Int* 1998 Aug;**63**(2):112-7.

(213) Karlsson MK, Linden C, Karlsson C, Johnell O, Obrant K, Seeman E. Exercise during growth and bone mineral density and fractures in old age. *Lancet* 2000 Feb 5;**355**(9202):469-70.

(214) Seabra A, Marques E, Brito J, Krustrup P, Abreu S, Oliveira J, et al. Muscle strength and soccer practice as major determinants of bone mineral density in adolescents. *Joint Bone Spine* 2012 Jul;**79**(4):403-8.

(215) Gunter K, Baxter-Jones AD, Mirwald RL, Almstedt H, Fuchs RK, Durski S, et al. Impact exercise increases BMC during growth: an 8-year longitudinal study. *J Bone Miner Res* 2008 Jul;**23**(7):986-93.

(216) Ferrari S, Rizzoli R, Slosman D, Bonjour JP. Familial resemblance for bone mineral mass is expressed before puberty. *J Clin Endocrinol Metab* 1998 Feb;**83**(2):358-61.

(217) Karasik D, Ferrari SL. Contribution of gender-specific genetic factors to osteoporosis risk. *Ann Hum Genet* 2008 Sep;**72**(Pt 5):696-714.

(218) Houshian S, Mehdi B, Larsen MS. The epidemiology of elbow fracture in children: analysis of 355 fractures, with special reference to supracondylar humerus fractures. *J Orthop Sci* 2001;**6**(4):312-5.

(219) Detter FT, Rosengren BE, Dencker M, Nilsson JA, Karlsson MK. A 5-year exercise program in pre- and peripubertal children improves bone mass and bone size without affecting fracture risk. *Calcif Tissue Int* 2013 Apr;**92**(4):385-93.

(220) Ma D, Jones G. Soft drink and milk consumption, physical activity, bone mass, and upper limb fractures in children: a population-based case-control study. *Calcif Tissue Int* 2004 Oct;**75**(4):286-91.

(221) Marshall SJ, Biddle SJ, Gorely T, Cameron N, Murdey I. Relationships between media use, body fatness and physical activity in children and youth: a meta-analysis. *Int J Obes Relat Metab Disord* 2004 Oct;**28**(10):1238-46.

(222) Wareham K, Johansen A, Stone MD, Saunders J, Jones S, Lyons RA. Seasonal variation in the incidence of wrist and forearm fractures, and its consequences. *Injury* 2003 Mar;**34**(3):219-22.

(223) Deakin DE, Crosby JM, Moran CG, Chell J. Childhood fractures requiring inpatient management. *Injury* 2007 Nov;**38**(11):1241-6.

(224) Gao Y. Children hospitalized with lower extremity fractures in the United States in 2006: a population-based approach. *Iowa Orthop J* 2011;**31**:173-80.

(225) Holick MF. Vitamin D deficiency. *N Engl J Med* 2007 Jul;**357**(3):266-81.

(226) Ryan LM, Teach SJ, Singer SA, Wood R, Freishtat R, Wright JL, et al. Bone mineral density and vitamin D status among African American children with forearm fractures. *Pediatrics* 2012 Sep;**130**(3):e553-e560.

(227) Winzenberg T, Powell S, Shaw KA, Jones G. Effects of vitamin D supplementation on bone density in healthy children: systematic review and meta-analysis. *BMJ* 2011 Jan 25;**342**:c7254.

(228) Stark AD, Bennet GC, Stone DH, Chishti P. Association between childhood fractures and poverty: population based study. *BMJ* 2002 Feb 23;**324**(7335):457.

(229) Lyons RA, Delahunty AM, Heaven M, McCabe M, Allen H, Nash P. Incidence of childhood fractures in affluent and deprived areas: population based study. *BMJ* 2000 Jan 15;**320**(7228):149.

(230) Gilbride SJ, Wild C, Wilson DR, Svenson LW, Spady DW. Socio-economic status and types of childhood injury in Alberta: a population based study. *BMC Pediatr* 2006 Nov 9;**6**:30.

(231) Menon MR, Walker JL, Court-Brown CM. The epidemiology of fractures in adolescents with reference to social deprivation. *J Bone Joint Surg Br* 2008 Nov;**90**(11):1482-6.

(232) Court-Brown CM, Brydone A. Social deprivation and adult tibial diaphyseal fractures. *Injury* 2007 Jul;**38**(7):750-4.

(233) Clark EM, Ness A, Tobias JH. Social position affects bone mass in childhood through opposing actions on height and weight. *J Bone Miner Res* 2005 Dec;**20**(12):2082-9.

(234) Khadilkar AV, Sanwalka NJ, Kadam NS, Chiplonkar SA, Khadilkar VV, Mughal MZ. Poor bone health in underprivileged Indian girls: An effect of low bone mass accrual during puberty. *Bone* 2012 Feb 18;**50**(5):1048-53.

(235) Gracia-Marco L, Ortega FB, Casajus JA, Sioen I, Widhalm K, Beghin L, et al. Socioeconomic status and bone mass in Spanish adolescents. The HELENA Study. *J Adolesc Health* 2012 May;**50**(5):484-90.

(236) Petit MA, McKay HA, Mackelvie KJ, Heinonen A, Khan KM, Beck TJ. A Randomized School-Based Jumping Intervention Confers Site and Maturity-Specific Benefits on Bone Structural Properties in Girls: A Hip Structural Analysis Study. *J Bone Miner Res* 2002 Mar 1;**17**(3):363-72.

(237) Ryan LM, Guagliardo M, Teach SJ, Wang J, Marsh JE, Singer SA, et al. The Association Between Fracture Rates and Neighborhood Characteristics in Washington, DC, Children. *J Investig Med* 2013 Mar;**61**(3):558-63.

(238) Cauley JA, Lui LY, Ensrud KE, Zmuda JM, Stone KL, Hochberg MC, et al. Bone mineral density and the risk of incident nonspinal fractures in black and white women. *JAMA* 2005 May 4;**293**(17):2102-8.

(239) Looker AC, Melton LJ, III, Harris TB, Borrud LG, Shepherd JA. Prevalence and trends in low femur bone density among older US adults: NHANES 2005-2006 compared with NHANES III. *J Bone Miner Res* 2010 Jan;**25**(1):64-71.

(240) Solomon L. Osteoporosis and fracture of the femoral neck in the South African Bantu. *J Bone Joint Surg Br* 1968 Feb;**50**(1):2-13.

(241) Bell NH, Shary J, Stevens J, Garza M, Gordon L, Edwards J. Demonstration that bone mass is greater in black than in white children. *J Bone Miner Res* 1991 Jul;**6**(7):719-23.

(242) Vidulich L, Norris SA, Cameron N, Pettifor JM. Differences in bone size and bone mass between black and white 10-year-old South African children. *Osteoporos Int* 2006;**17**(3):433-40.

(243) Micklesfield LK, Norris SA, Nelson DA, Lambert EV, van der Merwe L., Pettifor JM. Comparisons of body size, composition, and whole body bone mass between North American and South African children. *J Bone Miner Res* 2007 Dec;**22**(12):1869-77.

(244) Micklesfield LK, Norris SA, van der Merwe L., Lambert EV, Beck T, Pettifor JM. Comparison of site-specific bone mass indices in South African children of different ethnic groups. *Calcif Tissue Int* 2009 Oct;**85**(4):317-25.

(245) McVeigh JA, Norris SA, Cameron N, Pettifor JM. Associations between physical activity and bone mass in black and white South African children at age 9 yr. *J Appl Physiol* 2004 Sep;**97**(3):1006-12.

(246) Micklesfield LK, Norris SA, Pettifor JM. Determinants of bone size and strength in 13-year-old South African children: The influence of ethnicity, sex and pubertal maturation. *Bone* 2011 Jan 1;**48**:777-85.

(247) Warden SJ, Hill KM, Ferira AJ, Laing EM, Martin BR, Hausman DB, et al. Racial differences in cortical bone and their relationship to biochemical variables in Black and White children in the early stages of puberty. *Osteoporos Int* 2013 Jun;**24**(6):1869-79.

(248) Leonard MB, Elmi A, Mostoufi-Moab S, Shults J, Burnham JM, Thayu M, et al. Effects of sex, race, and puberty on cortical bone and the functional muscle bone unit in children, adolescents, and young adults. *J Clin Endocrinol Metab* 2010 Apr;**95**(4):1681-9.

(249) Bachrach LK, Hastie T, Wang MC, Narasimhan B, Marcus R. Bone mineral acquisition in healthy Asian, Hispanic, black, and Caucasian youth: a longitudinal study. *J Clin Endocrinol Metab* 1999 Dec;**84**(12):4702-12.

(250) Hui SL, Perkins AJ, Harezlak J, Peacock M, McClintock CL, Johnston CC, Jr. Velocities of bone mineral accrual in black and white American children. *J Bone Miner Res* 2010 Jul;**25**(7):1527-35.

(251) Rupich RC, Specker BL, Lieuw AF, Ho M. Gender and race differences in bone mass during infancy. *Calcif Tissue Int* 1996 Jun;**58**(6):395-7.

(252) Wang MC, Aguirre M, Bhudhikanok GS, Kendall CG, Kirsch S, Marcus R, et al. Bone mass and hip axis length in healthy Asian, black, Hispanic, and white American youths. *J Bone Miner Res* 1997 Nov;**12**(11):1922-35.

(253) McVeigh JA, Norris SA, Pettifor JM. Bone mass accretion rates in pre- and early-pubertal South African black and white children in relation to habitual physical activity and dietary calcium intakes. *Acta Paediatr* 2007 Jun;**96**(6):874-80.

(254) McVeigh JA, Norris SA, de Wet T. The relationship between socio-economic status and physical activity patterns in South African children. *Acta Paediatr* 2004 Jul;**93**(7):982-8.

(255) Rowe R, Maughan B, Goodman R. Childhood Psychiatric Disorder and Unintentional Injury: Findings from a National Cohort Study. *J Pediatr Psychol* 2004 Mar 1;**29**(2):119-30.

(256) Wren TA, Shepherd JA, Kalkwarf HJ, Zemel BS, Lappe JM, Oberfield S, et al. Racial Disparity in Fracture Risk between White and Nonwhite Children in the United States. *J Pediatr* 2012 Dec;**161**(6):1035-40.

(257) Gyepes M, Mellins HZ, Katz I. The low incidence of fracture of the hip in the negro. *JAMA* 1962;**181**(12):1073-4.

(258) Richter L, Norris S, Pettifor J, Yach D, Cameron N. Cohort Profile: Mandela's children: The 1990 birth to twenty study in South Africa. *Int J Epidemiol* 2007 Jun;**36**(3):504-11.

(259) Tanner JM, Healy M, Goldstein H, Cameron N. Assessment of skeletal maturity and prediction of adult height (TW3 method). 3rd ed. London: WB Saunders: Harcourt Publishers Ltd; 2001.

(260) Pate RR, Heath GW, Dowda M, Trost SG. Associations between physical activity and other health behaviors in a representative sample of US adolescents. *Am J Public Health* 1996 Nov;**86**(11):1577-81.

(261) Gordon-Larsen P, McMurray RG, Popkin BM. Adolescent physical activity and inactivity vary by ethnicity: The National Longitudinal Study of Adolescent Health. *J Pediatr* 1999 Sep;**135**(3):301-6.

(262) Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 2000 Sep;**32**(9 Suppl):S498-S504.

(263) Tanner JM. Growth at adolescence. 2nd ed. Blackwell, Oxford; 1962.

(264) Norris SA, Richter LM. Usefulness and Reliability of Tanner Pubertal Self-Rating to Urban Black Adolescents in South Africa. *Journal of Research on Adolescence* 2005;**15**(4):609-24.

(265) Pothiwala P, Evans EM, Chapman-Novakofski KM. Ethnic variation in risk for osteoporosis among women: a review of biological and behavioral factors. *J Womens Health (Larchmt)* 2006 Jul;**15**(6):709-19.

(266) Randsborg PH, Gulbrandsen P, Saltyte BJ, Sivertsen EA, Hammer OL, Fuglesang HF, et al. Fractures in children: epidemiology and activity-specific fracture rates. *J Bone Joint Surg Am* 2013 Apr 3;**95**(7):e42.

(267) Raustorp A, Ludvigsson J. Secular trends of pedometer-determined physical activity in Swedish school children. *Acta Paediatr* 2007 Dec;**96**(12):1824-8.

(268) Gyllencreutz L, Rolfsman E, Saveman BI. Non-minor injuries among children sustained in an outdoor environment - a retrospective register study. *Int J Inj Contr Saf Promot* 2013 Sep 11;**DOI:10.1080/17457300.2013.833945**.

(269) Meehan WP, III, Mannix R. A substantial proportion of life-threatening injuries are sport-related. *Pediatr Emerg Care* 2013 May;**29**(5):624-7.

(270) Tandon T, Shaik M, Modi N. Paediatric trauma epidemiology in an urban scenario in India. *J Orthop Surg (Hong Kong)* 2007 Apr;**15**(1):41-5.

(271) ROHL L. On fractures through the radial condyle of the humerus in children. *Acta Chir Scand* 1952 Nov 29;**104**(1):74-80.

(272) Mortensson W, Thonell S. Left-side dominance of upper extremity fracture in children. *Acta Orthop Scand* 1991 Apr;**62**(2):154-5.

(273) Fricke O, Land C, Semler O, Tutlewski B, Stabrey A, Remer T, et al. Subcutaneous fat and body fat mass have different effects on bone development at the forearm in children and adolescents. *Calcif Tissue Int* 2008 Jun;**82**(6):436-44.

(274) Ma DQ, Jones G. Clinical risk factors but not bone density are associated with prevalent fractures in prepubertal children. *J Paediatr Child Health* 2002 Oct;**38**(5):497-500.

(275) Jones S, Johansen A, Brennan J, Butler J, Lyons RA. The effect of socioeconomic deprivation on fracture incidence in the United Kingdom. *Osteoporos Int* 2004 Jul;**15**(7):520-4.

(276) Jones G, Dwyer T. Bone mass in prepubertal children: gender differences and the role of physical activity and sunlight exposure. *J Clin Endocrinol Metab* 1998 Dec;**83**(12):4274-9.

(277) Flynn J, Foley S, Jones G. Can BMD Assessed by DXA at Age 8 Predict Fracture Risk in Boys and Girls During Puberty?: An Eight-Year Prospective Study. *J Bone Miner Res* 2007 Sep;**22**(9):1463-7.

(278) Wetzsteon RJ, Hughes JM, Kaufman BC, Vazquez G, Stoffregen TA, Stovitz SD, et al. Ethnic differences in bone geometry and strength are apparent in childhood. *Bone* 2009 May;**44**(5):970-5.

(279) Lazcano-Ponce E, Tamayo J, Cruz-Valdez A, Diaz R, Hernandez B, Del CR, et al. Peak bone mineral area density and determinants among females aged 9 to 24 years in Mexico. *Osteoporos Int* 2003 Jul;**14**(7):539-47.

(280) Dimitri P, Wales JK, Bishop N. Fat and bone in children: differential effects of obesity on bone size and mass according to fracture history. *J Bone Miner Res* 2010 Mar;**25**(3):527-36.

(281) Rosen CJ, Bouxsein ML. Mechanisms of disease: is osteoporosis the obesity of bone? *Nat Clin Pract Rheumatol* 2006 Jan;**2**(1):35-43.

(282) Wetzsteon RJ, Petit MA, Macdonald HM, Hughes JM, Beck TJ, McKay HA. Bone structure and volumetric BMD in overweight children: a longitudinal study. *J Bone Miner Res* 2008 Dec;**23**(12):1946-53.

(283) Ducher G, Bass SL, Naughton GA, Eser P, Telford RD, Daly RM. Overweight children have a greater proportion of fat mass relative to muscle mass in the upper limbs than in the lower limbs: implications for bone strength at the distal forearm. *Am J Clin Nutr* 2009 Oct;**90**(4):1104-11.

(284) Davidson P, Goulding A, Chalmers D. Biomechanical analysis of arm fracture in obese boys. *J Paediatr Child Health* 2003 Dec;**39**(9):657-64.

(285) Laddu DR, Farr JN, Laudermilk MJ, Lee VR, Blew RM, Stump C, et al. Longitudinal relationships between whole body and central adiposity on weight-bearing bone geometry, density, and bone strength: a pQCT study in young girls. *Arch Osteoporos* 2013 Dec;**8**(1-2):156.

(286) Farr JN, Chen Z, Lisse JR, Lohman TG, Going SB. Relationship of total body fat mass to weight-bearing bone volumetric density, geometry, and strength in young girls. *Bone* 2010 Apr;**46**(4):977-84.

(287) Poopedi MA, Norris SA, Pettifor JM. Factors influencing the vitamin D status of 10-year-old urban South African children. *Public Health Nutr* 2011 Feb;**14**(2):334-9.

(288) Mouratidou T, Vicente-Rodriguez G, Gracia-Marco L, Huybrechts I, Sioen I, Widhalm K, et al. Associations of dietary calcium, vitamin D, milk intakes, and 25-hydroxyvitamin D with bone mass in Spanish adolescents: the HELENA study. *J Clin Densitom* 2013 Jan;**16**(1):110-7.

(289) Ioannou C, Javaid MK, Mahon P, Yaqub MK, Harvey NC, Godfrey KM, et al. The effect of maternal vitamin D concentration on fetal bone. *J Clin Endocrinol Metab* 2012 Nov;**97**(11):E2070-E2077.

(290) Gale CR, Javaid MK, Robinson SM, Law CM, Godfrey KM, Cooper C. Maternal size in pregnancy and body composition in children. *J Clin Endocrinol Metab* 2007 Oct;**92**(10):3904-11.

(291) Patel DN, Pettifor JM, Becker PJ, Grieve C, Leschner K. The effect of ethnic group on appendicular bone mass in children. *J Bone Miner Res* 1992 Mar;**7**(3):263-72.

(292) Jones G, Nguyen TV. Associations between maternal peak bone mass and bone mass in prepubertal male and female children. *J Bone Miner Res* 2000 Oct;**15**(10):1998-2004.

(293) Theintz G, Buchs B, Rizzoli R, Slosman D, Clavien H, Sizonenko PC, et al. Longitudinal monitoring of bone mass accumulation in healthy adolescents: evidence for a marked reduction after 16 years of age at the levels of lumbar spine and femoral neck in female subjects. *Journal of Clinical Endocrinology & Metabolism* 1992 Oct 1;**75**(4):1060-5.

(294) Faulkner RA, Bailey DA, Drinkwater DT, McKay HA, Arnold C, Wilkinson AA. Bone densitometry in Canadian children 8-17 years of Age. *Calcif Tissue Int* 1996 Nov;**59**(5):344-51.

(295) Thandrayen K, Norris SA, Micklesfield LK, Pettifor JM. Heterogeneity of fracture pathogenesis in urban South African children: the birth to twenty cohort. *J Bone Miner Res* 2011 Dec;**26**(12):2834-42.

(296) Hinton RY, Lincoln A, Crockett MM, Sponseller P, Smith G. Fractures of the femoral shaft in children. Incidence, mechanisms, and sociodemographic risk factors. *J Bone Joint Surg Am* 1999 Apr;**81**(4):500-9.

(297) Pressley JC, Kendig TD, Frencher SK, Barlow B, Quitel L, Waqar F. Epidemiology of bone fracture across the age span in blacks and whites. *J Trauma* 2011 Nov;**71**(5 Suppl 2):S541-S548.

(298) Pye SR, Tobias J, Silman AJ, Reeve J, O'Neill TW. Childhood fractures do not predict future fractures: results from the European Prospective Osteoporosis Study. *J Bone Miner Res* 2009 Jul;**24**(7):1314-8.

(299) Buttazzoni C, Rosengren EB, Tveit M, Landin L, Nilsson JA, Karlsson KM. Does a childhood fracture predict low bone mass in young adulthood? - A 27-year prospective controlled study. *J Bone Miner Res* 2013;**28**:351-9.

(300) Cheng S, Xu L, Nicholson PH, Tylavsky F, Lyytikainen A, Wang Q, et al. Low volumetric BMD is linked to upper-limb fracture in pubertal girls and persists into adulthood: a seven-year cohort study. *Bone* 2009 Sep;**45**(3):480-6.

