EFFECTIVENESS OF A SCHOOL-BASED PHYSICAL ACTIVITY INTERVENTION FOR INCREASING BONE STRENGTH IN CHILDREN: ACTION SCHOOLS! BC

by

HEATHER McGILLVRAY MACDONALD

BSc., The University of British Columbia, 1999

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE STUDIES

(Human Kinetics)

THE UNIVERSITY OF BRITISH COLUMBIA

JULY 2006

ABSTRACT

Introduction: Osteoporosis and related fracture are significant societal health burdens. Physical activity during childhood can result in significant bone health benefits, which may reduce the risk for osteoporosis later in life.

Aim: The primary aim was to evaluate the effectiveness of a school-based physical activity model, Action Schools! BC (AS! BC), for enhancing bone mass and strength in boys and girls using novel bone imaging technologies.

Methods:

Design and Participants: This was a 16-month cluster randomized, controlled, school-based intervention. Ten schools were randomized to Intervention (INT, 7 schools) or Control (CON, 3 schools). The bone-loading component of AS! BC was a daily, high-impact jumping program (Bounce at the Bell) plus 15 minutes/day of classroom physical activity. Participants were 514 children aged 9-11 years at baseline.

Bone Measurements: Tibial bone strength was assessed with peripheral quantitative computed tomography. Dual energy x-ray absorptiometry and hip structure analysis were used to assess femoral neck bone mineral content (BMC) and bone strength, respectively.

Results

Part 1: Cross-sectional Comparisons

In pre- and early pubertal boys tibial bone strength was 5-15% greater than in pre- and early pubertal girls. After adjusting for tibial length, muscle cross-sectional area was the primary explanatory variable of bone strength in both sexes.

Part 2: 16-Month Change – Tibial Bone Strength

Intervention boys (n = 147) tended to have greater gains in tibial bone strength than CON boys (n = 64); however, the intervention effect was only significant for prepubertal boys at the distal tibia. Action Schools! BC was not effective for increasing tibial bone strength in girls (n = 137 INT, 65 CON).

Part 3: 16-Month Change – Femoral Neck Bone Mass and Strength

Intervention girls tended to have greater gains in femoral neck bone strength and BMC than CON girls; however, the difference in change between groups was not significant. Action Schools! BC was not effective for increasing femoral neck bone mass or strength in boys.

Summary: Skeletal adaptations to the AS! BC intervention were sex-, maturity- and site-specific. Action Schools! BC offers promise as a simple and inexpensive strategy for increasing bone mass and strength in boys and girls.

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GLOSSARY OF TERMS AND ABBREVIATIONS

Bone Definitions

ABBREVIATION	DEFINITION
pQCT	Peripheral quantitative computed tomography. The XCT-2000 model is used in this thesis.
ToA	Total bone cross-sectional area (mm^2) as measured with pQCT.
CoA	Cortical bone cross-sectional area (mm^2) as measured with pQCT.
CavA	Area of the marrow cavity (mm^2) as calculated with pQCT outcomes of ToA and CoA. (CavA = ToA – CoA)
TrbA	Trabecular cross-sectional area (mm^2) as measured with pQCT.
CTh	Cortical thickness (mm) as measured with pQCT.
ToD	Total bone mineral density (mg/cm^3) as measured with pQCT.
CoD	Cortical bone mineral density (mg/cm^3) as measured with pQCT.
TrbD	Trabecular bone mineral density (mg/cm^3) as measured with pQCT.
BSI	Bone strength index (mg^2/mm^4) as calculated with pQCT outcomes of ToA and ToD ($BSI = ToA * ToD^2$).
SSI_p	Polar strength-strain index (mm^3) as measured by pQCT. Also known as the density-weighted polar section modulus.
SSI_x	Strength-strain index (mm^3) with respect to the x-bending axis as measured by pQCT.
SSI_y	Strength-strain index (mm^3) with respect to the y-bending axis as measured by pQCT.
MCSA	Muscle cross-sectional area (mm^2) as measured by pQCT.
DXA	Dual energy x-ray absorptiometry. The Hologic QDR 4500W model is used in this thesis.
BA	Bone area (cm^2) as measured by DXA.
BMC	Bone mineral content (g) as measured by DXA.
aBMD	Areal bone mineral density (g/cm^2) as measured by DXA.
HSA	Hip structure analysis. Refers to the computer algorithm applied to proximal femur DXA images to estimate bone structural variables. Version 3.0 is used in this thesis.
NN	Narrow neck. Refers to the narrowest region of the femoral neck that is analyzed with HSA.
CSA	Cross-sectional area (cm^2) as estimated by HSA.
CSMI	Cross-sectional moment of inertia (cm^4) as measured by HSA
Z	Section modulus (cm^3) as measured by HSA and (mm^3) as measured by pQCT

TERM	DEFINTION
Areal bone mineral density	The ratio of bone mineral content to the projectional area of bone (g/cm^2) as measured by DXA.
Bone architecture	The size and shape of a whole bone. Can also refer to properties of cortical or trabecular bone (i.e., cortical thickness, trabecular number or thickness).

Glossary continued

TERM	DEFINTION
Bone (cross-sectional) geometry	The surface dimensions of bone that quantify the amount of bone surface and its distribution about torsion and bending axes (i.e., cross-sectional area, cross-sectional moment of inertia).
Bone mass	Amount of bone material within a cross-section or region of interest (e.g. BMC by DXA).
Bone strength	Ultimate failure load of bone. In this thesis bone strength is estimated with pQCT-derived BSI, SSI_p, SSI_x and SSI_y and HSA-derived Z.
Bone structure	Properties of bone such as size, shape and distribution of material that contribute to bone strength.
Volumetric bone density	The amount of bone mineral averaged over a certain volume as measured by pQCT. Can be cortical (CoD), trabecular (TrbD) or total bone mineral density (ToD).

Maturity Definitions

TERM	DEFINITION
Tanner Staging	A self-report method of assessing the stage of reproductive (or sexual) maturity in girls and boys. In this thesis Tanner stage for girls refers to breast stage and Tanner stage for boys refers to pubic hair.
Prepuberty (PRE)	Tanner stage 1.
Early puberty (EARLY)	Tanner stage 2 or 3.
Peri-puberty (PERI)	Refers to a broad category of Tanner stages 2-4 (after prepuberty but before post puberty).
Post puberty (POST)	Tanner stage 5
Premenarcheal	Refers to a girl who has not yet experienced her first menstrual period.
Postmenarcheal	Refers to a girl who has experienced her first menstrual period.
Age at peak height velocity (PHV)	An indicator of somatic maturity in longitudinal studies of child and adolescent growth.

PREFACE: PUBLICATIONS ARISING FROM THIS THESIS

Sections of this thesis have been published as multi-authored manuscripts in peer-reviewed journals and are indicated with a * beside the publication below. Details of the authors' contributions are provided, where relevant. I agree with the stated contributions of the thesis author, as indicated below.

_____ _____Dr. Heather McKay (Thesis supervisor)

Published Papers

***Macdonald HM,** Kontulainen SA, Petit MA, Janssen PA, McKay HA. 2006. Bone strength and its determinants in pre- and early pubertal boys and girls. Bone. In Press.
Authors' contributions: Heather Macdonald was responsible for the original ideas behind the paper, analysis and presentation of findings and writing and editing of the original paper. Saija Kontulainen and Moira Petit stimulated discussion of results and provided editorial assistance. Patti Janssen provided statistical consultation and editorial assistance. Heather McKay guided all aspects of the research and was the key editor of this manuscript.

Rhodes RE, **Macdonald HM**, McKay HA. 2006. Predicting physical activity motivation and behaviour among children in a longitudinal sample. Social Science and Medicine; 62:3146-56.

*Naylor PJ, **Macdonald HM**, Reed KE, McKay HA. 2006. Action Schools! BC: A socio-ecological approach to modifying chronic disease risk factors in elementary school children. Preventing Chronic Disease [serial online]. Available from: URL: http://www.cdc.gov/pcd/issues/2006/apr/05_0090.htm.

*Naylor PJ, **Macdonald HM,** Zebedee JA, Reed KE, McKay HA. 2006. Lessons learned from Action Schools! BC - An 'active school' model to promote physical activity in elementary schools. Journal of Science and Medicine in Sport. In Press.

McKay HA, Reed KE, **Macdonald H**, Khan KM. 2003. Exercise interventions for health: time to focus on dimensions, delivery and dollars. British Journal of Sports Medicine; 37:98-99.

Papers submitted

Macdonald HM, Kontulainen SA, Khan KM, McKay HA. Is a school-based physical activity intervention effective for increasing tibial bone strength in boys and girls? Submitted to the Journal of Bone and Mineral Research, June 2006.
Authors' contributions: Heather Macdonald was responsible for the original ideas behind the paper, analysis and presentation of findings and writing and editing of the original paper. Saija Kontulainen and Karim Khan stimulated discussion of results and provided editorial assistance. Heather McKay guided all aspects of the research and was the key editor on this paper.

Macdonald HM, Kontulainen SA, Beck TJ, McKay HA. Effectiveness of a school-based physical activity model for increasing femoral neck bone mass and strength in boys and girls: The Action Schools! BC model. Submitted to Bone, May 2006.
Authors' contributions: Heather Macdonald was responsible for the original ideas behind the paper, analysis and presentation of findings and writing and editing of the original paper. Saija Kontulainen stimulated discussion of results and provided editorial assistance. Tom Beck provided training and guidance with HSA analysis, stimulated discussion of results and provided editorial assistance. Heather McKay guided all aspects of the research and was the key editor on this paper.

Petit MA, **Macdonald HM,** McKay HA. Growing bones: How important is exercise? Submitted to Current Opinion in Orthopaedics, June 2006.

Ahamed YA, **Macdonald HM,** Reed KE, Naylor PJ, McKay HA. Physical activity does not compromise academic performance of school children. Submitted to Medicine and Science in Sports & Exercise, February 2006.

Abstracts

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Macdonald HM, Manske SA, Reed KE, Khan KM, McKay HA. 2005. Action Schools! BC: Daily physical activity increases bone strength in prepubertal boys. Journal of Science and Medicine in Sport 8;4(Suppl):153. Presented orally at the Australian Conference of Science and Medicine in Sport, Fifth National Physical Activity Conference. Recipient of Asics Medal for Best Paper Overall.

Macdonald HM, Kontulainen SA, Petit MA, McKay HA. 2005. Determinants of bone geometry, density and strength in girls and boys. Journal of Bone and Mineral Research; 20 (S1): S33. Presented orally at the American Society for Bone and Mineral Research Annual Meeting, September 2006, Nashville TN. Young Investigator Award recipient.

Kontulainen S, Liu D, Jamieson M, **Macdonald H**, Manske S, Oxland T, McKay H. 2005. Defining cortical bone by pQCT: *In vitro* and *in vivo* accuracy of bone geometry. Journal of Bone and Mineral Research; 20 (S1): S338.

Macdonald HM, Kontulainen SA, Petit MA, McKay HA. 2005. Action Schools! BC: Effects of a 16-month school-based physical activity intervention on bone geometry, strength and the muscle-bone unit in pre- and early pubertal girls. Bone; 36:S56. Presented in poster format at the 3rd International Conference on Children's Bone Health, Sorrento, Italy, May 2005. Recognized as Selected Poster.

ACKNOWLEDGEMENTS

This thesis would not have been possible without the generous support of many people. First, I would like to gratefully acknowledge my supervisor, Dr. Heather McKay. Thank you Heather, for your expert guidance and continual encouragement and for always challenging me to reach outside my comfort zone. Your dedication to research has inspired me and your contribution to my growth both as a researcher and as an individual are immeasurable. Thank you to my other committee members, Dr. Karim Khan and Dr. Patti Janssen, for sharing your insight and knowledge and for helping me to see the big picture. Dr. Penny Brasher, thank you for your statistical help and for introducing me to the wonderful world of STATA. Thank you to Dr. Tom Beck and Lisa Semanick for your excellent tutelage and hospitality during my time in Baltimore.

I could not have asked for a better project to work on for the past 4 years. Action Schools! BC represents the efforts of an incredible group of people and I feel privileged to have had the chance to work closely with them. Kate Reed, thanks for coming to Vancouver when you did! You were a great companion on the many school visits and it was a pleasure to discuss stats with you over many tall Americanos. Bryna Kopelow, Jennifer Fenton and Sydney Millar at JW Sporta, the passion and enthusiasm you bring to your work are inspiring. Thank you for welcoming me into the mix and for developing such an amazing program. Debbie Keel and Judy Howard, thanks for making sure the classes did their jumps properly! PJ Naylor, thank you for the great data discussions. Josie McKay and Connie Waterman, without you this study could not have run so smoothly. Thank you for your time and efforts and your superb scheduling abilities! Thank you to the UBC Graduate Fellowship for supporting me throughout my studies. And of course, a huge thanks to the 514 children and their parents as well as the teachers and administrators who participated in Action Schools! BC.

I was fortunate to have three amazing women as mentors and friends throughout this journey. Dr. Kerry MacKelvie O'Brien, thank you for providing great footsteps for me to follow in and for being a trusted friend in and out of the lab. Dr. Moira Petit, thank you for helping me to keep everything in perspective, for being an excellent reviewer and a wonderful traveling companion. And Dr. Saija Kontulainen, I cannot imagine what these last few years would have been like without you! Your enthusiasm for research is incredible and I thank you for sharing it with me. Thank you for all that you have contributed to this thesis – from the many discussions of pQCT analysis to your careful review of the manuscripts. Kiitos!

To all of my amazing friends and colleagues in the Bone Health Research Group and the Division of Orthopaedic Engineering Research – to name you all would be a thesis in itself, but thanks to everyone for the great discussions, many laughs and of course, the coffee breaks! Special thanks to my officemates in Room 590 for always providing a listening ear and for sharing my sweet tooth.

Thank you to my family – Mom, Dad, Roy, Jayne and Polly Ann – for your unconditional love and support and most of all, your patience. Thank you to the girls – Emily, Hayley and Nicole for always being just a phone call away. I treasure our friendship and hope that one day the calls won't be long distance!

And last, but certainly not least, Jamie. Thank you for your unwavering support and endless encouragement and for making me laugh every day. I look forward to starting our post-grad school life together.

1 Introduction, Literature Review, Rationale, Objectives & Hypotheses

1.1 Introduction

Osteoporosis and related fractures are serious societal health burdens. In particular, hip fracture is a significant cause of morbidity and mortality worldwide (1). Annual direct health care costs of hip fracture in Canada are approximately 650 million dollars and in the absence of effective preventive strategies, this number is expected to rise to 2.4 billion dollars by 2041 (2). Based on the current level of evidence, regular physical activity may be the most cost-effective, safe and readily available method to prevent both osteoporosis and low-trauma falls that lead to osteoporotic fracture (3). More specifically, physical activity during childhood can result in substantial bone health benefits, which in turn may reduce the risk of osteoporosis later in life (3-6). Unfortunately, recent trends suggest that more than 50% of Canadian children are not active enough for optimal growth and development (7). Thus, there is an immediate need for effective interventions to promote physical activity and bone health among youth.

Schools, by nature, have a captive audience and are therefore an excellent arena in which to encourage positive physical activity behaviours. To date, the longest school-based exercise intervention (20 months) resulted in significant gains (+4.3-4.6%) in bone mineral content (BMC) as measured by dual energy x-ray absorptiometry (DXA) at the clinically significant femoral neck in boys (8) and girls (9). Despite the effectiveness of this program, and others like it (10-12), it is not likely to be sustainable in the elementary school setting due to the time required (10-20 minutes, 3 times per week) and the need for equipment and specially trained teachers. For a school program to gain acceptance on a population-wide basis, it must be effective, simple to administer, short in duration and possible to perform in the classroom (13). Recently, a school-based bone-loading program, Bounce at the Bell, was developed to meet these criteria (13). Bounce at the Bell was designed based on promising results from animal studies that have demonstrated significant gains in bone strength with short bouts of loading (14) and an improved osteogenic response to exercise sessions separated by rest periods (15). This program was effective for increasing proximal femur bone mass in boys and girls; however, its effects on bone structure and strength are not known.

In addition to changes in bone mass that occur in response to exercise, it is equally important to characterize bone structural changes as both properties contribute to ultimate bone strength (16). Currently, DXA is the most widely used method to evaluate bone mass in clinical and research settings (17). However, due to its planar technology, DXA is unable to assess bone structure or separate cortical and trabecular bone compartments which may respond differently to loading. A computer software algorithm, hip structure analysis (HSA), can be used to supplement conventional DXA measures of BMC with estimates of proximal femur bone geometry and strength (18), but it to is limited by DXA's planar technology. Peripheral quantitative computed tomography (pQCT) provides a means with which to directly evaluate cross-sectional geometry and (volumetric) bone mineral density of the appendicular skeleton, which together can be used to estimate bone strength (17,19). A number of cross-sectional (20-23) and longitudinal (24-26) studies have used pQCT to describe sex- and maturity-related differences in long bone development in the upper and lower extremities, but few pediatric intervention studies have used pQCT to determine the effect of high-impact physical activity on bone strength (11,27).

An additional advantage of pQCT is its ability to assess the muscle-bone relationship. Muscle contraction incurs the largest physiological load on the skeleton (28,29) and during growth, bones must continually adapt their geometry and mass to withstand loads from increases in both stature and muscle forces (30,31). Thus, there is a need for pediatric bone densitometric data to be interpreted in the context of these mechanical challenges (31). Muscle cross-sectional area as measured with pQCT provides a surrogate for muscle force (32) and together with pQCT-derived bone geometry and strength can be used to gain further insight into the functional muscle-bone unit.

Thus, the primary purpose of my thesis is to determine the effectiveness of a school-based physical activity intervention, which includes a high-impact jumping program, for increasing bone strength in boys and girls. The secondary focus is to define the muscle-bone relationship in the weight-bearing tibia in boys and girls. To provide a comprehensive evaluation of the growing skeleton I employ two novel bone imaging techniques, pQCT and HSA, in addition to DXA. My thesis is outlined in three parts. Part I describes sex differences in pQCT-derived tibial bone strength in pre- and early pubertal children and identifies determinants of bone strength in both boys and girls. Part II defines the site- and sex-specific bone structural response to a 16-month, school-based physical activity intervention using pQCT. Part III investigated the sex-specific effect of the 16-month physical activity intervention on bone structural adaptations and bone mineral accrual at the clinically relevant proximal femur using both HSA and DXA.

I provide relevant background literature in Chapter 1 including bone biology and biomechanics, measurement of bone mass and strength in children, sex- and maturity-related differences in skeletal development, determinants of bone strength in children with a focus on the role of muscle and the influence of physical activity on bone health in children. I conclude Chapter 1 with the rationale, specific objectives and hypotheses for the three studies that comprise this thesis and in Chapter 2 I provide a detailed description of the physical activity model and the methods employed. Chapter 3 describes the cohort of children who participated in the study. Chapters 4-6 provide the results of the three studies that are In Press (Part I) or have been submitted for publication (Parts II and III). Finally, in Chapter 7 I discuss the three studies as an integrated whole and propose future directions for pediatric bone research. In addition, I summarize the results of this thesis and present conclusions.

1.2 Literature Review

In this chapter I discuss relevant background information in 6 key areas: bone biology, bone biomechanics, measurement of bone health in children, maturity- and sex-related differences in skeletal development, determinants of bone strength in children and finally, the influence of physical activity on pediatric bone health.

1.2.1 Bone Biology and Bone Growth

Bone is a dynamic tissue with multiple functions. The primary function of bone is to be stiff and strong in order to resist deformation resulting from internal (mainly muscular) and external loads (33). In addition, bones serve as levers for locomotion, attachment sites for muscles, ligaments and tendons and as a central reservoir for calcium while also providing a site for haematopoiesis (formation of blood cells) and protecting organs (34,35). During growth, the skeleton must maintain these functions while dramatic changes in size and shape occur. Within the skeleton, the structure of bone tissue, and of whole bones, is complex and ultimately influences bone's mechanical properties.

1.2.1.1 Bone Tissue: Composition and Organization

Bone is a composite material comprised of an organic and inorganic form (36). The inorganic, or mineral, phase is composed mainly of a specific crystalline hydroxyapatite (calcium and phosphorus) while the organic phase is composed mainly of type I collagen. Collagen is organized into fibres, which are the major structural component of the bone matrix and give bone its flexibility and tensile strength. Collagen also provides a location for the deposition of the inorganic mineral crystals, which give bone rigidity and compressive strength (36).

Two types of bone tissue exist: woven and lamellar bone (36). Woven bone is a quickly formed, poorly organized tissue in which collagen fibres and mineral content demonstrate a random distribution. Woven bone is considered immature and is the only form of bone present in the embryonic and newborn skeleton. It can also be found in fracture callus, certain metaphyseal regions of the growing skeleton, certain bone tumours and patients with osteogenesis imperfecta (36). In contrast, lamellar bone is a slowly formed, highly organized material that results from remodeling of woven or pre-existing bone. The collagen and associated mineral are arranged in sheets (lamellae) which are organized according to the stress orientation of the collagen fibres (36,37). Differences in the structural properties of woven and lamellar bone are reflected in their mechanical characteristics. Woven bone is *isotropic*, which means the mechanical behaviour is similar regardless of the orientation of the force. Lamellar bone is *anisotropic*, which means the mechanical behaviour differs according to the orientation of the force (36).

Within the appendicular and axial skeleton, woven and lamellar bone are organized into cortical (or compact) and trabecular (spongy or cancellous) compartments (36). Although cortical and trabecular bone are made of the same material, there are structural and functional differences between them (38). Trabecular bone exists as a three-dimensional lattice structure composed of individual trabeculae and is found at the ends of long bones and in the vertebral bodies. The lattice organization determines the porosity of trabecular bone (75-95%), provides a vast surface area where metabolic activities such as bone turnover occur and houses bone marrow which functions in haematopoiesis.

Conversely, cortical bone is arranged in cylinders, is much less porous (5-10%) than trabecular bone and forms the diaphysis of long bones (39). Haversian bone is the most complex form of cortical bone, and is arranged in osteons, which consist of vascular channels circumferentially surrounded by lamellae of bone. The dense arrangement of osteons within cortical bone confers a higher degree of calcification when compared to trabecular bone (80-90% for cortical bone vs. 15-25% for trabecular bone). As a result cortical bone fulfills mainly, but not only, mechanical and protective functions (38). I discuss the structural and mechanical properties of trabecular and cortical bone in more detail in Section 1.2.2.

1.2.1.2 Whole Bone Structure

Within the human skeleton, bones can be roughly grouped as either long (e.g. tibia), short (e.g. metacarpal), flat (e.g. skull or scapula), irregular (e.g. vertebrae) or sesamoid (e.g. patella) (29). In this thesis, I focus on long bones.

As illustrated in Figure 1-1 a growing long bone consists of a tubular diaphysis that flares into two wide ends (the epiphyses). The epiphyses are separated from the funnel-shaped metaphyses by a layer of cartilage known as the growth plate which is the site of endochondral ossification (Section 1.2.1.3.1). The outer portion of the diaphysis contains cortical bone, whereas the inside contains bone marrow and is known as the medullary or marrow cavity. In contrast, the epiphyses are filled with moderately thick low-turnover trabeculae and the metaphysis is a transitional region of trabecular and cortical bone (40). The broad shape of bone ends serves to better distribute joint forces and reduce stress (force per unit area) that is transmitted by trabecular bone in the metaphysis to cortical bone in the diaphysis (41).

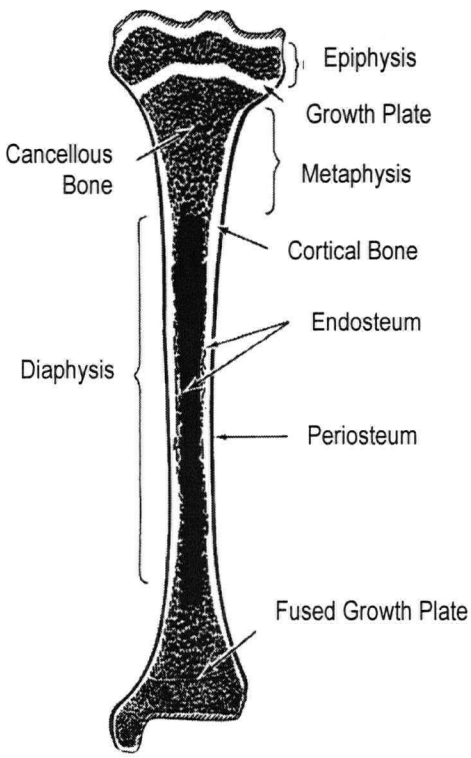


Figure 1-1. Illustration of a growing long bone. Adapted from Jee et al. (42).

The organization of the cortical and trabecular components within a long bone results in two bone surfaces that are in contact with soft tissue (Figure 1-1) (38). The external (periosteal surface or periosteum) and internal (endosteal surface or endosteum) surfaces of cortical bone are lined with osteogenic cells, and are therefore sites of bone tissue turnover. There are three cell types found in bone; *osteoblasts*, *osteoclasts* and *osteocytes*, each with specific roles in regulating bone turnover (36). Osteoblasts, or bone-forming cells, secrete osteoid, the unmineralized protein component of the bone matrix that forms the basic framework of bone tissue. Once an osteoblast has secreted and mineralized the osteoid, it becomes an osteocyte, the most abundant cell in fully formed bone (42). The osteocytes remain in contact with osteoblasts through gap junctions, and this linkage is thought to be important in transducing mechanical signals into biological activity (36). Osteoclasts, or bone resorbing cells, are usually found in cavities on bone surfaces called resorption pits. Osteoclasts secrete lysosomal enzymes and hydrogen ions that together, work to dissolve the bone matrix. During growth, osteoblasts and osteoclasts may function independently to modify the size and shape of bones during bone *modeling* or their cellular activities may be combined in the basic multicellular unit (BMU) which is responsible for bone *remodeling* (43). I discuss bone modeling and remodeling in further detail in Sections 1.2.1.3.2 and 1.2.1.3.3.

1.2.1.3 Physiology of Bone Growth and Bone Turnover

In this section I discuss the three processes that determine and maintain the architectural structure of bone: *growth*, *modeling* and *remodeling*.

1.2.1.3.1 Longitudinal Bone Growth

Growth refers to the enlargement of bones in width and length due to an increase in cell number, and occurs from birth through maturity (42). Longitudinal bone growth in the appendicular skeleton occurs via endochondral ossification, which is defined as the process of bone formation from pre-existing calcified cartilage (42). During bone development, endochondral ossification occurs in the epiphyseal growth plate (Figure 1-1) (44). Initially, the cartilage is calcified (primary spongiosum or primary trabeculae) and this allows for the deposition of more calcified material in the form of woven bone (secondary spongiosum or secondary trabeculae). Chondrocytes (cartilage producing cells) within the growth plate are organized according to their stage of maturation, with the most mature cells in the calcifying zone being incorporated into metaphyseal bone (44). With increasing distance to the growth plate, metaphyseal trabeculae located in the centre of the bone are thinned out and eventually resorbed leaving the diaphysis devoid of trabeculae (45). In contrast, metaphyseal trabeculae on the periphery serve to transfer loads from the growth plate to the metaphyseal cortex. Eventually the peripheral trabeculae coalesce and become part of the metaphyseal cortex (46).

Growth plate activity varies with age and the contribution of the distal and proximal growth plate to overall longitudinal growth varies between bones (47,48). For example, for the tibia, the proportion of growth at the *proximal* growth plate in girls varies from 50% at age 7 to 80% at age 14 (48). For boys, the proportion of growth at the proximal growth plate varies from 50% at age 7 to 80% at age 16. Similar variation with age occurs in the femur;

however, approximately 70% of femoral growth occurs at the *distal* growth plate (48). In the upper extremities, the proximal growth plate accounts for approximately 80% of growth in the humerus, whereas the distal growth plate accounts for 80% and 85% of growth in the radius and ulna, respectively (47).

Regulation of longitudinal growth is thought to occur on three levels: systemic, local and mechanical (45). At the systemic level growth hormone (GH), insulin-like growth factor-I (IGF-1), thyroid hormones and glucocorticoids regulate longitudinal growth during childhood, whereas sex hormones (estrogen and testosterone) are more influential during puberty (49). In boys and girls, estrogen is pivotal for epiphyseal fusion which, until recently, was commonly believed to be the central determinant of cessation of linear growth (50). More recent evidence suggests that epiphyseal fusion is only a marker of growth cessation that occurs after a decline in chondrocyte proliferation and subsequent 'growth-plate senescence' (51). Regulation of chondrocyte proliferation also occurs at the local level (within the growth plate) and involves a number of different growth factors (e.g., fibroblast growth factors, Indian hedgehog) (49). Little is known about mechanical regulation of longitudinal growth; however, according to Harold Frost's chondral growth response curve (45,52), mild tension and compression are thought to increase longitudinal growth while severe compression is thought to inhibit growth.

1.2.1.3.2 Bone Modeling

During growth, the size and shape of bones is modified through *modeling*, which involves the independent actions of osteoblasts and osteoclasts on bone surfaces (29). Continuous addition of bone to the periosteal surface by osteoblasts and simultaneous endosteal resorption by osteoclasts contributes to diaphyseal enlargement. This motion of surfaces in tissue space is known as *drift*, and may increase or decrease bone curvature according to the specific mechanical needs of the bone (29,53). Bone modeling during growth is thought to be regulated by mechanical strain (54). I discuss this in more detail in Section 1.2.2.2.

At metaphyseal sites, modeling also serves to decrease the diameter of newly formed metaphyseal bone (metaphyseal inwaisting) to match the cross-sectional size of the diaphysis (Figure 1-2) (53,55). At the distal radius (4% site), the rate of periosteal resorption is estimated to be 8 μm/day, while the rate of endocortical apposition is about 9.5-10 μm/day. The high rate of endosteal apposition is necessary to maintain the cortical thickness at this site (55). Once skeletal maturity is reached, the modeling rate is greatly reduced.

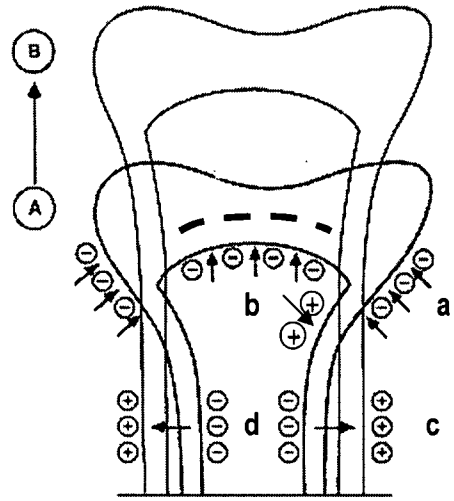


Figure 1-2. Formation (+) and resorption (-) during longitudinal bone growth. During growth from A to B, the funnel-like metaphysis is reduced to match the shape of the narrower diaphysis through osteoclastic resorption on the periosteal surface of the metaphysis (a). Thickening of the cortex occurs along the cortical endosteal surface of the metaphysis and enlargement of the marrow cavity occurs by resorption of metaphyseal trabecular bone (b). The diameter of the diaphysis increases by periosteal bone formation (c) and the marrow cavity of the diaphysis expands by bone resorption on the endosteal surface (d). Adapted from Jee (42) and Baron (38).

1.2.1.3.3 Bone Remodeling

Unlike modeling, bone *remodeling* continues throughout life. The primary function of remodeling is to maintain load bearing capacity, and this is accomplished by preventing and/or repairing fatigue damage through the replacement of old bone with newly formed bone (34). Remodeling occurs on bone surfaces (periosteal, endosteal, trabecular) and within cortical bone, and involves the tightly coupled activity of osteoblasts and osteoclasts in one unit, the basic multicellular unit (BMU). The BMU follows a regulated sequence of activation, resorption and formation during which time (~4 months: 3 weeks for resorption, 3 months for formation) a volume of damaged bone is removed by osteoclasts and replaced by osteoblasts (34). Activation occurs in the presence of chemical (hormones) or mechanical signals. In cortical bone, initiation of remodeling may also be related to the emergence of microcracks under conditions of fatigue loading. Specifically, osteocyte-mediated signalling pathways (56) and interstitial fluid flow (57) are thought to be two mechanisms associated with the activation of repair-damage remodeling. During growth there is a positive balance between bone formation and resorption due to high activation frequency (58). In contrast, during ageing there is a negative imbalance between osteoclast and osteoblast activity arises such that with each progressive remodeling cycle bone resorption exceeds formation. This uncoupling of bone formation and resorption may result from the absence of estrogen at menopause (29) or immobilization/disuse (59).

Within cortical bone, the BMU proceeds in the form of a tunnel at a rate of approximately 40 um/day and in adults is responsible for replacing about 5% of cortical bone each year (29). Cortical bone remodeling (intracortical or osteonal remodeling) results in the formation of secondary osteons with new Haversian canals that are bounded by cement lines. The activation frequency of cortical bone formation is highest during childhood as the primary osteons produced during modeling processes are quickly converted to secondary osteons (29). The greater activation

frequency during growth may be associated with increased levels of growth hormone, or age-related variations in the material properties of the bone matrix. Trabecular remodeling occurs in a similar fashion; however, BMUs work on the surface of trabeculae by digging and refilling trenches known as Howship lacunae (29). The rate of trabecular bone turnover (~25% per year in adults) is considerably higher than that of cortical bone; however, the rate is known to vary throughout the skeleton (29). In the growing skeleton a given location of trabecular bone surface undergoes approximately 1.04 remodeling cycles per year (60).

During remodeling, a number of BMUs are in the resorption phase, while others are in the formation phase. Therefore, at sites where remodeling is occurring there is a temporary loss of bone, or undermineralization (61). The immature skeleton tends to be more undermineralized than the mature skeleton due to the high rate of BMU activation associated with rapid longitudinal growth. This temporary deficit results in a low elastic modulus (stiffness) and higher strains for a given load (29). The increased strains may in turn increase fatigue damage and lead to increased activation frequency.

1.2.2 Bone Biomechanics

In this section I discuss whole bone mechanical properties as well as mechanical properties of cortical and trabecular bone. I then discuss theories of bone adaptation to mechanical stimuli and evidence from animal research that has furthered our understanding of the skeletal response to weight-bearing activity.

1.2.2.1 Mechanical Properties of Bone

Functionally, the most relevant property of bone is its strength. From an evolutionary standpoint, selection favours mechanisms that maintain bone's mechanical integrity by whatever means possible (31). Therefore, the goal during development is to create a strong skeleton that will withstand functional mechanical loads and prevent fracture later in life. In fashioning a stronger skeleton, bone development is controlled by the functional requirements of bone as an organ (31). The *mechanical properties* of long bones (stiffness, flexibility, strength and lightness) balance conflicting demands on the skeleton. For example, bone must be stiff to ensure efficient muscle action and yet compliant (less stiff) to absorb energy and avoid fracture (29).

The mechanical behaviour of whole bones under conditions of experimental or physiological loads is dependent not only on the mass and material properties, but also on bone geometry and architecture (16). Whereas the *material properties* of bone are classically defined by performing standardized mechanical tests on uniform specimens of bone, *structural properties* of bone are determined by whole bone structural tests (16,62). Such mechanical tests involve applying different types of loads, such as compression, bending and/or torsion, to whole bones from different skeletal regions including the lumbar vertebrae and long bones (62). Data generated from a mechanical test is used to generate a load-deformation curve, which defines the *extrinsic* (structural) properties of the bone including whole bone strength, stiffness and work (or energy) to failure. When the extrinsic properties are normalized for bone size (cross-sectional area, CSA), the load-deformation curve is converted to a stress-strain

curve, which defines the *intrinsic* (or material) properties of bone (63). The intrinsic properties include the ultimate stress (strength), elastic modulus and toughness.

1.2.2.1.1 Material Properties

The *material properties* of bone are the characteristics at the tissue level that contribute to overall bone strength. To better understand these properties it is important to discuss the underlying fundamental biomechanics. Under conditions of loading, bone will experience deformation from its original dimensions. This phenomenon is known as **strain**, and is equivalent to the change in length of the bone divided by the original length (16). The intensity of the load applied is referred to as **stress**, and is measured by force divided by the area of bone over which it acts (64). Bone can experience three types of stress: tension, compression and shear, which may occur independently or in combination according to specific loading configurations (65).

The *material properties* of stiffness, strength and toughness can be derived from the stress-strain curve (Figure 1-3). The slope of the linear portion of the curve represents the material stiffness, or the modulus of elasticity (**elastic region**). Before the **yield point**, any deformation experienced by the bone will be temporary meaning it will return to its original shape once the load is removed. After the **yield point**, the load will cause permanent deformation (**plastic region**) up to the point of maximum stress which ultimately results in bone **failure**. The area under the curve represents the material **toughness**; a tougher bone will be more resistant to fracture (62). The design of long bones is an appropriate combination of stiffness and toughness which, in the healthy skeleton, allows bones to bear the loads imposed upon them (41).

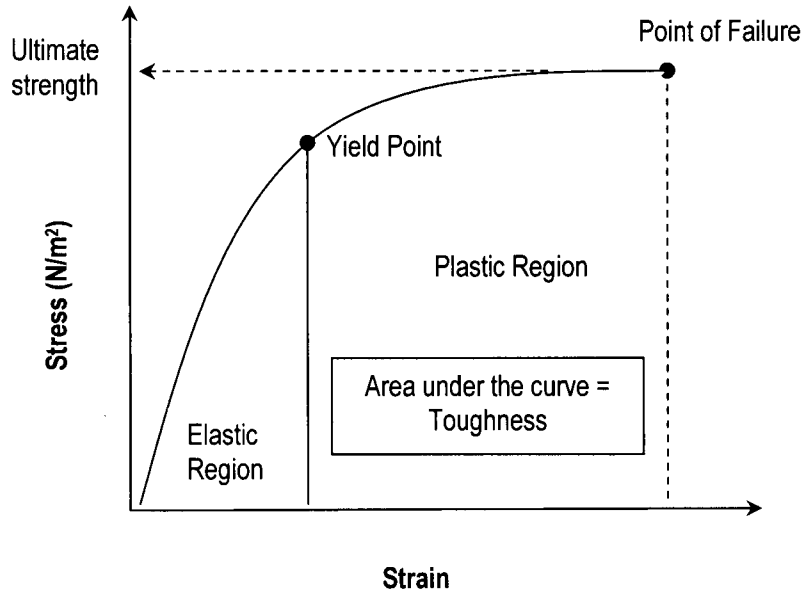


Figure 1-3. A standard stress/strain curve of a bone specimen produced during mechanical testing. This curve can also be used to represent whole bone properties (load/deformation curve). Adapted from Einhorn (16).

The mechanical properties of cortical and trabecular bone are influenced by the material properties of each bone compartment. Within cortical bone, characteristics of individual secondary osteons including the collagen fibre orientation as well as the overall cortical porosity and mineralization are known to be key determinants of mechanical integrity (29). In addition, microdamage due to fatigue may also alter cortical bone material properties. As cortical bone is a viscoelastic, or time-dependent, material its mechanical properties are highly dependent on strain rate (29).

The early cadaveric work of Currey and Butler (66) demonstrated age-related changes in the mechanical properties of bone tissue. The femoral midshaft of 18 cadavers aged 2 to 48 years was assessed under static loading conditions. Bending strength and modulus of elasticity increased with age, whereas the material toughness decreased. Further, significant correlations were found between ash content and bending strength, elastic modulus and material toughness. These results highlight the important relationship between the degree of mineralization and the mechanical properties of bone. In general, the elastic properties of bone are influenced solely by bone's mineral phase. However, the ultimate strength of bone is related to *both* the content and distribution of bone mineral within the matrix (16,33).

Trabecular bone is unique from other biological tissues due to its substantial heterogeneity across sites, ages and species (67). This heterogeneity contributes to differences in mechanical properties, and is a function of underlying variations in porosity (or apparent density), material properties of individual trabeculae (thickness) and orientation (anisotropy) of trabecular architecture (67,68). In the spine and at articulating joints, trabecular bone experiences mainly axial compression; however, axial torsion and horizontal shear stress also contribute to forces incurred on the surface of trabeculae in the axial skeleton (69). The compressive strength of trabecular bone is related to the square of apparent density, whereas elastic modulus demonstrates between a squared and cubic relationship with apparent density (70,71). The architecture of trabecular bone provides the requirements for optimal load transfer by combining appropriate strength and stiffness with minimal weight according to rules of mathematical design proposed by Wolff (72,73).

1.2.2.1.2 Bone Cross-sectional Geometry

Within the appendicular skeleton, long bone cross-sectional geometry is complex and varies along the length of the bone. The principle forces experienced at the *diaphysis* of long bones include axial compression, bending, shear and torsion or twisting (Figure 1-4) (16). Often these loads occur in combination, for example most long bone shafts experience mainly bending, but are also compressed and twisted to varying extents. Resistance to such forces is more a product of the distribution of cortical bone (cross-sectional properties) than the mass or density of the mineralized tissue (16,71). For a long bone such as the tibia, the most efficient cross-sectional shape is one in which the mineralized tissue is placed as far from the neutral axis of the load as possible. This geometric arrangement maximizes the greatest strength/lightness ratio, and is best described by the cross-sectional moment of inertia (*I* or CSMI) (Figure 1-5). The polar moment of inertia (*J*) is calculated as the sum of any two perpendicular measures of I (e.g., $I_x + I_y$) (74). The cross-sectional moment of inertia can also be used to calculate the section modulus (Z) as I / (D/2) where D is the cross-section's diameter in the bending plane (74,75). Age-related changes in

bone formation/resorption on the periosteal and endosteal surfaces contribute to the gain in bone strength during growth and strength maintenance during aging (76).

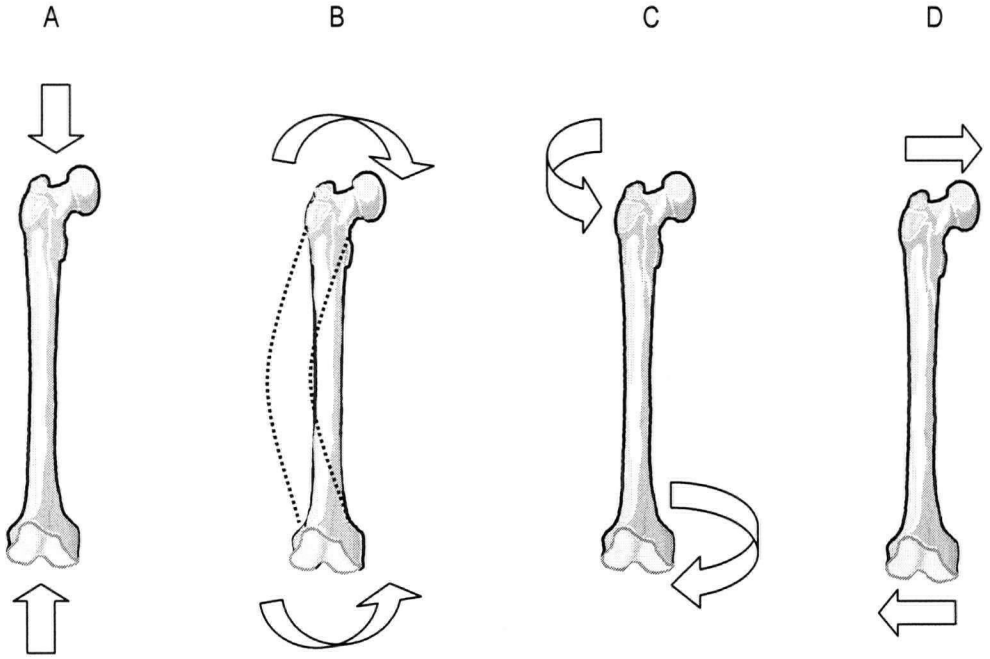


Figure 1-4. The principle loads experienced by bone in nature. Arrows indicate applied forces in (A) compression, (B) bending (tension on the convex side and compression on the concave side), (C) twisting (or torsion) and (D) shear. Adapted from Kontulainen (77) and Pearson and Lieberman (35).

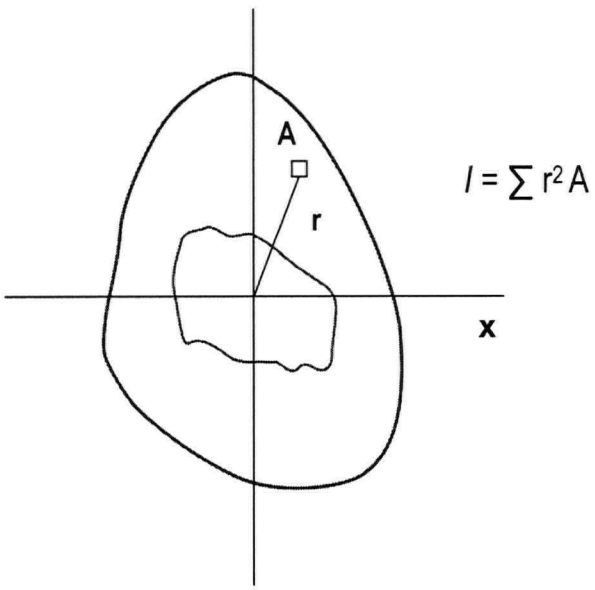


Figure 1-5. The cross-sectional moment of inertia (I, mm^4) for a bone cross-section describes the distribution of bone material about a defined axis. The cross-section is divided into many square regions of area *A* that are located at a distance (r) from the neutral axis for bending (x-axis). Adapted from Martin et al. (29).

1.2.2.2 Bone Adaptation to Mechanical Stimuli

The primary mechanical function of the skeleton is to provide rigid levers for muscles to act against as they work to hold the body upright in the presence of gravitational forces (78). Consequently, the skeleton is continually exposed to a loading environment. The mechanical stimuli encountered throughout life serve to sculpt the skeleton's genetic blueprint to match the loading requirements. This relationship between physical loads and bone structure was theorized over a century ago by Roux (79) (summarized by Roesler (80)) and is commonly referred to as *bone functional adaptation* (81-84). In a general sense, bone functional adaptation involves feedback loops that serve to maintain an "equilibrium" or "customary" strain level in the presence of bone strain (84). An increase in bone strain (e.g., through an increase in physical activity) results in bone formation, which in turn reduces bone strain to its original customary level. In contrast, a decrease in bone strain (e.g., through physical inactivity) results in bone resorption which again restores strain to the customary level. The customary strain level likely varies by skeletal location (33,82) and as proposed by Frost (30) may be altered by both mechanical and nonmechanical factors. In addition, characteristics of bone strain such as frequency and distribution, as well as the loading history of bone cells also influence the magnitude of the bone response (85,86).

1.2.2.2.1 Mechanotransduction

Although the specific cellular mechanisms underpinning bone adaptation are poorly understood, it is known that some form of mechanotransduction is required (78). Mechanotransduction is the conversion of a biophysical force into a cellular response. In bone it is proposed that four phases are involved: mechanocoupling, biochemical coupling, transmission of signal and the effector cell response. Mechanical loads induce strains in bone tissue that are detected by osteocytes, a process that is thought to be mediated by strain-induced interstitial fluid flow (87). Signals are then transmitted from the osteocytes to mechanoreceptors within the cell membrane and cytoskeleton where a signalling cascade is initiated. Once the signal reaches the effector cells (osteoblasts and osteoclasts), bone remodeling begins and ultimately results in architectural changes that adjust bone structure to match the requirements of the mechanical environment (78).

1.2.2.3 Mechanostat Theory

As discussed, it is now recognized that the customary strain level and regulation of bone adaptation involves more than simply mechanical strain. The mechanostat theory, proposed by Frost, suggests that the control of skeletal physiology involves the actions of many interlocking, and usually negative feedback loops that are influenced by both mechanical and nonmechanical factors (30,54). Rather than one customary strain level, Frost describes a threshold range that includes a minimum effective strain (MES) for both remodeling (MESr) and modeling (MESm) (Figure 1-6). During growth, the main mechanical challenges of increasing body weight and muscle loads function to increase bone strains towards the MESm and turn modeling on. Once skeletal maturity is reached, peak bone strains are reduced to the level needed to initiate "conservation-mode" remodeling. With decreased activity and with aging, decreasing muscle strength reduces the loads on bone and shifts strains below the MESr. This results in disuse-

mode remodeling, which causes a slow loss of bone next to marrow (88). The setpoints of the mechanostat may be altered by nonmechanical agents such as hormones and nutrition (31). It is suggested that estrogen may lower the MESm and MESr (on the endosteal surface, next to bone marrow) so that smaller strains are required to turn modeling and remodeling on (89).

Mechanostat theory has been verified in several animal experiments (90-93). For example, in growing dogs, disuse osteopenia in the casted forelimb was the result of both reduced modeling on the periosteal surface (decrease in periosteal expansion) and increased remodeling on the endosteal surface (increased endosteal expansion) (92). Remobilization of the dogs reversed both of these trends such that periosteal apposition increased and endosteal apposition was also restored.

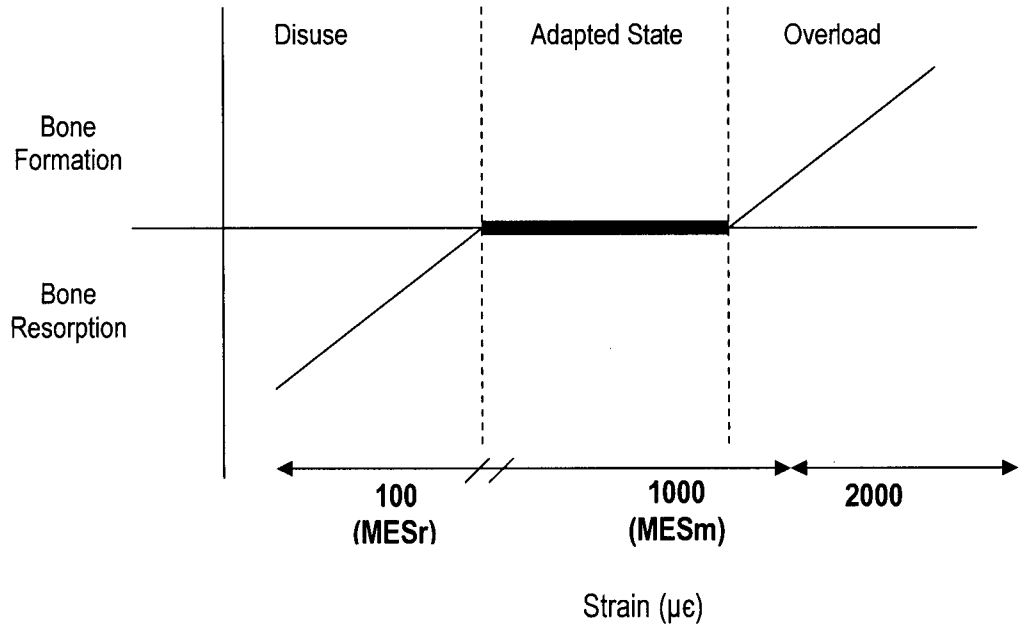


Figure 1-6. Schematic of the mechanostat theory for bone response to mechanical loading. MESm represents the minimum effective strain for bone modeling and MESr represents the minimum effective strain for bone remodeling. In the adapted state between MESr and MESm, bone turnover is minimal as typical strains change. During growth, increasing body weight and muscle loads should increase strains towards MESm and turn modeling on. In contrast, during aging, decreasing muscle strength should reduce the strains towards MESr and turn disuse remodeling on. Adapted from Frost (54,88).

1.2.2.3.1 Rules for Bone Adaptation to Mechanical Stimuli

The structural changes that result from bone adaptation can be predicted by three fundamental rules outlined by Turner (85): 1) adaptation is driven by dynamic, rather than static, loading; 2) extending the loading duration has a negative effect on bone adaptation, 3) adaptation is "error-driven", meaning abnormal strains drive structural change. These rules are important to consider when designing bone loading interventions. Results from

animal studies provide insight into how such interventions can be optimized to further the anabolic effect of mechanical loading.

Rule 1: Dynamic Loading. Studies in both growing (94) and mature (95) rats have demonstrated that bone adapts only in response to dynamic loads. Further, it appears that static loading may actually suppress normal longitudinal growth. Robling and colleagues (94) measured ulnar periosteal bone formation rates in three groups of growing male rats who received either a static (8.5 N or 17 N at 1 N sec^{-1}) or dynamic loading (17 N at a frequency of 2 Hz) protocol for 10 min/day for 2 weeks. Periosteal bone formation was suppressed by 28-41% in those rats who received static loading, and at the end of the 2-week period the loaded ulnae was 2 to 4% shorter than the contralateral control ulna in those animal who received the 17 N static load. In contrast, an osteogenic effect of dynamic loading was observed on both the periosteal and endosteal surfaces as bone formation rate increased by 78% and 300%, respectively, compared with the control limb (94). However, similar to the static load group, the dynamic load group also demonstrated significant growth suppression of the loaded limb. This was the result of a reduction in the number of proliferating chondrocyte lacunae in the distal growth plate and an increase in growth plate height. The suppression of longitudinal growth observed in this study may reflect tissue damage due to the high peak strains used in this loading model. In the male rat ulna, 17 N elicits a compressive strain on the medial surface of approximately 3500 με. This is considerably higher than peak strains recorded during running (1200 με) and jumping from a 30 cm height (2500 με) in growing rats (96) and peak strains at the human tibial midshaft during vigorous activity such as downhill running (< 2000 με) (97).

