"Bounce at the Bell": The effects of a 7-month intervention of brief bouts of moderate intensity exercise on bone mass, bone structure and bone strength in children.

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Abstract

INTRODUCTION: Adult bone mass is a function of the amount of bone gained during the years of growth, and the amount of bone lost with advancing age. Therefore, childhood bone mineral accrual is critical for bone health. The current cost of osteoporosis in Canada is estimated to be $1.3 billion per year. There is recent evidence that load-bearing exercise elicits a positive osteogenic response and that childhood is an opportune time to deliver an exercise program to optimize this response. No studies have been conducted to determine whether frequent, brief bouts of jumping exercise have an osteogenic effect in children.
OBJECTIVE: To examine the effects of a 7-month program of jumping on bone mass, strength and structure in early pubertal children.
METHODS: There were 51 children in the exercise group (mean age 10.2 ± 0.4 years, mean height 139.8 ± 7.0 cm, and mean weight 35.7 ± 9.1 kg) and 75 children in the control group (mean age 10.2 ± 0.4 years, mean height 140.6 ± 6.1 cm, and mean weight 35.4 ± 8.0 kg). We administered physical activity (PA), calcium intake (CA) and maturity questionnaires at baseline and final. We also assessed bone mineral content (BMC) at the total proximal femur (PF) and its subregions - trochanteric (TR), intertrochanteric (IT) and femoral neck (FN), as well as at the lumbar spine (LS), and total body (TB) using dual-energy x-ray absorptiometry (DXA, Hologic, QDR 4500). Using hip structural analysis (HSA) at the PF, areal bone mineral density (aBMD), subperiosteal width (SPW), estimated cortical width (AVG CORTEX) and bone cross-sectional area (CSA) - which is equivalent to cortical area and endosteal diameter - were measured at the narrow neck (NN), intertrochanteric (IT), and femoral shaft (S) regions. Section modulus (Z, a representative of bone strength) was then estimated from these measurements. The 7-month exercise intervention consisted of brief bouts of 5-10 jumps (interspersed 3 times throughout the school day) 5 days/week. Analysis of covariance (covariates: baseline maturity, age height, change in height, and average physical activity score) was used to determine differences between intervention and control groups in all the previously mentioned bone parameters.
RESULTS: There were no differences between groups for age, HT, WT, maturity level, Ca or PA at baseline or for change in these parameters across the trial period. BMC at the IT (3.5%, p=0.005) and PF (2.6%, p=0.012) increased significantly more in intervention children when compared with control children, but BMC was not significantly different between groups at other sites. There were no differences between groups for bone structure and bone strength, with the exception of NN SPW which changed significantly more in control (2.1%, p=0.014) compared with intervention children.
CONCLUSIONS: A progressive program of 5 – 10 jumps, 3 times throughout the day elicits a positive osteogenic response at the IT region and the PF. Further study is required to investigate whether or not these changes are maintained 12 months after withdrawal of the exercise stimulus.

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List of Terms

AVG CORTEX – estimated width of the cortex – a structural parameter from HSA

BMC – bone mineral content (grams) measured by DXA

aBMD – areal bone mineral density (g/cm^2) measured by DXA and also reported from HSA

BA – bone area (cm^2) measured by DXA

vBMD – true volumetric bone mineral density measured by pQCT (g/cm^3)

BMU – basic multicellular unit – the theory of bone adapting to load in small packets

BMFLM – bone mineral free lean mass (kg)

Bone mass – for the purposes of this thesis bone mass is interchangeable with BMC

Bone structure – refers to the geometric properties of bone which include CSA, SPW, AVG CORTEX, and aBMD by HSA which contribute to bone strength

Bone strength – refers to the ability of bone to withstand a given load which include CSMI and Z as outcomes from pQCT and HSA

Ca – calcium or calcium intake – measured by the Food Frequency Questionnaire in this study

CSA – cross-sectional area (cm) – structural parameter from HSA, MRI or pQCT

CSMI – cross-sectional moment of inertia CSMI = $\pi/4$ X ($r_t^4 - r_e^4$) where r_t is the total bone radius and r_e is the endocortical radius – CSMI is a strength parameter measured by HSA, MRI or pQCT

CV – coefficient of variation

DXA – dual energy x-ray absorptiometry

Early-pubertal – a stage of maturity indicated by Tanner stage 2 and 3

FITT – the exercise principle of frequency, intensity, time and type

FN – femoral neck – a sub-region of the total proximal femur as measured by DXA

HSA – Hip Structural Analysis – uses total proximal femur scan by DXA to analyze the structural parameters

Ht – height (cm)

I_{min} – represents the minimum distance from the center of mass to the outer cortex – measured by pQCT

I_{max} – represents the maximum distance from the center of mass to the outer cortex – measured by pQCT

IT – intertrochanteric region of the proximal femur as measured by DXA and a site reported from HSA

LS – total lumbar spine - a site measured by DXA

LT – loaded physical activity time per week

MES – minimal effective strain – the amount of stimulus required to maintain the skeleton

MRI – magnetic resonance imaging

NN – narrow neck region of the proximal femur reported from HSA

PA – physical activity score (score/5) measured by the PAQ-C – Physical Activity Questionnaire for Children

PF – total proximal femur – a site measured by DXA

PAV – peak bone accrual velocity

PHV – peak height velocity

PPM – Pearson Product Moment correlations

pQCT – peripheral Quantitative Computerized Tomography

Pre-pubertal – a measure of maturity indicated by Tanner stage 1

S – shaft region of the femur for HSA

SPW – sub-periosteal width a structural parameter from HSA

TB – total body measured by DXA

TR – trochanteric region – a sub-region of the total proximal femur as measured by DXA

Wt – weight or total mass (kg)

Z – section modulus Z = CSMI/ r_t - an expression of bending or torsional resistance – measured by pQCT and HSA

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Dedication

for my amazingly loving and supportive parents George and Gail Bryant

&

my soul mate Dave and sweet baby Georgia

Chapter 1: Introduction

Adult bone mass is a function of the amount of bone gained during the years of growth, the amount of bone conserved during adulthood, and the amount of bone lost with advancing age. There is now strong evidence to support the important role of childhood bone mineral accrual for optimal bone health. The current cost of osteoporosis in Canada is approximately $1.3 billion per year which means that over the next 25 years $32.5 billion will be spent on the treatment of osteoporotic fractures (Wiktorowicz, Goeree et al. 2001). These conservative estimates do not account for the cost of 50 – 75% of fractures in persons with mild to moderate low bone mass, who do not have osteoporosis (Seeman, 2002).

Recent evidence suggests that exercise elicits a positive osteogenic response and that childhood may be an opportune time to deliver an exercise program to promote this response (McKay and Khan 2000), (Bailey, Faulkner et al. 1996), (Bailey and McCulloch 1992). The World Health Organization has "red-flagged" inactivity in children as a major health risk that contributes to chronic diseases such as osteoporosis (WHO, 2001). Thus, exercise strategies aimed at promoting a healthy skeleton have the potential to provide major public health benefits.

Current knowledge regarding the normal process of bone gain during childhood comes from both large cross-sectional studies (Wang, Aguirre et al. 1997; Young, Hopper et al. 1995, Nguyen, Howard et al. 1998) and longitudinal studies (Theintz, Buchs et al. 1992; Bailey, McKay et al. 1999) of bone mass

using dual energy x-ray absorptiometry (DXA). Generally, these studies have identified a critical period, for both boys and girls, during growth when the tempo of bone mineral accrual accelerates and when as much as 26% of the adult skeleton is laid down (Bailey, McKay, 2000).

Cross-sectional studies of female racquet sport players found significantly greater side-to-side differences in areal bone mineral density (aBMD) and bone mineral content (BMC) ($p < 0.001$) in the upper extremity and lumbar spine (LS) between players and controls (Haapasalo, Kannus et al. 1994, Kannus, Haapasalo et al. 1995, Haapasalo, Kannus et al. 1998). These researchers also found that the starting age of exercise had an effect on BMC in the dominant arm. Those players who started before menarche had a 2 – 4 times greater bone gain than those athletes who began playing before menarche (Kannus, Haapasalo et al. 1995). This series of contralateral side studies provide strong evidence that exercise has a significant osteogenic effect in childhood and that starting age of exercise can have a significant positive effect on the amount of bone accrual in childhood.

In addition, a series of prospective pediatric intervention trials provide convincing evidence of the positive effect of mechanical loading on bone accrual (Fuchs, Bauer et al. 2001; Bradney, Pearce et al. 1998; Morris, Naughton et al. 1997; McKay, Petit et al. 2000; MacKelvie, McKay et al. 2001; Heinonen, Sievanen et al. 2000). These studies began to characterize the region-, sex-, maturity- and bone surface-specific response of immature bone to loading. However, the specific type, intensity and duration of exercise required to elicit a

significant bone response remains unknown. For the most part, these intervention trials were designed to deliver a greater strain magnitude than would normally be encountered in daily activities. Recently, it has been shown, in animals, that multiple bouts of exercise with long rest intervals resulted in similar or greater effects than higher intensity, low frequency exercise regimens (Robling, Burr et al. 2001; Robling, Hinant et al. 2002).

Few studies have outlined the effects of exercise interventions on bone strength and structure. Petit and colleagues (Petit, McKay et al. 2002) used hip structural analysis of the proximal femur and demonstrated that reduced endosteal expansion or increased endosteal apposition, along with, increased bone cross-sectional area underpin the bone strength and structural advantages observed in early-pubertal girls after a 7-month circuit-training intervention. Heinonen and colleagues (Heinonen, Sievanen et al. 2000) used peripheral quantitative computerized tomography (pQCT) of the tibia to investigate the bone strength and structural changes after a 9-month step-training and jumping intervention and noted no significant differences between intervention and control groups.

This thesis is comprised of a comprehensive literature review outlining the rationale for this study (Chapter 2), research questions and hypothesis (Chapter 3), methods (Chapter 4), results (Chapter 5), discussion (Chapter 6), conclusions and summary (Chapter 7).

In sections 2.1 to 2.3, I present a brief summary of the biology of bone, bone growth, modeling and remodeling followed by a discussion of the biomechanics of bone. Next, in part 2.4 and 2.5, I review how bone mineral content is assessed in children and describe the normal patterns of bone mineral accrual. In 2.6, methods to assess maturity are reviewed. In 2.7, I detail the effects of exercise on bone mineral and bone mineral accrual from cross-sectional athlete studies, prospective intervention trials of children and from animal models. In 2.8, I discuss whether bone mineral accrual gains are maintained after the cessation of exercise or following retirement from sport. The evidence from both human and animal studies is provided. Lastly in 2.9, I present the recognized limitations in the current body of literature.

2.1 Bone Biology – What is bone?

2.1.1 Bone Function

Bone is a multifunctional organ that is responsible for: 1) providing mechanical support, locomotion and lever action, 2) protecting soft tissues, 3) storing minerals such as calcium, phosphate, potassium, bicarbonate and magnesium, 4) calcium homeostasis and 5) providing the location for hematopoiesis (Khan, McKay et al. 2001). The primary focus of this thesis is the skeleton's function to bear the gravity- and muscle contraction mechanical forces imposed on it without breaking to thus, permit efficient locomotion (Jarvinen, Kannus et al. 2003).

2.1.2 Forms of Bone

Bone is composed of collagen (20-25%), water (5%), and crystalline calcium hydroxyapatite (70%) (Khan, McKay et al. 2001). The four types of bone are woven, lamellar, Haversian, and laminar. Woven bone, comprised of randomly arranged collagen, makes up all the bone in the body at birth and is replaced by the uniformly structured lamellar bone at about 4 years old. Lamellar bone is also found at fracture healing sites and sites of rapid or great mechanical load during adulthood (Currey 1984). Haversian bone is found when a matrix of bone encircles a blood vessel in the cortical bone (discussed in section 2.1.4) forming an osteon (Khan, McKay et al. 2001). Finally laminar bone is a plate-like bone formed in alternating layers of laminae when a bone needs to respond quickly to stress and growth, as is commonly found in larger mammals (Currey 1984).

2.1.3 Bone Cells

Osteoblasts, osteocytes, and osteoclasts are the three types of bone cells and are responsible for the process of bone remodeling. Osteocytes are mature bone cells responsible for the cellular communication of bone loading and are formed from the calcification of the matrix forming osteoblasts. Osteoblasts reside in the surface of the bone in groups where they synthesize, excrete and mineralize collagen, matrix protiens, noncollagen and regulatory factors (Puzas 1996). It is the responsibility of the osteoclasts to resorb bone, they are large, multi-nucleated cells that produce hydrogen ions proteolytic enzymes which allow

them to resrob bone (Mundy 1996). Osteocytes, osteobalsts, and osteoclasts work together to enable bone to respond to the different stresses and strains it experiences. That is, together these cells maintain homeostasis within the bone (Currey 1984).

2.1.4 Bone Structure and Arrangement

There are two primary bone compartments: trabecular and cortical. Trabecular bone is composed of vertical and horizontal interconnected plates called trabeculae which gives it a spongy appearance. Cortical bone forms the outer shell of long bones and is composed of long horizontally oriented collagen fibers making it dense in appearance and able to withstand force. Because trabecular bone has greater bone surface area, it is much more responsive to the shear forces created by fluid flow as a result of loading than cortical bone. In cortical bone the cells are much closer together and lack the lattice structure of trabecular bone; therefore, fluid can not move as easily through it (Lee and Einhorn 2001).

The skeleton is commonly divided into appendicular and axial regions. The appendicular skeleton refers to all the long bones such as the arms and legs. The axial skeleton refers to all flat bones, like the pelvis and scapula, and the vertebrae which make up the spine (Khan, McKay et al. 2001).

Figure1 illustrates the structure of a growing long bone. Cortical bone is located in the midshaft or diaphysis, whereas trabecular bone is found at the bone ends (epiphysis) and metaphysis (Khan, McKay et al. 2001). Frost (1997) and Schonau (1997) hypothesized that bone is constructed in this manner to

protect the bone ends from damage due to stress and to give the bone its strength in the axial direction (Frost 1997; Schonau 1997).

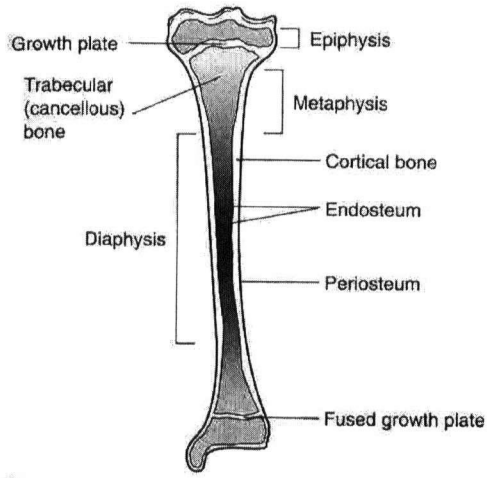


Figure 1 Diagram of a growing long bone (Khan, 2001)

2.2 Bone Growth, Modeling and Remodeling

Growth, modeling, and remodeling are the three distinct processes bone undergoes over the human lifespan (Barr and McKay 1998).

2.2.1 Growth

The first process, *growth*, is genetically predetermined and hormonally regulated. It is defined by the change in width and length of the bones that occurs from birth to the end of linear growth, usually the end of adolescence (Barr, McKay 1998). Increases in bone length and the size and number of the trabeculae are a function of endochondral ossification. Cortical bone increase and widening of the bone, on the other hand, are a function of periosteal apposition (Parfitt 1994).

2.2.2 Modeling

Modeling refers to the process of bone apposition, primarily during growth, that produces a net gain in bone at a specific loaded site. Prior to modeling, there is no bone resorption, as there is in the process of remodeling (Barr and McKay 1998). Modeling is active on trabecular, cortical-endosteal and periosteal surfaces of bone (Frost 1992). Subsequently, modeling results in the shaping of the bone in response to the load placed on it during growth. Modeling is characterized by the formation of a collegan-based extracellular matrix formed from chondrocytes, followed by deposition of calcium within this matrix and subsequent vascularization (Lee and Einhorn 2001). Two of the most important adaptive responses to bone loading during growth are an increase cortical thickness and bone cross-sectional area (Van der Meulen, Beaupre et al. 1993; Kannus, Sievanen et al. 1996; Moro, van der Meulen et al. 1996; Schonau 1997).

2.2.3 Remodeling

Although similar to modeling, *remodeling* requires that old or damaged bone be resorbed prior to the accrual of new bone. Remodeling is the primary response of bone to loading in adulthood; however it can occur during growth, and can modify the shape of the bone (Barr and McKay 1998). Longitudinal bone growth occurs at the epiphyseal (growth) plate. Bone remodeling during growth and development occurs at the metaphysis (Khan, McKay et al. 2001). Bone remodelling is a surface phenomenon and occurs on endosteal, periosteal, trabucular and Haversian canal surfaces and is primarily responsible for the way bone is gained, replaced or lost at specific sites and how bone structure evolves

over time (Lee and Einhorn 2001). The rate of trabecular bone remodelling are 5 to 10 times higher than cortical bone remodelling in adulthood. Cortical bone remodelling ranges from 50% at sites such as the midshaft of the femur in the first two years of life to 2 to 5% in old age (Lee and Einhorn 2001). The skeleton is comprised of individual structural units called bone metabolic units (BMU). Approximately 20% of the skeletal mass is made of trabecular bone and cortical bone approximately 80%. A cortical BMU is the haversian system or osteon (approximately 200 to 250 micro meters in diameter) and the trabecular BMU is much larger, approximately 600 micro meters long and 60 micro meters wide, and comprised of crescent shaped trabecular surface (Lee and Einhorn 2001).

2.3 The Biomechanics of Bone – How does bone respond to stress and strain?

Bone has the capacity to adapt to the loads imposed upon it. Stress is defined as the amount of force applied to a particular area and is expressed in Newtons/m^2 or Pascal (Pa). In other words, stress is the internal resistance that is generated within the bone to resist an applied external load, which is equal in magnitude, but opposite in direction (Lee and Einhorn 2001). Strain is defined as the amount of bone deformation caused by a particular stress and is measured as a % change in bone dimension from its original shape (Khan, McKay et al. 2001). In this section I discuss bone remodeling and the mechanostat theory of Frost (Frost 1997). I also review the process of mechanotransduction.

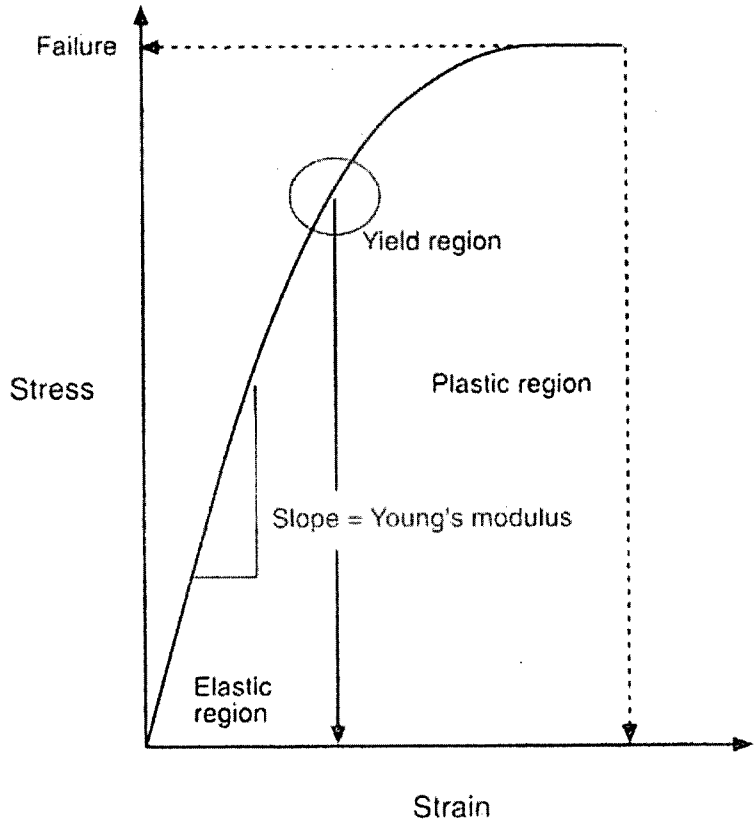


Figure 2. Stress-strain curve for a specimen of bone testing the material properties (Lee and Einhorn 2001).

Figure 2 demonstrates the stress-strain curve, which illustrates the material properties of bone which are stiffness and strength. The strength of a bone is measured by the load at the yield region, otherwise known as the failure point of the bone (Lee and Einhorn 2001).

2.3.1 Bone Mass, Density, Structure and Strength

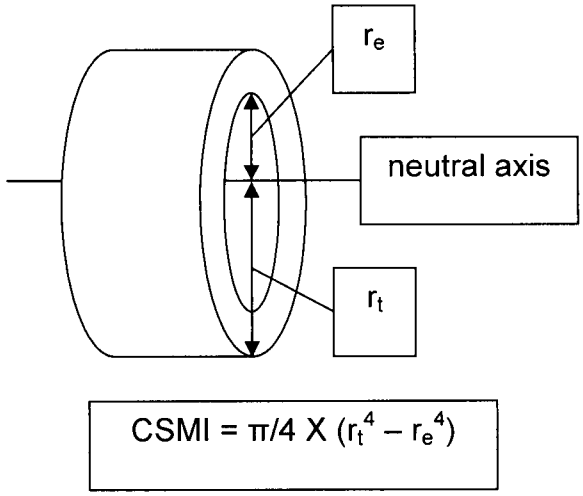
The mechanical competence of bone is a product of both its intrinsic properties (mass and density) and its geometric or structural properties (endosteal, periosteal, and cortical dimensions). Bone mass is defined as the

material composition of bone or bone mineral content (BMC, grams) as measured by dual-energy x-ray absorptiometry (DXA) (Khan, McKay et al. 2001).

Bone structure makes a significant contribution to bone strength (Frost 1997; Schonau 1997). Bones with different structural properties resist bending differently, even though they have similar cortical density and total cortical bone mass. The tubular shape of long bone is ideal for withstanding external loads (Beck, Ruff et al. 1990).

Cross sectional moment of inertia (CSMI) is related to bone bending strength. As cortical bone mass is distributed further from a bone's center of mass, the greater the CSMI or strength (Figure 3).

Figure 3. The cross sectional moment of inertia (CSMI) is a measure of a bone's resistance to bending and torsional loading. CSMI is calculated using the total bone radius (r_t) and endocortical radius (r_e) (Modlesky, Lewis et al. 2002)



In other words, the relative distance of the cortical bone shell from the center of gravity is proportional to bone stability, with the exception that when the cortical thickness becomes too thin, as in old age, the bone is susceptible to buckling (Beck, Ruff et al.1990). As this relationship is a fourth order exponential one, a small increase in the distance of cortical bone mass from the center of mass (r_t) will result in a dramatic increase in bone strength. Likewise, an increase in

endocortical apposition resulting in a decrease in the distance of the endocortical surface from the center of mass (r_e) will result in a dramatic increase in bone strength. (Forwood 2001; Rauch and Schoenau 2001; Modlesky, Lewis et al. 2002). For example, an increase of 1 mm in cortical cross-sectional area, in a growing child, results in a four-fold increase in bending strength (Forwood 2001)!