(301) Kawalilak CE, Baxter-Jones AD, Faulkner RA, Bailey DA, Kontulainen SA. Does childhood and adolescence fracture influence bone mineral content in young adulthood? *Appl Physiol Nutr Metab* 2010 Jun;**35**(3):235-43.

(302) Kuroda T, Onoe Y, Miyabara Y, Yoshikata R, Orito S, Ishitani K, et al. Influence of maternal genetic and lifestyle factors on bone mineral density in adolescent daughters: a cohort study in 387 Japanese daughter-mother pairs. *J Bone Miner Metab* 2009;**27**(3):379-85.

(303) Ohta H, Kuroda T, Onoe Y, Nakano C, Yoshikata R, Ishitani K, et al. Familial correlation of bone mineral density, birth data and lifestyle factors among adolescent daughters, mothers and grandmothers. *J Bone Miner Metab* 2010 Nov;**28**(6):690-5.

(304) Gueguen R, Jouanny P, Guillemin F, Kuntz C, Pourel J, Siest G. Segregation analysis and variance components analysis of bone mineral density in healthy families. *J Bone Miner Res* 1995 Dec;**10**(12):2017-22.

(305) Jouanny P, Guillemin F, Kuntz C, Jeandel C, Pourel J. Environmental and genetic factors affecting bone mass. Similarity of bone density among members of healthy families. *Arthritis Rheum* 1995 Jan;**38**(1):61-7.

(306) Park S, Park CY, Ham JO, Lee BK. Familial interactions and physical, lifestyle, and dietary factors to affect bone mineral density of children in the KNHANES 2009-2010. *J Bone Miner Metab* 2013 Sep;**DOI:10.1007/s00774-013-0515-0**.

APPENDIX A (Ethics clearance certificate)

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Thandrayen

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M071132**
PROJECT	Fractures and Bone Mass in Urban South African Children of Different Ethnic Backgrounds
INVESTIGATORS	Dr K Thandrayen
DEPARTMENT	Paediatrics Child Health
DATE CONSIDERED	07.11.30
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 08.01.31 **CHAIRPERSON** .....
(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr S Norris

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX B

Birth to Twenty – Year 15 - Adolescent Fracture Questionnaire

Bt20 ID Number:

Bone Health Number:

If the box states **YES** please complete **Section A and C**
If the box states **NO** please complete **Section B**

Section A – Verification

You told us you broke / fractured bones in your body _____ times. I would just like to make sure that we have the correct information:

Incident Number	Which side of your body? (Right / Left)	Which bone did you break / fracture?	When did this happen? (Year / Age)	How did this happen?
1.				
2.				
3.				
4.				

Section B – Please complete

Have you **ever** broken / fractured a bone in your body?

Yes	No

IF YES, how many **times in total** have you broken / fractured a bone in your body?

If Yes, please tell me about the different times this occurred.

Incident Number	Which side of your body (Right / Left)	Which bone did you break / fracture?	When did this happen? (Year / Age)	How did this happen?
1.				
2.				
3.				
4.				
5.				

Section C – Please complete

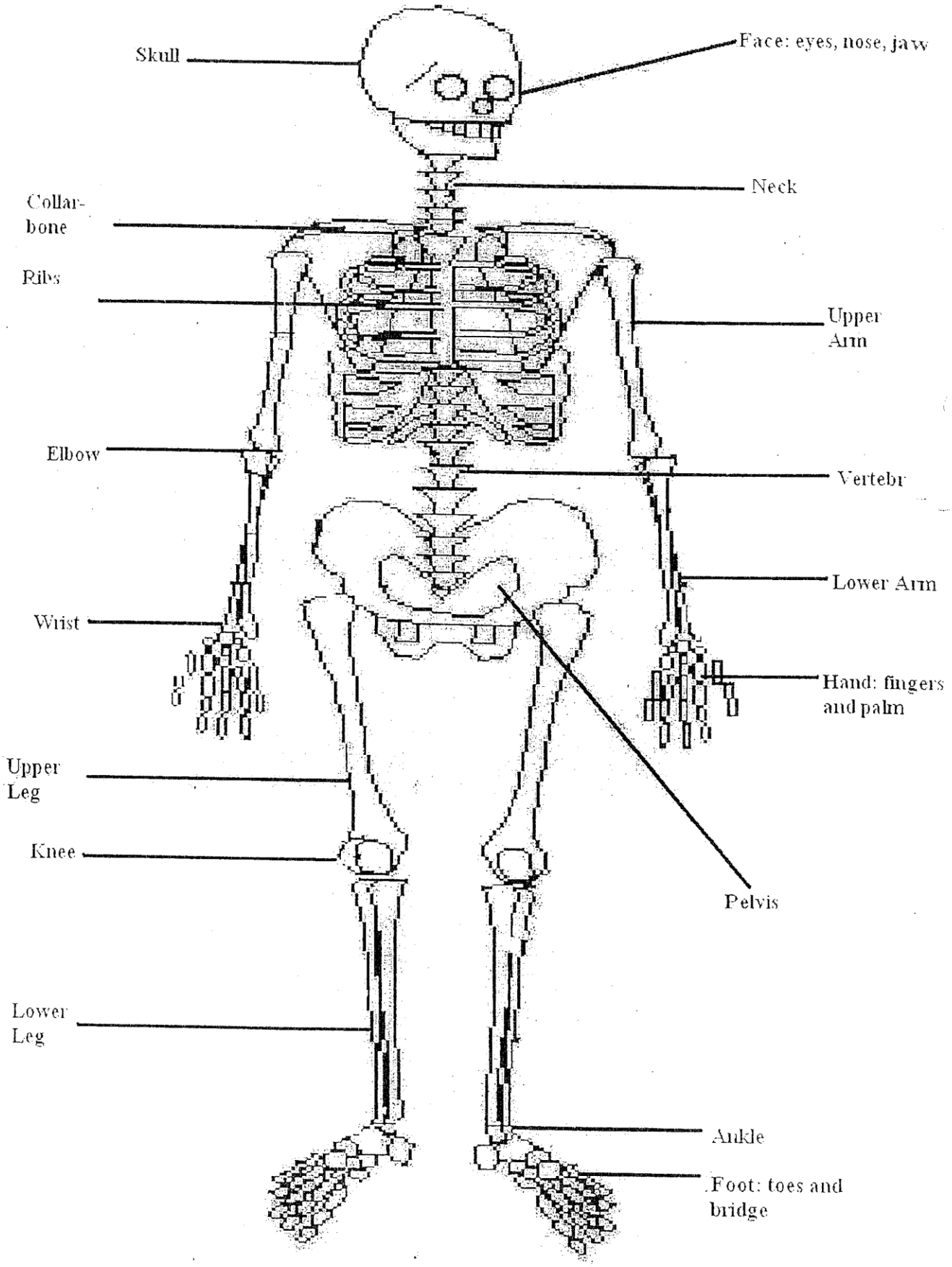
Did you break / fracture a bone in your body in the **past 12 months**?

Yes	No

If Yes, please tell me about this event/s.

Incident Number	Which side of your body (Right / Left)	Which bone did you break / fracture?	When did this happen? (Year / Age)	How did this happen?
2.				
3.				
4.				
5.				

Human Skeleton



APPENDIX C – Year 17 Adolescent fracture questionnaire



University of the Witwatersrand
Department of Paediatrics and Child Health

BIRTH TO TWENTY BARA SITE: 17TH YEAR ADOLESCENT FRACTURE QUESTIONNAIRE

BTT ID NUMBER : | | | | | | | |

Did you break / fracture a bone in your body in the **past 24 months (2 years)**?

Yes	**No**

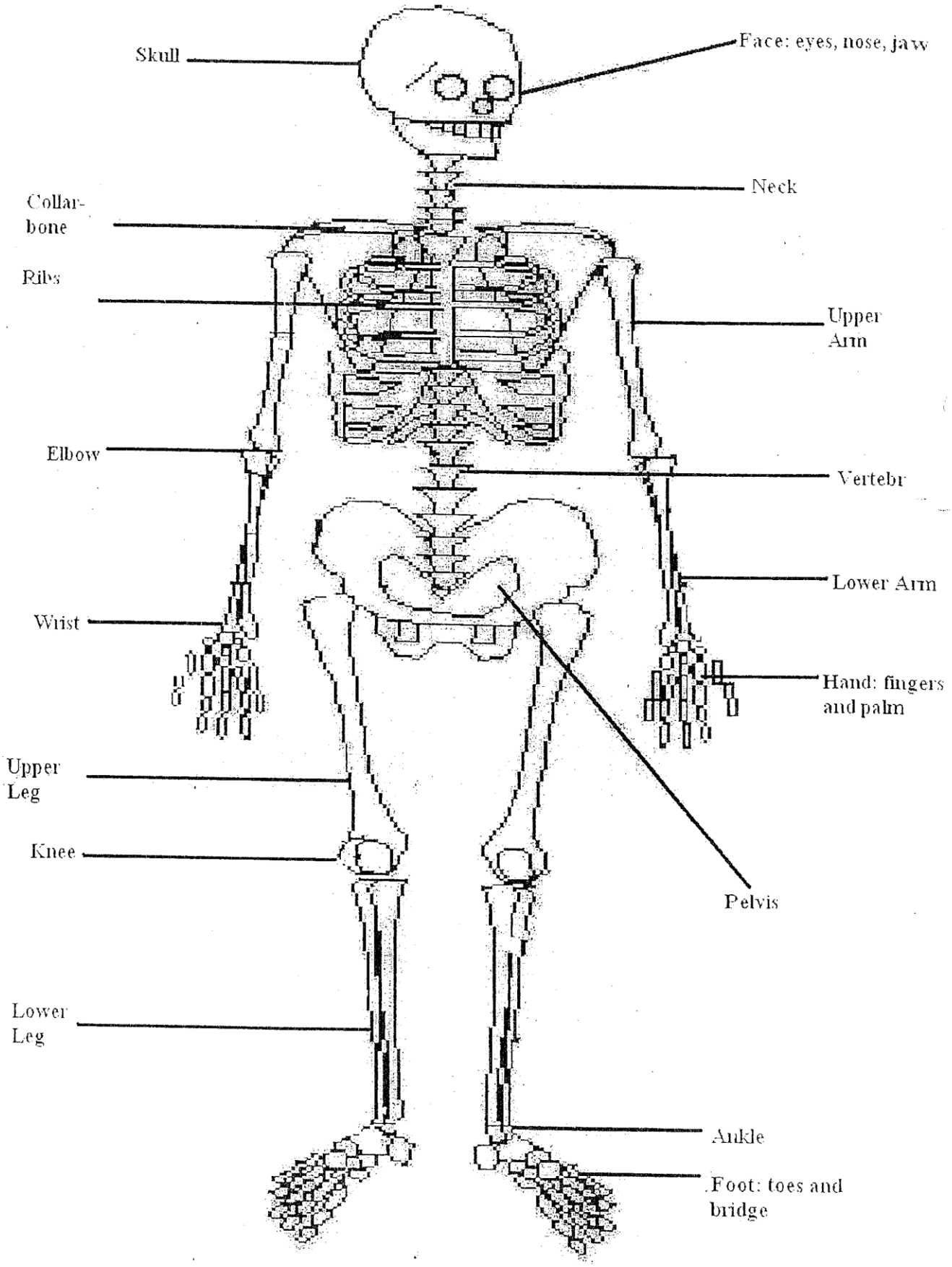
If **Yes**, please tell me about this event/s.

Incident Number	Which side of your body (Right / Left)	Which bone did you break / fracture? Please MARK the sites of fractures on the skeleton provided at the back of the page and number the fractures in order of occurrence with the year or age of occurrence next to the fracture.	When did this happen? (Year / Age)	How did this happen? Please choose from the options provided in the table below and enter for e.g. 2.2 and if not listed in the table then describe what happened
1.				
2.				
3.				
4.				
5.				

GRADE 1 (Slight trauma)
1.1 Falling to the ground from standing on the same level (e.g while walking you slipped and fell and had a fracture)
1.2 Falling from less than 0.5m (falling from stools, chairs and beds)
GRADE 2 (Moderate trauma)
2.1 Falling from between 0.5 – 3 m (e.g. a wall or jungle gym or tree)
2.2 Falling down stairs, from a bicycle, roller blades, skateboard or swing
2.3 Playground scuffles (e.g. wrestling or boxing)
2.4 Sport injuries (e.g. soccer, rugby, netball, hockey etc)
2.5 Slamming fingers into a door or knocking against a solid object
GRADE 3 (Severe trauma)
3.1 Falling from a height > 3 m (falls from windows or roofs)
3.2 Motor vehicle or pedestrian accidents
3.3 Injuries caused by heavy moving or falling objects (e.g. bricks or stones)
4. Do not recall or cannot remember

Quality checked by: _____ **Date:** _____

Human Skeleton



APPENDIX D

BIRTH TO TWENTY STUDY: 17TH YEAR CAREGIVER'S QUESTIONNAIRE ABOUT FRACTURES IN THEIR CHILDREN

BTT ID NUMBER: **BONE STUDY ID NUMBER:**

1. How many children do you have besides the child that is enrolled on the Birth to Twenty Study? _____

2. Of these siblings, have any of them fractured or broken a bone/s?

YES ☐ NO ☐ **If YES**, how many siblings have fractured? _____

AND please tell me about the gender and the different times this occurred in each sibling

SIBLING 1: Male ☐ Female ☐

Incident Number	Which side of your body? (Right / Left)	Which bone did you break / fracture? Please MARK the sites of fractures on the skeleton provided at the back of the page and number the fractures in order of occurrence with the year or age of occurrence next to the fracture.	When did this happen? (Year / Age)	How did this happen? Please choose from the options provided in the table on the next page and enter for e.g 2.2 and if not listed in the table then describe what happened
1.				
2.				
3.				
4.				
5.				

SIBLING 2: Male ☐ Female ☐

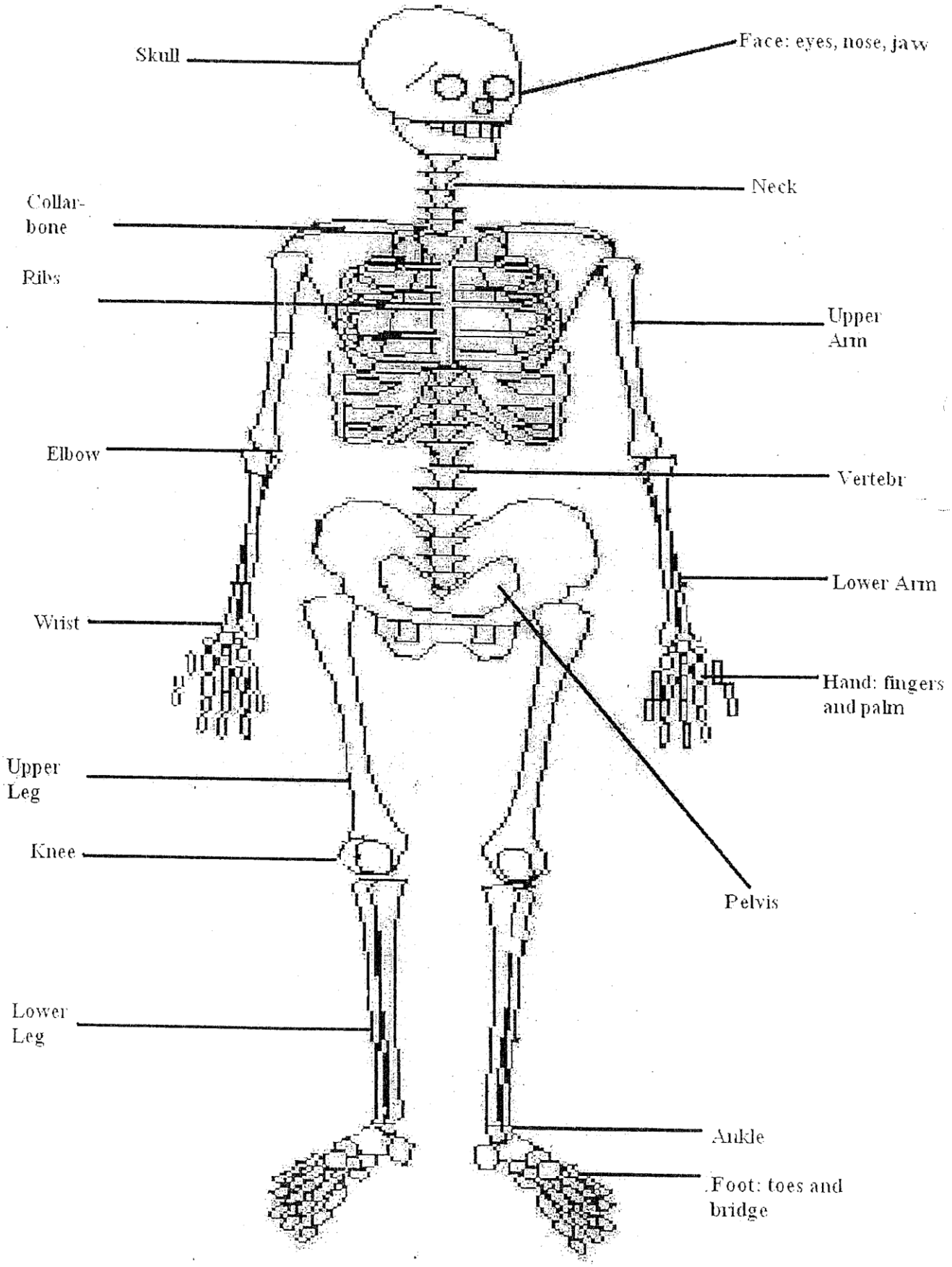
Incident Number	Which side of your body? (Right / Left)	Which bone did you break / fracture? Please MARK the sites of fractures on the skeleton provided at the back of the page and number the fractures in order of occurrence with the year or age of occurrence next to the fracture.	When did this happen? (Year / Age)	How did this happen? Please choose from the options provided in the table on the next page and enter for e.g 2.2 and if not listed in the table then describe what happened
1.				
2.				
3.				
4.				
5.				

SIBLING 3: Male ☐ Female ☐

Incident Number	Which side of your body? (Right / Left)	Which bone did you break / fracture? Please MARK the sites of fractures on the skeleton provided at the back of the page and number the fractures in order of occurrence with the year or age of occurrence next to the fracture.	When did this happen? (Year / Age)	How did this happen? Please choose from the options provided in the table on the next page and enter for e.g 2.2 and if not listed in the table then describe what happened
1.				
2.				
3.				
4.				
5.				

GRADE 1 (Slight trauma)
1.1 Falling to the ground from standing on the same level (e.g while walking you slipped and fell and had a fracture)
1.2 Falling from less than 0.5 metres (falling from stools, chairs and beds)
GRADE 2 (Moderate trauma)
2.1 Falling from between 0.5 – 3 metres (e.g a wall or jungle gym or tree)
2.2 Falling down stairs, from a bicycle, roller blades, skateboard or swing
2.3 Playground scuffles (e.g wrestling or boxing)
2.4 Sport injuries (e.g soccer, rugby, netball, hockey etc)
2.5 Slamming fingers into a door or knocking against a solid object
GRADE 3 (Severe trauma)
3.1 Falling from a height > 3 metres (falls from windows or roofs)
3.2 Motor vehicle or pedestrian accidents
3.3 Injuries caused by heavy moving or falling objects (e.g bricks or stones)
4. Do not recall or cannot remember

Human Skeleton



APPENDIX E

University of the Witwatersrand
Department of Paediatrics and Adolescent Health

BIRTH TO TWENTY STUDY: 17TH YEAR
MOTHER'S QUESTIONNAIRE ABOUT FRACTURES

DATE: Day ☐☐ **Month** ☐☐ **Year** ☐☐☐☐

BTT ID NUMBER: ☐☐☐☐☐☐☐

BONE STUDY ID NUMBER: ☐☐☐

1. Are you the biological mother of the adolescent enrolled in Birth to twenty?

YES ☐ NO ☐ **If YES**, how many times have you fractured in your childhood up to the age of 18 years? _____

AND please tell me about the different times this occurred if you can recall

Incident Number	Which side of your body? (Right / Left)	Which bone did you break / fracture? Please MARK the sites of fractures on the skeleton provided at the back of the page.	How did this happen? Please choose from the options provided in the table below and enter for e.g 2.2 and if not listed in the table then describe what happened
1.			
2.			
3.			
4.			
5.			