Dynamic loading conditions may involve variation in strain magnitude, strain frequency and/or strain rate; however, evidence suggests that bone adaptation is more responsive to rate-related phenomena (98). Mosley and Lanyon (99) investigated the effects of strain rate on the adaptive modeling response in the ulna of growing male rats subjected to 2 weeks of axial compressive loading. The loading protocol involved three strain rates (low, moderate, high) at a constant frequency of 2 Hz, and similar peak strain magnitudes across the three groups. The strain rate and frequency used were similar to those recorded by strain gauges (implanted on the ulna) during normal activity. At study completion, the high-strain-rate group demonstrated a 67% greater adaptive modeling response (as measured by change in bone volume) than the low-strain-rate group. It is suggested that strain rate may influence the magnitude of the load induced fluid flow, thus impacting the mechanotransduction process (99).

A more recent study in growing turkeys suggests that the effects of strain rate under certain loading conditions may be surface-specific (100). Judex and Zernicke subjected 10 young roosters to a 3 week drop jumping program. Roosters performed 200 drop jumps (from 50-60cm) daily. When compared to strain rates associated with baseline walking, the drop jumping protocol resulted in larger peak strain rates in the cortex of the middiaphyseal tarsometatarsus (TMT) (+740%). Strain magnitude was increased to a lesser extent (+30%) and strain distribution was unchanged. Although bone formation on the periosteal surface increased significantly (+40%), the increase on the endocortical surface was much more dramatic (+370%) despite smaller mechanical stimuli at this surface. Under normal loading conditions, the bone formation rate on the endocortical surface is lower than on the periosteal

surface. Therefore, these results suggest that the endocortical surface may have a greater potential for change in the presence of increased strain rates associated with axial compressive loading.

Although strain rate may be more osteogenic than strain magnitude, it is important to consider the changes in bone structure that are associated with varying dynamic loads. In growing rats, the adaptive modeling response has been shown to be greater in those animals receiving loads of greater magnitude (4000 με) than those experienced during normal locomotion (1000 to 2000 με) (96). However, it should be noted that in reference to the mechanostat hypothesis 4000 με represents the pathological overload zone for human bone, and may result in microdamage. In adults, strain magnitude at the tibial midshaft during vigorous activity (uphill and downhill zigzag running) is approximately 2000 με, which is nearly three times higher than strains recorded during walking (97).

Rule 2: Short Duration of Loading is More Osteogenic. In a now classic experiment, Rubin and Lanyon (95) used the avian ulnar loading model to demonstrate that the cellular response to mechanical loading saturates quickly. The results of this study showed that 36 cycles/day at physiological strain magnitudes (2000 με) were just as effective for eliciting an osteogenic response as 1800 cycles/day at the same strain magnitude. Further, beyond 36 cycles, the bone response was not enhanced. The saturation of the bone response to mechanical loads has also been described in growing bone. Umemura and colleagues (14) assigned immature female rats to one of five jump-trained groups (5, 10, 20, 40, or 100 drop jumps) or a control group. The jump training began at a jump height of 25 cm and progressed to 40 cm by the fourth week. After 8 weeks of jump training (5 days/week), the 5-jump group showed significant gains in bending rigidity at the femur and tibia (Figure 1-7) and in tibia cortical area compared with the control group. Although there was a trend towards an increased cortical area and rigidity with an increased number of jumps, the differences between the 10-, 20- and 40-jumps/day groups were small. These results suggest that short loading bouts were just as effective in initiating a bone response as prolonged loading bouts.

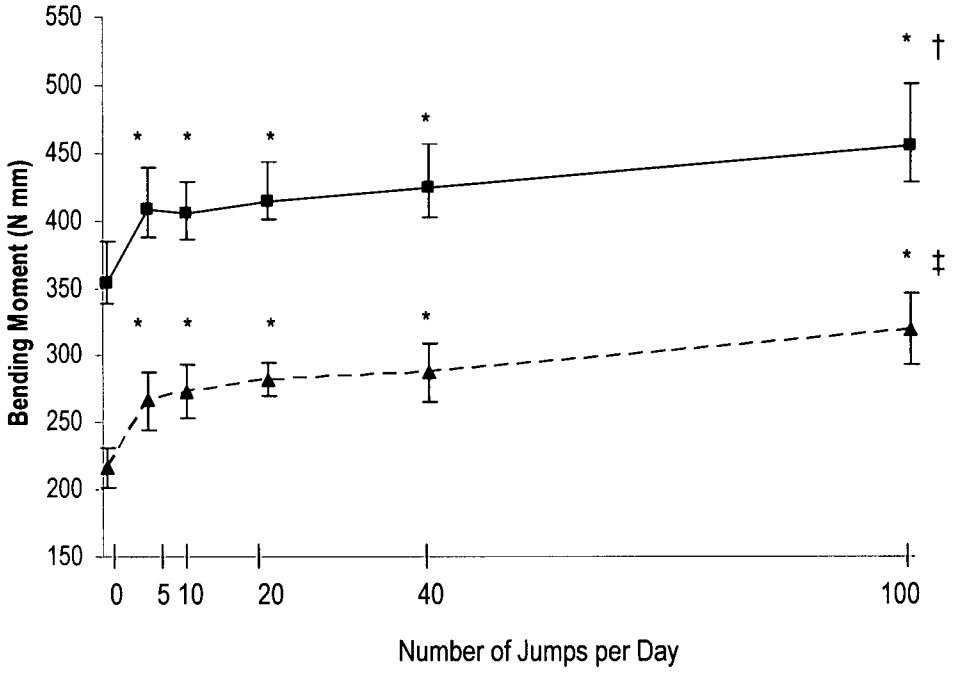


Figure 1-7. Maximum bending moments (N · mm) at the fracture test of the femur and tibia in the rats trained with different numbers of jumps per day. Values are means ± SD. * significantly ($p < 0.01$) different from the control group (0 jumps/day); † from 5-jump group and 10-jump group ($p < 0.05$); ‡ from the 5-, 10-, 20- and 40-jump groups ($p < 0.01$). Adapted from Umemura et al. (14).

An additional feature of bone cell saturation is that recovery periods either within a single loading bout, or between individual loading bouts, can re-establish mechanosensitivity. In adult rats, partitioning a daily loading protocol into brief sessions separated by recovery periods produced greater gains in bone mass, geometry and strength than one single loading bout (15). After 16-weeks, rats who received 4 bouts of 90 cycles/bout (90 x 4) with 3 hours of recovery between bouts showed a 70% greater BMC, 37% greater CSA and 46% greater minimum second moment of area at the tibial diaphysis than rats who received one uninterrupted bout (360 x 1). Similarly, Robling et al. (101) found that 14 seconds of rest between load cycles resulted in 66-190% higher relative bone formation rates on the loaded tibia of adult female rats. It is suggested that short-term recovery sessions may enhance the recruitment and/or activation of osteoblasts via fluid-flow mechanisms, while long-term recovery sessions may allow reorganization of the actin cytoskeleton (101). It is not known whether a similar loading protocol is effective in growing animals.

Rule 3: Abnormal strains drive bone adaptation. During mechanical loading, bone adaptation is dominated not by a large number of cycles of 'normal' strain distribution but rather by fewer cycles of relatively 'abnormal' strain distribution (102). Thus, adaptation is 'error-driven' in that bone responds to unusual strain distribution by making architectural changes to eliminate or reduce the perceived deviations from normal loading patterns (85). Using the avian ulnar model, Rubin and Lanyon (91) noted a linear relationship between strain magnitude and change in ulnar

cross-sectional area (CSA) such that loads less than 1000 με were associated with a reduction in CSA while loads between 1000 and 4000 με conferred a significant increase in CSA. Due to the artificial nature of the loading environment, the osteogenic response observed was attributed to an unusual strain distribution. The strain distribution error was sufficient to elicit a bone response even at strains of low magnitude.

More specifically, regional differences in strain distribution influence bone adaptation. At the tibial shaft, strain gauge data from animal (103,104) and human cadaver (105) studies indicate that the primary mode of loading is bending in the anterior-posterior direction. The strain distribution associated with bending loads results in tensile strain on the anterior cortex and compressive strain on the posterior cortex, the sites furthest away from the neutral axis of bending (medial-lateral direction) (71,105). Generally speaking, bone is preferentially added in regions of highest strain in order to return strains at these sites to the "customary" level (81). This has been demonstrated in several experiments with both young (96,99) and adult (106,107) animals. There may also be regional differences in cortical bone properties such as mineral content and porosity that are related to loading patterns (93). For example, Skedros and colleagues (93) reported increased mineralization in the compression cortex compared with the tension cortex in the immature mule deer calcaneus. This is likely related to the influence of loading on Haversian bone remodeling (35,108). Although the function of Haversian bone remodeling is not well understood, one hypothesis is that it prevents or repairs fatigue damage (microcracks) that results from high strain magnitudes and/or frequencies (33,35,98).

Based on results from these animal studies, Turner and Robling (109) generated an equation that can be used to estimate the osteogenic potential of an exercise protocol. Three parameters are required to calculate the osteogenic index (OI): intensity (peak ground reaction force, GRF), number of jumps (N), and time betweens sessions. The equation predicts that the OI for weekly exercise protocols is higher if the number of sessions per week is increased rather than the duration of the individual sessions. For example, 300 jumps per day (GRF = 3 x body weight), 2 times per week produces an OI of 33. However, if the 600 jumps are performed over 5 days (120 jumps per day) the OI is more than doubled (109). A similar increase in the OI is observed if one daily session is divided into two sessions separated by a recovery period. Although the OI may prove useful for identifying effective exercise programs, this equation has not been validated for use in animal or human studies.

1.2.2.3.2 Adaptive Differences between Cortical and Trabecular Bone

The aforementioned studies used animal models to evaluate adaptation of the cortical diaphysis. It is clear that the adaptive response to loading is complex, and is influenced by a number of properties within the loading environment. Less is known about loading characteristics that influence trabecular bone adaptation, possibly because of difficulties associated with applying and controlling loads at trabecular sites such as the metaphysis (110,111). Previous studies in growing rats have demonstrated osteogenic effects of endurance exercise on trabecular bone formation and microarchitecture (112,113); however, variations in loading protocols were not assessed in either study. Recently, van der Meulen and colleagues (111) developed a novel device to apply controlled loads to the distal lateral femoral condyle of the rabbit. They then used a similar loading protocol to that of

Robling et al. (15) to investigate the role of the number of loading cycles on trabecular bone volume fraction and architecture at the distal femur in 14 skeletally mature rabbits. Compared with loading cycles of 10 cycles/day and 25 cycles/day, the loading cycle of 50 cycles/day for 4 weeks increased bone volume fraction and trabecular thickness as measured by microCT (μCT). However, due to the small sample size, no conclusions could be made regarding the effects of load cycles on trabecular bone formation (mineral apposition rate) as measured with histomorphometry. Future investigations with this animal model will help to define other loading characteristics such as load magnitude and duration that influence trabecular bone functional adaptation.

The adaptive response of cortical bone in the growing skeleton involves mainly changes in periosteal bone formation and cross-sectional geometry, whereas the adaptive response of trabecular bone involves changes in trabecular microarchitecture. Joo et al. (113) studied the effects of 10 weeks of endurance exercise (treadmill running) on trabecular aBMD (by DXA) and microarchitecture (with μCT) at the distal femoral metaphysis in skeletally immature male rats. Compared with controls, exercised rats demonstrated a significant increase in trabecular aBMD which was the result of significant increases in trabecular thickness, number and connectivity and a significant decrease in trabecular separation. Although not tested directly, the authors interpreted the structural changes as an increase in trabecular bone strength based on established relationships between bone strength and microarchitectural parameters (114,115). Similar to the studies described previously, the adaptive response to treadmill running at the femoral diaphysis in these same animals involved an increase in periosteal bone formation (113). These results highlight how the adaptive response of bone to loading differs between regions of the same bone.

1.2.2.3.3 Adaptive Differences between Immature and Mature Bone

Evidence from animal studies suggests that the ability of bone to adapt to mechanical loading is much greater in the growing than in the non-growing skeleton (108,116-118). The age-related differences may be due to changes in the strain-related thresholds necessary to activate the (re)modeling response. Rubin and colleagues (116) found that following an 8-week loading program the increase in ulnar cortical area was significantly greater in young (1 year old) turkeys when compared to old (3-year old) turkeys (30% vs. -3%, respectively). Although this study suggests that the aging skeleton may not be responsive to loading, Turner et al. (117) found that the response to loading in older rats was dependent on a higher level of strain than was required in the younger animals. This may reflect a reduction in osteoblast or osteocyte function with aging (108,117).

More recently, Jarvinen et al. (118) examined the adaptive mechanisms of the growing and aged rat femoral neck in response to a 14-week running program. When compared to controls, both young and adult rats showed similar gains in the breaking load (+30% and +28%, respectively); however the mechanism underpinning this gain was age-dependent. Whereas young rats demonstrated a significant increase in pQCT-derived ToA (+25%) and non-significant gain in ToD (+11%), the adult rats had significant increases in ToD (+23%) and non-significant increases in ToA (+10%). Thus, it appears that the growing skeleton may preferentially adapt to mechanical loading through geometric changes while the mature skeleton responds mainly through increases in bone density (118).

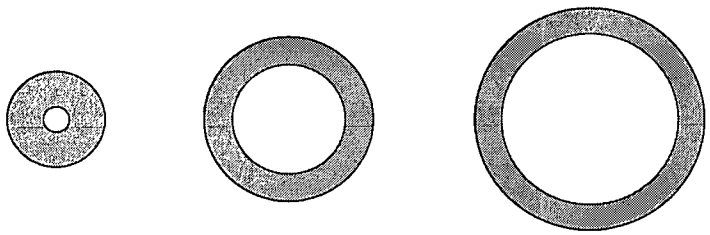
1.2.3 Measurement of Bone Parameters in Children

As discussed, the amount of bone within a cross-sectional area affects bone strength. In general, more bone equals a stronger bone. However, the architectural distribution of the bone mass (e.g., the diameter of the bone) also affects whole bone strength. Therefore, in order to understand the changes in bone strength that occur during growth, it is essential that both the material and architectural properties of the skeleton be assessed. This thesis will involve the use of three technologies that together, will provide a comprehensive evaluation of the growing skeleton. I discuss the strengths and limitations of each technology in this section.

1.2.3.1 Dual Energy X-Ray Absorptiometry

Currently, dual energy x-ray absorptiometry (DXA) is the most commonly used modality to assess bone mineral status of the growing skeleton in both clinical practice and research (119). DXA is a relatively inexpensive, noninvasive technology that requires a short scan time and is associated with low radiation exposure (119). The outcome variable of bone mineral content (BMC) in grams represents the attenuation values of photons that pass from an X-ray tube (source) through the region of interest. The common regions of interest in pediatric studies are the total body, lumbar spine and proximal femur. For each region, the projected, 2-dimensional area of bone (bone area, cm^2) analyzed is used to calculate the areal bone mineral density (aBMD, g/cm^2). In our laboratory (UBC Bone Health Research Group), the *in vivo* precision values (%CV) with the Hologic QDR 4500W are less than 2% in adults for all regions of interest (unpublished data). Due to ethical concerns associated with repeated scans, precision studies with children are uncommon. However, Litaker et al. (120) recently reported high reproducibility (intraclass correlation, ICC = 0.997) for total body BMC with the QDR 4500W in a large cohort (n = 219) of 13 to 18 year olds.

Although DXA-derived aBMD is a reasonable predictor of bone strength, and ultimately fracture risk (17,121-123), the planar nature of the measurement is a considerable limitation (17). Of particular relevance to longitudinal pediatric studies, DXA is unable to account for changes in bone size and geometry that occur during growth (119) (Figure 1-8). As a result, BMC and aBMD measures in a child with short stature (e.g., with smaller bones) will likely be underestimated while the opposite is true for a child with tall stature. To correct for the third dimension, a mathematical equation can be applied to the DXA outcomes to generate bone mineral apparent density (BMAD), or the amount of BMC per total bone volume (124). Underlying this correction is the assumption that bone cross-sectional shape is geometrically similar between subjects, and that bone thickness scales linearly with the measured projectional area (121,124). Although this assumption may hold true for skeletal sites that are considered cylindrical (femoral neck), it is likely not appropriate for more complex geometries such as those of the lumbar vertebrae (121). As will be discussed in more detail in Section 2.2.4.3 a prediction algorithm has been developed that can be applied to proximal femur scans to generate three-dimensional approximations of bone geometry and bone bending strength.



aBMD	**1**	**1**	**1**
Bending Strength	**1**	**4**	**8**

Figure 1-8. Schematic of the effect of bone cross-sectional geometry on long bone strength. Changes in distribution of bone mass that influence bone bending strength (i.e. cross-sectional moment of inertia) are not reflected in conventional measures of areal bone mineral density (aBMD) by dual energy x-ray absorptiometry.

Additional limitations of DXA include its inability to distinguish between cortical and trabecular bone, and inaccuracies associated with surrounding soft tissue (119). Within the DXA 2-component model, the composition and distribution of soft tissue in the region of interest is assumed to be absorptiometrically homogeneous (125). Corrections for soft tissue are based on a uniform distribution of fat around the bone (119) and thus, longitudinal DXA values in children may reflect changes in body size and composition associated with growth rather than true changes in BMC (119). More specifically, a nonuniform distribution of fat around the bone can result in inaccuracies in DXA measurements of aBMD in the range of 20-50% (126). Despite these limitations, DXA remains the most commonly used methodology to assess pediatric bone, especially in clinical settings (127).

1.2.3.2 Hip Structure Analysis

Structural parameters of the proximal femur can be estimated by applying the hip structure analysis (HSA) program to DXA images. HSA is a predictive computer algorithm that incorporates mechanical engineering principles into a software-specific analysis of bone mineral data (18). The principle used in the HSA program is that a line of pixels along the bone axis in a bone mass image is a projection of the corresponding cross-section (128). The dimensions of this projection are used to estimate bone cross-sectional geometry (18,128).

Bone mass profiles are generated at the femoral neck across its narrowest point ("narrow neck"; NN), the intertrochanteric (IT) region along the bisector of the shaft and femoral neck axes and the femoral shaft (FS) at a distance 1.5 times the femoral neck width (Figure 1-9) (18,129). At each site, five contiguous bone mass profiles are created and are spaced 1 pixel width apart. Thus, the total cross-section is approximately 5 mm thick. The profile integral is equivalent to bone surface area (CSA, cm^2) after removal of soft tissue voids and assuming a fixed average mineralization of 1.051 g/cm^3 (value for fully mineralized adult cortical bone). As such, CSA measures the amount of bone within the cross-section (like DXA-derived BMC) but the quantity is expressed in terms of cortical equivalent surface area rather than mineral mass (130). Subperiosteal width (SPW, cm) is the blur-corrected profile

width and cross-sectional moment of inertia (CSMI, cm^4) in the bending plane is derived as $CSMI = \sum a_i d_i^2$ where a_i is the pixel thickness x pixel spacing along the bone mass profile and d_i is the distance of the pixel from the centre of mass (131). The section modulus (Z, cm^3), an indicator of bone bending strength, is computed as $Z = CSMI/d_{max}$ where d_{max} is the maximum distance from the centre of mass medial or lateral cortical margin (131).

In modeling these regions, HSA assumes that the NN and shaft regions are circular and that the IT region is an asymmetric ellipse. In addition, each region is assumed to contain different proportions of cortical and trabecular bone: IT region, 50/50; NN region, 60/40; shaft region, 100% cortical bone (132). The HSA program was validated using 22 cadaver specimens (18). Estimated strength from HSA correlated well with measured bone breaking strength (r = 0.66-0.89). HSA-computed cross-sectional properties were also compared to those obtained from CT images. Agreement between the two methods was within 10% (18).

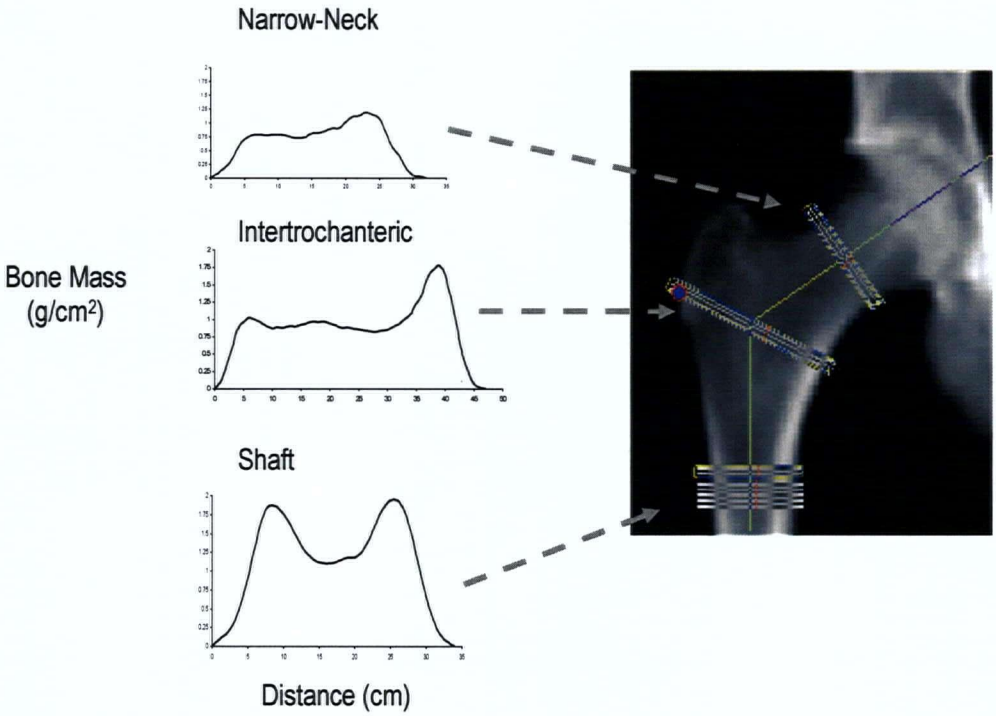


Figure 1-9. Proximal femur image from Hologic DXA scanner showing positions of analysis regions at the narrow neck, intertrochanteric and femoral shaft. To the left of the image are typical bone mass profiles used in measurement of geometric properties.

Bone structural outcomes from HSA can be used to supplement standard DXA outcomes of aBMD and BMC and have recently been shown to have similar predictive power to aBMD in determining fracture risk (133). To date, HSA has been used in several pediatric studies and has proven useful in evaluating sex differences in femoral neck bone geometry and strength (130) as well as in understanding the bone structural response to physical activity (8,134,135). However, there are clearly limitations in estimating three-dimensional properties using two-dimensional imaging techniques. In particular, CSMI and Z are only relevant for bending in the image plane and cannot be used to

estimate bending in other directions (18). Further, the mineralization density of pediatric bone is lower than that of adults. The assumption of adult mineralization in the HSA program therefore results in an underestimation of CSA, CSMI and Z in children (130).

The precision of HSA varies according to the manufacturer or model of the DXA instrument. Khoo et al. (129) recently assessed the in vivo short-term precision of key HSA variables from each of three regions of interest within the proximal femur using paired scans from two large clinical trials involving post-menopausal women. Precision error (CV%) for Z, CSMI, CSA and SPW for the Hologic QDR 4500 ranged from 2.3 – 5.1% at the narrow neck, 1.9-4.6% at the intertrochanteric region and 0.9 – 3.2% at the femoral shaft (129). Precision error tended to be poorer for CSMI and Z than CSA and SPW. This difference may be explained by the fact that similar to conventional DXA measures of BMC and BMC, CSA and SPW are relatively insensitive to patient positioning (129). In contrast, CSMI and Z estimate bending strength in the image plane only and in asymmetric cross-sections such as the IT region scans with differing rotations about the axis perpendicular to the cross-section will produce different values. Errors in positioning would affect CSMI and Z at the narrow neck and femoral shaft to a lesser degree due to the more symmetrical cross-sections. In addition, changes in femur position (hip rotation) may also alter the location and orientation of the image planes at the NN and IT regions (Figure 1-10). Regarding the precision of HSA analyses, results from our lab have shown intraoperator precision is <1.5% CV for all structural variables within the three regions (134).

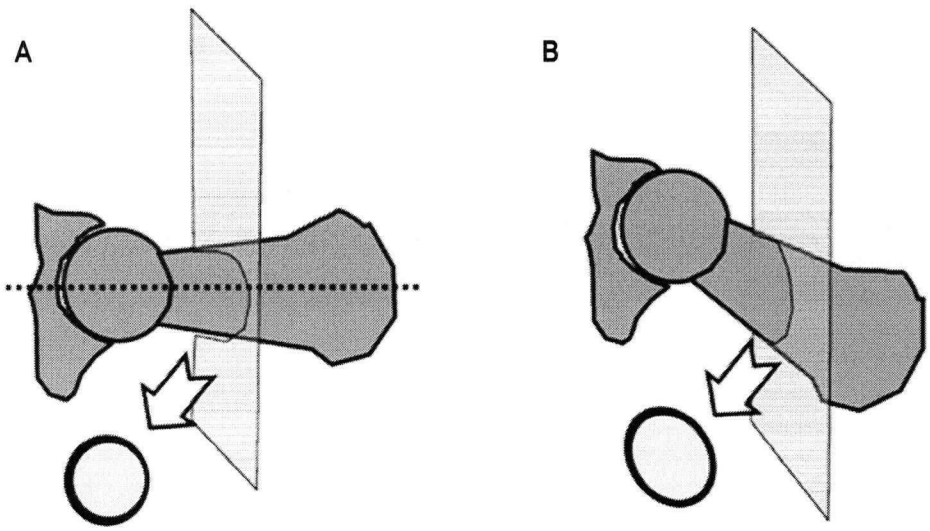


Figure 1-10. Illustration of the effect of femur repositioning on the location and orientation of the image plane. (A) Axial view of proximal femur, with the femoral neck axis positioned correctly (co-planar with the DXA scanning plane represented by the dotted line). (B) Repositioning error has placed the femoral neck axis out of the scanning plane and results in a distorted cross-section. Adapted from Khoo et al. (129) with permission from Elsevier.

1.2.3.3 Peripheral Quantitative Computed Tomography

Given the limitations of DXA, 3-dimensional imaging modalities such as pQCT are being employed more frequently in pediatric bone research. Peripheral QCT was developed specifically as an extension of the larger QCT systems, which are able to measure (volumetric) bone density in the axial and appendicular skeleton. Although both instruments are unique in their ability to separate cortical and trabecular bone, pQCT has several advantages over QCT including higher resolution, higher precision, lower radiation and lower cost (136-138). The two most common pQCT machines on the current market are the XCT 2000 (Stratec Medizintechnik GmbH, Pforzheim, Germany) and the Densiscan 1000 (Scanco Medical, Basserdorf, Switzerland). The UBC Bone Health Research Group owns one of the three XCT 2000 machines in Canada, and thus I focus my discussion of pQCT on this model.

1.2.3.3.1 pQCT Technology

Similar to DXA, pQCT measures the attenuation of radiation as it passes from the source to the detector through the object of interest. However, unlike DXA, pQCT scans a single tomographic slice and is used to assess bone geometry and apparent density of the axial skeleton (radius, tibia) (Figure 1-11). Peripheral QCT scans are performed using a translate/rotate mechanism, which involves a series of transverse measurements following successive, partial rotation displacements (12°) of the source-detector couple (19). This process continues until a 180° excursion is complete (15 rotations). The absorption of x-rays by the object of interest at each angular position creates multiple absorption profiles. Using a technique called filtered backprojection, the absorption profiles are mathematically combined to create a cross-sectional image which represents the original object (139). Each individual unit (voxel) within the image corresponds to an attenuation coefficient. These coefficients are transformed into volumetric mineral content and density by comparing the values to a reference hydroxyapatite phantom (19). The result is a value for apparent (volumetric) bone mineral density in the bone slice. It is important to note that due to limited resolution, pQCT is unable to measure the degree of mineralization within the cortex. Thus, the measure of apparent density (or BMDcompartment) is a volume that includes porous spaces such as osteonal canals and is related to cortical porosity (140).

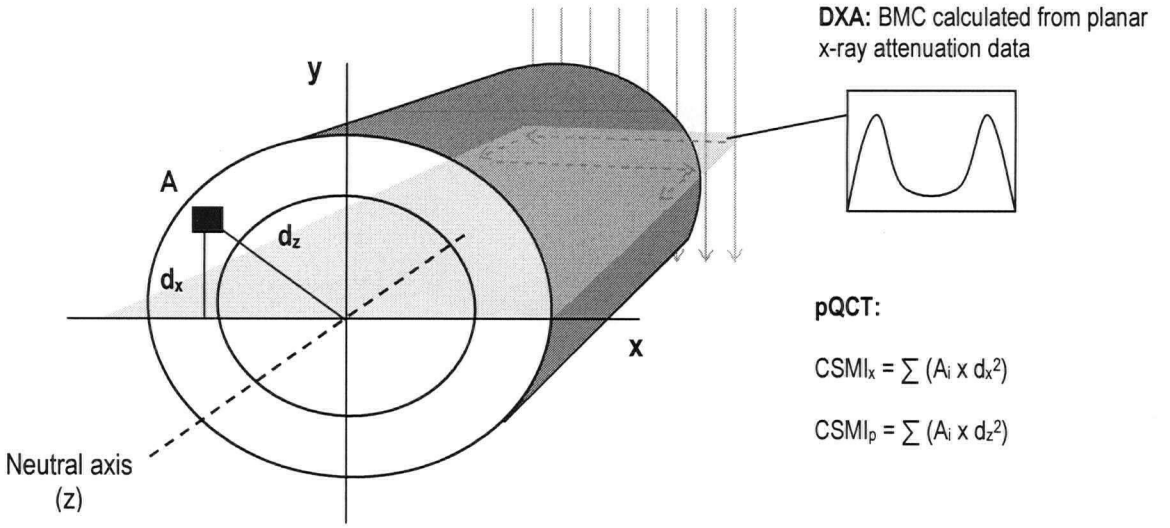


Figure 1-11. Schematic of a long bone and its biomechanical properties measured by DXA and pQCT. Whereas DXA calculates bone mineral content (BMC) from planar x-ray attenuation data, pQCT generates a three-dimensional cross-section from which geometric and material properties of the bone are obtained. For example, the bending and torsional cross-sectional moments of inertia ($CSMI_x$, $CSMI_p$) are obtained as the integral sum of the products of the area of each pixel (A_i) and the squared distance (d_x, d_y, d_z) to the corresponding bending (x, y) or torsion (z) axis. Adapted from Kontulainen (77) and Ferretti et al. (141).

1.2.3.3.2 Data Acquisition

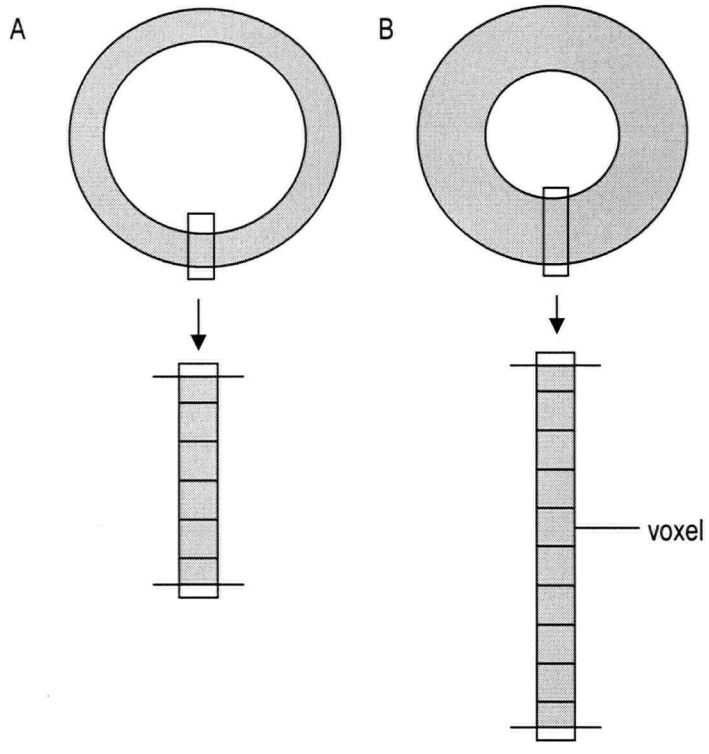
Unlike DXA, pQCT offers the operator a number of choices related to scan acquisition parameters. These include the resolution, scan time, reference line placement and scan site. Although these parameters influence outcomes of interest, it is uncommon for researchers to report their acquisition protocol(s) and there are currently no standardized protocols for pediatric pQCT studies. This poses significant challenges when comparing results across pQCT studies.

Peripheral QCT image quality is dependent on spatial resolution or voxel size. The number of voxels per scan field is fixed for each machine; however, the operator can change the field size. A smaller field size, and thus, a smaller voxel size, results in an improved resolution (19). Unfortunately, a small voxel size (e.g. 0.2 mm) requires a longer scan time to minimize the signal to noise ratio and therefore increases effective radiation dose. Thus, a voxel size of 0.4 mm or 0.5 mm is often used in pediatric pQCT studies. Although this resolution decreases radiation exposure, it does increase the potential for the partial volume effect (PVE) to influence bone outcomes. The PVE occurs when a voxel contains two or more tissues of different densities and is particularly relevant when assessing cortical bone (Figure 1-12). If the average density of the voxel is within the limit of the user-defined analysis threshold the partially filled voxel is included in the analysis and may contribute to an underestimation of the true apparent density. At the periosteal surface where the boundary between bone and soft tissue is well-defined, a partially filled voxel is not likely to be included in the analysis. However, at the endosteal surface the boundary between cortical bone, "subcortical bone", trabecular bone and marrow is less clear due to smaller differences in tissue densities. As a result, there is a greater chance that partially filled voxels would be included in the analysis. The PVE can be

minimized by choosing appropriate analysis modes and thresholds. Further, correction factors have been proposed; however, these may only be necessary when absolute rather than relative values are required (142).

In children, the PVE is also a concern when assessing skeletal sites with a thin cortical shell such as the distal radius or tibia (143,144). If the cortex is not sufficiently thick (<2-2.5 mm) to allow at least one voxel to lie fully within the periosteal and endosteal border the volume averaging errors increase (144). Thus, cortical bone should be evaluated with pQCT at shaft sites only.

An additional concern when assessing pediatric bone with pQCT is placement of the reference line. In order to determine the exact measurement site, a reference line must be defined at an anatomical landmark (139). This landmark is located using a scout scan that is performed prior to the real pQCT scan. Placement of the reference line is not standardized for pediatric pQCT studies and in many cases, researchers do not report the landmark used (11). The manufacturer recommends the reference line to be placed in the middle of the epiphyseal plate (139). However, at the distal radius, others place the reference line through the most distal portion of the growth plate in children with open growth plates or through the middle of the ulnar border of the articular cartilage in children whose growth plate is no longer visible (20). In my opinion, neither of these approaches is appropriate for prospective pediatric studies since reproducibility of the landmark is limited due to reliance on visual estimation and inevitable changes in the growth plate. The need for reproducible landmarks as well as standardization of other pQCT protocols was recently discussed by Ashe and colleagues (145) with reference to analysis of low density bone. A similar report has yet to be provided for pediatric pQCT studies.



pQCT result for CoD	4 x 710 mg/cm^3 + 2 x 469 mg/cm^3	8 x 710 mg/cm^3 + 2 x 469 mg/cm^3
Mean:	630 mg/cm^3	662 mg/cm^3

Figure 1-12. Schematic of the partial volume effect (PVE) as it pertains to the measurement of cortical bone mineral density (CoD) by pQCT. (A) At sites where the cortical wall is not sufficiently thick (< 2mm), partially filled voxels (assumed in this example to be filled by two-thirds) at the edge of the cortex will reduce the measured CoD. (B) At sites where the cortical wall is sufficiently thick, partially filled voxels have less of an influence on the measured CoD. Adapted from Schoenau et al. (23).

1.2.3.3.3 Data Analysis

The Stratec software that accompanies the XCT 2000 (Version 5.5 is used in this thesis) provides numerous analysis modes and thresholds from which the operator must determine the most appropriate combination for the particular region of interest (ROI). Similar to pQCT data acquisition, standardized pQCT analysis protocols for pediatric bone do not exist. As a result, default protocols provided by the manufacturer (139) are commonly used.

Total and trabecular bone areas and densities are obtained in two steps with iterative detection algorithms in the CALCBD function. In the first step soft tissue is separated from the outer bone edge to derive total bone outcomes (Contour Mode). In the second step trabecular bone outcomes are determined by peeling away the cortical and subcortical bone (bone that falls between the cortical and trabecular bone thresholds) (Peel Mode). Cortical area and density are obtained in the CORTBD function by removing all voxels in the ROI that have an attenuation

coefficient below the defined threshold (Separation Mode). The CALCBD and CORTBD functions produce a large number of bone outcomes; however, only a few are commonly reported in the current literature. These select variables are described in Table 1-1.

Bone areas and densities can be obtained accurately with the XCT 2000 (137,146) although the precision is generally poorer at trabecular sites such as the distal radius and tibia compared with cortical bone sites such as the radial and tibial shafts (146). The various modes and thresholds recommended by the manufacturer have not be validated for the assessment of cortical and trabecular bone properties in children. The *in vivo* precision of pQCT (Norland XCT 2000) at the tibia in children between 6 and 14 years is less than 2% (147). The major sources of imprecision associated with pQCT scanning are gross movements during scanning, subject positioning and limb alignment (148) and placement of the reference line. Imprecision can be minimized by having one trained operator perform the scans according to standardized procedures.

1.2.3.3.4 Measurement of Bone Strength with pQCT

A significant advantage of pQCT compared with DXA is that pQCT provides estimates of bone strength. As discussed, the distribution of cortical bone at diaphyseal sites such as the tibial midshaft influences both bone torsional and bending strength (16,62,71). With pQCT, the distribution of each pixel from the reference axis (x, y or z) is used to estimate CSMI (Figure 1-11). The polar moment of inertia is the sum of the principal moments of inertia (I_{max} and I_{min} or I_x and I_y) and is important in determining stress in torsion (74). However, pQCT-derived CSMI is a also a reliable indicator of bone bending strength in animal studies (149,150). Section modulus, an additional indicator of long bone bending strength (75), is derived by dividing CSMI by the maximum distance from the bending axis to the outer surface (d_{max}).

Bone bending strength is also dependent on the material stiffness of cortical bone (i.e., elastic modulus) (62). Material stiffness can only be determined with mechanical tests; however, it can be estimated with pQCT-derived bone mineral apparent density (151). The strength strain index (SSI or density-weighted section modulus) provided by the XCT-2000 combines architectural properties of the cross-section (section modulus) with apparent cortical density (normalized to the physiological density of 1200 mg/cm^3). This bone strength index has been validated against measurements of whole bone strength in animal studies (152).

At the metaphyses of long bones, compressive strength is dependent on the material and architectural properties of trabecular bone. Since the limited resolution of pQCT prevents assessment of the architectural properties of trabeculae, estimation of compressive strength must rely on measures of trabecular mass (trabecular BMC) or apparent density (141). Further, combinations of apparent density with an indicator of bone size such as cross-sectional area may also provide a reasonable assessment of compressive strength. Kontulainen and colleagues (153) calculated a compressive bone strength index (BSI) for the distal radius as the product of the square of pQCT-derived total density and total cross-sectional area (the load bearing area). At distal sites, total density is more a reflection of trabecular density than of cortical density and the square of the density is used based on relationships established in compression tests of trabecular bone (70,71,154).

1.2.3.3.5 Strengths and Limitations of pQCT

As discussed, pQCT offers several advantages over conventional DXA measures of BMC in the assessment of pediatric bone. In addition to bone areas, densities and estimated strength, pQCT can also estimate muscle cross-sectional area (MCSA) using similar user-defined modes and thresholds. I discuss this feature of pQCT in Section 1.2.5.4.1.2. With the exception of a lack of standardized acquisition and analysis protocols there are few limitations of pQCT. One concern for longitudinal studies is the long-term precision of pQCT measurements (155). As discussed, the contribution of the proximal and distal growth plates to overall long bone growth varies with age (47,48). Thus, it is not possible to reproduce the same exact location over time. However, the same relative location along the bone length can be determined using a fixed anatomical reference line.

Perhaps the most obvious limitation of pQCT is that this technology is unable to measure the clinically relevant proximal femur. Initially, it was anticipated that pQCT measurements of the upper and lower limbs might provide a means to estimate hip fracture risk. However, experimental pQCT data indicates that geometric and densitometric properties of the upper and lower limbs explain only 30-45% of the variability in femoral strength (156). This is less than the 50-60% explained by site-specific measurements of the femoral neck and proximal femoral shaft (156). Further, correlations between parameters of bone geometry and (volumetric) density display only moderate correlations across skeletal sites (156). Therefore, a comprehensive evaluation of both peripheral and axial regions of the growing skeleton can only be achieved with the use of multiple imaging techniques.

Table 1-1. Common bone outcomes in pediatric pQCT studies. The site of analysis, analysis mode and a brief description of each outcome are provided.

	Outcome (units)	Site of Analysis	Analysis mode	
Bone mass	Bone mineral content (BMC, mg/mm)	Distal, shaft	Contour mode	The amount of bone mineral within a cross-sectional slice of 1-mm thickness. Can be multiplied by the slice thickness to obtain total BMC in a 2.5 mm slice.
Bone geometry	Total bone cross-sectional area (ToA, mm^2)	Distal, shaft	Contour mode	The surface area of the entire bone cross-section including the cortex and marrow cavity. ToA directly reflects changes in bone size resulting from periosteal apposition (157).
	Trabecular bone cross-sectional area (TrbA, mm^2)	Distal	Contour mode, Peel mode	The surface area of the trabecular bone cross-section. This area is influenced by endocortical apposition or resorption.
	Cortical bone cross-sectional area (CoA, mm^2)	Shaft	Separation mode	The surface area of cortical bone within the cross-section. CoA is influence by periosteal apposition and endocortical apposition and resorption.
	Average cortical thickness (CTh, mm)	Shaft	Separation mode	The distance between the outer and inner border of the cortical shell. CTh is determined with the circular ring model which assumes a circular cross-section.
Volumetric Density	Total density (ToD, mg/cm^3)	Distal	Contour mode	ToD is the volumetric density averaged over the entire cross-section. It is influenced by the relative contributions and densities within both the cortical and trabecular bone compartments.
	Trabecular density (TrbD, mg/cm^3)	Distal	Peel mode	TrbD is the volumetric density averaged over the trabecular area of the cross-section. TrbD is influenced by trabecular number and thickness and the degree of mineralization at the material level.
	Cortical density (CoD, mg/cm^3)	Shaft	Separation mode	CoD is the volumetric density averaged over the cortical area of the cross-section. CoD is influenced by cortical porosity and the degree of mineralization at the material level.

Table 1-1 continued

	Outcome (units)	Site of Analysis	Analysis mode	Description
Strength Indices	Cross-sectional moment of inertia (CSMI, mm^4)	Shaft	Separation mode	$CSMI = \sum (A_i \times d_i^2)$ CSMI is proportional to the distribution of bone mass about the neutral axis and is an indicator of bone strength in bending or torsion (depending on which axis is used as a reference). It is calculated as the integral sum of the products of area (A) of each voxel and the squared distance (d^2) of the corresponding voxel to the bending (x, y) or torsion (z) axes (Figure 1-11) (19).
	Section modulus (Z, mm^3)	Shaft	Separation mode	$Z = CSMI/d_{max}$ where d_{max} is the maximum distance from the bending axis to the outer surface, in the plane of bending. Thus, Z approximates a cross-section's resistance to bending in a given plane (75)
	Strength-Strain Index (SSI, mm^3)	Shaft	Separation mode	$SSI = \sum_i \frac{[(a_i \times d_i^2)(CoD/ND)}{d_{max}}$ SSI is calculated as the integrated product of Z and CoD. The ratio of CoD and normal physiological density (ND = 1200 mg/cm^3) provides an estimate of the modulus of elasticity (158). Similar to CSMI, SSI can be determined with respect to the polar (z) axis or the bending (x, y) axes.
	Compressive Bone strength index (BSI, mg^2/mm^4)	Distal	Contour mode	$BSI = ToA * ToD^2$ At distal sites, compressive strength is estimated as the square of the total density and the total cross-sectional area (the load-bearing area) (70,71,153,154)

1.2.4 *The Growing Skeleton: Maturity- and Sex-Related Differences in Bone Geometry, Density and Strength*

In this section I first provide a description of the methods commonly used to assess physical maturity in children and provide a brief overview of the hormones that influence skeletal development. I then go on to discuss the maturity- and sex-related differences in skeletal development focusing on pediatric pQCT studies.

1.2.4.1 Assessing Maturity

While growth is defined as the increase in the size of the body as a whole or in parts, maturation refers to the tempo and timing of the physical changes associated with growth (159). Maturity, or biological age, does not follow the same temporal pattern as chronological age thereby conferring a large amount of variation in maturation among children of the same chronological age.

Measures of maturity vary according to the biological system being assessed. Historically, skeletal maturation is the most common method. The development of the skeleton spans the entire period of growth, and is fairly uniform with each bone progressing through standard changes from childhood to early adulthood (159). The progression of bone from an immature to a mature state can be characterized through specific changes observed on a hand-wrist X-ray that occur in a definite, irreversible order. Skeletal age is determined based on ratings provided by one of three methods: Greulich-Pyle, Tanner-Whitehouse and Fels (159). These methods are often used in clinical settings, but are of limited practicality in research settings due to ionizing radiation associated with radiography.

Given the limitations associated with measuring skeletal age, assessment of sexual maturation is more common in pediatric research. Originally described by Tanner (160), this method relies on criteria associated with the development of secondary sex characteristics, specifically breast and pubic hair development in girls and pubic hair and genitalia development in boys. The criteria are incorporated into a five-stage scale, which is then used to rate a child's sexual maturation. Tanner stage 1 represents prepuberty, Tanner stages 2 and 3 represent early puberty, Tanner stage 4 indicates the late stages of maturity and Tanner stage 5 represents reproductive maturity. These stages correlate well with testosterone and estrogen levels ($r=0.5$-0.8) in girls and boys (161). However, similar to skeletal development, the development of secondary sex characteristics is continuous. Therefore, a five-stage scale does not allow one to account for the large degree of variation that may be present between two children rated at the same Tanner stage (159). There are also known differences in the timing of sexual maturation between boys and girls that confound comparisons between sexes at the same Tanner stage (162,163).

Ratings in clinical settings are usually made by direct observation; however, due to the invasive nature of observation self-assessment methods are more common in research settings. Adolescents' self-assessment of maturity using line drawings of the 5 Tanner stages demonstrates favourable agreement with physician assessment (164,165), although there may be a tendency for children, mainly boys, to overestimate their development at early stages of maturation (165). In addition, the use of Tanner staging may be limited in overweight children. A recent study of 244 children between the ages of 6 and 12 years, 41% of whom were obese (BMI $\geq$ 95th percentile), found

that Tanner breast stage was overestimated in 38% of obese girls (166). This discrepancy may be due to the difficulties in distinguishing breast tissue from adipose tissue.

In order to assess the timing of growth, somatic methods such as age of peak height velocity (PHV) are commonly used in longitudinal studies (159). Age of PHV requires serial measurements of height (or sitting height, leg length etc.) from which individual growth trajectories can be identified. This approach can account for the wide variation amongst children's growth parameters at any chronological age, and in the rate of change of these parameters. In boys and girls, PHV occurs at a maturational point equivalent to 92% of adult stature (167) and the characteristics of the growth spurt in boys and girls are largely under genetic control (168). On average, PHV occurs earlier in girls (11.8 years, Tanner stage 3) than in boys (13.4 years, Tanner stage 4). In both sexes PHV occurs approximately 9 months before the peak in bone mineral accrual velocity (5,160) and between 5-7 months before the peak in estimated femoral neck strength velocity (Figure 1-13) (130). Mirwald and colleagues (169) recently developed a prediction equation to estimate age of PHV from one-time measurements of height, sitting height and leg length. Cross-validation with longitudinal growth data indicated that age at PHV could be predicted within 1 year of the actual value. Although this equation offers promise for estimating biological age in cross-sectional studies it has yet to be validated in ethnically diverse samples. In addition, this technique is only able to classify children as either pre- or post-PHV and thus, cannot be used to assess maturity prior to takeoff (initiation of the growth spurt). As such, maturity offset would be similar to the pre- and postmenarcheal categorization that is used for girls (169).

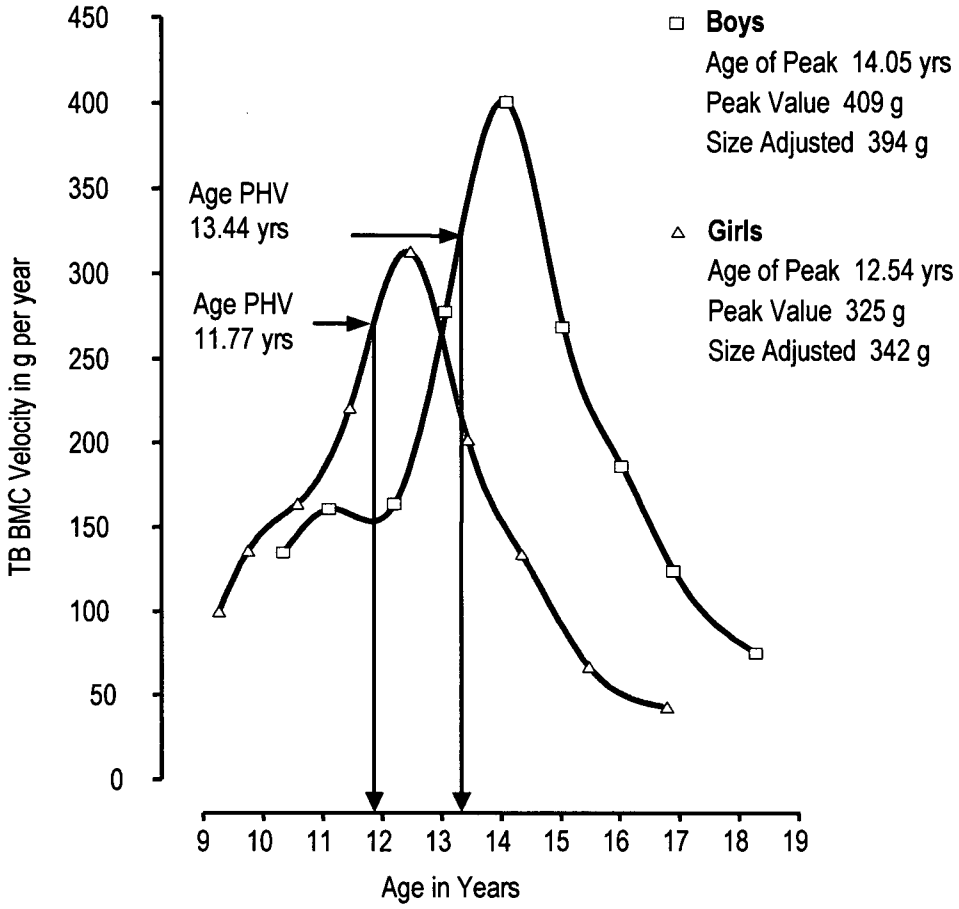


Figure 1-13. Graph illustrating total body bone mineral content (TB BMC) accrual velocity and ages at peak bone mineral content velocity and peak height velocity for boys (blue) and girls (red) according to chronological age. Adapted from Bailey et al. (5).

1.2.4.2 Hormonal Regulation of Bone Development

During puberty, dramatic alterations in linear growth and body composition occur as a result of the interactions of gonadal steroid hormones and the growth hormone (GH)/insulin-like growth factor (IGF-1) axis (170). In this section I discuss these interactions, with a specific focus on how they influence bone size and structure.

GH and IGF-1. Pubertal growth relies heavily on the activity of the growth hormone (GH)/insulin-like growth factor 1(IGF-1) axis. GH is secreted by the pituitary gland, and is necessary for the proliferation of cartilage cells at the epiphyseal plate (170). During prepuberty, GH works in concert with thyroid hormones to promote cartilage development and bone formation. GH also promotes the production and secretion of IGF-1 from the liver, as well as other sources (171). Similar to GH, IGF-1 plays an important role in cartilage and bone development as well as muscle tissue growth (171). The GH/IGF-1 axis undergoes a dramatic activation at the time of puberty due to the rising levels of sex hormones, with estrogen likely the dominant mediator (170). Increased physical activity may also influence activation of the GH/IGF-I axis in girls (172) and boys (173) during puberty. In girls, GH levels increase

around Tanner stage 2 and peak around the Tanner stage 3-4 transition (174) while in boys, the increase in GH occurs slightly later and peaks at Tanner stage 4 (Figure 1-14) (174). This temporal difference in GH secretion between girls and boys follows the pattern of change in height velocity (170). The rise in IGF-1 also occurs around Tanner stage 2 (in girls and boys) and peaks around Tanner stage 4-5 (175).