2.3.2 Wolff's Law – Skeletal Response to Loading

The principle that bone will remodel or optimize structure (bone mass, geometry, and material properties) in response to a physical force or applied load, measured in Newtons (N), has been attributed to Julius Wolff ((Wolff 1892)). However, there is some debate as to whether these principles are rightfully the brainchild of Wilhelm Roux (Bailey, Faulkner et al. 1996). The bone's response to an external load is referred to as mechanical loading. Mechanical loads are delivered to the bone via physical activity, exercise or loading system.

Physical activity is a catch-all term for any bodily movements performed by the skeletal muscles that produce an energy expenditure greater than the basal level (Sallis, Owen, 1998). Frequency, intensity, time and type are the characteristics of physical activity and commonly abbreviated to FITT. The manipulation of these characteristics of physical activity can result in different health outcomes, for example high-intensity vs low-intensity physical activity influencing an increase in the efficiency of the heart to circulate blood.

Exercise is defined as purposeful, repetitive, planned and structured physical activity that is performed with the objective of improving and maintaining

one or more aspects of physical fitness (Reid, Dyck et al. 1999). Load-bearing physical activity, that is any activity producing a force greater than or different from those experienced on a routine basis from gravity and muscle contraction, is associated with a positive osteogenic response in growing bone (Beck, Shaw et al. 2001).

To study the adaptive response of the growing skeleton to strain in animal studies, measurement of the mechanical load involves an instrument or loading system that will hold the limb to be effected and produce a controlled force onto that limb which allows the variables of strain rate, magnitude and frequency to be manipulated in a controlled manor to tease out the specific bone response to each (Mosley, Lanyon 2002; Robling, Hinant et al. 2002). In order to measure mechanical loading in humans, ground reaction forces (GRFs) must be measured. When an object creates a force against another object it creates a reaction force and this reaction force can be measured with a force platform. For example, children doing plyometric jumps (taking off with two feet) had GRFs measured at over six times their body weight (McKay, Tsang et al. submitted).

There are three types of load or stress: compressive, tensile and shear. Compressive loads are imposed when the force on the bone pushes it together; for example the axial load produced in the tibia by walking. A tensile load is the result of pulling or bending of the bone away from itself; for example, the inferior side of the femoral neck undergoes a tensile load in response to the transfer of the axial load from the femoral shaft to the femoral neck from activities such as running or jumping. Thirdly, shear stress is produced when two forces are

applied parallel to each other across the bone, also know as a torsion force (Khan, McKay et al. 2001).

There are three elements of strain: magnitude, rate, and frequency. The quantity of change in bone length, or the degree of deformation, under a mechanical load is referred to as strain magnitude. Strain rate is the speed at which strain develops within the bone and then releases. Strain frequency corresponds with the distribution of the strain bouts (Carter and Hayes 1976; Lanyon, Goodship et al. 1982). The varying and interactive effects of bone's response to these elements of strain are discussed in section 2.3.5.

2.3.3 The Mechanostat and the Utah Paradigm

The "mechanostat" refers to a concept first presented by Harold Frost in 1987 (Frost 1987). It maintains that bone responds to loading in order to maintain an appropriately supportive structure given the amount and type of load being placed on it. Thus, the skeleton requires a minimal effective strain (MES) stimulus to be maintained. In other words, bone requires at least a certain level of stress that, in turn deforms (strains) the bone enough so that it continues to remodel and maintain its bone mineral. If the MES is not maintained, then resorption will be greater than formation and bone mass will decline. Such is the case when a bone is immobilized due to fracture (Frost 1987; Frost 1987).

Further, Frost has proposed the Utah Paradigm which helps explain how load-bearing bones adapt to develop a structure to develop the strength to carry the largest loads required in order not to break. Muscle forces produce the greatest loads on bones due to lever effects. Those strains cause strain-

dependent signals which are detected at the cellular level and cause local modulation of osteoclasts and osteoblasts, from cell-to cell directional orientation communication, affecting bone growth, modelling and remodelling. The result is an adaptive response of both bone architecture and bone material quality, the two determinants of bone strength (Frost 2001). As mentioned above, the mechanostat refers to the concept of the homeostatic regulation of bone structure.

The newer component of this theory is the basic multicellular unit or BMU-based remodelling whereby small packets of bone can be turned over. The BMU can work in "disuse-mode" or "conservation-mode". When in "disuse-mode", BMUs make less bone than they resorb in bone next to the marrow, trabecular or endocortical bone in both children and adults (Frost 2001). In "conservation-mode" BMUs resorb and replace relatively equal amounts of bone so that there is no net loss or gain in bone mass. The mechanical effects on bone, especially through the muscle-bone-unit, determine over 40% of modelling and remodelling actions (Frost 2001).

2.3.4 Mechanotransduction

Mechanotransduction refers to the biological mechanisms by which bone communicates to maintain homeostasis or optimal levels of strain by adjusting its structure (Ko and McCulloch 2001). Mechanocoupling, biochemical coupling, transmission of the biochemical signal and effector (bone cell) response are the four steps in mechanotransduction (Duncan and Turner 1995).

First, a mechanical force on the bone triggers a signal to the cells; this process is called *mechanocoupling* (Duncan and Turner 1995). Similar to the movement of fluid through a sponge, fluid in the bone matrix is forced through the cell membranes of the osteocytes causing a fluid sheer stress within those membranes (Weinbaum, Cowin et al. 1994). Next, bone cells *biochemically couple* to integrins (glycoprotein) and attach to the collagen matrix. This process stimulates osteoblastic cells and the release of Ca^{2+} from the endoplasmic reticulum (Chen, Ryder et al. 2000).*Transmission of the biochemical signal* is likely conducted by osteoblasts that are stimulated in response to the load on the bone by intermediary biochemical compounds called second messengers. Osteoblasts communicate with osteocytes that stimulate the release of prostaglandins. Prostaglandins appear to be necessary for bone remodeling as rats incapable of prostaglandin production did not respond to a bone stimulus (Forwood 1996). Lastly, mechanotransduction requires *effector cells*, either osteoblasts or osteoclasts, to produce new, or rearranged bone (Duncan and Turner 1995).

2.3.5 The Elements of Strain

The three elements of strain: magnitude, frequency and rate, have varying and interactive effects on bone's response to loading. Further, strain distribution is also likely critical in bone adaptation and has been introduced as the 'error strain distribution' hypothesis (Lanyon 1996). Several animal studies have investigated the effects of strain magnitude, strain rate, strain frequency and

strain distribution on both growing and mature bone, and I these are summarized in the following sections.

2.3.5.1 Strain Magnitude

Bone structure is maintained when mechanical strains are maintained between 200 and 2500 microstrains or minimal effective strain (MES) and if these MESs are exceeded bone modelling will result in an increase in bone mass (Frost 1990). A study on turkey ulnae revealed that as strain magnitude increased, there was a resultant increase in bone formation and what bone response thresholds might be (Rubin and Lanyon 1985). The researchers immobilized the turkey ulnae for 8 weeks, which resulted in a 20% decrease in CSA. Rubin and colleagues (Rubin and Lanyon 1985) found that strains in excess of 4000 microstrains delivered in 100 load cycles resulted in a 40% increase in CSA and that strains of 1000 to 2500 microstrains resulted in endosteal and periosteal bone formation which maintained CSA.

Another more recent study subjected rats to a four-point bending apparatus which imposed two levels of strain (800 and 1000 microstrain) at four different cycle frequencies: 0, 40, 120 and 400 cycles per day. There was a 2.8-fold increase in periosteal bone formation rate at the 400 cycle/day, but not lower at the 800 microstrain level compared with controls (Cullen, Smith et al. 2001). At the 1000 microstrain level, formation rate of periosteal bone increased 8 to 10 fold and at the endosteal formation surface, at the 120 and 400 cycle frequencies, the formation rate doubled. The authors concluded that bone formation occurred at both periosteal and endosteal surfaces when higher strain

magnitudes are applied at moderate or high frequencies controls (Cullen, Smith et al. 2001).

2.3.5.2 Strain Rate

Judex and colleagues (Judex and Zernicke 2000) conducted a study with young roosters. Animals were assigned to either a sedentary control (n=10) or a dropping group (n=10). Those in the treatment group were dropped 200 X/day producing a peak strain rate of +740% and strain magnitude of +30%. After 3 weeks, researchers found a high correlation between strain rate and bone formation on the endocortical (+370%), but not periosteal surface (+40%). The authors concluded that the unusual strain rates were responsible for the significant osteogenic response (Judex and Zernicke 2000). This study also demonstrated the importance of evaluating the surface-specific response to loading.

The fluid flow required to stimulate new bone formation is dependent on the rate of change in bone strain (O'Connor, Lanyon et al. 1982). O'Connor and colleagues (O'Connor, Lanyon et al. 1982) demonstrated greater amounts of bone formation associated with peak strains applied at high strain rates and lower bone formation rates or bone resorption associated with peak strains applied at low strain rates. Evidence supports the theory that strain rate is an important component in the process of bone adaptation, in other words, if only strain magnitude and strain distribution were important than static loading would have an osteogenic effect (Lanyon and Rubin 1984).

2.3.5.3 Strain Frequency

In a study of strain frequency, the right forelimbs of adult rats were loaded 360 times/day, 3 days/week for 16 weeks. One group (n=13) received all 360 loads at a single time point whereas the other group (n=13) received 90 loads separated by 3 hours at 4 time points throughout the day for a total of 360 loads. The left forelimbs served as a control for all animals in addition to two control group of rats, one age-matched control (n=9) and baseline control (n=9). Although both exercise groups had significantly greater ulnar BMC by DXA (6.9%, p=0.016) in the right forelimb compared with the left and the multiple exercise bout group had significantly higher values (70% greater difference between right and left limb, p=0.001) than the single bout group, even though strain rate and magnitude were equal between groups. Similarly, strength measures by pQCT at the ulnar midshaft revealed significantly greater ($p<0.0001$) CSA, vBMD, I_{min} and I_{max} in the right forelimb compared with the left in both loaded groups. In addition, the multiple exercise group had significantly greater (37%, p=0.012) CSA than the single bout group. Therefore, strain frequency is also an important factor to consider when designing an exercise intervention. These researchers concluded that human exercise interventions aimed at improving bone mass may achieve greater success if the daily exercise program is broken down into smaller sessions separated by recovery periods as this enhances the mechanosensitivity of the bone to a loading stimulus (Robling, Hinant et al. 2002).

An earlier study by this group found that rats allowed an 8 hour recovery period between exercise bouts, had 100% greater bone formation rates at the tibia than those rats that had shorter recovery periods. Bone formation rates were directly related to the length of recovery period in the groups less than 8 hours - that is groups with no recovery period had very little bone formation. They concluded that 8 hrs was the approximate optimal time period required to restore mechanosensitivity to bone (Robling, Burr et al. 2001).

Umemura and colleagues (Umemura, Ishiko et al. 1997) found that tibiae of 5-week old rats (n=57) that performed 5 jumps/day had significantly larger cortical cross-sectional area ($p<0.05$), than their counterparts who were sedentary. There were no significant differences between the 5-jumps/day group and four other jump groups (10-, 20-, 40- and 100-jumps/day). The authors concluded that a large number of strains per day is not required for exercise-induced bone enhancement in rats (Umemura, Ishiko et al. 1997). This study demonstrated that more is not always better in that the bone has a mechanosensitivity threshold that once past, any further increase in the amount of exercise in a single session may not produce a bone response.

2.3.5.4 Strain Distribution

The 'error strain distribution' hypothesis refers to the theory that bone responds to reduce the error by making structural changes to respond to strain distributions that vary from the normal (Lanyon 1996). Strain distribution involves the combination of strain magnitude with strain rate to create strains that are unusual for the effected bone causing an osteogenic response. An osteogenic

response occurred when low strain magnitudes that were typical of regular daily activites (that would not typically cause an osteogenic response) were applied in an unusual distribution in sheep (Lanyon, Goodship et al. 1982) and in turkey ulnae (Rubin and Lanyon, 1985). The greatest osteogenic response seems to be the result of high strain magnitude and strain rate with an unusual strain distribution, as demonstrated by previously discussed experiment using roosters by Judex et al. (Judex and Zernicke 2000).

2.4 The Measurement of Bone

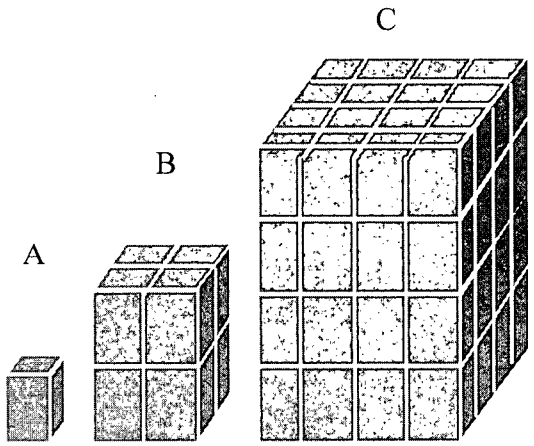
2.4.1 Dual Energy X-Ray Absorptiometry (DXA)

DXA is a precise, safe, relatively inexpensive and readily available measure of bone mineral. DXA measures bone mineral content (BMC, g), bone area (BA,cm^2), and areal bone mineral density (*a*BMD, g/cm^2) for the total body, lumbar spine, proximal femur and its sub regions: femoral neck (FN), intertrochanteric region (IT) and trochanteric region (TR). Areal BMD by DXA is a two dimensional (length and width) representation of a three-dimensional (length, width and depth) bone which does not reflect true, three-dimensional density (g/cm^3) (Khan, McKay, 2001). Figure 4 shows that even though "true" bone density (*v*BMD) does not change, an increase in bone size results in an increase in *a*BMD by DXA. Therefore, it is important to control for change in size as it can account for the change in *a*BMD, which may inappropriately be attributed to an adaptive response. Further, DXA cannot differentiate cortical and trabecular compartments of bone and does not evaluate bone structure and strength, but

provides only bone's material properties. Convention is currently that BMC be reported to avoid misinterpretation of bone outcomes.

Figure 4. Bone area, volume and BMD of 3 different size blocks made of identical material, weighing 1 g/cm^3 (Khan et al. 2001)

		A	B	C
HEIGHT	[L^1]	1 cm	2 cm	4 cm
AREA (side)	[L^2]	1 cm^2	4 cm^2	16 cm^2
VOLUME	[L^3]	1 cm^3	8 cm^3	64 cm^3
*a*BMD	g/cm^2	1 g/cm^2	2 g/cm^2	4 g/cm^2
vBMD	g/cm^3	1 g/cm^2	1 g/cm^3	1 g/cm^3



Although DXA has limitations, it is currently the most common assessment of bone mass in children and adults. It is also a safe method for measuring the clinically relevant sites at the hip and spine. In addition, large epidemiological trials have established a strong link between aBMD as measured by DXA and adult fracture rates (Melton, Wahner et al. 1986; Melton and Riggs 1987; Melton 1993; Goeree 1996; Wiktorowicz, Goeree et al. 2001). In an attempt to address DXA's inability to measure true density, some researchers have developed mathematical equations based on geometric assumptions that can estimate bone volume and applied them to DXA data. They termed these bone mineral apparent density (BMAD) or corrected BMD (corr BMD) (Beck, Ruff et al. 1990; Kroger, Kotaniemi et al. 1992).

2.4.2 Hip Structural Analysis (HSA)

The cross-sectional properties of bone make a considerable contribution to its strength as the relative distance of the cortical bone shell from the bone center of mass is proportional (to the fourth order) to bone stability (Frost 1997, Schonau 1997); therefore, it is important to measure exercise-induced changes in these properties. To this end, Dr. Tom Beck (John Hopkins University) has developed the Hip Structural Analysis (HSA) program (detailed in Methods). This program estimates geometrical properties of bone at the proximal femur from planar DXA scans (Beck, Ruff et al. 1990).

Three regions: the narrow neck (NN), intertrochanteric (IT) and femoral shaft (S) are analyzed using 5mm thick segments. Distribution of the bone mass across the segment is assessed to determine the cross-sectional area (CSA), the subperiosteal width (SPW), section modulus (Z) and areal bone mineral density (aBMD) and simple models using measured dimensions and assumptions of cross-sectional shape are used to estimate cortical thickness (AVG CORTEX). Z is determined by first determining the cross-sectional moment of inertia (CSMI) and then dividing that value by half the subperiosteal width for the NN and S. For the IT region, CSMI is divided by the distance from the region centriod to the lateral margin.

The advantage of HSA is that it acknowledges the relative contributions of cortical thickness, bone shape, diameter, trabecular and cortical bone distribution and the total amount of bone tissue. The limitation of this method is that because it uses the DXA scan, it too assumes the properties of a three dimensional object

from a two dimensional image. Therefore, HSA assumes that the femoral neck is shaped like an annulus and that the proportions of trabecular and cortical bone are fixed.

2.5 Bone Mineral Accrual in Children

2.5.1 Normal Pattern of Bone Accrual

The pattern of normal bone mineral accrual has been described from both cross-sectional (Theintz, Buchs et al. 1992; Young, Hopper et al. 1995) and longitudinal data (Bailey 1997; Martin, Bailey et al. 1997; McKay, Bailey et al. 1998; Bailey, McKay et al. 1999; Bailey, Martin et al. 2000). Bone mineral is accrued steadily throughout the growing years, accelerates rapidly at all skeletal sites with the onset of puberty, and reaches a plateau at sexual maturity (Theintz, Buchs et al. 1992; Bailey 1997; Bailey, McKay et al. 1999; Bailey, Martin et al. 2000). Peak bone mass is achieved, on average, by the second decade of life (Bailey, McKay et al. 1999), but as much as 95% of adult bone mass is gained by age 15 years in girls (McKay et al 1994).

2.5.2 Sex Differences

Important evidence regarding bone accrual in children comes from the six-year longitudinal University of Saskatchewan Bone Mineral Accrual Study (Bailey, McKay et al. 1999). Boys (n=60) and girls (n=53) were measured by DXA annually over a six-year period through critical stages of growth and development, providing a novel account of the timing of bone accrual through the different stages of puberty. The peak height velocity growth curve in Figure 5 demonstrates the approximate 3-month lag between peak height velocity (PHV)

and PAV (Bailey, McKay et al. 1999). It also demonstrates the relatively greater magnitude of bone accrual at peak in boys (394 g/yr) as compared with girls (342 g/yr). Approximately 26% of total body bone mineral is accrued during the two years (boys 13.1 – 15.1 years of age and girls 11.5 – 13.5 years of age) surrounding PHV. Figure 5 also illustrates the approximate two-year difference for PHV and peak bone accrual between boys (14.1 +/- 0.95 years of age) and girls (12.5 +/- 0.9 years of age). This supports the argument that the sexes must be compared at a similar biological landmark rather than chronological age (Bailey, McKay et al. 1999; Bailey, Martin et al. 2000). Two epidemiological studies of children revealed that the risk of fracture is twice as likely at peak height velocity when bone accrual lags behind linear growth (Bailey, Wedge et al. 1989; Blimkie, Lefevre et al. 1993).

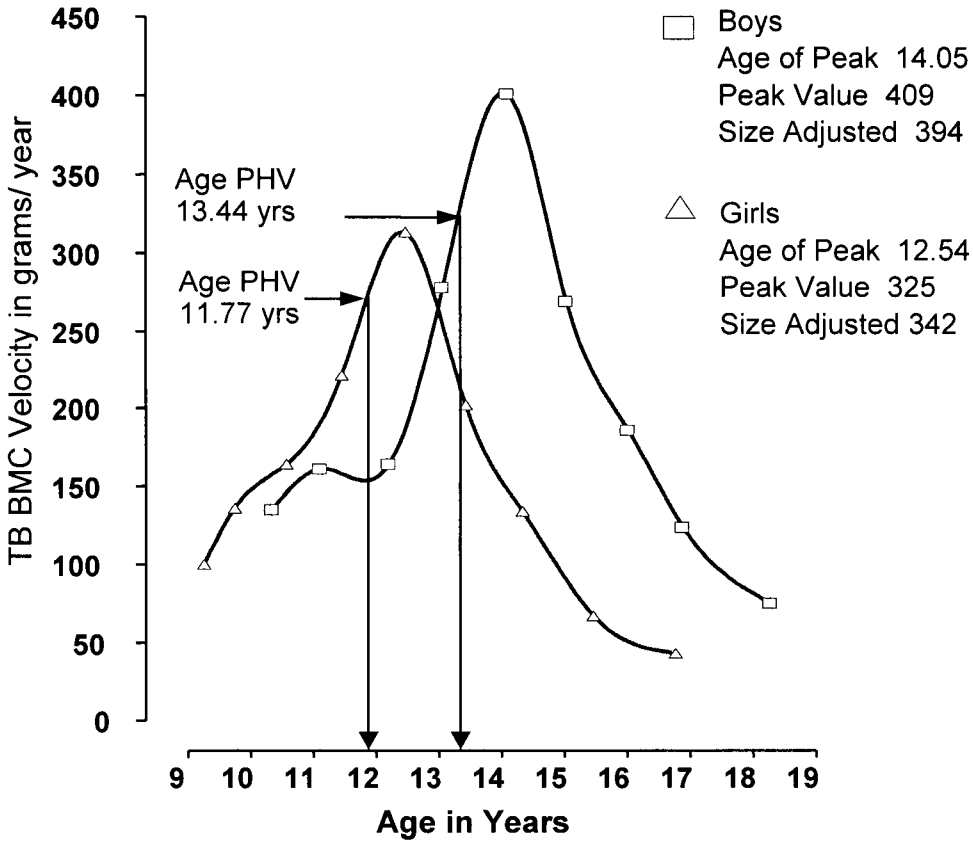


Figure 5. Velocity curves for bone mineral accrual for the total body for boys and girls. Note the difference in magnitude and timing of peak bone accrual velocities, with girls slightly ahead of boys, but boys with a greater peak magnitude. Bailey et al. 1999

2.5.3 Site Specificity

A three-year mixed longitudinal study of lumbar spine and femoral neck bone accrual in Caucasian children aged 6 to 14 years (n=90) found that almost one third of LS BMC was accrued during the three years around the onset of puberty (Slemeda, Reister, et al. 1994). The average rate of BMC gain in the LS during prepuberty was 0.027 g /cm^2 per year and 0.077 g /cm^2 per year during peripuberty ; whereas, the average rate of BMC gain at the femoral neck was 0.030 g /cm^2 per year during prepuberty and 0.047 g /cm^2 per year during peripuberty. This discrepency to rates of bone gain at different maturational

stages contributes to the theory that bone gains in childhood can be attributed to increases in bone length while bone gains in puberty can be attributed to periosteal apposition and endocortical contraction (Slemeda, Reister, et al. 1994).

Similarily, a two year mixed longitudinal study of Caucasian girls aged 6.9 to 16.6 years of age (n=109) provided evidence that bone is accrued in the leg and spine at different times during maturation (Bass, Delmas et al. 1999). At baseline, the girls were divided into three groups based on maturational development : Tanner stage 1 or prepubertal (6.9 – 11.9 years of age, n=36), Tanner stages 2 – 4 or peripubertal (10.1- 15.1 years of age, n=26) and Tanner stage 5 or postmenarcheal (11.4 – 16.6 years of age, n=36). BMC gain in the spine and legs were 38 and 240 grams from 7 to 11 years of age, peaking at 72 and 241 grams from 11 to 14 years of age and tailing off to 46 and 149 grams from 14 to 17 years of age respectively. Rapid growth in trunk length was represented by a rapid increase in sitting height between 12 and 13 years of age and was also reflected in rapid gains in spine BMC between 11 and 14 years of age, which is consistent with the findings of previous studies (Malina, Bouchard, 1991; Karlberg, 1989). BMC gain in the legs was relatively the same between 7 to 11 years of age and 11 to 14 years of age with a sharp decrease from 14 to 17 years of age, however, the girls had the greatest growth velocity in the legs during the 7 to 11 years of age interval, with the femoral length increasing on average 19.0% during that period, slowing to a 9.9% increase between 11 and 14 years of age (Bass, Delmas et al. 1999).