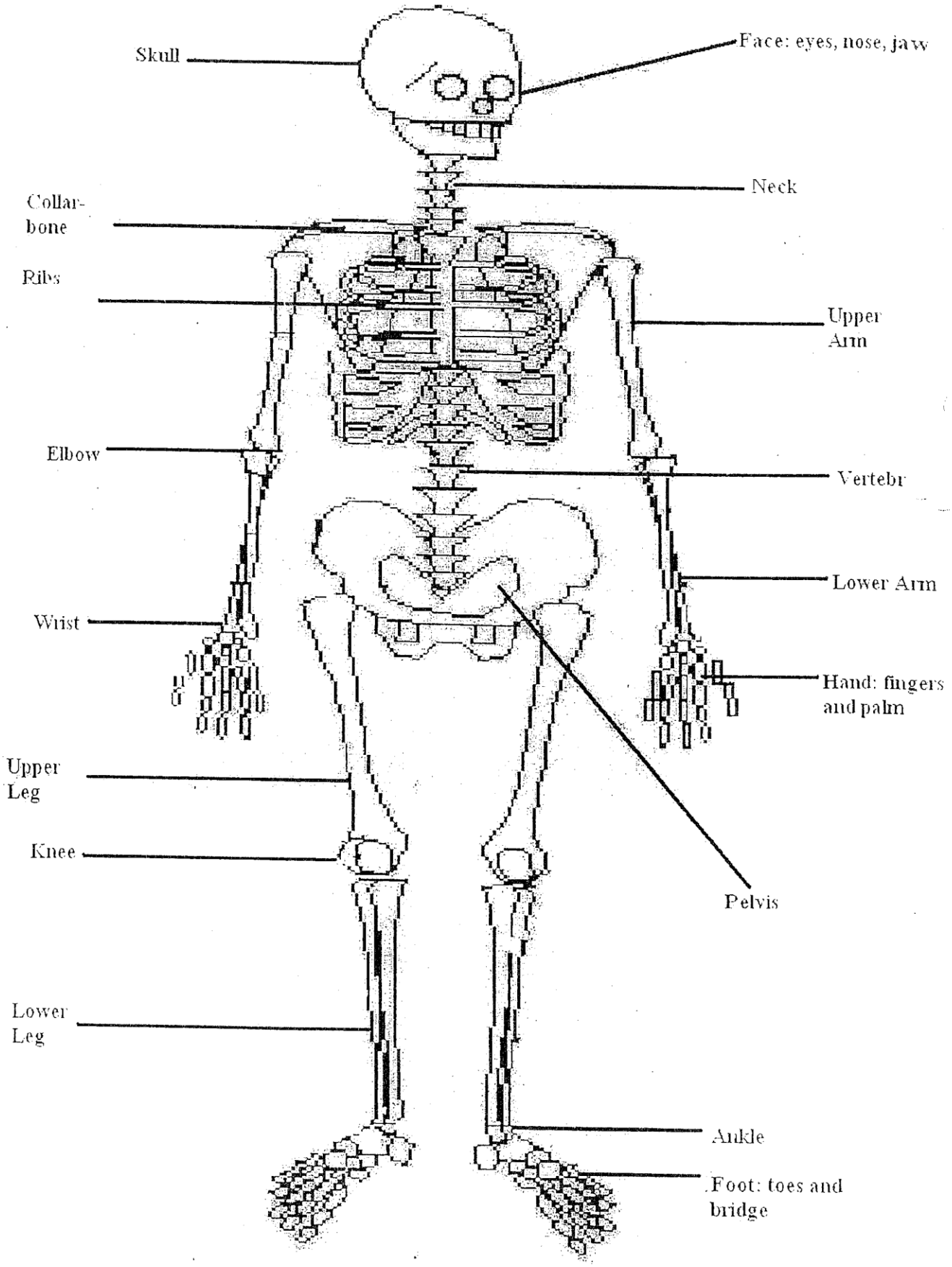
GRADE 1 (Slight trauma)
1.1 Falling to the ground from standing on the same level (e.g while walking you slipped and fell and had a fracture)
1.2 Falling from less than 0.5 metres (falling from stools, chairs and beds)

GRADE 2 (Moderate trauma)
2.1 Falling from between 0.5 – 3 metres (e.g a wall or jungle gym or tree)
2.2 Falling down stairs, from a bicycle, roller blades, skateboard or swing
2.3 Playground scuffles (e.g wrestling or boxing)
2.4 Sport injuries (e.g soccer, rugby, netball, hockey etc)
2.5 Slamming fingers into a door or knocking against a solid object

GRADE 3 (Severe trauma)
3.1 Falling from a height > 3 metres (falls from windows or roofs)
3.2 Motor vehicle or pedestrian accidents
3.3 Injuries caused by heavy moving or falling objects (e.g bricks or stones)
4. Do not recall or cannot remember

Research Assistant:		**Date:**	
Quality checked by:		**Date:**	

Human Skeleton



APPENDIX F

University of the Witwatersrand
Department of Paediatrics and Child Health

BIRTH TO TWENTY: 17TH YEAR ADOLESCENT VERIFICATION OF FRACTURES QUESTIONNAIRE

BTT ID NUMBER : | | | | | | | | Date: _____

Dear Caregiver or Adolescent:

You have been randomly selected from those adolescents who have previously reported fractures. Please can you assist us with verifying the information that was previously given to us with regard to the number of fractures that your child or you, the adolescent has had since birth. To further verify that the fractures were correctly diagnosed we require information on the whether the adolescent was seen by a doctor/hospital and whether xrays were done and treatment was given.

- Please can you confirm with me, how many times your child or you (the adolescent) has fractured a bone/s: _____

- Please can you confirm the side and site of the most recent fracture and how your child or you (the adolescent) had fractured that bone?

Which side of your body (Right / Left)	Which bone did you break / fracture?	When did this happen? (Year / Age)	How did this happen?

- For each fracture can you please complete the following questions :

Fractures	Who diagnosed the fracture (doctor, nurse or self-diagnosed)?	Have you been to a hospital, clinic or private doctor?	Have you had an xray done?	Do you have the xrays?	What was the treatment? (POP, sling, bandage, traction, operation)	Do you have any outpatient files or records of the fractures

- If you have any xrays with you can we fetch the xrays from you? Y/ N

Osteoporos Int
DOI 10.1007/s00198-008-0627-x

ORIGINAL ARTICLE

Fracture rates in urban South African children of different ethnic origins: The Birth to Twenty Cohort

K. Thandrayen · S. A. Norris · J. M. Pettifor

Received: 26 November 2007 / Accepted: 28 March 2008
© International Osteoporosis Foundation and National Osteoporosis Foundation 2008

Abstract
Summary Fracture rates were compared in children of different ethnic backgrounds from Johannesburg, South Africa. More white children fracture than black and mixed ancestry children. Reasons for this may be due to greater sports participation by whites and genetic protective factors in blacks. This has to be further investigated.
Introduction Fracture rates in childhood are as high as those in the elderly. Recent research has been undertaken to understand the reasons for this, but there is little information available on ethnic differences in childhood fracture rates.
Methods Using the birth to twenty longitudinal cohort of children, we retrospectively obtained information on fractures and their sites from birth to 14.9 years of age on 2031 participants. The ethnic breakdown of the children was black (B) 78%, white (W) 9%, mixed ancestry (MA) 10.5% and Indian (I) 1.5%.
Results Four hundred and forty-one (22%) children had sustained a fracture one or more times during their lifetime (males 27.5% and females 16.3%; $p<0.001$). The percentage of children fracturing differed between the ethnic groups (W 41.5%, B 19%, MA 21%, I 30%; $p<0.001$). Of the 441 children reporting fractures, 89(20%) sustained multiple fractures. The most common site of fracture was the upper limb (57%).
Conclusion More white children fracture than black and mixed ancestry children. This is the first study to show ethnic differences in fracture rates among children. The reasons for these differences have to be further elucidated. Greater sports participation by whites and genetic protective factors in blacks may be contributing factors.

Keywords Black · Children · Ethnicity · Fractures · Incidence · White

K. Thandrayen (✉) · S. A. Norris · J. M. Pettifor
MRC Mineral Metabolism Research Unit,
Department of Paediatrics,
Chris Hani Baragwanath Hospital,
PO Bertsham,
Johannesburg 2013, South Africa
e-mail: kebashni.thandrayen@wits.ac.za

Introduction

Fracture rates in childhood are as high as those in the elderly [1], and the incidence of childhood fractures is probably rising in the developed world [2, 3]. The type and incidence of fractures in childhood vary with gender, age and site; however there is little information on ethnic differences in childhood fracture rates. The incidence of fractures is lower in African-American post-menopausal women than in white women in the United States [4, 5]. A similar ethnic difference in hip fracture prevalence is seen between white and South African black women [6]. Information on the pattern and incidence of childhood fracture rates amongst the various South African ethnic groups has not been investigated previously. Thus, the aim of this study was to determine the rates of fractures and site distribution of and activity-related risk factors for fractures in children of different ethnic origins. We hypothesized that 1) South African black children would fracture less than white children, similar to the pattern in the post-menopausal South African population; and 2) all ethnic groups would have a similar age and sex-related distribution of fractures.

Materials and methods

Subjects

The Birth to Twenty study is a cohort of urban children, which included all neonates delivered within the public sector hospitals between April 23 to June 8 1990 and who were resident in the greater Johannesburg area six months after delivery, with the aim to track their growth, health, well-being and educational progress. 3273 singleton children were enrolled. The total cohort is demographically representative of long-term resident families living in Johannesburg–Soweto. However, the cohort under represents white children due to white families utilizing private practitioners and facilities and thus not being enrolled. To compensate for this, at the age of 10 years, we recruited a supplementary sample of 120 white children born during the same period in 1990 into the bone health sub-study of the Birth to Twenty cohort. Of the 3273 children in the cohort initially, contact has been maintained with more than 70% at the age of 16 years. A cohort profile describing the study sample, research objectives and attrition has been documented by Richter et al. [7]. Data from 2031 children were analyzed for this study. The ethnic breakdown of the study sample was predominantly black (B) (1600 [78%]), with the remainder of the cohort being made up of white (W) (188 [9%]), mixed ancestry (MA) (213 [10.5%]) and Indian(I) (30 [1.5%]). Children who had chronic diseases such as rheumatoid arthritis, epilepsy and asthma were excluded from the data analyses, as the use of certain medications and immobility are associated risk factors for low bone mass and may increase the incidence of fractures. All subjects provided assent and their parents provided written, informed consent; ethical approval having been obtained from the University of Witwatersrand Committee for Research on Human Subjects.

Questionnaire

A fracture questionnaire was completed by each adolescent at age 15 years and verified for completeness and accuracy by the parent or primary caregiver of the child. The questionnaire included information on previous fractures, their sites with the aid of a skeletal diagram, the causes and age at fracture. The grading of severity of trauma causing fractures was classified into slight (grade 1), moderate (grade 2) or severe (grade 3) (Table 1). The definitions were slightly modified from Landin [3] and Manias et al. [8] to be appropriate for local conditions.

Table 1 Grades of trauma causing fractures

Grade	Cause
Grade 1 (Slight)	Falling to the ground from standing on the same level
	Falling from less than 0.5 metres (falling from stools, chairs and beds)
Grade 2 (Moderate)	Falling from between 0.5 – 3 metres
	Falling down stairs, from a bicycle, roller blades, skateboard or swing
	Playground scuffles
	Sport injuries
Grade 3 (Severe)	Falling from a height >3 metres (falls from windows or roofs)
	Motor vehicle or pedestrian accidents
	Injuries caused by heavy moving or falling objects (e.g., bricks or stones)

Data analysis

Data were analyzed using Statistica statistical software version 7.0 (StatSoft, USA). Standard statistical measures such as chi-square were used where appropriate. A p-value of <0.05 was considered to be statistically significant. Fracture rates were calculated as the number of new cases or fractures divided by total person-time of observation. Because of the small number of subjects in the Indian ethnic group, statistical analyses generally did not include this group.

Results

Of the 2031 subjects, four hundred and forty-one (22%) children had one or more fractures during their lifetime. (Table 2) The highest percentage of children with a history of fractures was in the white population (41.5%), followed by the Indian (30%), mixed ancestry (21%) and the black

Table 2 The number of children who sustained fractures over the first 15 years of life according to ethnicity and sex

Ethnicity	All children	Number of children with fractures			
		Total children with fractures		Males	Females
	N	*N*	(%)	(%)	(%)
White	188	78	41.5	47	36
Indian	30	9	30	43	19
Mixed ancestry	213	44	21	26	15
Black	1600	310	19	25	14
Total	2031	441	22	27.5	16.3

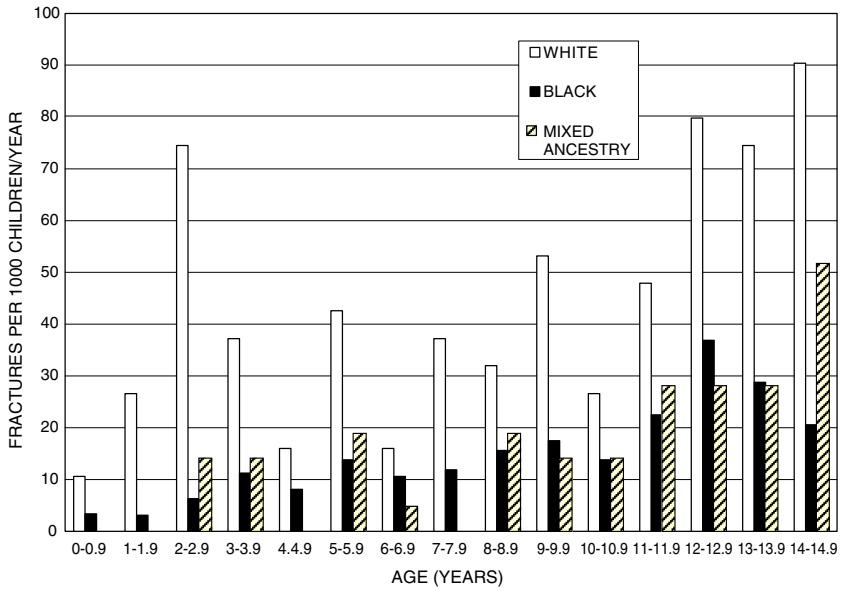


Fig. 1 Fracture rates per year by age and ethnicity

(19%) populations. (Table 2) There was a significant difference between the ethnic groups in the percentage of children who had fractures over the 15 years ($p<0.001$). No further data are shown on the Indian subjects as the results are unreliable due to low numbers. A higher percentage of white males (47%) and females (36%) had fractured compared to those in the black (25% and 14% respectively) and mixed ancestry (26% and 15% respectively) ethnic groups. (Table 2) The overall fracture rate over the first 15 years of life was 18.5/1000 children/annum. The age distribution and peak rates of fractures were similar between the black and mixed ancestry ethnic groups, but the fracture rates were higher at all ages in the white population. (Figure 1) The fracture rate over the first 15 years of life was three times greater in the white group than in the black and mixed ancestry groups (W 46.5 [95% CI 30.4–58.3]; B 15.4 [95% CI 9.8–20.1]; MA 15.6 [95% CI 7.7–23.5] /1000 children/annum, $p<0.001$). First frac-

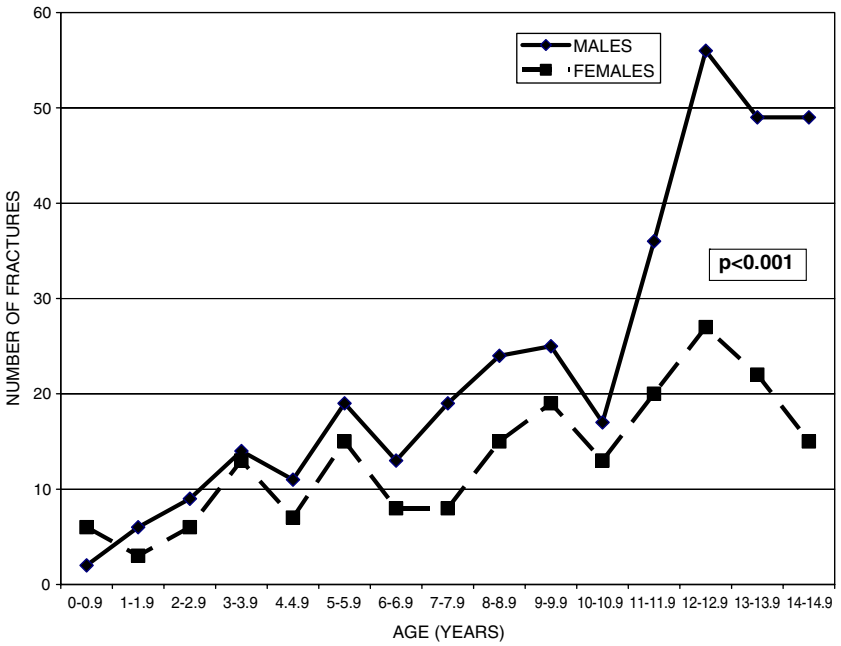


Fig. 2 Fractures per year by age and sex distribution. The number of males and females in the study were similar

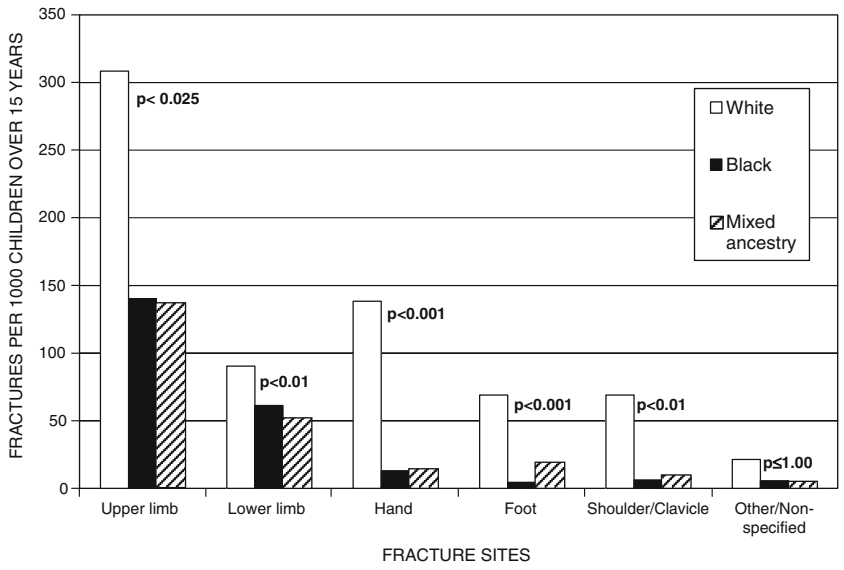


Fig. 3 Fracture rates over 15 years between ethnic groups at the different fracture sites. The *p* values indicate the significant difference between fracture rates of the white children and those of the black and mixed ancestry children

ture was more common in the white group than in the black and mixed ancestry groups (W 31.2 [95% CI 19–41.6]; B 12.9 [95% CI 8.7–16.4]; MA 13.8 [95% CI 6.9–20.6] /1000 children/annum; $p<0.001$).

More boys than girls sustained fractures (27.5% vs. 16.3%; $p<0.001$) throughout all age groups except in the first year of life. (Figure 2) Of all fractures, 64% occurred in males. The peak age of fractures was between 11–14.9 years for the sexes combined. The peak fracture rate for girls was between 11–13.9 years of age during which period 10% fractured and between 11–14.9 years of age for boys when 19% fractured. The fracture rate from 11–14.9 years of age in white males was almost three times higher than in black males (101.1 [95% CI 59.9–142.4] vs. 37.3 [95% CI 19.5–55.2] /1000 children/annum, $p<0.001$) and double that of the mixed ancestry group (49.5 [95% CI 10–89] /1000 children/annum, $p<0.002$). The fracture rate from 11–13.9 years of age in white females was three times greater than in black (60.6 [95% CI 17.1–104.1] vs. 17 [95% CI 9–25.1] /1000 children/annum; $p<0.001$) and mixed ancestry females (18.7 [95% CI -4.6–41.9] /1000 children/annum; $p<0.003$).