Several DXA studies have documented decreased aBMD in children with GH deficiency (176,177). In contrast, a recent pQCT study of GH deficient children (mean age 7.5yrs) showed that proximal radius CoD was normal compared to healthy, age-matched children while values for CoA and CTh were significantly lower (178). After one year of GH therapy, CoD decreased, which was proposed to be a result of increased bone turnover and catch-up growth. Similar to GH, the effects of IGF-1 are likely limited to the cross-sectional properties of bone rather than the material properties. Mora and colleagues (179) examined the relationship between IGF-1 and measures of bone ToA, CoA and CoD with QCT at the femoral shaft in 197 healthy children (94 girls, ages 7 to 18 years). Serum levels of IGF-1 were significantly correlated with ToA and CoA, but not with CoD. Thus, the GH/IGF-1 axis likely influences periosteal bone formation. This has been confirmed in studies of growth hormone deficient male and female rats (180).

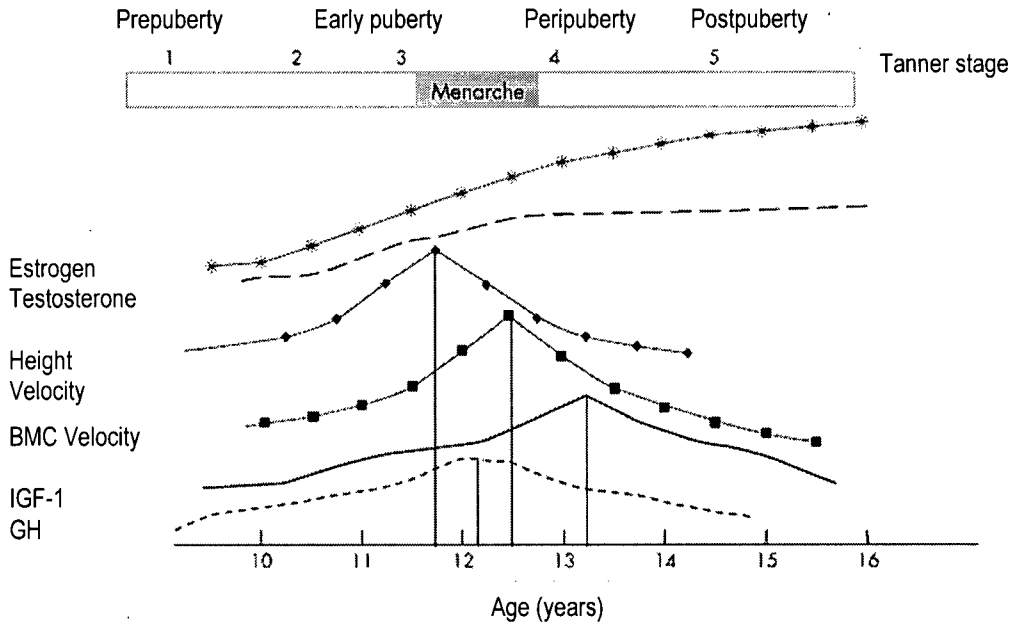


Figure 1-14. Peaks for height velocity and bone mineral content (BMC), amplitudes for growth hormone (GH) and insulin-like growth factor-I and trends for estrogen and testosterone levels in girls relative to chronological age and Tanner stage. Peaks (connected to age by solid lines) for height and BMC velocities and GH and IGF-I indicate the average age at which these peaks occur in girls as well as the corresponding approximate Tanner stage. In boys, peak height velocity and peak BMC velocity occur about 1.5 years later than girls (at 13.4 years (Tanner stage 3) and 14.0 years (Tanner stage 4), respectively). The relationship between peaks for height and BMC velocity and peaks for GH and IGF-I are similar for boys. Adapted from MacKelvie et al. (181) with permission from BMJ Publishing Group.

Sex steroids. Sex steroids play an essential role in skeletal development and in the maintenance of bone health throughout life (182). During puberty, estrogen and testosterone influence the secretion of GH and IGF-1, and are therefore key contributors to linear growth (171). In addition, estrogen plays a key role in epiphyseal fusion in girls and boys (49,183), and may inhibit periosteal bone formation and promote endosteal apposition in girls (184-186). In contrast, animal studies have demonstrated positive effects of androgens on periosteal apposition (184). The differential effects of estrogen and testosterone on the periosteal surface are thought to contribute to sexual dimorphism in bone size that begins to emerge during puberty (187).

Estrogen is also thought to influence bone adaptation to loading during growth in girls by lowering the theoretical mechanostat setpoint on the endosteal surface (88,89). As a result, exercise may have a more beneficial effect on bone formation in the presence rather than the absence of estrogen. In addition, signalling through the estrogen receptors, which are found in osteoblasts, osteoclasts and osteocytes, may also influence the bone surface-specific effects of exercise (188,189). In particular, absence of the α-form of the estrogen receptor (ER- α), which is expressed in osteoblasts and osteoclasts, limits bone's adaptive response in adult female mice (190,191). Polymorphisms in the ER-α gene may also modulate the effect of weight-bearing physical activity on aBMD at the lumbar spine and femur and ToD at the tibia in pubertal girls as was recently reported by Suuriniemi et al. (192); however, the mechanisms underlying this association remain unclear. Signalling through the second estrogen receptor, ERβ, is thought to act as an "antimechanostat" by suppressing osteoblastic activity in the presence of increased loading (189). Genotyping studies in humans are needed to confirm these relationships.

Results from a 4-year prospective study of 27 girls ages 8 to 18 years documented the correlations between changes in sex hormones and pubertal development (193). Estrogen levels begin to rise with the onset of breast development (Tanner stage 2), continue to increase until menarche is reached and remain relatively constant after menarche (Figure 1-14) (193). Testosterone levels show a similar progression in girls; however, the magnitude of the increase at Tanner 2 is less than for estrogen. The increase in estrogen levels during puberty is associated with the timing of peak bone mineral accrual velocity (Tanner 3) (5). Further, at the time of PHV (~11.8 yrs), estrogen levels in girls represent 72% of the concentration achieved at 15-16 years.

In boys, estrogen levels increase with advancing Tanner stage, although they remain considerably lower than in girls (194). In prepuberty, estrogen levels are already 8-fold higher in girls than in boys (195). The largest absolute increase in boys' estrogen levels occurs between Tanner stage 4 and 5 (Figure 1-14) (195). This rise correlates with the timing of PHV, and is influenced by the testosterone concentration which peaks one year before PHV. As growth velocity decreases in boys and epiphyseal fusion begins, estrogen levels remain elevated. Together with the pattern of change in estrogen levels for girls described previously, these data support a biphasic effect of estrogen on linear growth: at low levels estrogen stimulates onset of the pubertal growth spurt and at high levels estrogen influences growth plate senescence and epiphyseal fusion (183,188,193,196). The overall greater growth of boys is due to two additional years of prepubertal growth compared with girls and a greater magnitude of the pubertal growth spurt which is likely influenced by the pubertal increase in testosterone (188,197).

Few studies have investigated the effects of estrogen and testosterone on bone geometry or (volumetric) density in the growing skeleton (198,199). Most recently, Wang et al. (199) investigated the influence of estrogen and testosterone on cortical bone properties at the tibial shaft (60% site) in 258 girls aged 10 to 13 years over a 2-year period. To control for biological age, estrogen and testosterone concentrations were introduced into hierarchical linear models that controlled for time relative-to-menarche. Estrogen, which increased progressively to menarche and gradually decreased thereafter, was a positive predictor of ToD and CTh and a negative predictor of endosteal circumference. In contrast, testosterone was a negative predictor of ToD and a positive predictor of ToA and periosteal and endosteal circumferences. When combined with results of their previous study which demonstrated a gradual increase in marrow cavity area up to menarche and a decrease thereafter (26), these results suggest that estrogen-mediated endosteal apposition (or decreased resorption) is limited to the time after menarche. These results must be interpreted with caution due to the use of single measurements of serum hormone levels. In addition, the circular ring model was used to estimate periosteal and endosteal circumferences and CTh at the tibial shaft assuming the bone to be a perfect cylinder. This method may not be appropriate given the triangular shape of the tibial shaft.

1.2.4.3 Maturity- and Sex-Related Differences in Skeletal Development

To date, the growing skeleton has been characterized using mainly DXA-based bone outcomes. The cross-sectional (200,201), short-term (202) and longer-term prospective (203) studies conducted found that total body bone mass is similar for boys and girls before entering puberty (9 to 11 years of age). As they approach puberty, boys achieve greater bone mass at all measurable sites (204). An analysis of data from the University of Saskatchewan Pediatric Bone Mineral Accrual Study (PBMAS) that controlled for biological age, body size and body composition within a multilevel statistical model (204) showed that boys had statistically significantly higher total body (TB) and femoral neck (FN) BMC at all maturity levels (Figure 1-15). Less is known about changes in bone geometry and strength that occur during growth in boys and girls. An understanding of sex-specific developmental differences in these parameters may provide insight into the higher incidence of fragility fractures among women than men (187,205).

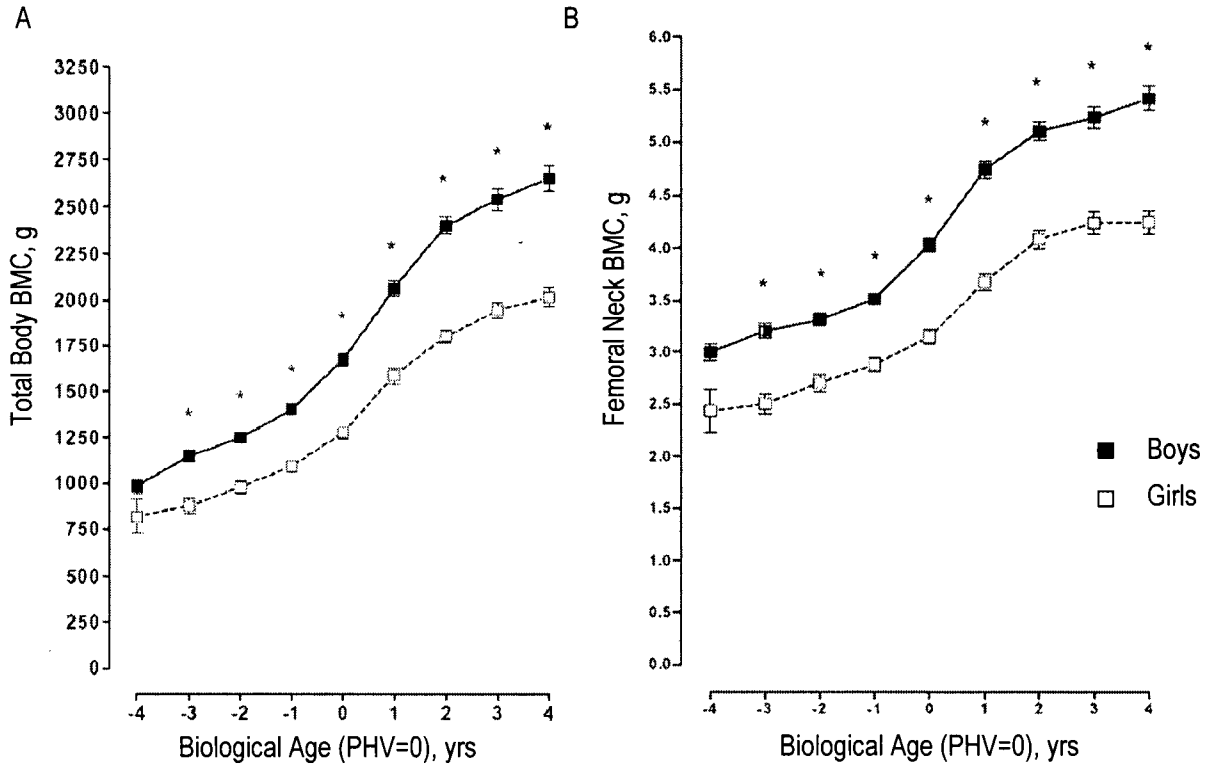


Figure 1-15. Total body (A) and femoral neck (B) BMC accrual for boys (solid squares) and girls (open squares) by biological age (years from age at peak height velocity, PHV). Values are means. * $p < 0.05$ between biological age groups. Adapted from Baxter-Jones et al. (204) with permission from Taylor and Francis.

1.2.4.3.1 Bone Geometry

A number of cross-sectional pQCT studies have described maturity- and/or sex-related developmental patterns associated with long bone growth in the upper and lower extremities (20,21,26,147). At the distal and proximal radius Neu et al. (20,21) reported an age-related difference in total bone area during growth in both sexes, although the magnitude of the difference was larger in boys. The sex difference in bone cross-sectional geometry (size) is thought to become evident during puberty when periosteal diameter expands to a greater extent in boys compared with girls (24,25,187,206). In turn, the larger bone size in boys is thought to confer greater bone bending strength in boys. However, there is disagreement in the literature as to when this sex difference emerges. Specifically, it is not clear if measures of bone geometry are greater in boys than girls as early as prepuberty. At the femoral diaphysis total and cortical bone areas (by QCT or MRI) are similar between prepubertal boys and girls (207,208), whereas radiographic data from the second metacarpal (186) and pQCT data from the radius (20,21) suggest that total and cortical bone areas are greater in prepubertal boys than girls. Of these investigations, the QCT and MRI studies of the femur (207,208) and the pQCT studies of the radius (20,21) provide the most accurate measurements of bone cross-sectional geometry. Although the discrepancy in the findings of these studies suggests possible differences between weight-bearing and non-weight-bearing bones, it is important to acknowledge that the

data for the proximal (21) and distal (20) radius were not expressed relative to body size (i.e., height, limb length, weight or muscle cross-sectional area) as they were for the mid-femur (207,208). Thus, it is possible that the sex difference in bone areas at the radius may not be apparent after accounting for the confounding effects of body size. Further studies of the upper and lower limbs are needed to confirm whether sex differences in bone cross-sectional geometry are evident in prepuberty. In particular, longitudinal studies that use an appropriate indicator of biological age, rather than maturity categories, are needed to determine when sexual dimorphism in bone geometry emerges.

At diaphyseal sites, changes in cortical bone area during growth are a function of bone formation on the endosteal surface, which also determines the area of the marrow cavity (or medullary area). In early radiographic studies of the metacarpals, Garn and colleagues (186,209,210) noted a sex difference in the magnitude and duration of endosteal bone formation that resulted in a narrowing of the marrow cavity in girls. They proposed that the observed endosteal apposition in girls resulted from the pubertal estrogen surge and served to create a calcium store for reproduction (186,209,210). However, the evidence regarding this surface-specific pattern of circumferential bone growth remains controversial. Cross-sectional comparisons of cortical bone structure by QCT (207), MRI (208) and pQCT (21) indicate that area of the marrow cavity increases with advancing maturation and age in both sexes. In contrast, a recent longitudinal HSA study of the femoral neck found that once biological age, height and lean mass were controlled for in a multilevel model, girls had greater CSA than boys after PHV (130). Since boys had significantly greater subperiosteal width, the authors proposed that greater CSA in girls must reflect greater bone gain on the endocortical surface in accordance with Garn's theory. Discrepancies in the aforementioned studies may reflect true site-specific differences, differences in imaging techniques (2-dimensional vs. 3-dimensional) or differences in estimation algorithms.

To date, only one pQCT study has attempted to substantiate Garn's theory using prospective data. Kontulainen et al. (25) compared 20-month changes in ToA, CoA, marrow cavity area (CavA) and cortical proportion (CoA/ToA) at the tibial midshaft in 128 girls and boys across early-, peri- and postpuberty. According to Garn's theory, endosteal apposition in peri- and postpubertal girls (those who reached menarche over the 20-months or were postmenarcheal at baseline) would be reflected by a decrease in CavA and an increase in CoA/ToA (an indicator of cortical thickness). However, the pQCT findings did not support this hypothesis. Similar to boys, both peri- and postpubertal girls experienced periosteal apposition and endosteal resorption as evidenced by increases in both ToA and CavA (Figure 1-16). Although this study was limited by cross-sectional comparisons across pubertal groups that were defined differently for boys and girls, these findings do suggest that the commonly accepted paradigm that endosteal apposition is a hallmark of bone development in postmenarcheal girls be re-evaluated. Prospective studies with a more appropriate indicator of biological age are needed to confirm these results.

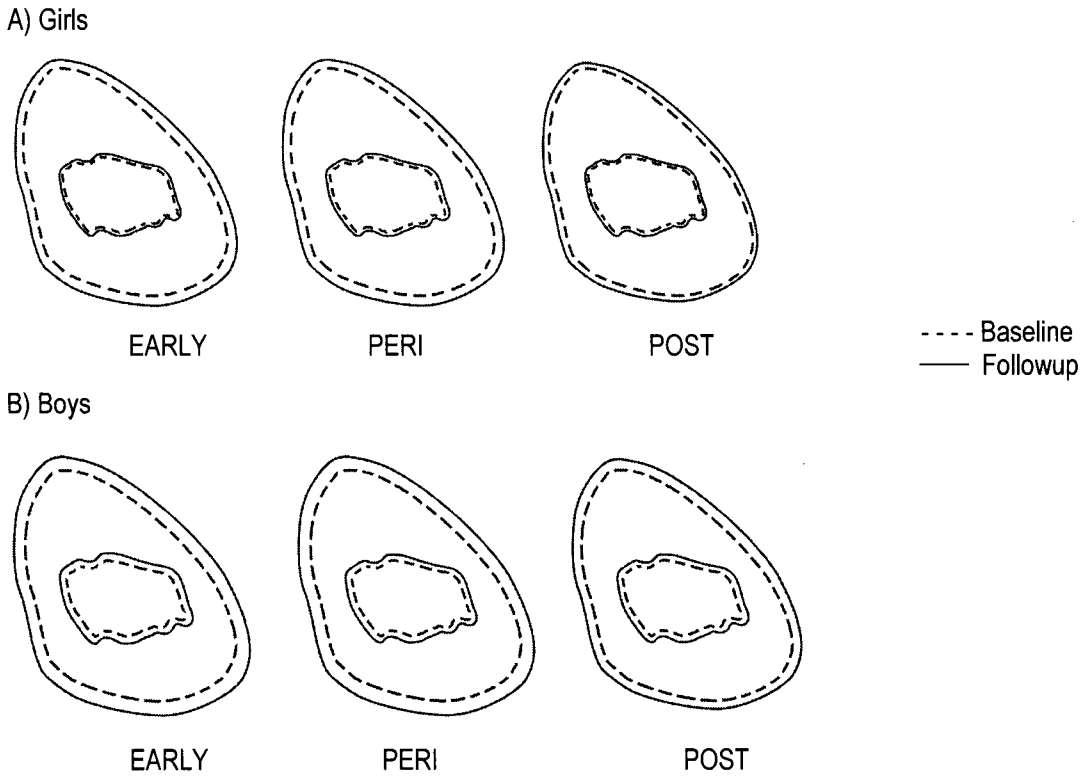


Figure 1-16. Schematic diagram depicting 20-month change in cortical bone in early-, peri- and postpubertal girls and boys. Average increases in total bone area and marrow cavity area are drawn to scale. Adapted from Kontulainen et al. (25).

1.2.4.3.2 Bone Density

When discussing the developmental changes in bone density (by pQCT) it is important to recognize that BMD (mass of mineral per unit volume) can be analyzed at three levels: bone material ($BMD_{material}$), trabecular and cortical compartments ($BMD_{compartment}$) and the entire bone (BMD_{total}) (140). Unlike DXA, pQCT is able to assess both $BMD_{compartment}$ and BMD_{total} and can therefore provide insight into underlying biological processes.

Based on current evidence, some discrepancy exists regarding sexual dimorphism in cortical density. In a cross-sectional study of the proximal radius, Schoenau et al. (23) observed similar values for pQCT-derived CoD for prepubertal boys and girls, but after Tanner stage 3 and through to adulthood, CoD was 3-4% higher among women than men (23). Cortical density is determined by two physical properties, cortical porosity and mean material density, which themselves are influenced by the rate of intracortical remodeling (140). It is suggested that higher CoD at the proximal radius in females is due to a lower rate of intracortical remodeling that is perhaps controlled by estrogen, but this has yet to be confirmed with histomorphometric analysis. Conversely, there was no sex difference in CoD at the femoral shaft as measured by QCT in a longitudinal study of girls and boys 8-18 years of age (211). The discrepancy in these findings may be related to differences in imaging resolution or detection algorithms or may reflect site-specific variation between the upper and lower limbs.

To date, two prospective pQCT studies have described growth-related changes in CoD at the tibia (26,212) and only the study from our group compared the change in CoD between boys and girls (212). Kontulainen et al. (212) used pQCT to assess maturity- and sex-specific differences in 20-month change of CoD at the tibial midshaft (50% site) in 127 early-, peri- and postpubertal boys and girls. Similar to the findings of Wang et al. (26) who reported a gradual increase in CoD at the tibial shaft (60% site) over 2 years in pubertal girls, CoD increased (2-4%) significantly across maturity groups of girls. The greatest increase was observed for peripubertal girls (those who reached menarche during the followup). In contrast, CoD increased in peripubertal boys only but the change was not significantly different from that of the other maturity groups. When CoD change was compared between sexes (within each maturity group), girls in each maturity group demonstrated a significantly greater increase (2-3%) in CoD than boys (212). These findings do not agree with the QCT results of the mid-femur from Loro et al. (213) discussed previously. However, it is important to note that the Loro et al. (213) study was limited by direct comparisons of boys and girls across Tanner stages 2-5. As highlighted previously for studies of bone geometry, future investigation of sexual dimorphism in cortical bone development would benefit from aligning boys and girls on biological age.

In a secondary analysis, Kontulainen et al. (212) investigated the change in CoD distribution using the radial distribution function in the Bonalyse software (Bonalyse 2.1, BonAlyse Oy, Jyväskylä). For peripubertal girls, CoD change was greatest in the subcortical region, whereas for postpubertal girls (post-menarcheal at baseline) CoD change was greatest in the high density mid-cortical region. Together with earlier findings from this cohort that showed expansion of the marrow cavity (rather than endosteal apposition) (25), these results suggest that pubertal girls appear to consolidate bone in the sub- and mid-cortical regions more than pubertal boys. Although pQCT has insufficient resolution to image cortical porosity or material density, regional differences in cortical density distribution are shown to be related to tissue porosity (214). In addition to the possible influence of estrogen on intracortical remodeling discussed previously, there is also the possibility that higher mechanical demands (i.e. larger body size and greater muscle force) in boys than girls may have caused more microdamage in boys' cortical bone, which in turn may have increased intracortical remodeling and in turn, cortical porosity (35). This has yet to be confirmed with histomorphometric analysis.

Measurements of trabecular density (TrbD) by pQCT represent the trabecular number, trabecular thickness and mean material density of the trabeculae (20). Values for TrbD are generally lower than those for CoD due to the differences in porosity between the two types of bone. Cross-sectional data from the distal (4% site) radius suggest that TrbD does not increase with age in girls, and may increase slightly in boys after Tanner stage 3 (20). As a result of these age-related differences, boys have 13% and 23% greater TrbD compared with girls at Tanner stage 5 and in adulthood, respectively. In contrast, sex differences in TrbD (by QCT) were not observed at the lumbar spine, although TrbD increased by approximately 18% between Tanner stages 2 and 5 in both sexes (213). The differences in TrbD at the axial and appendicular skeleton may reflect the more transient nature of the trabeculae within the metaphyseal region of the distal radius (20). To my knowledge, there have been no prospective pQCT studies of trabecular bone properties in children.

Recently, the development and validation of high-resolution three-dimensional pQCT systems have allowed trabecular microstructure to be evaluated non-invasively at the distal radius (215-217). In young adults (aged 20-29 yrs), trabecular bone volume/tissue volume and trabecular thickness at the distal radius were greater in men than women, whereas there was no sex difference in trabecular number or separation (217). This technology has not been used to evaluate trabecular microstructure in the growing skeleton.

1.2.4.3.3 Bone Strength

The relative rate of bone formation on the periosteal surface and bone formation and resorption on the endosteal surface together determine bone size, the amount of bone material within the bone envelope, and ultimately, whole bone strength (186,218). The magnitude of the growth-related increase in bone strength is substantial; when comparing section modulus (by pQCT) at the proximal radius between children (6 years of age) and adults (40 years of age) there is a difference of about 300-400% (22). Although both sexes experience age-related gains in radial bone strength, the larger bone size in boys confers a strength advantage that can be observed after Tanner stage 2 (22). Similarly at the tibial midshaft, we found that 20-month changes in section modulus were 14-16% greater in early-, peri- and post-pubertal boys compared with girls of similar maturity status and that the sex difference in bone strength change mirrored the sex difference in CoA change (24). Although larger body size likely explains part of this sex difference in bone strength, it is also thought that due to smaller musculature in women than men, the lower bone strength in women may result from adaptation to smaller forces and bending moments than in men (219). However, few studies have investigated sexual dimorphism in bone strength relative to sex differences in muscle mass or muscle forces (24,130,219). I discuss these studies in more detail in Section 1.2.5.4.4.

At the distal radius, the most common site for fracture in children (220,221), it appears that although bone size increases with age in both boys and girls, development of bone strength (as estimated with pQCT-derived strength-strain index) lags behind the increases in the product of forearm length and body weight, an indicator of a fall-related mechanical challenge (55). Based on estimated rates of endocortical apposition and periosteal resorption at the metaphyseal cortex, Rauch et al. (22) hypothesized that the lag in bone strength is due to an insufficient increase in metaphyseal cortical thickness relative to the increase in mechanical challenges during growth.

1.2.5 Determinants of Bone Strength

In this section I discuss several key factors that are known to influence bone strength during growth. These factors fall into two-categories: non-modifiable and modifiable. The non-modifiable factors include heredity (genetics) and ethnicity (or race) and the modifiable factors include dietary calcium and muscle forces. Physical activity is also a key determinant of bone mass and strength and is the focus of this thesis. I discuss the relationship between physical activity and bone strength in detail in Section 1.2.6.

1.2.5.1 Heredity

Numerous family (222-224) and twin (225-227) studies have shown that genetic factors may account for 60-70% of the interindividual variation in aBMD (by DXA). Further, familial resemblance for aBMD is present before

puberty (222). The heritability of aBMD is complex and does not demonstrate classic Mendelian recessive or dominant inheritance patterns that can be attributed to a single gene. Instead, aBMD is a polygenic trait explained by a collection of candidate genes including the vitamin D receptor (VDR) gene (228), the estrogen receptor gene (229), the parathyroid hormone receptor gene (230) and the COL1A1 gene (encodes the alpha I chain of type I collagen) (231) among others.

Twin studies have also highlighted the presence of shared genetic determinants of aBMD, BMC and other aspects of body size such as lean mass (226,232,233). Heritability of lean mass is thought to be between 50 and 80% (232,234), and when lean mass is controlled for the heritability estimate for bone mass is reduced by 5-20% (226,232,235). Thus, some of the genetic variability in bone mass reflects genetically-determined variability in body size (i.e. height, muscle mass) (235). The remaining 30-40% of the variation in bone mass is likely explained by environmental factors such as physical activity and nutrition as well as measurement error (235,236).

Unfortunately heritability estimates of bone mass do not provide estimates of the genetic variability in mechanically relevant parameters such as cross-sectional geometry. Few genetic studies of bone size or geometry have been conducted in humans (237-242), and most have used DXA estimates of bone size, HSA or radiographic analysis. At the femoral neck, heritability of parameters of cross-sectional geometry such as CSA and Z (estimated with HSA) range from 37% to 62% (241). Polymorphisms in several candidate genes responsible for variation in femoral neck bone geometry have been identified including the IGF-I gene (243), the tumour necrosis factor alpha (TNF-α) gene (244) and the ER-α gene (245). However, compared with aBMD, the genetics of bone geometry and strength are not well understood. Further, there have been no heritability or linkage studies of bone cross-sectional properties as measured with pQCT.

Recently, Volkman et al. (246,247) assessed the influence of genetic determinants of cortical bone geometry (assessed by μCT) in the mouse femur using quantitative trait loci (QTL) analysis. In contrast to the high heritability estimates of BMC and aBMD, genetic markers accounted for only 3-22% of trait variances in cross-sectional geometry (246,247). The authors discussed several ways that genes may influence bone structure: 1) directed activity of osteoblasts and osteoclasts, which in turn influence bone size and shape; 2) indirect action on factors such as muscle strength/force, which in turn alter mechanical load and thus bone structure; and 3) alter the mechanostat setpoint, which in turn would affect bone adaptation to loading (246). With the exception of the first proposed mechanism, these proposals highlight the interaction between genetic and environmental effects, specifically mechanical loading (84). Thus, although genetics plays a key role in shaping skeletal morphology, appropriate mechanical loading is necessary for the development of a healthy skeleton (31,84).

1.2.5.2 Race and Ethnicity

The terms race and ethnicity are often used interchangeably in the current literature. Further, researchers often fail to differentiate between these terms. This poses significant challenges when interpreting and comparing results across studies. Within bone research, there is currently no consensus regarding the definitions of race and

ethnicity. For the purposes of this review I will use the terminology as outlined by the authors and provide definitions if available.

Epidemiological studies have documented that the incidence of hip fracture across races is lower in non-Caucasians compared with Caucasians (248). However, among Asians there has been a dramatic increase in hip fracture rates over the past 3 decades. The highest rates were observed in urbanized countries (249). In addition, the rate of vertebral fracture was reported to be higher in Asians compared with Caucasians living in North America (250). The differences in fracture rates across races has been attributed primarily to variation in aBMD, with Blacks > Caucasians > Asians. Although this trend has also been partially explained by differences in bone size (251), very little is known about the contribution of bone geometry to fracture rates across races (252).

An apparent discrepancy is noted in the lower aBMD and lower fracture risk in Asians compared with Caucasians. DXA studies suggest that lower fracture risk may be related to shorter hip (or femoral neck) axis length (HAL or FNAL) (253) and a smaller femoral neck angle (254) in Asians. Recently, Wang et al. (255) demonstrated that racial differences in femoral neck size, cortical thickness and indices of bone strength (estimated with DXA) may be related to growth- and age-related differences in periosteal apposition and endocortical resorption. For example, young adult (Australian) Chinese women (~30 years of age) had a significantly shorter FNAL, narrower femoral neck (smaller periosteal diameter) and thinner cortex than young adult Caucasian women after adjusting for differences in body size. However, from young to old age (~70 yrs) similar increments in femoral neck periosteal and endosteal diameter occurred in Chinese and Caucasian women. As a result, in old age, Chinese women maintained a smaller femoral neck periosteal diameter, section modulus and buckling ratio (255). The authors proposed that racial-differences in the onset of puberty and peak growth velocity (i.e., Chinese earlier than Caucasians) may explain the structural differences in femoral neck dimensions such that earlier exposure to estrogen in Chinese children may result in a shorter leg length and FNAL compared with Caucasians (255). Several studies have shown that age of onset of puberty may be earlier in (mainland or Hong Kong) Chinese than Caucasian girls (256,257); however, this trend may not apply to Chinese children that live in westernized countries (258).

Of the few studies that examined race/ethnic differences in bone parameters during growth, most have focused on DXA measured BMC and aBMD. Results from cross-sectional and prospective studies suggest that after adjusting for body size, there is little to no difference in BMC or aBMD, or the gain in these parameters, between Asian and Caucasian (defined by country of origin) prepubertal children (259-264). However, ethnic differences in bone mineral may become more apparent in the later stages of puberty. MacKelvie et al. (261) compared Tanner stage 2 Asian and Caucasian girls and found substantial differences in BMC and aBMD across several skeletal sites in favour of Caucasian girls. This finding is in agreement with previous cross-sectional studies that suggested ethnic differences in bone mass may become apparent with advancing maturity (211,265,266).

To date, one cross-sectional study has examined racial differences in bone geometry during growth. Gilsanz and colleagues (211) used QCT to measure properties of the axial and appendicular skeleton in 80 Black and 80 Caucasian boys and girls between 8 and 18 years of age (definition for race not provided). The children were matched for age, gender, height, weight and Tanner Stage. Race did not influence the cross-sectional area of the

vertebral bodies. However, race did influence vertebral BMD as evidenced by higher BMD among Black children at puberty (211). In contrast, there was no difference for CoD at the femoral shaft between groups. There was, however, a significant difference between races for femoral shaft cross-sectional area and femoral length (211). When children across Tanner stages were collapsed, values for cross-sectional area were, on average, 3% and 8.4% greater in Black girls and boys, respectively compared with same sex Caucasian children (211). It is not known if similar differences in bone cross-sectional geometry and density exist between Asian and Caucasian children.

Genetics is likely a significant factor underlying race/ethnic differences in fracture rates and bone phenotypes (i.e., bone size or density). Asian and Caucasian populations have different patterns of variation in polymorphisms of candidate genes for osteoporosis such as the vitamin D receptor gene and the collagen type 1 alpha 1 (COL1A1) gene, among others (267-269). For example, the high-fracture risk allele "s" of the COL1A1 gene was found to be absent in East Asian populations and more frequent in Caucasian populations (0.15 to 0.32) (267). It is not known how genetic differences may interact with documented differences in environmental and lifestyle factors between races/ethnicities (260,261).

1.2.5.3 Dietary Calcium

Calcium is a major constituent of bone mineral and is thus an essential nutritional factor for optimal skeletal development. However, controversy exists over the amount of calcium that is necessary for bone health during growth (270,271) and whether calcium intake during childhood is related to fracture risk later in life (272,273). The majority of total body calcium forms hydroxyapatite crystals that comprise the inorganic phase of the bone matrix. The amount of calcium incorporated into the skeleton is determined by both calcium absorption (ingested – fecal) and retention (absorbed - (renal + dermal + endogenous secretion)) (274). Calcium retention is regulated by a complex homeostatic control mechanism that involves the actions of several calciotropic hormones (parathyroid hormone, vitamin D, calcitonin) (61) as well as possible genetic influences (275,276). From birth to the end of adolescence, 150 mg/day, on average, of calcium must be retained from the diet to meet the needs of the growing skeleton (277). The highest calcium retention is required during puberty, specifically for the 2 years around peak bone mineral accrual velocity (5). In the Saskatchewan PBMAS study, Bailey et al. (274) calculated peak calcium accretion rates in 130 children (60 boys) from longitudinal BMC measurements assuming a 32.2% calcium fraction in bone (278). Peak calcium accretion rates were 359 ± 81 mg/day at age 14 ± 1 yrs for boys and 282 ± 58 mg/day at age 12.5 yrs for girls. Slightly lower estimates of accretion rates (201) were used to determine the current adequate intake (AI) for calcium for children and adolescents (9-18 yrs: 1300 mg/day) (271). Although it is possible that higher intakes may be required during the adolescent growth spurt to optimize bone mineral accretion (275), calcium does exhibit threshold behaviour meaning that at a certain point there is little increase in retention with increased intake (279).

The current AI for calcium during growth is based, in part, on results from several randomized, double-blind, placebo-controlled trials that have shown positive effects for calcium supplementation on BMC and aBMD in children (280-283). However, only one of these trials reported maintenance of bone gains in the supplemented group several years after the end of the intervention (284). Bonjour and colleagues (284) also noted larger gains in height in the

previously supplemented group. They attributed the differences in longitudinal growth to the calcium intervention; however, maturity status was not controlled for within the analysis. Failure to adequately control for maturation and other confounding factors is one of several limitations of calcium supplementation trials that were recently discussed by Lanou and colleagues (270).

An additional limitation of the current calcium literature is that few pQCT studies have investigated the effects of dietary calcium on bone geometry, density and strength during growth (285-289). Moyer-Mileur et al. (287) conducted a 12-month randomized controlled trial (RCT) in which 71 early adolescent girls (aged 12 yrs, Tanner stage 2) were randomized to either treatment (daily supplement = 800 mg calcium carbonate, 400 IU Vitamin D) or control (placebo). Peripheral QCT was used to assess changes in trabecular bone properties at the distal tibia (10% site). After adjusting for body size and menarcheal status, girls in the treatment group gained significantly more trabecular BMC (+4.1% vs. -1.6%) and TrbD (+1.0% vs. -2.0%) than controls. There was no difference between groups for 12-month change in TrbA (+3.1% vs. +2.0%). In subsequent regression analyses, it was determined that supplementation accounted for 5.2% and 10.4% of the variability in trabecular BMC and TrbD change, respectively. Two other supplementation trials that used pQCT were unable to determine a causal relationship between calcium and ToD of the radial shaft (289) or cortical bone properties at the tibial shaft (288) due to a lack of pQCT data at baseline. There is a need for well-designed RCTs that span adolescent growth in boys and girls to more closely investigate the relationship between calcium and pQCT-derived measures of bone density, geometry and strength.

Calcium may have a more significant influence on skeletal development when in a deficient state (290); however, ethical concerns prevent such studies in children. Animal models have therefore been used to investigate the effects of low-calcium diets on the growing skeleton (291-293). In a recent histomorphometric study of growing female rats, Iwamoto et al. (293) found that rats fed a mild calcium deficient diet (0.1%) for 10 weeks had increased bone resorption and suppressed bone mineralization in trabecular bone at the proximal tibia compared with rats fed a normal calcium diet (0.5%). In addition, cortical area was significantly smaller in the low-calcium animals. Similar findings have been reported for the rat femur (291,292) with the ultimate result being a decrease in bone breaking strength (291). The negative effects of low dietary intake on skeletal development are likely mediated by the actions of parathyroid hormone (PTH) as levels of the hormone are significantly elevated in low calcium animals compared to controls (293).

1.2.5.3.1 Ethnic Differences in Calcium Intake

An additional limitation of the current AI for calcium during growth is that it has limited use across ethnic populations because the calculations were based on data from Caucasian children (271). Ethnic differences in calcium intake are well established (260,261,294,295). Previous studies from our lab (260,261) found that pre- and early pubertal Caucasian children consumed 35-41% more calcium than their Asian peers. It also appears that the sources of dietary calcium vary by ethnicity. In Asian diets, a large percentage of the calcium intake may come from non-dairy sources such as breads, cereals, vegetables and legumes (296). In contrast, Caucasians are more likely to obtain a large percentage of dietary calcium from dairy products. The bioavailability of calcium from non-dairy

sources is generally less than from dairy sources (297). The ethnic difference in calcium intake is also confounded by a higher prevalence of lactose intolerance among Asians (298). The dietary intake of calcium in Asian youths may have particular relevance to the incidence of hip fracture later in life as low calcium intakes among older Asian populations has been identified as a risk factor for hip fracture (299). However, it is not known if ethnic differences in dietary calcium are related to ethnic differences in bone strength at sites such as the proximal femur.

1.2.5.3.2 Calcium and Exercise Interactions

As will be discussed in detail in Section 1.2.6, physical activity is a significant determinant of bone strength in the growing skeleton. Whether dietary calcium and physical activity have a synergistic effect on bone during childhood and adolescence is controversial (300-302). Few randomized trials in children have investigated the combined effects of calcium and exercise (288,303-305) and evidence from these trials in support of an interaction is weak. Of these trials, one used pQCT to investigate the influence of a possible calcium and exercise interaction on cortical bone properties at the tibia (20% site) in young children (3-5 yrs) (288). Unfortunately due to the exclusion of a large number of baseline pQCT scans, 12-month change in pQCT outcomes could not be assessed. Thus, it remains unclear if calcium and physical activity together provide an osteogenic stimulus more beneficial than physical activity alone.

1.2.5.4 Muscle

The relationship between muscle and bone was acknowledged decades ago (306); however, it has only recently gained significant attention in pediatric bone research (31,307). As discussed, muscle forces incur the largest voluntary loads on the skeleton (30,88). During growth, the skeleton continually adapts to these loads to keep bone deformation within safe limits and in the absence of normal muscle forces, long bones fail to develop normal width, mass and longitudinal curvature (308). Due to the strong relationship between muscle and bone, an understanding of muscle development is important for pediatric studies of bone health. In this section I discuss measurement of muscle mass and force during growth as well as the few pediatric studies that have investigated the muscle-bone relationship in children.

1.2.5.4.1 Measurement of Muscle Mass

There are several methods available for determining skeletal muscle mass or muscle size in children including limb circumferences, creatinine excretion and imaging techniques such as DXA, (p)QCT and magnetic resonance imaging (MRI) (197,309). For the purpose of this thesis I discuss only DXA and pQCT.

1.2.5.4.1.1 DXA

DXA can safely and easily evaluate body composition in pediatric studies. The DXA body composition approach assumes that the human body consists of three components – fat, bone mineral and residual or "lean soft tissue" – that are distinguishable by their X-ray attenuation properties (310). Theoretically, three different photon energies are needed to separate the three different components. The two-energy DXA system circumvents this by

first separating pixels with only soft tissue (fat + lean) from pixels containing soft tissue + bone mineral based on the ratio, or R value, of attenuation characteristics within each pixel. Soft tissue pixels are then further separated into fat or lean soft tissue pixels according to assumptions of stable attenuation ratios for both tissues (311). Total body lean mass can be used as a surrogate for skeletal muscle mass (312) and it is estimated that during childhood and adolescence lean body mass accounts for 70% of total body mass (197). The appendicular skeleton, which is approximately 75% skeletal muscle mass, represents the largest contribution to total body lean mass. DXA-derived lean mass has been validated against chemical analysis (313,314) and precision (in adults) with repositioning (%CV) in our laboratory with the Hologic QDR 4500W is less than 0.5% (Bone Health Research Group, unpublished data). Similarly, a recent study with 13 to 18 year olds found high reproducibility (ICC = 0.997) of the QDR 4500W for repeated measurements of total body lean mass (120).

1.2.5.4.1.2 pQCT

In addition to characterizing bone geometry and density, pQCT can quantify muscle cross-sectional area (MCSA) in the appendicular skeleton. For the lower leg, the most common measurement site is the proximal two-thirds site, or 66% of total tibial length proximal to the distal end. In adults, this site correlates with the largest muscle belly (32); however, this relationship has not been defined in children. At the radius, MCSA is measured at 65% of total ulnar length proximal to the radial endplate because forearm circumference is largest at this site in adults (309). Similar to pQCT analysis for bone outcomes, MCSA is obtained with user-defined threshold driven algorithms. The analysis involves two steps: 1) separate muscle and bone from fat and 2) separate muscle from bone. If a small voxel size is used (0.4 mm), an additional step may be required to remove the skin from the total muscle cross-sectional area. There is good agreement between pQCT-derived MCSA and spiral CT-derived MCSA in adults (R^2 = 0.9) (315); however accuracy of this method has not been determined in children. Similarly, precision of pQCT-derived MCSA has not been determined in children, but Neu et al. (309) reported a precision error of 1.93% for MCSA in adult women.

1.2.5.4.2 Measurement of Muscle Force

According to mechanostat theory, it is muscle *force* that drives bone development, not muscle size (88). Direct measurements of muscle force can only be determined invasively with force transducers and thus, indirect methods such as dynamometry are used to estimate muscle force in children and adults (316,317). In addition, pQCT-derived MCSA can be used as a surrogate for potential force development of muscles (32,318). As proposed by Rittweger et al. (32), the bending moment that a muscle exerts may be estimated by the product of MCSA and the length of the lever arm (i.e., tibial length). The relationship between MCSA and muscle force is based on the well established association between physiological muscle cross-sectional area (PCSA) and maximum isometric muscle force (319). Physiological CSA is calculated as the ratio of muscle volume to muscle length and as such, represents muscle area assuming a constant area along the entire muscle length. In parallel-fibred muscles (e.g., biceps

brachii), maximum force increases linearly with PCSA. However, for pennate muscles (e.g. soleus), the force per anatomical cross-sectional area depends on pennation angle (319).

Both grip force by dynamometry and MCSA by pQCT are used to estimate muscle force. However, to my knowledge there are no published reports of the relationship between these measures in healthy children, nor are there data to support the relationship between pQCT-derived MCSA and maximal force production in the lower leg. There are, however, clinical pediatric pQCT data showing a strong association (r = 0.91) between forearm grip force and MCSA in children with juvenile rheumatoid arthritis (320). In the legs, a moderate to strong association (r = 0.5-0.7) was reported for thigh MCSA determined with MRI and isokinetic strength (maximum force under dynamic conditions) at the knee in 10-14 yr old children (321). However, in the MRI study, once stature and weight were accounted for in the multilevel regression model, the influence of MCSA was non-significant. This indicates that MCSA is not the sole determinant of muscle force. Additional factors that may influence muscle force production in children include muscle pennation angle and neuromuscular characteristics such as contractile properties (197).

Field measures of muscle performance include vertical and standing long jump (197). Jumping tests are used as indicators of muscle coordination and explosive power. In boys and girls, jump performance increases linearly with age and there are consistent sex differences in jump performance throughout childhood and adolescence (197). Force platforms such as the Leonardo Jumping Platform (Novotec GmbH, Pforzheim, Germany) measure both stationary forces (body weight) and variation in forces during vertical jumping (i.e., ground reaction forces) and can be used to assess muscle power (force x velocity) in children (322). Force platforms are a valuable research tool because they provide an indirect measure of the magnitude and rate of external load on the legs during weight-bearing activity; however, their use in pediatric research has been limited to date.

1.2.5.4.3 Sex Differences in Muscle Development

Early radiographic studies of muscle widths helped to characterize the sex-specific patterns of muscle development (323). A small sex difference in muscle widths of the arm and calf exists during childhood, with boys having slightly wider muscles. This difference is magnified when testosterone levels increase in boys and they begin their adolescent growth spurt in musculature and it persists into adulthood, especially in the upper limbs (197,323). Similarly, cross-sectional pQCT data from the forearm indicate that both MCSA and grip force are greater in boys than girls at all stages of maturity (309). However, specific grip force (grip force per MCSA) was similar between sexes at all stages of development and thus appears to be independent of sex hormones.

1.2.5.4.4 The Muscle-Bone Relationship during Growth

In this section I discuss the cross-sectional and longitudinal studies of the muscle-bone relationship during growth with a focus on studies that used pQCT.

1.2.5.4.4.1 Cross-sectional Studies

Eckhard Schoenau's group at the University of Cologne in Germany may be considered the pioneers of pediatric pQCT research. Since their first pQCT study in 1996 (324) this group has contributed a great deal to our

understanding of the functional muscle-bone unit in children and have highlighted the value of pQCT as a research tool. Initially, Schoenau (324) used the XCT-900 to evaluate the influence of muscle force on bone strength at the distal radius (20% site) in 168 males and females aged 3 to 62 years. Bone strength was estimated with a bone strength index (BSI) as the product of Z and CoD. Both BSI and isometric muscle force (as assessed by dynamometry) demonstrated an age-dependent course and appeared to peak between 25 and 30 years of age, especially in males. In addition, there was a strong association between BSI and muscle force ($r = 0.87$) at all ages.

As a followup to the aforementioned study, Schoenau et al. (325) examined the influence of muscle force on properties of both trabecular and cortical bone at the distal radius in 14 healthy children aged 6 to 13 years. Whereas grip force correlated significantly with ToA, CoA and BSI ($r = 0.8$-0.9), there were no significant associations between grip force and CoD or TrbD. Based on these findings, the authors proposed that adaptation to muscle loads in the growing skeleton is dependent on changes in bone geometry rather than changes in density. Similar to the previous study, these results are limited by the questionable accuracy of cortical bone measurements at the distal radius due to the thin cortical shell (143). Despite this limitation, these early pQCT studies provided valuable insight to the functional muscle-bone unit and mapped future directions for pediatric pQCT trials. There is a need for comparable both cross-sectional and prospective exploratory studies in the lower limbs.

A subsequent study assessed a much larger sample of children and adults (318 children, aged 6-22 yrs; 336 parents) who were participants in the DONALD study (Dortmund Nutritional and Anthropometric Longitudinally Designed Study) (326). In order to examine the influence of puberty on MCSA and CoA at the radial shaft (65% site), boys and girls were compared based on Tanner stage. Again, a strong correlation ($r = 0.77$) was observed between CoA and MCSA in all children, adolescents and adults. However, the authors noted that at Tanner stage 3, the ratio of CoA to MCSA was significantly greater in girls. Similar results were obtained when the ratio of radial shaft BMC (by pQCT) to MCSA was compared across Tanner stages and between sexes in the same cohort (327).

These pQCT findings complement earlier DXA studies that also described a sex difference in the muscle-bone relationship during puberty. Originally described by Ferretti and colleagues (200), and repeated by Schiessl et al. (328) using cross-sectional data from Zanchetta et al. (329), the ratio of total body BMC to lean body mass has been shown to be greater for females after puberty. One explanation put forward to explain this difference is that sex hormones, specifically estrogen, may affect the mechanostat setpoint (54). This theory, and evidence surrounding it, was recently discussed in detail by Jarvinen et al. (330). In brief, rising estrogen levels during puberty may lower the (re)modeling threshold and in turn sensitize the bone adjacent to marrow to mechanical loading. This would result in increased endocortical apposition (89). From an evolutionary perspective, the estrogen-induced "packing" of bone into the female skeleton during puberty may serve to fill a calcium reservoir that is needed for reproduction (330). As discussed, the postulated endocortical (or endosteal) apposition may in fact be consolidation of cortical bone that cannot be adequately described by planar imaging techniques (212).

Evidence also suggests that the muscle-bone relationship may be region and site-specific. Recent advances in magnetic resonance imaging (MRI) technology have allowed regional muscle mass and whole bone cross-sectional area to be quantified (331). Heinonen and colleagues (332) employed this technique to assess the muscle-

bone relationship at the tibial midshaft in growing girls. A unique aspect of this study was the division of the tibial cross-section into three anatomical sectors (posterior, anteromedial, anterolateral). Although ToA and total MCSA were strongly correlated, the only significant correlation between CoA and MCSA was observed in the anterolateral sector. Further, CoA and MCSA in this sector were significantly correlated with ground reaction forces during a side-to-side jump. These results highlight the region-specificity of the muscle-bone relationship in the lower limb; however, it is not clear how this relationship may change during growth or following an exercise intervention.

Finally, a recent HSA study in 40 overweight (body mass index [BMI] > 85th percentile) and 94 healthy weight (BMI ≤ 85th percentile) children and adolescents aged 4-20 years demonstrated the importance of assessing indices of muscle force separately from total body weight or fat mass (333). At the femoral shaft and narrow neck regions of the proximal femur, overweight subjects had 11% and 13%, respectively, higher estimated bone strength (section modulus) than healthy weight subjects when adjusted for height, maturation and sex. However, when lean mass was added to the regression model, femoral shaft and narrow neck bone strength were similar between overweight and healthy weight subjects. Total body fat mass did not contribute significantly to these models. Thus, in accordance with mechanostat theory (30,31), it is important to interpret estimated bone strength in the context of dynamic loads (indices of muscle force) rather than static loads represented by body weight.

1.2.5.4.4.2 Longitudinal Studies

Few longitudinal studies have attempted to describe the changes in the muscle-bone relationship during growth (24,130,219,334). Ruff (219) used upper and lower limb radiographs from a sample of 20 subjects who were measured on average 34.5 times from near birth through late adolescence. Section modulus was estimated from radiographic humeral and femoral diaphyseal breadth measurements assuming a cylindrically shaped section. Muscle breadths were also measured radiographically at the mid femur and at the maximum width of the humerus. In this sample, there was a marked sex difference in the muscle-bone relationship over the entire age range which was more pronounced in the upper limb (219). In males, growth in humeral muscle size was highly correlated with change in humeral strength, while in females the two were less closely related. Significant sex differences were also documented for the femur; however, they became nonsignificant after controlling for body size (body weight x bone length). These findings suggest that muscular strength has a less pronounced effect on femoral bone strength which may be explained by the significant influence of body size on the weight-bearing lower limb (219). Although these findings provide strong support for the importance of mechanical factors in the development of bone strength, they are limited by the use of planar techniques.

Recently, Rauch and colleagues (334) used longitudinal data from the University of Saskatchewan PBMAS to test the mechanostat hypothesis that increasing muscle force drives the development of bone strength during growth. Total body lean mass (LBM) and total body BMC were used as surrogates of muscle force and bone strength, respectively. As illustrated in Figure 1-17, PHV preceded the peak in LBM by an average of 0.30 years in boys and by 0.39 years in girls. In turn, the peak in LBM preceded the peak in BMC accrual velocity by an average of 0.36 years in boys and by 0.51 years in girls. Similar relationships were observed in the upper and lower extremities

in both sexes. Additional regression analyses revealed that of sex, PHV and peak velocity for LBM (PVLBM), PVLBM was the only independent predictor of peak velocity for BMC accrual accounting for 40 and 60% of the variance. Although these results provide only an approximation of the muscle-bone relationship, they are in agreement with the mechanostat theory that muscle development precedes bone development during puberty.