A third recently published study from the University of Saskatchewan capitalized on the 6-year mixed longitudinal data from the Saskatchewan Pediatric Bone Mineral Acrrual Study (detailed above) to develop a method of predicting years from peak height velocity as an alternative measure of maturity (Mirwald, Baxter-Jones et al., 2002). Using a regression equation that incorporates the varying tempo in gains in sitting height and leg length and height, the authors were able to validate an equation to estimate years from peak height velocity. These three studies provide evidence to suggest that rapid trabecular (spine) bone accrual, that is more hormonally dependant occurs in a shorter more 'critical' time period during puberty after the slower accumulation of cortical (leg) bone throughout mid-childhood to puberty.

2.5.4 Determinants of Bone Mass

The key determinants of bone mass are genetics, race, sex, size, maturity, physical activity and calcium.

2.5.4.1 Genetics

Studies of family units investigating patterns of total aBMD reveal that heredity explains between 46 - 62% (Krall and Dawson-Hughes 1993) and 39 – 84% (Gueguen, Jouanny et al. 1995) of the variance in bone mass after controlling for environmental factors such as calcium intake, physical activity, smoking and alcohol intake. However, some of the strongest evidence that aBMD is a result of the interaction between genes, environmental and lifestyle factors comes from monozygotic (identical) twin studies (Nguyen, Howard et al. 1998). Nguyen and colleagues (Nguyen, Howard et al. 1998) found a 10 – 20% difference in aBMD

within 112 female twin pairs (mean age 52 years). At the lumbar spine, genetic heritability was estimated to be 78%, 76% for femoral neck, and 79% for total body aBMD (Nguyen, Howard et al. 1998). A second twin study assessed lean mass, LS, FN and total forearm aBMD of female monozygotic (n=122) and dizygotic (fraternal twins, n=93) pairs 10-26 years of age over a four-year period (Hopper, Green et al. 1998). Results revealed that the greatest similarity in aBMD occurred between 10 to 13 years of age and that environmental factors were a greater influence on femoral neck and lumbar spine aBMD between 13 to 17 years of age, lessoning again between 17 to 26 years of age (Hopper, Green et al. 1998). These twin studies confirm that lean mass is one of the strongest predictors of both change in and absolute aBMD during growth and in adulthood, respectively (Hopper, Green et al. 1998, Nguyen, Howard et al. 1998).

2.5.4.2 Race

Caucasians and Asians have greater fracture rates than Blacks (Horlick, Thornton et al. 2000). However, the relationship between ethnicity, race and aBMD in children has been less studied. Black youth had greater bone mass than Caucasian and non-Black youth (Bachrach 1994; Bhudhikanok, Wang et al. 1996; Nelson and Barondess 1997; Wang, Aguirre et al. 1997; Bachrach, Hastie et al. 1999; Horlick, Thornton et al. 2000). Asian boys and girls residing in the United States had similar aBMD at several sites in pre- and early puberty (Tanner Stages 1-2) as compared to same sex- and maturity-matched Caucasian children (Bhudhikanok, Wang et al. 1996).

Three studies from the University of British Columbia Bone Health Research Lab (UBC BHRL) have reported aBMD changes in Asian and Caucasian children (McKay, Petit et al. 2000; McKay, Petit et al. 2000; MacKelvie, McKay et al. 2001). The first cross-sectional study reported no apparent differences in PF aBMD between Asian (n=58) and Caucasian (n=110) prepubertal (8.9 +/- 0.7 years) boys and girls, with the exception of Caucasian boys (+8%), despite the fact that physical activity (+15%) and calcium intake (+35%) were much greater in the Caucasian children (McKay, Petit et al. 2000). The second study was the 8-month follow-up to the previous study and revealed that the Asian and Caucasian children aBMD changed similarly in numerous skeletal sites (McKay, Petit et al. 2000). Lastly, an investigation of TB, LS, PF, FN, and TR aBMD of Asian (n=56) and Caucasian (n=75) in pre- and early-pubertal girls revealed no differences in aBMD at any site between Asian and Caucasian pre-pubertal girls, despite significantly lower calcium intake ($p<0.001$) and general physical activity score ($p<0.05$) (MacKelvie, McKay et al. 2001). However, there was a 9 – 14% lower aBMD in early-pubertal Asian than Caucasian girls, even though the Asian girls had a significantly lower calcium intake ($p<0.001$) and participation in loaded physical activities and extracurricular sports ($p<0.05$), but no difference in general physical activity. Authors concluded that there was an increase in the difference between Asian and Caucasian girls in lifestyle factors related to bone health and bone mineral accrual with increasing maturation (MacKelvie, McKay et al. 2001). These studies provide

evidence that although there are some racial differences in aBMD gain in childhood, that these differences are greatly influenced by lifestyle factors.

2.5.4.3 Calcium

During growth, in infancy and adolescence, calcium (Ca) requirements are the greatest. Daily Ca accretion for pubertal children was 284 +/- 58 mg/day for girls and 359 +/- 81 mg/day for boys in the University of Saskatchewan Bone Mineral Accrual Study (Martin, Bailey et al. 1997). These estimations are based on the assumption that bone is comprised of 32.2% Ca (Matkovic and Heaney 1992). Boys in the University of Saskatchewan study consumed 1140 +/- 392 mg/day and girls consumed 1113 +/- 378 mg/day (Martin, Bailey et al. 1997). The resorption rate for young adults was reported as 144 +/- 133mg/day in a meta-analysis of subjects (n=519) from 34 different studies (Matkovic and Heaney 1992). In 1998 the daily recommended intake of Ca for this age group was 1300 mg/day (Yates, Schlicker et al. 1998).

The other determinants of bone mineral, that have been consistently reported for children, include body weight, height, lean mass, physical activity and maturity (Haapasalo, Kannus 1998; Faulkner, Bailey 1996; Petit, McKay 1999; McKay, Petit 2000; Frost 1996; MacKelvie, McKay et al. 2001; MacKelvie, McKay et al. 2002).

2.6 Maturity Assessment

2.6.1 Self-Assessed Tanner Staging

As evidenced by the Saskatchewan Bone Mineral Accrual Study, chronological age can not be used as a marker of the amount and timing of

physiological change during growth (Bailey, McKay et al. 1999). Children of the same chronological age can vary in their maturational development by up to 6 years developmentally (Malina and Bouchard, 1991). Another confounding factor is that children move through maturational stages at varying rates (Bailey, 1997). Therefore, it is necessary to record and report both level of maturational development and age in bone studies in children. Currently, the most common method is self-assessed Tanner stage, a modification of Tanner Staging (Tanner, 1978).

Tanner Staging was originally developed for clinicians to assess if a child, boy or girl, was developing normally or whether he or she may be developmentally delayed or advanced (Tanner, 1978). This method is rather invasive in nature, as it requires a clinician to observe the child naked and would not be cost effective in large, non-clinical studies. Therefore, self-assessment of Tanner stage is used, as it is private, cost-effective and has good reliability with physician-rating (Duke, Litt et al. 1980). Self-assessment of Tanner stage involves the child identifying themselves with a developmental diagram of breast and pubic hair development for girls and genitalia and pubic hair development for boys that range from Tanner stage 1 (no development) to stage 5 (fully developed). Children in Tanner stage 1 are considered pre-pubertal, those in Tanner stage 2 or 3 are said to be in early puberty, children in Tanner stage 4 are considered to be late-pubertal and finally those in Tanner stage 5 are classified as reproductively mature (Appendix 2).

2.7 How does physical activity affect growing bone?

2.7.1 Assessment of Physical Activity

One of the most common methods of assessing moderate to vigorous general physical activity in studies of bone mineral accrual in children is the Physical Activity Questionnaire for Children (PAQ-C) (Crocker, Bailey et al. 1997). The PAQ-C is self-administered 7-day recall of physical activity. It can be easily administered to large groups and is inexpensive (Crocker, Bailey et al. 1997). Because subjects need to be able to read and interpret the questions, this method is not recommended for children under 9 years of age (Sallis, Owen et al. 1999).

The PAQ-C was validated to distinguish physical activity levels between children who have high, average or low activity levels, during the six-year Saskatchewan Bone Mineral Accrual Study (Kowalski, Crocker et al. 1997). When compared to motion sensors, other self-administered physical activity measures and interview-assisted recall, the PAQ-C was found to be significantly, moderately related ($r=0.39 – 0.45$) (Kowalski, Crocker et al. 1997; Crocker, Bailey et al. 1997) and strongly related to a 5 point self-rating of physical activity ($r=0.63$), while accounting for differences in the level of activity throughout the year, as well as, the differences between boys and girls (Crocker, Bailey et al. 1997). These differentiations are important because the rate of bone accrual can change throughout the year depending on the season (Mirwald, Bailey et al. 1997) and there may be an interaction effect of sex and activity on aBMD (Matkin, Bachrach et al. 1998). The PAQ-C is limited to monitoring the effect of

general physical activity on bone accrual and cannot assist in the determination of specific exercises that may enhance bone accrual.

2.7.2 General Physical Activity and Bone

The University of Saskatchewan Peak Bone Mineral Accrual Study also demonstrated a greater rate of bone mineral gain at peak bone accrual velocity (PAV) and a greater magnitude of bone accumulation during the two years around PAV, for children in the highest quartile for physical activity over those in the lowest quartile. The most active boys and girls had a 9% and 17%, respectively, greater total body BMC than their least active counterparts one year after the age of peak bone mineral accrual (Bailey, McKay et al. 1999).

Recent evidence suggests that there is a longitudinal relationship between physical activity and lumbar spine bone mass in young adults (Bakker, Twisk et al. 2003). Bakker and colleagues (Bakker, Twisk et al. 2003) completed a ten-year longitudinal investigation of the relationship between bone mass and physical activity as part of the Amsterdam Growth and Health Longitudinal Study (males n=225, females n=241), bone measurements were taken at mean ages 27, 32 and/or 36 years. Results revealed that mechanical physical activity (loaded PA), as measured by a physical activity interview, was a significant positive linear predictor of lumbar spine aBMD for males ($r = 0.09$; $p < 0.001$), but not for females. The authors concluded that loaded physical activity or mechanical loading has a small positive influence on lumbar spine aBMD in young male adults (Bakker, Twisk et al. 2003). It is unfortunate that these researchers did not perform bone measures earlier on in this study as it began

when the subjects were a mean age of 13 years. A more effective analysis of the effects of exercise on bone mass could have been made over that longer period and while bone mass was still in the accrual phase during growth.

2.7.3 Evidence from Athlete Studies

Investigators from the University of Saskatchewan recently published evidence of bone mass, bone strength and bone structural differences between premenarchial elite female gymnasts (n=30) and sex and age-matched controls (n=30) at the hip using Hip Structural Analysis (HSA) (Faulkner, Forwood et al. 2003). Results revealed that the gymnasts had significantly greater BMC ($p <$ 0.001) at all sites (TB, LS, PF, FN, TR) when adjusted for body size. Structure and strength indices at the narrow neck (aBMD, CSA and Z) where significantly greater ($p < 0.02$) in the gymnasts when adjusted for height and weight. Endosteal diameter was significantly greater in the controls ($p < 0.001$). At the femoral shaft the gymnasts had significantly greater aBMD, CSA, Z, CSMI and subperiosteal width (SPW). Interestingly when adjusted for lean mass, all significant differences between the groups disappeared, except aBMD at the NN. This finding indicates that lean mass may be the primary contributor to bone changes in this group of gymnasts (Faulkner, Forwood et al. 2003).

Longitudinal data were collected in 37 competitive Australian female tennis players (aged 8 – 17 years) over 1.1 ± 0.01 years (Bass, Saxon et al. 2002). Players were divided into pre- (n=6), peri- (n=15) and post-pubertal stages (n=16) at final. Bone geometry, mass and strength of three sections (mid-, distal and proximal regions) were measured using magnetic resonance imaging (MRI)

between the 30 – 60% site of the distal humerus. After 12 months, the cortical area of the distal region increased 4% more in the loaded arm compared with the non-loaded arm in the post-pubertal players as a result of contraction of the mudullary area (2%, $p < 0.05$) and periosteal expansion (2%, NS)(Bass, Saxon et al. 2002). At baseline, peri-pubertal girls had 7 – 11% greater cortical area in the loaded vs non-loaded arm, which resulted in an 11 – 14 % greater side-to side difference in humeral BMC ($p < 0.01$). The authors suggest that the greater cortical area is a result of greater periosteal expansion than medullary expansion at the midhumerus, but at the distal humerus it is a result of greater periosteal expansion alone (Bass, Saxon et al. 2002). Further, the authors suggest that during growth, the pattern of bone formation and resorption differs on both the endosteal and periosteal surfaces. They propose that during peri-puberty, bone is resorbed on the endosteal surface while there is periosteal bone formation, whereas post-puberty is a time of both endosteal (only at the distal humerus) and periosteal formation. These surface-specific changes are site dependant as well, with more periosteal bone formation occurring at the mid humerus compared with the distal humerus during peri-puberty (Bass, Saxon et al. 2002). A limitation of this study by Bass and colleagues, is that many of the conclusions about changes in growth and the effects of loading were drawn from the baseline, cross-sectional data. Further study using longitudinal data may give a clearer picture as to the surface- and site-specific changes that occur as a result of growth and loaded physical activity.

A 12-month longitudinal study by Bennell and colleagues (Bennell, Malcolm et al. 1997) investigated bone mass and bone turnover in young adult (17 - 26 years old) power athletes (n=50, 23 females, 27 males), endurance athletes (n=61, 30 females, 31 males), and non-athlete controls (n=55, 28 females, 27 males). At baseline the power athletes had significantly higher ($p < 0.05$) aBMD at the lower limb, upper limb and LS than the controls; whereas the endurance athletes only had significantly greater aBMD ($p< 0.05$) in the lower limbs than the controls. After 12-months, all groups, including controls, had significant gains in TB BMC and femoral aBMD ($p < 0.001$) and the changes were independent of exercise status, except at the LS, where the power athletes gained significantly more aBMD. The authors concluded that bone response to loading is site and magnitude specific (Bennell, Malcolm et al. 1997). This study may indicate that specific exercise may contribute to a higher total bone mineral accrual during growth; however, it is unclear as to whether power athletes have a genetic predisposition to higher bone mass.

A cross-sectional retrospective female athlete study explored the effect of weight-bearing exercise on aBMD of the LS, FN, and forearm (Etherington, Harris et al. 1996). Researchers recruited 83 ex-elite female athletes between the ages of 40 to 65 from middle and long distance running (n=67) and tennis (n=16) and 585 age-matched female controls; recruited from 1003 females (aged 44 to 67) who participated in a general population survey. The subjects were split into four groups: ex-athletes, active controls (>1hr vigorous activity/week, n=22), low active (inconsistent or moderate levels of activity, n=216) and inactive (< 15

mins of activity/week, n=347). Ex-athletes had significantly greater LS (8.7%, p<0.001) and FN (12.1%, p<0.001) aBMD than controls after controlling for age, weight, height and smoking. Ex-tennis players had significantly greater LS (12%, p=0.0004) and FN (6.5%, p=0.066) aBMD than ex-runners. Lastly, active controls had significantly greater FN (8.3%, p=0.004) and LS (7.9%, p=0.009) aBMD than the inactive controls. Researchers concluded that regular (> 1 hr/week), vigorous physical activity is associated with greater aBMD within normal populations (Etherington, Harris et al. 1996).

In another cross-sectional retrospective female athlete study, regional (arms, legs, spine (L2-4), and skull from the total body scan) and total body BMD was measured in 36 retired female gymnasts (25.0+/- 0.9 years old), and 15 age, height and weight matched adult controls (average exercise 1.8 +/- 0.7 hours/week) (Bass, Pearce et al. 1998). Areal BMD for the retired gymnasts was 0.7 to 1.4 SD greater than the controls at all sites except the skull regardless of time since withdrawal from training (Bass, Pearce et al. 1998). Data from these retrospective cross-sectional athlete studies suggest that exercise from elite sport may induce greater aBMD gains during childhood and adolescence and that these greater gains persist into adulthood after cessation of the sport.

2.7.4 Evidence of the Importance of Starting Age from Unilateral Controlled Trials

Several cross-sectional unilateral controlled studies from the UKK Institute in Finland, compared side-to-side differences in aBMD and BMC in several sites of the upper extremities of female racquet sport players. The first study examined national level female squash players (n=19), mean age 25.4 ± 4.0 years and

healthy age, sex, height and weight-matched controls (n=19) and found that the side-to-side differences in the players was significant at all sites, the greatest being at the proximal humerus (BMD 15.6%, BMC 17.8%, $p < 0.001$) (Haapasalo, Kannus et al. 1994).

In the second study, national level female squash and tennis players (n=105), mean age 27.7 ± 11.4 years, were divided into six groups according biological age (years before menarche) that they started playing: 5 years before, 3 – 5 years before, 0 – 2 years before, 1 – 5 years after, 6 – 15 years after and more than 15 years after in order to investigate the effect of starting age of physical activity on BMC in the dominant arm of racquet sport players (Kannus, Haapasalo et al. 1995). When compared with matched controls (n=50), mean age 27.2 ± 9.2 years, players had a significantly greater side-to-side difference in BMC at all sites: proximal humerus, humeral shaft, radial shaft and distal radius ($p<0.0001$). Interestingly, these researchers found that the girls who started playing tennis before menarche had a 2 - 4 times greater side-to-side difference in BMC than those players who started after menarche (Kannus, Haapasalo et al. 1995).

The third study found that young females elite tennis players (n=91, age 7 – 17 years old), when compared with healthy females controls (n=51), had significantly greater side-to-side differences between dominant and non-dominant arms at some sites (1.6 – 15.7%, $p<0.05$ – $p<0.001$) at all Tanner stages, but not until Tanner breast stage III (mean age 12.6 years) were those differences significant uniformly across all variables and sites (Haapasalo,

Kannus et al. 1998). Lumbar spine aBMD was also measured in this study and significant differences between players and controls were not found until Tanner stage IV (mean age 13.5 years, 8.7%, $p<0.05$) and V (mean age 15.5 years, 12.4%, $p<0.05$) (Haapasalo, Kannus et al. 1998).

2.7.5 Longitudinal Intervention Trials in Children

Evidence from labs other than ours will be summarized first. Next, recent studies outlining physical activity interventions with calcium supplementation will be discussed, followed by the multiple school-based interventions from our own lab, the University of British Columbia Bone Health Research Lab (UBC BHRL).

2.7.5.1 Pre-Pubertal Children

Bradney and colleagues (Bradney, Pearce et al. 1998) conducted a randomized controlled trial of prepubertal Caucasian boys (n=20) and age, sex, ethnicity, height, sitting height, weight, baseline aBMD and maturity matched control children (n=20). The intervention boys were from one school and the control boys were from another socioeconomically equivalent school, designation of intervention and control school was randomized and both schools had 2 hrs of physical education classes per week as part of the curriculum. The intervention was conducted by one physical education teacher, during out-of-school hours. The intervention was 30 minutes of weight-bearing activities (basketball, weight-training, aerobics, soccer, volleyball, gymnastics, folk and line dancing), 3 times/week for 8 months. The compliance was reported as 96%. The primary outcomes were a 4.5% (p=.001) greater increase in BMC of the femoral shaft and a 1.2% and 2.8% (p=.001) greater increase in TB and LS (L3) vBMD of the

intervention children when compared with control children (Bradney, Pearce et al. 1998). Some limitations of this study were that it was not specified if the boys were matched at all sites for aBMD and baseline weight was reported as being matched between intervention and control boys; however, the intervention boys had a mean weight of 36.9 ± 2.0 kg and the control boys had a mean weight of 40.1 ± 1.6 kg, a difference of 3 kgs!

Fuchs and colleagues (Fuchs, Bauer et al. 2001) conducted a 7-month program of high impact loading comprised of a progression of 50 to 100, 2-footed drop jumps from a 61cm height box onto a wooden floor, 3 times/week in mainly Caucasian, prepubertal boys and girls (n=45) compared with control children (n=44). The intervention (20 mins) took place during school hours on separate days from the regularly scheduled physical education classes (30 mins, 1x/week). The drop jumps imposed greater ground reaction forces (approx 8 X body weight (BW)) (Bauer, Fuchs et al. 2001) than a previous intervention from the UBC BHRL (2 to 5 X BW) (MacKelvie et al. 2000). This intense program resulted in a 3.1% ($p < 0.05$) greater BMC and 2.0% ($p < 0.01$) greater aBMD at the LS and a 4.5% ($p < 0.001$) greater FN BMC in favour of the intervention children when compared with the control children (Fuchs, Bauer et al. 2001). Interestingly, despite the high strain magnitude and rate, the bone response to the intervention was similar to that reported in the Morris and colleagues' study, to be discussed next, in which the activities were more diverse (Morris, Naughton et al. 1997).

2.7.5.2 Early-Pubertal Girls

Morris and colleagues (Morris, Naughton et al. 1997) conducted a non-randomized controlled trial of early-pubertal, premenarchial girls (n=38), mean age of 9.5 +/- 0.9 years and age, height, weight and maturity matched control girls (n=33). One physical education teacher conducted the intervention in the mornings prior to the start of school. It consisted of three, 30-minute sessions/week of vigorous, loaded physical activity (aerobics, modified soccer, Australian Rules football, step aerobics, bush dance, skipping, ball games, modern dance and 10 weeks of weight training, including a 20-station weight-bearing, strength training circuit) for 10 months. Compliance with the intervention was reported to be 96% midway through the study and 92% at the end of the study. The intervention girls gained significantly more aBMD at the TB (2.3%), LS (3.6%), PF (3.2%), and FN (10.3%) ($p < 0.05$); however, when controlled for change in size (ht and wt) these results are no longer significant at the FN. Results also included a 5.5% greater increase in TB BMC for intervention girls when compared with control girls. A multiple regression analysis revealed that change in lean mass was the primary determinant of TB, LS, PF and FN aBMD (Morris, Naughton et al. 1997).

2.7.5.3 All Maturity Groups

Heinonen and colleagues (Heinonen, Sievanen et al. 1999) studied 139 healthy girls aged 10 to 15 years who spanned all five maturity groups and were categorized as either pre- (Tanner 1,2,3) or post- (Tanner 3,4,5) menarcheal. Sixty-four girls (25 pre- and 29 post-menarcheal) participated in a nine-month

intervention that was somewhat similar to Fuchs and colleagues (Fuchs, Bauer et al. 2001) in that the girls performed 100 two-foot jumps at floor level progressing to 100 two-foot jumps from a 30 cm box by the end of the third month, 125 two-foot and 25 one-foot jumps from the box for the next three months and 150 two-foot and 50 one-foot jumps from the box for the last three months along with 15 min of aerobic exercises 2 X/week. Sixty-two girls (33 pre- and 29 post-menarcheal) made up the control group and were asked to maintain regular physical activity levels over the 9-month period. A 3.3% (p = 0.012) greater LS BMC and 4.0% (p = 0.014) greater FN BMC, was reported for the pre-menarcheal intervention girls when compared with their pre-menarcheal controls. There were no significant differences between the intervention and control post-menarcheal girls (Heinonen, Sievanen et al. 1999). This adds support to the theory that the optimal time for additional bone mineral accrual from an exercise intervention or sport may exist prior to achieving reproductive maturity (Haapasalo, Kannus 1998; MacKelvie, McKay 2001).