Of the 441 children reporting fractures, 80% sustained a single fracture and 20% fractured on more than one occasion. More boys than girls sustained two or more fractures (23% vs. 15% of those fracturing; $p<0.001$). The maximum number of fractures sustained by an individual was five.

The most common site of fracture for both sexes across the ethnic groups was the upper limb (57%) (Fig. 3). Other fracture sites included the neck, ribs, pelvis, face, vertebrae and skull. The fracture rate at each site was highest in white children ($p<0.025$) (Fig. 3). Fracture rates at the different sites were similar in the black and mixed ancestry groups, but lower than in white children.

Most fractures occurred as a consequence of grade 2 trauma within all ethnic groups. There was a statistically significant difference in the grades of trauma causing

Table 3 Grades of trauma causing fractures versus ethnicity and sex

Grades of trauma causing fractures	All fractures occurring in individuals according to grades of trauma					
	Black*		White		Mixed ancestry	
	Males** *n* (%)	Females *n* (%)	Males *n* (%)	Females *n* (%)	Males *n* (%)	Females *n* (%)
Grade 1	61 (25)	41 (32)	10 (13.5)	9 (16)	9 (26)	7 (44)
Grade 2	151 (62)	70 (55)	56 (76)	38 (67)	21 (62)	7 (44)
Grade 3	28 (12)	16 (12.5)	7 (9.5)	9 (16)	3 (6)	2 (12)
Do not recall	2 (1)	1 (0.5)	1 (1)	1 (1)	1 (3)	0 (0)

Note: The Indian group was excluded due to small number of subjects

* $p<0.025$ Fractures in blacks associated with lower grades of trauma than in whites

** $p<0.035$ Fractures in black males associated with lower grades of trauma than in white males

fractures between the white and black ethnic groups ($p<$ 0.025), with whites generally fracturing at more severe levels of trauma. (Table 3).

Discussion

This study shows that fracture rates in children in South Africa vary across the different ethnic groups, with the percent of children reporting fractures in the white ethnic group being almost double that of the black and mixed ancestry groups. As far as we can ascertain, this is the first comparative study of children's fractures across ethnic groups reported in the world. Numerous studies from developed countries have reported on the incidence of childhood fractures in defined populations [3, 9–13] and in longitudinal cohort studies [14], but none have reported on ethnic differences in childhood fracture patterns and rates. The lower fracture incidence in black than white children is similar to that noted for femoral neck fractures in adults in South Africa [6].

The risk of osteoporotic fractures in the elderly is related to gender and ethnicity. The National Osteoporosis Risk Assessment (NORA) longitudinal observational study of osteoporosis among postmenopausal women in primary care practices compared white, Asian, Hispanic and Native American women in terms of osteoporosis risk and showed that these ethnic groups are more at risk for osteoporosis than African-American women [15]. Similarly African-American women have a lower fracture risk than white women at every level of bone mineral density and this relationship is largely explained by environmental and genetic factors that need to be further investigated [16].

Although only 22% of children in the combined cohort reported fractures, 41.5% of white children suffered one or more fractures; this latter figure being comparable to that found in the Dunedin Multidisciplinary Health and Development study whose participants were predominantly Caucasian [14]. The percentage of fractures in white boys and girls in the present study is also similar to those reported by Landin where by the age of 16 years, 42% of boys and 27% of girls had suffered a fracture [3]; however they are somewhat higher than those reported from a cross-sectional study in Poland, in which 30% of 1246 respondents had fractured by the age of 16 to 20 years [13]. In the current study, the fracture rate in white children were threefold that found in the black and mixed ancestry groups and more males than females sustained multiple fractures, the latter finding being in keeping with other population based studies[3, 9, 12–14,17]. The reasons for the increased fracture rate in boys may be due to the fact that males are more involved in contact and high impact team sports than girls and tend to spend more time outdoors playing [13]. Landin reported a fivefold increase in fracture rates caused by sports between 1950 and 1979 in Sweden [3]. The fact that more males sustained multiple fractures supports the evidence for sport playing a role in the increased fracture rate in males. There was a significant difference in the grading of trauma associated with fractures between the white and black children suggesting that sport and physical activity plays a role in the increased rate of fractures in the white group. We have previously reported lower physical activity levels in black children [18], which is related to the lack of organized sports in schools attended mainly by black subjects and the poorer socio-economic status of the black families [19]. McVeigh et al. previously reported that white males at age 9 and 10 years from the same Birth to Twenty longitudinal study had the highest physical activity levels and those white male children falling into the highest quartile of activity exhibited bone mass benefits at the whole body, total hip and lumbar spine sites [20]. Despite the highest physical activity levels in white male children, black children still had a higher hip, mid-radial and lumbar spine (girls only) bone mass and similar values to their white peers at other sites[18, 20]. These findings support the hypothesis of a genetic protection against low bone mass and fracture in blacks. Fractures on average were reported to have occurred at a higher energy level in white children but this is unlikely to have been due to different interpretations of the questions by the ethnic groups as a single researcher classified the degree of trauma resulting in fractures according to the answers given as to how the fractures happened. Further, a single interviewer helped with the questionnaires to eliminate the problem with language and interpretation of questions.

Upper limb or radial fractures have been repeatedly reported to be the most common site of fracture in both sexes [3, 9, 12, 14, 17]. This study confirms these findings in all the ethnic groups. Peak age of fractures for both males and females found in this study correlate with stages of pubertal growth and peak height velocities which are compatible with other studies[3, 9, 13, 14].

Limitations of the study include the fact that the results for Indian children are unreliable due to very small number of subjects included in the cohort. Recall bias might be another limitation as the diagnosis of all fractures was based on recall by the subject and the parent or caregiver and was not confirmed with radiological assessments; however this was probably not a major factor in the study as at all ages the findings were consistent between the ethnic groups. The methodology of year 15 data collection on fractures was able to confirm the age, site and cause of previous fractures that had been recorded at year 13 and also collected information on new fractures occurring between 13 and 15 years. In addition, all questionnaires had a skeletal diagram attached to verify the site of fracture and the information was verified for accuracy and completeness by the parent or primary caregiver.

The chances of a fracture not being diagnosed in the different ethnic groups are unlikely to have differed despite having access to different levels of health care as health care in the public sector is free for all children. Both public and private health facilities in urban areas would perform routine radiological assessments to confirm fractures. Further limitations are that there are currently no comparative analyses of bone mass, potential fracture-associated risk factors, dietary intake of calcium or vitamin D and measurements of calcium homeostasis and vitamin D status between the ethnic groups. Rather than to look at risk factors, the aim of the present report is to describe the pattern of childhood fractures amongst different ethnic groups in South Africa.

Conclusion

This is the first study to show that white children fracture more than children from black and mixed ancestry groups. When comparing whites to blacks, these findings are similar to the pattern in the post-menopausal population. The reasons for this could be more active participation in sport and physical activity in white children and genetic protective factors in blacks, which has to be further investigated.

Acknowledgements Birth to Twenty is funded by the Wellcome Trust (UK), Medical Research Council of South Africa, Human Sciences Research Council of South Africa, and by the Friedel Sellschop Award to Dr Norris from the University of the Witwatersrand, Johannesburg. The Bone Health sub-cohort is supported by a National Research Foundation grant.

Conflicts of interest None.

References

1. Heaney RP, Abrams S, Dawson-Hughes B et al (2000) Peak bone mass. Osteoporos Int 11:985–1009
2. Khosla S, Melton LJ III, Dekutoski MB et al (2003) Incidence of childhood distal forearm fractures over 30 years: a population-based study. JAMA 290:1479–1485
3. Landin LA (1983) Fracture patterns in childrenAnalysis of 8,682 fractures with special reference to incidence, etiology and secular changes in a Swedish urban population 1950–1979. Acta Orthop Scand Suppl 202:1–109
4. Luckey MM, Meier DE, Mandeli JP et al (1989) Radial and vertebral bone density in white and black women: evidence for racial differences in premenopausal bone homeostasis. J Clin Endocrinol Metab 69:762–770
5. Perry HM III, Horowitz M, Morley JE et al (1996) Aging and bone metabolism in African American and Caucasian women. J Clin Endocrinol Metab 81:1108–1117
6. Solomon L (1968) Osteoporosis and fracture of the femoral neck in the South African Bantu. J Bone Joint Surg Br 50:2–13
7. Richter L, Norris S, Pettifor J et al (2007) Cohort Profile: Mandela's children: The 1990 Birth to Twenty Study in South Africa. Int J Epidemiol 36:504–511
8. Manias K, McCabe D, Bishop N (2006) Fractures and recurrent fractures in children; varying effects of environmental factors as well as bone size and mass. Bone 39:652–657
9. Cooper C, Dennison EM, Leufkens HG et al (2004) Epidemiology of childhood fractures in Britain: a study using the general practice research database. J Bone Miner Res 19:1976–1981
10. Lyons RA, Sellstrom E, Delahunty AM et al (2000) Incidence and cause of fractures in European districts. Arch Dis Child 82:452–455
11. Lyons RA, Delahunty AM, Heaven M et al (2000) Incidence of childhood fractures in affluent and deprived areas: population based study. BMJ 320:149
12. Rennie L, Court-Brown CM, Mok JY et al (2007) The epidemiology of fractures in children. Injury 38:913–922
13. Konstantynowicz J, Bialokoz-Kalinowska I, Motkowski R et al (2005) The characteristics of fractures in Polish adolescents aged 16–20 years. Osteoporos Int 16:1397–1403
14. Jones IE, Williams SM, Dow N et al (2002) How many children remain fracture-free during growth? a longitudinal study of children and adolescents participating in the Dunedin Multidisciplinary Health and Development Study. Osteoporos Int 13:990–995
15. Pothiwala P, Evans EM, Chapman-Novakofski KM (2006) Ethnic variation in risk for osteoporosis among women: a review of biological and behavioral factors. J Womens Health (Larchmt) 15:709–19
16. Cauley JA, Lui LY, Ensrud KE et al (2005) Bone mineral density and the risk of incident nonspinal fractures in black and white women. JAMA 293:2102–2108
17. Lyons RA, Delahunty AM, Kraus D et al (1999) Children's fractures: a population based study. Inj Prev 5:129–132
18. McVeigh JA, Norris SA, Cameron N et al (2004) Associations between physical activity and bone mass in black and white South African children at age 9 yr. J Appl Physiol 97:1006–1012
19. McVeigh JA, Norris SA, de Wet T (2004) The relationship between socio-economic status and physical activity patterns in South African children. Acta Paediatr 93:982–988
20. McVeigh JA, Norris SA, Pettifor JM (2007) Bone mass accretion rates in pre- and early-pubertal South African black and white children in relation to habitual physical activity and dietary calcium intakes. Acta Paediatr 96:874–880

ORIGINAL ARTICLE

JBMR

Heterogeneity of Fracture Pathogenesis in Urban South African Children: The Birth to Twenty Cohort

Kebashni Thandrayen,[1] Shane A Norris,[1] Lisa K Micklesfield,[1,2] and John M Pettifor[1]

[1]MRC/Wits Developmental Pathways for Health Research Unit, Department of Paediatrics, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa

[2]UCT/MRC Research Unit for Exercise Science and Sports Medicine, Department of Human Biology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

ABSTRACT

South African black children fracture less than white children. Differences in bone mass, body composition, and physical activity may be contributing risk factors. This study aimed to investigate the association between fracture prevalence, bone mass, and physical activity in South African children. Using the Bone Health cohort of the Birth to Twenty longitudinal study, we retrospectively obtained information of lifetime fractures until age 15 years in 533 subjects. Whole-body bone mineral content (BMC), bone area (BA), fat mass (FM), and lean mass (LM) (measured by dual-energy X-ray absorptiometry [DXA]), anthropometric data, physical activity scores, and skeletal maturity were obtained at ages 10 and 15 years. Nonfracturing black females were used as the control group and comparisons were made between those who did and did not fracture within the same sex and ethnic groups. Of the 533 subjects, 130 (24%) reported a fracture (black, 15%; white, 41.5%; $p < 0.001$). White males who fractured were significantly taller (10 years, $p < 0.01$), more physically active (15 years, $p < 0.05$) and had higher LM (10 years, $p = 0.01$; 15 years, $p < 0.001$), whereas white females who fractured were fatter (10 and 15 years, $p = 0.05$ and $p < 0.05$, respectively), than their nonfracturing peers. White males who fractured had greater BA and BMC at all sites at 10 and 15 years compared to their nonfracturing peers after adjusting for differences in height and weight; BA and BMC were similar in each of the other sex and ethnic groups. No anthropometric or bone mass differences were found between black children with and without fractures. The factor associated with fractures in white males appears to be participation in sports activities, while in white females obesity appears to play a role. No contributing factors in black males and females were found, and needs further elucidation. © 2011 American Society for Bone and Mineral Research.

KEY WORDS: FRACTURES; BONE DENSITOMETRY; PHYSICAL ACTIVITY; SOUTH AFRICA; CHILDREN; BONE MASS

Introduction

Adult studies have documented ethnic differences in bone mass and fracture risk.[1,2] African American adults fracture less and have greater areal bone mineral density (BMD) than white adults,[1] and similarly, South African black women have greater hip bone mass[3,4] and fracture less compared to South African white women.[5]

We have previously shown that South African black children fracture less than white children[6] and at various ages have greater BMD than their white peers at some sites.[7–10] Recently, Micklesfield and colleagues[11] have reported that South African black children, despite having a lower body weight than white children at age 13 years, have greater diaphyseal bone strength, as measured by peripheral quantitative computed tomography (pQCT). This could possibly explain the lower fracture incidence previously reported in South African black children. The role of lifestyle factors such as physical activity in determining bone mass differences has been investigated by McVeigh and colleagues,[10] who showed an association between physical activity and bone mineral content (BMC) and BMD only in South African white children at 9 years of age in the same cohort. No such relationship was found in black children of the same age.

In South African children, differences in bone mass and geometry, and physical activity between the ethnic groups may be contributing risk factors for the different fracture rates observed. Recent studies in the United Kingdom conclude that white children have significantly higher fracture rates than other ethnic groups but the reasons as to why have not been elucidated.[12,13] To our knowledge there are no studies that have investigated the contribution of bone mass and physical activity to ethnic differences in fracture risk. Therefore, the aim of this

Received in original form April 28, 2011; revised form July 11, 2011; accepted July 29, 2011. Published online August 23, 2011.
Address correspondence to: Kebashni Thandrayen, MBBCh, FCPaed(SA), Mmed, Department of Paediatrics, Chris Hani Baragwanath Hospital, PO Bertsham 2013, South Africa. E-mail: kebashni.thandrayen@wits.ac.za

Journal of Bone and Mineral Research, Vol. 26, No. 12, December 2011, pp 2834–2842
DOI: 10.1002/jbmr.491
© 2011 American Society for Bone and Mineral Research

study was to investigate the associations between fracture prevalence, bone mass, body composition, and physical activity in urban South African children.

Methods

Study population

Data from 533 children from the Bone Health subcohort of the Birth to Twenty (Bt20) longitudinal study of child health and development were used. All eligible children (3273) born within a 7-week period (April 23 to June 8, 1990) in the greater Johannesburg metropolitan area in South Africa were originally recruited for the Bt20 study. The cohort profile has been previously described by Richter and colleagues.[14] The child's ethnic classification was defined by the race classification currently in use in South Africa for demographic and restitution purposes. Although the South African government currently classifies race into black (ethnic Africans), white (Europeans, Jews, and Middle Easterners), colored (mixed race), and Indian (Asian), only children for whom both parents were classified as either white or black were included in this study. The Bone Health study was constituted as a subcohort of Bt20 when the children were 9 years of age to investigate in more detail factors influencing bone mass accretion during puberty and adolescence. A supplementary sample of 120 white children born during the same period was recruited at the age of 10 years to increase the white sample size. These supplementary 120 white children were born during the cohort enrolment dates, but not in the area; however, there were no differences in birth weight, maternal age and education, and socioeconomic status between the supplementary children and the original white participants of the cohort.

Children who had chronic illnesses such as asthma and epilepsy were not included in the bone health subcohort, as the use of certain medications and immobility are associated risk factors for low bone mass and may increase the incidence of fractures. Participants were born prior to the human immunodeficiency virus (HIV) epidemic in South Africa and thus were unlikely to suffer from HIV or tuberculosis. The reported child mortality in the original Birth to Twenty cohort of some 3200 participants by age 10 years was 28 participants and this number had increased to 40 by age 15 years. The cause of death was mainly accident/trauma related. Thus the bone mass demographics were unlikely to be affected by chronic illnesses or death. All subjects provided assent and their parents/guardian provided written, informed consent; ethical approval was obtained from the University of Witwatersrand Committee for Research on Human Subjects.

Fracture questionnaire

A fracture questionnaire was completed by each adolescent with the help of his/her parent or guardian at age 15 years. The questionnaire included information about previous fractures, their sites with the aid of a skeletal diagram, and the causes and age at fracture. Due to the retrospective nature of the fracture data collection, the fractures could not be verified by X-ray.

Anthropometric measurements, skeletal maturity, and dual-energy X-ray absorptiometry–derived parameters

Anthropometric measurements, skeletal maturity, and bone mass data were obtained annually but data at age 10 years (pre- or early puberty) and 15 years (mid- or late puberty) were used for this study. Height was measured to the nearest millimeter using a stadiometer (Holtain, Crosswell, UK). Weight was measured to the last 100 g using a digital scale (Dismed, Halfway House, South Africa) with participants wearing light clothing and no shoes. Skeletal maturity was assessed by a trained expert by scoring bone age from hand radiographs using the Tanner-Whitehouse bone-specific scoring technique (TWIII 20).[15]

Total body less head bone area (TBLH BA), total body less head bone mineral content (TBLH BMC), whole body composition (fat mass and lean mass), and site-specific measurements of bone area (BA) and BMC at the radius (R), hip (H), hip neck (HN), and lumbar spine (LS) were performed using an Hologic QDR 4500A dual-energy X-ray absorptiometer (DXA) (Hologic, Inc., Waltham, MA, USA) according to standard procedures (software version 11.2; Hologic).

Assessment of physical activity levels

Questionnaires quantifying total physical activity (PA) for the previous 12 months were administered at ages 10 and 15 years via interview. The questionnaire was modified from previous studies to be appropriate for South African children and results obtained on this cohort at 9 years of age have been published previously.[10] The intensity, frequency, and duration of all physical activities (physical education, extramural school and club sport, informal physical activity, and active commuting to and from school) and sedentary activities were recorded. Formal activities were inclusive of sporting activities at school and club level, and informal activities included play activities at home or in the neighborhood outside of school. Physical activity was scored in minutes per week multiplied by metabolic equivalents (MET, 1 MET is defined as the energy expenditure for sitting quietly, which for the average adult is approximately 3.5 mL of oxygen/kg body weight/min) according to the classification of Ainsworth and colleagues,[16] to obtain a measure of physical activity related energy expenditure (METmins/week). The total, formal, and informal physical activity scores were thereafter converted to *Z*-scores by using the largest nonfracture group (black females) as the reference group for comparison between those who did and did not sustain a fracture.