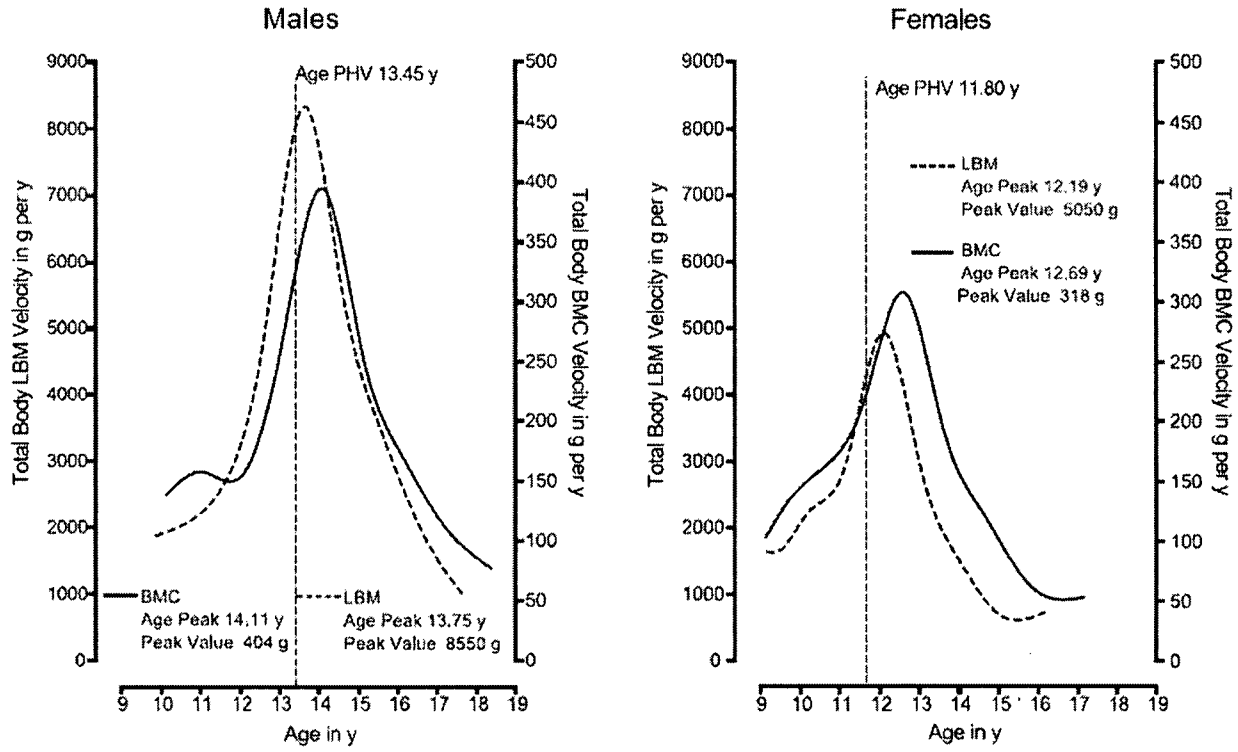


Figure 1-17. Velocities of total body lean body mass (LBM) and total body bone mineral content (BMC) velocity during puberty in males and females. From Rauch et al. (334) with permission from Elsevier.

The PBMAS data was also used to address the mechanostat hypothesis (54,335) that based on greater muscle mass and force in boys before PHV (336) bone strength should also be greater in boys than girls before PHV (130). As discussed, femoral neck CSA per unit lean mass was greater in girls than boys 2 and 3 years after PHV which would suggest greater axial bone strength in girls than boys (130). However, the authors argue that this sex difference has little mechanical relevance for the femoral neck where bending forces dominate the loading history (130). In contrast to the CSA findings, Z per unit lean mass was significantly greater in boys than girls at all biological ages due to boys' greater subperiosteal width (130). Although this finding agrees with mechanostat theory that estrogen may only alter the mechanostat setpoint on the endosteal surface next to bone marrow and not on the periosteal surface (89), the authors suggest that because the sex difference in Z was small and close to the error of measurement it was not biologically significant (130). It is interesting to note, however, that the sex difference was consistent across all biological ages. It is likely that an accurate picture of sexual dimorphism in femoral neck bone strength cannot be obtained with HSA due to the underlying limitations of planar DXA technology.

To date, only one prospective pQCT study has evaluated the muscle-bone relationship during growth (24). Using 20-month followup data from the Healthy Bones Study II (HBS II) (8,9,261-263), we assessed changes in two bone-muscle strength indices (BMSI) for the tibial midshaft in 128 early, peri- and post pubertal boys and girls. Bone-muscle strength indices represent the strength of bone relative to its mechanical environment and provide a means to compare bone strength in groups where body size and muscle mass differ. As discussed, the tibia is subject to both compressive and bending stresses. Thus, we calculated a BMSI for compression as the ratio of CoA to MCSA (CoA/MCSA) and a BMSI for bending as the ratio of lever arm-adjusted section modulus [Z/(tibial length/2)] to MCSA. Based on the results of Schoenau and colleagues (326,327), girls would be expected to demonstrate an increase in both BMSIs over the 20-months and have higher values than boys for both ratios. However, our results did not provide support for the theory of estrogen-mediated changes in the mechanostat threshold. Both early and peripubertal girls experienced a slight decrease in BMSIs, while BMSIs were maintained in postpubertal girls (Figure 1-18). Further, comparisons between sexes within each maturity group showed a significantly greater increase in BMSIs in early- and peripubertal boys compared with early- and peripubertal girls. Although our findings were limited by the cross-sectional comparisons within maturity groups and different criteria used to assess maturity in boys and girls, they do provide insight to the muscle-bone relationship in the lower limbs during puberty. Differences between these results at the tibial midshaft and those of Schoenau et al. (326) at the radius may reflect site-specificity of the muscle-bone relationship or may be a function of differences in study design. There is a need for prospective pQCT studies similar in design to that of the Saskatchewan PBMAS to clarify the maturity- and sex-specific development of the muscle-bone relationship in the upper and lower limbs.

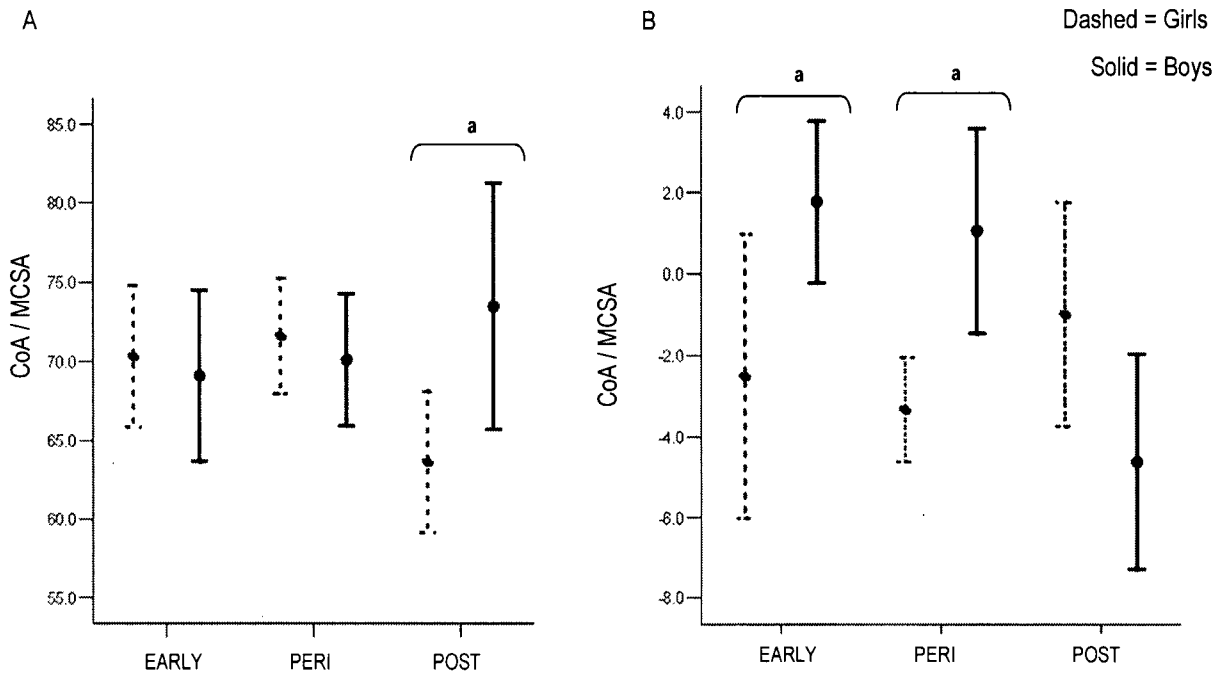


Figure 1-18. Baseline (A) and 20-month absolute change (B) values for cortical area to muscle area ratio (CoA / MCSA, bone-muscle strength index for compression) for girls (dotted lines) and boys (solid lines) across early

pubertal (EARLY), peri-pubertal (PERI) and post-pubertal (POST) maturity groups. Bars indicate 95% confidence intervals. (a) Boys > Girls, $P < 0.05$. Adapted from Macdonald et al. (24) with permission from Elsevier.

1.2.5.4.5 Effects of Exercise on the Functional Muscle-Bone Unit during Growth

The strong biomechanical link between muscle and bone suggests that increased muscle size, strength or force due to physical activity would lead to greater strain on bone and a resultant increase in bone mass, size and strength (307,337). However, there is little evidence to support the hypothesis that an exercise-induced increase in muscle size, strength or force directly influences bone adaptation to loading during growth. As I will discuss in more detail in Section 1.2.6, several HSA studies in children have shown how the relationship between physical activity and bone strength during growth is mediated by estimated muscle force (i.e., total body lean mass) (135,338,339), but they do not provide evidence of a cause-effect relationship. Similarly, in a recent cross-sectional MRI study, Daly et al. (340) investigated differences in the muscle-bone relationship between the playing and non-playing arms of 47 competitive female tennis players (aged 8 to 17 years). Similar to other studies of racquet sport players, muscle size and bone mass, size and strength were greater in the playing arm. Further, percent side-to-side differences in muscle area were positively associated with the percent side-to-side differences in BMC, CoA, ToA and polar moment of inertia. However, in regression analysis side-to-side differences in muscle area accounted for only 12-16% of the variance in side-to-side differences in bone parameters. This suggests that other factors associated with loading may contribute to skeletal adaptations to exercise. The effect of exercise on the muscle-bone relationship in children has yet to be studied prospectively.

1.2.6 Physical Activity and Bone Health in Children

As discussed in Section 1.2.2.2 mechanical loading provides a significant osteogenic stimulus to the immature (animal) skeleton. The relationship between physical activity and bone health during human growth has been reviewed extensively (6,181,341,342) and it is clear that the same principles of adaptation observed in animal studies hold true in the human skeleton. To date, the majority of studies that evaluated the effects of physical activity on the growing skeleton used DXA and thus, much of the existing literature focuses on the relationship between physical activity and peak bone mass. Although the use of imaging modalities such as pQCT and programs such as HSA are becoming more widespread, there are still only a handful of studies that assessed the relationship between physical activity and bone geometry, density and estimated strength indices in children using cross-sectional (135,338,343-345) or longitudinal (339) data or controlled intervention trials (8,11,13,27,134,346,347).

In this section I first briefly discuss the measurement of physical activity in children, in particular the Physical Activity Questionnaire for Children (PAQ-C). Next I review cross-sectional and prospective studies that either used pQCT to compare bone geometry, density and strength between athlete and non-athlete populations or to evaluate the role of physical activity as a determinant of cortical and trabecular bone properties in the growing skeleton. Finally, I discuss 6 physical activity intervention trials that evaluated the bone structural response to increased activity using either pQCT or HSA.

1.2.6.1 Measurement of Physical Activity in Children

Accurate methods assess children's physical activity are essential to determine current levels of activity, describe the relationship between physical activity and health outcomes and assess the effectiveness of interventions designed to increase physical activity (348,349). Physical activity is "bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above the resting level" (350). Based on this definition, the criterion standards for physical activity assessment are direct observation, doubly labelled water (DLW) and indirect calorimetry (348). Unfortunately, these methods are not practical for large studies as they require expensive equipment (DLW, calorimetry) and are associated with high researcher burden (direct observation) (351). Therefore, a wide range of methods have been developed to *estimate* a child's energy expenditure. These include objective measures such as heart rate monitoring, accelerometry and pedometry and subjective measures such as self-report questionnaires (348). Many of the objective measures are also inappropriate for large scale field research projects due to high costs and potential for subject reactivity. Further, it is difficult to determine the most appropriate method for research as many of these methods have not been validated against a gold standard (351). In addition, one must consider the strengths and weaknesses of each method, the size and characteristics of the study population and the specific research objectives. Ultimately, the method chosen should be valid, reliable, practical and nonreactive (352). Self-report instruments are most commonly used to assess children's physical activity levels (353). This is likely due to the low costs, low researcher burden, relatively quick administration time and thus, the ability to measure large numbers of children in a short time period (354).

This thesis will focus on one self-report questionnaire, the Physical Activity Questionnaire for Children (PAQ-C), which has been used previously in several prospective studies including the University of Saskatchewan Bone Mineral Accrual Study and the UBC Healthy Bones Studies (5,10,262,263).

1.2.6.1.1 Physical Activity Questionnaire for Children

The PAQ-C is a self-administered 7-day recall questionnaire that was designed to assess habitual MVPA in children aged 8-14 years participating in the 6-year University of Saskatchewan Bone Mineral Accrual Study (5,354). It was developed through a multi-step process that included item modification based on feedback from students, research assistants and item analysis. The final questionnaire consisted of ten items, nine of which are used to calculate a summary activity score. The other question assesses whether the child was sick in the previous week, or was prevented from normal activity as a result of other events. Within each PAQ-C item, physical activity is described as "sports, games, or dance that make your legs feel tired, or make you sweat", and all items are scored on a 5-pont scale (1 = low activity to 5 = high activity, continuous scale). The PAQ-C has since been modified to include an estimate of time per activity session (item 1) as well as involvement in extracurricular activities (sports, music lessons, tutoring, language lessons, etc.), the number of nights per week spent in organized sporting activities, and the number of hours of television watched and/or video/computer games played per day (355).

The PAQ-C has been validated against other self-administered questionnaires, teacher rating, uniaxial accelerometer counts (Caltrac), fitness test (step test) and interview-assisted recall (r = 0.28-0.63) (356). The

moderate correlation between the Caltrac and the PAQ-C (r = 0.39) is similar to correlations found with other self- and interview-administered questionnaires (357). The lack of strong association in validation studies of self-report is attributed to limitations in memory and recall skills, particularly in young children (less than 10 yrs), overestimation of physical activity and bias due to social desirability (348,357,358). A further limitation of the PAQ-C is that it does not discriminate between specific activity intensities (i.e., moderate and vigorous). Despite these limitations, the PAQ-C is a cost- and time-effective instrument that is useful in studies of large-scale populations.

However, the PAQ-C was a reliable means to assess physical activity levels when administered several times during one school year. Crocker and colleagues (354) found acceptable levels of test-retest reliability for both girls (r = 0.82) and boys (r = 0.75) aged 9 to 14 years after one week. Further, when the questionnaire was administered during the fall, winter and spring seasons, correlations were greater than 0.80 for the average of two or three responses. Similarly, across the 6 PAQ-C measurements for the Healthy Bones Study (355) the reliability improved for both girls and boys when the average of multiple assessments was used (single assessment: r = 0.34-0.59; multiple assessments: r = 0.75-0.90).

Crocker et al. (354) also noted that the PAQ-C was a sensitive means to detect physical activity differences between boys and girls, and differences across seasons. This feature is especially relevant as a substantial body of literature supports both seasonal (359) and sex (360,361) differences in physical activity. Currently, the PAQ-C is unable to discriminate between group activity levels; however, this has been identified as an area to examine in future (356).

1.2.6.2 Cross-sectional Studies in Children – General Physical Activity

Few studies have investigated the relationship between general physical activity and bone geometry or strength during growth using HSA or pQCT. In the Iowa Bone Development Study, Janz and colleagues (135) used both accelerometry and parental report to determine the relationship between physical activity and bone geometry (CSA, Z) as estimated with HSA in 467 young children (mean age 5.2 yrs). This study represents the first time accelerometers were used to determine the relationship between physical activity intensity and bone structural variables in children. After adjusting for age, weight and height, participation in vigorous (≥ 2818 accelerometer counts) activity was positively correlated (r = 0.19 to 0.32) with CSA and Z at each of the three regions of the proximal femur in boys and girls. Moderate (≥ 527 counts) activity was also significantly associated with CSA and Z but the relationship varied between sexes and sites. In contrast, sedentary activity (< 152 counts) was negatively associated with CSA and Z at each region in girls only. When the relationship between vigorous activity and bone geometry was explored further in linear regression models, vigorous activity was found to explain, on average, 7% of the variance in CSA and Z at each region in boys and girls. When lean mass was included in the regression model as an estimate of muscle force the amount of variance explained by vigorous activity decreased to approximately 4%. Thus, lean mass explains some, but not all, of the relationship between physical activity and bone geometry (135). Given that current physical activity guidelines for children include both moderate and vigorous physical activity (362), it would be interesting to know how much, if any, of the variance in CSA and Z is accounted for by moderate activity.

Recently, Wang et al. (344) used pQCT to evaluate the influence of leisure-time physical activity on cortical bone properties at the tibial diaphysis (60% site) in 242 pre- and early pubertal Finnish girls. A physical activity score was calculated for each participant from a self-report questionnaire. The score incorporated the frequency, estimated intensity and duration of weekly physical activities as well as an indication of whether the activity was weight-bearing or not. Girls were classified as low-, moderate- or high-active based on their score and were also categorized into low- or high-impact physical activity groups according to whether their "favourite" activity was weight-bearing. In the prepubertal girls, there was no consistent trend in the differences in tibial bone properties between the three activity groups. High-active girls had a 7% larger ToA than moderate-active girls and a 2% greater CoD and 4% greater CTh than low-active girls, but low-active girls had larger ToA and CTh than moderate-active girls. When the prepubertal girls were compared based on participation in weight-bearing activity, all bone outcomes were significantly greater in the high-impact group. There were no significant differences in any cortical bone properties between activity groups of early pubertal girls. Based on these findings, the authors suggest that prepuberty may be the most beneficial time for physical activity to effect bone development. It is interesting to note, however, that there was a trend for lean mass to be greater in the low-active group of Tanner II girls. Therefore, an association between physical activity and cortical bone properties may have been observed if lean mass had been controlled for in the analysis. Alternatively, differences between groups may have been confounded by inaccuracies associated with the questions and calculations used to determine the activity score since these had not been used in previous studies, nor had they been validated.

Similar associations between physical activity and cross-sectional bone properties have not been reported in boys. However, a recent population-based study of 1068 Swedish men (mean age 19 yrs) found that men who began participating in regular physical activity before age 13 had significantly greater CoA at the tibial shaft (25% site) and trabecular density at the distal tibia (4%) site than boys who began participating in physical activity at age 13 or later. This result is similar to those reported from pQCT studies of male (363) and female racquet-sport athletes (153). I discuss these studies in more detail in Section 1.2.6.4.

1.2.6.3 Longitudinal Studies in Children – General Physical Activity

With the exception of the few intervention studies discussed in Section 1.2.6.6, there have been no prospective pQCT studies of the relationship between physical activity and bone geometry or strength in healthy children. Results from the Saskatchewan PBMAS provided conclusive evidence that active children (with PAQ-C activity scores in the highest quartile) have greater absolutes values for DXA-derived bone mineral content and greater bone mineral accrual than their less-active peers (5).

To followup the work of Bailey et al. (5), Forwood et al. (339) applied HSA to proximal femur scans of the PBMAS cohort to investigate the influence of physical activity on femoral neck bone strength during adolescence. Children were classified as *physically inactive* if their age-sex-specific z score for the PAQ-C fell below the lowest quartile, *physically active* if their z score fell in the highest quartile and of *average activity* if their z score fell between the lowest and highest quartile. To account for repeated measures within individuals and individual growth

characteristics sex-specific hierarchical random-effects models were created using a multi-level modeling approach. Within these models maturation was controlled for using age at peak height velocity. In both boys and girls, physical activity was a significant predictor of narrow neck CSA and Z but not SPW. Differences in Z between inactive and active boys and girls are illustrated in Figure 1-19. It is not clear whether differences between activity groups were significant for all biological age groups. Importantly, when leg length and leg lean mass were entered into the random-effects models (instead of height and weight), the significant effects of physical activity were no longer apparent. Similar to the results of Janz et al. (135) discussed above, the effects of physical activity on bone strength are likely mediated by the relationship between physical activity and lean mass, which provides an estimate of muscle force.

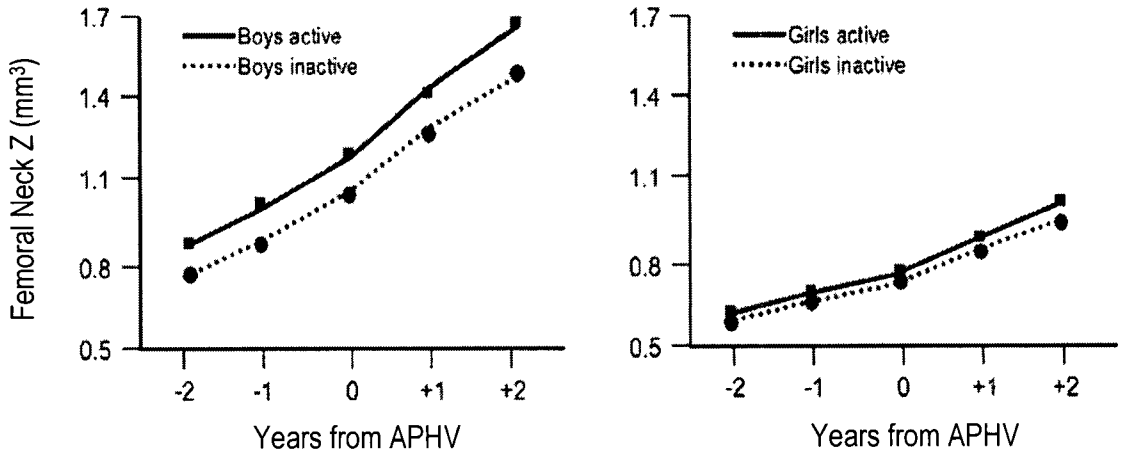


Figure 1-19. Growth curves for femoral neck (narrow neck region) section modulus (Z) comparing 17 active boys to 17 inactive boys (A) and17 active girls to 17 inactive girls (B). Values for Z represent adjusted means (height, weight) and are plotted against biological age groups (years from age of peak height velocity, APHV). Adapted from Forwood et al. (339) with permission from Elsevier.

1.2.6.4 Cross-sectional Studies in Adults - Racquet-sport Athletes

Racquet-sport athletes provide an excellent model to study the relationship between physical activity and bone health. Loaded-to-unloaded arm comparisons reduce the influence of confounding factors such as genetics, hormones and nutrition. Several unilateral control studies (153,363-365) conducted at the UKK Institute in Finland contributed significantly to the bone and physical activity literature and advanced our understanding of how the skeleton adapts to mechanical loading.

Initially, DXA was used to compare BMC and estimated bone strength (CSMI, Z) at the humerus and radius in players who had started their training in childhood (young starters) or before menarche and those who began their careers later in adulthood (old starters) or after menarche (364,365). Kannus et al. (364) divided players into groups according to the number of years before or after menarche that their training began. Among all players, the side-to-side difference in BMC at all measured sites was significantly greater than controls. However, women who began training before or at menarche had a two to four times greater side-to-side difference in BMC at the humerus and

radius than women who began their training 15 years after menarche. As a followup to this study, Haapasalo et al. (365) evaluated side-to-side differences in BMC and estimated CTh, CSMI and Z in 67 male and female tennis players and 57 sedentary controls. The female players were either young or old starters whereas all male players were young starters. Compared with controls, the players' relative side-to-side differences in BMC and estimated geometry and strength were significantly larger (+6 to +45%). Further, the side-to-side differences were much larger in young starters (+12 to +45%) compared with old starters (+3 to +12%). Together these findings suggest that intense physical activity, if begun during childhood or adolescence, has a pronounced positive effect on the growing skeleton.

With the advent of pQCT, the UKK group was able to further investigate skeletal adaptations in adult racquet-sport athletes by focusing on side-to-side differences in bone geometry and estimated strength indices. In their first pQCT study, Haapasalo et al. (363) compared 12 former national-level male tennis players (25-35 yrs) who began their training during childhood with 12 age-matched controls. They measured trabecular and cortical bone properties at the distal, shaft and proximal sites of the radius and humerus and found that the significantly greater side-to-side difference in BMC and estimated bone strength (BSI, minimum and maximum moments of inertia: I_{min}, I_{max}) in the players was due to enlarged bone area (ToA, CoA) and not greater (volumetric) bone density (CoD, TrbD). The side-to-side differences in bone geometry (12-32%) and strength (23-67%) in the players were significantly greater than those for controls (geometry: 0.5-6%; strength: 5-16%). In the players, a side-to-side difference in CoD was only observed at the distal humerus where CoD was slightly greater (2%) in the non-playing arm.

Similar findings were reported for female racquet-sport athletes who began training before or at menarche (young starters) (153). Compared with athletes who started training after menarche (old starters), young starters demonstrated greater side-to-side differences in humeral shaft ToA, CoA and CTh (13-20%), which in turn resulted in greater estimated bone strength of the playing arm (+26%) as measured by the torsional bone strength index (BSIt, density-weighted polar section modulus) (Figure 1-20). There were no side-to-side differences for CoD in young starters. Similar adaptations were observed in the old starters; however, the magnitude of the side-to-side difference in BSIt was significantly smaller (+11%) due to less periosteal expansion (+2.6%). At the distal radius, a significant side-to-side difference was found for total BMC (9%) and TrbD (+5%) in the young starters compared with controls, but not in ToA. Although these findings from the upper limbs do not represent the entire skeleton, they do suggest that during growth the immature skeleton adapts to increased loading mainly through periosteal expansion at shaft sites and through increased TrbD at distal sites. As discussed, these adaptations serve to improve bone bending/torsional and compressive strength at the shaft and distal sites, respectively, according to the type of load incurred at each site (62,64,71).

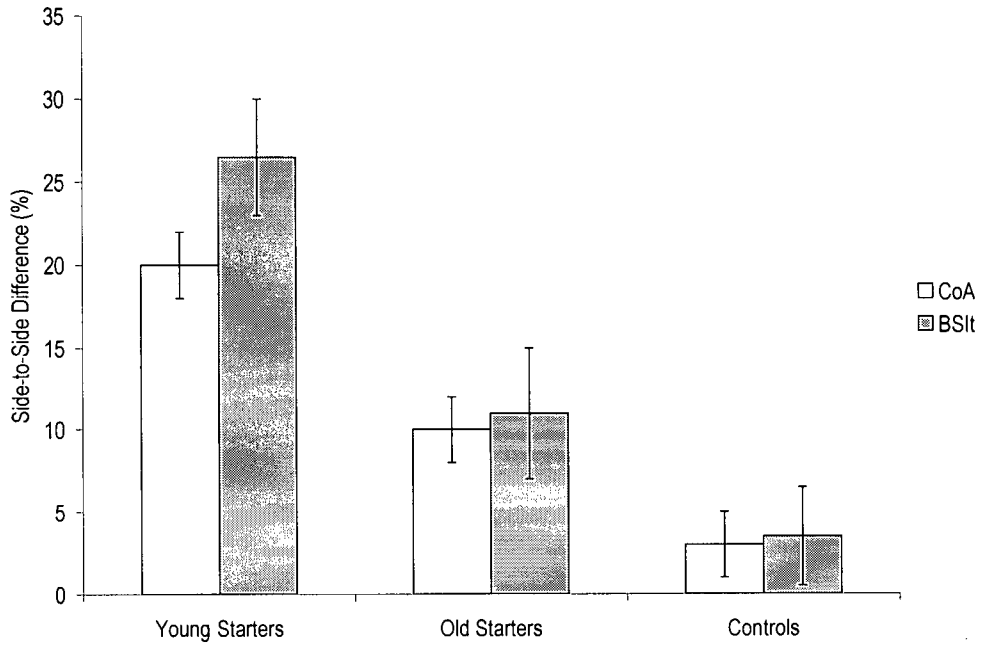


Figure 1-20. Side-to-side differences (%) in cortical area (CoA) and torsional bone strength index (BSIt) at the humeral midshaft in young starters (began training before menarche), old starters (began training after menarche) and controls (no training). Bars are 95% confidence intervals. Adapted from Kontulainen et al. (153).

1.2.6.5 Cross-sectional Studies in Children – Athlete Populations

The literature provides few cross-sectional comparisons of bone structural adaptations of loading between child athletes and non-athlete controls. Most recently, Ward and colleagues (345) conducted a study with 44 young male and female pre-pubertal gymnasts and 42 controls of a wide age range (5-12 yrs). Peripheral QCT was used to assess bone geometry, density and estimated strength (SSI) at the distal radius (4% of forearm length), radial midshaft (50% of forearm length), distal tibia (10 mm from the distal metaphysis) and proximal two-thirds tibia (65% of tibial length). At both shaft sites, gymnasts had 5-13% greater SSI than controls and this strength advantage was a result of a 5-8% greater CoA with no differences in CoD at either shaft site. Gymnasts also had a significantly greater MCSA (4%) than controls at the proximal two-thirds tibia. In contrast, at distal sites of the radius and tibia, gymnasts had 5-21% greater ToD and TrbD than controls, but bone areas were not significantly different between the two groups. These findings are consistent with the aforementioned studies of racquet-sport players and again highlight the site-specific differences in bone adaptation (within and between bones) according to the loads experienced at the distal and shaft sites.

Similar site-specific differences in bone structure were observed by Faulkner et al. (338) in an HSA study of the proximal femur in 30 premenarcheal gymnasts and 20 age-matched controls. At both the narrow neck and shaft sites of the proximal femur, size-adjusted bone bending strength (Z) was significantly greater for gymnasts than controls. However, geometric adaptations that contributed to the greater strength varied between the regions of interest at the proximal femur. At the narrow neck region, gymnasts' CSA was larger due to a smaller endocortical

diameter. Despite a smaller subperiosteal width in gymnasts, the distribution of mass was sufficient to confer greater bending strength at this site. In contrast, the gymnasts' greater bending strength at the femoral shaft was a result of a greater subperiosteal width and moment of inertia. This site-specificity may reflect differences in loading conditions between the narrow neck and femoral shaft, but it must be noted that HSA is unable to evaluate bone geometry outside of the image plane. The strength advantages observed in the gymnasts disappeared after lean mass was controlled for. Consistent with HSA findings discussed previously (135,339), these results provide further support for the strong biomechanical link between physical activity, muscle forces and bone strength.

In addition to pQCT and HSA, magnetic resonance imaging (MRI) has also been used to evaluate the relationship between physical activity and bone cross-sectional geometry. Bass et al. (343) used MRI to evaluate side-to-side differences in ToA, CoA and CavA at the distal and midshaft sites of the humerus in 47 competitive female tennis players aged 8-17 yrs. To determine if maturity status influenced the bone response to loading, the players were classified as either pre-, peri- or postpubertal according to Tanner stage. In the prepubertal group side-to-side differences in CoA were associated with greater periosteal expansion (larger ToA) whereas in the postpubertal group side-to-side differences were associated with greater endocortical contraction (smaller CavA). The side-to-side differences in bone strength (measured by the polar second moment of inertia) appeared to be greater among the prepubertal girls, but were similar between peri- and postpubertal girls. The authors suggest that because endocortical expansion predominated during the later stages of puberty that no additional gains in bone bending strength were achieved. Unfortunately, due to the cross-sectional design of this study and the lack of comparison between side-to-side differences in control participants it is difficult to accurately assess changes in bone geometry that occurred as a result of growth and those that occurred as a result of physical activity.

1.2.6.6 Exercise Interventions with Children

To date, most intervention trials with children have used conventional DXA measures of BMC and aBMD to evaluate the bone response to increased physical activity. Results from the UBC Healthy Bones Studies (HBS I and II) (8-10,262,263) represent a significant contribution to the pediatric bone and exercise literature. In addition to being the first (and longest, 20-months) school-based intervention to implement a bone-loading program within the physical education curriculum, HBS II identified a "window of opportunity" during puberty when bone is highly responsive to loading and demonstrated the effectiveness of a simple exercise program on gains in bone mass in Asian and Caucasian girls and boys during growth (8-10,262,263).

Most pediatric physical activity intervention studies are conducted in schools and there are a number of reasons why this is so. First, it is suggested that since children spend a significant portion of their formative years in school the school setting may provide the best opportunity to positively influence childhood physical activity behaviours (366). Second, schools cater to large and diverse numbers of children. This is advantageous from a public health perspective as it increases intervention reach (367). Finally, schools typically have facilities and resources required to provide physical activity opportunities (368). Therefore, activity programs and/or exercises that

are part of an intervention study can be implemented within physical education (PE) classes or can use existing activity space and equipment within the school.

In randomized trials of school-based interventions, the school (cluster) is most often the unit of randomization, whereas the children are the unit of analysis. This design is advantageous as it prevents contamination that would occur if intervention and control children attended the same school. However, in this situation, children within a school cannot be regarded as independent observations, and as a result the effective sample size is less than the total number of individual participants (369,370). The reduction in sample size depends on the average cluster size and the degree of correlation between clusters (369). The correlation between clusters is known as the intracluster (or intraclass) correlation coefficient (ICC or ρ) and is the proportion of the total variance of the outcome that can be explained by the variation between clusters (371). Statistical software and methods are available to adjust for the ICC in an analysis (372). However, of the school-based studies discussed below, those that randomized by school (8,134,346) did not account use appropriate statistical techniques. As a result, the variability of the intervention effect may be underestimated (372).

Only 7 intervention studies have used pQCT, HSA or estimates from DXA scans to describe changes in bone geometry, density or estimated strength that occurred in response to an exercise regime or physical activity program (8,11,13,27,134,346,347). The results of these studies are summarized in Table 1-2. In addition, one 12-month randomized controlled trial used pQCT to evaluate the effects of calcium supplementation and physical activity on cortical bone properties at the tibial shaft (20% site) in 3-5 year old children (288). Unfortunately, 12-month change in pQCT outcomes could not be evaluated in that study due to poor quality (movement artefacts) of pQCT scans at baseline.

1.2.6.6.1 Exercise Interventions with Prepubertal Children

Two of the 6 studies described in Table 1-2 involved boys who were prepubertal at baseline (8,346). It is difficult to compare results between these studies due to differences in the: 1) change in maturational status of the cohort, 2) type and length of the intervention and 3) techniques used to assess changes in bone structure. These factors may help to explain why the observed structural adaptation to increased loading differed between the two studies. In the 8-month study of Bradney et al. (346) intervention boys demonstrated a greater gain in cortical thickness compared with control boys. However, this was a result of a greater decrease in endocortical (medullary) diameter rather than a greater increase in periosteal diameter as was observed in intervention boys in the HBS II study (8). At diaphyseal sites such as the mid-femur, resistance to bending forces is achieved through increased periosteal bone formation (76). In addition, increasing testosterone levels in boys during puberty may stimulate periosteal expansion (373). Thus, the surface-specific response to increased loading may be related to maturational stage and the associated growth velocity of each bone surface. It is possible that the advanced maturational stage of the boys in the 20-month HBS II study (77% advanced to early puberty) may have conferred a readiness for adaptation at the femoral neck, whereas boys in the Australian study remained prepubertal at followup and had not yet experienced rapid growth-related changes at the periosteal surface.

Alternatively, the type of loading associated with each intervention may explain the differences in structural adaptation. The activities performed by the Australian boys involved essentially normal loading but increased magnitude (346). The authors suggest that these stresses may not have been sufficiently unusual in distribution to increase strains at the periosteal surface and that opposing muscle contraction may have generated axial stress that in turn would increase endocortical apposition (346). In contrast, the high-impact jumping circuit in the HBS II study was designed to provide dynamic strains to the growing skeleton in order to maximize the osteogenic potential of the intervention (8). This exercise program may have been more effective for increasing strains at the periosteal surface.

Finally, it is possible that the ruler function used by Bradney et al. (346) may lack the precision necessary to detect small changes in periosteal dimensions. In addition, neither the DXA ruler function nor HSA are able to evaluate structural changes in other planes that may be important to overall bone strength. This highlights the need for 3-dimensional imaging technologies to assess bone structural and surface-specific adaptations that contribute to bone strength.

Most recently, Valdimarsson et al. (347) investigated the effects of increased general physical activity on bone mineral accrual and estimated bone width in grade 1 and 2 girls aged 7 to 9 yrs. Unlike previous studies, this 12 month intervention did not involve any activities designed to be osteogenic. Instead, the one intervention school provided daily PE (40 minutes/day) which included general activities as part of the Swedish school curriculum (i.e., ball games, running and jumping). The control participants continued with their regular PE curriculum of 60 minutes/week. Although the intervention was effective for increasing lumbar spine BMC and estimated bone width of the third lumbar vertebrae, it had no effect on change in femoral neck BMC or bone width. Further, the lumbar spine results are questionable due to the significantly greater gain in fat mass in intervention girls. This may have resulted in an overestimation of changes in bone mass by DXA (126).

Interestingly, Valdimarsson et al. (347) suggest that because no additional resources were required and that the intervention could be led by classroom teachers, this type of intervention could "instantly be organized in all schools". In addition, they suggest that by continuing with regular PE, children would be more motivated to participate than if they had to perform repetitive jumping activities (347). These points are debatable for several reasons. First, daily PE may not be feasible in all schools due to limited access to the school gymnasium. Second, studies of children's activity levels in physical education suggest that less than 50% of class time is spent in moderate-to-vigorous activity (MVPA) (374,375). Factors contributing to low levels of MVPA in PE include low student motivation, poor teaching skills or lack of adequate resources, space, training, and administrative support for PE (374). Thus, if this type of intervention is to be implemented on a wide-scale it is likely that additional resources and teacher training would be required to ensure delivery of high-quality physical activity.

1.2.6.6.2 Exercise Interventions with Mixed-Maturity Cohorts

Exercise intervention studies that included children in distinct maturational categories at baseline identified the early pubertal years as a window of opportunity when osteogenic effects of exercise are magnified. In particular, exercise-induced gains in BMC and aBMD observed in the HBS II were specific to early pubertal girls while bone

mineral changes in prepubertal intervention girls did not differ from same-maturity controls (263). Few studies (11,27,134) have investigated maturity-specific changes in bone geometry or strength in response to increased loading.

As a followup to the work of MacKelvie et al. (263), Petit and colleagues (134) investigated whether structural adaptations (estimated with HSA) in response to the HBS II intervention would also be maturity-specific. Similar to the DXA findings, there was no significant difference in change between prepubertal intervention and control girls for CSA, CTh or Z at any of the three proximal femur regions. However, early pubertal intervention girls demonstrated greater gains in CSA, CTh and Z at the narrow neck than early pubertal controls. Significant bone structural adaptations in the early pubertal girls may reflect an interaction between increased estrogen levels and the bending forces associated with the specific jumps. Estrogen may promote bone formation on the endosteal surface in the presence of increased loads by lowering the theoretical mechanostat threshold (88). In contrast, estrogen may counteract the positive effects of exercise on the periosteal surface via activation of the ERβ receptor (189). It is not known if a similar maturity-specific window of opportunity exists at other skeletal sites.

Based on the results from studies of racquet sport athletes that demonstrated a 2-fold greater skeletal benefit of loading in women who began their training before menarche (364,376), Heinonen and colleagues (11) compared the bone response to a 9-month high-impact exercise intervention between pre- (Tanner stages 1-3) and postmenarcheal (Tanner stages 2-5) girls. Consistent with their previous investigations (364,376), high-impact exercise had a significant effect on BMC accrual in premenarcheal girls only. This finding provided further support for the concept that the premenarcheal period is a critical time during which the osteogenic potential of exercise is maximized. However, despite significantly greater gains in BMC at the lumbar spine and femoral neck (3 and 4%, respectively) in the premenarcheal exercising girls, they observed no group differences in CoD, CoA or BSI (density-weighted section modulus) at the tibial shaft (Figure 1-21) (11). Given the wide range of Tanner stages within the premenarcheal group, it is possible that the growth-related changes in bone size may have been large enough to mask the effects of the exercise stimulus in the lower limbs (11).

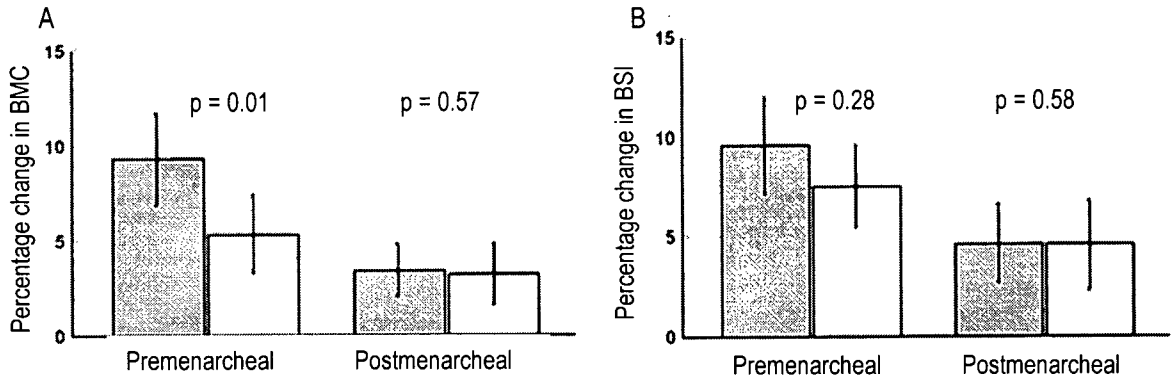


Figure 1-21. Nine-month percent change in femoral neck bone mineral content (BMC) (A) and tibial midshaft bone strength index (BSI) in pre- and postmenarcheal intervention (shaded bars) and control (white bars) girls. Significance values for group comparisons within the pre- and postmenarcheal groups are provided. Bars are 95% confidence intervals. Adapted from Heinonen et al. (11)

Johannsen and colleagues (27) attempted to identify a maturity-specific response to high-impact activity in both boys and girls. Compared with the aforementioned interventions, this study was unique by way of the novel jumping program employed. Intervention children performed 25 drop jumps per day from a 45 cm box, 5 days per week for 12 weeks. This program was designed based on results from animal studies that demonstrated significant gains in bone strength in growing rats with a minimum of 5 jumps per day (14). Despite the unique bone-loading program, this study is fraught with a number of methodological limitations. First, the authors aimed to compare the bone response to the intervention between pre-, peri- and pubertal children. However, due to the small overall sample size (n = 54) of both boys and girls, exclusion of 28% of baseline pQCT scans and the large variability in the age and maturity status of participants it would seem that this study was underpowered to detect a maturity-specific effect. Second, the intervention lasted only 12-weeks. Given that a complete bone remodeling cycle in children may take up to 4 months (29) and that an intervention period of at least 10 months is recommended to account for the bone remodeling transient (61), it would seem that a 3-month intervention period is insufficient. In light of these limitations, the noted gains in BMC and ToD (by pQCT) at the distal tibia (4% site) among pubertal children (Tanner stage 4 and 5) in the intervention group are difficult to interpret. A longer study with participants in a narrower maturational range is needed to determine the effectiveness of this jumping program.

The efficacy of a similar jumping program, Bounce at the Bell, was recently evaluated by McKay et al. (13). Children at intervention schools performed 10 high-impact countermovement jumps 3 times daily at the time of the morning, noon and afternoon bell for 8-months. Although this study was limited by the non-randomized study design, the results suggest that short bouts of high-impact activity separated by rest periods offer promise as a simple and cost-effective strategy to increase proximal femur bone mass in pre- and early pubertal children. The effects of Bounce at the Bell on bone structure in the pilot study were less clear possibly due to the small sample size of boys and girls. There is a need for a larger randomized controlled trial of Bounce at the Bell to determine the effectiveness of this program for increasing bone strength in boys and girls.

1.2.6.7 Exercise during Growth: Effects on Bone Later in Life

It is apparent that increased mechanical loading during growth has beneficial effects on both the material and structural properties of the skeleton. Whether these exercise-induced adaptations are preserved in the absence of ongoing intervention is currently a contentious issue (377). In addition, due to the logistics of conducting a large, long-term randomized controlled trial, it is not known (and may never be) whether enhanced bone structure during childhood contributes to reduced fracture risk (378). Several studies of former athletes suggest that vigorous activity during childhood contributes to the maintenance of skeletal health in both men (379,380) and women (381,382). In addition, sports-exercise history during adolescence predicts 16% to 22% of the variance in HSA-derived femoral neck and shaft bone strength in young adult women (383) although this relationship may be explained, in part, by lean mass (384). Finally, epidemiological data support the association between physical activity during childhood and adolescence and decreased fracture risk (380,385,386).

Of the pediatric intervention trials discussed, only the trial conducted by Heinonen et al. (11) assessed maintenance of the bone gains in a followup study (387). One-year after the end of the intervention, trainees demonstrated a 5% advantage in lumbar spine BMC accrual compared with controls and tended to have a greater gain in proximal femur BMC (2-3%). The tibial midshaft was not assessed in the followup study so it is not known if the slightly greater gains in CoA and BSI observed in the trainees after the 9-month intervention was maintained.

Several deconditioning studies in growing animals provide evidence that skeletal benefits achieved during training are lost in the absence of the exercise stimulus (118,388,389). However, when discussing the effects of "detraining" on skeletal health, it is important to consider the physical activity behaviours of children in the absence of intervention. There is a considerable body of evidence that supports the tracking of physical activity patterns from childhood through adolescence (390) and, although the correlations are generally low, also into adulthood (391,392). Therefore, active children who participate in a physical activity intervention will likely continue to be active once the program is stopped. Unfortunately, it is also a reality that activity levels among adolescents tend to decline, especially among girls (393). In order to curb this decline, it is imperative that physical activity promotion strategies be tailored towards children and adolescents so that we may attempt to instil positive, long-lasting health behaviours in this population. In addition, there is a need for simple, targeted bone-loading programs such as Bounce at the Bell, to become part of the regular physical activity program in elementary schools in order to optimize development of the growing skeleton.

Table 1-2. Physical activity interventions with prepubertal children and mixed maturity cohorts

First Author	Subjects and Design	Intervention	Statistical approach	Results
Bradney (346)	Subjects: BOYS, Caucasian n = 20 INT (10.4 yrs at baseline, all prepubertal) n = 20 CON (age, ht and baseline aBMD matched to INT boys) 2 schools randomly allocated to INT or CON DXA: Lunar DPX-L	**Program**: Extra weight-bearing physical activity (B-ball, weight training, aerobics, soccer etc) in addition to regular PE class **Frequency & duration**: 30 min, 3x/week, 8 months **Progression**: none stated	INT and CONT boys matched for age, sitting height, height and baseline aBMD Unpaired t-tests: 8-month changes different between groups Did not account for within school variance.	Femoral midshaft: **Peri diam**: NS **Endo diam**: INT – ↓ 9%, CON - +2.3% **CTh**: +6.4% **CSMI**: +2.4% (CON > INT) **Z**: +1.6% (CON > INT)
MacKelvie (8)	Subjects: BOYS, 44% Asian, Tanner stage 1 at baseline n = 31 INT n = 33 CON Randomized by school (stratified by number of participants) DXA: Hologic QDR 4500W with HSA analysis	**Program**: Classroom-based high impact jumping program **Frequency & Duration**: 10-12 min, 3x/week, 2 school years **Progression**: # jumps & height of jump (progressed through levels) advanced every 8-10 weeks Yr 1: 50 (baseline) to 100 (final) jumps Yr 2: 55 jumps (baseline) to 132 (final) jumps	Independent t-tests: baseline comparisons ANCOVA: 20-month change in DXA and HSA outcomes - covariates: baseline bone, change in height, final Tanner stage Bivariate correlations: body composition and bone bending strength Did not account for within school variance.	INT > CON: **NN CSA**: +2.5%, NS **NN SPW**: +2.6%, NS **NN CSMI**: 12.4%, $p < 0.05$ **NN Z**: +7.4%, $p < 0.05$ **NN ED**: + 2.9%, NS **NN CTh**: NS **IT CSA**: NS ($p = 0.07$) **IT SPW, CSMI, Z, ED**: NS **IT CTh**: NS ($p = 0.07$) **FS**: NS

Table 1-2 continued.

First Author	Subjects and Design	Intervention	Statistical approach	Results
Valdimarsson (347)	Subjects: GIRLS, Caucasian, Tanner stage 1 at baseline n = 53 INT n = 50 CON NOT randomized: 1 school assigned to INT, controls were volunteers from 3 neighbouring schools DXA: Lunar DPX-L version 1.3z	**Program**: Increased number of physical education classes. Classes included both indoor and outdoor general physical activity (i.e., ball games, running, jumping) **Frequency & Duration**: 40 min/day (200 min/wk) **Progression**: none stated	Univariate and multivariate ANCOVA: baseline age and annual increments in height and weight as covariates	INT > CON **TB BMC**: NS **LS BMC**: +4.7% **FN BMC**: NS **Leg BMC**: NS Bone width: **L3**: +2.9% **FN**: NS
Heinonen (11)	Subjects: GIRLS, Caucasian N = 58 Premenarcheal (25 INT, 33 CON, ~ 11 yrs at baseline) N = 68 Postmenarcheal (39 INT, 33 CON, ~14 yrs at baseline) NOT randomized: schools self-selected into INT group DXA: Norland XR-26; pQCT: Norland XCT 3000	**Program**: Jump training sessions, two- and one-foot jumps, used jump boxes, also did aerobic exercises **Frequency & Duration**: 50 min (20 min jumping), 2x week, 9 months **Progression**: Month 1: 100 2-foot jumps, no box Months 7-9: 150 two-foot and 50 one-leg box jumps (multidirectional)	ANCOVA: baseline values and age as covariates (within each maturity group) Individual BMC values obtained from the ROI were normalized by the length of the ROI	*Pre-menarcheal (INT>CON)*: **LS BMC**: + 3.3% **FN BMC**: + 4.0% **Troch BMC**: NS Tibia: 50% site **CoD, CoA, BSI**: INT ↔ CON *Post-menarcheal*: INT ↔ CON (at all sites)

Table 1-2 continued.

First Author	Subjects and Design	Intervention	Statistical approach	Results
Petit (134)	Subjects: GIRLS, 34% Hong Kong Chinese, 57% white N = 68 Prepubertal (43 INT, 25 CON, 10 yrs at baseline) N = 106 Early-pubertal (43 INT, 63 CON, 10.5 yrs at baseline) Randomized by school (stratified by ethnicity) DXA: Hologic QDR 4500 with HSA analysis	**Program**: Classroom-based high impact jumping program **Frequency & Duration** : 10-12 min, 3x/week, 7 months **Progression**: # jumps and height of jump (progressed through levels) - started with 50 jumps per session and progressed to 100 jumps per session	Separate analyses for each maturity group: ANCOVA (baseline wt, change in ht, Tanner Breast stage and sport nights) Did not account for within school variance.	*Prepubertal*: INT ↔ CON *Early-pubertal* (INT > CON): **NN BMD**: + 2.6% **IT BMD**: + 1.7% **NN CSA**: + 2.3% **IT CSA**: NS **NN CTh**: + 3.2% **IT CTh**: NS **NN ED**: NS **IT ED**: -1.4% **NN Z**: + 4.0% **IT Z**: NS **FS**: NS
Johannsen (27)	Subjects: GIRLS & BOYS, ethnicity not stated N = 26 CON (14 girls, 12 boys, 10.0 ± 5.1 yrs at baseline, 13 Pre, 7 Peri, 6 Post) N = 28 INT (17 girls, 11 boys, 10.3 + 5.3 yrs at baseline, 13 Pre, 5 Peri, 10 Post) Randomized (blocks of 2) by gender and age group DXA: Hologic 4500A ; pQCT: Stratec XCT 2000	**Program**: High-impact jumping program conducted in schools and childcare centres **Frequency & Duration** : 25 jumps/day, 5x/week, 12 weeks **Progression**: None stated (children jumped off 45 cm – high box, GRFs 4-5x BW	t-tests: baseline differences between INT and CON ANCOVA: baseline weight, sex, Tanner stage Least-square means & Tukey-Kramer HSD test: interaction of pubertal stage and intervention group (baseline wt, calcium, sex as covariates)	Main effects: DXA: **TB BMC**: INT > CON (~ 1%) **Leg BMC**: INT > CON (~1.5%) pQCT: NS Interaction effects (group x maturity): **Tib BMC** (4% site): p = 0.04 **LS BMC**: p = 0.10 **ToD** (4% site): p = 0.03 Intervention effect in pubertal group only (Tanner stage 4 or 5)

Table 1-2 continued.

First author	Subjects and Design	Intervention	Statistical approach	Results
McKay (13)	Subjects: Girls & Boys, 48% Asian N = 51 INT N = 73 CON (from HBS II study) 65% Tanner I at baseline, ~10 yrs of age 3 schools volunteered for the intervention DXA: Hologic QDR 4500W with HSA analysis	**Program**: "Bounce at the Bell" - simple jumping program (countermovement jumps) **Frequency & Duration**: 10 jumps, 3x/day, 8 months **Progression:** none	ANOVA: to compare baseline bone and descriptive variables and 8-month change in descriptive variables ANCOVA: 8-month change in bone variables - covariates: baseline bone, weight, change in height, final Tanner stage, PA load time	INT > CON: **TB BMC**: +0.9% (p = 0.004) **TB BA**: +1.4% (p = 0.036) **PF BMC**: +2.1% (p = 0.019) **IT BMC**: +2.7% (p = 0.017) **NN Z**: +3.3% (NS) **NN CSA**: +2% (NS) **NN CTh**: +1.2% (NS) No sex x group interactions

INT = intervention; CON = control; yrs = years; ht = height; aBMD = areal bone mineral density (g/cm^3); DXA = dual energy x-ray absorptiometry; Peri diam = periosteal diameter (mm); Endo diam = endosteal diameter (mm); CTh = cortical wall thickness (mm); CSMI = cross-sectional moment of inertia (mm^4); Z = section modulus (mm^3); HSA = Hip Structural Analysis; Peri circ = periosteal circumference (cm); Endo circ = endosteal circumference (cm); CoA = cortical bone cross-sectional area (mm^2); CSA = cross-sectional area (cm^2); NN = narrow neck; IT = intertrochanteric region; FS = femoral shaft; SPW = subperiosteal width (cm); ED = endosteal diameter (cm); NS = non-signficant; LS = lumbar spine; BMC = bone mineral content (g); FN = femoral neck; L3 = third lumbar vertebrae; Troch = trochanteric region; ↔ = no difference; BSI = bone strength index; GRF = ground reaction force; BW = body weight

1.2.7 Summary of Directions for New Research on Bone Strength in the Growing Skeleton

The preceding literature review highlighted the need for further studies of bone strength in the growing skeleton using imaging techniques such as pQCT and HSA. In particular, there is a paucity of data characterizing the bone structural response to physical activity in boys and girls.