2.7.5.4 Adolescents

Two exercise intervention studies have been conducted with post-menarcheal adolescent girls (Blimkie, Rice et al. 1996; Witzke and Snow 2000). Blimke and colleagues randomized 32 girls (16 control and 16 intervention) mean age of 16.2 $\pm$ 0.2 years (range 14-18yrs), from one high school into either a resistance training program using hydraulic machines (13 exercises, 10-12 reps each X 4 sets) 3 times/week or a control group who continued with regular physical activity for 6.5 months. Subjects were matched for physical activity

levels, height, weight and age between the groups. There were no significant differences in LS bone mass variables between the exercise intervention and control girls after the training period (Blimkie, Rice et al. 1996), which agrees with the results of the post-menarcheal girls from the previous study (Heinonen, Sievanen et al. 1999) in which the intervention was much more intense.

Similarly, there were no significant intervention effects on bone mass in the Witzke and colleagues controlled exercise study (Witzke and Snow 2000). The cohort consisted of post-menarcheal (22.7 ±14.0 months past menarche) girls (29 control and 27 intervention) with a mean age of 14.6 ± 0.5 years (range 13 - 15 years). Bone mineral content of the TB, LS, PF and its subregions FN and TR was assessed by DXA. The first 3 months of the exercise intervention were comprised of progressive resistance training and plyometrics, followed by 6 months of plyometrics including bounding, hopping and jumping on a soft surface 30-45 minutes, 3 X/week for 9 months. The subjects were not randomized and recruited from 2 different high schools. The program was conducted during physical education classes for credit and compliance ranged from 71-97% with an average of 86% (Witzke and Snow 2000). There were no differences between groups at baseline; however the control group had participated in more sports prior to the intervention and had a trend (p =0.07) toward higher initial leg strength and power when compared with the intervention girls. Also, during the study, control girls averaged 5.6 hours/week of physical activity outside of PE classes while the intervention girls only averaged 2.6 hours/week. Authors reported a trend in greater increases in BMC at all sites for intervention girls

when compared with control girls. A limitation to this study was the differing activity levels between intervention and control girls and the fairly large standard of deviations in change in BMC at various sites, some as large as 3 times the mean.

2.7.5.5 Exercise and Calcium Interventions

Results from a recently published study suggest that not only does an exercise intervention have a positive osteogenic response, but that there is an interactive effect between prescribed exercise and calcium (Iuliano-Burns, Saxon et al, 2003). Pre-pubertal girls (n=66) with a mean age of 8.8 ± 0.1 years were randomly assigned to one of four groups: moderate-impact exercise with or without fortified calcium foods (434 +/- 19 mg/day) and low-impact exercise with or without fortified calcium foods (434 +/- 19 mg/day) for 8.5 months. The exercise intervention was part of the regular physical education classes 20 minutes 3X/week. The high impact exercise group (intervention) participated in moderate-impact activities such as hopping-, jumping- and skipping-based activities with GRF ranging between 2 to 4 times body weight and hand weights were added in the last 8 weeks of the intervention. The low-impact (control) exercise group participated in low-impact (approximately 1 times body weight) activities such as stretching and low-impact dance routines. Body composition and TB and LS BMC were assessed using DXA. Leg (femur and tibia-fibula) and arm (humerus and ulna-radius) BMC values were identified as separate sites from the TB scan analysis. Researchers found an interaction effect between Ca and exercise at the femur (7.1%, $p< 0.05$), but not at the tibia-fibula region. Also,

all exercise groups, regardless of calcium, had a significant increase (3%, $p<$ 0.05) in BMC at the arm including both the humerus and ulna-radius sites. As well non-exercise, calcium supplemented girls had significantly greater BMC at the humerus (2.2%, $p<$ 0.09) and radius-ulna (4.0%, $p<$ 0.01) sites when compared with the non-exercise placebo group (Iuliano-Burns, Saxon et al, 2003). The authors concluded that greater increases in BMC may occur when moderate exercise, conferring region-specific effects, is combined with an increase in calcium intake, producing generalized effects (Iuliano-Burns, Saxon et al, 2003). The limitations of this study are that regional measures were taken from the total body DXA scan, introducing questions of reproducibility and error. Precision for this analysis method was not reported. Secondly, the mechanism of an interaction effect between calcium intake and increased bone mineral accrual during exercise is not clearly outlined or understood.

Another recently published study revealed the effect of a 15.5 month calcium supplementation and exercise intervention on bone mineral in adolescent girls (n= 144) with a mean age of 17.4 ± 0.3 years and 4.7 ± 0.2 years post-menarche (Stear, Prentice et al, 2003). Subjects were randomly assigned to one of four groups: exercise group and placebo (n= 38) or calcium supplementation (n=37), or non-exercise group and placebo (n= 28) or calcium supplementation (n= 28). The calcium intervention was comprised of two double-blinded groups: calcium supplement (500 mg orange flavoured tablet 2X/day)(n= 65) and placebo (n=66) for 15.5 months. Compliance was calculated to be 70 ± 27% or 700 mg/day for the supplemented group. The exercise intervention,

which occurred at the lunch break or directly after school, was stratified by Ca supplementation to ensure equal numbers of supplemented and placebo girls in the exercise group (n= 75) and not invited to exercise group (n= 56). The exercise classes were 45 minutes 3 X/week, including a warm-up and cool-down with a 30 minute moderate-to-vigorous intensity, exercise-to-music workout of moderate-to-high intensity high impact, weight bearing movements for 24 weeks. Compliance with the exercise intervention was 36 ± 25%. BMC and BA were measured for the TB, LS, non-dominant forearm (total, ultradistal, and distal third radius and PF (including FN, TR and IT). A significant increase in size-adjusted BMC (BMC adjusted for BA, weight and height) in the calcium supplemented groups, in subjects classified as having good compliance (>75%), was reported for TB (0.8 ± 0.3%, $p \leq 0.01$), LS (1.9 ± 0.5%, $p \leq 0.001$), PF (2.7 ± 0.6%, $p \leq 0.001$), FN (2.2 ± 0.7%, $p \leq 0.001$), and TR (4.8 ± 0.9%, $p \leq 0.001$). Participants that attended >50% of the exercise sessions reported a significant increase in BMC at the PF (1.4 ± 0.7%, $p \leq 0.05$) and TR (2.6 ± 1.2%, $p \leq 0.05$). No interaction effect between calcium and exercise was found. A decrease was observed in size-adjusted BMC at the PF, FN and TR for the placebo and exercise group and placebo and no-exercise group, who also had a decrease at the IT region. Researchers attributed this loss to peak bone mass having been achieved, reorientation of the hip with increasing age, redistribution of bone mineral within the hip, or a variation in edge detection by DXA. Limitations in this study included poor compliance with the Ca supplementation and poor attendance to the exercise sessions, which resulted in the researchers stratifying

the subjects into two groups for attendance of the exercise sessions (>50% and <50% attendance) and Ca supplement intake (>75% and <75%) upon completion of the study. These researchers concluded that both exercise and calcium supplementation increase bone mineral accrual in adolescent girls who had good compliance with the intervention (Stear, Prentice et al, 2003).

A third recently published randomized 12-month trial measured the effects of exercise and calcium supplementation on TB BMC and BA and regional measures, arm and leg BMC and BA, from the TB scan, as measured by DXA and bone structure (periosteal and endosteal circumferences, cortical area and cortical thickness) of 20% site of the distal tibia as measured by peripheral quantitative computerized tomography (pQCT) in pre-pubertal children aged 3 to 5 years (n=239 at baseline) (Specker and Binkley, 2003). Children were randomized to one of four groups, as in the previous two studies, fine motor and calcium (n=57 at baseline, n=45 at final), fine motor and placebo (n=57 at baseline, n=45 at final), gross motor and calcium (n=62 at baseline, n=43 at final), and gross motor and placebo (n=57 at baseline, n=45 at final). The calcium intervention was comprised of two 500 mg tablets/day or placebo 5 day/week for 12 months. The exercise intervention was 30mins/day 5 days/week of either gross motor movements, jumping, hopping and skipping activities, or fine motor activities that kept the children sitting for 30 minutes. Results revealed an increase in leg BMC in the gross motor group over the fine motor group in children who were calcium supplemented (9.7%, $p<0.05$) when compared with those receiving placebo. Peripheral QCT results revealed significant increases in

cortical thickness, from a mean of 1.20 ± 0.06 mm to a mean of 1.43 ± 0.04 mm, and cortical area, from a mean of 52.5 ± 2.0 mm^2 to a mean of 62.9 ± 1.4 mm^2 (both, $p<0.02$) in children who were in the gross motor with calcium supplement group. Interestingly, the opposite occurred in children receiving placebo; cortical thickness and area were smaller with gross motor activity than fine motor activity. Periosteal and endosteal circumferences increased independent of calcium supplementation in the gross motor groups ($p<0.05$). The authors concluded that an increase in bone circumference, content and cortical area and thickness occurs as a response to exercise in combination with higher calcium intake in young children (Specker and Binkley, 2003). Limitations to this study include a report of poor scan quality on 51% of the baseline pQCT scans, the resolution of the pQCT scans was not reported and it is debatable as to whether or not pQCT currently has the resolution and precision to measure such small changes in the cortex of the small bones in children of this age.

These exercise intervention with calcium supplementation studies reveal that there may be a link between bone's response to an exercise stimulus and the amount of calcium intake in children of varying ages. Follow-up of these children would to determine whether bone response continues after cessation of the exercise intervention and/or the calcium supplementation.

2.7.5.6 Healthy Bones Trials

In 1997, Dr. McKay established the Healthy Bones Research Program at UBC BHRL and in a series of prospective, randomized, controlled exercise trials, this research group demonstrated that the growing skeleton's response to

exercise is maturity and anatomical site, but not race, specific (McKay, Petit 2000, MacKelvie, McKay 2001, Petit, McKay 2002, MacKelvie, McKay 2001 McKay Petit 2000, McKay, Petit 2000). In the Healthy Bones Study I (HBS I), (McKay and Petit et al. 2000) examined the lifestyle, size and shape determinants of bone mass in 168 pre-pubertal Asian and Caucasian Canadian girls and boys (mean age 8.9±0.7). They found that Asian children consumed significantly less dietary calcium (35%) on average and were significantly less active (15%) than Caucasian children ($p<0.001$) (McKay and Petit et al. 2000). Even at this young age, Asian boys had significantly lower FN BMC (11%) than same size and age Caucasian boys. Lean mass, sex and physical activity explained 37% of the total variance in bone mineral density ($p<0.05$).

In HBS II, the effects of an 8-month high impact exercise intervention (jumping, hopping and skipping activities), administered three times per week for 10 minutes were investigated in pre- and early-pubertal children (n=382). Girls were divided into four groups: pre-pubertal (PRE; Tanner breast stage 1, 10.0 +/- 0.6 years old) intervention (n = 43) and control (n = 25), and early-pubertal (EARLY; Tanner stages 2 and 3, 10.5 +/- 0.6 years old) intervention (n = 43) and control (n = 63). There were significantly greater gains in bone in early- (but not pre-) pubertal girls after 8 (MacKelvie, McKay 2001) (Figure 6) and 20 months (MacKelvie 2003) compared with the control group. Eight-month differences ranged from 1.2% to 3%, depending on anatomical site and bone variable. MacKelvie et al. (MacKelvie, McKay 2001) found that the ethnic difference in

physical activity, calcium intake and PF BMC was more pronounced as girls matured.

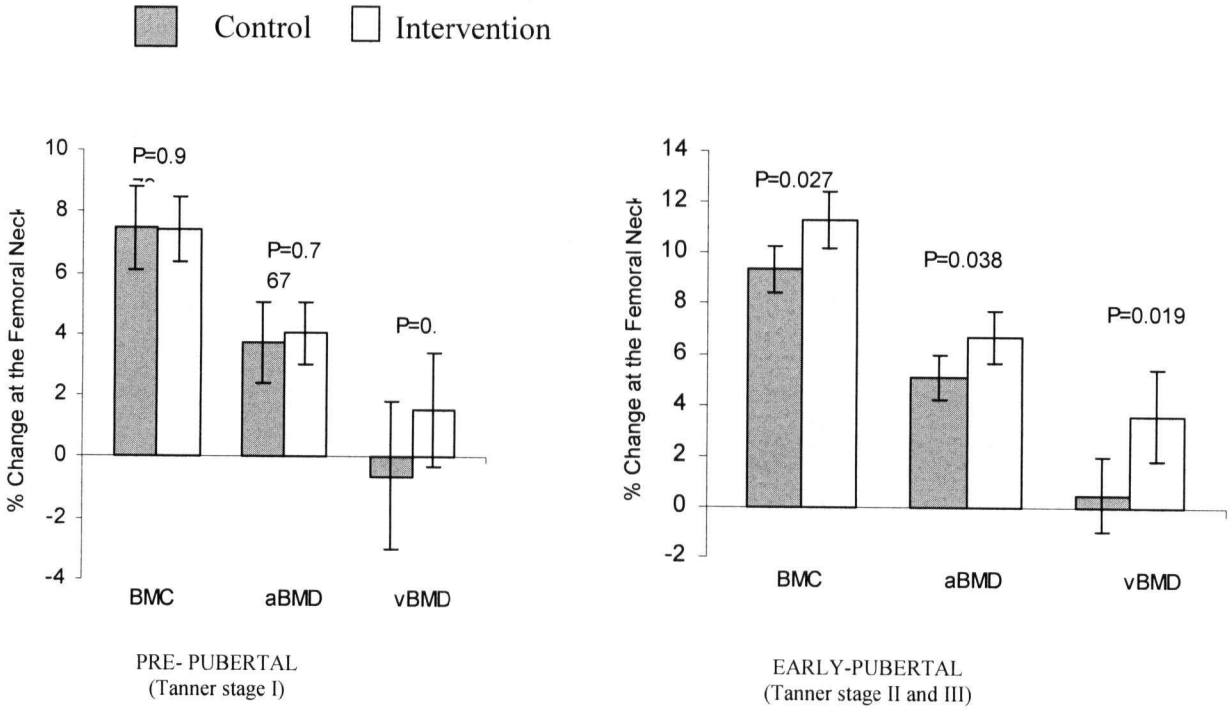


Figure 6. Percent change in BMC, areal BMD (aBMD) and volumetric BMD (vBMD) at the femoral neck in pre- vs. early-pubertal control (blue bars) and intervention (white bars) groups (MacKelvie, McKay et al., 2001, J of Peds).

A subsequent analysis of the Asian- and Caucasian-Canadian boys (10.3+/-0.6 years) in HBS II showed that the intervention group (n=61) gained 1.6% more TB BMC ($p < 0.01$) and 1% more PF aBMD ($p < 0.05$) than the control group after controlling for baseline weight, change in height, loaded physical activity and age (MacKelvie, McKay et al. 2002). In a secondary analysis, researchers examined 41 Asian and 50 Caucasian boys (10.2+/-0.6

years) who were below the 75th percentile (19.4 kg/m2) of the cohort mean for baseline body mass index (BMI). Intervention group boys gained significantly more TB and LS BMC, PF aBMD, and TR aBMD (2%, $p<0.05$) than control group boys. There were no differences in bone changes between Asians and Caucasians. There were no significant differences between control (n = 16) and intervention (n = 14) boys whose baseline BMI fell in the highest quartile (10.5+/-0.6 years and 49.1+/-8.2 kg). The authors concluded that bone mineral accrual, at several regions, was augmented by jumping exercise equally in prepubertal Asian and Caucasian boys of average or low BMI, and that there was no intervention effects on bone mineral in high BMI prepubertal boys (MacKelvie, McKay et al. 2002).

HBS II also examined bone structural properties of pre- and early-pubertal girls (Petit, McKay et al. 2002). Hip structural analysis (HSA) (Beck, Ruff et al. 1990) was used to assess bone mineral density (BMD), endosteal diameter, subperiosteal width, and cross-sectional area and to estimate cortical thickness, and section modulus at the femoral neck (FN), intertrochanter (IT), and femoral shaft (FS) regions. No significant differences were found between the PRE groups; however, the EARLY intervention group had significantly greater gains in IT (+1.7%, $p = 0.02$) and FN (+2.6%, $p = 0.03$) BMD and increased gains in bone cross-sectional area, reduced endosteal expansion and greater gain in section modulus (bending strength) at the FN (+4.0%, $p = 0.04$). There was no difference between groups for change in subperiosteal dimension. This study provided

important information about geometric changes and resultant exercise-induced gain in bone strength in early-pubertal girls (Petit, McKay et al. 2002).

In summary, randomized controlled trials demonstrated differences in modifiable lifestyle factors and FN BMC between Asian and Caucasian children and clearly support the central role that exercise may play in enhancing material and structural properties of the growing skeleton. There have been no exercise or jumping interventions designed to evaluate the effect of short bouts of exercise performed at intervals throughout the school day. For a program of exercise to have universal appeal and measurable health benefits it must be efficient, inexpensive and delivered with minimal training to a large population. Thus, schools provide the optimal vehicle to disseminate such programs to children.

2.8 Are gains from exercise interventions maintained after the withdrawal of the intervention?

2.8.1 Follow-up of Exercise Interventions in Children

A recent study by Fuchs and colleagues (Fuchs and Snow 2002) examined the effects of a 7-month detraining period after a 7-month exercise intervention (Fuchs, Bauer et al. 2001) in prepubertal children. As discussed earlier, this intervention was comprised of the children jumping 100 times from a 61 cm box for 7 months and significant results were found at the PF (4.5%, $p < 0.001$) and LS (3.1%, $p < 0.05$). At follow-up BMC and aBMD at the PF and LS were measured by DXA in 74 returning children (n=37 intervention, originally n=45, n=37 controls, originally n=44), an attrition rate of 18%, non-return was mostly attributed to time constraints for parents to bring their child to testing,

along with moving away from the area and parental concern about exposing their child to further radiation. The jumpers maintained a 4% BMC ($p < 0.05$) and BA ($p < 0.01$) advantage when compared with the control children at the PF, but not the LS. A limitation of this study is that 8 of the children were classified as early-pubertal at follow-up which may have confounded their results, but they reported no change in the outcomes after removing these children from the analysis. Another limitation is that it was unclear whether or not the intervention children had refrained from jumping all together even though the no longer had access to the 61cm boxes, both the intervention and control children reported participation in a variety of sports and physical activities during the follow-up period including running, jumping and gymnastics (all high impact activities). This study reveals that exercise induced bone mineral accrual may be maintained for a short interval, at certain skeletal sites, despite the withdrawal of the specific exercise intervention stimulus whether these advantages persist into adulthood is unknown or whether these differences would be maintained if the children were inactive is doubtful.

2.8.2 Follow-up Evidence in Athlete Studies

Evidence, from retrospective studies of adults who were involved in competitive sport or dance as children, suggests that exercise-induced bone gain in childhood is retained in adulthood. Khan and colleagues (Khan, Bennell et al. 1998) measured aBMD at the PF, LS and forearm in 99 female dancers (mean age 51 +/- 14 years) and age, height, weight and menopausal status matched controls (n=99), in a retrospective cohort study. There was a significant positive

relationship between aBMD values at the femur (FN p= 0.001, PF p < 0.01) and number of hours spent training per week between the ages of 10 and 12 (Khan, Bennell et al. 1998).

Kontulainen and colleagues (Kontulainen, Kannus et al. 1999) examined 13 former competitive *male* tennis players and 13 controls (mean age 26 years). They found that tennis players, who had started playing before the end of puberty, had maintained their side-to-side BMC difference (26% at the humeral midshaft) advantage over the controls after a four year follow-up period despite the fact that their training intensity and frequency had significantly declined ($p < 0.05$) from an average of 7.6 ± 7.2 hours/week to an average of 3.3 ± 2.hours/week (Kontulainen, Kannus et al. 1999).

In a second study by this same research group, 64 *female* racquet sports players and 27 controls were assessed after a 5-year follow-up period. Subjects were divided into two groups; those that started playing before menarche (n=36, mean age 21.6 +/- 7.6 yrs) and those that started playing after menarche (n=28, mean age 39.4 +/- 10.5 yrs). Despite a dramatic reduction in training (approximately 70%) both groups maintained their exercise-induced side-to-side bone gain advantage over controls (humeral shaft BMC 22% greater in young starters, 10% greater in the older starters). Those subjects who started playing before the onset of menarche maintained a 1.3 - 2.2 times greater bone advantage over the later starters, even though the total years of playing were equal. The authors concluded that exercise-induced bone gain can be

maintained with reduced training and that bone maintenance is independent of starting age of an activity (Kontulainen, Kannus et al. 2001).

2.8.3 Evidence from Animal Studies

There seems to be some evidence from animal studies that the starting age, or maturity level, when exercise began has an effect on the response of bone to withdrawal of exercise stimulus (Kiuchi, Arai et al. 1998), (Silbermann, Schapira et al. 1991). A randomized control trial of a 10-week training period followed by a 10-week period of withdrawal of training in young male rats (cont, n=25, exer, n=28) revealed that significant gains in BMC at the femur (16.6%, p=0.01), tibia (11.7%, p=0.01) and humerus (12.5%, p=0.01) were retained over the ten week withdrawal of exercise period ((Kiuchi, Arai et al. 1998). Likewise, rats that started treadmill running at 6 weeks of age for a duration of 5 months maintained their beneficial bone gains after not training for at least 12 months (Silbermann, Schapira et al. 1991)). Thus, it appears that benefits of a targeted program of loading persist over the short term.

In a randomized controlled trial of 50, 10 wk old female rats, animals were divided into five groups; 4 weeks jumping exercise (n=10) and sedentary control (n=10), 8 weeks jumping exercise (n=10) and sedentary control (n=10), and 4 weeks of jumping exercise followed by 4 weeks of sedentary rest (n=10) (Singh, Umemura et al. 2002). The bone mass, measured by fat-free dry weight and the breaking force, measured with a three-point bending until fracture servo-controlled electromechanical testing system, of the tibia were measured after the rats were killed at 4 and 8 weeks. All exercise groups had significantly stronger

($p < 0.01$ to $p < 0.001$) and denser ($p < 0.01$ to $p < 0.001$) tibia than controls and the 8-week group had significantly ($p < 0.05$) larger cortical area, measured after fracture, than the 4-week groups. The group that had a 4-week cessation of exercise after 4 weeks of training maintained their bone advantage at 8-weeks (Singh, Umemura et al. 2002).

These animal detraining studies suggest that exercise-induced bone gains may be maintained over a relatively short time with complete cessation of exercise. However, further longer-term study is required to determine if exercise-induced bone gains, if accrued at an early age, are maintained throughout the lifespan.

2.9 Limitations in Existing Knowledge

The preceding review has highlighted the following limitations that this study aims to overcome.

- There are currently no trials to identify the effects of brief bouts of loading interspersed throughout the day on bone mass in pre- and early-pubertal children.
- There are currently no trials to identify the effects of brief bouts of loading interspersed throughout the day on bone structure in pre- and early-pubertal children.

Also further investigation is warranted to discover the effects of the withdrawal of an exercise intervention for 12 months and longer in pre- and early-pubertal children.