Statistical analyses

Data were analyzed using the Statsoft (Statistica v7.0, 2006; Statsoft, Inc., Tulsa, OK, USA) package. Individual anthropometric measurements (height-for-age *Z*-score [HAZ] and body mass index [BMI]-for-age *Z*-score [BAZ]) were calculated using the World Health Organization (WHO) Anthroplus software (http://www.who.int/growthref/tools/en). Using logistic regression analyses, ethnicity and sex were found to be important factors predicting fracture risk in the entire cohort; therefore, analyses were performed for each sex and ethnic group separately. Data

were summarized as means (standard deviations [SDs]) or medians (interquartile range), depending on the distribution. Comparisons were made between those who had and had not fractured within the same sex and ethnic group using chi-square analysis. A p value of <0.05 was considered to be statistically significant. The largest nonfracturing group (black females) were used as the control or reference group to compare with other groups for whole-body composition and bone mass measurements and physical activity scores. Individual whole-body composition measurements were compared with the control group (nonfracturing black females) by calculating Z-scores, by subtracting the control mean from the participant's specific measurement and dividing by the control SD. Bone mass, height, and weight variables were log-transformed, then BA and BMC were adjusted for height and weight of the whole cohort using multiple regression analyses. Thereafter, Z-scores for BA and BMC of each of the sexes and ethnic groups were derived using data from nonfracturing black females as the control. Unadjusted physical activity Z-scores were derived from the control group. Fracture rates were calculated as the number of subjects who reported a fracture or the number of fractures divided by total person-time of observation.

Results

Fracture patterns

Of the 533 subjects in the cohort at 15 years of age, 186 (35%) were white (W) and 347 (65%) were black (B). The total number of children who sustained fractures over the first 15 years of life was 130 (24%). Of the 130 children reporting fractures, 70% had sustained a single fracture and 30% had had more than one fracture.

The percentage of white children who reported a fracture in the first 15 years of life was 41.5% ($n = 78$) compared to 15% ($n = 52$) in black children ($p < 0.001$). The proportions of white males (WM) and females (WF) who had fractured were significantly higher than for black males (BM) and females (BF), respectively (WM 47% versus BM 37%; $p < 0.001$ and WF 18% versus BF 11%; $p < 0.001$).

The overall fracture rate for the first 15 years of life was 23 per 1000 children per annum. White males had the highest fracture rates per annum followed by white females and then black males and females (Table 1).

The fracture incidence rates for all sites except the lower limb were significantly higher in the white population (Fig. 1). The most common site of fracture for the entire cohort was the upper limb (48%).

Table 1. Fracture Rates Over the First 15 Years of Life

Ethnic group	Fracture rate per 1000 children per annum	95% Confidence intervals
White males	52.4*	28.3–76.5
Black males	14.4	7.6–21.3
White females	37.1**	24.6–49.5
Black females	8.4	4.1–12.7

*$p < 0.01$ between white and black males.
**$p < 0.001$ between white and black females.

Anthropometric and whole body composition characteristics

Ethnicity ($p < 0.001$) and sex ($p = 0.024$) were shown by logistic regression (data not shown) to be important predictors of fracture risk in the entire cohort, thus further analyses were performed within the same sex and ethnic groups. Complete anthropometric and whole body composition measurements were available on 304 of the 347 black children with fracture data at mean age of 10.5 years and on 332 of the 347 children at mean age of 15.5 years. Seven of the 43 black children (16%) at age 10 years and 2 of the 15 (13%) at age 15 years with incomplete data had reported a fracture (proportions very similar to those with complete data, suggesting no selection bias in those used in the analyses).

Comparing the same ethnic and sex groups with and without fractures, there were no statistically significant differences in anthropometry or body composition measurements at age 10 or 15 years between black males or females with and without a history of fractures at age 15 years (Table 2). Comparing body mass variables of black males with those of nonfracturing black females, black males at 10 years and 15 years had a lower fat mass ($p < 0.001$) and at 15 years had a greater lean mass ($p < 0.001$) (Table 2).

Complete anthropometric and whole-body composition measurements were available from 101 of the 186 white children with fracture data at a mean age of 10.6 years and from 116 of the 186 white children at a mean age of 15.7 years. The major reason for the lack of complete data at the two time points was an unwillingness of parents or children to take time off from school for the DXA and radiological studies. Thirty-four of the 85 white children (40%) at age 10 years and 34 of the 70 (48.5%) at age 15 years with incomplete data had reported a fracture (proportions very similar to those with complete data, suggesting no selection bias in those used in the analyses).

Comparing the same ethnic and sex groups with and without fractures, white males who had fractured in the first 15 years of life were significantly taller ($p < 0.01$) and had a higher lean body mass ($p = 0.01$) at the age of 10 years, and remained with greater lean mass ($p < 0.001$) at age 15 years compared to their nonfracturing peers (Table 2). White females who had fractured had a higher lean body mass at age 15 ($p < 0.05$) and a higher BMI at age 10 years ($p = 0.05$) and 15 years ($p < 0.05$) compared to the white females who had not fractured (Table 3).

Comparing body mass variables of the different ethnic and sex groups with those of nonfracturing black females, white males at 10 and 15 years and white females at 15 years had a greater lean mass (Table 3).

Associations between fractures, bone mass characteristics, and physical activity

TBLH BA and TBLH BMC Z-scores adjusted for height and weight at 10 and 15 years of age were compared between the controls and the other sex and ethnic groups; and within the same sex

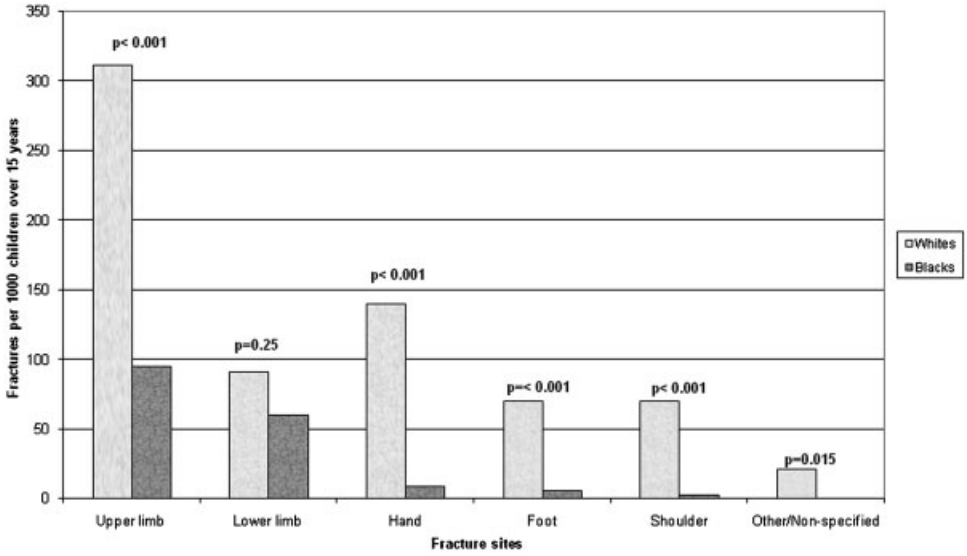


Fig. 1. Fracture incidence rates per annum at the different fracture sites in white and black children.

and ethnic groups for those who did and did not report a fracture during the first 15 years of life (Tables 4 and 5).

Comparing the same ethnic and sex groups with and without fractures, white males who reported a previous fracture/s during the first 15 years of life had greater BA and BMC at all sites at age 10 years (Table 4), and at 15 years (Table 5) than their nonfracturing peers. There were no significant differences in either BA or BMC at age 10 or 15 years in black or white females or in black males between those who did or did not fracture at age 10 and 15 years (Tables 4 and 5).

Comparing bone mass variables of the different ethnic and sex groups with those of nonfracturing black females, white males with fractures and white females with and without fractures at 10 years had greater BA and BMC at most sites and black males without fracture had lower BA and BMC at all sites (Table 4). The number of black males with fractures was too small to make a meaningful comparison. At 15 years, all white males and females and black males had greater BA and BMC compared to the nonfracturing black female controls (Table 5).

Table 6 compares total physical activity *Z*-scores (combining formal and informal activities) at ages 10 and 15 years between children with and without a history of fractures at age 15 years. White males who reported a fracture during the first 15 years of life participated in more physical activity at age 10 years (formal only; $p < 0.05$) and at 15 years (total and informal; $p < 0.05$ and $p < 0.01$, respectively) compared to white males with no fracture history. Fracture risk was positively associated with physical activity; at age 15 years for every 1 SD increase in formal physical activity (*Z*-score of METmins/week) the odds ratio for fracturing was 2.2 (95% CI, 1.22–3.97; $p < 0.01$) and for every 1 SD increase in total physical activity (*Z*-score METmins/week) the odds ratio for fracturing was 1.78 (95% CI, 1.06–3.00; $p < 0.05$). There was no

Table 2. Anthropometric and Body Composition Measurements at 10 and 15 Years of Age of Black Males and Females With and Without a History of Fractures at 15 Years of Age

	Black females at 10 years		Black females at 15 years		Black males at 10 years		Black males at 15 years	
	Without fractures ($n = 128$)	With fractures ($n = 16$)	Without fractures ($n = 140$)	With fractures ($n = 17$)	Without fractures ($n = 131$)	With fractures ($n = 29$)	Without fractures ($n = 142$)	With fractures ($n = 33$)
Chronological age (years)	10.5 (0.26)	10.5 (0.28)	15.6 (0.24)	15.5 (0.25)	10.6 (0.27)	10.5 (0.28)	15.6 (0.26)	15.5 (0.28)
Bone age (years)	9.9 (1.10)	9.8 (0.88)	14.7 (0.62)	14.7 (0.50)	9.9 (0.70)	9.9 (0.76)	14.8 (1.30)	14.73 (1.16)
HAZ score[a]	−0.41 (0.95)	−0.67 (0.65)	−0.48 (0.89)	−0.52 (0.99)	−0.52 (0.90)	−0.41 (1.04)	−0.13 (0.97)	0.04 (1.01)
BAZ score[a]	0.16 (1.21)	−0.28 (0.91)	0.60 (1.10)	0.16 (0.94)	0.07 (1.12)	−0.11 (0.94)	0.02 (1.13)	−0.14 (1.05)
Lean mass *Z*-score[b]	0.00 (1.00)	−0.46 (0.43)	0.00 (1.00)	−0.37 (0.48)	0.02 (0.80)	−0.08 (0.72)	1.51 (1.35)*	1.38 (1.16)*
Fat mass *Z*-score[b]	0.00 (1.00)	−0.33 (0.53)	0.00 (1.00)	−0.29 (0.49)	−0.52 (0.82)*	−0.61 (0.48)*	−1.06 (0.93)*	−1.09 (0.79)*

Data presented as mean (SD). There were no significant differences within the same sex and age groups.
HAZ = height age *Z*-score; BAZ = BMI age *Z*-score.
[a]Computed using WHO Anthroplus software.
[b]The *Z*-scores of lean and fat masses of each ethnic and sex groups were derived from the values obtained from the black nonfracturing females.
*$p < 0.001$ significant differences in lean and fat mass *Z*-scores comparing nonfracturing black females to other ethnic and sex group.

Table 3. Anthropometric and Body Composition Measurements at 10 and 15 Years of Age of White Males and Females With and Without a History of Fractures at 15 Years of Age

	White females at 10 years		White females at 15 years		White males at 10 years		White males at 15 years	
	Without fractures ($n = 28$)	With fractures ($n = 20$)	Without fractures ($n = 44$)	With fractures ($n = 19$)	Without fractures ($n = 29$)	With fractures ($n = 24$)	Without fractures ($n = 30$)	With fractures ($n = 23$)
Chronological age (years)	10.6 (0.27)	10.6(0.27)	15.7(0.28)	15.7 (0.26)	10.6 (0.22)	10.7 (0.25)	15.7 (0.24)	15.74 (0.25)
Bone age (years)	10.0 (1.24)	10.2 (1.26)	14.6 (0.71)	14.8 (0.48)	10.1 (0.66)	10.2 (0.72)	15.3 (1.06)[c]	15.8 (0.86)
HAZ score[a]	0.17 (1.16)	0.20 (1.17)	0.51 (1.03)	0.25 (1.01)	−0.08 (1.15)[d]	0.88 (1.11)	0.43 (1.11)	0.90 (1.08)
BAZ score[a]	−0.12 (1.06)[c]	0.52 (1.11)	0.13 (0.94)[c]	0.73 (1.07)	0.01 (0.86)	0.29 (1.06)	0.02 (0.76)	0.49 (1.02)
Lean mass *Z*-score[b]	0.34 (1.04)	0.63 (1.15)[g]	0.51 (0.96)[c,f]	1.18 (1.30)[h]	0.36 (0.83)[d,f]	1.12 (0.77)[h]	2.78 (1.60)[e,h]	4.05 (1.51)[h]
Fat mass *Z*-score[b]	−0.14 (0.77)[f]	0.27 (0.90)[h]	−0.27 (0.71)	0.15 (1.17)	−0.53 (0.50)[g]	−0.28 (0.66)	−1.09 (0.78)[h]	0.87 (0.75)[h]

Data presented as mean (SD).
HAZ = height age *Z*-score; BAZ = BMI age *Z*-score; BMI = body mass index; WHO = World Health Organization.
[a]Computed using WHO Anthroplus software.
[b]The *Z*-score of lean and fat masses of each ethnic and sex groups were derived from the values obtained from the black nonfracturing females.
[c]$p \leq 0.05$.
[d]$p < 0.01$.
[e]$p < 0.001$: significant differences within the same sex and age groups.
[f]$p < 0.05$.
[g]$p < 0.01$.
[h]$p < 0.001$: significant differences in lean and fat mass *Z*-scores comparing nonfracturing black females to other ethnic and sex groups.

Table 4. Bone Area and Bone Mineral Content *Z*-Scores (Adjusted for Height and Weight) at 10 Years of Age With and Without a History of Fractures at Age 15 Years

	Females at 10 years				Males at 10 years			
	Blacks		Whites		Blacks		Whites	
Bone mass measurements (Z scores)	Without fractures ($n = 128$)	With fractures ($n = 16$)	Without fractures ($n = 28$)	With fractures ($n = 19$)	Without fractures ($n = 130$)	With fractures ($n = 29$)	Without fractures ($n = 29$)	With fractures ($n = 24$)
TBLH BA	0.00 (1.00)	−0.36 (0.52)	0.32 (1.01)	0.59 (1.14)[c]	−0.30 (0.88)[d]	−0.33 (0.72	**0.11 (0.93)**[b]	**0.78 (0.79)**[e]
R 1/3 BA	0.00 (1.00)	−0.33 (0.53)	0.45 (1.07)[c]	0.63 (1.19)[d]	−0.31 (0.92)[d]	−0.30 (0.84)	**0.21 (1.02)**[b]	**0.95 (0.90)**[e]
R mid BA	0.00 (1.00)	−0.30 (0.55)	0.54 (1.11)[d]	0.65 (1.21)[d]	−0.32 (0.94)[c]	−0.28 (0.92)	**0.27 (1.06)**[b]	**1.05 (0.97)**[e]
R ultra distal BA	0.00 (1.00)	−0.28 (0.57)	0.59 (1.13)[d]	0.66 (1.22)[d]	−0.32 (0.96)[c]	−0.26 (0.98)	**0.31 (1.09)**[b]	**1.11 (1.02)**[e]
R total BA	0.00 (1.00)	−0.30 (0.55)	0.54 (1.11)[d]	0.65 (1.21)[d]	−0.32 (0.94)[c]	−0.28 (0.93)	**0.27 (1.06)**[b]	**1.05 (0.97)**[e]
H BA	0.00 (1.00)	−0.26 (0.59)	0.63 (1.15)[d]	0.66 (1.22)[d]	−0.31 (0.97)[c]	−0.25 (1.01)	**0.33 (1.11)**[b]	**1.15 (1.06)**[e]
HN BA	0.00 (1.00)	−0.31 (0.54)	0.50 (1.10)[c]	0.65 (1.20)[d]	−0.32 (0.93)[d]	−0.29 (0.89)	**0.24 (1.04)**[b]	**1.01 (0.94)**[e]
LS BA	0.00 (1.00)	−0.21 (0.64)	0.69 (1.16)[d]	0.66 (1.21)[d]	−0.30 (1.00)[c]	−0.21 (1.09)	**0.39 (1.13)**[b]	**1.22 (1.13)**[e]
TBLH BMC	0.00 (1.00)	−0.36 (0.53)	0.31 (1.00)	0.58 (1.14)[c]	−0.30 (0.87)[d]	−0.33 (0.71)	**0.10 (0.92)**[b]	**0.76 (0.78)**[e]
R 1/3 BMC	0.00 (1.00)	−0.35 (0.52)	0.38 (1.04)	0.61 (1.17)[d]	−0.31 (0.89)[d]	−0.32 (0.77)	**0.15 (0.96)**[b]	**0.85 (0.83)**[e]
R mid BMC	0.00 (1.00)	−0.33 (0.53)	0.45 (1.08)[c]	0.63 (1.19)[d]	−0.31 (0.92)[d]	−0.31 (0.84)	**0.20 (1.02)**[b]	**0.95 (0.89)**[e]
R ultra distal BMC	0.00 (1.00)	−0.36 (0.53)	0.29 (1.00)	0.57 (1.13)[c]	−0.30 (0.87)[d]	−0.33 (0.70)	**0.09 (0.91)**[a]	**0.75 (0.78)**[e]
R total BMC	0.00 (1.00)	−0.34 (0.53)	0.41 (1.06)[c]	0.62 (1.18)[d]	−0.31 (0.90)[d]	−0.31 (0.81)	**0.18 (0.99)**[b]	**0.90 (0.86)**[e]
H BMC	0.00 (1.00)	−0.33 (0.53)	0.45 (1.07)[c]	0.63 (1.19)[d]	−0.31 (0.91)[d]	−0.30 (0.83)	**0.20 (1.01)**[b]	**0.94 (0.89)**[e]
HN BMC	0.00 (1.00)	−0.37 (0.53)	0.26 (0.99)	0.56 (1.12)[c]	−0.29 (0.86)[d]	−0.34 (0.68)	**0.07 (0.89)**[a]	**0.70 (0.76)**[e]
LS BMC	0.00 (1.00)	−0.31 (0.54)	0.50 (1.10)[c]	0.64 (1.21)[d]	−0.32 (0.93)[d]	−0.30 (0.88)	**0.24 (1.04)**[b]	**1.00 (0.93)**[e]

Data presented as mean (SD). Bold values denote significant differences in BA and BMC Z-scores comparing nonfracturing and fracturing white males.
BA = bone area; BMC = bone mineral content; TBLH = total body less head; R = radius; H = total hip; HN = hip neck; LS = lumbar spine.
[a]$p < 0.05$.
[b]$p < 0.01$, significant differences within the same sex and age group.
[c]$p < 0.05$.
[d]$p < 0.01$.
[e]$p < 0.001$: significant differences in BA and BMC *Z*-scores comparing nonfracturing black females to fracturing and nonfracturing white males, white females, and black males, respectively.