1.2.7.1 Sex Differences, Muscle and Tibial Bone Strength

There is disagreement in the current literature as to whether sex differences in long bone cross-sectional geometry, (volumetric) density and strength are evident as early as prepuberty. Results from pQCT studies of the distal and proximal radius suggest that a strength advantage in favour of boys exists during prepuberty (20,21), whereas at weight-bearing sites (femur) bone geometry is similar between prepubertal boys and girls (207,208,213). Sex differences in tibial bone strength have yet to be investigated in pre- and early pubertal children using pQCT. Further, given the significant mechanical challenge posed by increasing muscle forces on the growing skeleton, there is a need for pQCT data to be interpreted in the context of a functional model of bone development (31,88). In addition to the influence of muscle, there is also need to understand the role of other biological (maturity, ethnicity) and lifestyle (physical activity, dietary calcium) factors on tibial bone strength in pre- and early pubertal children.

1.2.7.2 Physical Activity and Bone Strength in the Growing Skeleton

Peripheral QCT is a novel imaging technique that evaluates skeletal adaptations to a physical activity intervention in children. To date, only two controlled intervention studies have used pQCT to investigate the effects on high-impact exercise on tibial bone geometry, density and strength and results from these trials were inconclusive (11,27). There remain unanswered questions regarding the type and duration of exercise required to elicit a bone structural response at the tibia and whether such a response may differ between metaphyseal and diaphyseal sites within the same bone. Results from animal studies suggest that short bouts of high-impact activity separated by rest periods may provide a significant osteogenic stimulus (14,15); however the effectiveness of a similarly designed bone-loading program (13) for increasing tibial bone strength in boys and girls has yet to be determined. In addition to evaluating the appendicular skeleton, there is a need to determine the effectiveness of a novel bone-loading program on bone strength at the clinically relevant proximal femur. Results from the HBS II trial (8,134) indicated that HSA is a valuable tool that can be used to supplement conventional measures of proximal femur bone mass with estimates of bone cross-sectional geometry and strength.

From a public health perspective, effective school-based physical activity programs have the potential to positively influence pediatric bone health on a population-wide basis. However, to be feasible in the school and classroom setting bone-loading programs must be inexpensive and easily administered by generalist teachers. As few of the previous school-based interventions have met these criteria there is a need for development of an innovative physical activity model and the subsequent evaluation of this model in a large cohort of children using novel bone imaging techniques.

1.3 Rationale, Objectives and Hypotheses

In this chapter, I outline the rationale, objectives and hypotheses for each of the three studies that make up this thesis. In addition, I provide the scientific contribution that each study will make to the pediatric bone health field.

1.3.1 Part I: Bone Strength and its Determinants in Pre- and Early Pubertal Boys and Girls

Rationale. Higher fracture rates in women than men may be related to a sex difference in bone strength that may emerge during growth (187). Despite a number of pediatric DXA studies that address this (5,203,204,232,261,394), there is still confusion about when the sex difference in bone strength appears and which factors (i.e., body weight, muscle mass or force) have the greatest influence on bone strength during growth. This confusion is due, in part, to the use of BMC or aBMD as surrogates of bone strength as DXA outcomes ignore the contribution of bone geometry to bone strength. Peripheral QCT-derived bone strength indices which combine geometry and (volumetric) density provide a more accurate means to investigate sexual dimorphism in long bone strength. Peripheral QCT can also evaluate muscle cross-sectional area (MCSA) which is a surrogate for muscle force. Mechanostat theory postulates that the greatest direct mechanical challenges on the skeleton during growth come from increasing bone length and muscle forces, whereas additional modulating factors such as maturity, physical activity and nutrition may affect the mechanostat indirectly by influencing either longitudinal bone growth or muscle force (31). Although a number of pQCT studies evaluated bone strength in the growing skeleton (20,21,285,286), few interpreted their data in the context of the mechanostat model (24,326). Further, no pQCT study has evaluated the influence of ethnicity on tibial bone strength in boys and girls.

Objectives. The *primary objective* is to determine if there is a sex difference in tibial bone strength and its components (geometry and density) in pre- and early puberty. The *secondary objective* is to evaluate the contribution of MCSA, a surrogate of muscle force, and modulating factors including maturity, ethnicity, physical activity, dietary calcium and vertical jump height to tibial bone strength.

Primary Hypothesis. After adjusting for tibial length and MCSA, tibial bone strength will be similar between pre- and early pubertal boys and girls.

Secondary Hypothesis. After adjusting for tibial length, MCSA will be the primary explanatory variable of tibial bone strength in boys and girls.

Contribution. This will be the first study to evaluate sex differences in tibial bone strength in pre- and early pubertal children using pQCT. In addition, this study will provide further insight into the muscle-bone relationship during growth and the relationships between non-modifiable (maturity, ethnicity) and modifiable factors (physical activity, dietary calcium, physical performance) and tibial bone strength. Results from this cross-sectional study will identify factors that contribute to bone strength in children. Based on these findings, researchers can develop intervention trials that address these factors.

1.3.2 *Part II: Sixteen-Month Longitudinal Study of a School-Based Physical Activity Intervention on Tibial Bone Strength in Boys and Girls.*

Rationale. The osteogenic effects of exercise on the growing skeleton are well recognized (4,6,341). A previous 20-month, school-based, bone-loading intervention in an ethnically diverse cohort of pre- and early pubertal boys and girls reported significant gains (+4.3-4.6%) in BMC at the clinically significant femoral neck (8,9,262,263). Few studies have assessed the bone structural adaptations to physical activity in children using pQCT (11,27,288). Only one of these trials (11) evaluated tibial bone strength and none of the studies evaluated bone strength at both distal and midshaft sites. Thus, it is not known if the bone response to physical activity differs between primarily trabecular (distal) and cortical (midshaft) sites of the tibia. Further, it is not known if adaptations to increased loading within a bone cross-section occur in a site-specific manner as no pQCT studies have investigated changes in tibial bone strength in the x- and y-bending planes. Finally, many school-based interventions have involved modifications to existing physical education curriculum (8,9,134,262,346,355). In light of current curricular demands this type of intervention may not be feasible or sustainable. Thus, there is a need for a novel and effective physical activity program for elementary schools that incorporates a simple bone-loading component.

Objectives. The *primary objective* is to compare changes in bone strength at the distal tibia and tibial midshaft as estimated with pQCT-derived bone strength indices between children who participate in a 16-month school-based physical activity program, Action Schools! BC, and same-sex, non-participating controls. The *secondary objective* is to determine if, at the tibial midshaft, structural adaptations to increased loading differ in the x- and y-bending planes.

Primary Hypothesis. Changes in bone strength indices will be greater in both boys and girls participating in Action Schools! BC compared with sex-matched, non-participating controls. Differences in change between intervention and control children will be similar at the distal tibia and tibial midshaft.

Secondary Hypothesis. Changes in bone strength at the tibial midshaft will be similar in the x- and y-bending planes.

Contribution. This is the largest school-based physical activity intervention undertaken to date in elementary schools. I use a novel assessment tool (pQCT) to determine the effects of physical activity on bone strength at the distal and midshaft tibia in boys and girls. This has not been achieved previously. Beyond what has been done before, this study will characterize the bone structural response to a novel bone loading program implemented within a larger school-based physical activity model, Action Schools! BC. If effective, this program will offer a simple and inexpensive means to improve bone strength in elementary school children.

1.3.3 *Part III: Sixteen Month Longitudinal Study of a School-Based Physical Activity Intervention on Femoral Neck Bone Mass and Strength in Boys and Girls.*

Rationale. Our research group previously reported enhanced bone mass and structure compared with controls in both boys (8,262) and girls (9,134,263) who participated in a school-based, high-impact circuit training intervention for 20-months. Despite the effectiveness of HBS II, a model that modifies the physical education curriculum is not likely to be sustainable in elementary schools. Based on findings from animal studies (14,15) that demonstrated osteogenic effects of short bouts of high-impact loading separated by rest periods, our group designed the Bounce at the Bell program. Bounce at the Bell is a simple, inexpensive and feasible bone-loading model that can be easily implemented by generalist teachers. Action Schools! BC is a school-based physical activity model that incorporates Bounce at the Bell as part of the required classroom-based physical activity component. Bounce at the Bell was effective for increasing proximal femur bone mass in a combined sample of boys and girls. The effects of this program on boys' or girls' femoral neck bone strength as estimated with HSA were less clear. Hip structure analysis provides a means to estimate bone structure and strength in response to this novel intervention at the clinically relevant proximal femur.

Objectives. The *primary objective* is to compare changes in HSA-estimated bone bending strength at the femoral neck between boys and girls participating in a 16-month school-based physical activity program, Action Schools! BC, and same-sex, non-participating controls. The *secondary objective* is to compare changes in DXA-derived total proximal femur, lumbar spine and total body BMC and bone area between intervention children and controls.

Primary Hypothesis. Boys and girls who participate in Action Schools! BC will have a greater change in estimated femoral neck bone strength than same-sex controls.

Secondary Hypothesis. Boys and girls who participate in Action Schools! BC will have a greater change in proximal femur, lumbar spine and total body BMC compared with same-sex controls.

Contribution. This study builds on previous school-based physical activity interventions conducted by our research group. The novel aspects of the Action Schools! BC model were described for Part II. If proven effective, the Action Schools! BC physical activity model that includes Bounce at the Bell will offer a feasible, and potentially sustainable, school-based strategy for enhancing bone strength at the clinically relevant proximal femur.

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2 Methods[1]

In this chapter I outline the study design and the methods common to Parts I, II and III. I begin with a detailed description of the school-based physical activity model, Action Schools! BC, which provides the foundation of this thesis.

2.1 Action Schools! BC Overview

Action Schools! BC (AS! BC) is a school-based model that aims to integrate physical activity and healthy school environments into school health policy and, ultimately, into the social fabric of elementary schools. Further, the goal of AS! BC is to provide "more opportunities for more children to be more active more often" to achieve long-term, measurable and sustainable health benefits. In this section I discuss development and delivery of the AS! BC model.

2.1.1 Development of the Action Schools! BC Model

The AS! BC model incorporates a menu of "best practice" interventions gleaned from models of school health being implemented across Canada and around the world. Best practices were determined through a comprehensive evaluation of internet, direct contact, print media and scientific literature resources, and were compiled into a user-friendly compendium for teachers (Action Pages!) (1). Further critical evaluation of these resources identified the "best of the best practices" based on four health targets: Healthy Heart, Healthy Bones, Healthy Self and Healthy School. These practices were incorporated into the AS! BC model.

The AS! BC model provides a tool for schools to create individualized physical activity Action Plans that contribute to the health of children, as well as the overall health and well-being of the school community. To help schools promote physical activity and healthy school policies, the AS! BC model is divided into 6 Action Zones: School Environment, Extracurricular, Family and Community, School Spirit, Scheduled Physical Education and Classroom Action (Figure 2-1). Within each Zone, the AS! BC model provides numerous Action Ideas and resources that help schools achieve their individual goals. I will provide a brief description of each zone; however, for the purposes of this thesis, I will focus on the required components that target bone health within the Classroom Action Zone (Section 2.2.6).

In the **School Environment Zone**, AS! BC supports active living policies and helps schools to create safe and inclusive environments for physical activity. Action Ideas for this Zone include providing bike racks or creating bike storage spaces in safe locations on school grounds and providing Professional Development opportunities for teachers. The **Scheduled Physical Education Zone** supports the curricular goal of 150 minutes per week of scheduled physical education (PE) as recommended in the BC Instructional Resources Package (IRP) (2). Action

[1] A version of this chapter has been published. Naylor PJ, Macdonald HM, Reed KE, McKay HA. *Action Schools! BC*: A socioecological approach to modifying chronic disease risk factors in elementary school children. Preventing Chronic Disease [serial online]. Available from: URL: http://www.cdc.gov/pcd/issues/2006/apr/05_0090.htm.
A version of this chapter has been accepted for publication. Naylor PJ, Macdonald HM, Zebedee JA, Reed KE, McKay HA. Lessons learned from Action Schools! BC – An 'active school' model to promote physical activity in elementary schools. Journal of Science and Medicine in Sport 2006.

Ideas include providing basic skill instruction to all students to ensure confidence and competence with various activities. The **Classroom Action Zone** provides creative, alternative classroom physical activity ideas that complement scheduled PE and incorporate physical activity into the classroom setting. Action Ideas include implementing the 15 (minutes) x 5 (days per week) program and developing indoor and/or outdoor activity circuits. In the **Extra-curricular Zone**, AS! BC balances Classroom Action and PE with a variety of opportunities for children, school staff and families to be physically active before and after school and during lunch. Action Ideas include organizing walk or cycle to school days and making physical activity equipment available to students throughout the school day. The **Family and Community Zone** fosters the development of partnerships with families and community practitioners to create and promote opportunities for children and their families to be active. Action Ideas include contacting local community facilities to explore new physical activity opportunities (e.g. skating, swimming). The **School Spirit Zone** cultivates school spirit by encouraging physical activity throughout the whole school. Action Ideas include organizing physical activity events for students and staff (e.g. mini-Olympics, bike rodeos) and by having a physical activity component in school assemblies.

Figure 2-1. The six Action Zones of Action Schools! BC.

2.1.2 Organizational Structure of Action Schools! BC

AS! BC represents a partnership between government, researchers, educators and the health, recreation and sport sectors. Thus, the development and delivery of AS! BC was managed by the coordinated efforts of several committees and teams which I will describe briefly (Figure 2-2). The committees and teams were under the direction of Dr. McKay (HAM) who was the Principal Investigator for this study. I was the Research Director for the Healthy Bones component of the AS! BC evaluation. I discuss my role in further detail below.

AS! BC Advisory Committee. The AS! BC Advisory Committee had representation from government, community, health and education stakeholders. The aim of this group was to work with the AS! BC Support Team to identify strategies to guide the development and implementation of AS! BC and to communicate the model and the mandate to their membership. Further, this committee helped to identify barriers to the success and sustainability of AS! BC. Stakeholders included: 2010 LegaciesNow; BC Ministry of Health (formally BC Ministry of Health Services), BC Ministry of Tourism, Sport and the Arts (formally BC Ministry of Children, Women and Aboriginal Services); BC

Ministry of Education; Provincial Health Services Authority; BC Parks and Recreation; BC School Trustees and BC Confederation of Parent Advisory Councils among others (Appendix 1).

AS! BC Technical Team. This group included teachers, principals, University Professors and Instructors, Physical Education Consultants and Sport Administrators with specific expertise and proven success in delivering physical activity and sport in the school or community setting. They provided expert opinion and guidance to the AS! BC Support Team (below) regarding development, implementation and course adjustment of the AS! BC model.

AS! BC Support Team. This Team was comprised of sports skills and education specialists from JW Sporta (Bryna Kopelow, Jennifer Fenton). JW Sporta is a creative British Columbia based consulting and marketing company responsible for the design and province-wide delivery of the Premier's Sport Awards Program (PSAP) that teaches fundamental motor skills to children. The Support Team oversaw the design and facilitation of the AS! BC model under the 'best practices' framework. The AS! BC Facilitators (Debbie Keel, Judy Howard), were elementary teachers seconded by the Program Team to train teachers and to liaise between the Support Team and the School Action Team (below) to facilitate the implementation of AS! BC.

School Action Team. The success of AS! BC lies in ownership of the model by the school community. At initial planning meetings, principals and the Support Team engaged staff to identify teachers willing to 'champion' AS! BC. Together with the AS! BC Facilitator, principals, 'Champion' teachers and supportive parents formed the School Action Team. This group was responsible for creating and promoting a customized program of activities (Action Plan) that reflected the diversity, personality and perceived needs of the school community.

Evaluation Team. The Evaluation Team involved research directors representing each of the measurement arms: Healthy Bones (myself); Healthy Heart (Darren Warburton, Kate Reed); Healthy Eating (Ryna Levy-Milne); Academic Performance (Kadriye Ercikan); Healthy Weight (Jean-Pierre Chanoine, Kerry MacKelvie O'Brien) and Policy, Tracking and Process Evaluation (PJ Naylor, Janelle Zebedee). As research director for the Healthy Bones component I consulted on development of the AS! BC model, chose measurement tools and methods and provided expertise on the type and dose of physical activity required for bone health. In addition, I was responsible for hiring, training and supervising the Healthy Bones measurement team. I also assisted the AS! BC Administrators (Josie McKay, Connie Waterman) with scheduling of laboratory and school measurement sessions. The AS! BC Administrators oversaw all aspects of the evaluation and facilitated communication between research teams.

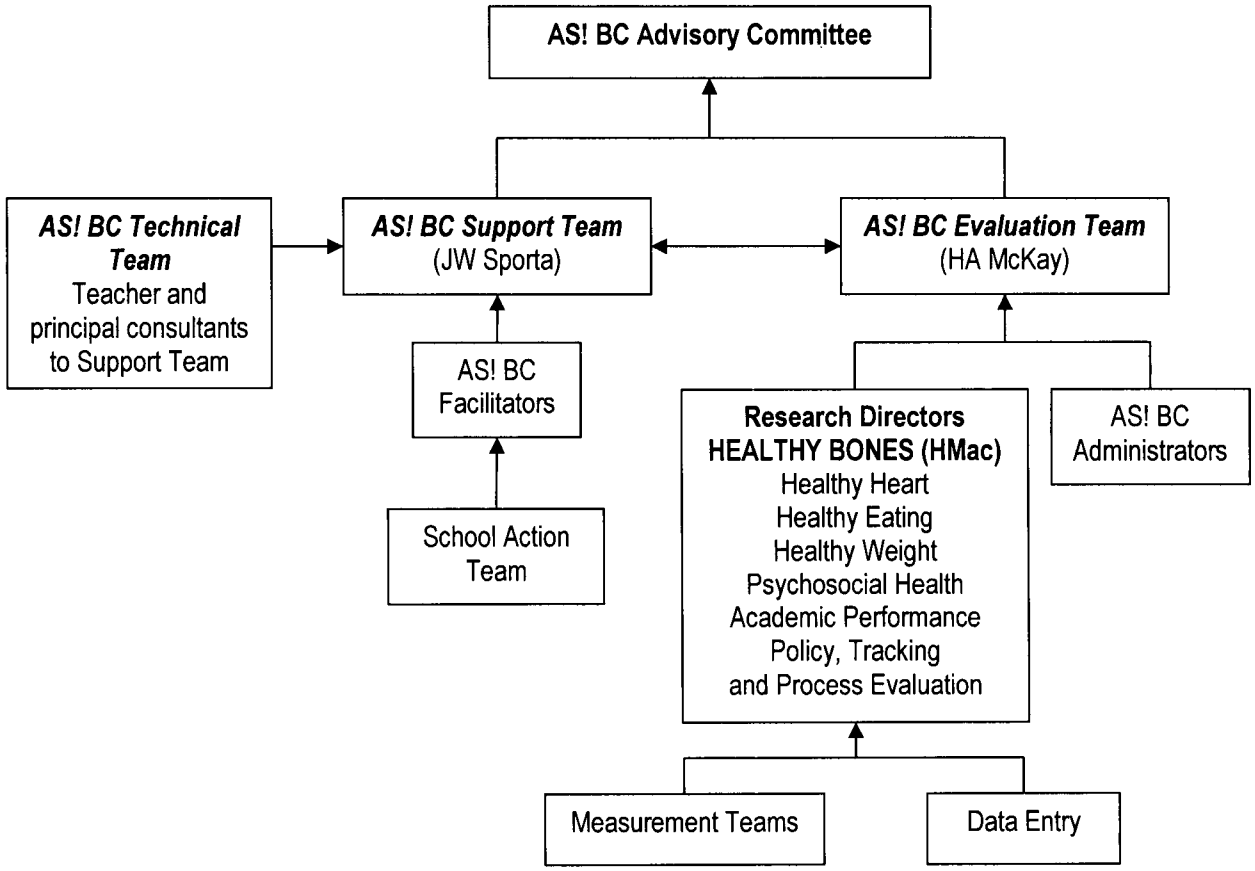

Figure 2-2. Flowchart outlining the organizational structure of Action Schools! BC (AS! BC).

2.2 AS! BC: Evaluation

In this section I discuss all aspects of study design including school, teacher and student recruitment methods, model delivery and a detailed description of the components of AS! BC that were designed and implemented as they relate to this thesis.

2.2.1 Study Design

This was a cluster randomized, controlled, school-based prospective study involving children in Grades 4 and 5 (at baseline) from 10 elementary schools in the Vancouver and Richmond School Districts. The study timeline is provided (Figure 2-3). The total study duration was 16-months with a median followup time of 14 months (range: 13 – 15). The total intervention time was 11 months: Phase I (3 months) and Phase II (8 months) were separated by a 2-month summer holiday. Part I of this thesis utilized baseline data to conduct a cross-sectional comparison of tibial bone strength between boys and girls. Part II utilized 16-month change data to evaluate the effectiveness of AS! BC for enhancing tibial bone strength in boys and girls. Part III utilized 16-month change data to evaluate the effectiveness of AS! BC for increasing proximal femur bone mass and strength. Ethical approval was obtained for all parts of this thesis from the UBC Clinical Research Ethics Board (Appendix 2).

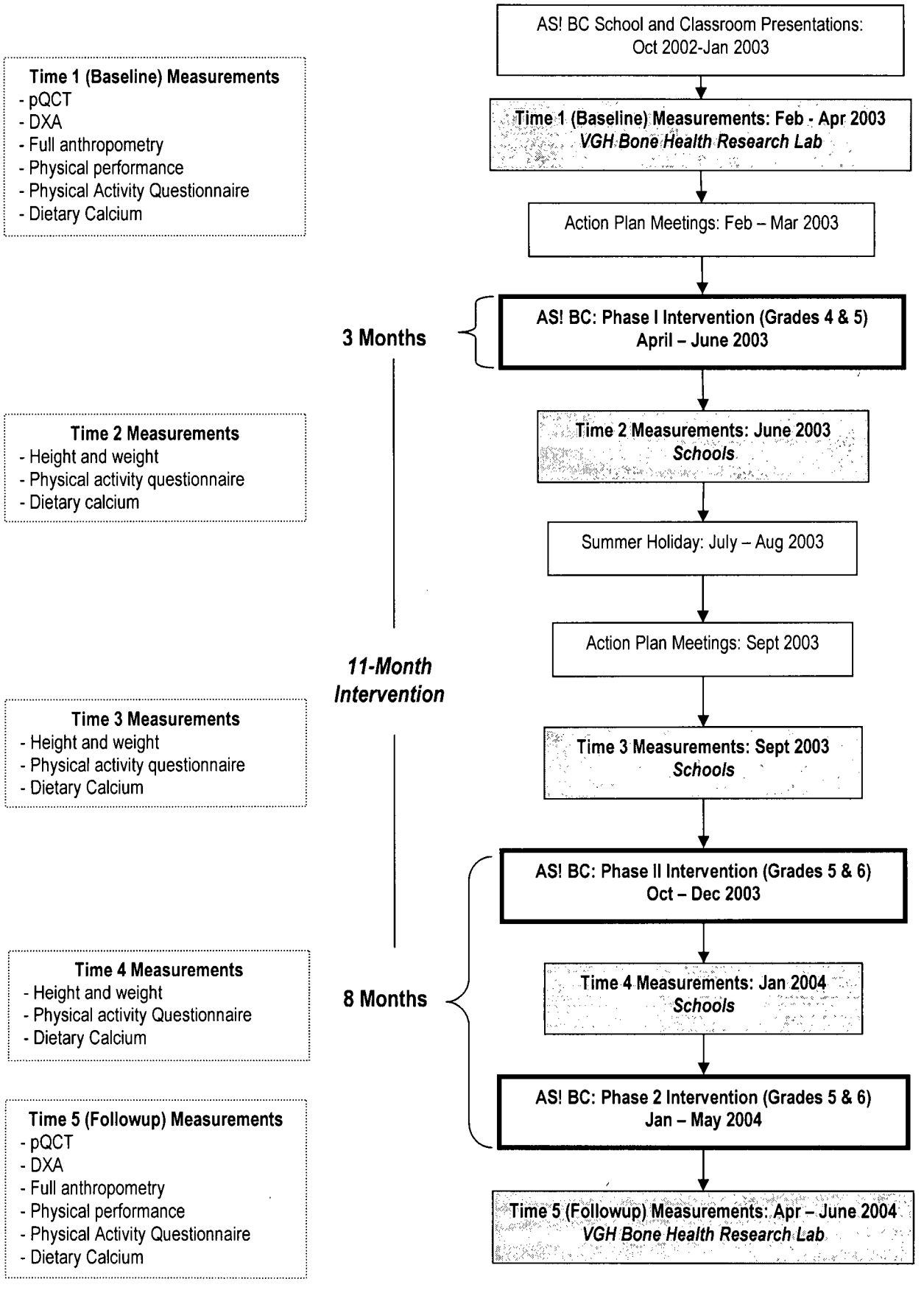

Figure 2-3. Study timeline.

2.2.2 *Recruitment - Schools*

Between 1997 and 2001 the UBC Bone Health Research group conducted two school-based interventions in the Richmond School District (3,4), and as a result established a positive rapport with principals and teachers in a large number of elementary schools. In addition, a formal partnership was established between the UBC Faculty of Education and the Vancouver School Board that allows research projects (with Board approval) to be conducted in the Greater Vancouver School Districts. AS! BC represents the first time that our research group has worked with the Vancouver School District.

Presentations to Principals and Vice-Principals were made at District (Richmond) and Area (Vancouver) meetings (October-November 2003) (Figure 2-3). Interested Principals and/or Vice-Principals contacted the AS! BC Administrators for further information. From the 103 public elementary schools in the two districts (75 in Vancouver, 38 in Richmond), 20 (19%) schools volunteered to participate in the AS! BC evaluation. To discriminate between schools who were already undertaking physical activity initiatives from those who were not, the AS! BC Evaluation Team used results from the 2002 BC Ministry of Education Satisfaction Survey (5) to finalize school participation based on student and parental response related to exercise participation in school. The survey was administered to children in grades 4 and 7 and their parents and one question in the human and social development section asked;

Children: "At school, do you get exercise (for example, physical activity or sports)?
Parents: "At school, does your child get exercise (for example, physical activity or sports)?

For both the child and parent surveys, responses were provided on a 5-point scale: 1 = At no time; 2 = Few times; 3 = Sometimes; 4 = Many times; 5 = All of the time. From the pool of 20 volunteer schools we invited those schools with a mean score of 3 or less to participate (n = 11 schools). One Principal withdrew his school (before randomisation) after determining there was a chance their school could be randomly selected as a control school. Thus, 10 schools (3 Richmond schools, 7 Vancouver schools) participated in the study.

Once participation was established the AS! BC Support and Evaluation Teams organized meetings with the Principal and Vice-Principal and Grade 4 and 5 teachers at participating schools (Figure 2-3). The purpose of these meetings was to introduce teachers to AS! BC, present the project timeline and outline specific responsibilities of teachers, should they choose to participate. Regarding incentives, teachers were told that if their school was randomly selected as an intervention school they would receive physical activity related resources and if their school was randomly selected as a control school they would not receive such resources.

Following completion of these meetings at all 10 schools, the schools were randomly assigned to one of three study arms: *Liaison* (Level 1 Intervention), *Champion* (Level 2 Intervention) or *Usual Practice* (Control). Randomization was determined remotely by random draw (by a third party) and was performed in 2 steps. First, to ensure the Richmond District was represented in each study arm, each Richmond school was randomly assigned to one of the 3 groups. Second, the Vancouver schools were stratified by size (300 < total school population > 300) because of the large range in school size (min = 275 students, max = 610 students). The 7 schools were then

randomized to one of the 3 groups. As will be discussed (Sections 2.2.5 and 2.2.6), the level of external support differed between the 2 intervention arms, but the required components of the AS! BC were the same for Level 1 and 2 schools. Thus, for the purpose of this thesis, the Level 1 and 2 schools were collapsed into one Intervention group.

2.2.3 *Recruitment – Children*

To inform children about AS! BC, I conducted presentations in grade 4 and 5 classes in each of the 10 participating schools (January 2003). In addition to describing the program, I answered children's questions and distributed information and consent forms and health history questionnaires (Appendix 2) to children to be taken home to parents/guardians. The forms were translated into 3 languages (Chinese, Punjabi and Vietnamese) prior to distribution. Following the presentations, and based on information from teachers, the ethnic breakdown of each class was assessed and forms in the appropriate languages were distributed. I distributed approximately 1100 information and consent forms.

Incentives for children to participate included 2 trips to the Bone Health Research Laboratory at VGH for measurements where children received snacks, AS! BC stickers, pencils, socks and Frisbees as well as detailed individual and group results which were mailed home in the summer following the final measurement (Appendix 7).

2.2.4 *Consent, Health History and Ethnicity*

Signed consent forms were returned to each child's teacher and were collected by a research assistant. Once all forms were collected baseline measurements were scheduled for each school.

In addition to the consent form, parents completed a health history questionnaire for their child. This questionnaire was designed to identify children with medical conditions that interfered with normal physical activity or bone metabolism. We administered a modified version of this questionnaire in the laboratory at the followup measurement (April-June 2004) to assess change in medical status (Appendix 2). I excluded children from data analyses *only*, as appropriate.

In addition to health status, we used the health history questionnaire to determine each child's ethnicity based on parents' or grandparents' place of birth. We classified children as '*Asian*' if both parents or all 4 grandparents were born in Hong Kong or China, India, Philippines, Vietnam, Korea or Taiwan or '*Caucasian*' if both parents or all 4 grandparents were born in North America or Europe. We classified children of other ethnic origins (i.e. Black or Hispanic) or mixed ethnicity as 'other'.

2.2.5 *Action Schools! BC Implementation*

Level 1 intervention schools received assistance from the AS! BC Support Team and an AS! BC Facilitator (DK). The AS! BC Support Team met with school principals and staff, convened the self-identified School Action Team, introduced program components and weekly logging responsibilities, facilitated the development of school and teacher Action Plans and provided resources (Classroom Action Bin, Action Pages) and workshops required by the school to deliver their Action Plan. I describe the Action Plan and resources in further detail below. The AS! BC Support Team also engaged principals in discussions of healthy school policy and with them, identified areas for

change in the school environment (e.g. vending machines, bike racks, professional development). Finally, the AS! BC Support Team engaged parent groups and relevant community partners (e.g. Parks and Recreation and provincial sport organizations) deemed key to successful implementation of the model.

Within each Level 1 school the AS! BC Facilitator worked with a self-appointed contact person (i.e. teacher or vice-principal) to schedule in-service training for teachers. In addition, the AS! BC Facilitator assisted the contact person with completion of an inventory of available space, equipment and other physical activity related resources as well as a School Health Inventory related to healthy school policy and current physical activity (including PE) practices (Appendix 3). The AS! BC Facilitator provided one-on-one consultation and ongoing support to participating teachers. In total, these tasks required approximately 2 – 4 contact hours per school per week.

Level 2 intervention schools were similar to Level 1 schools with a few exceptions. A principal, teacher, parent or community champion (rather than an AS! BC Facilitator) was self- identified to facilitate development and delivery of the teacher and school Action Plans. The 'Champion' conducted an inventory of available space, equipment and other physical activity related resources and completed the School Health Inventory. As before, the AS! BC Support Team guided the development of the school Action Plan, provided teacher training workshops, instruction and resource manuals as well as a basic Classroom Action Bin. Contact with the AS! BC Facilitator (JH) was infrequent following teacher training (0.5 – 1 contact hour per school per week) although there was ongoing telephone and email communication with and facilitation by the Support Team on a weekly basis.

Within the Usual Practice condition, control schools continued with their regular physical activity practices and we made no active attempt to modify the school environment.

2.2.5.1 Creating an Action Plan

The School Action Team and the AS! BC Support Team worked together to create individualized Action Plans for the whole school and individual classes (Grades 4 and 5 in Phase I and Grade 5 and 6 in Phase II). The planning sessions occurred twice during the evaluation period (Figure 2-3). The Action Plan was based on school and classroom goal statements within each Action Zone that were determined by the School Action Team or by individual teachers. To achieve school/classroom goals, Action Ideas were chosen from the list of 'best practices' activities and resources provided in the Action Pages! (1). The Action Plan served to outline and clarify the AS! BC model for classroom teachers, and ensured that activities were chosen that fulfilled the Healthy Bones and Healthy Heart requirements (Section 2.2.6). A sample Action Plan worksheet is provided (Appendix 3).

2.2.5.2 Classroom Action Bin

The AS! BC Support Team provided Grade 4, 5 and 6 classes in the Level 1 schools with a customized bin that contained equipment (exercise bands, hand grippers, skipping ropes), teaching resources (game and activity manuals) and tools (videos) to support the individualized Action Plans (Appendix 3). The AS! BC Support Team added new materials and tools to the bin as requested and as they became available. The Level 2 schools received a basic bin only. The AS! BC Support Team (with the AS! BC Facilitators) introduced the bins and provided instructions

on how to use the available resources at teacher training workshops conducted before the start of each phase of the intervention (Spring 2003 and Fall 2003).

2.2.6 *Action Schools! BC Model: Required Components*

Intervention teachers were instructed to implement two required components in the Classroom Action Zone, Classroom Action 15 x 5 and Bounce at the Bell *in addition to* regular physical education. The intervention was 11 months in duration: *Phase I* was from April - June 2003 and *Phase II* was from October 2003 to May 2004 (Figure 2-3). Teacher training for 15 x 5 and Bounce at the Bell was conducted at the start of each phase by the AS! BC Facilitators. Training sessions were workshop based and took place during regular school hours. Teacher-on-call funding was provided to schools to support the release of classroom teachers for AS! BC training.

2.2.6.1 *Classroom Action 15 x 5*

The Classroom Action 15 x 5 program required teachers to provide their students with a total of 15 minutes of physical activity a day, each day of the school week, for a goal of 75 minutes of weekly classroom-based (for the most part) physical activity. The 15 minutes could be accumulated throughout the school day and teachers chose from a menu of moderate to vigorous activities that targeted three health outcomes: Healthy Hearts, Healthy Self and Healthy Bones. The activities included skipping, dancing, playground circuits and simple resistance exercises with exercise bands, among others.

2.2.6.2 *Classroom Action: Bounce at the Bell*

In addition to the 15 x 5 program, intervention teachers were required to implement Bounce at the Bell a minimum of four days per week. Children performed Bounce at the Bell in the classroom three times daily at the time of the school bell (or on instruction of teacher if there was no school bell). This program was designed to provide *short, frequent, high-impact* loading bouts with *various strain rates* based on the animal work of Umemura et al. (6) and Robling et al. (7). Teachers were provided with laminated 8.5 x 11" diagrams of four specific jumps and a Bounce at the Bell manual (Appendix 4). Teachers instructed their students to perform either counter movement jumps (two foot take off, clutch knees, two foot landing) or side to side jumps (one foot take off, opposite foot landing). During Phase I, children performed 10 one-foot landing jumps (5 on each leg, or 5 two-foot landing jumps) at the morning, noon and final school bell, 4 days per week. In Phase II students began with 10 one-foot landing jumps and increased the number of jumps each month until they achieved a maximum of 36 jumps per day (Table 2-1). Ground reaction forces for these jumps were measured previously by our group in an independent sample of 70 girls and 70 boys (8-12 yrs) and were found to be 3.5-5.0 times body weight (8).

Table 2-1. Bounce at the Bell program for Phase II.

Month	Number of 1-foot Landing Jumps	Number of 2-foot Landing Jumps	Number of Sessions per Day	Total Number of Jumps per Leg
October	10 (5 on each leg)	5	3	15
November	12 (6 on each leg)	6	3	18
December	14 (7 on each leg)	7	3	21
January	16 (8 on each leg)	8	3	24
February	18 (9 on each leg)	9	3	27
March	20 (10 on each leg)	10	3	30
April	22 (11 on each leg)	11	3	33
May	24 (12 on each leg)	12	3	36

2.2.7 Program Compliance

To monitor compliance with the 15 x 5 and Bounce at the Bell programs, we asked teachers at intervention schools to complete weekly activity logs (Appendix 4). Each day, teachers recorded the type, frequency and duration of all activities (across all 6 Action Zones) undertaken with their students including their scheduled physical education classes. Intervention teachers also recorded the frequency of Bounce at the Bell and the number of jumps performed at each session. We asked teachers at control schools to complete a modified version of the activity log (Appendix 4). The logs were collected bi-weekly by the AS! BC Facilitator and were entered into the AS! BC database. From these logs, I determined the minutes per week of activity delivered by teachers at intervention and control schools.

2.2.8 Data Collection

2.2.8.1 Data Collection Overview

There were 5 data collection sessions during the 16-month study period (Figure 2-3). Baseline and followup sessions took place at the Bone Health Research Lab. The lab is located in the Vancouver Coastal Health Research Institute at 828 West 10th Avenue in Vancouver, BC. Consenting children were released from class for approximately 3 hours and were transported to VGH via minivan in groups of 5-6 (Table 2-2). The distance between schools and VGH ranged from 3.8 km to 16.1 km (9). Children were supervised en route by a chaperone. While at the lab, children rotated through 4 stations: Bone densitometry (DXA and pQCT), Anthropometry, Performance Measures and Questionnaires. Children were supervised by a member of the measurement team at all times.

Table 2-2. Transportation schedule for study participants to and from Vancouver General Hospital (VGH).

	Depart School	Arrive at VGH*	Depart VGH*	Arrive at School*
Group 1	9:00 am	9:30	11:15	11:45
Group 2	10:40	11:10	12:50	1:20
Group 3	12:15 pm	12:45	2:30	3:00

*Times are approximate and varied according to distance between each school and VGH.

Three additional measurement sessions took place in the schools (June 2003, September 2003, January 2004). Students were released from class in groups of 10 for approximately 1 hour. The sessions were held in the school library or general purpose room and research assistants facilitated the completion of questionnaires by children. The ratio of children to research assistants was 2:1.

2.2.8.2 Measurement Team Training

Prior to each measurement period I conducted a 3-4 hr training session for a measurement team of 6-8 research assistants (RA). The RAs were trained to administer questionnaires, instructed in the correct techniques for anthropometric and physical measures and advised on the ethics of data collection. The RAs were given the opportunity to practice all measurements during the training session under my supervision. It was anticipated that we would retain approximately 60% of the RAs between sessions. Across the 5 measurement sessions, 6 RAs worked once (40%), 6 worked twice (40%) and 3 worked more than 3 times (20%).

2.2.8.3 Bone Densitometry

2.2.8.3.1 DXA

Bone area (BA, cm^2) and bone mineral content (BMC, grams) were measured at the proximal femur (PF), lumbar spine (LS) and total body (TB) at baseline and followup using a Hologic QDR 4500W bone densitometer (Hologic Inc, Waltham, MA). Measurements were made by one of three trained and qualified technologists (Leslie Bryant-MacLean, KR or Teresa Liu-Ambrose) under the supervision of HAM. The procedure required that each child lie on the padded examination table for positioning and measurement (~15 minutes) (Figure 2-4). The children wore light clothing free of metal zips and snaps and removed jewellery and/or glasses for measurement. A spine phantom was scanned daily to satisfy the mandatory Hologic quality control procedures. One research assistant (LBM) analyzed all DXA scans using standardized procedures outlined in the Hologic Users Guide (10). This protocol has been used extensively in previous studies in our lab (3,4,11,12). The precision of the 4500W with repositioning was determined in 14 healthy adult volunteers (7 men, 8 women; aged 26-50 yrs). The precision (%CV) ranged from 0.6% for TB BMC to 2.2% for FN BMC (UBC Bone Health Research Group, unpublished data). Bone densitometry by DXA is a safe, painless procedure, is associated with an extremely low dose of radiation and is used routinely in modern medical practice. For the three scans, the effective dose for children is, on average, 60 μSv (13).

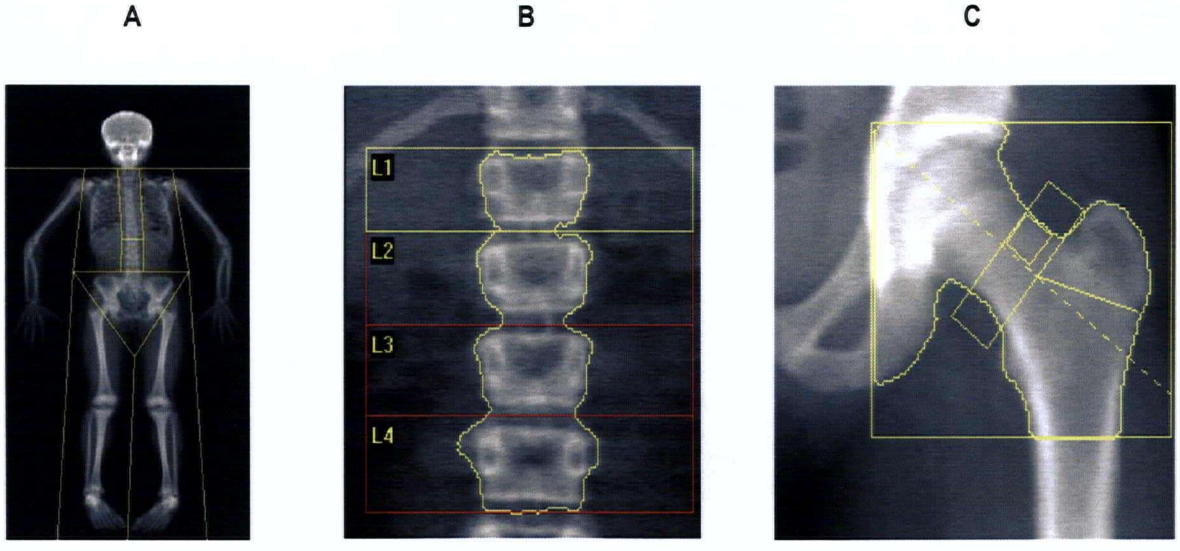

Figure 2-4. Images of (A) total body, (B) lumbar spine and (C) proximal femur scans acquired with the Hologic 4500W bone densitometer. The lines on each image outline the regions of interest defined in the DXA analysis.

2.2.8.3.2 HSA

I analyzed proximal femur scans for bone structural characteristics using the hip structure analysis (HSA, Version 3.0) program designed by Dr. Tom Beck at Johns Hopkins University (Baltimore, MD, USA). Our group has used this method in previous pediatric studies (14,15). For the purpose of this thesis I report bone structural variables for the narrow neck (NN) region (across the narrowest segment of the femoral neck) (Figure 1-9) only. A detailed description of HSA is provided in Section 1.2.3.2. Briefly, the HSA program extracts the pixel distribution across the bone axis and uses this to estimate bone cross-sectional geometry. For precision, measurements are averaged over five parallel lines (~1 mm apart) across the bone axis. Bone cross-sectional area (CSA, cm^2) is derived as the integral of the profile of pixel values converted to centimetres and subperiosteal width (cm) is the blur-corrected width of the profile. The cross-sectional moment of inertia (CSMI, cm^4) for bending in the plane of the image is derived as the integral of the bone mass profile weighted by the square of the distance from the centre of mass (16). The section modulus (Z, cm^3), an indicator of bone bending strength, is computed as $Z = CSMI/d_{max}$ where d_{max} is the maximum distance from the centre of mass medial or lateral cortical margin (16). I received training in HSA analysis from Dr. Tom Beck and Lisa Semanick at Johns Hopkins University and I analyzed all scans with their guidance. For the purpose of this thesis I report only bone structural variables (CSA, SPW, Z) for the narrow neck region. To determine intraoperator precision for HSA analysis, I performed repeated analysis on 20 randomly selected scans. Coefficients of variation for analysis of narrow neck CSA, SPW and Z were 0.1%, 0.6% and 0.6%, respectively.

2.2.8.3.3 pQCT- Acquisition

I acquired and analyzed all pQCT scans for this thesis. I acquired a single 2.3 mm slice at the distal (8%), midshaft (50%) and proximal two-thirds (66%) sites of the left tibia (Figure 2-5) using the XCT-2000 (Norland/Stratec

Medizintechnic GmbH, Pforzheim, Germany). I positioned each child's leg in a similar fashion using a customized leg hold designed by Dan Schiferl (Bone Diagnostic Inc.). I used a Velcro strap to ensure each child's leg remained stationary during scan acquisition (Figure 2-5a). I used a scan speed of 30 mm/sec and a sampling resolution (voxel size) of 0.4 mm according to manufacturer recommendations (17). To locate the anatomic reference line I performed a 30 mm planar scout view over the joint line (Figure 2-5b). The relative location of the distal and midshaft sites was automatically adjusted to this reference (Figure 2-5c). For the proximal two-thirds site, I determined the site location (66% of the total tibial length) from the tibial length measurement (Section 2.2.8.5) and marked the location on the leg with non-permanent ink. I then placed the gantry and positioning laser on the mark. The total time required for all three scans was approximately 10 minutes. Similar to DXA, bone densitometry by pQCT is a safe, painless procedure and is associated with an extremely low dose of radiation. The skin dose for one scan is 90 μSv and 35 μSv for the scout scan. Thus, the total skin dose for three scans is 155 μSv. However, the effective dose equivalent (risk from exposure of a single tissue in terms of an equivalent risk from exposure of the whole body) is only 0.22 μSv (17). In addition, each scan is associated with a small amount of scatter radiation (<1 μSv). The total radiation dose for the pQCT scans is significantly less than the radiation dose associated with one chest X-ray (100 μSv) and normal annual background radiation in Canada (~1800 μSv/year) (18). Quality assurance was performed daily using the cone phantom provided by the manufacturer.

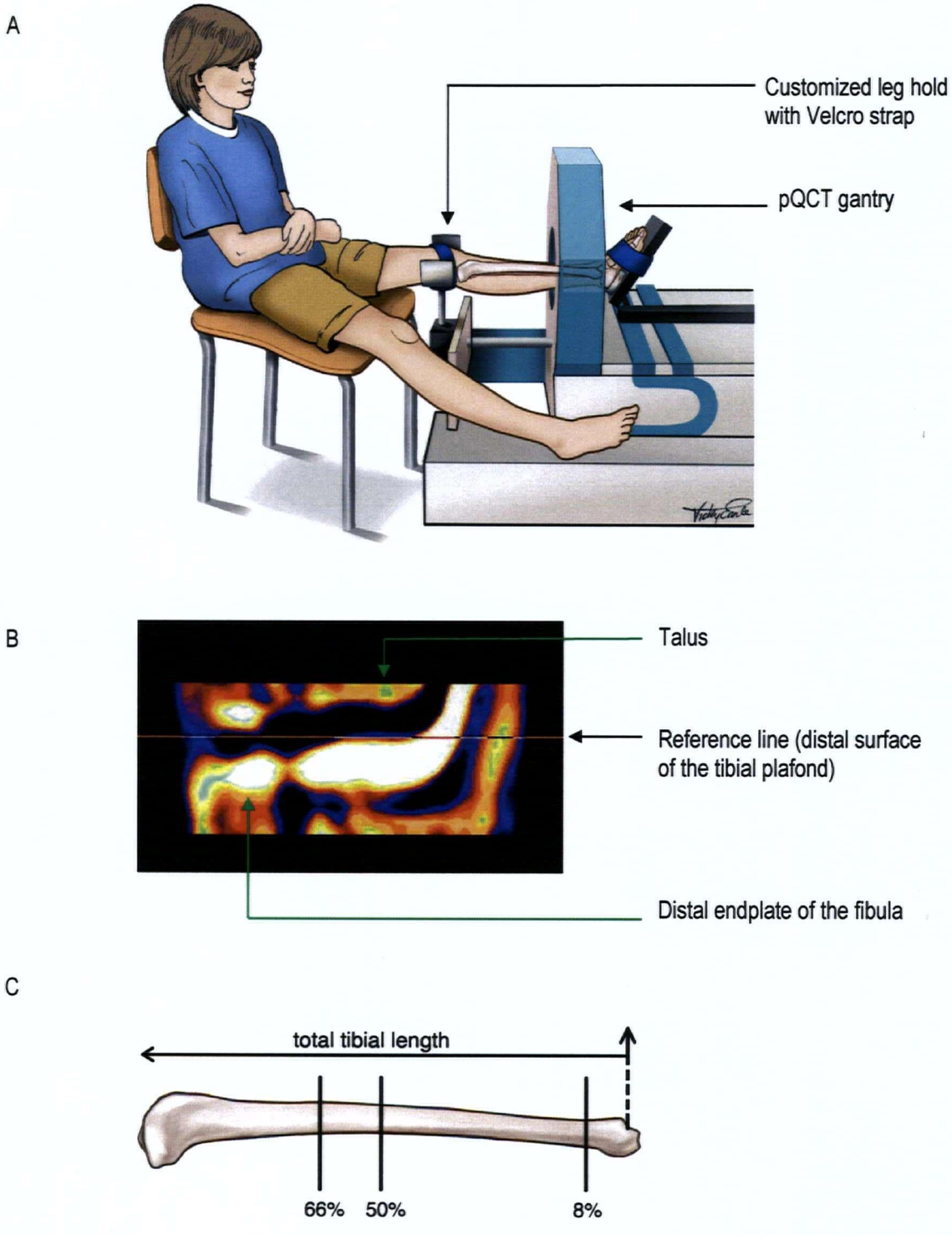

Figure 2-5. Peripheral quantitative computed tomography (pQCT) scan acquisition. (A) The child sits comfortably in a chair with adjustable height, places their left leg through the pQCT gantry, rests their leg in the customized leg hold and rests their left foot in the foot rest. A Velcro strap is fastened around the left knee and foot to minimize movement during scan acquisition. (B) A scout scan is performed to determine placement of the reference line at the distal surface of the tibial plafond. (C) Single 2.3 mm slice measurements are obtained at the distal (8%), midshaft (50%) and proximal two-thirds (66%) sites. Figures (A) and (C) from Vicky Earle, Medical Illustrator, UBC, The Media Group.

2.2.8.3.4 pQCT – Analysis

I analyzed all pQCT scans using Stratec software (Version 5.50) according to standardized procedures outlined in the Stratec Users Manual (17). Briefly, for each scan I positioned the cursor in the centre of the tibia marrow cavity. I then activated the edge detection algorithm (with a mouse-click) which drew an automatic region of interest (ROI) around the tibia. The algorithm uses the operator set modes and thresholds to determine a large number of variables. The modes, thresholds and outcome variables used in this thesis are presented (Table 2-3). As discussed (Section 1.2.3.3.3), there are currently no standardized analysis protocols for pediatric pQCT studies. Therefore, the modes and thresholds used in this thesis are similar to those used in previous studies by our group (19) and are based on the manufacturer's recommendations (17).

In our laboratory, precision with repositioning was determined for 13 healthy adults (10 women, 3 men; mean age 27 yrs). The coefficient of variation (CV, %) varied from 0.65 (ToA) to 1.66 (TrbD) at the distal tibia and from 0.72 (ToA) to 0.94 (CoA) at the midshaft.

Table 2-3. Analysis modes, thresholds and outcome variables for pQCT measurements at the distal (8%), midshaft (50%) and proximal two-thirds (66%) sites of the tibia.

Site	Analysis Mode (Threshold)	Variable
Distal (8%)	Contour Mode 3 (200 mg/cm^3) Peel Mode 5 (Automatic) Separation Mode 3 (default, 169 mg/cm^3)	Total bone cross-sectional area (ToA, mm^2) Total density (ToD, mg/cm^3)
Shaft (50%, 66%)	Contour Mode 1 (711 mg/cm^3) Peel Mode 2 (540 mg/cm^3) Separation Mode 1 (default, 711 mg/cm^3)	Total bone area (ToA, mm^2) Cortical area (CoA, mm^2) Cortical density (CoD, mg/cm^3)
Shaft (50%, 66%)	Contour Mode 1 (711 mg/cm^3) Peel Mode 2 (540 mg/cm^3) Separation Mode 1 (480 mg/cm^3)	Polar strength-strain index (SSI_p, mm^3)
Shaft (66%)	Contour Mode 1 (-100 mg/cm^3) Peel Mode 2 (40 mg/cm^3) Separation Mode 1 (default, 711 mg/cm^3)	Muscle cross-sectional area (MCSA, mm^2)

2.2.8.4 Body Composition and Muscle Cross-sectional Area

Total body fat mass and bone-mineral free lean mass were generated from total body DXA scans. In our lab the precision for these measures (with repositioning) in healthy adults is 1.9% for total body fat mass and 0.33% for total body lean mass (UBC Bone Health Research Group, unpublished data). The acquisition and analysis protocols were the same as those described for DXA-derived bone outcomes.

Muscle cross-sectional area (MCSA) of the left lower leg was determined from the single slice pQCT measurement obtained at the proximal two-thirds site (66% site). Similar to pQCT analysis for bone outcomes, the analysis of MCSA is an automated process but requires specification of a ROI and separation thresholds. The ROI for muscle analysis is automatically positioned around the entire cross-section therefore includes all of the soft tissue and bone. The modes and thresholds used to determine MCSA are presented in Table 2-3.