Chapter 3: Research Questions and Hypotheses

3.1 Objectives

3.1.1 Primary Objectives

This seven-month program of high impact loading was designed to; 1) assess the effects of a novel intervention on change in bone mineral content (BMC) at the total body, proximal femur and lumbar spine and 2) to assess the adaptation of structural parameters at the proximal femur by Hip Structural Analysis (HSA).

The primary research questions are:

1. Is there a difference in bone mass accrual between children who participated in a novel exercise program and control children?
2. Is there a difference in bone structural parameters at the proximal femur between children who participate in a novel exercise program and controls?

3.2 Hypotheses

3.2.1 Primary Hypotheses

Compared with normally active controls, children who participated in a 7-month program of frequent bouts of exercise 3 times per day will demonstrate:

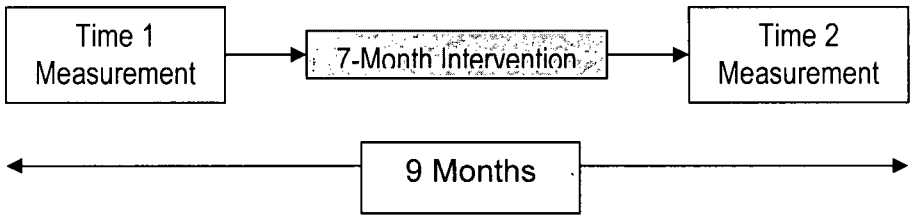
1. A greater increase in BMC at the total body, the lumbar spine and the total proximal femur and its subregions as measured by DXA.
2. A greater increase in BMD, CSA, SPW, and AVG CORTEX of the NN, S, and IT regions, resulting in a greater increase in section modulus (Z) a measure of bone strength as determined by HSA.

Chapter 4: Methods

4.1 Study Design

"Bounce at the Bell" was a 7-month, 2 group by 2 time point controlled trial of frequent bouts of jumping exercise using extant baseline data. The study was conducted as a companion study to the larger Healthy Bones II Study in the Richmond School District (MacKelvie, McKay et al. 2002; MacKelvie, McKay et al. 2001). Baseline measurement (Time 1) was conducted in October 2000, and I performed Time 2 measurement in all 51 intervention children after 7-months of intervention in June 2001 (Figure 7). [1]

Figure 7: Study Timeline



4.2 Subjects

HBS II subjects were recruited on three levels. First, our research group established a rapport with several teachers and principals in the Richmond School district during the first study Healthy Bones I in 1997-98. In May of 1999, the project was presented at the annual principals' meeting and the principals were then asked to approach teachers at their schools to become involved.

[1] Even though the baseline data were collected before I started my Master's program, I was personally involved in data collection at time point 2. As well, I analyzed all scans from all time points for both intervention and control children.

Second, the project was presented to teachers at the individual schools (n=15) who expressed an interest in taking part in the study. Third, the project was presented (n=16) in September 1999 in the classrooms for students and parents and information letters and consent forms (Appendix 1) were distributed (n=780) (MacKelvie, 2002). Control subjects (n=75) for this study were randomly selected from the HBS II control group (n=107). Selection criteria included sex, age, ethnicity, height and maturity so that the ratio of boys, girls, ethnic groups and maturity levels matched those of the intervention group.

4.2.1 Recruitment and Informed Consent

Three control schools in the Richmond School District (Ferris, Errington, and Thomas Kidd) volunteered to participate in the Bounce at the Bell intervention. All healthy children in grades 5 and 6 were eligible to participate. Approval from the University of British Columbia Clinical Research Ethics Board (CREB) was obtained to conduct this study. Fifty-one intervention subjects (28 girls and 23 boys) in Tanner stages 1 and 2 agreed to participate and consent was obtained from each child and his/her parents or guardian (Appendix 1).

4.3 *Data Collection*

Data collection was performed at the University of British Columbia Bone Health Research Laboratory. Children were excused from classes for two and a half hours and transported in groups of 6 from their schools, to UBC and back, by minivan with a qualified driver and chaperone. The children rotated through four stations: bone measurements (30 min), anthropometry (10 min), strength

measures (10 min), and questionnaires (20 min). Thus, the entire protocol required approximately 70 minutes to complete.

4.3.1 Body Composition

Subjects removed their shoes and wore light clothing for the anthropometric measurements. All measurements where taken twice unless there was a difference of more than +/- 0.4cm (height, calf girth) or +/-0.2kg (weight), in which case a third measure was taken. We used the average of two values or the median of three values for statistical analysis.

i) Stretch stature of sitting height and height were measured using a customized wall-mounted stadiometer to the nearest 0.1/cm. Gentle upward pressure was applied to the mastoid process to provide traction for the stretch stature.

ii) Weight was measured to the nearest 0.1kg using an electronic scale (Seca).

iii) The greatest girth of the calf was measured using a metal tape measure.

iv) The total body (TB) DXA scans provided body composition estimates of bone mineral free lean mass and fat mass. Our bone densitometer had an *in vivo* precision, CV of 0.30+/- 0.15%, for total body lean mass and a CV of 1.42 +/-0.78% for total body fat mass.

The whole body (WB) DXA scans provided body composition estimates of bone mineral free lean mass and fat mass. Our bone densitometer had an *in vivo* precision, CV of 0.30+/- 0.15%, for whole body lean mass and a CV of 1.42 +/- 0.78% for whole body fat mass.

4.3.2 Lifestyle Factors

4.3.2.1 Calcium Intake

Calcium (Ca) intake was assessed three times throughout the school year (October, January and June) with a researcher administered Food Frequency Questionnaire that has been used in the past by our group (MacKelvie, McKay et al. 2001; MacKelvie, McKay et al. 2002)(Appendix 2). This instrument has previously been validated against 7-day food recalls in this age group (Barr 1994). Children must indicate the frequency either per month, per week or per day of specified servings of calcium-rich food items.

4.3.2.3 Health History and Ethnicity

The parents were asked to fill out a health history and ethnicity questionnaire at baseline. The country that the child, their parents and grandparents were born in as well as the duration of time the family has lived in Canada was identified. The parents were also asked to report any illnesses or medical conditions that the child may have experienced (Appendix 2).

4.3.2.3 Physical Activity

A 7-day recall questionnaire (PAQ-C) was administered at three times throughout the school year (October, January and June) to assess moderate to vigorous, general, habitual physical activity (Appendix 2). The PAQ-C assesses physical activity over the past 7-days scored from 1 (low activity) to 5 (high activity) (Crocker, Bailey et al. 1997). The questionnaire also included questions regarding loaded activities including loading of the upper limbs (ie. volleyball, tennis, gymnastics) and an indication of the number of nights per week the child

participated in organized sports (sport nights). Thus, three physical activity variables were calculated: average physical activity (score from 1-5); loaded physical activities (min/wk) and sport nights (days/wk of organized sports). There has previously been validation of interviewer- versus self-administered questionnaires in this age group (Sallis, Strikmiller et al. 1996).

4.3.3 Dynamic Power Measure

Dynamic muscle strength was assessed with a vertical jumps test at each bone data collection time. In a study of young women this measure was significantly correlated (r=0.7, p<0.01) to strength of the ankle, knee and hip extensor muscles (Blackburn and Morrissey 1998). The average of two recorded jumps, preceded by two practice jumps, was reported.

(i) Vertical jump was comprised of a maximum two-foot takeoff jump from a standing position one-elbow length from the wall. The distance between the highest point touched (with an ink-marked finger) and the maximum reach with both feet flat on the floor was measured to the nearest 0.1cm (CPAFLA 1998).

4.3.4 Maturity

Tanner Stage (Tanner 1978) was parent- or self-assessed to identify maturational stage at each bone data collection time. A series of 5 developmental stages (breast and pubic hair for girls and pubic hair for boys) is depicted by line drawings in this method. The child (or parent) chose the drawing that he/she feels most closely resembled themselves (the child) (Appendix 2). Breast stage for girls was used when there was a discrepancy between breast

and pubic hair ratings. Duke and colleagues (Duke, Litt et al. 1980) found that self-assessment of sexual maturation in adolescents' agreed well with physician ratings. In this study, children in Tanner Stage 1 were considered to be pre-pubescent, Tanner Stage 2 and 3 represented early puberty, Tanner Stage 4 was considered late or peri-puberty, and Tanner Stage 5 corresponded with post-puberty.

4.3.5 Bone Mineral Content

Bone mineral content (BMC, grams) was measured at the left proximal femur (PF) (including the femoral neck (FN), greater trochanter (TR) and intertrochantric (IT) subregions), lumbar spine (LS), and for the total body (TB) using a Hologic QDR 4500 bone densitometer. Two qualified research assistants (KJ MacKelive and LB MacLean) performed the scans. I analyzed all scans for all participants (including control subjects), using the standard Hologic analysis protocol (Hologic 1996). Bone densitometry, routinely used in clinical practice, is a safe, painless, extremely low dose (10 millirem per session) radiation procedure. The radiation is equivalent to the amount that one would receive flying from Vancouver to Toronto. The children wore light clothing that was free of any metal and removed all jewellery. All three scans took approximately 15 minutes and required the child to lay stationary on a padded table.

Spine and anthromorphic phantoms were scanned every morning before measurement to ensure quality assurance. The *in vitro* spine precision for our lab's Hologic QDR 4500 was maintained between 0.3 and 0.6% (coefficients of variation (CV)) for all bone parameters over the duration of the study. A short-

term *in vivo* precision study was conducted in our lab with 17 young healthy adults (3 measurements in one hour) with and without repositioning to measure BMC of the TB, LS, and PF [including FN and TR]. The CV for the TB and LS for BMC was less than 0.7%. The CV for the PF, FN, and TR for BMC was 1.4, 2.6, and 3.5%.

4.3.6 Bone Structure and Bone Strength

Proximal femur DXA scans were further analyzed using the Hip Structural Analysis (HSA) program (Beck, Ruff et al. 1990) to assess the structure and geometry of the hip. HSA assesses the distribution of bone mass across three narrow regions of bone as illustrated (Figure 8). Reported measures include cross-sectional area (CSA), subperiosteal width (SPW), and section modulus (Z), which is calculated using the cross-sectional moment of inertia (CSMI).

$Z = CSMI/(d_s/2)$ where d_s is the SPW for the NN and S regions and distance from the lateral margin to the centroid for the IT region and

$CSMI = (\Pi/4)\ X\ (r_1^4 - r_2^4)$ where r_1 is the distance from the centroid of the bone region to the endosteal surface and r_2 is the distance from the centroid to the periosteal surface

Simple models that employ assumptions of cross-section shape along with measured dimensions are used to estimate cortical thickness (AVG CORTEX).

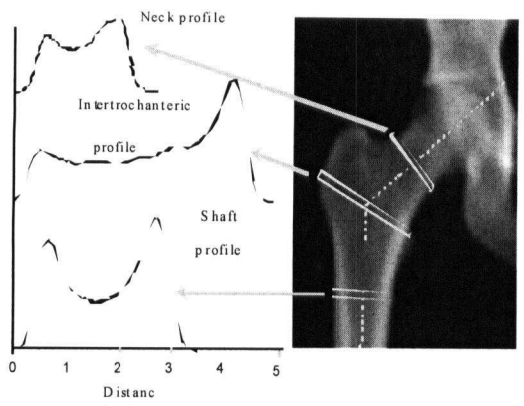


Figure 8. Hip image from a Hologic DXA scanner showing analysis regions across the femur at the narrow neck (NN), intertrochanteric (IT), and shaft (S) and their typical bone mass profiles.

Areal bone mineral density (aBMD) is also calculated but as the three regions of interest do not have Hologic counterparts, the calculated absolute aBMD values may differ from the standard aBMD analysis. This approach was used in previous studies in our lab and has been tested in clinical groups (Beck 2000, personal communication).

4.4 Exercise Intervention

Teachers were provided an instruction manual with diagrams of the prescribed jumps (Appendix 3). A Bounce at the Bell research assistant met with teachers to describe, demonstrate and review the jumping protocol three times throughout the school year. Teachers asked children in their classroom to perform five, two-foot or 10, alternating foot jumps, 3 times every school day (once at morning bell, once at noon bell, and once at home time bell). Control children, who were in different classes and schools, continued with their regular daily school routine. Teachers recorded the average number of jumps children in their classes performed daily.

4.5 Statistical Analysis

Descriptive analysis of independent and dependant variables were conducted (Table 4.5.1). Pearson product moment (PPM) correlations between selected independent and dependant variables were also determined (Table 4.5.1). I conducted ANCOVA to compare change in primary outcomes over the intervention. I selected covariates based on previous studies and on the relationship between independent and dependant variables. They were baseline maturity, age, height, change in height and physical activity score unless otherwise noted.

Table 4.5.1. Reported independent and dependent variables.

Independent variables:		Dependent variables:
Baseline Age	7-Month Change in:	Bone Mass (DXA):
Sex	Height	Total Body BMC
Ethnicity	Weight	Lumbar Spine BMC
Physical Activity Score	Bone Mineral	Proximal Femur BMC
Load Time	Free Lean Mass	Femoral Neck BMC
Total Calcium	Fat Mass	Trochanteric Region BMC
Baseline:	Vertical Jump	Intertrochanteric Region BMC
Height		
Weight		Bone Structure (HSA) of the Narrow Neck,
Sitting Height		Intertrochantric Region and Shaft:
Leg Length	Final Maturity	Areal Bone Mineral Density
Calf Girth		Cross Sectional Area
Maturity		Sub-Periosteal Width
Lean Mass		Estimated Cortical Width
Fat Mass		
Dynamic Power:		Bone Strength (HSA) of the NN, IT, and S:
Vertical Jump		Section Modulus

4.5.1 Power analysis

A power of 0.83 was calculated for this study based on a 3% difference in bone parameters between the groups with a common standard deviation of 4% and 30 participants per group (MacKelvie 2002).

Chapter 5: Results

There were 51 intervention children (mean age 10.1 ± 0.5; boys n=23, girls n=28) and 75 control children (mean age 10.2 ± 0.4; boys n=36, girls n=39) at baseline. The baseline age range for intervention children was 8.9 to 10.8 years and 9.2 to 11.0 years for the controls. In section 5.1 I include results regarding compliance to the intervention. In sections 5.2 through 5.4 I outline the descriptive data including body composition, lifestyle factors and maturity. In section 5.5 I present the results of the PPM correlations for selected variables. In sections 5.6 and 5.7 I outline the results for bone mass, bone structure and bone strength measures.

5.1 Exercise Intervention

Attendance sheets and jump records were collected at the end of the study to determine compliance to the intervention. Along with personal communication between the research assistant (Leslie B. MacLean) and the six teachers at the three schools who were participating in the intervention, jump records and attendance sheets were collected at the end of the school year. All teachers reported that the children performed 10 jumps at least 2-3 times per day, from 2-5 days per week. One class performed 10 jumps 3 times per day, 2 times per week with ball throwing, running and jumping on the other days. The average jumps/week was 90.2 ± 34.1. Jumps were highly correlated with the significant changes in bone mass at the PF and IT ($r = 0.93$, $p < 0.001$). The average school attendance of the intervention children was 96.8% with a range

of 0 to 25 missed days of school not including statutory and school holidays and teacher professional development days.

5.2 Body Composition

There were no significant differences between intervention and control children in baseline body composition values (Table 5.1).

Table 5.1 Body composition (height, weight, sitting height, leg length, calf girth, bone mineral free lean mass, and fat mass) values for intervention and control children at baseline (mean ± std dev (range)).

	Intervention (n=51)	Control (n=75)
Height (cm)	139.8 ± 7.0 (122.5 -154.3)	140.6 ± 6.1 (127.3 - 153.1)
Weight (kg)	35.7 ± 9.1 (22.0 – 69.2)	35.4 ± 8.0 (22.6 – 68.6)
Sitting Height (cm)	73.9 ± 3.8 (63.1 – 81.7)	74.6 ± 3.5 (66.7 – 83.1)
Leg Length (cm)	65.8 ± 3.6 (59.1 – 74.5)	66.0 ± 3.4 (57.2 – 74.1)
Calf Girth (cm)	28.3 ± 5.2 (21.7 – 38.2)	29.1 ± 2.9 (23.1 – 37.0)
Bone Mineral Free Lean Mass (kg)	24.3 ± 4.4 (15.8 – 37.9)	25.2 ± 4.0 (17.9 – 37.5
Fat Mass (kg)	8.9 ± 4.9 (3.1 – 27.9)	8.9 ± 4.9 (3.4 – 29.4)

Children in the intervention group changed similarly to children in the control group with respect to body composition over 7-months, with the exception of calf girth (Table 5.2). Calf girth increased significantly more in intervention children when compared with control children (p=0.001).

Table 5.2 Unadjusted body composition (height, weight, sitting height, leg length, calf girth, bone mineral free lean mass, and fat mass) 7-month change values for intervention and control children (mean ± std dev (range)).

	Intervention (n=51)	Control (n=75)
Height (cm)	4.3 ± 1.3 (2.0 – 7.8)	4.1 ± 1.2 (1.6 – 6.6)
Weight (kg)	2.6 ± 2.0 (-4.4 – 8.4)	2.9 ± 1.5 (-0.4 – 7.8)
Sitting Height (cm)	1.9 ± 0.9 (0.4 – 4.2)	1.8 ± 1.4 (-2.9 – 4.9)
Leg Length (cm	2.6 ± 1.3 (-0.2 – 4.3)	2.3 ± 1.4 (-1.9 - 8.2)
Calf Girth (cm)	1.6 ± 3.7* (-0.03 – 2.6)	0.6 ± 1.1 (-2.5 – 2.6)
Bone Mineral Free Lean Mass (kg)	2.1 ± 1.0 (0.6 – 4.2)	2.1 ± 1.1 (-.06 – 5.8)
Fat Mass (kg)	0.7 ± 1.3 (-2.7 – 5.1)	0.6 ± 1.1 (-2.3 – 3.7)

Intervention children had significantly greater change in calf girth when compared with controls (p = 0.001)

5.3 Lifestyle Factors

5.3.1 Calcium Intake

Mean calcium intake at baseline was not significantly different between intervention (776 ± 390 mg/day, range 253 to 2472 mg/day) and control children (798 ± 379 mg/day, range 48 to 1944 mg/day) (Table 5.4). The average of the three calcium intake data points (fall, winter and spring) revealed no significant differences between intakes of intervention (821 +/- 377 mg/day, range 264 to 1813 mg/day) versus control (834 +/- 377 mg/day, range 133 to 1950 mg/day) children. However, there was a significant sex difference for average calcium intake (boys mean intake 939 ± 403 mg/day and girls mean intake 731 ± 322 mg/day (p=0.004)).

5.3.2 Health History and Ethnicity

There were no reports of any illness or medical conditions subjects experienced prior to the study that would affect participation in the study. Similarly, during the study, there were no reports of injury or illness that would have affected continued participation in the study. The study participants or their parents reported the country where they, their parents and grandparents were born and the duration the family had lived in Canada. The children were then divided into one of three ethnic groups: Asian, Caucasian and Other (Table 5.3).

Table 5.3 Ethnic breakdown of cohort (n (%)).

	Intervention (n=51)		Control (n=75)	
	Boys (n=23)	Girls (n=28)	Boys (n=36)	Girls (n=39)
Asian	10 (43)	15 (54)	15 (42)	20 (51)
Caucasian	12 (52)	7 (25)	19 (53)	10 (26)
Other	1 (5)	6 (21)	2 (5)	9 (23)

5.3.3 Physical Activity

There were no statistically significant differences between groups for general physical activity score at baseline, but there was a significant difference for time spent in *loaded* physical activity (Table 5.4). Intervention children participated in significantly more loaded activities per week compared with control children ($p = 0.04$). Within groups, boys (mean load time 7.3 ± 6.7 hours per week) participated in significantly more loaded physical activity than girls (mean load time 4.2 ± 4.2 hours per week)($p = 0.01$). Similarly, boys had a significantly higher general physical activity score (mean score 3.0 ± 0.6 /5) than girls (2.8 ± 0.6 /5) ($p = 0.02$) at baseline.

Table 5.4 Baseline values for physical activity, dynamic power (vertical jump), and calcium intake values (mean ± std dev (range)).

	Intervention (n=51)	Control (n=75)
Physical Activity Score (/5)	3.0 ± 0.7 (1.2 – 4.5)	2.9 ± 0.6 (1.6 – 4.4)
Load Time (hr/wk)	6.8 ± 6.8* (0.3 – 35.3)	4.9 ± 4.7 (0 – 21.3)
Vertical Jump (cm)	23.4 ± 6.1 (8.4 – 38.1)	23.6 ±5.8 (12.9 – 35.8)
Calcium Intake (mg/day)	776 ± 390 (253 – 2472)	798 ± 379 (48 – 1944)

* Intervention children significantly greater than controls (p= 0.04)

There was no significant difference between intervention children average 7-month physical activity score compared with control children. However, intervention children had significantly greater average 7-month loaded physical activity time compared with control children ($p = 0.05$) (Table 5.5). There was one girl and one boy in the intervention group who had extremely high values for average 7-month loaded physical activity and when these two subjects were removed the difference between groups was no longer significant. Boys had a significantly greater average 7-month physical activity score (3.2 ± 0.6 /5) and average loaded physical activity time (8.1 ± 5.7 hours per week) when compared

with girls average physical activity score (2.8 ± 0.5 /5; $p = 0.002$) and average loaded physical activity time (4.7 ± 3.7 hours per week; $p < 0.001$).

Table 5.5 Average 7-month values for physical activity and calcium intake and unadjusted 7-month change for vertical jump.

	Intervention	Control
Physical Activity Score (/5)	3.0 ± 0.6 (1.7 – 4.3)	3.0 ± 0.5 (2.1 – 4.1)
Load Time (hr/wk)	7.2 ± 5.9* (0.5 – 28.7)	5.6 ± 4.3 (0.3 – 18.8)
Vertical Jump (cm)	3.6 ± 4.3 (-6.6 – 14.1)	3.2 ± 3.9 (-5.6 – 13.6)
Calcium Intake (mg/day)	821 ± 377 (264 – 1813)	834 ± 377 (133 – 1951)

* Intervention children significantly greater than controls (p= 0.05)

5.4 Dynamic Power

Performance values for vertical jump, used to represent dynamic power of the lower body, were not significantly different between groups at baseline (Table 5.4). There were no significant differences in dynamic power between intervention and control children after 7 months (Table 5.5).

5.5 Maturity

There were no statistically significant differences between groups for Tanner stage at baseline. The girls were distributed across Tanner stages 1 – 3 and the boys were distributed across Tanner Stage 1 and 2 (Table 5.6). Forty-six percent of the intervention girls and 41% of control girls were classified as pre-pubertal (Tanner 1). Fifty-four percent of intervention girls were early-pubertal (Tanner 2 and 3) compared with 59% of controls. For boys, 78% of the intervention and 97% of control boys were pre-pubertal. Only 22% in intervention and 3% of control boys were early-pubertal.