Table 5. Bone Area and Bone Mineral Content *Z*-Scores (Adjusted for Height and Weight) at 15 Years of Age With and Without a History of Fractures at Age 15 Years

	Females at 15 years				Males at 15 years			
	Blacks		Whites[a]		Blacks[b]		Whites[c]	
Bone mass measurements (*Z*-scores)	Without fractures ($n = 147$)	With fractures ($n = 19$)	Without fractures ($n = 45$)	With fractures ($n = 20$)	Without fractures ($n = 146$)	With fractures ($n = 33$)	Without fractures ($n = 30$)	With fractures ($n = 25$)
TBLH BA	0.00 (1.00)	−0.20 (0.65)	0.60 (0.92)	0.90 (1.23)	0.64 (1.13)	0.72 (0.94)	**1.61 (1.13)**[e]	**2.43 (1.01)**
R 1/3 BA	0.00 (1.00)	−0.01 (1.02)	1.03 (1.02)	1.05 (1.25	1.19 (1.19)	1.38 (1.25)	**2.33 (1.23)**[e]	**3.12 (1.21)**
R mid BA	0.00 (1.00)	−0.04 (0.98)	0.99 (1.01)	1.05 (1.26)	1.14 (1.19)	1.31 (1.22)	**2.27 (1.23)**[e]	**3.08 (1.19)**
R ultra distal A	0.00 (1.00)	−0.08 (0.90)	0.92 (1.00)	1.03 (1.26)	1.04 (1.19)	1.20 (1.16)	**2.16 (1.22)**[e]	**2.98 (1.16)**
R total BA	0.00 (1.00)	−0.04 (0.97)	0.99 (1.01)	1.05 (1.26)	1.13 (1.19)	1.30 (1.22)	**2.26 (1.23)**[e]	**3.07 (1.19)**
H BA	0.00 (1.00)	0.04 (1.10)	1.10 (1.03)	1.05 (1.23)	1.29 (1.19)	1.49 (1.30)	**2.41 (1.22)**[d]	**3.16 (1.23)**
HN BA	0.00 (1.00)	−0.04 (0.97)	0.99 (1.01)	1.05 (1.26)	1.13 (1.19)	1.31 (1.22)	**2.26 (1.23)**[e]	**3.07 (1.19)**
LS BA	0.00 (1.00)	0.02 (1.07)	1.08 (1.03)	1.05 (1.24)	1.26 (1.19)	1.46 (1.29)	**2.39 (1.22)**[d]	**3.15 (1.23)**
TBLH BMC	0.00 (1.00)	−0.21 (0.61)	0.55 (0.91)	0.87 (1.22)	0.58 (1.12)	0.65 (0.91)	**1.52 (1.11)**[e]	**2.33 (0.99)**
R 1/3 BMC	0.00 (1.00)	−0.12 (0.81)	0.81 (0.97)	0.99 (1.26)	0.91 (1.17)	1.03 (1.09)	**1.99 (1.20)**[e]	**2.82 (1.11)**
R mid BMC	0.00 (1.00)	−0.16 (0.74)	0.72 (0.95)	0.96 (1.25)	0.80 (1.16)	0.91 (1.03)	**1.84 (1.17)**[e]	**2.67 (1.07)**
R ultra distal BMC	0.00 (1.00)	−0.27 (0.52)	0.35 (0.86)	0.74 (1.18)	0.33 (1.07)	0.35 (0.80)	**1.13 (1.03)**[e]	**1.89 (0.90)**
R total BMC	0.00 (1.00)	−0.18 (0.69)	0.66 (0.93)	0.93 (1.24)	0.72 (1.14)	0.81 (0.98)	**1.72 (1.15)**[e]	**2.54 (1.04)**
H BMC	0.00 (1.00)	−0.11 (0.85)	0.85 (0.98)	1.01 (1.26)	0.96 (1.18)	1.10 (1.11)	**2.06 (1.20)**[e]	**2.89 (1.13)**
HN BMC	0.00 (1.00)	−0.22 (0.61)	0.55 (0.91)	0.87 (1.22)	0.57 (1.11)	0.64 (0.91)	**1.51 (1.11)**[e]	**2.32 (0.99)**
LS BMC	0.00 (1.00)	−0.23 (0.58)	0.50 (0.89)	0.84 (1.21)	0.51 (1.10)	0.57 (0.88)	**1.42 (1.10)**[e]	**2.21 (0.96)**

Data presented as mean (SD). Bold values denote significant differences in BA and BMC Z-scores comparing nonfracturing and fracturing white males.
BA = bone area; BMC = bone mineral content; TBLH = total body less head; R = radius; H = total hip; HN = hip neck; LA = lumbar spine.
[a] $p < 0.05$ for all BA and BMC *Z*-scores between nonfracturing black females and white females with and without fractures.
[b] $p < 0.01$ for all BA and BMC *Z*-scores between nonfracturing black females and black males with and without fractures except for the RA ultra distal BMC *Z*-score in black males with fractures.
[c] $p < 0.001$ for all BA and BMC *Z*-scores between nonfracturing black females and white males with and without fractures.
[d] $p < 0.05$.
[e] $p < 0.01$, significant differences within the same sex and age group.

significant difference in physical activity at age 10 or 15 years in black or white females or in black males between those who did or did not report a previous fracture.

Discussion

This is the first study to demonstrate heterogeneity in the pathogenesis of fractures in children of different ethnic groups. White males who reported a previous fracture were more physically active at ages 10 and 15 years and had greater BA and BMC at the same ages at all sites than their nonfracturing white peers. Thus increased physical activity seems to be the key contributory factor in the pathogenesis of fractures in white urban South African males. These differences were not present in white females or in black children; however, in white females, BMI and lean mass appeared to be contributory factors. The association with BMI in females has been reported in other studies,[17,18] but the differences in lean mass have not been reported previously. No anthropometric or bone mass and size factors were found to be associated with fractures in black children when performing comparisons within the same sex and ethnic groups. Comparing body and bone mass variables of the different ethnic and sex groups with those of nonfracturing black females had shown that white males at 10 and 15 years, white females, and black males at 15 years had a greater lean mass; and white males and females and black males at 15 years had higher BA and BMC at all sites.

Our findings support those of Clark and colleagues[19] in a high-income country setting, who described the relationship between physical activity, bone mass, and fracture risk in mainly white Caucasian children (3.1% were of nonwhite ethnicity) and showed that despite having a higher BMD, daily or more vigorous physical activity increased fracture risk. To the best of our knowledge, the current study is the first to investigate the relationship between physical activity, bone mass, and fracture risk in children of different ethnic origins.

There are both bone-dependent and bone-independent factors that contribute to fracture risk in childhood.[20] Many studies have investigated the influence of physical activity, socioeconomic status, exposure to sunlight, breastfeeding in early life, and maternal smoking during childhood on bone mass.[21–24] Flynn and colleagues[25] prospectively followed 8-year-old children for 8 years and concluded that there was an inverse relationship between bone mass at 8 years of age and upper limb fracture risk at 16 years of age, and that overweight or obesity at 8 years of age was also associated with an increased risk of fracture. In the Avon Longitudinal Study of Parents and

Table 6. Total Physical Activity *Z*-Scores at 10 and 15 Years in Children With and Without a History of Fractures at Age 15 Years Compared to Nonfracturing Black Females

	Physical activity *Z*-scores																	
	10 years								15 years									
	Without fractures				With fractures				Without fractures				With fractures					
	n	Total	Formal	Informal	*n*	Total	Formal	Informal	*n*	Total	Formal	Informal	*n*	Total	Formal	Informal		
Black females	136	0.0 (−0.6 to 0.4)	−0.5 (−0.6 to 0.3)	0.0 (−0.7 to 0.4)	16	0.2 (−0.4 to 0.4)	0.0 (−0.6 to 0.5)	0.0 (−0.7 to 0.4)	145	−0.3 (−0.6 to 0.1)	−0.4 (−0.4 to −0.1)	−0.4 (−0.6 to 0.1)	18	−0.2 (−0.6 to 0.3)	−0.4 (−0.4 to 0.1)	−0.3 (−0.6 to −0.1)		
White females	28	−0.8 (−1.3 to −0.5)	0.4 (−0.6 to 3.0)	−1.1 (−1.3 to −0.8)	20	−0.8 (−1.2 to −0.5)	0.8 (−0.0 to 2.1)	−1.1 (−1.3 to −0.8)	38	0.0 (−0.6 to 1.1)	0.8 (−0.1 to 2.5)	−0.5 (−0.6 to 0.0)	18	−0.3 (−0.5 to 1.0)	0.2 (−0.2 to 1.7)	−0.4 (−0.6 to 0.3)		
Black males	129	0.2 (−0.3 to 0.8)	−0.3 (−0.6 to 1.7)	0.1 (−0.3 to 0.6)	31	0.2 (−0.2 to 1.0)	0.1 (−0.6 to −1.1)	0.1 (−0.3 to 0.6)	140	0.1 (−0.4 to 0.9)	0.01 (−0.4 to 1.1)	−0.1 (−0.5 to 0.3)	32	0.2 (−0.2 to 0.9)	0.6 (−0.4 to 1.5)	−0.3 (−0.6 to 0.5)		
White males	23	−0.7 (−1.0 to 0.4)	**0.8 (−0.2 to 2.2)**[a]	−0.7 (−1.2 to −0.1)	20	−0.5 (−0.9 to −0.2)	**1.7 (0.5 to 3.8)**	−0.7 (−1.2 to −0.1)	24	**0.0 (−0.5 to 0.6)**[a]	**0.2 (−0.3 to 0.9)**[b]	−0.2 (−0.4 to 0.6)	22	**0.8 (0.0 to 2.1)**	**1.6 (0.6 to 3.8)**	0.0 (−0.4 to 0.4)		

Data presented as median (interquartile range). Each of the physical activity components of the black nonfracturing females were used as the control to create *Z*-scores for the other sex and ethnic groups. Bold values denote significant differences in physical activity *Z*-scores comparing nonfracturing and fracturing white males.

[a] $p < 0.05$.

[b] $p < 0.01$: significant differences within the same sex and age.

Children (ALSPAC) prospective study, an 89% increased risk of fracture per 1 SD decrease in size-adjusted BMC at age 9.9 years was found.[26] Despite the inverse relationship observed between fracture risk and bone mass, Clark and colleagues[26] were the first to suggest that the higher bone mass associated with increased physical activity in children does not necessarily compensate for the increased exposure to injuries and higher fracture risk.[19] Studies indicate that African American and Hispanic children have a significantly higher bone strength than white children, due to greater bone density at the distal trabecular bone regions and greater bone density and area at the cortical sites of the radius and tibia[27]; the authors suggest that the differences in fracture rates reported between different ethnic groups in adulthood may be traced back to these differences in bone strength in childhood. Several studies on the Bt20 cohort have reported greater BMD in black compared to white children at 9 and 10 years of age[7–9] and more recently Micklesfield and colleagues[11] have shown that South African black children have greater bone strength as measured by pQCT; however, the association between fracture risk and bone strength or geometry in South African children has to be further investigated. We postulate that structural differences in bone geometry may provide protection against fractures in black South Africans.

We have previously shown in the Bt20 cohort that there was a significant difference in the grading of trauma associated with fractures between white and black children, with white children fracturing at more severe levels of trauma than black children.[6] McVeigh and colleagues[10] have shown in the same cohort that white males with the highest physical activity scores have a greater BMD. Therefore, although more physically active white males may have higher BMD, this does not appear to protect them from fracturing.

We have also previously documented that black children are less physically active than white children,[10] but this does not seem to negatively impact their bone mass because black children have a greater hip bone mass, and black girls have a greater lumbar spine bone mass, than their white peers.[10] Despite South African black children being less active and consuming a diet lower in calcium (whites 703–711mg/day versus blacks 297–331mg/day) than white children,[28] we have now shown that they fracture less as well. The complexities of bone turnover and geometry have to be further investigated in the different ethnic groups to explain the possible pathogenesis of ethnic differences in fracture rates and bone mass among children.

A higher BMI at 10 and 15 years of age was the only difference between white females with and without a history of fractures. There were no significant differences in any bone mass or anthropometric measurements in black females with and without fractures. The Dortmund Nutritional and Anthropometric Longitudinal Designed (DONALD) study conducted in Germany on healthy children highlighted the inverse association between the accrual of bone mass and subcutaneous adipose tissue in prepubertal females and found that pubertal females with relatively high subcutaneous fat area (high ratio fat area/fat mass) were characterized by lower bone strength.[17] Our finding of increased adiposity being associated with greater fracture risk

in white girls is in keeping with previous studies conducted in white individuals. Goulding and colleagues[18] found that girls with fractured forearms are often overweight and those with recurrent fractures and high body weight have a substantially higher fracture risk than girls with a history of a single fracture.[29] We have yet to investigate the reasons why increased adiposity in white females is associated with increased fracture risk. No previous studies have compared body composition characteristics and fracture risks in black individuals and this is the first study to suggest that there does not appear to be an association between fat mass, or adiposity, and fracture risk in black girls or boys, despite an increasing (but similar) prevalence of overweight or obesity in both black and white females. At age 15 years, 24% of BF were overweight and 8% were obese; 22% of WF were overweight and 5% were obese; 8% of BM were overweight and 7.5% were obese; and 14% of WM were overweight and 4% were obese.

There are three potential limitations to this study: first, the small number of subjects in the white group, which was influenced by the original sampling method that represented the demographics of racial proportions in urban South Africa. Despite the small number of white children we were able to document statistically significant differences in bone size and area and physical activity between the white boys who did and did not fracture. Further, in white girls we were able to show an association between adiposity and fracture risk.

Second, we did not adjust for potential modifiers (socioeconomic, nutrition, and vitamin D status). Vidulich and colleagues[7] found no effect of nutritional factors on bone mass and stated that the site-specific ethnic differences in bone mass were not the result of poor nutrition or poorer households in South African black children but suggested rather that genetic factors might play a role. Poopedi and colleagues[30] found no significant relationship between vitamin D status and BMC in either black and white subjects in the same cohort; however, an inverse relationship between fat mass and 25-hydroxyvitamin D was found in both black and white children.[31] Despite black children having lower levels of 25-hydroxyvitamin D than white children, this does not appear to influence their bone health.[30]

Third, the lack of radiological confirmation of fractures might be considered a limitation of this study; the fracture rates for whites and blacks previously reported from the Bt20 cohort were similar to those reported in the current smaller subcohort and the previous findings were similar between the ethnic groups at all ages. Furthermore, fracture data that had been previously collected at year 13 and those collected in the current year-15 questionnaires confirmed the previous fracture rates. The use of skeletal diagrams also verified the site of fracture and were filled in with the help of the parent or caregiver for accuracy and completeness. Although there was no available radiological proof of fractures, both public and private health facilities in urban areas would have performed radiological assessments to confirm fractures, so self-reported data are likely to be reliable. Despite the lack of X-ray verification, there are no known systematic differences in the presentation of children from the different ethnic groups with fractures. All children less than 6 years old receive free health care at public hospitals and only a minimal fee for those older than 6 years is charged. Furthermore, primary and community health care clinics offer free services to all, thus individuals of a lower socioeconomic status can seek medical attention without any hindrance when warranted; it is therefore unlikely that fractures go undiagnosed. Unfortunately, there are no data available to confirm this.

In view of the more complete bone mass measurements for the black as opposed to the white children, there may be a potential ascertainment bias with regard to the bone mass findings; however, because the proportions of fractures in participants with fracture but no bone mass measurements are similar to those with bone mass measurements in both the black and white children, this bias is highly unlikely.

The present study did not explore ethnic differences in bone geometry and volumetric BMD measurements using peripheral quantitative computed tomography, or their relationship to fractures; it is possible that further insights into the reasons for the ethnic differences in fracture risk may come to light.

Conclusions

The pathogenesis of fractures in South African children appears to differ between ethnic groups. The white males with fractures were taller and had greater lean tissue mass than their nonfracturing peers. However, it appears that increased physical activity (formal sport), possibly leading to a greater opportunity for injury, is the contributory factor to the increased incidence of fractures despite greater bone mass and size. In white females with fractures, a higher BMI was found, in keeping with other studies. No such associations between physical activity or body composition and fractures were found in the black children. Further studies are necessary to investigate the relationship between bone geometry and fracture risk in children of different ethnic groups worldwide to determine whether genetic or other environmental factors are important contributory factors.

Disclosures

All authors state that they have no conflicts of interest.

Acknowledgments

Birth to Twenty is funded by the Wellcome Trust (UK), Medical Research Council of South Africa, Human Sciences Research Council of South Africa, National Research Foundation, and the University of the Witwatersrand, Johannesburg. We are grateful to all the participants and their families in this study, and to the entire Birth to Twenty team, which includes interviewers, technicians, clerical workers, research scientists, nurses, and receptionists.

Authors' roles: KT was involved in the conception, acquisition of data, analysis, and interpretation of data and drafting of manuscript and approval of the final version of submitted manuscript. SAN, LKM, and JMP were involved in the design, critical revision, and approval of the final version of the submitted manuscript.

References

1. Cauley JA, Lui LY, Ensrud KE, Zmuda JM, Stone KL, Hochberg MC, Cummings SR. Bone mineral density and the risk of incident nonspinal fractures in black and white women. JAMA. 2005;293: 2102–8.
2. Looker AC, Melton LJ III, Harris TB, Borrud LG, Shepherd JA. Prevalence and trends in low femur bone density among older US adults: NHANES 2005–2006 compared with NHANES III. J Bone Miner Res. 2010;25:64–71.
3. Daniels ED, Pettifor JM, Schnitzler CM, Russell SW, Patel DN. Ethnic differences in bone density in female South African nurses. J Bone Miner Res. 1995;10:359–67.
4. Chantler S, Dickie K, Goedecke JH, Levitt NS, Lambert EV, Evans J, Joffe Y, Micklesfield LK. Site-specific differences in bone mineral density in black and white premenopausal South African women. Osteoporos Int. 2011 Mar 3. [Epub ahead of print].
5. Solomon L. Osteoporosis and fracture of the femoral neck in the South African Bantu. J Bone Joint Surg Br. 1968;50:2–13.
6. Thandrayen K, Norris SA, Pettifor JM. Fracture rates in urban South African children of different ethnic origins: the Birth to Twenty cohort. Osteoporos Int. 2009;20:47–52.
7. Vidulich L, Norris SA, Cameron N, Pettifor JM. Differences in bone size and bone mass between black and white 10-year-old South African children. Osteoporos Int. 2006;17:433–40.
8. Micklesfield LK, Norris SA, Nelson DA, Lambert EV, van der Merwe L, Pettifor JM. Comparisons of body size, composition, and whole body bone mass between North American and South African children. J Bone Miner Res. 2007;22:1869–77.
9. Micklesfield LK, Norris SA, van der Merwe L, Lambert EV, Beck T, Pettifor JM. Comparison of site-specific bone mass indices in South African children of different ethnic groups. Calcif Tissue Int. 2009;85:317–25.
10. McVeigh JA, Norris SA, Cameron N, Pettifor JM. Associations between physical activity and bone mass in black and white South African children at age 9 yr. J Appl Physiol. 2004;97:1006–12.
11. Micklesfield LK, Norris SA, Pettifor JM. Determinants of bone size and strength in 13-year-old South African children: the influence of ethnicity, sex and pubertal maturation. Bone. 2011;48:777–85.
12. Clark EM, Ness AR, Tobias JH. Bone fragility contributes to the risk of fracture in children, even after moderate and severe trauma. J Bone Miner Res. 2008;23:173–9.
13. Rowe R, Maughan B, Goodman R. Childhood psychiatric disorder and unintentional injury: findings from a national cohort study. J Pediatr Psychol. 2004;29:119–30.
14. Richter L, Norris S, Pettifor J, Yach D, Cameron N. Cohort profile: Mandela's children: the 1990 Birth to Twenty Study in South Africa. Int J Epidemiol. 2007;36:504–11.
15. Tanner JM, Healy M, Goldstein H, Cameron N. *Assessment of skeletal maturity and prediction of adult height (TW3 method)*. 3rd ed. London: WB Saunders, Harcourt Publishers Ltd; 2001. 128 p.
16. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR Jr, Schmitz KH, Emplaincourt PO, Jacobs DR Jr, Leon AS. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc. 2000;32:S498–504.
17. Fricke O, Land C, Semler O, Tutlewski B, Stabrey A, Remer T, Schoenau E. Subcutaneous fat and body fat mass have different effects on bone development at the forearm in children and adolescents. Calcif Tissue Int. 2008;82:436–44.
18. Goulding A, Jones IE, Taylor RW, Manning PJ, Williams SM. More broken bones: a 4-year double cohort study of young girls with and without distal forearm fractures. J Bone Miner Res. 2000;15: 2011–8.
19. Clark EM, Ness AR, Tobias JH. Vigorous physical activity increases fracture risk in children irrespective of bone mass: a prospective study of the independent risk factors for fractures in healthy children. J Bone Miner Res. 2008;23:1012–22.
20. Ma DQ, Jones G. Clinical risk factors but not bone density are associated with prevalent fractures in prepubertal children. J Paediatr Child Health. 2002;38:497–500.
21. Jones IE, Williams SM, Goulding A. Associations of birth weight and length, childhood size, and smoking with bone fractures during growth: evidence from a birth cohort study. Am J Epidemiol. 2004;159:343–50.
22. Jones S, Johansen A, Brennan J, Butler J, Lyons RA. The effect of socioeconomic deprivation on fracture incidence in the United Kingdom. Osteoporos Int. 2004;15:520–4.
23. Arabi A, Nabulsi M, Maalouf J, Choucair M, Khalife H, Vieth R, El-Hajj FG. Bone mineral density by age, gender, pubertal stages, and socioeconomic status in healthy Lebanese children and adolescents. Bone. 2004;35:1169–79.
24. Jones G, Dwyer T. Bone mass in prepubertal children: gender differences and the role of physical activity and sunlight exposure. J Clin Endocrinol Metab. 1998;83:4274–9.
25. Flynn J, Foley S, Jones G. Can BMD assessed by DXA at age 8 predict fracture risk in boys and girls during puberty?: an eight-year prospective study. J Bone Miner Res. 2007;22:1463–7.
26. Clark EM, Ness AR, Bishop NJ, Tobias JH. Association between bone mass and fractures in children: a prospective cohort study. J Bone Miner Res. 2006;21:1489–95.
27. Wetzsteon RJ, Hughes JM, Kaufman BC, Vazquez G, Stoffregen TA, Stovitz SD, Petit MA. Ethnic differences in bone geometry and strength are apparent in childhood. Bone. 2009;44:970–5.
28. McVeigh JA, Norris SA, Pettifor JM. Bone mass accretion rates in pre- and early-pubertal South African black and white children in relation to habitual physical activity and dietary calcium intakes. Acta Paediatr. 2007;96:874–80.
29. Goulding A, Cannan R, Williams SM, Gold EJ, Taylor RW, Lewis-Barned NJ. Bone mineral density in girls with forearm fractures. J Bone Miner Res. 1998;13:143–8.
30. Poopedi MA, Norris SA, Pettifor JM. Factors influencing the vitamin D status of 11 year old urban South African children. Bone. 2009;45: S84.
31. Poopedi MA, Norris SA, Pettifor JM. Factors influencing the vitamin D status of 10-year-old urban South African children. Public Health Nutr. 2011;14:334–9.