2.2.8.5 Anthropometry

The Bone Health Research Group has used all of the following procedures extensively in previous studies (3,4,11,12). Stretch statures for both standing height and sitting height (without shoes) were measured by standard method, applying gentle upward traction from the base of the mastoid process. Measurements were recorded to the nearest millimetre, using a wall-mounted stadiometer (Seca Model 242, Hanover, MD). Total leg length was derived as the difference between standing height and sitting height. Weight was measured on a calibrated electronic scale (Seca Model 840, Hanover, MD) to the nearest 0.1 kg. For sitting and standing height and weight, duplicate measures were taken unless measures differed by ±0.4 cm (height) or ±0.2 kg (weight), when we took a third measurement. The average of 2 values was used for analysis. If three measures were taken, the two values within 0.4 mm were used to determine the average value. Maximum calf girth and tibial length were measured to the nearest millimetre by standard method using an anthropometric tape. All anthropometric measures were recorded on the Personal Data Form (Appendix 6).

2.2.8.6 Physical Performance

Vertical and horizontal jump tests were used to assess lower limb dynamic muscle power. Vertical jump performance was evaluted using the Vertec™ device (Fitness Source, Concord, ON), which provides jump heights in 1/2" increments. First, the child's highest reaching point (highest Vertec™ slat reached) was determined while the child stood with feet flat on the ground (no shoes) beside the Vertec™. Second, the child performed a maximum two-foot takeoff jump from a standing position and we recorded the highest slat reached. The difference between the jump height and the standing height was converted to centimetres. For the horizontal jump, children performed a barefoot, two-foot take-off from a matted surface according to ACSM protocol (20). The feet were chalked to mark the landing and the recorder measured the distance, to the nearest mm, from the starting line to the most proximal heel mark. For both vertical and horizontal jumps, children took 2 practice jumps, followed by 3 recorded performances. The best of the three performances was used for analysis.

2.2.8.7 Questionnaires

2.2.8.7.1 Maturity

Stage of sexual maturity was assessed at baseline and followup using self-report Tanner Staging (21). This method requires a child to choose from a series of line drawings that depict the 5 stages of development of secondary sex characteristics the drawing(s) that he/she feels best represent(s) his/her physical appearance. The

line drawings include breast development and pubic hair for girls and pubic hair for boys (Appendix 6). The diagrams are accompanied by brief descriptions of the visual appearance of the stages. In our lab, children completed the form in private following instructions from a research assistant. Children returned the completed form in a sealed envelope to the research assistant. At baseline and followup girls were also asked if they had had their first period (menarcheal status), and if yes, they were asked to provide the approximate date of this event.

Due to the differences in timing between onset of pubic hair and breast development (22,23) and the association between estrogen levels and breast development (24), I used breast stage only to determine maturational stage in girls. Self-assessment of maturity correlates well with physician ratings; coefficients of variations were 0.81, 0.91 and 0.88 respectively for girls' breast, girls' pubic hair and boys' pubic hair (25).

2.2.8.7.2 Physical Activity

Leisure-time physical activity was assessed using the Physical Activity Questionnaire for Children (PAQ-C) (26,27) (Appendix 6). A research assistant guided the children in completing the PAQ-C. Where appropriate, cues to facilitate children with time estimates were provided (i.e., recess is 15 minutes long, lunch time is 45 minutes long, etc.). In addition to baseline and followup, the PAQ-C was administered 3 other times during the study period (Figure 2-3) to account for seasonal variation in children's activity levels. Our group has modified the original 10-item, 7-day recall questionnaire to include 12 items and an estimation of time spent in physical activity:

Item 1. The child recalls from a list of common sports and activities any activity they participated in during the previous week. An estimate of the minutes per session for each activity was added to Item 1. (*modification to original questionnaire*)

Items 2-7. The child recalls the amount of physical activity participation at different times during the previous weekdays (P.E. classes, recess, lunch, after school, evening) and weekend.

Item 8. The child selects a statement which best describes their level of activity (number of times they were active) over the previous 7 days.

Item 9. The child reports how many hours of television they watched or video games they played each day during the previous week. (*modification to original questionnaire*)

Item 10. The child reports whether they were sick at any point over the past week, and if so, if this prevented them from participating in regular physical activity.

Item 11. The child describes their level of activity (none to very often) on each day of the previous week.

Item 12. The child reports if they participate in any extra-curricular sports or activities, and if so how many days/nights during the week they do the activity(ies). (*modification to original questionnaire*)

For this thesis, I report 2 physical activity variables: general physical activity score and load time. The general physical activity score (*PA score*) was calculated as an average of Items 1-8 and Item 11, in a continuous range between 1 (low active) and 5 (high active). Physical activity time was calculated as the average number of minutes per day of physical activity reported in Item 1. The activity time was further broken down into the time spent

in loaded physical activities (those activities with an estimated impact greater than walking, *load time*, hours/week). Finally, from Item 12, I report the number of days/nights per week spent in extra-curricular sporting activities (*sport nights*, scored as 0 through 7).

Reliability of single assessments and of the average of 5 assessments was tested with the intraclass correlation coefficient (ICC). The ICC for a single assessment of PA score was 0.55 for boys and 0.49 for girls and for a single assessment of load time was 0.41 for boys and 0.46 for girls (all $p < 0.001$). The reliability improved with multiple assessments. The ICC for 5 reports of PA score was 0.86 for boys and 0.83 for girls and for 5 reports of load time was 0.78 for boys and 0.81 for girls (all $p < 0.001$). Correlations between average PA score (average of 5 reports) and average load time (average of 5 reports) was 0.62 ($p < 0.001$).

2.2.8.7.3 Dietary Calcium

I used a food frequency questionnaire (FFQ) to assess dietary intake of calcium (Appendix 6). This questionnaire is valid for use with Asian and Caucasian adolescents (28), has low respondent burden and short administration time. An RA assisted one or two children at a time and provided cues to facilitate recall such as "Do you have this food in your lunch every week day?" or "How many times have you had this food in the last month?" In addition, food models in appropriate portion sizes were available to assist the children. The FFQ was used to estimate a daily calcium intake (mg/day) based on the calcium content of the food items. This questionnaire was administered 5 times during the study period in order to assess mean and seasonal variation in calcium intake.

Similar to the PAQ-C, reliability of the FFQ improved with multiple assessments. The ICC for a single assessment was 0.50 for boys and 0.51 for girls and for 5 assessments was 0.83 for boys and 0.84 for girls ($p < 0.001$).

2.2.9 Statistical Analysis

In this section I provide an overview of the statistical analyses used in this thesis. The specific analyses used for Parts I-III are presented in the Methods section of each chapter. Data were analyzed using both SPSS statistical software, Windows Version 13.0 (SPSS Inc., Chicago, IL) and STATA software, Version 9.0 (StataCorp LP., College Station, TX).

2.2.9.1 Statistical Power

The primary independent variable of interest in this thesis is bone strength. However, as outlined, I used two methodologies to evaluate bone strength at different skeletal sites. As a result, there are different primary outcomes associated with each imaging modality. For the pQCT analysis, the primary outcomes were change in polar strength strain index (SSI_p) at the tibial midshaft and bone strength index (BSI) at the distal tibia. For the HSA analysis the primary outcome was change in narrow neck section modulus (Z). Of these variables, an intervention effect has previously been shown in Z only (14,15). Based on the findings of Petit et al. (14), sufficient power was required to detect a difference of 4% in the primary outcome, change in Z. Based on a 2:1 randomization (assuming Level 1 and 2 intervention schools will be collapsed in the analysis), 80% power, a Type I error of 5% (2-sided) and a standard

deviation of 5%, a total of 60 children were required. To allow for within-sex and between maturity-group comparisons and an attrition rate of 10% between school years a total of 264 children were required. However, all children in grades 4 and 5 in each of the 10 schools were invited to participate and the consent rate (47%) was greater than expected. Thus, a larger number of children (n = 514) were randomized.

It should be noted that this sample size calculation does not account for the clustered study design (schools randomized, not individual children). Estimates of sample size in cluster randomized trials should account for both the within- and between-cluster variation (29). Often, in cluster randomized trials, responses or scores of individuals within a cluster tend to be more similar than those between individuals in different clusters. If the effect of clustering is ignored, the variability of the intervention effect may be underestimated due to falsely narrow confidence intervals (30). Since the variance is affected by cluster design, the sample size required for a certain power is also affected. The degree to which the sample size is affected is determined by an inflation factor (design effect) that accounts for both cluster size and the intracluster correlation coefficient (ICC) (31). The ICC (ρ_I) calculated as:

$$\rho_I = s_c^2 / (s_c^2 + s_w^2) \qquad \text{(Equation 1)}$$

where s_c^2 equals the variance between clusters and s_w^2 equals the variance within clusters (31). The design effect (or variance inflation factor) is then calculated as:

$$D = 1 + (m-1)^* \rho_I \qquad \text{(Equation 2)}$$

where m equals the number of observations per cluster and ρ_I equals the ICC.

To date, there have been no published reports of the ICC for any bone outcomes in pediatric intervention studies that employed a clustered design. However, based on data from the HBS II study I estimated the design effect for DXA-derived BMC. In HBS II the variability *between* schools (FN BMC: SD = 0.00001 and LS BMC: SD = 0.13) was far less than the variability within *schools* (FN BMC: SD = 0.20 and LS BMC: SD = 2.70) (32). If these standard deviations are converted to variance, the ICC can be calculated as the ratio of the between school variance to the sum of the between and within school variance. For HBS II, the ICC was 0.002. With this ICC, I then estimated the design effect for the current study in which there are 10 clusters with a median of 49 participants per cluster. Therefore, D = 1 + (49-1)*0.002 = 1.096. Thus, based on the ICC for BMC, the sample size should be approximately 10% greater (n = 290) than that required for a trial where children are randomized individually. The large number of children randomized in the present study may account for this estimated design effect. However, it is not known if the same inferences can be made for the between- and within-school variance in pQCT or HSA outcomes. Thus, for the analyses of change in Parts II and III I employ statistical techniques that account for the clustered design (mixed linear model, robust standard error). I report the ICC for all analyses and discuss the effects on sample size estimation for future school-based studies in the discussion of Parts II and III.

2.2.9.2 Mixed Linear Model

The mixed linear model is an extension of the general linear regression model in which an additional term is added to model the random effect due to clustering. A simplified version of the model can be summarized as:

$$y_{ij} = \alpha + \beta_1 x_{1ij} + \beta_2 x_{2ij} + \mu_j + e_{ij} \quad \text{(Equation 3)}$$

where y_{ij} is the outcome for the i^{th} individual in the j^{th} cluster, α is the intercept or constant, β is the slope or regression coefficient that describes the relationship between x and y, μ_j is the random effect of the j^{th} cluster and e is the random error term (residual) (30,33).

For Part II, I fit the mixed linear model using STATA. In addition to group (intervention or control, *fixed effect*) and school (*random effect*), covariates were included in the models for change in pQCT outcomes. Covariates were chosen based on relationships established in Part I and on established biological and biomechanical relationships. In addition, I evaluated the influence of group imbalances in baseline characteristics on the overall model (coefficients, standard errors, confidence intervals). Variables which demonstrated a significant influence were also included as covariates. Generally covariates fell into one of four categories: baseline bone or body size, rate of linear growth (change in tibial length), rate of increase in MCSA and maturity (final Tanner stage). Separate models were created for boys and girls.

For Part III, I attempted to use the mixed linear model for DXA and HSA outcomes. However, due to small values for within school variance (indicated by the small ICC values at baseline, Appendix 10) combined with the relatively small number of clusters, the software failed to arrive at a solution (i.e., the mixed linear model failed to converge) for some of the DXA and HSA outcomes. Therefore, I used linear regression to estimate the intervention effect. I used the design effect (or variance inflation factor) to adjust the variance of the intervention effect as outlined by Murray (34). The design effect was determined using a conservative estimate of the ICC (0.05). Similar to Part II, separate models were created for boys and girls and independent variables in the regression models included baseline body size, rate of linear growth (change in height), rate of increase in total body lean mass and maturity (final Tanner stage).

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3 Overview of the Cohort

3.1 Participants

A total of 515 children (258 boys, 257 girls) and their parents/guardians provided informed consent to participate in this study. However, 1 boy from a control school had parental consent for the questionnaire component but not for bone densitometry. Thus, 514 children had consent for all parts of the bone health evaluation at baseline. This represents 47% of the total grade 4 and 5 student population across the 10 schools (Table 3-1). Importantly, although only 47% of children participated in the study, all children (n = 1212) in grade 4 and 5 classes and in grade 3/4 and 5/6 split classes in each of the 10 schools were exposed to the intervention.

The number of children in Level 1 (n = 188), Level 2 (n = 171) and Control (n = 155) was balanced. As discussed (Section 2.2.2), the two intervention arms were collapsed for the purpose of this thesis. As a result, there were more Intervention (n = 359) than Control (n = 155) children. The consent rate and number of participants at each school is provided (Table 3-1) as is the breakdown of the cohort by sex and ethnicity at baseline and followup (Table 3-2). Overall, 54.3% of the children were Asian, 33.5% were Caucasian and 12.2% were of other ethnicities.

Descriptive characteristics and values for select bone outcomes at baseline for Intervention and Control children and for boys and girls at baseline are provided (Table 3-3 and Table 3-4, respectively). Based on parental report in the health history questionnaire we excluded 5 children from all analyses, although these children still participated in data collection. We excluded 2 Intervention boys and 3 girls (2 Intervention, 1 Control) based on conditions that could affect normal physical activity or bone development. These conditions included leukemia, fetal alcohol syndrome, malignant brain tumour, mild osteogenesis imperfecta and Type I diabetes. Thus, baseline values for descriptive characteristics and select bone outcomes are presented for 509 children (355 Intervention, 153 Control; 255 boys, 254 girls).

At baseline, boys and girls were of a similar age and ethnic distribution. The majority of boys were in Tanner stage 1 (62%) with a smaller percentage in Tanner stage 2 (32%) and Tanner stage 3 (6%). In contrast, the majority of girls were in Tanner stage 2 (53%) with a smaller percentage in Tanner stage 1 (37%) and Tanner stage 3 (10%). A small number of girls (8%) were post-menarcheal at baseline.

Table 3-1. Summary of consent rates across Control (CON) and Intervention (INT) schools at baseline. Intervention schools 1 through 4 are Level 1 intervention schools and schools 5-7 are Level 2 intervention schools.

School	Teacher ID	Class size	No. of eligible students (grade 4 or 5)	No. of students with consent	% with consent
CON - 1	1	31	31	12	
	2	30	30	7	
	3	30	30	5	
Totals		91	91	24	26
CON - 2	17	29	14	8	
	18	28	28	18	
	19	21	10	4	
	20	24	16	7	
	21	25	25	16	
Totals		127	93	53	57
CON - 3	22	29	29	6	
	23	29	29	8	
	24	31	31	14	
	25	31	31	24	
	26	30	30	22	
	27	30	10	4	
	28	30	9	0	
Totals		210	169	78	46
INT - 1	4	28	28	9	
	5	30	30	20	
	54	23	11	8	
Totals		81	69	37	54
INT - 2	12	31	31	15	
	13	32	32	11	
	14	29	29	17	
	15	30	30	8	
	52	23	7	0	
Totals		145	129	51	40
INT - 3	35	27	27	8	
	36	30	30	12	
	38	31	31	12	
	51	29	29	4	
Totals		117	117	36	31
INT - 4	47	28	28	15	
	48	28	28	14	
	49	30	30	16	
	50	30	30	19	
Totals		116	116	64	55

Table 3-1 continued.

School	Teacher ID	Class size	No. of eligible students (grade 4 or 5)	No. of students with consent	% with consent
INT - 5	6	26	26	7	
	7	26	26	8	
	8	28	28	10	
	10	27	27	13	
	11	22	16	9	
Totals		129	123	47	38
INT - 6	29	24	13	5	
	30	30	30	23	
	32	30	22	18	
	33	30	30	23	
	53	31	31	25	
Totals		145	126	94	74
INT - 7	45	26	26	14	
	44	25	25	16	
Totals		51	51	30	58
TOTALS		1212	1084	514	47

Table 3-2. Boys and girls by group and ethnicity at baseline (N = 514: 359 Intervention, 155 Control) and followup (N = 443: 312 Intervention, 131 Control).

			Boys	Girls	Total (%)
Baseline	Intervention	Asian	99	102	201 (56)
		Caucasian	61	56	117 (33)
		Other	17	24	41 (11)
	Control	Asian	41	37	78 (50)
		Caucasian	26	29	55 (35)
		Other	13	9	22 (14)
	Total Group	Asian	140	139	279 (54)
		Caucasian	87	85	172 (33)
		Other	30	33	63 (12)
Followup	Intervention	Asian	89	84	173 (55)
		Caucasian	56	48	104 (33)
		Other	15	20	35 (11)
	Control	Asian	32	32	64 (49)
		Caucasian	21	27	48 (37)
		Other	12	7	19 (15)
	Total Group	Asian	121	116	237 (53)
		Caucasian	77	75	152 (34)
		Other	27	27	54 (12)

Table 3-3. Age, maturity, body size and composition, lifestyle variables, physical performance, tibial bone geometry, density and strength indices, bone mineral content (BMC) and femoral neck geometry and strength at baseline for Intervention and Control children.

	Intervention			Control		
	Mean (SD)	Minimum	Maximum	Mean (SD)	Minimum	Maximum
N	355	-----	-----	154	-----	-----
# Tanner 1/2/3/4/5	175/151/29/0/0	-----	-----	79/65/10/0/0	-----	-----
# Post-menarcheal	6	-----	-----	2	-----	-----
Age (yrs)	10.2 (0.6)	8.9	11.7	10.3 (0.6)	9.2	11.3
Height (cm)	141.2 (7.3)	123.9	161.1	141.4 (7.3)	126.3	166.3
Weight (kg)	36.8 (8.9)	20.0	80.4	38.2 (9.6)	22.9	77.1
Sitting height (cm)	74.3 (3.7)	64.7	85.6	74.7 (3.8)	65.0	85.5
Tibial length (cm)	32.9 (2.4)	27.5	39.5	32.8 (2.2)	27.1	39.4
Lean mass (kg)	25.0 (4.0)	14.6	39.1	25.4 (4.5)	16.6	43.2
Fat mass (kg)	9.8 (5.3)	3.0	37.7	10.8 (5.6)	3.2	35.4
MCSA (mm^2)	3372.7 (534.2)	2195.7	5025.8	3385.3 (537.5)	2362.2	5180.3
Physical activity score	2.6 (0.5)	1.3	3.7	2.6 (0.5)	1.2	3.8
Load time (hrs/week)	4.9 (4.0)	0	25.5	5.1 (4.0)	0	17.9
Sport Nights (#/week)	2.0 (2.0)	0	7	1.0 (2.0)	0	7
Long jump (cm)	127.2 (17.1)	83.6	172.6	126.8 (18.5)	84.9	187.2
Vertical jump (cm)	26.6 (5.4)	15.2	45.7	26.5 (5.2)	13.0	43.2
Dietary calcium (mg/day)	897 (479)	88	2687	876 (437)	102	2368
ToA – 8% site (mm^2)	529.7 (84.7)	333.3	878.4	531.3 (85.9)	328.2	797.9
ToD – 8% site (mg/cm^3)	300.5 (34.3)	222.6	395.2	303.2 (32.6)	231.9	407.2
BSI – 8% site (mg^2/mm^4)	4798.8 (1151.0)	2163.7	8498.8	4914.2 (1201.1)	2571.1	9160.8
CoA – 50% site (mm^2)	193.7 (31.8)	115.2	294.6	193.9 (30.9)	123.5	274.2
CoD – 50% site (mg/cm^3)	1052.0 (34.9)	910.3	1126.2	1050.1 (31.0)	939.2	1119.3
SSI – 50% site (mm^3)	979.7 (228.2)	495.4	1818.0	984.9 (222.5)	553.8	1592.0
Total body BMC (g)	1056.9 (197.3)	616.6	1694.0	1070.6 (188.6)	686.3	1623.0
Lumbar spine BMC (g)	23.6 (5.4)	12.0	42.4	23.8 (4.9)	14.7	38.5
Proximal femur BMC (g)	15.6 (3.4)	7.4	26.9	15.6 (3.3)	9.0	25.2
Femoral neck BMC (g)	2.7 (0.4)	1.7	4.3	2.7 (0.5)	1.6	4.0
Narrow Neck CSA (mm^2)	1.61 (0.26)	0.99	2.48	1.64 (0.26)	0.97	2.51
Narrow Neck Z (mm^3)	0.59 (0.13)	0.28	1.10	0.61 (0.14)	0.31	1.08
Narrow Neck Width (mm)	2.60 (0.20)	1.95	3.33	2.64 (0.19)	2.22	3.25

MCSA = muscle cross-sectional area; ToA = total bone cross-sectional area; ToD = total density; BSI = bone strength index; CoA = cortical bone cross-sectional area; CoD = cortical density; SSI = strength-strain index; CSA = cross-sectional area; Z = section modulus; Width = subperiosteal width.

Table 3-4. Boys' and girls' age, ethnic distribution, maturity, body size and composition, lifestyle variables, physical performance, tibial bone geometry, density and strength indices, bone mineral content (BMC) and femoral neck bone geometry and strength at baseline.

	Boys			Girls		
	Mean (SD)	Minimum	Maximum	Mean (SD)	Minimum	Maximum
N	255	-----	-----	254	-----	-----
# Asian/Caucasian/Other	145 / 85 / 30	-----	-----	138 / 83 / 33	-----	-----
# Tanner 1 / 2 / 3 / 4 / 5	159 / 82 / 14 / 0 / 0	-----	-----	95 / 134 / 25 / 0 / 0	-----	-----
# Post-menarcheal	-----	-----	-----	8	-----	-----
Age (yrs)	10.2 (0.6)	8.9	11.4	10.2 (0.6)	9.2	11.7
Height (cm)	141.3 (7.1)	124.0	159.4	141.1 (7.6)	123.9	166.3
Weight (kg)	38.1 (9.7)	22.3	80.4	36.4 (8.4)	20.0	65.7
Sitting height (cm)	74.4 (3.5)	65.0	85.5	74.5 (4.0)	65.0	85.5
Tibial length (cm)	32.9 (2.3)	27.5	39.5	32.9 (2.4)	27.1	39.4
Lean mass (kg)	25.9 (4.1)	16.5	43.2	24.3 (4.1)	14.6	35.6
Fat mass (kg)	10.1 (5.9)	3.0	37.7	10.1 (4.8)	3.5	27.3
MCSA (mm^2)	3412.6 (530.7)	2072.2	5180.3	3330.1 (565.2)	2049.4	5069.3
Physical activity score	2.6 (0.5)	1.2	3.8	2.5 (0.5)	1.3	3.7
Load time (hrs/week)	5.8 (4.4)	0	25.5	4.1 (3.2)	0	16.7
Sport Nights (#/week)	1.6 (2.0)	0	7	1.3 (1.8)	0	7
Long jump (cm)	132.8 (18.3)	87.1	187.2	121.5 (14.5)	83.6	155.0
Vertical jump (cm)	27.7 (5.5)	15.2	45.7	25.5 (4.8)	13.0	43.2
Dietary calcium (mg/day)	944 (497)	140	2687	836 (429)	88	2159
ToA – 8% site (mm^2)	548.9 (88.6)	339.8	878.4	511.1 (76.8)	328.2	815.0
ToD – 8% site (mg/cm^3)	306.4 (31.1)	232.7	407.2	296.2 (35.6)	222.6	395.2
BSI – 8% site (mg^2/mm^4)	5151.5 (1086.4)	2842.1	9160.8	4472.7 (1137.2)	2163.7	8498.8
CoA – 50% site (mm^2)	197.8 (31.7)	115.2	294.6	189.8 (30.8)	118.1	274.2
CoD – 50% site (mg/cm^3)	1046.6 (34.5)	910.3	1126.2	1056.2 (32.4)	952.4	1125.3
SSI – 50% site (mm^3)	1010.6 (233.5)	495.4	1818.0	952.7 (215.0)	553.8	1592.0
Total body BMC (g)	1081.4 (186.9)	695.9	1694.0	1040.6 (200.4)	616.6	1636.1
Lumbar spine BMC (g)	23.3 (4.7)	12.9	36.7	24.0 (5.7)	12.0	42.4
Proximal femur BMC (g)	15.9 (3.2)	10.3	26.9	15.2 (3.5)	7.4	25.9
Femoral neck BMC (g)	2.8 (0.4)	1.9	4.3	2.5 (0.4)	1.6	4.1
Narrow Neck CSA (mm^2)	1.68 (0.25)	1.15	2.48	1.56 (0.26)	0.97	2.51
Narrow Neck Z (mm^3)	0.63 (0.13)	0.34	1.10	0.56 (0.12)	0.28	1.08
Narrow Neck Width (mm)	2.64 (0.21)	1.95	3.25	2.58 (0.18)	2.10	3.33

MCSA = muscle cross-sectional area; ToA = total bone cross-sectional area; ToD = total density; BSI = bone strength index; CoA = cortical bone cross-sectional area; CoD = cortical density; SSI = strength-strain index; CSA = cross-sectional area; Z = section modulus; Width = subperiosteal width.

3.2 Participants Lost to Followup

Seventy-one children (47 INT, 24 CON) were lost to followup; 59 children (40 INT, 19 CON) moved either out of the province or to other schools in the Vancouver or Richmond Districts (that were not participating in the study) and declined participation the followup measurement, 7 children (4 INT, 3 CON) remained in the same school but declined participation in the followup measurement, and 5 children (3 INT, 2 CON) could not be scheduled for the final measurement (Figure 3-1and Figure 3-2). There were no significant differences in any of the descriptive characteristics or bone variables between children lost to followup and those who remained in the study. Eleven children (7 INT, 4 CON) moved to a different school (not participating in the study) but returned for followup. Two boys moved to another school participating in the study; 1 moved from an INT to a CON school and 1 moved from one INT school to another. Both boys returned for followup measurements. One INT boy was excluded from the analysis because of a broken femur sustained during Phase II (September 2003 – June 2004) which caused him to miss several months of school. The number of acceptable scans for each bone imaging technique is provided (Table 3-5). The numbers presented incorporate both participants lost to followup and scans that could not be analyzed due to movement artefacts.

Baseline and 16-month absolute and percent change for select descriptive characteristics and bone outcomes for each school are presented (Table 3-6). The narrowest range for change between schools was for height (4.8% - 5.6%) and the widest range was for change in proximal femur BMC (19.9% - 28.9%).

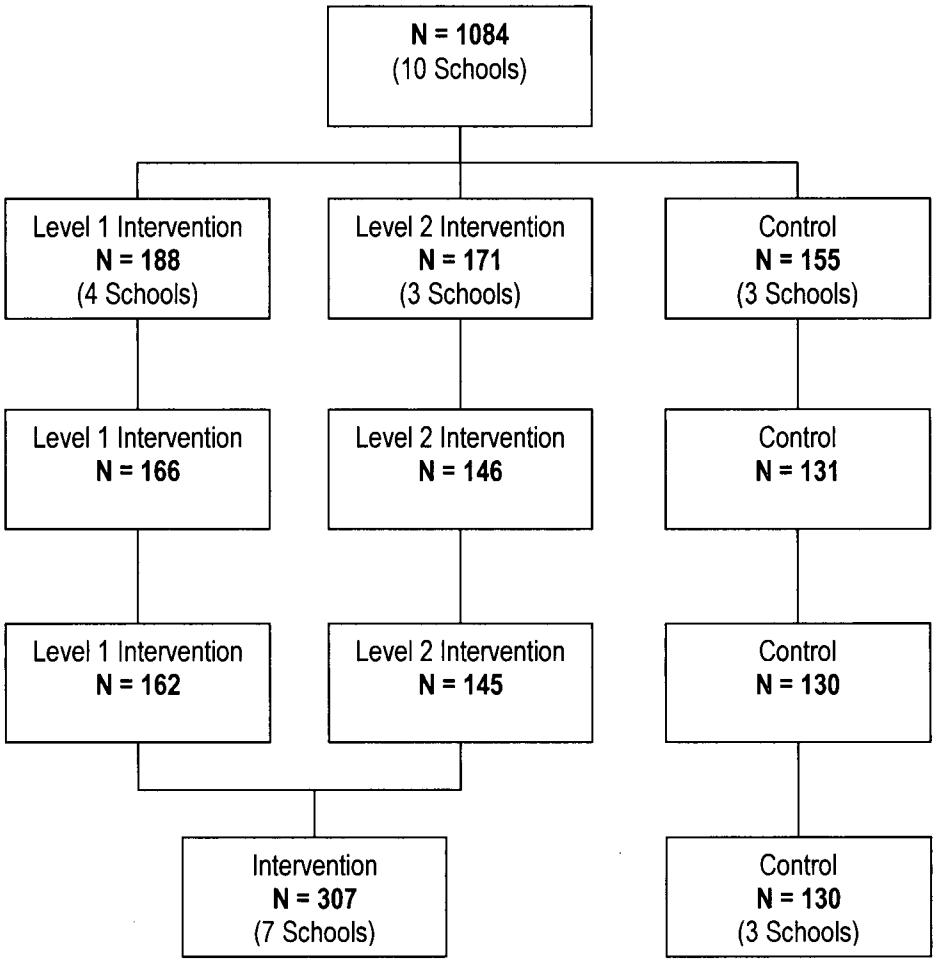

Figure 3-1. Flow of participants through trial (simplified view).

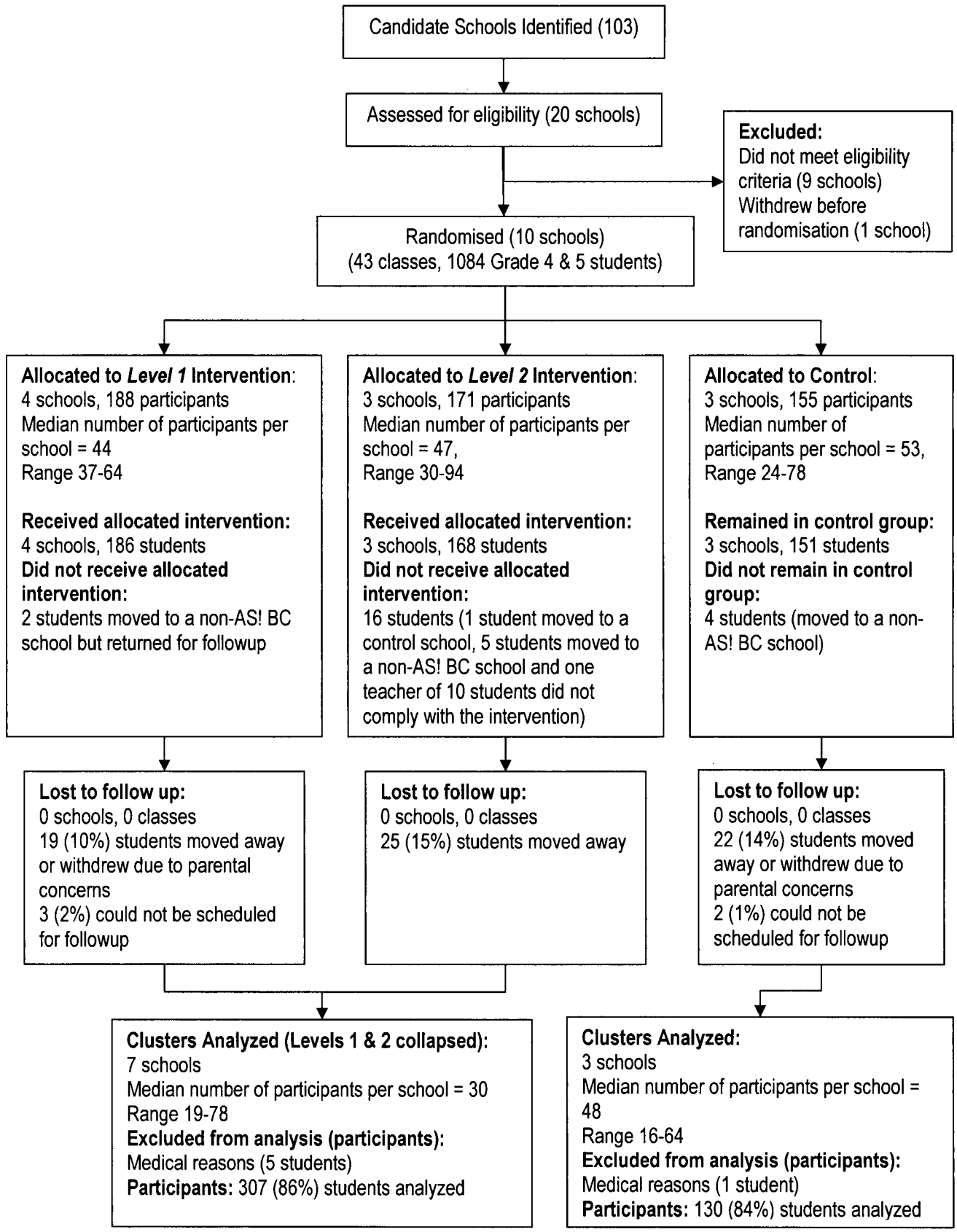

Figure 3-2. Flow of participants through trial [detailed view according to CONSORT guidelines (1)].

Table 3-5. Number of acceptable scans for dual energy X-ray absorptiometry (DXA), hip structure analysis (HSA) and peripheral quantitative computed tomography (pQCT) analysis at baseline and followup for boys and girls in intervention and control groups.

Instrument - Site	Group	Baseline n (Boys / Girls)	Baseline Total (INT + CON)	Followup n (Boys / Girls)	Followup Total (INT + CON)
DXA – Total Body	Intervention	355 (175 / 180)	508	307 (157 / 150)	437
	Control	153 (80 / 73)		130 (65 / 65)	
DXA – Proximal Femur	Intervention	354 (174 / 180)	507	305 (155 / 150)	435
	Control	153 (80 / 73)		130 (65 / 65)	
DXA – Lumbar Spine	Intervention	353 (174 / 179)	505	306 (156 / 150)	435
	Control	152 (80 / 72)		129 (65 / 64)	
HSA – Narrow Neck	Intervention	346 (170 / 176)	493	294 (151 / 143)	415
	Control	147 (79 / 68)		121 (63 / 58)	
pQCT – Distal (8%)	Intervention	307 (154 / 153)	465	269 (140 / 129)	391
	Control	158 (76 / 72)		122 (59 / 63)	
pQCT – Midshaft (50%)	Intervention	325 (161 / 164)	475	280 (145 / 135)	408
	Control	150 (79 / 71)		128 (64 / 64)	
pQCT – Proximal Two-Thirds (66%)	Intervention	313 (156 / 157)	457	269 (140 / 129)	391
	Control	144 (74 / 70)		122 (59 / 63)	

Table 3-6. Baseline, 16-month absolute and percent (%) change (Δ) for height, weight, proximal femur bone mineral content (PF BMC), polar strength strain index (SSI_p) and narrow neck section modulus (NN-Z) and 16-month average dietary calcium intake, physical activity score (PA Score) and load time for Control (CON) and Intervention (INT) schools. Mean (SD).

	CONTROL			INTERVENTION						
School	**CON - 1 (n = 17)**	**CON - 2 (n = 48)**	**CON - 3 (n = 64)**	**INT - 1 (n = 28)**	**INT - 2 (n = 44)**	**INT - 3 (n = 32)**	**INT - 4 (n = 55)**	**INT - 5 (n = 37)**	**INT - 6 (n = 78)**	**INT - 7 (n = 27)**
Baseline Age (yrs)	10.3 (0.4)	10.4 (0.5)	10.2 (0.6)	10.1 (0.6)	10.3 (0.7)	10.3 (0.5)	10.3 (0.6)	9.9 (0.6)	10.1 (0.6)	10.2 (0.5)
Baseline Height (cm)	142.2 (6.9)	141.9 (7.5)	139.7 (6.7)	140.4 (7.3)	140.6 (7.9)	143.3 (6.8)	140.3 (6.4)	138.9 (6.7)	141.3 (7.2)	144.4 (9.1)
Height Δ (cm)	6.9 (1.5)	7.1 (2.0)	7.8 (2.0)	7.6 (2.0)	7.7 (2.0)	6.7 (1.8)	6.8 (1.8)	6.9 (1.7)	7.6 (2.2)	7.0 (1.9)
Height % Δ	4.8 (1.1)	5.0 (1.4)	5.6 (1.4)	5.4 (1.3)	5.5 (1.4)	4.7 (1.2)	4.8 (1.2)	5.2 (1.2)	5.4 (1.5)	4.9 (1.3)
Baseline Weight (kg)	42.0 (12.4)	38.0 (9.2)	36.2 (9.4)	37.5 (8.6)	36.1 (8.2)	38.0 (11.2)	36.0 (7.6)	35.9 (8.7)	36.4 (9.3)	38.5 (10.4)
Weight Δ (kg)	6.2 (3.9)	6.6 (3.7)	6.1 (2.2)	6.3 (2.8)	5.3 (2.4)	5.4 (2.1)	5.4 (2.5)	6.0 (3.3)	6.4 (2.8)	5.4 (2.5)
Weight % Δ	14.6 (7.7)	17.4 (8.3)	17.2 (7.0)	16.8 (7.0)	14.8 (6.0)	14.3 (5.1)	15.1 (5.9)	15.6 (9.3)	17.9 (7.2)	14.8 (6.7)
Baseline PF BMC (g)	15.8 (3.4)	15.8 (3.7)	14.8 (2.8)	15.7 (3.6)	14.7 (3.1)	16.5 (3.6)	16.0 (2.6)	15.1 (3.5)	15.7 (3.6)	16.1 (4.9)
PF BMC Δ (g)	3.1 (1.6)	4.2 (1.7)	3.8 (1.7)	3.9 (1.7)	4.3 (1.9)	3.8 (2.1)	3.2 (1.6)	3.5 (1.6)	3.5 (1.7)	3.7 (1.9)
PF BMC % Δ	20.1 (9.7)	27.0 (9.8)	25.9 (10.0)	24.8 (8.8)	28.9 (11.1)	23.2 (12.0)	19.9 (8.7)	22.9 (10.0)	22.6 (9.3)	24.1 (12.6)

Table 3-6 continued.

School	CON - 1 (n = 17)	CON - 2 (n = 48)	CON - 3 (n = 64)	INT - 1 (n = 28)	INT - 2 (n = 44)	INT - 3 (n = 32)	INT - 4 (n = 55)	INT - 5 (n = 37)	INT - 6 (n = 78)	INT - 7 (n = 27)
Baseline SSI_P (mm^3)	994.7 (199.4)	986.9 (248.8)	956.4 (210.2)	997.4 (220.1)	934.5 (220.4)	1021.7 (232.2)	965.4 (212.4)	904.2 (173.0)	1002.8 (253.8)	1028.4 (266.4)
SSI_P Δ (mm^3)	156.7 (46.6)	185.0 (76.0)	178.3 (63.3)	209.9 (107.1)	187.4 (84.5)	183.5 (69.6)	165.5 (67.9)	205.4 (72.4)	182.2 (76.5)	184.2 (76.9)
SSI_P % Δ	16.2 (5.7)	18.7 (5.9)	18.9 (5.7)	20.5 (8.1)	19.9 (7.4)	18.2 (6.5)	17.0 (5.8)	22.7 (7.0)	18.4 (6.3)	18.4 (7.0)
Baseline NN-Z (mm^3)	1.72 (0.26)	1.71 (0.29)	1.56 (0.22)	1.58 (0.23)	1.53 (0.24)	1.66 (0.27)	1.72 (0.23)	1.57 (0.24)	1.59 (0.26)	1.63 (0.36)
NN-Z Δ (mm^3)	0.08 (0.05)	0.09 (0.07)	0.11 (0.05)	0.13 (0.08)	0.11 (0.06)	0.12 (0.06)	0.09 (0.05)	0.09 (0.05)	0.10 (0.05)	0.10 (0.06)
NN-Z % Δ	13.6 (8.4)	14.8 (10.8)	19.4 (9.4)	22.0 (12.4)	20.5 (9.6)	19.5 (9.8)	15.0 (8.1)	16.4 (9.0)	18.1 (8.5)	17.5 (11.2)
PA Score (1-5)	2.5 (0.3)	2.8 (0.4)	2.6 (0.3)	2.6 (0.5)	2.6 (0.4)	2.6 (0.3)	2.7 (0.3)	2.7 (0.3)	2.7 (0.4)	2.8 (0.3)
Load time (hrs/wk)	4.9 (3.7)	6.1 (3.7)	5.8 (4.1)	5.8 (4.2)	5.0 (3.7)	5.3 (3.5)	4.7 (3.5)	6.4 (3.9)	7.4 (4.8)	6.0 (4.0)
Dietary Calcium (mg/day)	741 (277)	974 (396)	812 (382)	812 (521)	755 (293)	910 (395)	1042 (507)	798 (329)	810 (300)	1006 (399)

Note: Values do not account for clustering.

References

1. Campbell MK, Elbourne DR, Altman DG 2004 CONSORT statement: extension to cluster randomised trials. BMJ **328:**702-8.

4 Part I: Bone Strength and its Determinants in Pre- and Early Pubertal Boys and Girls[2]

4.1 Introduction

Higher fracture rates in women than men may be related to a sex difference in bone strength that is thought to emerge during growth (1). Despite a plethora of cross-sectional and longitudinal pediatric dual energy x-ray absorptiometry (DXA) studies (2-7), there is still disagreement in the literature about when the sex difference in bone strength appears and which factors have the greatest influence on bone strength. Furthermore, it is not known if sex differences in bone strength in childhood and adolescence persist and are related to sex differences found in the elderly. This disagreement surrounding sex differences in bone strength is due, in part, to the use of bone mineral content (BMC) and areal bone mineral density (aBMD) as surrogates for bone strength because they do not fully account for bone size and ignore the geometry component of bone strength. In addition, BMC and aBMD are subject to a systematic inaccuracy introduced by assuming a uniform distribution of fat and lean tissue (8). Assessment of bone strength indices, bone geometry and (volumetric) density using techniques such as pQCT can provide further insight into sexual dimorphism in bone strength and the determinants of bone strength in boys and girls.

One hypothesis for the greater fracture rate in women is that their smaller skeleton incurs greater architectural damage and adapts less effectively by periosteal bone formation during aging (1,9). Sexual dimorphism in long bone geometry (size) and strength is thought to become evident during puberty when periosteal diameter expands to a greater extent in boys compared with girls (1,10-12). However, there is disagreement in the literature as to whether the sex difference in bone geometry, density and strength is evident in prepuberty. At the femoral diaphysis bone geometry is similar between prepubertal boys and girls (13-15), whereas at the second metacarpal (16) and radius (17,18) bone geometry, density and strength are greater in prepubertal boys than girls. When boys and girls were aligned on biological age, boys had significantly greater bone bending strength (section modulus) at the femoral neck than girls at all biological ages (19). It is not known whether a sex difference in bone strength is evident at the tibia in prepuberty.

During growth, bones must continually adapt their geometry and mass to withstand loads from increases in stature and muscle mass and forces (20,21). The mechanostat model postulates that the growing skeleton regulates its strength to maintain structural integrity and to keep mechanical strains within an acceptable range (21,22). During growth the primary mechanical challenges to the mechanostat come from increases in bone length and muscle force. In addition, the theoretical mechanostat is modulated by hormones, nutrition and physical activity. These factors may *indirectly* affect the mechanostat via their influence on the primary challengers (longitudinal growth or muscle force), the theoretical mechanostat setpoint (that determines the strain magnitude at which bone tissue will react) and/or the basic multicellular unit (osteoblasts and osteoclasts) (21,22).

[2] A version of this chapter has been accepted for publication. Macdonald HM, Kontulainen SA, Petit MA, Janssen PA, McKay HA. Bone strength and its determinants in pre- and early pubertal boys and girls. Bone 2006.

A number of pQCT studies have evaluated bone geometry, density and strength in the appendicular skeleton (radius, tibia) in healthy children (10,17,18,23-26). An advantage of pQCT is its ability to measure muscle cross-sectional area (MCSA) of the upper and lower limbs which is accepted as a reasonable surrogate for muscle force (27). However, only two of these studies have interpreted their data in the context of the mechanostat model using estimates of muscle forces (12,28). At the proximal radius, MCSA was a strong predictor of CoA in boys and girls (28). Whether this relationship between muscle and bone is similar at the distal or shaft sites of the tibia for boys and girls has not yet been determined.

Therefore, the objectives of this cross-sectional study were to 1) determine if there is a sex difference in tibial bone strength and its components (geometry and density) in pre- and early puberty and 2) evaluate the contribution of muscle force (using muscle cross-sectional area as a surrogate) and modulator variables (maturity, ethnicity, physical activity, dietary calcium and vertical jump height) to tibial bone geometry (total and cortical cross-sectional areas), density (total and cortical density) and estimated strength indices (bone strength index, strength strain index) in boys and girls. The primary hypothesis was that after adjusting for differences in bone length and MCSA bone strength indices, geometry and density would be similar between boys and girls in pre- and early puberty. The secondary hypothesis was that after adjusting for bone length, MCSA would be the primary explanatory variable of tibial bone strength indices and bone geometry in boys and girls and that modulating factors would have a small influence on these bone outcomes in both sexes. Due to the small degree of variation in bone density during pre- and early puberty (6,25,29) it was anticipated that MCSA and other modulating factors would not have a significant influence on total or cortical bone density.

4.2 Methods

This study is the cross-sectional, baseline report of a school-based physical activity intervention. Detailed methods are provided in Chapter 2 of this thesis, and are briefly summarized here.

4.2.1 Subjects

Of the original cohort of 514 children, this study involves 424 children (218 boys, 206 girls) aged 9 to 11 years. Children were considered Asian (N = 259) if both parents (or all 4 grandparents) were born in: Hong Kong or China (51%), India (10%), Philippines (11%), Vietnam (10%), Korea (4%), Taiwan (3%) or other Asian countries (12%) or Caucasian (N = 165) if both parents (or all 4 grandparents) were born in North America or Europe. Children of Hispanic, Oceanic and mixed ethnicities were not included in the present analysis (N = 30 girls, 30 boys). Three girls and two boys were excluded from the analysis based on conditions that could affect normal physical activity or bone development (brain surgery for malignant tumour, osteogenesis imperfecta, Type 1 diabetes, fetal alcohol syndrome, childhood leukemia). Eight girls were excluded from analysis because they were post-menarcheal at baseline. Seventeen children (10 girls, 7 boys) were excluded because they did not have a baseline pQCT scan.

4.2.2 Measurements

Detailed acquisition and analysis procedures for pQCT are provided in Chapter 2 (Sections 2.2.8.3.3 and 2.2.8.3.4). Briefly, single slice measurements were acquired at the distal (8%), midshaft (50%) and proximal two-thirds (66%) sites of the left tibia using pQCT (XCT-2000). At the distal tibia total bone cross-sectional area (ToA, mm^2) and total bone mineral density (ToD, mg/cm^3) were used to calculate a bone strength index (BSI, mm^2/mg^4) for compression. At the midshaft and proximal two-thirds sites measures of cortical bone area (CoA, mm^2), cortical bone mineral density (CoD, mg/cm^3) and polar strength strain index (SSI, mm^3) were obtained. Muscle cross-sectional area (MCSA, mm^2) was also assessed at the proximal two-thirds tibia. Of the two tibial shaft sites, the proximal two-thirds site is more commonly assessed as it is associated with the largest muscle belly in adults (30). However, the midshaft incurs the greatest strains during bending in animal studies (31) and is the site of choice for strain gauge studies in humans (32). Thus, both sites were included in this study.

Standing height was measured to the nearest 0.1 cm using a digital wall-mounted stadiometer and weight was measured to the nearest 0.1 kg with an electronic scale. Tibial length was measured (to the nearest 0.1 cm) as the distance from the distal edge of the medial malleolus to the tibial plateau using an anthropometric tape. For each variable the mean of two measures was used for analysis. Maturity was assessed with self-report Tanner staging (33). Children were categorized as either prepubertal (PRE, Tanner stage 1) or early pubertal (EARLY, Tanner stage 2 or 3) based on self-report breast stage for girls and pubic hair stage for boys.

Physical activity level was assessed with a modified version of the Physical Activity Questionnaire for Children (PAQ-C) (34). The outcomes of interest were: 1) general activity score (*PA score*) which represents activity level on a 1 (low activity) to 5 (high activity) scale and 2) loaded activity time (*Load time*, hrs/wk) which is an estimation of time spent in common sports and activities designated as loaded (impact > walking). Dietary calcium (mg/day) was estimated with a validated food frequency questionnaire (FFQ) (35). Research assistants administered the PAQ-C and FFQ. Lower limb power was estimated with vertical jump height (cm) using the Vertec™ device (Fitness Source, Concord, ON). Children performed three jumps and the maximum height was used for analysis.

4.3 *Statistical Analysis*

For comparisons between sexes across maturity groups, the analysis was performed in two steps. First, a two factor (sex, maturity group) univariate analysis of variance (ANOVA) was used to compare all continuous variables (unadjusted bone outcomes, body size, MCSA, physical activity, dietary calcium, vertical jump height). Significant sex x maturity interactions were assessed by tests of simple main effects to determine which maturity group demonstrated a sex difference. Second, a two factor (sex, maturity group) univariate analysis of covariance (ANCOVA) was used to compare bone outcomes between groups with tibial length and MCSA as covariates. These covariates were chosen in order to compare bone outcomes between boys and girls after accounting for estimates of the physiological loads on the skeleton (21,36). Again, tests of simple main effects were used if a significant sex x maturity interaction was detected. Chi-squared tests were used to compare the distribution of ethnicities between groups.

The determinants of bone geometry, density and strength were identified in two steps. First, bivariate correlations were used to identify significant relationships between bone outcomes (dependent variables) at each site (8%, 50%, 66%) and independent variables (tibial length, MCSA, ethnicity, maturity group, physical activity, dietary calcium, vertical jump height) for boys and girls. These independent variables were chosen in order to represent the challengers (tibial length, MCSA) and potential modulators (ethnicity, maturity group, physical activity, dietary calcium, vertical jump height) of the theoretical mechanostat (21,22). Pearson correlations were used for continuous variables and Spearman's rank correlations were used for categorical variables (maturity, ethnicity). Second, multivariable regression models were created to evaluate the contribution of independent variables once tibial length was controlled for. Separate models were created for each bone variable at each site for boys and girls. Variables were entered in the following order: 1) tibial length; 2) MCSA; 3) ethnicity (0 = Asian, 1 = Caucasian) and maturity group (0 = PRE, 1 = EARLY) (non-modifiable factors); 4) physical activity, dietary calcium and vertical jump height (modifiable factors). We used residual plots to check the data for normality, linearity and homoscedascity. Due to collinearity between the two physical activity variables (PA Score, load time), only one physical activity variable was used in the multivariate models for boys (PA Score) and girls (load time). The physical activity variable was chosen based on the strength of its relationship with the dependent variable noted in the bivariate correlations (Table 4-3). For the multivariate models I report the unstandardized regression coefficients (β) and the standard error (SE) are reported in the tables and the percentage of variance explained is reported in the text. Data were analyzed using SPSS statistical software, Windows version 13.0 (SPSS Inc., Chicago, IL, 2003). Significance was set at $p < 0.05$.

4.4 Results

4.4.1 Comparisons between Sexes - Descriptives

Values for descriptive variables for boys and girls in each maturity group are presented (Table 4-1). Boys and girls were of a similar ethnic distribution across maturity groups. In both sexes, EARLY children were significantly older than PRE children (0.14 yrs; 95% CI: 0.03, 0.26). There was a significant main effect of maturity group (EARLY > PRE) for height (3.4 cm; 95% CI: 2.0, 4.8) and tibial length (1.0 cm; 95% CI: 0.6, 1.5) and a main effect of sex (boys > girls) for vertical jump height (2.3 cm; 95% CI: 1.3, 3.3), load time (1.6 hrs/wk; 95% CI: 0.9, 2.4) and dietary calcium (126 mg/day; 95% CI; 37, 217). A significant sex x maturity group interaction was found for MCSA. Post-hoc analyses (simple main effects) indicated that PRE boys had larger MCSA than PRE girls (290.2 mm^2; 95% CI; 141.7, 438.6), but there was no significant difference in MCSA between EARLY boys and girls. A similar trend was observed for weight; however, the sex x maturity group interaction was not statistically significant ($p = 0.06$). There were however, significant main effects of both sex and maturity for weight with boys heavier than girls (3.0 kg; 95% CI; 1.2, 4.7) and EARLY children heavier than PRE children (4.7 kg; 95% CI; 3.0, 6.5).

4.4.2 Comparisons between sexes - Bone geometry, density and strength

Peripheral QCT variables for PRE and EARLY boys and girls at all sites are presented (Table 4-2). At the distal tibia ToA (unadjusted) was 8% larger in boys than girls across both maturity groups (42.3 mm^2; 95% CI: 25.5, 59.1). This difference remained significant after adjusting for tibial length and MCSA although the magnitude of the difference decreased slightly (28.7 mm^2; 95% CI: 16.0, 41.3). Before adjusting for tibial length and MCSA there were significant sex x maturity group interactions for both ToD and BSI with a sex difference apparent in the PRE group only. PRE boys had 8% greater ToD (23.4 mg/cm^3; 95% CI: 14.0, 32.7) and a higher BSI (+29%, $P < 0.05$) than PRE girls. After adjusting for tibial length, the interaction remained significant for ToD and only the main effect of sex was significant for BSI with boys having 15% greater BSI than girls (653.4 mg^2/mm^4; 95% CI: 463.3, 843.4).