Table 5.6 Tanner stage distribution of cohort at baseline

	Intervention (n=51)		Control (n=75)	
	Boys (n=23)	Girls (n=28)	Boys (n=36)	Girls (n=39)
Tanner stage 1	18	13	35	16
Tanner stage 2	5	13	1	23
Tanner stage 3	0	2	0	0

The distribution of the cohort in Tanner stages after 7 months is outlined (Table 5.7). Only 25% of intervention and 15% of control girls remained pre-pubertal (Tanner 1). Seventy-five percent of intervention and 85% of control girls were early-pubertal (Tanner 2 and 3) after 7 months. Twenty-six percent of intervention boys and 56% of control boys remained in pre-puberty. Meanwhile, 70% of the intervention and 44% of the control boys entered early-puberty. One boy from the intervention group was classified as late-pubertal (Tanner stage 4) at final. Note that the majority of children changed similarly over the 7 months, with the exception of the boy in the intervention group who progressed from Tanner stage 1 to Tanner stage 4. The data were analyzed with and without this individual and results did not change. After 7 months, 25%, 73% and 2% of intervention children and 35%, 65% and 0% of control children were in pre-, early- and late-pubertal stages of maturity, respectively.

Table 5.7 Tanner stage distribution of cohort at final (7 months).

	Intervention (n=51)		Control (n=75)	
	Boys (n=23)	Girls (n=28)	Boys (n=36)	Girls (n=39)
Tanner stage 1	6	7	20	6
Tanner stage 2	14	15	15	26
Tanner stage 3	2	6	1	7
Tanner stage 4	1	0	0	0

The relationship between maturity at baseline and baseline and 7-month change in BMC (Table 5.11), baseline (Table 5.14) and 7-month change in bone structure and bone strength (Table 5.15) is provided.

4.6 Bone Mineral Content

There were no significant differences in BMC at baseline between intervention and control children (Table 5.8).

Table 5.8. Baseline BMC at the total body (TB), lumbar spine (LS), proximal femur (PF) and its sub regions femoral neck (FN), trochanteric region (TR) and intertrochanteric region (IT) for intervention and control children (mean ± std dev (range)).

	Intervention (n=51)	Control (n=75)
BMC (g)		
TB	1054 ± 197 (661 – 1549)	1056 ± 176 (760 – 1564)
LS	24.6 ± 5.1 (15.7 – 40.4)	24.5 ± 4.6 (14.8 – 37.4)
PF	16.2 ± 3.4 (9.4 – 24.2)	15.8 ± 3.5 (9.8 – 27.0)
FN	2.7 ± 0.4 (1.9 – 3.7)	2.7 ± 0.5 (1.8 – 3.9)
TR	2.9 ± 0.9 (1.1 – 5.6)	2.8 ± 0.9 (1.3 – 6.4)
IT	10.5 ± 2.2 (6.4 – 15.4)	10.3 ± 2.3 (6.4 – 16.8)

Table 5.9 provides the unadjusted 7-month change values between intervention and control groups.

Table 5.9 Bone mineral content (BMC) unadjusted 7-month change values for intervention and control children at the total body (TB), lumbar spine (LS), proximal femur (PF) and its sub regions femoral neck (FN), trochanteric region (TR) and intertrochanteric region (IT) (mean ± std dev (range)).

	Intervention (n=51)	Control (n=75)
BMC (g)		
TB	99 +/- 50 (23 – 205)	107 +/- 49 (24 – 295)
LS	2.8 +/- 2.0 (-0.4 – 8.7)	2.8 +/- 1.8 (0.3 – 10.3)
PF	2.4 +/- 1.1 (0.7 – 6.0)	1.9 +/- 1.2 (-0.8 – 6.9)
FN	0.20 +/- 0.14 (-0.1 – 0.5)	0.20 +/- 0.15 (-0.2 – 0.7)
TR	0.63 +/- 0.32 (0.04 – 1.5)	0.57 +/- 0.9 (-0.4 – 2.6)
IT	1.5 +/- 0.8 (0.02 – 3.6)	1.2 +/- 0.8 (-1.0 – 3.6)

Children who participated in the intervention had significantly greater increases in adjusted BMC at the proximal femur (PF) (p= 0.012) and the intertrochanteric region (IT) (p= 0.005) (Figure 9). Adjusted BMC changes were not significantly different between groups at other sites (Table 5.10).

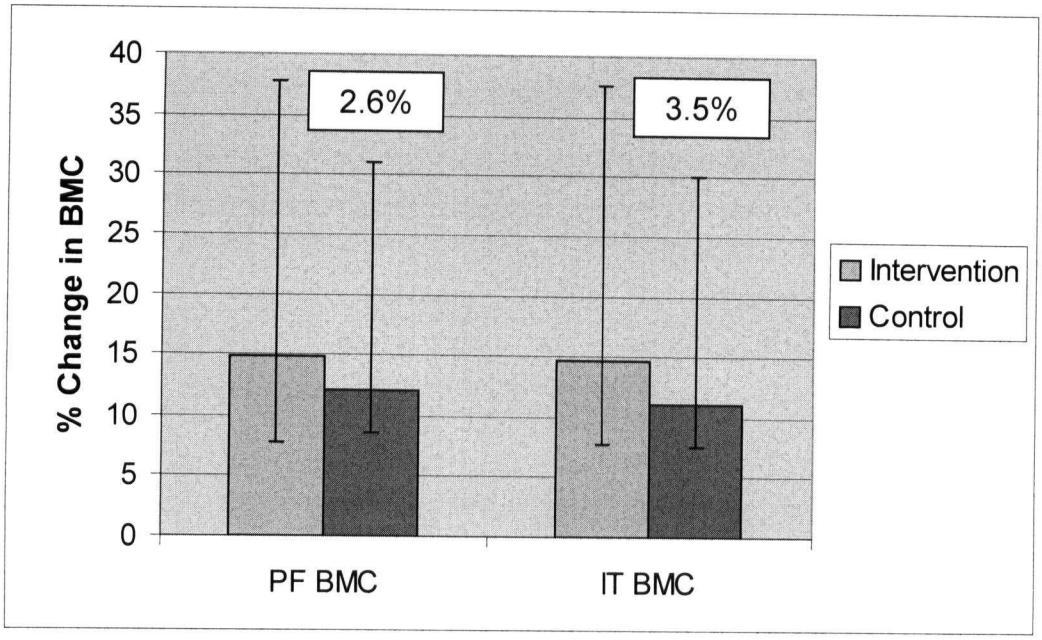


Figure 9. Comparison of % change in bone mineral content (BMC) at the proximal femur (PF) (p = 0.012) and its sub region the intertrochanteric region (IT) (p = 0.005) of intervention children with control children.

Table 5.10 Change in BMC values for intervention and control children after 7 months, values were adjusted for baseline maturity, age, height, 7-month change in height and average physical activity score.

	Intervention (n=51)	Control (n=75)
BMC (g)		
TB	99 +/- 49	107 +/- 49
LS	2.9 +/- 2.0	2.8 +/- 1.8
PF	2.4 +/- 1.3*	1.9 +/- 1.2
FN	0.20 +/- 0.14	0.20 +/- 0.16
TR	0.63 +/- 0.32	0.56 +/- 0.44
IT	1.5 +/- 0.8*	1.2 +/- 0.8

*Intervention children changed significantly more than controls (p<0.01).

Pearson Product Moment correlations between baseline BMC values and age, Tanner stage, height, weight, bone mineral free lean mass and fat mass are provided (Table 5.11). Of note, none of the baseline bone mass variables were related to physical activity score or calcium intake. However, loaded physical

activity time moderately correlated with PF and IT BMC and highly correlated with FN BMC.

Similar relationships between unadjusted *change* in all bone mass variables and descriptors are also provided. Of note, none of the change in bone mass variables were correlated with average physical activity score, loaded physical activity time, average calcium intake or baseline dynamic power.

Table 5.11 Pearson Product Moment correlations between baseline and 7-month change in BMC parameters and selected independent baseline and change variables in the study whole cohort.

Change in bone mass:	Age (yrs)	Tanner	Height (cm)	Weight (cm)	BMF Lean Mass (g)	Fat Mass (g)	Δ Height (cm)	PA Score (/5)	Load Time (hr/wk)	Vertical Jump (cm)	Calcium Intake (g)
Total Body BMC (g)	0.34**	0.27**	**0.81****	**0.71****	**0.82****	0.45**	0.18*	0.04	0.12	0.17	-0.01
Δ Total Body BMC (g)	0.29*	**0.49****	0.44**	0.46**	**0.50****	0.34**	**0.54****	-0.02	0.08	0.05	-0.04
Lumbar Spine BMC (g)	0.33**	0.33**	**0.72****	**0.52****	**0.70****	0.24**	0.27**	-0.02	0.09	0.28**	-0.07
Δ Lumbar Spine BMC (g)	0.25**	**0.51****	0.36**	0.33**	0.36**	0.24**	**0.61****	-0.10	-0.04	0.06	-0.15
Proximal Femur BMC (g)	0.27**	0.22*	**0.71****	**0.61****	**0.76****	0.34**	0.20*	0.12	0.18*	0.24**	0.02
Δ Proximal Femur BMC (g)	0.17	0.35**	0.39**	0.31**	0.36**	0.17	**0.58****	0.02	0.13	0.06	-0.09
Trochanteric BMC (g)	0.30**	0.38**	**0.67****	**0.55****	**0.66****	0.32**	0.34**	0.02	0.05	0.22*	-0.05
Δ Trochanteric BMC (g)	0.21*	0.30**	0.34**	0.24**	0.39**	0.12	**0.54****	0.01	0.08	0.16	-0.01
Intertrochanteric BMC (g)	0.25**	0.10	**0.66****	**0.61****	**0.72****	0.31**	0.12	0.16	0.20*	0.25**	0.03
Δ Intertrochanteric BMC (g)	0.13	0.25**	0.28**	0.24**	0.26**	0.13	**0.49****	0.07	0.15	0.03	-0.12
Femoral Neck BMC (g)	0.24**	0.13	**0.69****	**0.61****	**0.76****	0.34**	0.09	0.17	0.24**	0.21**	0.09
Δ Femoral Neck BMC (g)	0.21*	0.17	0.30**	0.20*	0.28**	0.07	0.22*	-0.02	0.03	0.10	-0.01

* $p < 0.05$; ** $p < 0.01$

5.7 Bone Structure and Bone Strength

There were no significant differences in bone strength or bone structure at baseline (Table 5.12). The HSA was unable to analyze PF scans for one boy and two girls in the intervention group.

Table 5.12 Baseline bone strength, areal bone mineral density (aBMD), cross-sectional area (CSA), subperiosteal width (SPW), and estimated cortical width (AVG CORTEX) and bone structure, section modulus (Z) values at the narrow neck (NN), intertrochanteric region (IT) and femoral shaft (S) for intervention and control children (mean ± std dev (range).

	Intervention (n=48)	Control (n=75)
Bone Structure:		
Narrow Neck (NN)		
aBMD (g/cm^2)	0.83 ± 0.13 (0.58 – 1.2)	0.82 ± 0.11 (0.57 – 1.2)
CSA (cm^2)	1.9 ± 0.4 (1.3 – 3.0)	1.9 ± 0.3 (1.3 – 2.9)
SPW (cm)	2.4 ± 0.2 (2.0 – 2.8)	2.4 ± 0.2 (1.9 – 2.9)
AVG CORTEX (cm)	0.16 ± 0.03 (0.11 – 0.24)	0.16 ± 0.02 (0.11 – 0.23)
Intertrochanteric Region (IT)		
aBMD (g/cm^2)	0.82 ± 0.12 (0.64 – 1.2)	0.81 ± 0.12 (0.60 – 1.1)
CSA (cm^2)	3.1 ± 0.6 (2.3 – 5.2)	2.9 ± 0.5 (2.0 – 4.4)
SPW (cm)	4.0 ± 0.4 (3.3 – 4.9)	3.8 ± 0.3 (2.8 – 4.5)
AVG CORTEX (cm)	0.35 ± 0.07 (0.24 – 0.58)	0.33 ± 0.05 (0.20 – 0.46)
Femoral Shaft (S)		
aBMD (g/cm^2)	0.99 ± 0.15 (0.79 – 1.5)	0.99 ± 0.13 (0.69 – 1.3)
CSA (cm^2)	2.0 ± 0.4 (1.4 – 3.3)	2.0 ± 0.3 (1.4 – 2.8)
SPW (cm)	2.2 ± 0.2 (1.8 – 2.5)	2.2 ± 0.2 (1.6 – 2.6)
AVG CORTEX (cm)	0.36 ± 0.07 (0.27 – 0.66)	0.36 ± 0.06 (0.24 – 0.50)
Bone Strength:		
NN Section Modulus (cm^3)	0.7 ± 0.2 (0.38 – 1.2)	0.7 ± 0.2 (0.47 – 1.2)
IT Section Modulus (cm^3)	2.1 ± 0.6 (1.2 – 4.0)	1.8 ± 0.4 (0.97 – 3.1)
S Section Modulus (cm^3)	0.84 ± 0.2 (0.49 – 1.4)	0.83 ± 0.2 (0.42 – 1.3)

The PPM correlations between baseline bone structural parameters and selected descriptors are provided (Table 5.14). Generally, total body mass and fat mass were most consistently and positively associated with bone structure

and bone strength outcomes. Unadjusted 7-month change for bone structure and bone strength are provided (Table 5.15).

Table 5.13 Unadjusted 7-month change for areal bone mineral density (aBMD), cross-sectional area (CSA), subperiosteal width (SPW), and estimated cortical width (AVG CORTEX) and section modulus (Z) at the narrow neck, intertrochanteric region and femoral shaft for intervention and control children (mean ± std dev (range)).

	Intervention (n=48)	Control (n=75)
Bone Structure:		
Narrow Neck (NN)		
aBMD (g/cm^2)	0.02 ± 0.09 (-0.29 – 0.36)	0.02 ± 0.06 (-0.20 – 0.19)
CSA (cm^2)	0.09 ± 0.10 (-0.93 – 1.3)	0.11 ± 0.17 (-0.49 – 0.58)
SPW (cm)	0.04 ± 0.15 (-0.40 – 0.50)	0.09 ± 0.08 (-0.10 – 0.32)
AVG CORTEX (cm)	0.005 ± 0.018 (-0.06 – 0.07)	0.003 ± 0.012 (-0.04 – 0.04)
Intertrochanteric Region (IT)		
aBMD (g/cm^2)	0.02 ± 0.07 (-0.19 – 0.35)	0.01 ± 0.05 (-0.12 – 0.21)
CSA (cm^2)	0.22 ± 0.53 (-1.6 – 2.6)	0.24 ± 0.28 (-0.28 – 1.6)
SPW (cm)	0.17 ± 0.29 (-1.0 – 1.2)	0.23 ± 0.15 (0.01 – 1.0)
AVG CORTEX (cm)	0.01 ± 0.04 (-0.13 – 0.19)	0.01 ± 0.03 (-0.06 – 0.15)
Femoral Shaft (S)		
aBMD (g/cm^2)	0.05 ± 0.09 (-0.25 – 0.36)	0.04 ± 0.07 (-0.14 – 0.20)
CSA (cm^2)	0.21 ± 0.29 (-0.79 – 1.4)	0.17 ± 0.16 (-0.13 – 0.62)
SPW (cm)	0.10 ± 0.12 (-0.41 – 0.50)	0.09 ± 0.07 (-0.05 – 0.42)
AVG CORTEX (cm)	0.02 ± 0.04 (-0.11 – 0.15)	0.01 ± 0.03 (-0.08 – 0.09)
Bone Strength:		
NN Section Modulus (cm^3)	0.04 ± 0.16 (-0.47 – 0.68)	0.06 ± 0.08 (-0.28 – 0.26)
IT Section Modulus (cm^3)	0.27 ± 0.63 (-2.0 – 3.0)	0.28 ± 0.29 (-0.19 – 1.6)
S Section Modulus (cm^3)	0.12 ± 0.16 (-0.47 – 0.80)	0.10 ± 0.08 (-0.07 – 0.40)

Table 5.14 Pearson Product Moment correlations between selected independent variables and baseline bone structure and bone strength at the narrow neck, intertrochanteric region and femoral shaft.

Bone Structure:	Age (yrs)	Tanner	Height (cm)	Weight (kg)	Δ Height (cm)	BMF Lean Mass (g)	Fat Mass (g)	PA Score (/5)	Load Time (hr/wk)	Vertical Jump (cm)	Calcium Intake (g)
Narrow Neck CSA (cm^2)	-0.00	**0.21***	0.17	0.17	0.04	0.04	0.16	-0.04	-0.04	0.13	0.00
Narrow Neck aBMD (g/cm^2)	0.01	0.15	0.18	0.18	-0.01	0.05	0.11	-0.02	-0.03	0.13	0.13
Narrow Neck SPW (cm)	-0.03	0.17	0.05	0.05	0.09	-0.00	0.16	-0.06	-0.01	0.06	-0.25**
Narrow Neck AVG CORTEX (cm)	0.01	0.15	0.17	0.18*	-0.02	0.06	0.11	-0.02	-0.03	0.13	0.14
Intertrochanteric CSA (cm^2)	0.06	0.16	0.13	0.09	-0.01	0.11	0.05	-0.05	-0.06	0.20*	-0.01
Intertrochanteric aBMD (g/cm^2)	0.11	0.07	0.13	0.08	-0.05	0.05	0.11	-0.01	-0.07	0.17	0.10
Intertrochanteric SPW (cm)	-0.06	**0.21***	0.08	0.08	0.05	0.13	0.05	-0.10	-0.01	0.14	-0.17
Intertrochanteric AVG CORTEX (cm)	0.06	0.06	0.11	0.10	-0.02	0.12	0.04	-0.03	-0.04	0.20*	0.09
Femoral Shaft CSA (cm^2)	0.08	**0.22***	**0.20***	0.17	0.02	**0.20***	0.10	-0.04	-0.07	0.11	-0.09
Femoral Shaft aBMD (g/cm^2)	0.10	0.15	**0.21***	**0.21***	0.03	**0.23***	0.15	-0.02	-0.06	0.11	-0.01
Femoral Shaft SPW (cm)	0.01	**0.22***	0.06	0.00	-0.01	0.03	-0.03	-0.07	-0.06	0.04	-0.18*
Femoral Shaft AVG CORTEX (cm)	0.09	0.13	**0.19***	**0.20***	0.03	**0.22***	0.14	-0.01	-0.06	0.10	0.02
Bone Strength:											
Narrow Neck Section Modulus (cm^3)	-0.02	**0.24****	-0.07	0.02	-0.05	0.02	0.17	-0.08	-0.06	0.12	-0.05
Intertrochanteric Section Modulus (cm^3)	0.00	0.17	0.13	0.09	0.05	0.12	0.02	-0.10	-0.04	0.19*	-0.10
Femoral Shaft Section Modulus (cm^3)	0.07	**0.26****	**0.19***	0.14	0.04	**0.18***	0.08	-0.05	-0.07	0.10	-0.16

* $p < 0.05$; ** $p < 0.01$

Table 5.15 Pearson Product Moment correlations between selected independent variables and unadjusted 7-month change in bone structure and bone strength at the narrow neck, intertrochanteric region and femoral shaft.

Change in Bone Structure:	Age (yrs)	Tanner	Height (cm)	Weight (kg)	Δ Height (cm)	BMF Lean Mass (g)	Fat Mass (g)	PA Score (/5)	Load Time (hr/wk)	Vertical Jump (cm)	Calcium Intake (g)
Narrow Neck CSA (cm^2)	-0.00	-0.05	0.07	**0.22***	-0.04	0.14	**0.25****	0.01	-0.04	-0.14	0.02
Narrow Neck aBMD (g/cm^2)	-0.02	-0.10	0.02	0.19*	-0.08	0.10	**0.21***	0.04	0.00	-0.11	-0.01
Narrow Neck SPW (cm)	0.00	0.04	0.12	0.16	0.06	0.14	**0.18***	-0.04	-0.13	-0.12	0.07
Narrow Neck AVG CORTEX (cm)	-0.02	-0.10	0.02	0.18*	-0.08	0.10	**0.21***	0.04	0.00	-0.10	-0.02
Intertrochanteric CSA (cm^2)	-0.11	-0.06	0.11	**0.31****	0.07	**0.23****	**0.31****	0.10	0.11	-0.11	0.03
Intertrochanteric aBMD (g/cm^2)	-0.12	-0.07	0.15	**0.30****	0.05	**0.26****	**0.26****	0.14	**0.18***	-0.02	0.05
Intertrochanteric SPW (cm)	-0.11	-0.07	-0.01	**0.21***	0.10	0.10	**0.27****	0.07	0.01	-0.22*	-0.01
Intertrochanteric AVG CORTEX (cm)	-0.08	-0.04	0.15	**0.31****	0.03	**0.24****	**0.32****	0.13	0.13	-0.12	0.06
Femoral Shaft CSA (cm^2)	-0.11	-0.03	0.02	**0.23****	0.08	0.17	**0.23****	0.06	0.06	-0.05	0.02
Femoral Shaft aBMD (g/cm^2)	-0.07	-0.01	0.04	**0.21***	0.01	0.15	**0.22****	0.07	0.07	-0.05	0.06
Femoral Shaft SPW (cm)	-0.16	-0.09	-0.07	0.07	0.13	0.05	0.07	0.01	0.01	-0.00	-0.08
Femoral Shaft AVG CORTEX (cm)	-0.06	-0.00	0.05	**0.22***	-0.01	0.15	0.22*	0.06	0.06	-0.06	0.06
Change in Bone Strength:											
Narrow Neck Section Modulus (cm^3)	-0.01	-0.04	0.08	**0.22***	-0.06	0.15	**0.24****	0.02	-0.04	-0.12	0.01
Intertrochanteric Section Modulus (cm^3)	-0.09	-0.04	0.15	**0.31****	0.02	**0.23****	**0.34****	0.04	0.05	-0.17	-0.03
Femoral Shaft Section Modulus (cm^3)	-0.13	-0.01	0.01	**0.23***	0.10	0.17	**0.22***	0.04	0.01	-0.05	-0.02

* $p < 0.05$; ** $p < 0.01$

The Pearson Product Moment correlations for selected independent variables and 7-month change values for bone structure and bone strength are provided (Table 5.15). Generally, change in bone structural parameters at all sites, except femoral shaft SPW, is positively correlated with baseline fat mass ($p < 0.05$ and $p < 0.01$) (Table 5.14). Similarly, change in bone structural parameters at all sites, except femoral shaft SPW and narrow neck SPW, is correlated with baseline weight ($p < 0.05$ and $p < 0.01$) (Table 5.14). Change in intertrochanteric CSA, aBMD and AVG CORTEX are highly correlated with bone mineral free lean mass ($p < 0.01$) (Table 5.14). Only change in intertrochanteric aBMD is moderately correlated to loaded physical activity time ($p < 0.05$)(Table 5.14). Generally, 7-month change in section modulus (representing bone strength) was positively correlated ($p < 0.01$) with baseline total body mass and fat mass at most measured sites (NN, IT and S).

There were no significant differences between intervention and control children for adjusted change in bone structure, with the exception of NN SPW (Table 5.16). Adjusted change in NN SPW was significantly greater in control children (3.8%), compared with intervention children (1.7%) ($p = 0.014$).

Table 5.16 Adjusted values for areal bone mineral density (aBMD), cross-sectional area (CSA), subperiosteal width (SPW), and estimated cortical width (AVG CORTEX) and section modulus (Z), 7-month change values at the narrow neck (NN), intertrochanteric region (IT) and femoral shaft (S). Values are adjusted for baseline maturity, age, height, change in height and average physical activity score for intervention and control children.