Osteoporos Int
DOI 10.1007/s00198-013-2477-4

ORIGINAL ARTICLE

Fracture patterns and bone mass in South African adolescent–mother pairs: the Birth to Twenty cohort

K. Thandrayen · S. A. Norris · L. K. Micklesfield · J. M. Pettifor

Received: 13 March 2013 / Accepted: 26 July 2013
© The Author(s) 2013. This article is published with open access at Springerlink.com

Abstract
Summary The associations of fracture prevalence and bone mass in adolescents with maternal fracture history and bone mass have not been investigated previously in South Africa. Maternal bone mass has a significant inverse association with their adolescents' fracture rates and bone mass across all ethnic groups.
Introduction Differences in fracture rates and bone mass between families and individuals of different ethnic origins may be due to differing lifestyles and/or genetic backgrounds. This study aimed to assess associations of fracture prevalence and bone mass in adolescents with maternal fracture history and bone mass, and sibling fracture history.
Methods Data from 1,389 adolescent–biological mother pairs from the Birth to Twenty longitudinal study were obtained. Questionnaires were completed on adolescent fractures until 17/18 years of age and on sibling fractures. Biological mothers completed questionnaires on their own fractures prior to the age of 18 years. Anthropometric and bone mass data on adolescent–biological mother pairs were collected.
Results An adolescent's risk of lifetime fracture decreased with increasing maternal lumbar spine (LS) bone mineral content (BMC; 24 % reduction in fracture risk for every unit increase in maternal LS BMC Z-score) and increased if they were white, male, or had a sibling with a history of fracture. Adolescent height, weight, male gender, maternal bone area and BMC, and white ethnicity were positive predictors of adolescent bone mass. White adolescents and their mothers had a higher fracture prevalence (adolescents 42 %, mothers 31 %) compared to the black (adolescents 20 %, mothers 6 %) and mixed ancestry (adolescents 20 %, mothers 16 %) groups.
Conclusion Maternal bone mass has a significant inverse association with their adolescent off-springs' fracture risk and bone mass. Furthermore, there is a strong familial component in fracture patterns among South African adolescents and their siblings.

Keywords Adolescents · Biological mothers · Bone mass · Family patterns · Fractures · South Africa

K. Thandrayen · S. A. Norris · L. K. Micklesfield · J. M. Pettifor
MRC/Wits Developmental Pathways for Health Research Unit, Department of Paediatrics, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

S. A. Norris
e-mail: Shane.norris@wits.ac.za

L. K. Micklesfield
e-mail: Lisa.Micklesfield@uct.ac.za

J. M. Pettifor
e-mail: John.pettifor@wits.ac.za

K. Thandrayen (✉)
Department of Paediatrics, Chris Hani Baragwanath Hospital, PO Bertsham, Johannesburg 2013, South Africa
e-mail: Kebashni.thandrayen@wits.ac.za

Introduction

Heritability [1, 2] and lifestyle factors [3] of both mother during pregnancy and child influence the accrual of peak bone mass and impact the risk of osteoporosis in later adulthood. Intrauterine programming and environmental influences during early childhood may modify peak bone mass accrual. There is no consistent long-term effect of low birth weight on bone mineral density and hip fracture risk later in life [4] but thinness in childhood may be a risk factor for fracture in later life [5]. A meta-analysis and systematic review showed that higher birth weight is associated with greater bone mineral content (BMC) in adulthood [6] and, in almost all of those studies, this relationship was independent of body size. Cooper et al. [7] concluded that infant growth and physical activity in childhood are important determinants of peak bone mass in women. However, it has also been shown that gains in bone

Published online: 14 August 2013

mineral accretion during childhood via interventions such as increased physical activity and nutrient supplementation may only be transient, thus promoting the hypothesis that bone mass is ultimately governed by a homeostatic system which tends to return towards a yet-to-be defined set point [8]. Whether this set point is genetically predetermined needs to be further investigated. Our research group has shown that heritability of bone area (BA) and BMC by maternal descent is approximately 30 % in South African pre/early pubertal black and white children, despite ethnic differences in both body and bone size, as well as in lifestyle [9]. The pattern of ethnic differences in bone strength in youth [10, 11] is similar to the reported ethnic differences in fracture rates in adults [12–14], suggesting that these differences in fracture rates may track back to differences in bone strength in childhood and adolescence.

Although heritability has been shown to be an important determinant of bone mineral accrual and fracture risk in other countries [15], no information is available on the differences in bone mass and fracture patterns between families of different ethnic backgrounds in South Africa. In this study, we were interested in assessing the associations between bone mass and fracture history of mothers with those of their adolescent children. We hypothesized that as there is a strong association between the bone mass measurements of adolescent–biological mother pairs, maternal bone mass will influence fracture prevalence in their adolescent offspring and that a history of fractures in the mother or other siblings will be associated with an increased risk of fractures in the adolescent.

Methods

Study population

Data from 1,389 adolescent–biological mother pairs from the Birth to Twenty (Bt20) longitudinal study of child health and development were used. All eligible neonates (n=3,273) born within a 7-week period (April 23 to June 8, 1990) in the greater Johannesburg metropolitan area in South Africa were recruited at birth into the Bt20 study. Although the total cohort is demographically similar to long-term resident families living in Soweto, Johannesburg, the cohort under represents white children due to white families generally utilizing private practitioners and facilities which were excluded during initial enrolment. To compensate for this, at the age of 10 years, we recruited a supplementary sample of 120 white children born during the same period as the cohort children in 1990 into the bone health sub-study of the Bt20 cohort. Of the 3,273 children in the cohort initially, contact has been maintained with more than 70 % at the age of 16 years. A cohort profile describing the study sample, research objectives and attrition has been documented by Richter et al. [16]. An adolescent's ethnic classification was defined by the race classification currently used in South Africa for demographic and restitution purposes. The South African government currently classifies race into black (B; ethnic Africans), white (W; Europeans, Jews and Middle Easterners), coloured or mixed ancestry (MA; mixed race) and Indian (South Asian), and only adolescents whose parents were classified as being of the same ethnic group were included. Data from 1,389 adolescent–biological mother pairs were analysed for this study. The ethnic breakdown of the study sample was predominantly B (1,170 (84.2 %)), with the remainder of the cohort being made up of W (91 (6.6 %)) and MA (128 (9.2 %)). Indian adolescents and their mothers were excluded as the number of participants was too few to make meaningful comparisons. Children who had chronic diseases such as rheumatoid arthritis, epilepsy and asthma were excluded from the data analyses, as the use of certain medications and immobility are associated risk factors for low bone mass and may increase the incidence of fractures. All subjects provided assent and their parents/guardian provided written, informed consent. Ethical approval for the study was obtained from the University of the Witwatersrand Committee for Research on Human Subjects.

Fracture questionnaire

A fracture questionnaire was completed by each adolescent with the assistance of his/her parent or caregiver at 15 and 17/18 years of age. The questionnaire at age 15 included information on previous fractures from birth until 15 years of age, including site of fracture with the aid of a skeletal diagram, and the causes and age at fracture. At age 17/18, the fracture questionnaire included information on fractures that had occurred since their previous questionnaire. Mothers/caregivers also completed a questionnaire on fractures occurring since birth in the adolescent's sibling(s). Biological mothers completed questionnaires on their own fractures prior to the age of 18 years. Due to the retrospective nature of the fracture data collection, the fractures could not be verified by radiographs.

Anthropometric measurements and dual-energy X-ray absorptiometer-derived parameters

Anthropometric measurements and bone mass data on the subjects at the age of 17/18 years were used for this study. Biological mothers' anthropometric data and bone mass measurements had been collected over 2 years when the adolescents were approximately 13 years of age. Height was measured to the nearest millimetre using a stadiometer (Holtain, Crosswell, UK). Weight was measured to the last 100 g using a digital scale (Dismed, Halfway House, South Africa), with participants wearing light clothing and no shoes. Tanner staging of pubertal development was assessed by the adolescents privately using a validated protocol based on Tanner's Sexual

Maturation Scale [17]. This scale, which had been previously validated for black South Africans [18], consists of drawings and explanations of the five Tanner stages of secondary sexual characteristics (breast development in females and genital development for males), ranging from stage 1 (pre-pubertal) through stage 5 (post-pubertal). Same sex researchers were available to assist the adolescents if necessary.

Total body (TB) and lumbar spine (LS) BA and BMC were measured in both the adolescents and biological mothers using a Hologic QDR 4500A dual-energy X-ray absorptiometer according to standard procedures using the same software version for both the adolescents and biological mothers (software version 11.2, Hologic, MA, USA).

Statistical analyses

The data were analysed using SAS (version 9.3) package. In the descriptive analysis of the adolescent–biological mother pair characteristics, the baseline data were summarized as means (standard deviations). ANOVA was used to test for differences in age and anthropometric measurements; ANCOVA, adjusting for height and weight, was used to test for differences in bone mass (bone mineral content and bone area) measurements between ethnic groups. Bonferonni correction was used for post hoc comparisons of individual groups. Categorical data were summarized as numbers and percentages. Comparisons were made between those who had and had no fracture(s) using chi-square or Fisher's exact analysis. A p value of <0.05 was considered to be statistically significant. Ethnicity was dummy coded in all regression models, with whites as the reference group. The pubertal stages of the adolescents were recorded into early puberty (Tanner 1–3) and late puberty (Tanner 4–5) for use in the regression models. Multiple forward selection and backward elimination stepwise regression analyses examined the independent contributions of various factors to adolescent TB and LS BA and BMC, and all variables left in the model are significant at 0.15 level for inclusion or exclusion. Logistic regression analyses were performed to determine the factors influencing fracture risk in the adolescents before and after adjusting for confounding variables. The maternal bone mass measurements used in the logistic regressions were converted to Z-scores using the entire cohort of mothers as the reference group.

Results

Of the 3,273 neonates originally enrolled in the Bt20 cohort, fracture and bone mass data were available on 1,389 adolescents at age 17/18. Bone mass measurements were available on nearly all of their biological mothers (WB=1,383 and LS=1,261); however, information on previous fractures was only available on 688 (~50 %) of these. There were no differences in age, anthropometric data and bone mass measurements between those mothers who did complete the fracture questionnaire and those who did not (data not shown). Figure 1 depicts the attrition of subjects in the cohort from birth until 17/18 years of age. The figure also shows the numbers of fracture questionnaires and bone mass measurements available at age 17/18 on adolescent–biological mother pairs as well as the number of fracture questionnaires on the siblings of the 17/18-year-old adolescents.

Anthropometric and bone mass measurements

The baseline descriptive data of the adolescent–biological mother pairs of the different ethnic groups are shown in Tables 1 and 2. White adolescent males were heavier, had a greater BMI and were taller than black and MA adolescent males. White adolescent females were taller than black and MA adolescent females, but black adolescent females were heavier and had a greater BMI than the MA adolescent females.

After adjusting for height and weight, white males had a greater TB BA, LS BA and LS BMC than the males of the other ethnic groups. Mixed ancestry adolescent females had significantly lower TB BA than the black and white adolescent females. Adjusted TB BMC was not significantly different between the ethnic groups in either the adolescent males or females. Pubertal development was less advanced in black adolescent males than in other ethnic groups.

There were no differences in age or weight between the mothers in the different ethnic groups. White mothers were taller and had a lower BMI than their black and mixed ancestry peers. After adjusting for height and weight, black mothers had greater TB BA and BMC than mothers in the other two groups.

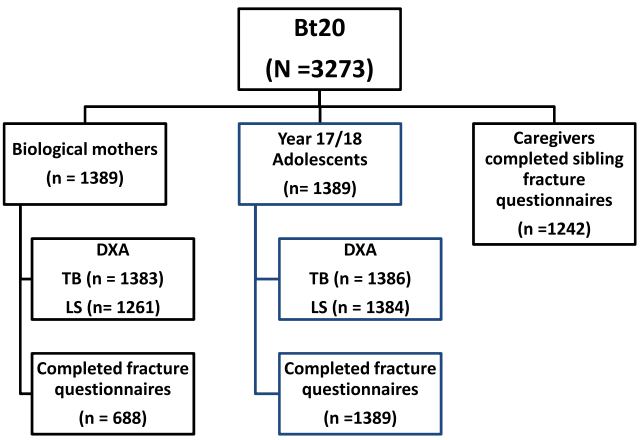


Fig. 1 Flow diagram describing the attrition of study participants from birth until 17/18 years of age including the number of adolescent–biological mother pairs and their siblings with fracture and bone mass data

Table 1 Anthropometric and bone mass measurements of 17/18-year-old adolescents

Anthropometric and bone mass measurements	Whites				Blacks				Mixed ancestry				*p* Values	
	Males		Females		Males		Females		Males		Females		Males	Females
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)		
Age (years)	41	17.8 (0.3)	50	17.8 (0.2)	577	17.9 (0.4)	593	17.9 (0.4)	61	18.2 (0.5)	67	18.2 (0.5)	MA>B* MA>W*	MA>B* MA>W*
Weight (kg)	41	72.3 (12.4)	50	61.7 (12.9)	577	59.1 (8.9)	590	59.2 (11.9)	61	59.4 (12.6)	67	53.8 (11.7)	W>B* W>MA*	W>MA** B>MA**
Height (m)	41	1.78 (0.09)	50	1.66 (0.07)	577	1.71 (0.07)	590	1.60 (0.06)	61	1.71 (0.07)	67	1.60 (0.06)	W>B* W>MA*	W>B* W>MA*
BMI (kg/m^2)	41	22.6 (3.1)	50	22.4 (4.1)	577	20.1 (2.6)	590	23.2 (4.5)	61	20.3 (3.8)	67	21.1 (4.2)	W>B* W>MA***	B>MA*
TB BA (cm^2)	41	2,336.2 (225.3)	50	2,010.7 (176.8)	577	2,086 (180.2)	593	1,883 (165.1)	61	2,045 (205.3)	67	1,781 (157.6)	W>B* W>MA*	W>B* W>MA* B>MA*
Adjusted TB BA (cm^2)[a]	41	2,087.8 (13.6)	50	2,026.8 (11.9)	577	2,051.4 (3.8)	590	2,008.2 (4.4)	61	2,013.4 (10.8)	67	1,956.9 (10.6)	W>B*** W>MA* B>MA***	W>MA* B>MA*
TB BMC (g)	41	2,694.8 (446.5)	50	2,144.5 (282.8)	577	2,308.9 (344.2)	593	2,034.2 (282.9)	61	2,310.0 (388.1)	67	1,894.5 (268.2)	W>B* W>MA*	W>MA* B>MA**
Adjusted TB BMC (g)‡	41	2,354.2 (37.2)	50	2,158.6 (32.4)	577	2,277.5 (10.4)	590	2,185.3 (12.0)	61	2,280.9 (29.5)	67	2,130.9 (28.9)	NS	NS
LS BA (cm^2)	41	68.9 (6.2)	50	57.8 (5.4)	575	62.7 (6.0)	593	54.5 (5.9)	61	61.8 (5.6)	67	53.2 (5.8)	W>B* W>MA*	W>B** W>MA*
Adjusted LS BA (cm^2)[a]	41	62.8 (0.8)	50	58.8 (0.7)	575	60.7 (0.2)	590	58.8 (0.2)	61	60.0 (0.6)	67	57.8 (0.6)	W>B** W>MA**	NS
LS BMC (g)	41	71.8 (12.6)	50	56.1 (10.0)	575	58.3 (10.8)	593	53.1 (9.6)	61	59.0 (10.9)	67	50.1 (8.5)	W>B* W>MA*	W>MA***
Adjusted LS BMC (g)[a]	41	62.8 (1.4)	50	56.8 (1.2)	575	56.7 (0.4)	590	58.0 (0.5)	61	57.6 (1.1)	67	56.5 (1.1)	W>B* W>MA**	NS
Pubertal status														
Stage 1	0	0 %	0	0 %	0	0 %	0	0 %	0	0 %	0	0 %		
Stage 2	0	0 %	0	0 %	2	0.4 %	0	0 %	0	0 %	0	0 %	W>B*	
Stage 3	1	2.4 %	5	10 %	74	13.8 %	81	14.3 %	3	7 %	4	9.3 %	MA>B**	NS
Stage 4	14	34.2 %	22	45 %	319	59.5 %	275	48.7 %	20	46.5 %	18	41.9 %		
Stage 5	26	64.4 %	22	45 %	141	26.3 %	209	40.0 %	20	46.5 %	21	48.8 %		

Data are presented as number (*n*) and percentage (%) or means (SD). Data compared between groups using ANOVA for continuous data and chi-square or Fisher's exact for categorical data

NS not significant, *TB* total body, *LS* lumbar spine, *BA* bone area, *BMC* bone mineral content

P values presented for ethnicity in male and females separately (*W* white, *B* black, *MA* mixed ancestry): *$p<0.001$, **$p<0.01$, ***$p<0.05$

[a] Adjusted BA or BMC is adjusted for weight and height, and is presented as means

Predictors of BA and BMC in 17–18-year-old adolescents

To determine factors that made a significant contribution to adolescent TB and LS BA and BMC, ethnicity, gender, adolescent height, adolescent weight, Tanner stage (sub-divided into early or late puberty), maternal height, maternal weight, maternal TB and LS BA and BMC were chosen as candidate explanatory variables for the multivariate stepwise regression analyses. The results from regression models are presented in Table 3. Puberty was excluded from the analyses due to a lack of correlation. Including adolescent height, weight and maternal BA (except of TB that contributed minimally) and BMC resulted in the highest partial R^2 values for the respective adolescent bone variables. Maternal height and weight were

Table 2 Anthropometric and bone mass measurements of mothers

Anthropometric and bone mass measurements	Whites		Blacks		Mixed ancestry		*p* Value
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	
Age (years)	91	39.9 (5.1)	1,170	40.0 (7.0)	128	41.1 (6.7)	NS
Weight (kg)	91	72.2 (16.4)	1,165	75.7 (16.3)	127	73.8 (16.5)	NS
Height (m)	91	1.65 (0.06)	1,165	1.59 (0.06)	127	1.59 (0.07)	W>B*, W>MA*
BMI (kg/m^2)	91	26.5 (6.2)	1,165	30.1 (6.2)	127	29.0 (6.4)	W<B*, W<MA**
TB BA (cm^2)	91	2,016.5 (149.5)	1,170	1,953.5 (154.8)	128	1,903.9 (171.7)	W>B*, W>MA*, B>MA**
Adjusted TB BA (cm^2)[a]	91	1,955.5 (8.1)	1,165	1,986.4 (2.4)	127	1,933.7 (6.8)	B>W*, B>MA*, W>MA***
TB BMC (g)	91	2,229.5 (276.9)	1,170	2,211 (315.6)	128	2,139 (336.7)	B>MA***
Adjusted TB BMC (g)[a]	91	2,149.2 (24.7)	1,165	2,252.4 (7.4)	127	2,181.5 (20.6)	B>W*, B>MA**
LS BA (cm^2)	91	60.6 (5.4)	1,067	55.4 (5.8)	107	55 (5.5)	W>B*, W>MA*
Adjusted LS BA (cm^2)[a]	91	58.0 (0.5)	1,064	57.1 (0.2)	106	55.8 (0.4)	W>MA*, B>MA***
LS BMC (g)	91	61.5 (10.7)	1,067	56 (10.8)	107	55.1 (10.7)	W>B*, W>MA*
Adjusted LS BMC (g)[a]	91	58.1 (1.0)	1,064	58.1 (0.3)	106	56.6 (0.9)	NS

Data are presented as means (SD). Data compared between groups using ANOVA for continuous data

P values presented for ethnicity (*W* white, *B* black, *MA* mixed ancestry): *$p<0.001$, **$p<0.01$, ***$p<0.05$

NS not significant, *TB* total body, *LS* lumbar spine, *BA* bone area, *BMC* bone mineral content

[a] Adjusted BA or BMC is adjusted for weight and height, and presented as means (SE)

negative predictors of adolescent BA and BMC, but contributed minimally to the overall variance. White ethnicity was a positive predictor of TB BA and BMC and LS BMC, and male gender was a positive predictor of TB BA and BMC and LS BA.