At the midshaft, there were significant sex x maturity group interactions for CoA and SSI (unadjusted) with a sex difference apparent in the PRE group only. PRE boys had 12% larger CoA (21.5 mm^2; 95% CI: 12.3, 30.6) and 17% greater SSI (145.5 mm^3; 95% CI: 83.1, 207.8) than PRE girls. After adjusting for tibial length and MCSA the sex x maturity group interaction was not significant, but there was a significant main effect of sex for both CoA and SSI. Boys had 4% larger CoA (+7.2 mm^2; 95% CI: 3.3, 11.0) and 6% greater SSI (52.0 mm^3; 95% CI: 26.1, 77.8) than girls. In contrast, girls in both maturity groups had 1% greater CoD than boys (10.1 mg/cm^3; 95% CI: 3.4, 16.8) and this difference remained significant after adjusting for tibial length and MCSA.

Results at the proximal two-thirds site were similar to those for the midshaft. There were significant sex x maturity group interactions for CoA and SSI (unadjusted) with a sex difference apparent in the PRE group only. PRE boys had 11% larger CoA (18.7 mm^2; 95% CI: 10.2, 27.1) and 16% greater SSI (165.9 mm^3; 95% CI: 95.8, 236.1) than PRE girls. After adjusting for tibial length and MCSA, the sex x maturity group interaction remained significant for CoA but not SSI. PRE boys had 4% larger CoA (7.3 mm^2; 95% CI: 1.7, 12.9) than PRE girls and there was no sex difference in the EARLY group. For SSI, there was a significant main effect of sex; boys had 5% greater SSI (58.9 mm^3; 95% CI: 26.8, 90.9) than girls. In contrast, girls in both maturity groups had 1% greater CoD than boys (8.2 mg/cm^3; 95% CI: 2.2, 14.1) and this difference remained significant after adjusting for tibial length and MCSA.

4.4.3 Determinants of Bone Geometry, Density and Strength in Boys and Girls

4.4.3.1 Distal Tibia

There were significant positive associations between ToA, BSI and tibial length and MCSA in boys and girls and a weak association between ToD and MCSA in girls only (Table 4-3, Figure 4-1 and Figure 4-2). For boys and girls, relationships between ToA, ToD, BSI and other predictor variables were weak, and not all were statistically significant. In the multivariate analysis, MCSA accounted for an additional 10 - 16% of the variability in ToA and BSI for boys and girls and 3% of the variability in ToD at the distal site for girls only after adjusting for tibial length (Table 4-4). When all other variables were held constant, our models suggest that for a 10% increase in MCSA, we would expect approximately a 306 mg^2/mm^4 (6%) increase in BSI for boys and a 300 mg^2/mm^4 (9%) increase in BSI for girls. The addition of maturity and ethnicity to the models for ToA, ToD and BSI did not result in a significant change in R^2 for boys or girls. The addition of physical activity, dietary calcium and vertical jump height to the models

resulted in a significant change in R^2 for ToD (boys) and BSI (boys and girls). For boys, a one unit increase in PA score yielded approximately a 10% increase in BSI. For girls, a one hour per week increase in loaded physical activity yielded approximately a 2% increase in BSI.

4.4.3.2 Tibial Shaft

At the tibial midshaft and proximal two-thirds site we observed strong relationships between CoA, SSI and tibial length and MCSA in boys and girls and a weak negative relationship between CoD and tibial length and MCSA in girls only (Table 4-3). The relationships between midshaft bone outcomes and MCSA are presented in Figure 4-2 and Figure 4-3. With the exception of the moderate correlation between CoA, SSI and maturity group in girls, the relationships between CoA, CoD and SSI and other predictor variables were weak for boys and girls. In the multivariate analysis, MCSA accounted for an additional 10-16% of the variance in CoA and SSI after adjusting for tibial length (Table 4-4). These models suggest that a 10% increase in MCSA would result in an approximately 69 mm^3 (7%) increase in midshaft SSI for boys and a 66 mm^3 (7%) increase in midshaft SSI for girls. The influence of MCSA was similar at the proximal two-thirds site for boys and girls.

For girls, ethnicity, maturity group and dietary calcium accounted for an additional 4% of the variance in midshaft CoA. Caucasian girls had significantly greater CoA (4%) than Asian girls and there was a trend for EARLY girls to have larger CoA than PRE girls (3%). Ethnicity was also a significant predictor of CoD in girls accounting for 3% of the variance. Asian girls had significantly higher CoD than Caucasian girls although the difference was small (1%). At the proximal two-thirds site, ethnicity and maturity group did not contribute to a significant change in R^2 for CoA, whereas the modifiable factors (load time, dietary calcium, vertical jump height) together accounted for 2% of the variance in CoA. Similar to midshaft CoA, ethnicity was a significant predictor of CoA at the proximal two-thirds site; however, ethnicity and maturity group together did not contribute to a significant change in R^2 for CoD. None of the non-modifiable or modifiable factors contributed to a significant change in R^2 for girls' SSI at either shaft site.

For boys, ethnicity contributed to a small but significant change in R^2 for midshaft CoA. Similar to girls, Caucasian boys had a larger midshaft CoA than Asian boys (3%). PA score and dietary calcium accounted for an additional 2-4% of the variance in midshaft CoA and SSI. At the proximal two-thirds site, ethnicity and maturity did not contribute to a significant change in R^2 for CoA or SSI, whereas physical activity score and dietary calcium appeared to have a similar influence on CoA and SSI at the proximal two-thirds site as they did on midshaft CoA and SSI. Dietary calcium was a weak but significant predictor of CoD at both shaft sites in boys; however, the overall models for CoD were not significant.

Table 4-1. Descriptive characteristics of pre- and early pubertal boys (n= 218) and girls (n = 206). Values are mean (SD) unless otherwise indicated.

	Prepubertal		Early pubertal		Two-way ANOVA[a]		
	Boys (n = 139)	Girls (n = 78)	Boys (n = 79)	Girls (n = 128)	Sex	Maturity	Interaction
Age	10.2 (0.6)	10.1 (0.6)	10.3 (0.6)	10.3 (0.6)	0.24	0.01	0.26
No. Asian/Caucasian	95 / 44	48 / 30	38 / 41	78 / 50	-----	-----	-----
Height (cm)	140.5 (6.7)	138.3 (6.6)	142.8 (7.5)	142.9 (7.0)	0.14	< 0.001	0.10
Tibial Length (cm)	32.5 (2.3)	32.0 (2.2)	33.3 (2.5)	33.3 (2.1)	0.26	< 0.001	0.21
Weight (kg)	36.9 (9.4)	32.2 (6.5)	40.0 (10.4)	38.6 (8.2)	0.001	< 0.001	0.06
MCSA (mm^2) [b]	3418.4 (523.7)	3120.4 (495.0)	3444.4 (495.6)	3445.2 (539.9)	0.02	< 0.001	0.003*
Vertical Jump Height (cm)	27.4 (5.5)	25.2 (5.2)	28.2 (5.8)	25.7 (4.5)	< 0.001	0.30	0.75
PA Score (1-5)	2.6 (0.5)	2.6 (0.5)	2.6 (0.5)	2.5 (0.5)	0.19	0.37	0.32
Load time (hours/week)	5.3 (4.0)	3.8 (3.1)	6.1 (4.9)	4.2 (3.3)	< 0.001	0.14	0.67
Dietary Calcium (mg/day)	927 (521)	829 (409)	967 (434)*	808 (433)	0.006	0.58	0.30

Prepubertal = Tanner stage 1; Early pubertal = Tanner stage 2 or 3; MCSA = muscle cross-sectional area; PA Score = physical activity score

a ANOVA = analysis of variance, *p* values presented for main effects (sex, maturity) and interaction (sex x maturity)

b Boys: n = 212, Girls: n = 194

* Post-hoc (simple main effects): Sex difference in the prepubertal group: Boys > Girls, $p < 0.001$; Maturity difference in girls only: early pubertal > prepubertal, $p < 0.001$

Table 4-2. Mean (SD) values for pQCT bone outcomes (unadjusted) at the distal tibia (8% site), tibial midshaft (50%) and proximal two-thirds tibia (66%) for pre- and early pubertal boys and girls.

		Prepubertal		Early pubertal		Two-way ANCOVA[a]		
Site		Boys	Girls	Boys	Girls	Sex	Maturity	Interaction
Distal (8%)[b]	ToA (mm^2)	541.6 (85.3)	489.9 (71.1)	559.2 (90.4)	526.3 (76.4)	< 0.001	0.68	0.46
	ToD (mg/cm^3)	309.8 (30.8)	286.4 (32.7)	303.7 (31.9)	297.7 (34.7)	< 0.001	0.85	0.04*
	BSI (mg^2/mm^4)	5203.9 (1126.9)	4051.0 (1061.2)	5151.8 (1084.1)	4673.8 (1062.2)	< 0.001	0.91	0.10
Midshaft (50%)[c]	CoA (mm^2)	196.2 (34.0)	174.2 (28.7)	200.5 (29.3)	196.2 (27.9)	< 0.001	0.59	0.10
	CoD (mg/cm^3)	1046.8 (36.6)	1060.4 (30.2)	1045.6 (31.4)	1052.5 (32.3)	0.005	0.32	0.41
	SSI (mm^3)	1003.5 (242.5)	853.7 (176.3)	1026.1 (240.9)	987.9 (197.3)	< 0.001	0.48	0.25
Proximal two-thirds (66%)	CoA (mm^2)	190.5 (31.1)	171.9 (26.6)	191.3 (28.0)	191.1 (27.3)	0.05	0.10	0.04*
	CoD (mg/cm^3)	1038.0 (31.3)	1047.5 (28.5)	1032.3 (25.4)	1039.1 (29.3)	0.02	0.12	0.87
	SSI (mm^3)	1207.9 (268.4)	1042.0 (195.3)	1237.9 (295.0)	1188.3 (241.9)	< 0.001	0.90	0.43

SD = standard deviation; Prepubertal = Tanner stage 1; Early pubertal = Tanner stage 2 or 3; ToA = total cross-sectional area; ToD = total density; BSI = bone strength index; CoA = cortical area; CoD = cortical density; SSI = strength strain index

a ANCOVA = analysis of covariance with tibial length and MCSA as covariates, *p* values presented for main effects (sex, maturity) and interaction (sex x maturity)

b Boys: n = 127 PRE, 75 EARLY; Girls: n = 68 PRE, 120 EARLY

c Boys: n = 136 PRE, 77 EARLY; Girls: n = 74 PRE, 124 EARLY

* Post-hoc (simple main effects): PRE boys > PRE girls for ToD and CoA (66% site)

Table 4-3. Bivariate correlations (Pearson's R) of pQCT bone outcomes at the distal tibia (8% site), tibial midshaft (50% site) and proximal two-thirds tibia (66% site) with tibial length, muscle cross-sectional area (MCSA), maturity, ethnicity, physical activity, dietary calcium and vertical jump for boys and girls.

	Site		Tibial length	MCSA	Maturity[a]	Ethnicity[a]	PA Score	Load time	Dietary calcium	Vertical jump height
Boys	**8%**	ToA	0.60***	0.59***	0.09	0.16*	0.20**	0.16*	0.12	0.07
		ToD	-0.02	0.12	-0.08	-0.02	0.24**	0.13	0.18*	0.04
		BSI	0.40***	0.54***	-0.02	0.01	0.36***	0.24**	0.25***	0.10
	50%	CoA	0.71***	0.63***	0.07	0.20*	0.22**	0.18*	0.21***	0.05
		CoD	0.03	0.04	-0.02	-0.09	-0.01	-0.01	0.13	0.10
		SSI	0.75***	0.64***	0.04	0.11	0.21**	0.22**	0.19**	0.06
	66%	CoA	0.68***	0.57***	0.01	0.17*	0.22**	0.19**	0.26***	0.09
		CoD	-0.04	-0.02	-0.10	-0.10	-0.09	-0.07	0.07	0.06
		SSI	0.70***	0.63***	0.02	0.13	0.22**	0.23**	0.24**	0.09
Girls	**8%**	ToA	0.54**	0.65**	0.26**	0.05	0.04	0.11	0.10	0.10
		ToD	0.15*	0.20**	0.17*	0.05	0.14	0.19*	.010	0.12
		BSI	0.45**	0.55**	0.31***	0.06	0.18*	0.26**	0.15*	0.18*
	50%	CoA	0.71***	0.75***	0.36***	0.18*	0.04	0.16*	0.17*	0.16*
		CoD	-0.26***	-0.26***	-0.11	-0.22**	-0.003	0.008	0.01	0.004
		SSI	0.75***	0.73***	0.33***	0.12	0.03	0.15*	0.14*	0.13
	66%	CoA	0.73***	0.72***	0.33***	0.11	0.03	0.12	0.15*	0.19*
		CoD	-0.36***	-0.27***	-0.13	-0.22**	-0.001	-0.03	0.000	0.07
		SSI	0.74***	0.72***	0.30***	0.08	0.03	0.13	0.14	0.14*

a Spearman's rank correlation

* P < 0.05; ** P < 0.01; ***P < 0.001

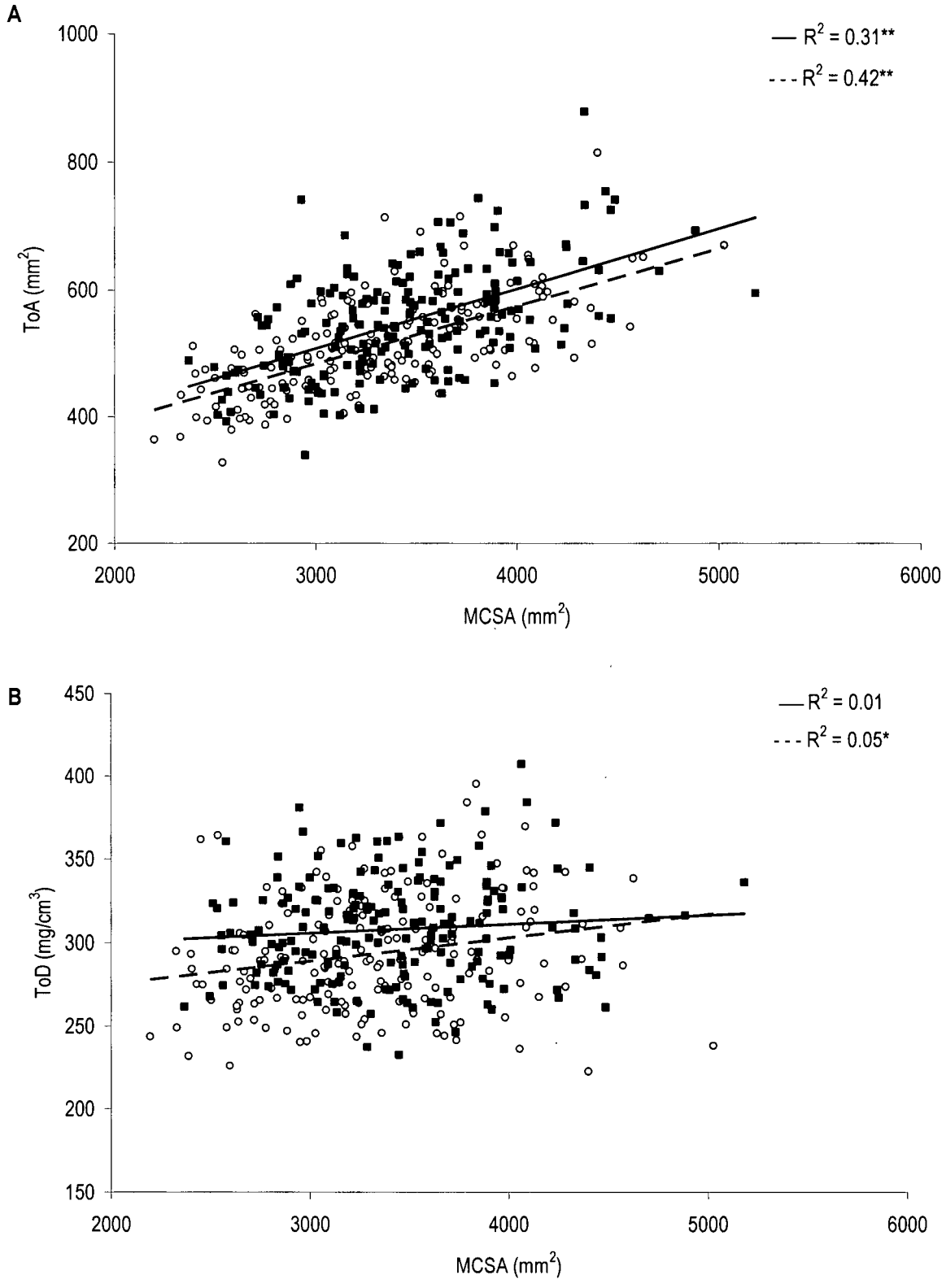

Figure 4-1. Scatterplots of muscle cross-sectional area (MCSA) and distal tibia (A) total bone cross-sectional area (ToA) and (B) total density (ToD) for boys (solid squares, solid line) and girls (open circles, dashed line).

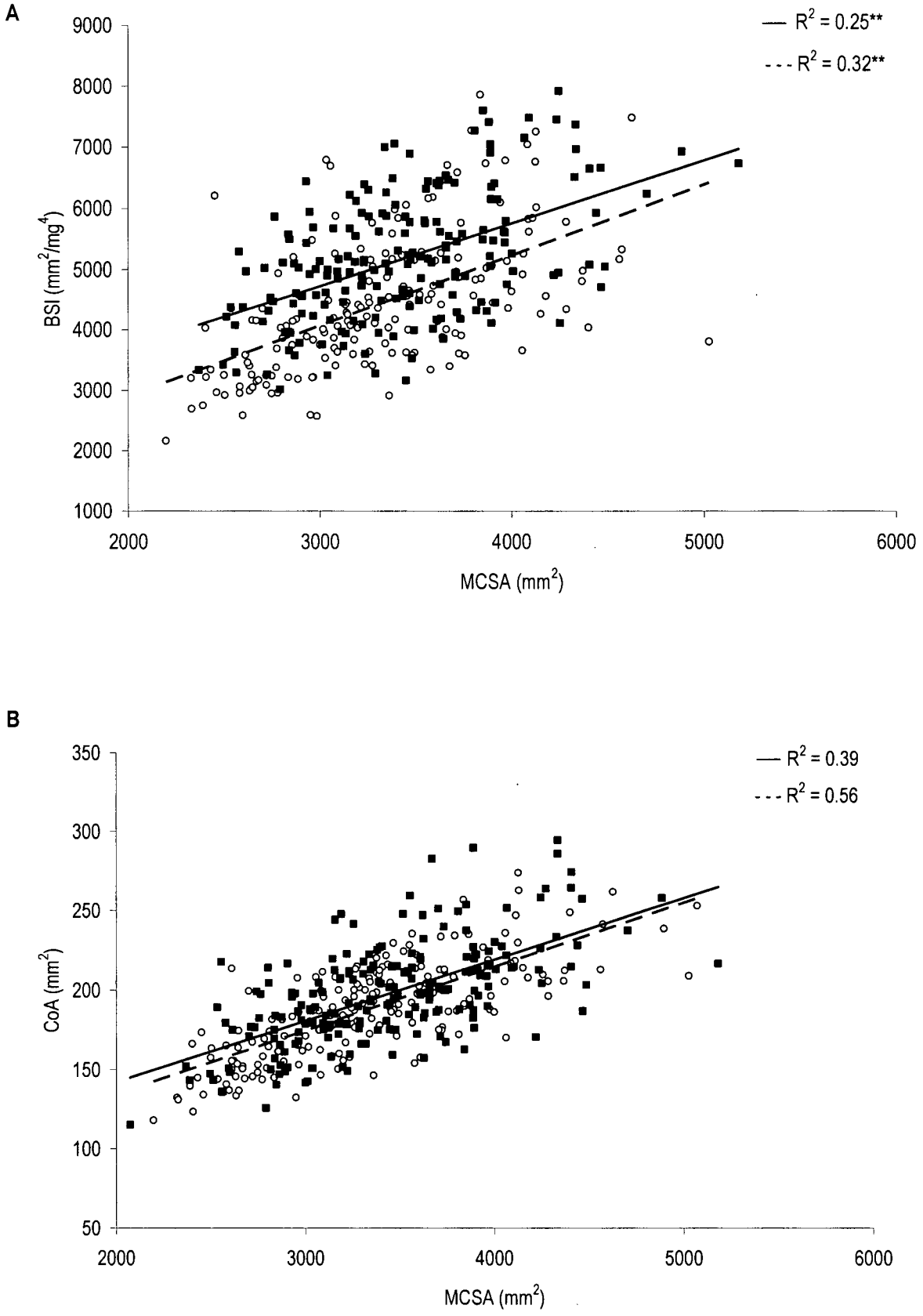

Figure 4-2. Scatterplots of muscle cross-sectional area (MCSA) and (A) distal tibia bone strength index (BSI) and (B) tibial midshaft cortical area (CoA) for boys (solid squares, solid line) and girls (open circles, dashed line).

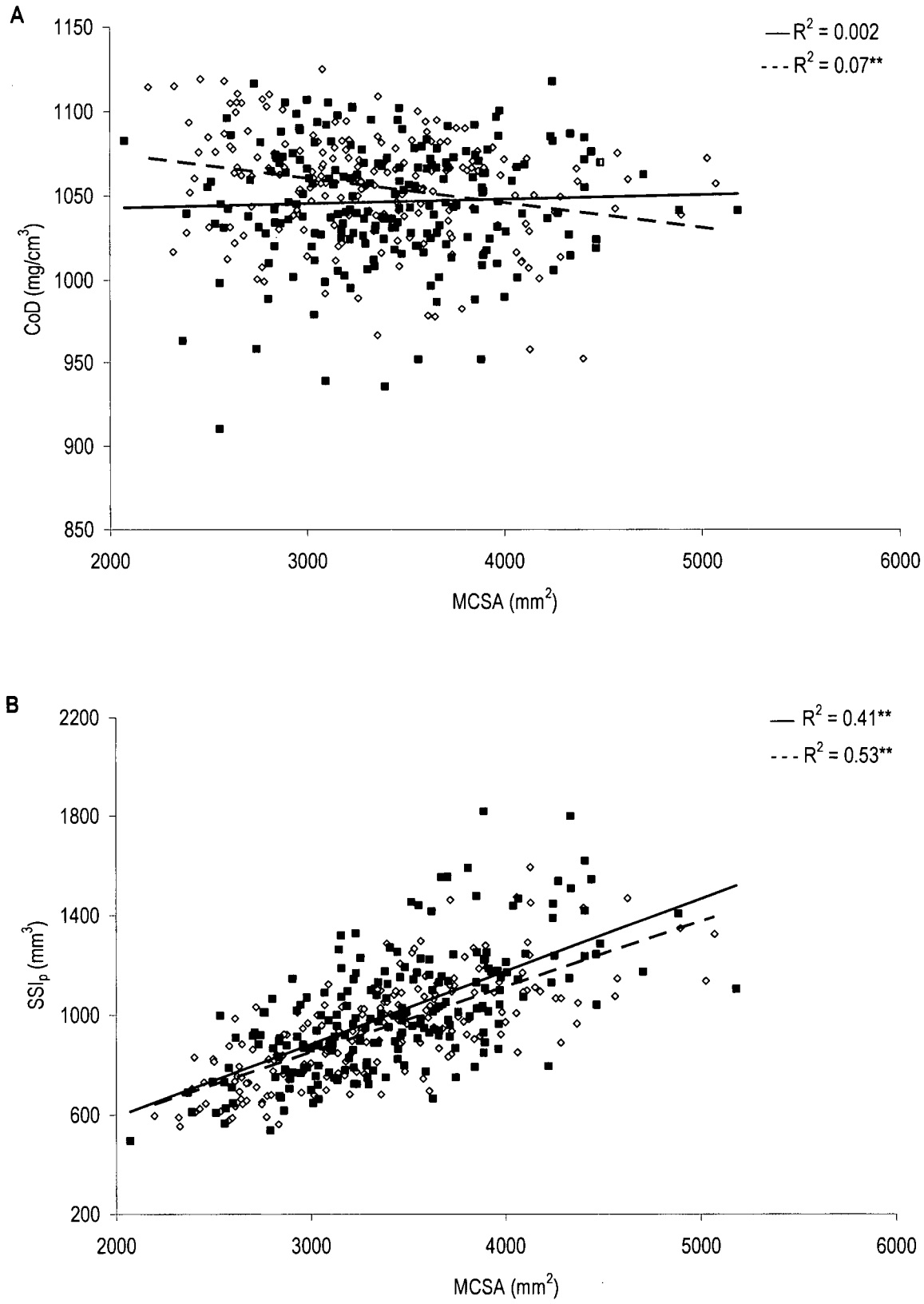

Figure 4-3. Scatterplots of muscle cross-sectional area (MCSA) and (A) cortical density (CoD) and (B) polar strength-strain index (SSI_p) at the tibial midshaft for boys (solid squares, solid line) and girls (open circles, dashed line).

Table 4-4. Multiple regression models for pQCT variables at the distal tibia (8%), tibial midshaft (50%) and proximal two-thirds tibia (66% site) for boys and girls.

		BOYS				***GIRLS***			
Site	DV	IV	B (SE)	P value	R^2	IV	B (SE)	P value	R^2
8%	**ToA**	Tibia length	1.5 (0.2)	<0.001	0.357**	Tibia length	0.9 (0.3)	<0.001	0.339**
		MCSA	0.07 (0.01)	<0.001	0.490**	MCSA	0.07 (0.01)	<0.001	0.468**
		Ethnicity[a]	16.9 (9.8)	0.09		Ethnicity	3.3 (9.3)	0.7	
		Maturity group[b]	0.02 (9.6)	0.9	0.495	Maturity group	4.7 (9.4)	0.6	0.465
		PA Score	13.5 (9.0)	0.1		Load time	1.7 (1.4)	0.2	
		Dietary calcium	0.006 (0.01)	0.5		Dietary calcium	0.008 (0.01)	0.5	
		Vertical jump	0.8 (0.8)	0.3	0.499	Vertical jump	0.05 (0.9)	0.9	0.464
	ToD	Tibia length	-0.1 (0.1)	0.3	0.005	Tibia length	-0.2 (0.1)	0.3	0.003
		MCSA	0.006 (0.005)	0.2	0.005	MCSA	0.01 (0.006)	0.02	0.029*
		Ethnicity	-2.9 (4.8)	0.5		Ethnicity	4.4 (5.3)	0.4	
		Maturity group	-5.3 (4.7)	0.2	0.000	Maturity group	5.9 (5.4)	0.3	0.033
		PA Score	12.1 (4.3)	0.006	0.059*	Load time	1.2 (0.9)	0.2	
		Dietary calcium	0.01 (0.005)	0.04		Dietary calcium	0.004 (0.006)	0.5	
		Vertical jump	0.02 (0.4)	0.9		Vertical jump	-0.08 (0.6)	0.9	0.053
	BSI	Tibial length	9.2 (3.0)	0.003	0.165**	Tibia length	3.2 (3.9)	0.4	0.176**
		MCSA	0.9 (0.1)	< 0.001	0.319**	MCSA	0.9 (0.2)	< 0.001	0.309**
		Ethnicity	62.3 (132.4)	0.6		Ethnicity	169.3 (140.2)	0.2	
		Maturity group	-191.7 (129.6)	0.1	0.321	Maturity group	182.4 (142.6)	0.2	0.319
		PA Score	505.2 (122.4)	0.001		Load time	71.3 (21.2)	0.001	
		Dietary calcium	0.4 (0.1)	0.003		Dietary calcium	0.2 (0.2)	0.3	
		Vertical jump	8.9 (10.9)	0.4	0.416**	Vertical jump	15.9 (14.0)	0.3	0.370*

Table 4-4 continued		***BOYS***				***GIRLS***			
Site	DV	IV	B (SE)	P value	R^2	IV	B (SE)	P value	R^2
50%	**CoA**	Tibial length	0.7 (0.07)	< 0.001	0.509**	Tibia length	0.5 (0.07)	< 0.001	0.504**
		MCSA	0.02 (0.003)	< 0.001	0.626**	MCSA	0.03 (0.003)	< 0.001	0.660**
		Ethnicity	6.0 (2.9)	0.04		Ethnicity	7.6 (2.6)	0.005	
		Maturity group	-4.8 (2.9)	0.10	0.636*	Maturity group	5.2 (2.7)	0.05	0.682**
		PA Score	5.4 (2.7)	0.05		Load time	0.7 (0.4)	0.08	
		Dietary calcium	0.007 (0.003)	0.02		Dietary calcium	0.007 (0.003)	0.03	
		Vertical jump	0.2 (0.2)	0.5	0.653**	Vertical jump	0.3 (0.4)	0.2	0.699**
	CoD	Tibial length	0.01 (0.1)	0.9	-0.004	Tibia length	-0.3 (0.1)	0.06	0.08**
		MCSA	0.004 (0.005)	0.5	-0.006	MCSA	-0.008 (0.005)	0.1	0.087
		Ethnicity	-7.8 (5.3)	0.1		Ethnicity	-12.8 (4.8)	0.008	
		Maturity group	-1.1 (5.2)	0.8	-0.009	Maturity group	-2.8 (4.9)	0.6	0.110*
		PA Score	-2.3 (5.0)	0.6		Load time	0.3 (0.7)	0.7	
		Dietary calcium	0.01 (0.005)	0.02		Dietary calcium	0.005 (0.006)	0.4	
		Vertical jump	0.6 (0.4)	0.2	0.013	Vertical jump	0. (0.5)	0.8	0.102
	SSI	Tibial length	6.0 (0.5)	< 0.001	0.569**	Tibia length	4.1 (0.5)	< 0.001	0.567**
		MCSA	0.2 (0.02)	< 0.001	0.684**	MCSA	0.2 (0.02)	< 0.001	0.682**
		Ethnicity	1.1 (20.2)	0.9		Ethnicity	28.6 (17.7)	0.1	
		Maturity group	-36.5 (20.0)	0.07	0.685	Maturity group	20.7 (18.0)	0.3	0.688
		PA Score	33.6 (19.0)	0.08		Load time	4.9 (2.7)	0.07	
		Dietary calcium	0.05 (0.02)	0.008		Dietary calcium	0.03 (0.02)	0.1	
		Vertical jump	1.8 (1.7)	0.3	0.702**	Vertical jump	1.0 (1.8)	0.6	0.696

Table 4-4 continued		*BOYS*				*GIRLS*			
Site	DV	IV	B (SE)	P value	R^2	IV	B (SE)	P value	R^2
66%	CoA	Tibial length	0.7 (0.07)	< 0.001	0.467**	Tibia length	0.5 (0.07)	< 0.001	0.518**
		MCSA	0.02 (0.003)	< 0.001	0.565**	MCSA	0.02 (0.003)	< 0.001	0.653**
		Ethnicity	2.9 (2.9)	0.4		Ethnicity	3.9 (2.6)	0.1	
		Maturity group	-6.2 (2.9)	0.03	0.572	Maturity group	4.7 (2.7)	0.09	0.661
		PA Score	5.1 (2.8)	0.07		Load time	0.7 (0.4)	0.09	
		Dietary calcium	0.009 (0.003)	0.002		Dietary calcium	0.004 (0.003)	0.2	
		Vertical jump	0.4 (0.2)	0.09	0.607**	Vertical jump	0.4 (0.3)	0.1	0.674*
	CoD	Tibial length	-0.04 (0.1)	0.7	-0.004	Tibia length	-0.4 (0.1)	0.001	0.139**
		MCSA	0.001 (0.005)	0.9	-0.009	MCSA	-0.005 (0.005)	0.3	0.137
		Ethnicity	-4.1 (4.6)	0.4		Ethnicity	-9.9 (4.2)	0.02	
		Maturity group	-5.2 (4.5)	0.2	-0.009	Maturity group	-1.8 (4.3)	0.7	0.156
		PA Score	-6.2 (4.3)	0.2		Load time	0.4 (0.7)	0.6	
		Dietary calcium	0.008 (0.005)	0.09		Dietary calcium	0.002 (0.005)	0.7	
		Vertical jump	0.4 (0.4)	0.3	0.003	Vertical jump	0.4 (0.4)	0.3	0.151
	SSI	Tibial length	6.3 (0.6)	< 0.001	0.493**	Tibia length	4.9 (0.6)	< 0.001	0.545**
		MCSA	0.2 (0.03)	< 0.001	0.631**	MCSA	0.2 (0.02)	< 0.001	0.662**
		Ethnicity	3.4 (25.5)	0.9		Ethnicity	14.0 (21.7)	0.5	
		Maturity group	-29.6 (24.9)	0.2	0.630	Maturity group	31.5 (22.1)	0.2	0.664
		PA Score	40.3 (29.1)	0.2		Load time	5.0 (3.4)	0.1	
		Dietary calcium	0.07 (0.03)	0.004		Dietary calcium	0.03 (0.03)	0.2	
		Vertical jump	3.5 (2.1)	0.1	0.660**	Vertical jump	1.5 (2.2)	0.5	0.669

DV = dependent variable; IV = independent variable; B = unstandardized regression coefficient; SE = standard error; MCSA = muscle cross-sectional area; PA Score = physical activity score a dummy variable: 0 = Asian, 1 = Caucasian; b dummy variable: 0 = prepubertal, 1 = early pubertal; * R^2 change significant at $P < 0.05$; ** R^2 change significant at $P < 0.001$

4.5 Discussion

This study describes tibial bone strength and its components (geometry and density) as measured with pQCT in a large cohort of 9-11 year old pre- and early pubertal boys and girls. The primary hypothesis was rejected as indices of bone strength (BSI and SSI) were 5-15% greater in both pre- and early-pubertal boys than girls after adjusting for tibial bone length and muscle cross-sectional area (MCSA). This was due largely to greater bone areas (ToA and CoA) in boys. A sex difference in total density (ToD) was evident in prepuberty only, with boys having 8% greater ToD than girls. In contrast, cortical density (CoD) was slightly greater (1%) in girls compared with boys in both maturity groups.

The secondary hypothesis was accepted as MCSA (a surrogate for muscle force) was the primary explanatory variable of bone strength and geometry at both measured sites after adjusting for tibial length in both boys and girls. This result is consistent with a functional model of bone development whereby both longitudinal growth and muscle forces are the primary factors influencing bone strength (Figure 4-4) (21). This study also demonstrates that modulators of the theoretical mechanostat such as physical activity and dietary calcium are weak, but significant contributors to tibial bone geometry and strength.

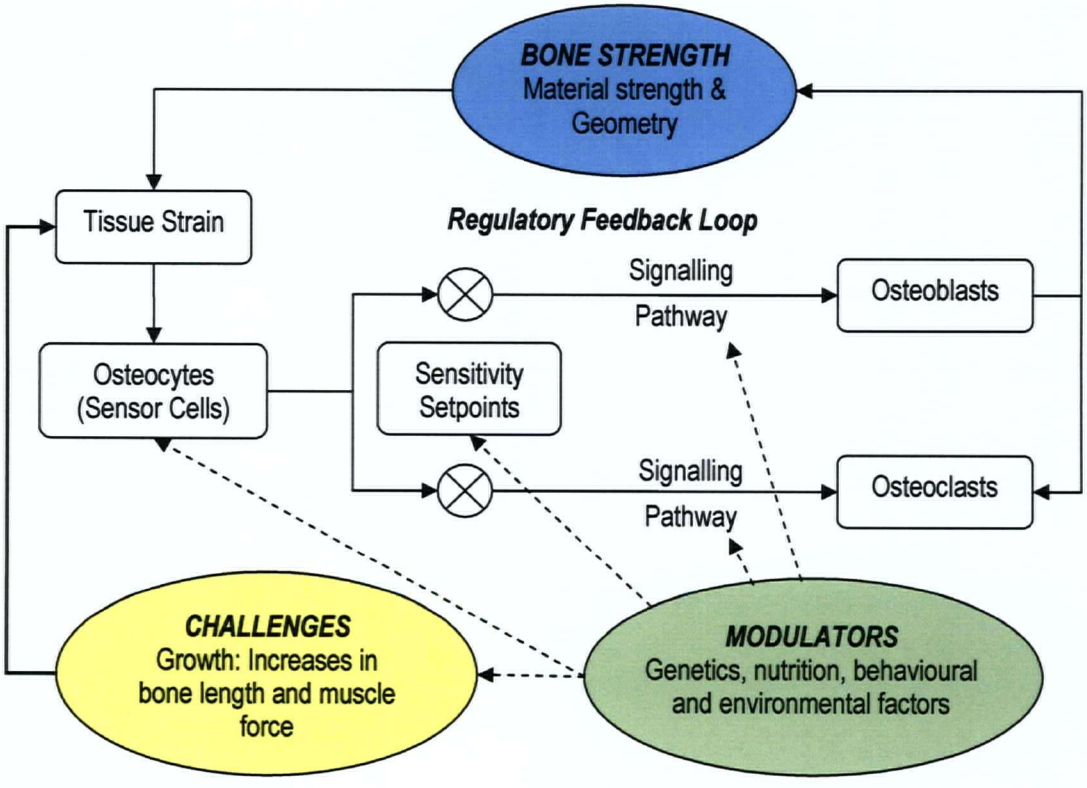

Figure 4-4. A functional model of bone development based on the mechanostat theory (22) and related approaches (37,38). The central component of the regulation of bone development is the feedback loop between bone deformation (tissue strain) and bone strength. During growth, this homeostatic system must continually adapt to external challenges (increases in bone length and muscle force) to keep tissue strain close to a preset level (sensitivity setpoint). Various modulating factors influence aspects of the regulatory system as indicated by the dashed arrows. Adapted from Rauch et al. (21) and Petit et al. (36).

4.5.1 Sex Differences in Bone Geometry, Density and Strength

Although a number of studies compared bone strength and its components between boys and girls at various stages of maturation, it is difficult to compare results across studies due to different sites of measurement, measurement technologies (radiography, DXA, MRI, QCT, pQCT) and scan acquisition and analysis protocols (2,4,10,12-19,39). However, many of the findings of the present study of the tibia agree with previous pQCT investigations of sex differences in long bone geometry and strength of the distal and proximal radius (17,18). Although rates of periosteal apposition cannot be inferred from these cross-sectional data it appeared that both PRE and EARLY boys experienced greater periosteal expansion than girls resulting in larger bone areas (ToA, CoA) and greater bone strength (BSI, SSI) at the distal and shaft sites of the tibia. These differences remained significant after adjusting for differences in tibial length and MCSA. This indicates that for a given tibial length and MCSA, a pre- or early pubertal boy has a larger bone area and greater bone strength than girls at approximately the same stage of maturity. These results could be interpreted to mean that bone strength is not adapted to muscle forces. However, MCSA is only a surrogate for muscle force and does not capture intrinsic properties of muscle which are known to affect force production such as fibre length to muscle length ratio and pennation angle (30). Thus, it is possible that boys had a greater specific muscle force (as indicated by the higher vertical jump height) for their size and this higher force may explain the remaining difference in bone area and strength between sexes. These data highlight the need for studies incorporating measures of muscle *force*, rather than MCSA alone.

These results are in contrast with MRI and QCT findings at the weight-bearing femoral diaphysis which showed no sex difference in bone area (13-15). This discrepancy may be due to differences in measurement technologies, in the study sample or in measurement sites and true regional differences in bone geometry and strength. Further, the studies of the femur did not include an estimation of bone strength. It is possible that even small differences in femoral cross-sectional geometry between boys and girls may have contributed to greater bone bending strength in boys.

At the femoral neck, Forwood and colleagues (19) found a small but significant sex difference in estimated bone bending strength (HSA-derived Z) when boys and girls were aligned on biological age (peak height velocity). Although the authors questioned the significance of the small difference (3.2% at peak height velocity) in bone strength, the finding was consistent across all biological age bands after controlling for stature and lean mass. To date, there have been no prospective pQCT studies that compared bone strength between boys and girls at the same biological age.

Greater ToD at the distal tibia among PRE boys compared with PRE girls agrees with results from the distal radius (18). Total density as measured by pQCT at the distal tibia represents the mean tissue density of both the thin cortical compartment (1.4 mm, on average, data not shown) and the larger trabecular compartment together with bone marrow (29). Thus, a difference in ToD could reflect a true difference in bone material density, marrow composition or the bone to marrow ratio. In their study of the distal radius, Neu et al. (18) reported greater trabecular density among PRE boys and acknowledged the limitations of obtaining measures of CoD at metaphyseal sites due

to the partial volume effect. In the present study, trabecular density was greater in both PRE and EARLY boys compared with same-maturity girls (data not shown).

In contrast to all other bone outcomes, CoD at the tibial midshaft was higher in girls compared with boys in both maturity groups. Higher CoD in girls was also reported at the proximal radius (25), although the sex difference was only observed in Tanner stages 4 and 5. A sex difference in CoD at the proximal radius may not have been evident in Tanner stages 1 through 3 due to limitations associated with the thin cortical shell (average < 2mm) in both girls and boys at that site (40). In contrast, we assessed CoD at the tibial shaft where average cortical thickness even in PRE and EARLY girls was >3.2 mm (data not shown). The biological underpinnings of the sex difference in CoD remain unclear; however, it is thought that intracortical remodelling is higher in boys which may contribute to differences in intracortical porosity (25). Mechanostat theory posits that higher mechanical demands on the tibial shaft in boys due to their larger body size and greater muscle force may cause more microdamage in boys' cortical bone. In turn, microdamage may increase intracortical remodelling (41) thereby leading to greater intracortical porosity and lower tissue material density in boys compared with girls. Due to limitations associated with Tanner staging (33,42,43), it is also possible that the pre- and early maturity categories were unable to capture differences in biological age between boys and girls. Prospective studies in which children are aligned on biological age (i.e., age at peak height velocity) are needed to confirm sex differences in CoD development.

4.5.2 Determinants of Bone Geometry, Density and Strength

4.5.2.1 Muscle Cross-sectional Area

During growth, muscle forces together with increasing bone length present a significant mechanical challenge to the developing skeleton (21). To maintain structural integrity, bone must adapt both its mass and geometry to keep strains within a functional range. Thus, our finding that MCSA, as a surrogate of muscle force, was predictive of bone geometry and strength at the distal and shaft sites of the tibia is not surprising. Previous pQCT studies of the tibia identified body weight as a key predictor of bone density and strength in young girls (aged 11-15 yrs); however, these studies did not evaluate the influence of MCSA (23,24). Although gravitational forces associated with body weight place significant loads on bone, they are small relative to those imposed by muscle forces (44,45). In the present study when MCSA was replaced by body weight in the regression models for bone geometry and strength indices, the variance explained by body weight was between 2 and 4% less than that explained by MCSA (data not shown). Further, when body weight replaced MCSA, vertical jump performance significantly predicted bone geometry and strength. Together body weight and vertical jump performance explained approximately the same amount of variance as MCSA alone. This finding suggests MCSA may be a more appropriate indicator of skeletal load than body weight as it represents both body size and an estimate of muscle force. It is interesting to note, however, that correlations between MCSA and vertical jump performance were low for boys and girls ($r = 0.2$ and 0.1, respectively). Although vertical jump height provides an *estimate* of muscle power (46), jumping performance is related to body size and is a measure of the energy storing capacity of the musculo-tendinous apparatus (not muscle power directly). Studies of lower leg power in adults have shown that an accurate prediction of muscle power from

vertical jump performance can be achieved if body weight is included in the prediction equation (47). Similar equations for children to estimate muscle force and power from vertical jump would be useful if a force platform were unavailable.

Based on these cross-sectional data it is not possible to determine a cause-effect relationship between muscle forces and bone geometry and strength. Given the shared genetic determinants between bone and muscle growth as well as body size (5) it is possible that many of these associations could be accounted for by genetic links (6). However, the temporal relationship between muscle and bone growth as reported by Rauch et al. (48) suggests that increasing muscle forces positively influence bone strength during growth.

The amount of variance in bone area and strength explained by MCSA (10-16%) in our multivariate models is substantially less than the 77% of the variance that MCSA explained for CoA at the proximal radius (28). This may be due to the fact that Schoenau and colleagues did not include an estimate of moment arm length (radial length) in their regression model. As recommended by Petit et al. (36), the best approach to represent the functional muscle-bone unit is to incorporate surrogates of muscle force, bone strength and moment arm length.

With the exception of girls' ToD at the distal tibia, MCSA was not a significant determinant of density. Given the small amount of variability in density, especially CoD, in this population, this result is not surprising. This finding agrees with studies in children (49) and animals (50) where no relationship between muscle strength or increased muscle mass and bone density (cortical or trabecular) was observed. Thus, it appears that peripheral skeleton adapts to mechanical loads during growth mainly through changing geometry while mineral properties and cortical porosity remain relatively constant.

4.5.2.2 Non-modifiable Factors: Ethnicity and Maturity

Although not the focus of this study, the contribution of ethnicity to bone outcomes was also evaluated. To my knowledge this is the first pQCT study to evaluate the influence of ethnicity (Asian and Caucasian) on bone strength and its components. With all other independent variables controlled for, Caucasian boys and girls had larger midshaft CoA compared with Asian boys and girls (3-4%). In contrast, Asian girls had significantly greater CoD at both shaft sites compared with Caucasian girls, although the absolute difference was small (1%). There was also a tendency for Asian boys to have greater CoD at both shaft sites; however, the influence of ethnicity on boys' CoD was not statistically significant. The biological underpinnings of these ethnic differences are not clear. Similar to the explanation for the sex difference in CoD, lower CoD and greater CoA in Caucasian boys and girls may be a result of higher intracortical remodelling, increased porosity and outward drift (periosteal expansion) due to greater strains incurred at the tibial midshaft than in Asian children. Interestingly, ethnicity was a significant determinant of girls' CoD at the proximal two-thirds site but was not a significant predictor of CoA. If we accept that strains are greater at the tibial midshaft compared with more proximal (or distal) sites then this increased strain magnitude might explain the differences in bone geometry between Asian and Caucasian children. Despite the differences in bone geometry and density, ethnicity was not a significant determinant of bone strength after tibial length, MCSA and other modulating factors were accounted for.

Maturity-related differences in bone geometry, density and strength in boys and girls are well documented (10,12,17-19). Tanner stage and menarcheal status have previously been identified as significant determinants of ToD at the distal and shaft sites of the tibia in adolescent girls (23,24). In the present study there was no main effect of maturity group nor was maturity group a significant predictor of bone strength in boys or girls after anthropometric differences were controlled for. Thus, in this cohort of mainly prepubertal boys and early pubertal girls, differences in bone strength were related to body size and musculature. Age, rather than maturational stage, is often used as a grouping or matching variable. In the present study, age was not a significant predictor of any bone outcome when used in place of maturity group (data not shown).

4.5.2.3 Modifiable Factors: Physical Activity and Dietary Calcium

Mechanical strain associated with physical activity plays a significant role in the regulation of the mechanostat. Physical activity increases muscle forces acting on the skeleton, which in turn should lead to an increase in bone strength. In the present study, physical activity was a significant determinant of bone strength at the distal tibia in both sexes. This relationship was likely mediated by the association between physical activity and total density. This has been previously documented in pQCT studies of the distal radius and tibia in young gymnasts (51) and the distal radius in racquet-sport athletes (52). Together, these findings suggest that physical activity offers a feasible target for intervention strategies designed to increase bone strength at trabecular bone sites in children.

In addition to physical activity, adequate nutrition (total energy, protein, calcium) is essential for growth and development. However, although calcium is a major constituent of bone, the growing skeleton appears to make the necessary adaptations so that bone mass is essentially maintained across a wide range of dietary calcium intakes (53). Further, a recent systematic review of pediatric calcium supplementation studies found no evidence to suggest that increased consumption of dietary calcium results in bone health benefits as measured by DXA (54). In light of these reviews and previous studies from our group, it is surprising that in the present study dietary calcium was a weak, but significant, predictor of bone strength at all sites in boys only. It is possible that the relationship between dietary calcium and tibial bone strength may be mediated by physical activity. Boys reported more hours of weight-bearing physical activity per week than girls and it would be expected that overall energy intake (including dietary calcium) would be greater in more active children. Indeed, boys reported a significantly greater dietary calcium intake than girls. Correlations between physical activity (PA score, load time) and dietary calcium were weak but significant for boys ($r = 0.22$-0.23, $p < 0.001$), whereas the correlations were not significant for girls. Additional pQCT studies are needed to clarify the relationship between dietary calcium and tibial bone strength during growth.

4.5.3 Limitations

This study has several limitations. First, maturational status was determined with Tanner staging. Although a valid and reliable means to assess secondary sex characteristics in boys and girls, Tanner staging is not able to capture differences in the tempo and timing of growth between sexes (43). In an attempt to overcome this limitation, boys and girls were compared according to pre- (Tanner stage 1) and early (Tanner stage 2-3) maturity groups rather

than undertaking direct comparisons between boys and girls across all three Tanner stages. To further explore sexual dimorphism in appendicular bone strength prospective pQCT studies are needed in which boys and girls are aligned on biological age.

Second, there are limitations associated with children's self-report of physical activity (55) and dietary calcium (56) which are particularly relevant for this cohort as this was their first exposure to the questionnaires. Reliability of children's self-report generally improves with age and repeated measurements (55,56). Thus, longitudinal studies that investigate determinants of *change* in bone strength may benefit from using average scores for physical activity and dietary calcium across several time points. Further, use of a more objective measure of children's physical activity such as accelerometers would overcome limitations of self-report and would also provide a means to assess the influence of activity intensity on tibial bone strength.

Finally, there are currently no published recommendations that state which sites should be measured with pQCT in the growing skeleton. In addition, pQCT acquisition and analysis protocols are not standardized for pediatric studies. Thus, it is difficult to compare results across studies. Several recent reports provide recommendations regarding pQCT outcomes (36,57,58); however, there is currently no consensus as to which analysis modes and thresholds should be used or which sites should be measured.

4.6 Summary

In summary, sexual dimorphism in tibial bone strength, and its components (geometry and density), is evident in pre- and early puberty. Prospective pQCT studies that span all stages of maturation are needed to further clarify the sex-specific differences in appendicular bone strength. This study also demonstrated that after accounting for differences in tibial length, muscle cross-sectional area, is a significant explanatory variable of bone geometry and strength in pre- and early pubertal Asian and Caucasian boys and girls. Our data are consistent with a functional model of bone development in which growing bone adapts its structure and strength to withstand mechanical loads, primarily from muscle contractions. The influence of other biological and lifestyle factors on bone geometry, density and strength were minimal, but may differ between girls and boys. In conclusion, intervention studies that address these relationships are warranted. In addition, future investigations of skeletal development should include an assessment of muscle force, bone geometry and strength, rather than bone density or mass alone.

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5 Part II: Effectiveness of a School-Based Physical Activity Intervention for Increasing Tibial Bone Strength in Boys and Girls: A Cluster Randomized Controlled Trial[3]

5.1 Introduction

There is great potential for physical activity interventions during childhood to be adopted as inexpensive, safe and far-reaching strategies to improve bone strength and, if activity is maintained, prevent osteoporosis and related fractures later in life (1). Schools provide an excellent arena to reach large numbers of children from broad socioeconomic background. Previous school-based exercise interventions demonstrated that increased mechanical loading effectively enhanced bone mineral content (BMC) and areal bone mineral density (aBMD) as measured by dual energy x-ray absorptiometry (DXA) in boys and girls (2-8). These studies made a substantial contribution to our understanding of how growing bone responds to exercise. However, only a partial picture emerged as 2-dimensional DXA measurements do not assess all components of bone strength. Additional tools now exist to assess how physical activity affects bone geometry, (volumetric) density and bone strength.

Peripheral QCT (pQCT) provides the opportunity to investigate how bone structure adapts to increased mechanical loading. Results from cross-sectional pQCT studies in children (9) and adults (10,11) and controlled studies in animals (12) suggest that mechanical loading improves bone strength at diaphyseal sites mainly through changes in cross-sectional geometry rather than through changes in density. In contrast, distal sites appear to adapt to compressive forces through increased density (9,11). Further, adaptations to increased loading within a bone cross-section occur in a site-specific manner in response to the direction of the loads imposed (13-15). To date, only 2 controlled trials evaluated the effects of increased high-impact physical activity on the preadolescent skeleton using pQCT (16,17). One of these trials assessed changes in tibial bone strength (16); however, only diaphyseal bone strength was assessed and bone strength changes in the bending planes were not investigated.

To maximize the osteogenic potential of exercise, activities should be high-impact and impose dynamic and abnormal strains of varying distribution on the skeleton (18,19). In addition, frequent and short bouts of activity that are separated by a rest period maximize mechanosensitivity, or bone's response to loading, in growing rats (20). Recently, our group reported that Bounce at the Bell, implemented over 8 months, was a simple and inexpensive intervention based on these principles of bone adaptation. Bounce at the Bell enhanced proximal femur bone mass (by DXA) in a mixed maturity sample of boys and girls (21). In the present study Bounce at the Bell was implemented as the main bone-loading component within a larger program of daily physical activity, Action Schools! BC (AS! BC).