	Intervention (n=48)	Control (n=75)
Bone Structure:		
Narrow Neck (NN)		
aBMD (g/cm^2)	0.02 +/- 0.09	0.02 +/- 0.06
CSA (cm^2)	0.09 +/- 0.10	0.11 +/- 0.17
SPW (cm)	0.04 +/- 0.15	0.09 +/- 0.08*
AVG CORTEX (cm)	0.005 +/- 0.018	0.003 +/- 0.012
Intertrochanteric Region (IT)		
aBMD (g/cm^2)	0.02 +/- 0.07	0.01 +/- 0.05
CSA (cm^2)	0.22 +/- 0.53	0.24 +/- 0.28
SPW (cm)	0.17 +/- 0.29	0.23 +/- 0.15
AVG CORTEX (cm)	0.01 +/- 0.04	0.01 +/- 0.03
Femoral Shaft (S)		
aBMD (g/cm^2)	0.05 +/- 0.09	0.04 +/- 0.07
CSA (cm^2)	0.21 +/- 0.29	0.17 +/- 0.16
SPW (cm)	0.10 +/- 0.12	0.09 +/- 0.07
AVG CORTEX (cm)	0.02 +/- 0.04	0.01 +/- 0.03
Bone Strength:		
NN Section Modulus (cm^3)	0.04 +/- 0.16	0.06 +/- 0.08
IT Section Modulus (cm^3)	0.27 +/- 0.63	0.28 +/- 0.29
S Section Modulus (cm^3)	0.12 +/- 0.16	0.10 +/-0.08

* Control children had significantly greater subperiosteal width at the narrow neck when compared with intervention children (p = 0.014).

Chapter 6: Discussion

This study examined whether an seven-month program of brief bouts of jumping performed at 3 timepoints throughout an elementary-school day would; 1) effect greater change in BMC at the TB, LS, PF and its subregions IT, FN and TR in intervention as compared with control children, and 2) result in an advantageous adaptation of structural parameters at the proximal femur by Hip Structural Analysis (HSA) in the intervention children compared with controls. I also assessed what the primary correlates with bone structural change amoung these children.

6.1 Body Composition

Although the "Bounce at the Bell" cohort was limited to 51 children of varying sex, ethnicity and maturity level, the cohort was a representative sample. Body composition variables such as average height, weight, sitting height, leg length and calf girth were similar between the intervention and control groups and agree with data from previous, much larger, studies from our lab with a similarly aged, mature and ethnically diverse cohort (MacKelvie, McKay et al. 2001; MacKelvie, McKay et al. 2002).

Changes in body composition of the cohort were essentially similar to those found in other studies, with the exception that this study found a significantly greater increase in calf girth of the intervention children compared with the control children. This significantly greater increase may indicate an increase in muscle gained in the calf region due to the daily jumping.

Fat mass changed similarly to pre- and early-pubertal girls after a 7-month jumping intervention (10 minutes, 3 times per week) (MacKelvie, McKay et al. 2001). Our data showed a strong relationship between both total body mass and fat mass with measures of bone structure at the proximal femur. To my knowledge, this has not been demonstrated previously. Note that lean mass did not display the same relationship. A recent study that used HSA to assess strength indices of the PF in pre-pubertal female gymnasts found a relationship between lean mass and increased bone strength, but not fat mass (Faulkner, Forwood et al. 2003).

Our data also showed a strong relationship between lean mass and bone mineral and these results agree with results from previous Healthy Bones studies (MacKelvie, McKay et al. 2001; MacKelvie, McKay et al. 2002) as well as previous studies from other labs (Young, Hopper et al. 1995; Pietrobelli, Faith et al. 2002). As well as lean mass, there was a strong relationship between fat mass, height and weight and bone mass at baseline. These findings agree with those from Healthy Bones II (MacKelvie 2002) and provide support for using height and weight as variables in the analyses of covariance when detecting differences in bone mass change between groups of children who participate in an exercise intervention and control children.

6.2 Lifestyle Factors

6.2.1 Calcium Intake

According to the recently published Dietary Reference Intakes (DRIs) the daily recommendation for calcium intake for children and adolescents is 1300

mg/day (Yates, Schlicker et al. 1998), which is well above intakes reported in this study, an average of 776 ± 390 mg/day for intervention children and 798 ± 378 mg/day for controls. Morris and colleagues (Morris, Naughton et al. 1997) reported much higher baseline averages of 960 ± 310 mg/day and 1016 ± 261 mg/day for Australian intervention and control pre-menarcheal girls, respectively. Another study of American pre-pubertal children reported higher calcium intakes, on average 1242 mg/day for jumpers and 1243 mg/day for controls, than ours also (Fuchs, Bauer et al. 2001); however a confounding factor may be the measurement instrument with which these values are calculated, in this case, the Harvard Youth Frequency Food Frequency Questionnaire. HBS II data, which used the same measurement instrument as our study, showed somewhat higher values for calcium intake at baseline, 819 ± 428 mg/day for girls, but not for boys 853 ± 442 mg/day (MacKelvie 2002) than the data from this study (girls 731 ± 322 mg/day and boys 939 ± 403 mg/day).

Given the recent evidence from randomized controlled trials of exercise intervention with calcium supplementation, it may be advisable to recommend that participants try to intake the DRI for calcium, in order to maximize any effects of an exercise intervention. In our study, there was no correlation between calcium intake and baseline or change in bone mass; however there was a negative correlation between bone structural parameters, NN SPW ($r = -0.25$, $p < 0.001$) and S SPW ($r = -0.18$, $p < 0.05$) at the proximal femur and calcium intake. To my knowledge, there have been no reports of a negative correlation between calcium intake and bone structural parameters at the proximal femur. A

randomized controlled trial stratified by various levels of calcium intake and change in PF bone structure would likely provide further evidence into the validity and repeatability of this finding.

6.2.2 Health History and Ethnicity

A unique aspect of this study was that the percentage of Asian to Caucasian subjects was greater than past studies, 54% and 51% of the intervention and control girls, respectively, were Asian. In HBS II, the percentage of Asian children was 35%, Caucasian 45% and Other was 20% for girls. Corresponding percentages for boys were 39%, 44% and 17% for boys, respectively (MacKelvie 2002). Since there has been little evidence to support a difference in bone accrual rates for Asian, Caucasian and Other children, exclusive of lifestyle factors (MacKelvie, McKay et al. 2001; MacKelvie, McKay et al. 2002), I grouped all children for analysis, but I also ensured that ethnicities were approximately represented in both boys and girls in both the intervention and control groups.

6.2.3 Physical Activity

Intervention children had significantly greater loaded physical activity (average 6.8 hours per week) when compared with control children (average 4.9 hours per week), but this amount was less than the average loaded physical activity time of 5.8 to 8.2 hours per week for boys (MacKelvie, McKay, 2002) and slightly more than the average of 4.5 to 5.7 hours per week for girls (MacKelvie, McKay, 2001) in previous studies from our lab. Also, I found that the boys participated in significantly greater loaded physical activity and had significantly

higher physical activity scores than girls in our study, which is consistent with the findings in previous studies (McKay, Petit at al 2000; MacKelvie, 2002).

Boys, who averaged 8.1 hours per week, participated in almost twice as much loaded physical activity than girls, who averaged 4.7 hours per week, over the 7-month period. There was a similar difference in loaded physical activity time between boys (7.6 ± 6.4 hours/week) and girls (5.0 ± 4.2 hours/week) in HBS II (MacKelvie 2002).

There was no correlation between average loaded physical activity time or physical activity score and change in BMC at any sites; however there was a relationship between loaded physical activity, but not physical activity score and baseline PF BMC ($r = 0.18$, $p < 0.05$), IT BMC ($r = 0.20$, $p < 0.05$) and FN BMC ($r = 0.24$, $p < 0.001$). This finding agrees, in part, with results from the U of S Bone Mineral Accrual Study that found correlations, higher than ours, between physical activity and TB, FN, and LS bone mineral accrual for boys ($r = 0.39 – 0.40$) and girls ($r = 0.38 – 0.47$). These findings were in older, more mature children at the time of peak bone mineral accrual (Bailey, McKay et al. 1999). As children in the present study were primarily pre- and early-pubertal, the effect of exercise on bone accrual may not be as pronounced yet. Most other exercise intervention studies report the differences or similarities between groups for physical activity, but not its relationship with bone accrual, because they are investigating the differences between groups for a specific exercise intervention and want to control for external-to-the-intervention physical activity (Fuchs, Bauer et al. 2001; Heinonen, Sievanen et al. 2000; Bradney, Pearce et al. 1998).

6.3 Dynamic Power

We measured one index of dynamic power, vertical jump, as a check between groups to ensure that there are no significant differences between groups at baseline, which could confound the results of the intervention. Secondly, any changes in dynamic power may indicate a benefit in the intervention group or a confounding factor in the control group. For example, if children in the control group participated in exercise that would increase dynamic power in the legs and resultantly increase bone mineral accrual or positively enhance bone structure and bone strength changes masking any greater increases in these parameters in the intervention group.

In this study, there were no significant differences between the intervention and control children for vertical jump at baseline and the average value for this dynamic power measure was similar to those found in HBS II (MacKelvie, 2002). Change in vertical jump was not significant between intervention and control children in this study. In HBS I, McKay and colleagues (McKay, Petit et el. 2000) found a significant increase in vertical jump in the intervention group over 7 months ($p = 0.003$) when compared with the control group and this difference was greater for girls than for boys with a significant interaction effect ($p = 0.043$).

6.4 Maturity

Age had a significant correlation with bone mineral at baseline, but not change in bone mineral accrual, whereas maturity had a strong correlation with both baseline bone mineral and bone mineral accrual. This finding agrees with

previous findings (MacKelvie, McKay et al. 2001). A greater, but not significant, percent of control children (33%) matured from Tanner stage 1 (pre-pubertal) to Tanner stage 2 (early-pubertal) than intervention children (24%). After 7 months, there were more total intervention children in early-puberty (73%) when compared with control children (63%); however none of the changes in maturity between groups was significantly different. Advanced maturational status could confer greater gains in bone mineral, thus I controlled for maturity. Results did not change when I controlled for final Tanner stage instead of baseline Tanner stage. Girls were significantly more mature when compared with boys after 7 months, which agrees with results from HBS II (MacKelvie 2002) and conforms to the findings of the U of S Bone Mineral Accrual Study in which girls, on average, were 22 months ahead of boys in maturational status at the same age (Bailey, McKay et al. 1999). Heinonen and colleagues (Heinonen, Sievenan et al. 2000) found significant increases in FN (4%) and LS (3.3%) BMC in pre-menarcheal girls (60% Tanner stage 2 or 3 at baseline), after a nine month intervention of high impact exercise 3 times per week.

The correlations found between baseline Tanner stage and baseline and change in bone mass parameters are largely consistent with those found in HBS II (MacKelvie 2002), with the exception of PF BMC (r =0.30, $p < 0.01$) and FN BMC (r =0.31, $p < 0.01$) which were not correlated as much or at all, respectively, in the present study. Intertrochanteric BMC was not reported in HBS II (MacKelvie 2002). Baseline Tanner stage was not correlated with any change in bone strength or structural parameters and only moderately correlated ($p < 0.05$)

with three baseline bone structural parameters (IT SPW, S CSA, and S SPW) and highly correlated ($p < 0.001$) with two out of three bone strength parameters NN and S section modulus. The Petit and colleagues (Petit, McKay et al. 2000) analysis of the randomized controlled trial (HBS II) of exercise and bone strength and bone structure using HSA did not report correlations, nor did the Faulkner and colleagues (Faulkner, Forwood et al. 2003) HSA study of PF strength indices in gymnasts. Therefore, to my knowledge, my findings on the correlation of maturational status and bone strength and bone structure are unique.

6.5 Bone Mineral Content

The bone response to this intervention was region- and site-specific. Previous studies (HBS II) from our lab have demonstrated significant gains in BMC at the LS and FN after 7 months of exercise, longer in duration (10 minutes), but only 3 times per week, in a similar cohort (MacKelvie, McKay et al. 2001, 2002). Results have been maturity- and sex-specific as well in that a significant response at the proximal femur was found in early- but not pre-pubertal girls (MacKelvie, McKay et al. 2001). The present study was not powered to separate the cohort into boys and girls or analyze the data by maturity group. However, these variables were controlled for in ANOVA.

Other previous studies have shown larger percent differences at more skeletal sites between intervention and control girls (Heinonen, Sievenen et al 2000; Morris, Naughton et al 1997) and boys and girls (Fuchs, Bauer et al. 2001) for example up to 5.5% versus 2.6% and 3.5% in this study. This may have been due to the longer, more intense nature of those interventions. However, these

interventions that took place in out-of-school hours (20 to 40 minutes in duration), were much less easily administered than ours, which was incorporated right into the classroom and only took a few minutes at three intervals throughout the school day.

The novel intervention I report, promoted bone gain at the proximal femur and intertrochanteric region in pre- and early-pubertal boys and girls which is different from the pattern of intervention promoted bone gain in early-pubertal girls in past studies at the femoral neck and lumbar spine, but not at the proximal femur or trochanteric region (MacKelvie, McKay et al. 2001; Heinonen, Sievenen et al 2000). The intervention did not promote bone gain at the lumbar spine and this may be because impact forces are greatly attenuated before reaching that region (Wosk and Voloshin 1981). Bone gain at the lumbar spine is more likely due to stress and strain caused by the action of the muscles of the abdomen, back and hip (Hodges and Richardson 1997). Further investigation is warranted into the effects of program designed to increase muscle strength in order to affect change in bone mass in children as has been demonstrated in adults (Lohman, Going et al. 1995; Kohrt, Ehsani et al. 1997).

Assuming that gains from childhood are maintained into adulthood with normal physical activity levels, the 2.6 to 3.5% greater gain in BMC at the proximal femur is clinically relevant (Bachrach 2000). One follow-up study of a 7-month intervention in pre-pubertal children demonstrated that 4% gains in BMC at the femoral neck, but not the lumbar spine, were maintained 7 months after the end of the jumping intervention (Fuchs and Snow 2002). During the follow-up

period, the children maintained average physical activity levels. Bone gains, such as those made at the proximal femur in this study, if maintained translate to an approximate 20% decrease in risk of fracture in old age (Hui, Slemenda et al. 1990). However, no study to date, has assessed the effects of a childhood exercise intervention past 7 months nor have the long-term effects from a longer intervention (more than on year) been investigated.

I reported BMC, and not aBMD, because changes in both bone geometry and density occur during growth and it is difficult to represent these three dimensional changes with a two-dimensional adjustment (Hayes and Bouxsein 1997). The limitation of vBMD is that it is based on the assumption of the geometric shape of the bone. The use of BMC avoids these limitations.

6.6 Bone Structure and Bone Strength

Hip structural analysis is a method used to investigate the changes in bone structure, the expansion or contraction at the periosteal and endosteal surfaces, and bone strength and as a result of growth and mechanical loading in children. We would expect to see an increase in periosteal expansion in response to loading as was demonstrated in animal studies (Mosely, March et al. 1997; Raab-Cullen, Theide et al. 1994). However it may not be appropriate to compare results from animal studies to those from human interventions (Petit, McKay et al. 2000). Petit and colleagues found that an increase in endosteal apposition or lack of contraction on the endosteal surface, but no increase in periosteal apposition in early-pubertal girls in response to an exercise intervention (Petit, McKay et al. 2000). Studies of racquet sport players reveal

surface-specific response to bending and torsional strains (Haapasalo, Kannus et al. 1996; Haapasalo, Kontulainen et al. 2000). Players who began sport during adolescence had greater periosteal apposition and bone size. A bone with a greater bone surface (greater CSA) will resist compressive loads, were as a wider bone (greater SPW) is better for resisting bending and torsional loads (Haapasalo, Kontulainen et al. 2000). If bone increases in width, but not in CSA, then a resultant drop in aBMD will occur (Petit, McKay et al. 2000). The axial forces produced in jumping interventions in children will most likely result in an increase in endosteal bone formation as the forces are evening distributed throughout the bone unlike the torsional or bending loads that would induce a periosteal surface response. This was recently demonstrated in an animal study where roosters were dropped resulting in a 350% greater increase in endosteal bone formation and only a 40% greater increase in periosteal bone formation of intervention compared with controls (Judex and Zernicke, 2002).

This intervention did not have a positive effect on bone structure or bone strength changes as assessed by HSA in pre- and early-pubertal children. As I was unable to separate the children into pre- and early-pubertal groups, it is possible that gains made by the latter may have been masked by no response to the intervention in the pre-pubertal groups. As we saw a significant increase in PF and IT BMC, we would expect to see an increase in IT CSA as it is equivalent to BMC by DXA. However, due to the fact that the analyzed section from HSA may not represent the entire IT region by DXA the results can vary. Petit and colleagues (Petit, McKay et al. 2000) reported a 2.3% greater increase in NN

CSA (p = 0.040) and 3.2% greater increase in NN AVG CORTEX (p = 0.032) resulting in a 4.0% greater increase in NN section modulus (p = 0.034), a measure of bone strength, in early-pubertal girls, but not pre-pubertal girls. However, they did find an apparent trend toward lower values for periosteal apposition in the intervention group at the NN and IT regions. That finding agrees with our finding of a significantly greater NN SPW in the control children when compared with intervention children (+2.1 %, p =0.014). As this change in SPW did not result in a corresponding change in bone strength as measured by section modulus, HSA may lack the sensitivity to detect such small estimated changes in the bone structure variables in pre-pubertal children. A 4.3% increase in SPW and a 6.9% increase in AVG CORTEX resulted in a 15.7% increase in section modulus in the study by Petit and colleagues (Petit, McKay et al. 2000). Another limitation of HSA is that it attempts to assess a three dimensional object from a two-dimensional image, for instance, it assumes an annular shape for the femoral neck. As well, HSA assumes a fixed compartment for trabecular and cortical bone mass. However it still remains a viable way to analyze bone structure and bone strength at clinically relevant sites using DXA scans.

6.7 Exercise Intervention

Our novel exercise intervention of short bouts of jumping interspersed throughout the school day is a safe, effective, inexpensive and easy method for enhancing bone mineral accrual in children. This is the first study to demonstrate that an easily administered program of short bouts of jumping performed in the classroom can have similar results to less-easily administered out-of-school

interventions requiring 30-35 minutes, 3 times per week in pre- and early-pubertal children (Bradney,Pearce et al. 1998) (Morris, Naughton et al. 1997). The jumping exercises were high impact in nature, therefore causing a greater strain rate and magnitude than the usual daily activities of the intervention children, despite the significantly greater participation of the intervention children in loaded physical activity prior to the start of the intervention.

Compliance with this intervention was very high likely due to the fact that it was administered in the classroom and had a novel and fun theme of "bouncing at the bell". Teachers reported that the children enjoyed participating in the jumping program and that it was easy to administer. This unique intervention was designed to elicit a positive bone response in children who were already active by undertaking an average 7.2 hours per week of loaded recreation activity. If the positive effects I report are confirmed in future studies with larger subject numbers, this intervention should be evaluated for maintenance of bone health over the longer term.

A limitation to this study was the small sample size, which made it impossible to separate the group into boys and girls and different maturational groups or ethnicities. Further study is warranted to determine if our unique intervention can confer gains in bone strength, as well as, structure in early-pubertal girls and boys.

Chapter 7: Summary, Conclusions and Future Directions

7.1 Summary

7.1.1 Primary Outcomes

1. This seven-month program of brief bouts of jumping performed at frequent intervals had a significant and positive effects on BMC gain, specifically the intertrochanteric and proximal femur regions ($p = 0.005$ and 0.012 respectively), between children who participated in this novel exercise program and control children.
2. There were no significant differences in bone structural parameters at the proximal femur between children who participated in this novel exercise program and controls.

7.2 Conclusions and Future Directions

1. This protocol may be an effective means for the delivery of an inexpensive bone building program in elementary schools.
2. Childhood may be a responsive time for proximal femur adaptation to loading activity.
3. Bounce at the Bell provided an inadequate stimulus to elicit a response in bone structure similar to the response in bone mineral content found in this group of children.
4. Further study is required to investigate whether or not the observed benefits will be maintained 12 months or longer after withdrawal of the exercise stimulus.
5. An additional study should be conducted, with a sample size large enough to determine the difference in response to the novel intervention for differing maturity groups, sexes and ethnicities. Further, to investigate site- and surface-specific responses to the novel intervention using additional, complementary technologies such as pQCT and MRI.

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Appendix 1:

Procedures:

- Your child's continued participation in the project will involve two testing sessions (approximately three hours each, including transportation time), one at the beginning and one at the end of the school year at the University of British Columbia in Vancouver. Each session will include the following procedures:

1. Measures of height, seated height, calf girth and weight will be taken again. Your child will be asked to complete questionnaires that will assess their physical activity, and calcium intake and perform a standing long jump and vertical jump test just as they have over the last two years. A trained study staff person will discuss the importance of these assessments with the children. A brief health history questionnaire will be sent home to be completed by a parent or guardian if not completed previously.

2. Following individual instruction, the children will be asked to complete the physical maturity assessment forms. There is a space in our laboratory where they may do this in private, seal the results and return the envelope to us. Results remain confidential and data entry is by subject number only so that children can not be identified. Parents wishing to complete this form for their children may indicate so by attaching a note to the returned consent form.2.

3. Characteristics of the bone in the tibia area will be assessed by quantitative ultrasound. This is a very simple procedure that only requires that your child remain still for 1 minute each for three measurements with his or her leg resting flat on the table. There are neither risks or discomfort associated with this procedure.

4. Your child's whole body, hip and spine bone status will be evaluated by a bone densitometer. This procedure is painless and routinely used in modern medical practice. It requires only that the child lies still on the padded measurement table for about 15 minutes. Although the bone measurement is X-ray based, the total patient effective dose per session will be less than 10 millirem which is similar to the background radiation one would receive making a one-way flight from Vancouver to Halifax. To put this in perspective, the annual background radiation in Vancouver due to natural sources is around 150 millirem per year. The current permissible level for the general population is 500 millirem per year. These values can be used to compare the relative risk of less than 10 millirem exposure from the bone density procedure. All bone density measurements will be conducted by a trained operator. Less than 15 minutes is required for all the bone measurement procedures.

5. Analysis of bone geometry of the lower leg will be performed using images generated by peripheral Quantitative Computerized Tomography pQCT. The pQCT involves a minimal amount of radiation (0.1 miscroSV), that's 1 tenth the radiation of a normal chest x-ray, similar to the radiation exposure one would receive flying to Toronto from Vancouver. The child will have to remain still with their leg extended into the device for three measures of the lower leg one at 10, 30 and 50% of the length of the lower leg from the ankle. A trained operator will conduct the 7-minute scan. There is no risk or discomfort to the child in this procedure.

Bounce at the Bell CONSENT FORM

Parent's Consent Statement:

I, _____
(please print the name of one or both parents)
understand the purpose and procedures of this study as described and I voluntarily agree to allow my child, _____, to participate in (please 4):

____The Healthy Bones Study (height, weight, questionnaires, bone mineral density, ultrasound, and pQCT measurements).

Your confidentiality will be respected. No information that discloses your identity will be released or published without your specific consent to the disclosure. However, research records and medical records identifying you may be inspected in the presence of the Investigator or his or her designate by representatives of UBC Bone Health Research Group, Health Canada, and the UBC Research Ethics Board for the purpose of monitoring the research. However, no records which identify you by name or initials will be allowed to leave the Investigators' offices.