Factors associated with fractures in 17/18-year-old adolescents

Of the 1,389 adolescents with fracture data, 91 (6.6 %) were W, 1,170 (84.2 %) were B and 128 (9.2 %) were MA. Twenty-

Table 3 Regression models describing the relationship between predictors and adolescent bone area and bone mineral content

	TB BA (*n*=1,269)			TB BMC (*n*=1,269)			LS BA (*n*=1,169)			LS BMC (*n*=1,169)		
	Parameter estimate	SE	Partial R^2	Parameter estimate	SE	Partial R^2	Parameter estimate	SE	Partial R^2	Parameter estimate	SE	Partial R^2
Intercept	−525.3	77.3		−672.2	190.5		−27.1	3.9		−28.9	7.4	
Whites	39.21	9.6	0.002*	62.4	24.9	0.002**	–			2.2	1.0	0.003**
Males	53.9	6.7	0.006*	115.6	17.4	0.018*	2.3	0.4	0.019*	–		
Adolescent height (m)	1,345.9	42.5	0.660*	1,486.5	110.3	0.409*	51.7	2.3	0.580*	47.8	3.0	0.275*
Adolescent weight (kg)	8.47	0.2	0.170*	14.0	0.6	0.170*	–			0.25	0.02	0.051*
Late Tanner stage	–			27.3	17.9	0.001	–			–		
Maternal height (m)	−485.8	66.9	0.005*	−709.4	132.4	0.007*	−10.7	3.0	0.004*	−14.1	5.0	0.003**
Maternal weight (kg)	−1.4	0.2	0.003*	−2.9	0.4	0.012*	–			−0.03	0.02	0.004***
Maternal bone measurement	0.32	0.03	0.004*	0.37	0.03	0.029*	0.29	0.03	0.021*	0.28	0.03	0.084*
Total R^2	0.852*			0.648*			0.624*			0.420*		

Mother's bone measurement corresponds to the respective TB or LS BA or BMC value for each column. All variables left in the model are significant at the 0.15 level

TB total body, *BA* bone area, *BMC* bone mineral content, *LS* lumbar spine

*$p<0.001$, **$p<0.05$, ***$p<0.01$

two percent of the adolescents reported a history of having fractured a bone previously. The percentage of white children who reported fractures was double that of the other groups (W 42 % vs. B 20 % and MA 20 %; both $p<0.001$).

Twenty-two percent of adolescents who had siblings had a history of fractures. Of these adolescents who had fractures, 23 % of their siblings had also sustained a fracture, while for those adolescents without a fracture history, only 14 % of their siblings had fractures (23 vs. 14 %; $p<0.01$).

Of the 688 biological mothers, who completed the fracture questionnaire, 60 (9 %) indicated that they had sustained a fracture before the age of 18 years (white mothers 31 %, mixed ancestry 16 %, black mothers 6 %; W>B, $p<0.001$; MA>B, $p=0.01$). Unlike the pattern of fracture incidence among the adolescents and their siblings, there was no difference in the prevalence of fractures among the adolescents of mothers who had or did not have a history of fractures.

Bivariate logistic regression analyses were initially performed for the whole group to assess if any confounding variables, such as weight, height, ethnicity, gender, pubertal stage, adolescents' and mothers' BA and BMC (TB and LS), and sibling history of fracture or maternal history of fracture, were individually associated with adolescent fracture risk. In these analyses, the adolescent's risk of fracture was higher if a sibling had a history of fracture (OR=1.6, 95 % CI 1.12–2.32, $p=0.01$), but was not associated with maternal history of fracture (OR=1.09, 95 % CI 0.63–1.86, $p=0.762$). Neither adolescent weight nor pubertal stage was associated with fracture risk of the entire cohort; however, height was positively associated with the risk of fracture (OR=9.85, 95 % CI 2.31–41.83, $p<0.01$), and males were at greater risk of fracture compared to females (OR=1.73, 95 % CI 1.33–2.24, $p<0.001$). Adolescent TB BA (OR=1.0008, 95 % CI 1.0002–1.001; $p<0.05$) and TB BMC (OR=1.0004, 95%CI 1.000002–1.0007, $p<0.05$) were both marginally associated with increased fracture risk. Maternal LS BMC was inversely associated with fracture risk in their adolescent offspring (OR=0.80, 95 % CI 0.7–0.93; $p<0.01$). White adolescents had a greater risk of fracture than other ethnic groups (OR=2.82, 95 % CI 1.82–4.37, $p<0.001$).

Multivariate logistic regression analyses were performed on the entire group ($n=1099$) to determine the risk factors for fractures in the adolescents. The factors which had been found to be significantly associated in simple logistic regression and multiple regression analyses were included in the model, namely gender, ethnicity, sibling history of fracture, adolescent and maternal heights, adolescent TB BA and BMC, and maternal LS BMC. Only the significant risk factors for adolescent fracture risk are shown in Table 4. White ethnicity and male gender remained significant, with a greater risk of adolescent fracture. The adolescent's risk of fracture was 50 % greater if a sibling had a history of fracture (OR=1.5, 95 % CI 1.02–2.21, $p<0.05$). Maternal LS BMC was protective against the risk of fracture in the adolescent (24 % reduction in fracture risk for every 1 unit increase in maternal BMC Z-score).

Table 4 Odds ratios for fractures in 17/18-year-old adolescents

Fractures ($n=1,099$)	Adjusted odds ratio	95 % Confidence interval
Whites	3.16*	1.89–5.32
Males	1.94**	1.25–2.99
Sibling history of fracture	1.50***	1.02–2.21
Maternal LS BMC (Z-score)	0.76**	0.63–0.91

Odds ratios are adjusted for all other variables in the table and for adolescent–mother pair heights and adolescent TB BA and BMC

LS lumbar spine, *BMC* bone mineral content

*$p<0.001$, **$p<0.01$, ***$p<0.05$

Discussion

To our knowledge, this is the first paper to describe the familial patterns of fracture risk in adolescents and its relationship with bone mass measurements in adolescent–biological mother pairs of different ethnic backgrounds. The main findings of this study were that an adolescent's risk of fracture was decreased if his/her mother had a greater lumbar spine BMC (24 % reduction in fracture risk for every SD increase in maternal BMC), but was increased if a sibling had a history of fracture or if the adolescent was white or male. Adolescent height and weight, maternal BA and BMC, males and white ethnicity were positive predictors of adolescent bone mass. Lastly, there was a higher prevalence of fractures in white mothers prior to 18 years of age compared to the other ethnic groups, a pattern similar to that of their adolescent children, which we have reported previously [19]. However, we were unable to show any association between a maternal history of childhood/adolescent fractures and the prevalence of fractures in their adolescent offspring.

Maternal influences such as gestational height, adiposity and vitamin D status have been postulated to be important in intrauterine programming and in the tracking of skeletal development and body composition from infancy to adulthood [20, 21]. These maternal influences are beyond the scope of this paper, but it will be important to determine if these factors predict or influence fracture risk and bone mass in adolescents from the different ethnic groups in South Africa.

Although the positive relationship between the mother's bone mass and her offspring's has been researched and documented worldwide [1, 22–24], the finding that maternal bone mass might influence her offspring's fracture prevalence during childhood and adolescence has not been reported

previously. Intuitively, this association should not be surprising as several studies, although not all [25–28], have shown that children who had fracture(s) tend to have reduced BMC and BA compared to their peers who had no fractures, and genetic inheritance (maternal and paternal bone mass) plays a large role in determining childhood BMC, BA and peak bone mass [29]. However, in our earlier study of the Bt20 cohort [30], we did not find an inverse association between fracture history prevalence and bone mass at two time points during childhood and adolescence. In fact, in white males, there was a positive association between fracture risk and bone mass [30], possibly associated with increased contact sport participation [19]. Thus, the association between maternal LS BMC and adolescent fracture risk might be a proxy for structural differences in the adolescents, with low maternal BMC indicating poorer adolescent bone strength rather than differences in bone mass per se.

In addition to predicting adolescent fracture, maternal bone mass was also an independent predictor of adolescent BA and BMC. Twin- and family-based studies have indicated that 60–85 % of the variance in BMD is genetically determined [1, 22–24, 31]. All of these studies indicate that the bone mass of pre- and post-menarche daughters is related to the BMD of their mothers. Most workers have found correlations between 0.22 and 0.58 in parent/children pairs or mother/children pairs [1, 29]. We found similar heritability rates (approximately 30 %) by maternal descent in pre-pubertal and early pubertal South African children [9], indicating that genetics plays an important role in determining bone mass in black, white and mixed ancestry South African children.

The pattern of differences in fracture prevalence between ethnic groups was similar in the biological mothers to that of their adolescent offspring, with the white mothers and adolescents reporting the highest prevalence of fractures (white mothers 31 % vs. blacks 6 % vs. MA 16 %). It is likely that the actual prevalence is higher than that recorded as the fractures were historic, occurred during childhood and had no means of verification. However, these figures are higher than those reported by an older group of men and women (>50 years of age) participating in the European Prospective Osteoporosis Study (EPOS). They reported a fracture prevalence between the ages of 8 and 18 years of 8.9 % in men and 4.5 % in women [32]. We were unable to show any association between the history of childhood/adolescent fractures in mothers and the prevalence of fractures in their adolescent offspring within each ethnic group (data not shown). The findings support those of Ma and Jones who did not observe any association between the prevalence of childhood fractures in offspring and maternal fracture history (but the number of participants was small) [33]. However, we did show an association within the same family, as the prevalence of sibling fractures was significantly higher in families who had adolescents who had fractures (23 %) than in families whose adolescents had no fractures (14 %). Similar evidence of fracture association among siblings has been reported from Poland, where more than 50 % of adolescents with multiple fractures indicated that at least one family member had sustained a fracture, while only 29 % of the adolescents who had no fractures had a family member who had fracture(s) [34].

We were unable to show an association between the risk of childhood fractures and bone mass measurements at 17/18 years of age for the entire group. There are conflicting results concerning the association between childhood fractures and bone mass around the time of peak bone mass attainment. Several studies have found that childhood fractures are associated with low adult BMD [35],[36], but this was not confirmed by Kawalilak et al. [37]. The EPOS study conducted in over 50-year-old adults supports the latter study in that BMD was similar among those who did and did not report sustaining a fracture during childhood [32].

This study has several limitations. It relies heavily on the self-reporting of historical childhood fractures in adolescents, their siblings and their mothers. Being historical, we could not verify the occurrence of the fracture, its site, or if X-rays confirmed the presence of a fracture. Thus, we are dependent on memory of fracture events which is likely to be influenced by the severity of the fracture and the time between completing the questionnaire and the fracture event, which in the case of the mothers was at least 20 to 30 years. Potential differences in literacy between the black and white participants are not relevant as questionnaires were completed with the help of a research assistant. To assess data quality, the fractures were verified telephonically in 51 (17 %) of the adolescents who reported fractures. Forty-eight (94 %) confirmed having one or more fractures. Of the remaining three, two had reported strains as fractures, and one had reported no history of fractures in the initial questionnaire. Of the reported fractures, 46 (96 %) were said to have been diagnosed by a doctor, and one by a nursing sister. Eighty-nine percent (42/48) had confirmed that they had had a radiograph performed, three did not and two could not remember. Finally, this study did not include confounding variables such as vitamin D levels, calcium intake, physical activity scores or socioeconomic status, but the relationship between sports activities and fractures has been reported previously in this cohort [30].

Conclusions

We have shown that fracture history in South African adolescents is significantly associated with maternal bone mass as well as a fracture history in their siblings. There is also a strong ethnic component in fracture patterns within South Africa as the prevalence of fractures is higher in white South African families compared to the other ethnic groups. It has been reported that bone strength is lower in whites or Caucasians compared to other ethnic groups [10, 11], probably increasing their risk of fracture.

Thus, further studies, using different techniques such as pQCT, are required to tease out the underlying physiological mechanisms for the differences in fracture rates among children of different ethnic groups within South Africa.

Acknowledgments Birth to Twenty is funded by the Wellcome Trust (UK), Medical Research Council of South Africa, Human Sciences Research Council of South Africa, National Research Foundation and the University of the Witwatersrand, Johannesburg. We are grateful to all the participants and their families in this study, and the entire Birth to Twenty team which includes interviewers, technicians, clerical workers, research scientists, nurses and receptionists.

Conflicts of interest None.

Open Access This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and the source are credited.

References

1. Krall EA, Dawson-Hughes B (1993) Heritable and life-style determinants of bone mineral density. J Bone Miner Res 8:1–9
2. Runyan SM, Stadler DD, Bainbridge CN et al (2003) Familial resemblance of bone mineralization, calcium intake, and physical activity in early-adolescent daughters, their mothers, and maternal grandmothers. J Am Diet Assoc 103:1320–1325
3. Ondrak KS, Morgan DW (2007) Physical activity, calcium intake and bone health in children and adolescents. Sports Med 37:587–600
4. Dotsch J (2011) Low birth weight, bone metabolism and fracture risk. Dermatoendocrinol 3:240–242
5. Javaid MK, Eriksson JG, Kajantie E et al (2011) Growth in childhood predicts hip fracture risk in later life. Osteoporos Int 22:69–73
6. Baird J, Kurshid MA, Kim M et al (2011) Does birthweight predict bone mass in adulthood? A systematic review and meta-analysis. Osteoporos Int 22:1323–34
7. Cooper C, Cawley M, Bhalla A et al (1995) Childhood growth, physical activity, and peak bone mass in women. J Bone Miner Res 10:940–947
8. Gafni RI, Baron J (2007) Childhood bone mass acquisition and peak bone mass may not be important determinants of bone mass in late adulthood. Pediatrics 119(Suppl 2):S131–6
9. Vidulich L, Norris SA, Cameron N et al (2011) Bone mass and bone size in pre- or early pubertal 10-year-old black and white South African children and their parents. Calcif Tissue Int 88:281–93
10. Wetzsteon RJ, Hughes JM, Kaufman BC et al (2009) Ethnic differences in bone geometry and strength are apparent in childhood. Bone 44:970–975
11. Micklesfield LK, Norris SA, Pettifor JM (2011) Determinants of bone size and strength in 13-year-old South African children: the influence of ethnicity, sex and pubertal maturation. Bone 48:777–85
12. Baron JA, Barrett J, Malenka D et al (1994) Racial differences in fracture risk. Epidemiology 5:42–47
13. Barrett-Connor E, Siris ES, Wehren LE et al (2005) Osteoporosis and fracture risk in women of different ethnic groups. J Bone Miner Res 20:185–94
14. Solomon L (1968) Osteoporosis and fracture of the femoral neck in the South African Bantu. J Bone Joint Surg Br 50:2–13
15. Lei SF, Chen Y, Xiong DH et al (2006) Ethnic difference in osteoporosis-related phenotypes and its potential underlying genetic determination. J Musculoskelet Neuronal Interact 6:36–46
16. Richter L, Norris S, Pettifor J et al (2007) Cohort profile: Mandela's children: the 1990 Birth to Twenty study in South Africa. Int J Epidemiol 36:504–11
17. Tanner JM (1962) Growth at adolescence. Blackwell, Oxford
18. Norris SA, Richter LM (2005) Usefulness and reliability of Tanner pubertal self-rating to urban black adolescents in South Africa. J Res Adolesc 15:609–24
19. Thandrayen K, Norris SA, Pettifor JM (2009) Fracture rates in urban South African children of different ethnic origins: the Birth to Twenty cohort. Osteoporos Int 20:47–52
20. Ioannou C, Javaid MK, Mahon P et al (2012) The effect of maternal vitamin D concentration on fetal bone. J Clin Endocrinol Metab 97:E2070–E2077
21. Gale CR, Javaid MK, Robinson SM et al (2007) Maternal size in pregnancy and body composition in children. J Clin Endocrinol Metab 92:3904–11
22. Ferrari S, Rizzoli R, Slosman D et al (1998) Familial resemblance for bone mineral mass is expressed before puberty. J Clin Endocrinol Metab 83:358–61
23. Kuroda T, Onoe Y, Miyabara Y et al (2009) Influence of maternal genetic and lifestyle factors on bone mineral density in adolescent daughters: a cohort study in 387 Japanese daughter-mother pairs. J Bone Miner Metab 27:379–85
24. Ohta H, Kuroda T, Onoe Y et al (2010) Familial correlation of bone mineral density, birth data and lifestyle factors among adolescent daughters, mothers and grandmothers. J Bone Miner Metab 28:690–695
25. Clark EM, Tobias JH, Ness AR (2006) Association between bone density and fractures in children: a systematic review and meta-analysis. Pediatrics 117:e291–e297
26. Goulding A, Cannan R, Williams SM et al (1998) Bone mineral density in girls with forearm fractures. J Bone Miner Res 13:143–48
27. Goulding A, Jones IE, Taylor RW et al (2001) Bone mineral density and body composition in boys with distal forearm fractures: a dual-energy X-ray absorptiometry study. J Pediatr 139:509–15
28. Ma D, Jones G (2003) The association between bone mineral density, metacarpal morphometry, and upper limb fractures in children: a population-based case–control study. J Clin Endocrinol Metab 88:1486–91
29. Jouanny P, Guillemin F, Kuntz C et al (1995) Environmental and genetic factors affecting bone mass. Similarity of bone density among members of healthy families. Arthritis Rheum 38:61–67
30. Thandrayen K, Norris SA, Micklesfield LK et al (2011) Heterogeneity of fracture pathogenesis in urban South African children: the Birth to Twenty cohort. J Bone Miner Res 26:2834–42
31. Gueguen R, Jouanny P, Guillemin F et al (1995) Segregation analysis and variance components analysis of bone mineral density in healthy families. J Bone Miner Res 10:2017–22
32. Pye SR, Tobias J, Silman AJ et al (2009) Childhood fractures do not predict future fractures: results from the European Prospective Osteoporosis Study. J Bone Miner Res 24:1314–18
33. Ma DQ, Jones G (2002) Clinical risk factors but not bone density are associated with prevalent fractures in prepubertal children. J Paediatr Child Health 38:497–500
34. Konstantynowicz J, Bialokoz-Kalinowska I, Motkowski R et al (2005) The characteristics of fractures in Polish adolescents aged 16–20 years. Osteoporos Int 16:1397–403
35. Buttazzoni C, Rosengren EB, Tveit M et al (2013) Does a childhood fracture predict low bone mass in young adulthood? A 27-year prospective controlled study. J Bone Miner Res 28:351–59
36. Cheng S, Xu L, Nicholson PH et al (2009) Low volumetric BMD is linked to upper-limb fracture in pubertal girls and persists into adulthood: a seven-year cohort study. Bone 45:480–486
37. Kawalilak CE, Baxter-Jones AD, Faulkner RA et al (2010) Does childhood and adolescence fracture influence bone mineral content in young adulthood? Appl Physiol Nutr Metab 35:235–43