I understand that at any time during the study we will be free to withdraw without jeopardizing any medical management, employment or educational opportunities. I understand the contents of all three pages of this form, the proposed procedures and possible risks. I have had the opportunity to ask questions and have received satisfactory answers to all inquiries regarding this study. I acknowledge that I have received a copy of this consent form. I understand that signing this consent form in no way limits my legal rights against the sponsor, investigators, or anyone else.

_____ _____
Signature of Parent/Guardian Date

_____
Please Print Name

_____ _____
Signature of Investigator Date

_____
Please Print Name

_____ _____
Signature of Witness Date

_____
Please Print Name

Bounce at the Bell CHILD'S ASSENT FORM

Child's Statement:
I understand the purpose and procedures of this study as described and I voluntarily agree to participate. I understand that at any time during the study, I will be free to withdraw without jeopardizing any medical management, employment or educational opportunities. I understand the contents of the consent form, the proposed procedures and possible risks. I have had the opportunity to ask questions and have received satisfactory answers to all inquiries regarding this study.

_____ _____
Signature of Child Date

_____
Please Print Name

_____ _____
Signature of Witness Date

_____
Please Print Name

Appendix 2:

Bounce at the Bell
Food Frequency Questionnaire – Fall 2003

Name/Grade:_____ Date:_____

We would like to know about some of the foods you eat. For each food listed please fill in how often you usually eat a portion of the size stated. If you eat the food:

- every day or more than once a day, fill in how many times you have it per day
- less than once a day but more than one a week, fill in the times per week
- less than once a week, but more than once a month, fill in the times per month
- less often than once a month, or never eat it, put an 'X' under 'do not eat'.

Example: Janice has a glass of orange juice every morning, along with two slices of toast. She usually has two sandwiches at lunch, and eats french fries about 3 times per week. She almost never eats cauliflower.

	Per day	Per week	Per month	Don't eat
Orange Juice, 1 cup	___1___	_____	_____	
French fries, regular serving	_____	___3___	_____	
Cauliflower, ½ cup (125 ml)	_____	_____	_____	___X___
Bread or toast, 1 slice	___6___	_____	_____	

NUMBER OF TIMES I EAT THE FOOD

	Per day	Per week	Per month	Don't eat
Bread or toast, 1 slice or 1 roll	_____	_____	_____	___-
Muffin, 1 large	_____	_____	_____	___-
Pizza, 1 medium slice	_____	_____	_____	___-
Cheeseburger or veggieburger with cheese	_____	_____	_____	___-
Cheese: 1 slice processed OR 1 piece hard cheese (plain or in sandwich)	_____	_____	_____	___-

Broccoli, ½ cup (125 ml)	_____	_____	_____	___-
____				
Gai-lan (Chinese broccoli), ½ cup	_____	_____	_____	___-
				____
Bok- choi (Chinese cabbage), ½ cup	_____	_____	_____	_____
				_____
Ice cream (large scoop)	_____	_____	_____	___-
____				
Frozen yogurt (large scoop)	_____	_____	_____	___-
____				
Fast food milkshake	_____	_____	_____	___-
____				
Cottage cheese, ½ cup	_____	_____	_____	___-
____				
Yogurt, small (174 ml) carton or equivalent	_____	_____	_____	___-
____				
Canned salmon or sardines with bones, ½ small can	_____	_____	_____	___-
____				
Soft drink, 1 can or large glass	_____	_____	_____	_____
				_____

	Per day	Per week	Per month	Don't eat
Tofu, 2 oz (60 gm)	_____	_____	_____	___-
____				
Milk on cereal	_____	_____	_____	___-
____				
Orange juice, 1 cup	_____	_____	_____	___-
____				

Milk (any type including chocolate), 1 cup_____ _____ _____ ___-

____

Macaroni & cheese, 1 cup (250 ml) _____ _____ _____ ___-

____

I usually drink (choose one only)

_____milk OR
_____chocolate milk OR
_____soy milk OR
_____rice milk

Are you allergic to any foods?

_____NO
_____YES: (what foods?_____)

Do you use any **vitamin and/or mineral** supplements? **(This question is not about medications)**

	Daily	>3x/week	1-3x/week	<1/week
Multivitamin	_____	_____	_____	_____
Multivitamin/mineral	_____	_____	_____	_____
Iron	_____	_____	_____	_____
Vitamin C	_____	_____	_____	_____
Calcium	_____	_____	_____	_____
Other	_____	_____	_____	_____

What is the brand/name of the supplement?_____

THANK YOU!

Bounce at the Bell
Food Frequency Questionnaire Instructions

1. This questionnaire is designed to be ADMINISTERED (one-on-one with a child is best). Kids shouldn't be completing this without supervision or direction, but they may want to.

2. Read the instructions at the top of the page to the child. Go through the example with them.

3. Go through the checklist one item at a time – hold a ruler or a piece of paper on each line as you go down the list with the child.

4. Note the quantities of each item – this is important. On item # 1 – bread or toast – remember to tell them that a sandwich is 2 pieces of bread (so a sandwich = 2 servings). If they have 2 pieces of pizza every time they have pizza, and they have pizza twice a month, that's 4 servings per month.

5. Direct children to look at food posters if they are confused about cottage cheese or tofu.

6. Fast Food milkshake – can include homemade milkshakes here too.

7. Canned salmon or sardines – HAS TO HAVE BONES IN IT. Canned tuna doesn't count.

8. Milk on cereal should be considered separately from milk in a glass.

9. The vitamin and mineral question is difficult for them – just see if you can get the best description possible if they are taking anything. This is definitely NOT about drugs and medications – they don't have to tell you anything about that – don't ask.

10. CHECK EACH QUESTIONNAIRE FOR COMPLETENESS –THIS IS REALLY IMPORTANT! IF A CHILD DID ANY PART OF THE QUESTIONNAIRE WITHOUT YOUR DIRECT SUPERVISION, QUESTION THEM TO MAKE SURE IT MAKES SENSE.

if **no**, at what age did she/he start drinking milk every day? _____ years old.

_____NO: if **no**,

Has your child ever drank one or more cups of milk per day (after being weaned from breast or bottle)?

_____ yes: at what age did she/he stop drinking milk every day? _____ years old.

How many cups did he/she drink until that age? _____ cups per day.

_____no (never drank milk on a daily basis after being weaned)

1.3 Is your child on a special diet? _____ yes _____no

If **yes**, _____ vegetarian

_____ low sodium

_____ low cholesterol

_____other

Please specify_____

2.0 Medical history and status

2.1 Has your child ever bee treated for any of the following conditions?

	yes	no
food allergies	O	O
hypothyroidism	O	O
other allergies	O	O
hyperthyroidism	O	O
asthma	O	O

other conditions (please list)_____

_____

_____

2.2 Is your child currently taking any medications? _____ yes _____ no

If **yes**, what medication(s) is your child taking? _____

_____

_____

_____

What are these medication(s) for?

_____

_____

_____

3.0 Bone History

3.1 Has your child ever been hospitalized, confined to bed or had a limb immobilized (i.e., arm in a cast)?

_____ yes _____ no

If **yes**, list condition, approximate date and time involved

(Example:	wrist fracture	summer, 1990	10 weeks)
	Reason	**Date**	**Time Involved**

_____

3.2 Is there a history of wrist, hip, or spine fractures in your family? _____ yes _____ no
If **yes**, indicate who was affected

_____ mother _____ father
_____ maternal grandmother _____ paternal grandmother
_____ maternal grandfather _____ paternal grandfather

3.3 Is there a history of osteoporosis in your family? _____ yes _____ no
If **yes**, indicate who was affected

_____ mother _____ father
_____ maternal grandmother _____ paternal grandmother
_____ maternal grandfather _____ paternal grandfather

3.4 Is there a history of any other bone disease in your family?
_____ yes _____ no
If **yes**, please indicate the family member(s) affected
1. _____
2. _____

What is the name of the condition(s) affecting this family member?
1. _____
2. _____

4.0 Physical Acitivity

4.1 How would you rate the physical activity level of your child? (physical activity is defined as vigorous activity that makes them sweat and/or breathe hard)

_____ Inactive
_____ Sometimes active
_____ Moderately active
_____ Often active
_____ Very active

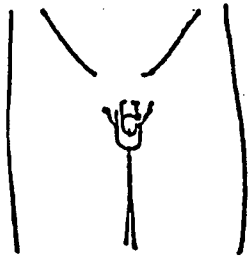
THANK YOU FOR YOUR PARTICIPATION

Bounce at the Bell - Fall 2003

STUDY IDENTIFICATION #:

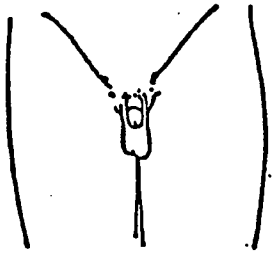
BOYS: After reading the descriptions under each drawing, please place a check mark above the drawing that looks closest to your stage of pubic hair development. Seal your response in the envelope provided. Thank you!

1 _____



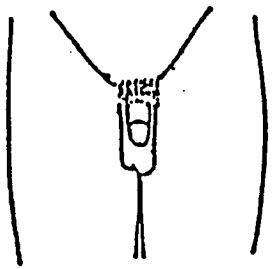
There is no pubic hair at all.

2 _____



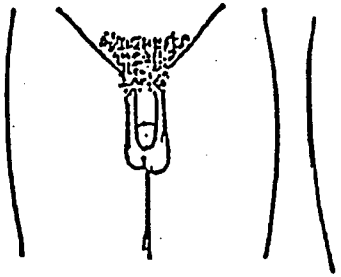
There is a small amount of long, lightly coloured hair. This hair may be straight or a little curly.

3 _____



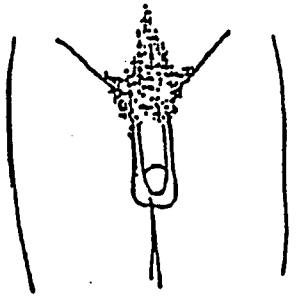
There is hair that is darker, curlier and thinly spread out to cover a somewhat larger area than in stage 2.

4 _____



The hair is thicker and more spread out, covering a larger area than in stage 3.

5 _____



The hair now is widely spread and covering a large area, like that of an adult male.

Bounce at the Bell

Self Assessment of Maturity Status: Boys

As you keep growing over the next few years, you will see changes in your body. These changes happen at different ages for different children, and you may already be seeing some changes, others may have already gone through some changes. Sometimes it is important to know how a person is growing without having a doctor examine them. It can be hard for a person to describe themselves in words, so doctors have drawings of stages that all children go through.

There are 5 drawings of pubic hair growth which are attached for you to look at. All you need to do is pick the drawing that looks like you do now. Put a check mark above the drawing that is closest to you stage of development for pubic hair. Put the sheet in the envelope and seal it so your answer will be kept private.

Bounce at the Bell - Fall 2003

STUDY IDENTIFICATION #:

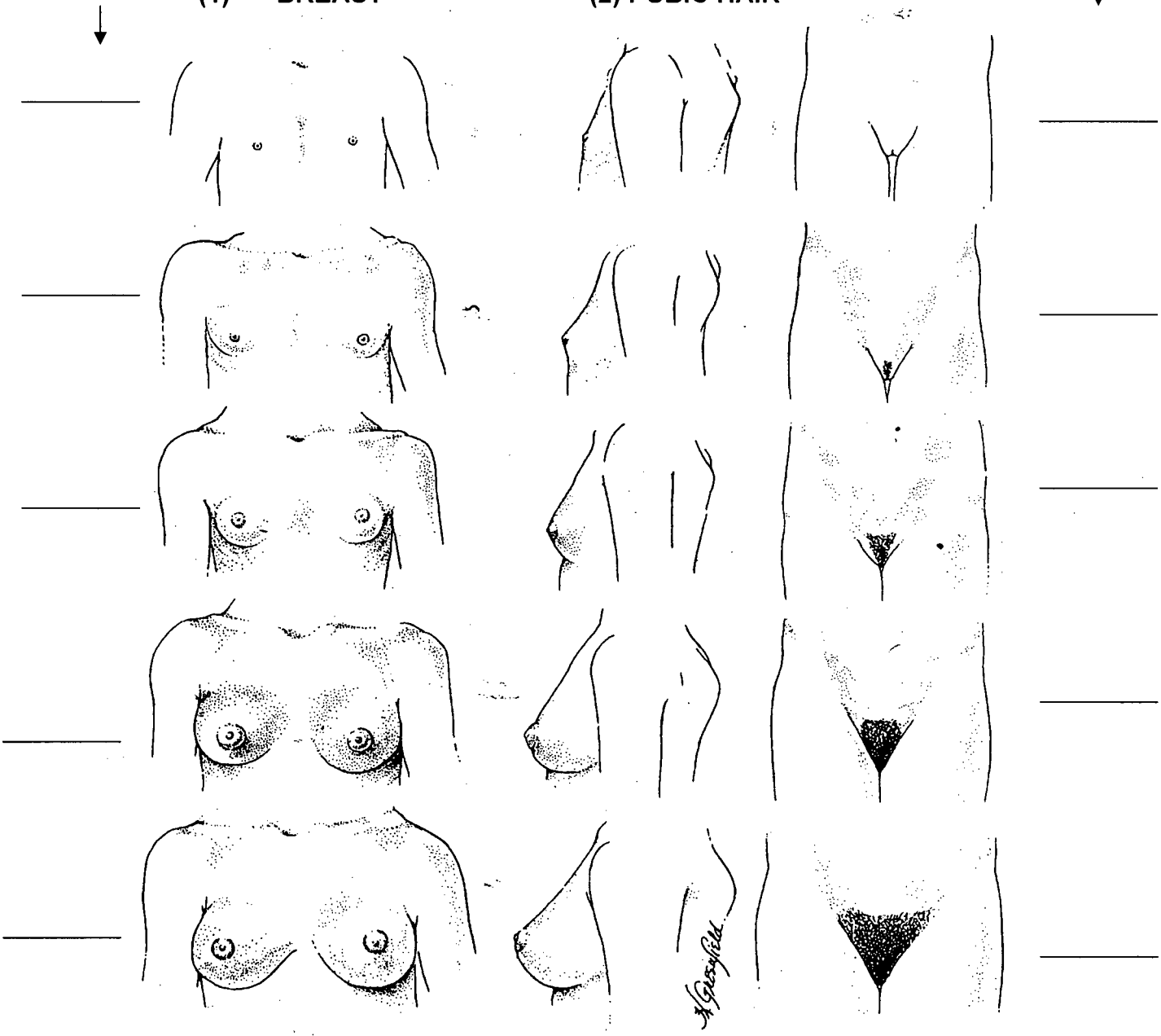
Please put a check mark on the drawing that looks most like (1) your stage of breast development, and (2) your stage of pubic hair development. Seal your response in the envelope provided. Thank you!

Choose one:

(1) BREAST

Choose one:

(2) PUBIC HAIR



Have you had your 1st period? Yes _____ No _____

If yes, do you remember when? Month _____ Year _____

THANK YOU.

Bounce at the Bell

Self Assessment of Maturity Status: Girls

As you keep growing over the next few years, you will see changes in your body. These changes happen at different ages for different children. You may already be seeing some changes, and some of your friends may have already gone through some changes. Sometimes it is important to know how a person is growing without having a doctor examine them. It can be hard for a person to describe themselves in words, so doctors have drawings of stages that all children go through. There are 5 drawings of breast growth, and 5 drawings of pubic hair growth on the next page. All you need to do is pick the drawings that look like you now. Put one check mark on the line at the drawing that is closest to your stage of development for breast growth, and one check mark at the drawing that is closest to your stage of pubic hair growth. Put the sheet in the envelope and seal it so that your answer will be kept private.

Appendix 3:

Tait

Jesse Wowk

Garden City

Brighouse

Diefenbaker

Kilgour

Mitchell

Ferris

Errington

Westwind

Thomas Kidd

Walter Lee

The Healthy Bones Study
2000-2001

"Bounce at the Bell"

"Bounce at the Bell"

The Healthy Bones Study began in the Richmond School District as a pilot project in 1997. In the early stages, 10 elementary schools were involved, with almost 200 Grade 3 and 4 students participating. In 1999, we began a larger study in Richmond, with nearly 400 Grade 4, 5, and 6 students involved from 14 elementary schools. During the 2000-2001 school year, we are attempting to follow a subset of these students for one more year. By doing so, we will be able to study the effects of a 2-year physical activity intervention on growing bone. After year two, this will be the longest study of this nature in the world. In conjunction with this study we are implementing an alternative intervention, the "Bounce at the Bell" program, in three schools (they are underlined on the cover page). The rationale for this intervention is that in laboratory studies a number of short bouts of jumping of modest impact throughout the day was as effective for stimulation bone formation as high impact loads three times per week. The contribution of teachers, students and principals at all participating elementary schools is critical and of tremendous importance to bone health research in Canada and worldwide. We consider you our partners in research, so thank you so very much for your participation.

Lifestyle habits such as physical activity and dietary calcium contribute significantly to the health of our bones throughout life. Although we cannot control the influence of genes on our bones, we can make well-informed decisions about physical activity and nutrition that may play an important role in preventing

bone loss and subsequent osteoporosis in later life. Our previous research and that of others suggests that the greatest effects of physical activity on the skeleton are observed when activities are undertaken during the active growing years. During the years from 10 through puberty our bones may be as responsive to loading through weight-bearing exercise as they will ever be. That's not to say that adults don't benefit from weight-bearing physical activity - they do. As we age the primary task of our skeleton becomes one of conserving, rather than increasing, bone mass.

Children often get a fair amount of exercise through running, but less frequently experience extra loads on their skeletons' through jumping. This is not true for those children involved in sports such as figure skating or gymnastics or dance who experience loads on their skeletons that approximate 10-15 times their body weight! Higher impacts from jumping result in positive adaptations in the growing skeleton and - not surprisingly - stronger bones. Our goal as individuals (and as researchers) is to design a program that is easy to do and that will reap the maximum rewards for the skeleton during the growing years and thus, reduce the risk for osteoporotic fractures in later life.

Initial results from our project in 1999-2000, as well as results from the 1997-1998 study in younger Richmond children (Appendix 1), have shown us that there is, indeed, a positive benefit from an 8-month, school based jumping program. The reason we are working with some of the same students in the 2000-2001 school year is to answer <u>three</u> as yet unanswered questions. (1) Do the positive benefits we observed in the jumping schools after one year persist over time? (2) Will there be further gains in bone strength from jumping after a second year in the

program? And finally, as there is still considerable discussion around the 'optimal' time and type (in relation to the onset of puberty) of mechanical load that bone responds optimally to. Therefore, our third question is; (3) What are the effects of different types of physical activity programs on bone in children?

Students who participate in the study will be measured at UBC twice during the 2000-2001 school year. At these times, we will assess bone status, growth and physical performance in jumping tasks by direct measurement. We will also assess physical development, calcium intake, and general levels of physical activity by questionnaire. We sincerely believe that the results of this unique study will provide important information regarding the roles of physical activity and calcium nutrition in the prevention of osteoporosis.

Again, thank you for your contribution to our research program. We look forward to working with you during this school year.

The 'Healthy Bones' Research Team

The "Bounce at the Bell" Study Intervention: 2000-2001

I. Format:

This straight-forward intervention involves five jumps, three times a day, every day for the entire school year. We suggest that you plan to do these jumps at morning bell, lunch bell and last recess bell. There is, however, no set formula so you can get your class jumping whenever it fits into your teaching schedule! You might choose to change the time of day as well as the year progresses so that it does not become too tedious.

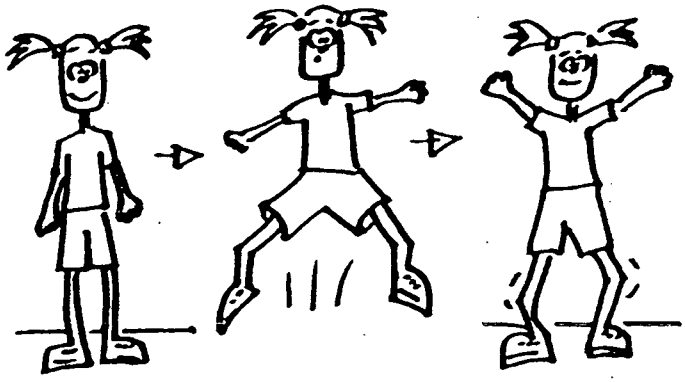
On the next page we have illustrated 4 jump alternatives that may be introduced throughout the year to mix things up a bit. Please remember that 1 jump refers to a takeoff and landing on both feet. If the children are doing single leg landings (such as for Disco Dancer or Terrific Triathlete) you must double the number of jumps so that five landings are experienced on each leg. Another idea to retain class interest and involvement is to chart the number of jumps that the class performs on a "Jumpometer" with a goal of reaching 100,000 jumps by the end of the year.

We have attached a calendar so that you can check off those days when you "Bounced at the Bell" with your class. We will also ask for the attendance records for the study participants on a regular basis so that we are aware of prolonged illness or absence that may have prevented a student's participation in the study.

Good luck!

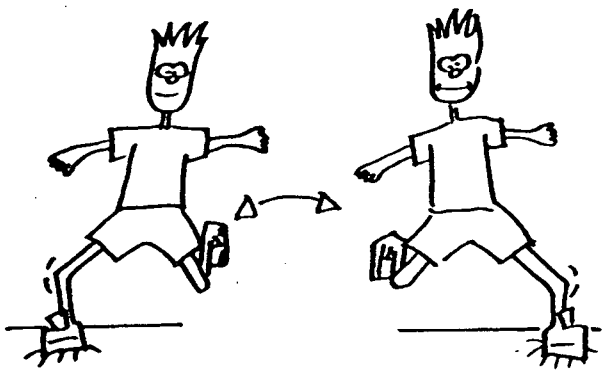
Bon Chance!

And Happy Hopping!

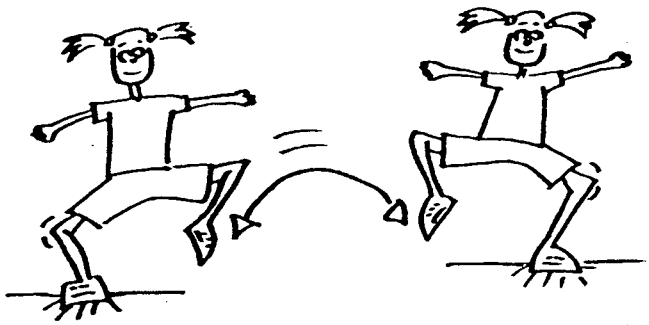


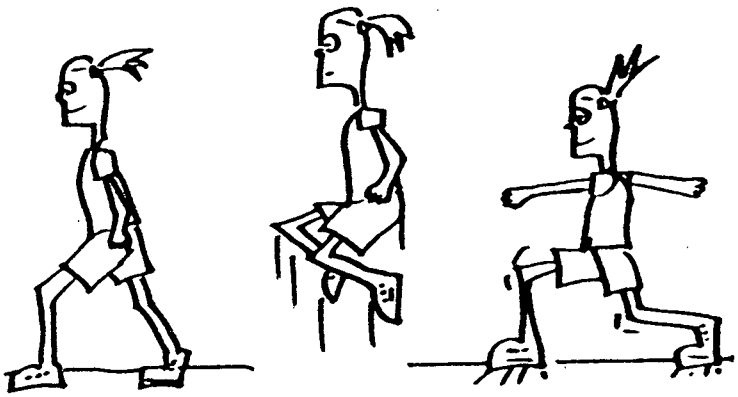
Jumping Jack Flash

Terrific Triathlete



Disco Dancer





Leapin' Lizards