The primary objective of this trial was to determine the effectiveness of a school-based physical activity model, AS! BC, for increasing tibial bone strength as estimated with the bone strength index (BSI) at the distal tibia and the polar strength strain index (SSI_p) at the midshaft in boys and girls. The secondary objective was to was to determine the effectiveness of AS! BC for increasing tibial midshaft bone strength along the x and y bending axes

[3] A version of this chapter has been submitted for publication. Macdonald HM, Kontulainen SA, Khan KM, McKay HA. Is a school-based physical activity intervention effective for increasing tibial bone strength in boys and girls?

(SSI_x, SSI_y). Based on the literature and our previous findings (21), it was hypothesized that compared with same-sex controls, both boys and girls participating in AS! BC would have a greater increase in bone strength at both the distal tibia and tibial midshaft and also along both bending axes at the tibial midshaft.

5.2 *Methods*

A comprehensive description of the Action Schools! BC model is provided in Chapter 2 as are detailed methods for school, teacher and subject recruitment, data collection and measurement protocols. The methods are briefly summarized here.

5.2.1 *Study Design*

This was a cluster randomized, controlled, school-based intervention trial. From a pool of 20 volunteer schools, 10 schools that met the study entry criteria were invited to participate. Seven schools were from the Vancouver School District and 3 were from the Richmond School District. Schools were randomly assigned to control (CON, 3 schools), Level 1 intervention (4 schools) or Level 2 intervention (3 schools). To ensure both Districts were represented in each group, the Richmond schools were randomized first. The Vancouver schools were then stratified by size (<300 or >300 total students) and randomly assigned to one of the three groups. Randomization was performed remotely by a third party using random number draw. The intervention arms differed in the amount of facilitation provided to teachers and not in the activity delivered to students. Thus, the two intervention arms were collapsed into one intervention group (INT, 7 schools) for the present analysis.

Baseline measurements were performed between February and April 2003. The intervention was 11 months in duration (Phase I: April - June 2003, Phase II: October 2003 – May 2004) and followup measurements were performed between April and June 2004. The median followup time was 14.0 months (interquartile range = 13.8 to 14.1 months). A detailed study timeline is presented in Chapter 2 (Figure 2-3).

5.2.2 *Participants*

Children were recruited from all grade 4 and 5 classes in participating schools. At baseline, 514 children (257 boys, 257 girls) received parental consent to participate. This represented 47% of the population of grade 4 and 5 students. Three girls (1 CON, 2 INT) and 2 boys (INT) were excluded from this analysis based on conditions that could affect normal physical activity or bone development (osteogenesis imperfecta, Type I diabetes, fetal alcohol syndrome, childhood leukaemia, brain tumour). At baseline, 41 (14 CON, 27 INT) grade 4 and 5 teachers agreed to participate in the study.

5.2.3 *Intervention*

For the present study, we introduced a two-component targeted bone-loading program into the Classroom Action Zone of AS! BC. Teachers at intervention schools delivered this program in addition to two 40 minutes classes (on average) of regular physical education per week. For the first component, teachers at INT schools were required to provide their students with an additional 15 minutes of physical activity, 5 days a week. Teachers chose from a

number of different activities including skipping, dancing, playground circuits and simple resistance exercises with exercise bands. All activities required minimal equipment and could be performed in the classroom, hallway or on the school playground. Teachers were given a Classroom Action Bin that contained equipment and resources to facilitate these activities.

The second required component was Bounce at the Bell. We asked INT teachers to implement this short activity (~3 min/day) in their classroom 3 times a day (at the morning, noon and end of day school bell), 4 days a week. Teachers instructed students to perform either counter movement jumps (two foot take off, clutch knees, two foot landing) or side to side jumps (one foot take off, opposite foot landing). During Phase I, students performed 5 two-foot landing jumps (or 10 one-foot landing jumps) at each session. During Phase II teachers were instructed to increase the number of jumps (starting from 5 per session) over each month of the school year until a maximum of 36 jumps per day was achieved. Children in CON schools participated in their regular program of physical education (PE) which involved two 40-minute PE classes per week according to curriculum guidelines.

In-school training of teachers at INT schools (N = 48 across Phases I and II) was conducted by the AS! BC Support Team. To monitor compliance with program delivery, we asked INT teachers to complete activity logs (Appendix 5). Teachers recorded the type, frequency and duration of each activity undertaken with their class each day of the school week. Intervention teachers also recorded the number of sessions of Bounce at the Bell and the number of jumps per session that their students performed each day of the school week. The physical activity level of CON schools was also monitored using a modified version of the activity log.

5.2.4 Descriptive Outcomes

Standing height was measured to the nearest 0.1 cm using a wall-mounted digital stadiometer (Seca Model 242, Hanover, MD) and body weight was measured to the nearest 0.1 kg using an electronic scale (Seca Model 840, Hanover, MD). Length of the left tibia was measured as the distance from the distal edge of the medial malleous to the tibial plateau (to the nearest 0.1 cm) using an anthropometric tape. For each variable the mean of two measures is reported. Muscle cross-sectional area (MCSA, mm^2) was assessed at the proximal two-thirds site of the left tibia with pQCT (XCT-2000).

Maturity status was assessed at baseline and followup using self-report Tanner staging (breast stage for girls, pubic hair stage for boys) (22). Girls' menarcheal status at baseline and followup was determined by self-report questionnaire. To estimate lower limb power, maximal height (cm) for vertical jump was measured using the Vertec™ device (Fitness Source, Concord, ON) and maximal distance (cm) for standing long jump was assessed according to standard protocol (23). A modified version of the Physical Activity Questionnaire for Children (PAQ-C) was used to assess physical activity (24,25). A general physical activity score (*PA Score*) was calculated as an average of the 10 PAQ-C items in a continuous range between 1 (low activity) and 5 (high activity) and an estimate of time (hrs/wk) spent in common sports and activities designated as loaded (impact > walking, *load time*) was generated from Item 1. A validated food frequency questionnaire (FFQ) (26) was used to determine dietary calcium (mg/day). The PAQ-C

and FFQ were administered at baseline and followup plus 3 additional times during the study period. The average across the 5 reports is presented for PA Score, load time and dietary calcium.

5.2.5 *Primary and Secondary Outcomes*

To address the primary objective, I used pQCT (XCT-2000) to assess change in bone strength index (BSI, mg^2/mm^4) at the distal tibia and change in polar strength strain index (SSI_p, mm^3) at the tibial midshaft. Detailed acquisition and analysis procedures are provided in Chapter 2 (Sections 2.2.8.3.3 and 2.2.8.3.4).

Briefly, a 30 mm planar scout view was acquired over the joint line to locate a standard anatomical reference (distal surface of the tibial plafond) from which the distal site (8% of total tibial length) and the tibial midshaft (50% of total tibial length) were measured proximally. I analyzed all scans using Stratec software, Version 5.5. At the distal tibia, contour mode 1 (200 mg/cm^3) was used to determine secondary outcomes of total bone cross-sectional area (ToA, mm^2) and total bone mineral density (ToD, mg/cm^3), which in turn were used to calculate BSI (ToA * ToD^2). At the midshaft, Separation mode 1 (480 mg/cm^3) was used to determine SSI_p. Secondary outcomes at the midshaft were total area (ToA, mm^2), cortical area (CoA, mm^2; Separation mode 1, 480 mg/cm^3) and cortical density (CoD, mg/cm^3; Separation mode 1, 711 mg/cm^3). The lower threshold of 480 mg/cm^3 was chosen for CoA in order to match the threshold used for the primary outcome (SSI_p), whereas 711 mg/cm^3 was chosen for CoD in order to minimize the partial volume effect.

To address the secondary objective, I used pQCT to assess change in SSI along the x- and y-bending axes (SSI_x, SSI_y). These outcomes estimate bone bending strength in the x- and y-planes, respectively (27). Precision and quality assurance procedures for pQCT are provided in Chapter 2 (Section 2.2.8.3.3).

5.3 *Statistical Analysis*

To account for the clustered study design, a linear mixed effects model was used to compare the change in primary (BSI, SSI_p, SSI_x, SSI_y) and secondary (distal tibia: ToA, ToD; midshaft: ToA, CoA, CoD) outcomes between intervention and control groups. Group (intervention or control) was designated as the *fixed effect* and school as a *random effect*. Separate mixed effects models were created for boys and girls due to known differences in the tempo and timing of growth and maturation between sexes (22). Covariates were chosen based on known biological and biomechanical relationships with the primary and secondary bone outcomes, relationships established in cross-sectional analyses detailed previously (Chapter 6) and the strength of associations noted in univariate analyses (Appendix 9). For boys, covariates in the final mixed effects models were baseline bone value, tibia length change and MCSA change. For girls, covariates were baseline bone value, tibia length change, MCSA change and final Tanner stage. Based on results from previous studies that identified differences in the bone response to increased loading between maturity groups (5,28), the effect of the intervention was also evaluated between maturity groups (pre- and early pubertal) by adding an interaction term (group x maturity category). Standard residual plots were used to assess normality, linearity and homoscedascity and plots of Cook's distance values were used to identify outliers. All analyses were performed using an intention-to-treat approach. Interactions at $p < 0.1$ were considered significant.

If the interaction was significant, the lincom function in STATA was used to determine standard errors for all linear combinations of coefficients.

5.4 Results

5.4.1 Participants and Compliance

A detailed description of the flow of participants through the trial is provided in Chapter 3 (Figure 3-1 and Figure 3-2). Briefly, 71 (14%) children were lost to followup and 6 (1%) were excluded from all analyses due to medical conditions known to affect bone metabolism or that prevented participation in regular physical education. In addition, 17 children from one Intervention school did not have a baseline pQCT scan and baseline scans from 10 other children (9 Intervention, 1 Control) could not be analyzed due to movement artefacts. Thus, the present analysis includes 410 children (281 Intervention: 145 boys, 136 girls; 129 Control: 64 boys, 65 girls) who had pQCT scans at baseline and followup.

Due to the short duration of Phase I, only compliance during Phase II is considered for this analysis. Median compliance with Activity Logs was 97% (interquartile range, IQR: 89-100%) across CON schools and 94% (IQR: 92 – 100%) across INT schools during Phase II. Teachers at INT schools delivered approximately 60 minutes more physical activity per week than teachers at CON schools (+58.9 min/wk; 95% CI, 25.4-92.4). Median compliance with Bounce at the Bell 74% (IQR: 50 – 89%) across INT schools. Fifteen teachers (44%) reported completing at least 80% of the required Bounce at the Bell sessions. Student attendance determined from school records averaged 96% across all schools over the course of the study.

5.4.2 Descriptives

Descriptive characteristics of boys and girls at baseline are presented (Table 5-1). Overall, 53% of the children were Asian, 34% were Caucasian and 13% were of mixed or other ethnicities. For boys and girls, the ethnic distribution was similar between groups. The majority of boys were prepubertal (67%) whereas the majority of girls were early pubertal (60%). Despite randomization, slight imbalances appeared in descriptive characteristics between groups. For boys, baseline weight and MCSA tended to be greater in the CON group, whereas for girls, baseline height, weight and MCSA tended to be greater in the INT group.

Regarding change in descriptive characteristics, INT boys tended to have a greater improvement in long jump (7.6% vs. 5.2%) and vertical jump (16.6% vs. 9.9%) performance compared with CON boys. Change in Tanner stage was similar between INT and CON boys (Table 5-2).

Girls in the INT group tended to have smaller gains in height (5.5% vs. 5.8%), tibial length (4.9% vs. 5.5%), weight (16.7% vs. 18.5%) and MCSA (12.9% vs. 15.6%) and a greater improvement in long jump performance (7.6% vs. 3.4%) than CON girls. Change in Tanner stage was similar between INT and CON girls (Table 5-2) and a similar proportion of INT and CON girls were post-menarcheal at followup (Table 5-1).

5.4.3 Primary outcomes

Baseline, followup and adjusted difference for change in primary and secondary pQCT outcomes for boys and girls are presented (Table 5-3). In diagnostic checks of the distal tibia outcomes, two boys (1 CON, 1 INT) had Cook's distance values 2.5 times greater than the next closest value. Thus, these boys were excluded from the distal tibia analysis. Similar checks of tibial midshaft outcomes resulted in the exclusion of one INT boy from the tibial midshaft analysis. These three scans were checked closely for movement artefacts and errors in pQCT analysis and none were discernible.

5.4.3.1 Boys

At baseline, bone strength indices (unadjusted) were 2-5% greater in CON boys than INT boys. At the distal tibia, adjusted 16-month change in BSI tended to be greater for INT boys (+774.6 mg^2/mm^4; 95% CI: 672.7, 876.4) than CON boys (+650.9 mg^2/mm^4; 95% CI: 496.4, 805.4), but this difference was not statistically significant. There was, however, a significant group x maturity interaction for change in BSI (Figure 5-1). Prepubertal INT boys had a significantly greater increase in BSI compared with prepubertal CON boys, whereas there was no significant difference in change between early pubertal INT and CON boys.

At the tibial midshaft, adjusted 16-month change in SSI_p, SSI_x and SSI_y tended to be greater for INT boys, but the difference in change between groups was not significant. The group x maturity interaction was not significant for strength indices at the tibial midshaft; however, there was a tendency for prepubertal INT boys to have greater gains in SSIp, SSIx and SSIy compared with prepubertal CON boys (Table 5-4 and Figure 5-1).

5.4.3.2 Girls

For girls, baseline values for bone strength indices were 4-5% greater in INT girls compared with CON girls. At the distal tibia, 16-month adjusted change in BSI tended to be greater in INT girls (+918.4 mg^2/mm^4; 95% CI: 844.2, 992.6) than CON girls (+829.2 mg^2/mm^4; 95% CI: 721.5, 936.9); however, this difference was not statistically significant (Table 5-3). At the tibial midshaft, there was no difference in change between INT and CON girls for SSI_p, SSI_x or SSI_y. Further, there were no significant group x maturity interactions for change in bone strength indices at either site.

5.4.4 Secondary Outcomes

5.4.4.1 Boys

At baseline, distal tibia ToA (unadjusted) was similar between CON and INT boys whereas ToD was approximately 3% greater in CON boys than INT boys. Control boys tended to have a greater change in ToA than INT boys, whereas the opposite was true for ToD (Table 5-3). Similar to results for BSI, a significant group x maturity interaction was found for ToD (Table 5-4). Prepubertal INT boys had a significantly greater increase in ToD (+3.2 mg/cm^3; 95% CI: -0.03, 6.5) compared with CON boys who demonstrated a decrease in ToD (-3.3 mg/cm^3; 95% CI: -8.2, 1.6). There was no significant group x maturity interaction for change in ToA.

At the tibial midshaft, baseline values for ToA, CoA and CoD were similar between CON and INT boys. There was a tendency for INT boys to have a greater gain in CoA; however, the difference in change between groups was not significant (Table 5-3). There were no significant group x maturity interactions for change in ToA, CoA or CoD (Table 5-4) although prepubertal INT boys tended to have a greater increase in CoA (+29.5 mm^2; 95% CI: 26.8, 32.2) than prepubertal CON boys (+25.8 mm^2; 95% CI: 22.0, 29.6).

5.4.4.2 Girls

Baseline values for distal tibia ToA and ToD were 1-2% greater in INT girls than CON girls. Similar to boys, 16-month adjusted change in ToA tended to be greater in CON girls (+62.0 mm^2; 95% CI: 53.5, 70.6) than INT girls (+53.8 mm^2; 95% CI: 48.0, 59.5) and change in ToD tended to be greater in INT girls (+12.5 mg/cm^3; 95% CI: 9.2, 15.7) than CON girls (+8.3 mg/cm^3; 95% CI; 3.4, 13.2) (Table 5-3). There were no significant group x maturity interactions for change in ToA or ToD.

At the tibial midshaft, baseline values for ToA and CoA were 3% greater for INT than CON girls, whereas CoD was similar between groups. There was no significant difference in change between groups for ToA, CoA or CoD (Table 5-3), nor were there any significant group x maturity interactions for change in ToA, CoA or CoD.

Table 5-1. Baseline and change (where appropriate) in descriptive characteristics for Control and Intervention boys and girls.

	BOYS				*GIRLS*			
	Control (N = 64)		**Intervention (N = 145)**		**Control (n = 65)**		**Intervention (N = 136)**	
	Baseline	**Change (95% CI)**	**Baseline**	**Change (95% CI)**	**Baseline**	**Change (95% CI)**	**Baseline**	**Change (95% CI)**
Baseline Age (yrs)	10.3 (0.6)	-----	10.2 (0.6)	-----	10.3 (0.5)	-----	10.2 (0.6)	-----
No. Asian/Caucasian/Other	31/21/12	-----	79/51/15	-----	31/27/7	-----	76/41/19	-----
Baseline Tanner Stage (1/2/3/4/5)	45/17/2/0/0	-----	88/50/7/0/0	-----	27/35/3/0/0	-----	52/71/13/0/0	-----
Final Tanner Stage (1/2/3/4/5)	25/26/12/1/0	-----	46/58/34/6/1	-----	9/24/30/2	-----	17/56/57/6	-----
No. Post-menarcheal at Baseline	-----	-----	-----	-----	1 (2%)	-----	6 (4%)	-----
No. Post-menarcheal at Followup	-----	-----	-----	-----	10 (15%)	-----	24 (18%)	-----
Height (cm)	141.2 (6.8)	6.6 (6.2, 7.1)	141.5 (7.2)	6.8 (6.5, 7.2)	140.2 (7.5)	8.1 (7.6, 8.6)	141.5 (7.5)	7.5 (7.2, 7.9)
Tibial Length (cm)	32.8 (2.2)	1.6 (1.4, 1.7)	32.9 (2.4)	1.7 (1.6, 1.8)	32.5 (2.3)	1.8 (1.6, 1.9)	33.0 (2.4)	1.6 (1.4, 1.7)
Weight (kg)	39.7 (9.6)	6.1 (5.4, 6.7)	37.2 (9.3)	5.6 (5.2, 6.0)	35.2 (8.7)	6.4 (5.7, 7.0)	36.3 (8.4)	5.8 (5.4, 6.3)
MCSA (cm^2)*	35.1 (5.4)	4.1 (3.5, 4.6)	33.8 (5.2)	4.2 (3.3, 5.1)	32.2 (5.3)	5.0 (4.4, 5.5)	33.3 (5.7)	4.3 (3.9, 4.7)
Long Jump (cm)	133.2 (20.9)	6.3 (2.4, 10.1)	133.2 (17.6)	9.2 (6.7, 11.6)	120.9 (15.1)	4.1 (0.8, 7.3)	121.2 (14.7)	8.1 (5.7, 10.4)
Vertical Jump (cm)	28.3 (5.2)	2.4 (1.0, 3.8)	27.7 (5.8)	4.1 (3.2, 5.1)	24.9 (5.1)	3.2 (1.8, 4.4)	25.6 (4.6)	3.0 (2.1, 3.9)
Average PA Score (/5)	2.7 (0.4)	-----	2.7 (0.4)	-----	2.6 (0.3)	-----	2.6 (0.4)	-----
Average Load Time (hrs / week)	6.8 (4.2)	-----	6.7 (4.3)	-----	4.7 (3.2)	-----	4.8 (3.4)	-----
Average Dietary Calcium (mg/day)	931 (450)	-----	928 (433)	-----	800 (290)	-----	807 (362)	-----

Note: Means, SD and 95% CI do not account for clustering

Physical activity and dietary calcium variables are the average of 5 reports.

SD = standard deviation; CI = confidence interval; MCSA = muscle cross-sectional area; PA = physical activity

* MCSA measured in mm^2 but presented in cm^2.

Table 5-2. Tanner stage at baseline and followup for Control and Intervention boys and girls.

		BOYS		*GIRLS*	
	Baseline – Followup Tanner Stage	**Control**	**Intervention**	**Control**	**Intervention**
Prepubertal	1-1	26 (58%)	46 (52%)	9 (33%)	17 (33%)
	1-2	15 (33%)	32 (36%)	13 (48%)	30 (58%)
	1-3	4 (9%)	10 (11%)	5 (19%)	5 (10%)
	Total	45 (100%)	88 (100%)	27 (100%)	52 (100%)
Early Pubertal	2-2	10 (53%)	26 (46%)	11 (29%)	26 (33%)
	2-3	6 (32%)	21 (37%)	22 (58%)	39 (50%)
	2-4	1 (5%)	3 (5%)	2 (5%)	1 (1%)
	3-3	2 (11%)	3 (5%)	3 (8%)	8 (10%)
	3-4	0	3 (5%)	0	4 (5%)
	3-5	0	1 (2%)	0	0
	Total	19 (100%)	57 (100%)	38 (100%)	78 (100%)

Table 5-3. Baseline, followup and adjusted difference in change in distal tibia and tibial midshaft pQCT outcomes for Control (CON) and Intervention (INT) boys and girls.

		BOYS					*GIRLS*				
Outcome	**Group**	**Baseline Mean (SD)**	**Followup Mean (SD)**	**Difference in Change (95% CI)***	***p***	**ICC**	**Baseline**	**Followup**	**Difference in Change (95% CI)***	***p***	**ICC**
Distal[a]											
BSI (mg^2/mm^4)	CON	5322.7 (1136.7)	6005.4 (1290.1)	123.8 (-62.1, 309.8)	0.2	0.06	4351.2 (1136.0)	5193.9 (1383.6)	82.0 (-50.1, 214.1)	0.2	0.01
	INT	5087.5 (1074.2)	5855.5 (1254.5)				4562.3 (1178.7)	5470.2 (1524.4)			
ToA (mm^2)	CON	548.1 (88.1)	625.3 (94.7)	-4.1 (-11.4, 3.2)	0.3	0.01	503.4 (80.0)	569.1 (90.9)	-8.1 (-18.4, 2.3)	0.1	0.05
	INT	552.4 (88.2)	626.2 (100.6)				509.7 (74.7)	561.8 (77.6)			
ToD (mg/cm^3)	CON	311.6 (32.2)	309.8 (34.0)	4.2 (-1.5, 9.8)	0.2	0.08	292.8 (32.3)	300.9 (34.6)	3.9 (-2.0, 9.8)	0.2	0.06
	INT	303.5 (30.4)	305.6 (29.9)				298.2 (36.4)	310.3 (41.1)			
Midshaft[b]											
SSI_P (mm^3)	CON	1029.8 (211.6)	1208.0 (250.4)	20.9 (-7.1, 48.9)	0.1	0.06	915.5 (221.3)	1093.5 (264.5)	2.1 (-16.3, 20.5)	0.8	0.02
	INT	1006.1 (241.4)	1204.2 (295.5)				954.4 (218.8)	1124.3 (251.5)			
SSI_X (mm^3)	CON	653.2 (151.1)	779.6 (184.6)	9.0 (-7.9, 26.0)	0.3	0.03	595.4 (164.2)	720.3 (193.5)	4.2 (-8.8, 17.3)	0.5	0.01
	INT	635.6 (167.7)	770.7 (205.1)				617.4 (157.3)	738.5 (181.6)			
SSI_Y (mm^3)	CON	528.6 (99.0)	614.9 (124.5)	15.8 (-5.9, 37.5)	0.2	0.09	457.8 (105.5)	541.1 (128.3)	0.6 (-9.8, 11.0)	0.9	0.002
	INT	517.7 (126.6)	617.7 (152.0)				481.5 (103.3)	560.9 (121.4)			

Table 5-3 continued

		BOYS					*GIRLS*				
Outcome	**Group**	**Baseline Mean (SD)**	**Followup Mean (SD)**	**Difference in Change (95% CI)***	***p***	**ICC**	**Baseline Mean (SD)**	**Followup Mean (SD)**	**Difference in Change (95% CI)****	***p***	**ICC**
Midshaft											
ToA (mm^2)	CON	340.5 (49.9)	376.8 (58.6)	1.5 (-3.1, 6.1)	0.5	0.03	312.4 (53.7)	345.7 (56.9)	0.3 (-3.7, 4.3)	0.9	0.03
	INT	335.5 (54.0)	374.1 (62.1)				322.1 (51.6)	352.4 (54.2)			
CoA (mm^2)	CON	221.4 (30.6)	249.1 (36.6)	2.2 (-2.2, 6.5)	0.3	0.03	205.2 (36.5)	232.2 (41.6)	0.5 (-2.5, 3.5)	0.8	0.04
	INT	219.1 (36.0)	249.3 (42.8)				211.0 (33.1)	236.5 (37.5)			
CoD (mg/cm^3)	CON	1046.0 (30.6)	1046.0 (35.8)	0.4 (-4.7, 5.5)	0.9	0.01	1058.6 (29.9)	1067.0 (32.8)	3.3 (-1.4, 7.8)	0.2	< 0.001
	INT	1047.5 (35.8)	1047.3 (35.7)				1057.2 (33.7)	1073.4 (35.8)			

SD = standard deviation; CI = confidence interval; ICC = intracluster correlation coefficient; BSI = bone strength index; ToA = total area; ToD = total density; SSI_p = polar strength-strain index; SSI_x = strength-strain index relative to the x-axis; SSI_y = strength-strain index relative to the y-axis; CoA = cortical area; CoD = cortical density.

* Change adjusted for baseline bone value, tibial length change and muscle cross-sectional area change.

** Change adjusted for baseline bone value, tibial length change, muscle cross-sectional area change and final Tanner stage.

a Boys: n = 60 CON, 136 INT; Girls: n = 63 CON, 126 INT

b Boys: n = 64 CON, 142 INT; Girls: n = 64 CON, 134 INT

Table 5-4. Adjusted difference in change (Intervention – Control) in pQCT outcomes at the distal tibia (8% site) and tibial midshaft (50% site) for pre- (PRE) and early pubertal (EARLY) boys.

Outcome	Maturity Group	Difference in Change (95% CI)*	p**
Distal Tibia			
BSI (mg^2/mm^4)	PRE†	222.9 (31.2, 414.5)	0.03
	EARLY‡	-57.0 (-294.3, 180.4)	
ToA (mm^2)	PRE	-5.2 (-14.1, 3.7)	0.67
	EARLY	-1.9 (-16.6, 12.8)	
ToD (mg/cm^3)	PRE	6.5 (0.7, 12.4)	0.07
	EARLY	-0.3 (-7.4, 6.9)	
Midshaft			
SSI_p (mm^3)	PRE	28.5 (-1.5, 58.6)	0.24
	EARLY	5.5 (-31.7, 42.8)	
SSI_x (mm^3)	PRE	16.2 (-2.4, 34.7)	0.13
	EARLY	-5.3 (-29.8, 19.1)	
SSI_y (mm^3)	PRE	18.7 (-4.6, 42.0)	0.51
	EARLY	9.9 (-17.7, 37.6)	
ToA (mm^2)	PRE	1.8 (-3.5, 7.1)	0.87
	EARLY	1.1 (-5.9, 8.1)	
CoA (mm^2)	PRE	3.7 (-1.0, 8.4)	0.24
	EARLY	-0.6 (-6.9, 5.6)	
CoD (mg/cm^3)	PRE	-1.4 (-6.9, 4.2)	0.31
	EARLY	-9.7 (-17.8, -1.6)	

CI = confidence interval; BSI = bone strength index; ToA = total bone cross-sectional area; ToD = total density; SSIp = polar strength strain index; SSIx = strength-strain index relative to the anatomical x-axis; SSIy = strength-strain index relative to the anatomical y-axis; CoA = cortical cross-sectional area; CoD = cortical density.
* Adjusted for baseline bone value, tibial length change, muscle cross-sectional area change
** *p* value for the group x maturity interaction
† n = 45 Control, 89 Intervention
‡ n = 19 Control, 58 Intervention

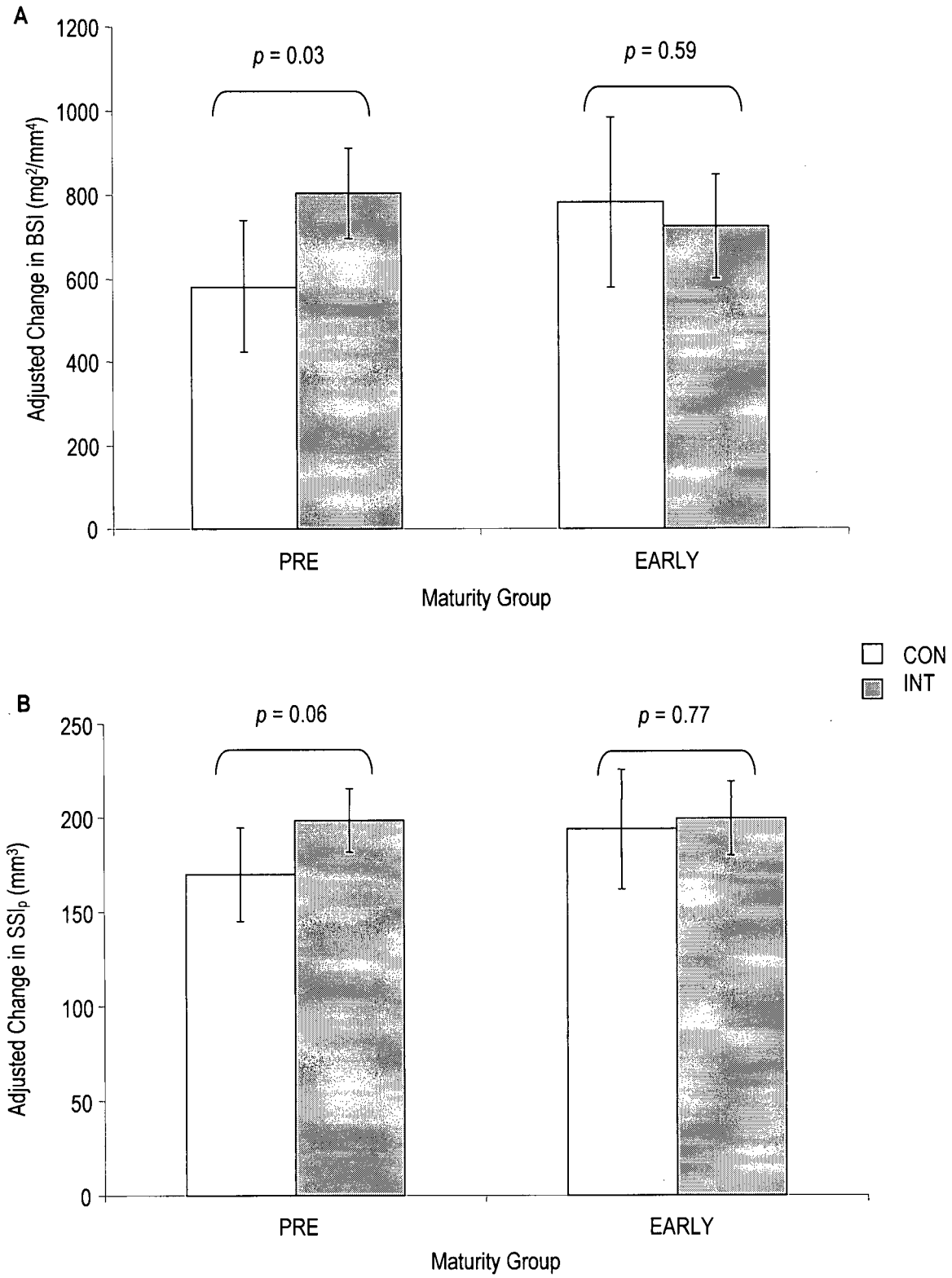

Figure 5-1. Adjusted change in (A) bone strength index (BSI) at the distal tibia and (B) polar strength strain index (SSI_p) at the tibial midshaft between prepubertal (PRE) and early pubertal (EARLY) Intervention (INT) and Control (CON) boys. Bars are 95% confidence interval and *p* value is for the group x maturity interaction. Change in bone strength indices adjusted for baseline bone value, tibial length change, and muscle cross-sectional area change.

5.5 Discussion

This is the first study to prospectively investigate the effects of increased physical activity on tibial *bone strength* in both boys and girls using pQCT. Action Schools! BC (AS! BC) was effective for increasing bone strength only at the distal tibia in prepubertal boys; it was not effective for increasing tibial bone strength in early pubertal boys or pre- or early pubertal girls. The novel aspects of this study are 1) the unique, pragmatic intervention and 2) the use of pQCT to estimate bone strength changes at two skeletal sites and in two bending planes.

5.5.1 Action Schools! BC: A Unique Intervention

The AS! BC model aimed to increase physical activity opportunities within the classroom setting and provided *generalist teachers* with ideas to achieve this without the need for special equipment or access to the school gymnasium. Within the broader activity component (Classroom Action), Bounce at the Bell was a simple bone-loading exercise that required only 3 minutes each school day to implement.

The osteogenic potential of physical activity is determined by the magnitude of the external load, the dynamic nature of the load, the rate at which the load is introduced and the duration of the loading bout (18,29). Previous school-based studies have incorporated these principles into the design of physical activity interventions and some have proven effective for increasing bone mineral accrual (2,4-8,16) and estimated bone strength (3,28,30) in boys and girls. However, in these trials the duration of the activity sessions ranged from 10-90 minutes and the sessions were only performed once a day, 2-3 times per week. In contrast, animal studies have demonstrated that multiple, short bouts of loading interspersed with recovery periods are equally as effective as longer loading bouts suggesting that the cellular response to loading saturates quickly (20,31). Bounce at the Bell, a program of short bouts of high-impact jumping separated by rest periods, was designed in accordance with these findings. In a pilot study of Bounce at the Bell, McKay and colleagues (21) found that this simple bone-loading program was effective for improving proximal femur bone mass in boys and girls aged 9-11 years.

In the current study, although intervention children performed Bounce at the Bell, they also performed a variety of other weight-bearing activities such as skipping and running. Also, boys and girls in this cohort were already active performing an average of 7 and 5 hours of leisure-time loaded activity per week, respectively, and many of the activities involved running. Thus, the contribution of these other weight-bearing activities to bone adaptation cannot be ruled out. Activities such as running and skipping impose greater loads on the skeleton than does walking (32,33), but the strains may not be sufficiently unusual in magnitude and/or distribution to elicit an osteogenic response at the tibia. In contrast, the maximum ground reaction forces (GRF) of the two-foot countermovement jumps used in Bounce at the Bell are approximately 5 times body weight (34). In addition, data from human strain gauge studies indicate that multidirectional activities similar to the jumps performed in Bounce at the Bell produce higher strains and strain rates and more unusual strain distributions than walking or running (35). Thus, it is likely that of the AS! BC activities undertaken in the present study, Bounce at the Bell provided the most consistent and unique bone-loading stimulus in the AS! BC intervention.

The AS! BC model was designed for the generalist teacher rather than physical education specialists. As a result, the success of the program is highly dependent on teacher uptake and compliance. Acceptance of the overall program was excellent as only one intervention teacher out of 48 chose not to participate. However, compliance with the Classroom Action component, and more specifically with Bounce at the Bell, varied across intervention teachers (within and between intervention schools). This variation in compliance may have influenced the primary analysis and resulted in an underestimation of the intervention effect. Interestingly, those teachers that complied with Bounce at the Bell were also more likely to meet the overall goal of 150 minutes per week of physical activity. Although the AS! BC process evaluation identified barriers and facilitators to teacher delivery of the overall AS! BC model (36), there is a need to further examine factors underlying the variation in teacher compliance with Bounce at the Bell.

5.5.2 pQCT - A Novel Imaging Modality

To date, three intervention studies have used pQCT to evaluate the effects of increased physical activity on the growing skeleton (16,17,37). There were a number of distinct differences between these trials that preclude a comparison between them. These differences include the age and sex of participants, length and type of the intervention, pQCT acquisition and analysis protocols, bone sites measured and outcome variables reported. This highlights the need for standardized analysis, acquisition and reporting protocols for pediatric pQCT studies.

The present study is unique in that change in estimated bone strength was evaluated at both the distal tibial and tibial midshaft. At the distal tibia, which experiences mainly compressive forces, bone strength is dependent on trabecular (apparent) density (38). In addition to a relatively dense trabecular bone structure, a large cross-sectional area would be optimal to resist compressive loads (11). Thus, bone strength at the distal tibia was estimated using BSI – a measure that incorporates both density and cross-sectional area. This index has been used in previous studies (11). In contrast, the tibial shaft experiences mainly bending and torsional forces and resistance to such forces is determined primarily by the distribution of cortical bone as well as its material stiffness of cortical bone (39,40). Therefore, bone torsional and bending strength at the tibial midshaft were estimated using the pQCT-derived polar strength-strain index (SSI_p) and SSI along the bending.

Given the strong association between compressive bone strength and apparent density (38), it is not surprising, that the greater gain in BSI in prepubertal INT boys was associated with a greater gain in ToD rather than ToA. Total density reflects the contribution of both trabecular density (TrbD) and CoD; however, CoD cannot be measured accurate at this site because of the thin cortical shell at the distal tibia (< 2 mm, on average, data not shown) (41). Prepubertal INT boys did tend to have a greater change in TrbD than prepubertal control boys (data not shown). These results extend previous cross-sectional pQCT findings in young gymnasts (9) and racquet-sport players (11). Although they did not assess estimated bone strength, Ward et al. (9) reported significantly greater ToD at the distal tibia in male and female gymnasts (5-12 yrs of age) compared with similar aged controls and no difference in ToA between groups after adjusting for age, sex and height. Similarly, Kontulainen et al. (11) reported significantly greater side-to-side differences in TrbD at the distal radius in female racquet-sport athletes (young starters) compared with controls. There was a tendency for athletes to have a greater side-to-side difference in BSI

as well. Results from animal studies suggest that gains in trabecular density in response to mechanical loading may be due to changes in trabecular microarchitecture such as increases in trabecular thickness and/or trabecular number as well as a decrease in trabecular separation (42).

At the tibial midshaft, prepubertal intervention boys tended to have a greater increase in SSI_p than prepubertal control boys; however, the difference in change between groups was not statistically significant. In a subgroup analysis that included only prepubertal intervention boys in classes that were at least 80% compliant with Bounce at the Bell the intervention effect was significant (data not shown). Although this finding must be interpreted with caution due to bias associated with subgroup analyses and the small number of intervention boys included (n = 35), it does suggest that teacher compliance is crucial to the effectiveness of the intervention.

The trend for greater change in SSI_p in prepubertal intervention boys compared with prepubertal control boys was associated with a trend for greater gain in CoA. As changes in SSI_p and CoA were not statistically significantly different between groups, I can only speculate on possible surface-specific adaptations to the intervention. At the midshaft, an increase in CoA may result from either an increase in periosteal bone formation or a decrease in endocortical bone resorption (or increased apposition), or a combination of both. In the present study, although prepubertal intervention boys had slightly greater (non-significant) gains in ToA they also tended to have a smaller increase in the area of the marrow cavity (data not shown) than control boys. Although periosteal expansion is the most effective means to increase bone torsional and bending strength at the shaft, increasing the amount of cortical bone within the cross-section (indicated by CoA) also increases bone strength, but to a lesser degree (43). Similar findings (cross-sectional) were reported for young gymnasts at the 65% site of the tibia shaft (9). Greater SSI_p in male and female gymnasts was associated with larger CoA, smaller area of the marrow cavity and similar ToA when compared with controls. In addition, Bradney et al. (3) reported smaller changes in DXA-derived area of the marrow cavity at the femoral midshaft in prepubertal intervention boys compared with controls following an 8-month exercise intervention.

There are several possible explanations for why the present investigation did not detect a significant effect on periosteal expansion. First, it is likely that an intervention-related increase in periosteal bone formation would be small relative to periosteal expansion associated with normal growth (44-46). Due to limited resolution, pQCT may be unable to detect such small changes on the outer bone surface. However, it is important to acknowledge that the contribution of bone surface to SSI_p varies exponentially with distance from the centre of mass of the cross-section. Thus, even small gains at the periosteal surface such as those observed for prepubertal intervention boys may contribute to an increase in bone bending strength. Second, the tibia experiences a combination of bending and axial compressive forces during weight-bearing activity (47). For long bones, strength in compression is inversely related to bone cross-sectional area (47,48). Decrease bone resorption on the endosteal surface (or increased apposition) would therefore serve to increase cross-sectional area and reduce the compressive strains. A longer intervention period would help to clarify the surface-specific adaptations to AS! BC in young boys.

The intervention tended to have a positive effect on indices of bone bending strength in both the x- and y-planes in prepubertal boys, but differences between groups were not statistically significant. As discussed, the magnitude of the intervention effect may increase given a longer intervention period. The x- and y-axes generated by the Stratec software are anatomical axes and therefore only approximate the planes of the maximum and minimum moments of area, respectively. At the tibial midshaft, running and walking cause bending in the anterior-posterior (AP) direction (49). Human strain gauge studies indicate that under such loads, the neutral axis of bending runs in the medial-lateral direction (ML, x-axis) and the anterior and posterior cortices experience the greatest tensile and compressive strains, respectively (49). In this plane gains in bone strength (SSI_x) are achieved through periosteal apposition (or decreased endocortical resorption) in the anterior and/or posterior regions of the cross-section. In contrast, bending strength in the ML direction (about the AP or y-axis, SSI_y) may be increased through apposition (or decreased resorption) in the medial and/or lateral regions. Studies of growing animals (13,15) have shown that changes in rates of bone formation and resorption on the medial, lateral, anterior and posterior surfaces in response to increased loading are directly related to strain gradient, or the distribution of the mechanical signal, in the cross-section. The strain gradient and strain distribution associated with the Bounce at the Bell jumps are not known, but it is possible that the multidirectional nature of the countermovement jumps (side-to-side, zigzag and front-to-back) may have resulted in an unusual strain distribution at the tibial midshaft such that strains were increased in both the AP and ML directions. Unfortunately current pQCT technology does not permit accurate assessment of region-specific changes that may have occurred in response to possible variation in strain distribution.

Although the muscle-bone relationship was not the focus of this study, it is interesting to note that despite greater gains in tibial bone strength among prepubertal INT boys, these gains were not associated with a greater change in muscle cross-sectional area compared with CON boys. A strong biomechanical link between muscle and bone is well-established (50); however, the effects of increased loading on the muscle-bone relationship are unclear. Muscle CSA is often used as a surrogate of muscle force, but changes in muscle force and strength can be achieved without a change in muscle size due to improvements in neuromuscular recruitment (51). It is possible that the greater gains in long and vertical jump performance in INT boys may indicate an increase in muscle force that is independent of the change in MCSA.

5.5.3 Sex- and Maturity-specificity of the Bone Response

Although boys and girls in intervention schools received the same program of physical activity AS! BC was effective for increasing tibial bone strength in prepubertal boys only. There are several possible explanations for the lack of an intervention effect in girls. First, physical activity levels are known to be lower in girls than boys at the same chronological age (52,53) and previous school-based intervention have reported challenges in promoting physical activity among girls (54). Thus, it is possible that girls were less motivated to participate in Bounce at the Bell and other Classroom Action activities than boys. Unfortunately, observational or teacher report data on children's participation in Bounce at the Bell and other activities were not available for the present study. The trend for intervention girls to have a greater improvement in distal tibia bone strength suggests that the program does have

potential to elicit an osteogenic response in girls. Direct observation of classroom activities may be warranted to clarify possible sex differences in participation as well as in execution of Bounce at the Bell jumps.

Second, the lack of an intervention effect in girls may be related to hormonal influences on bone development, specifically increased estrogen in girls during puberty. It has been proposed that in the female skeleton, estrogen modulates the bone response to loading indirectly via two mechanisms: 1) modifications in bone structure such as increased cortical density and relatively thicker cortices compared with the male skeleton (55,56) and 2) inhibition of periosteal bone formation due to activation of estrogen receptor beta (57). In the present study CoD was slightly greater in girls than boys at baseline and girls tended to have a greater increase in CoD than boys. This difference likely reflects differences in maturation as 67% of girls were early pubertal and 60% of boys were prepubertal. From a structural perspective, higher CoD is associated with increased bone stiffness and results in a decrease in the magnitude of deformation for a given load (55,58). Thus, as recently theorized by Sievanen (55), the more rigid female skeleton may require an approximately 20% greater strain to elicit similar deformations to those experienced in the male skeleton under normal loading conditions. It is possible that the strains associated with the present intervention were not sufficient to elicit an osteogenic response at the tibial midshaft in girls. This relationship may be further confounded by sex differences (boys > girls) in rate of change in muscle force and maximum muscle force associated with the countermovement jumps in Bounce at the Bell (34).

It is not clear what modifications to Bounce at the Bell and other Classroom Action activities may be required to increase the osteogenic potential of the AS! BC intervention at the tibia in girls. Heinonen et al. (16) implemented a more intensive jumping program (20-min of drop jump-training, 2 x/week) in their 9-month controlled trial and similar to the present study, did not observe an increase in bone strength at the tibial midshaft in intervention girls. However, based on current evidence from animal models this exercise program of infrequent and longer loading bouts would not be expected to maximize the adaptive response (18,19). It may be necessary to include more multidirectional jumps or zig-zag hopping in Bounce at the Bell as Milgrom et al. (35) found this type of activity was associated with the highest principal compression, tension and shear strains and compression strain rates when compared with activities such as walking, jogging, one- or two-leg vertical jumps and unidirectional hopping.

In boys, AS! BC was effective for increasing tibial bone strength in prepubertal, but not early pubertal boys. Of the few exercise interventions that have evaluated the bone response to loading in boys (3,7,30) all have included prepubertal boys only. Although results from the current study suggest that prepuberty may offer a "window of opportunity" for adaptation at the tibia similar to that described for girls at the femoral neck during early puberty (5,59), these findings should be interpreted with caution given the relatively small number of early pubertal boys. An alternative explanation for the maturity-specific intervention effect may be related to the boys' physical activity levels. Prepubertal intervention boys tended to report lower levels of leisure-time weight-bearing physical activity compared with early pubertal intervention boys (6.1 vs. 7.7 hrs/week). Since early pubertal intervention boys were already participating in more than one hour of loaded activity per day, it is possible that a more intense bone-loading program than Bounce at the Bell may have been required to elicit an osteogenic response in this group. To further investigate

this relationship within the clustered study design, a larger number of schools would be required to ensure adequate power for subgroup analyses.

5.5.4 Limitations

There are several methodological limitations of this study. First, although the cluster design was managed by the statistical approach, sample size was calculated without accounting for the clustered study design. Based on the intracluster correlation coefficient (ICC) for the primary outcomes at baseline (Appendix 9) and for change in the primary outcomes (Table 5-3), a conservative estimate of the ICC in this cohort is 0.05. However, it should be noted that due to the small number of schools, the precision of this estimate is limited (60). There is a need for appropriately designed pilot studies to determine an accurate estimate of the ICC for pQCT outcomes in boys and girls. In turn, this estimate can be used to plan future school-based interventions.

Second, an inclusion criterion for this study was that participating schools could not be undertaking any school-based physical activity initiatives as indicated by results from the province-wide Satisfaction Survey (61). Selecting these schools may have introduced bias into the study as the schools may have been more, or less, eager to participate in the intervention.

Third, this cohort was ethnically diverse with more than 50% of the children of Asian descent. As discussed in Part I of this thesis, there are differences in tibial bone geometry and density between Asian and Caucasian children. However, it was not the aim of the present study to investigate possible differences in the bone response to physical activity between ethnic groups. Further, the distribution of ethnicities was similar between intervention and control groups. In order to assess ethnic differences in skeletal adaptations to a school-based intervention, there is a need for estimates of the ICC for pQCT outcomes across ethnic groups.

Finally, there are several limitations associated with pQCT measurements. First, longitudinal bone growth in the tibia is disproportionate due to the greater contribution of the proximal growth plate (60%) compared with the distal growth plate (40%) (62). As a result it is not possible to determine the same exact location along the length of the tibia over time. However, a fixed anatomical landmark (distal edge of the tibia plafond) was used to locate the same relative region along the tibia length at the followup measurement. Second, placement of the anatomical axes used to determine SSI_x and SSI_y is influenced by leg position in the pQCT gantry. If the position is not accurately reproduced in repeated measurements, a systematic inaccuracy in the location of the axes within the cross-section and thus in the derived strength indices can occur. This potential source of error was minimized by having one trained technician acquire all scans at baseline and followup using standard positioning protocols.

5.5.5 Implications of the Findings

The results of the present study do not provide conclusive evidence regarding the effectiveness of AS! BC for increasing tibial bone strength in boys and girls; however, the findings in prepubertal boys are promising given the relatively modest intervention. It is not known if the observed gains in tibial bone strength will persist in the absence of intervention. However, results from two followup studies of school-based interventions (63,64) provide support for

the maintenance of gains in DXA-derived BMC 12-months after cessation of an exercise program. A followup study of the AS! BC cohort is needed to determine whether the skeletal advantage will be preserved in prepubertal boys. In addition, further investigation is required to determine if AS! BC is effective for increasing bone strength at clinically relevant sites such as the proximal femur. However, it is well established that physical activity during childhood is associated with reduced fracture risk in the elderly (65-67).

Due to declining resources for physical education in elementary schools and increasing curriculum demands on generalist teachers it is unlikely that interventions requiring modifications to an existing physical education curriculum will be a feasible or sustainable option. Thus, the AS! BC model offers an alternative means for elementary schools to increase daily physical activity opportunities for all students regardless of skill level. Importantly, although 50% of grade 4 and 5 children had consent to participate in the study, all children in grades 4 and 5, as well as children in grade 3/4 and 5/6 split classes were exposed to the intervention. This represents approximately 1400 children.

Finally, although teachers were provided with training, resources and the opportunity to design their own Action Plan, there were barriers to implementation such as lack of time and competing curricular demands (36). These factors need to be considered if wide-scale implementation of AS! BC is to be effective.

5.6 Summary

In summary, results of this study indicate that the Classroom Action component of AS! BC, which includes Bounce at the Bell, was an effective means to increase bone strength as estimated with pQCT at the distal tibia in prepubertal boys. The physical activity program was not similarly effective in girls. Future studies are needed to determine whether AS! BC is effective for increasing bone strength at clinically relevant sites such as the proximal femur in both boys and girls. The AS! BC model provided schools and generalist teachers with the tools and resources to increase physical activity opportunities in the classroom setting. As such, this model offers promise for wide-scale implementation.

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6 Part III: Effectiveness of a School-based Physical Activity Intervention for Increasing Femoral Neck Bone Mass and Strength in Boys and Girls[4]

6.1 Introduction

Physical activity during growth is beneficial not only for bone mineral accrual (1), but also for more functionally relevant properties such as bone cross-sectional geometry and ultimately, bone strength (2,3). More specifically, if begun before or at puberty, the benefits of physical activity on bone mass and (estimated) strength are more than two-fold greater than those achieved if activity is started after puberty (2,4). Unfortunately, recent statistics suggest that more than 50% of Canadian children are not active enough for optimal growth and development (5). If this trend continues it will likely contribute to an elevated risk for osteoporosis, falls and fracture among this population. Thus, it is important to identify effective physical activity programs that aim to optimize musculoskeletal development in children.

A number of intervention studies have demonstrated the effectiveness of various exercise programs for increasing bone mass in the growing skeleton (6-11). However, only one school-based study has provided a comprehensive evaluation of changes in *both* bone mass and estimated bone strength at the clinically relevant proximal femur in boys (12,13) and girls (14-16) in response to increased activity. The Healthy Bones Study II (HBS II) intervention was implemented within the school curriculum and the high-impact circuit program required 10-12 minutes, 3 times a week. Despite the effectiveness of HBS II, this program is not likely to be sustainable in elementary schools given competing curricular demands facing classroom teachers and limited access to gymnasium space and equipment. Therefore, in the absence of modifications to the existing physical education curriculum, it is important to identify an effective, school-based bone loading program that is simple to administer in the classroom setting, is short in duration and requires minimal equipment.

Building on the HBS II intervention, McKay and colleagues (17) recently reported the results of a pilot study in which they evaluated the effects of a short, high-impact jumping program, Bounce at the Bell on bone mass and structure in pre- and early pubertal boys and girls. Bounce at the Bell required children to perform 10 counter-movement jumps, 3 times daily at the time of the school bell. The design of this program incorporated principles of bone adaptation to loading defined in animal studies. Specifically, Umemura et al. (18) found that five jumps per day was sufficient to induce significant gains in bone mass and breaking force in growing rats. Additional experimental data from animal models showed that mechanosensitivity of bone declines shortly after initiation of loading and that inserting a rest period between loading bouts significantly improves the osteogenic response (19,20). In the Bounce at the Bell pilot study, a combined group of boys and girls had significantly greater gains in proximal femur bone mass than controls, but the bone structural response to the intervention as estimated with hip structure analysis (HSA) was unclear. To date, only one other study has incorporated these principles of bone adaptation into an

[4] A version of this chapter has been submitted for publication. Macdonald HM, Kontulainen SA, Beck TJ, McKay HA. Effectiveness of a school-based physical activity intervention for increasing femoral neck bone strength in boys and girls: The Action School! BC model. Submitted to Bone. June 2006.

intervention design; however, Johannsen et al. (21) did not assess the bone response to their 12-week jumping program at the proximal femur.

In the present study, Bounce at the Bell was implemented as the targeted bone-loading component within a larger classroom based program of physical activity, Action Schools! BC (AS! BC). The *primary objective* of this study was to evaluate the effectiveness of AS! BC for enhancing bone strength (section modulus, Z) at the clinically relevant femoral neck region of the proximal femur as estimated with HSA in boys and girls. To assess changes in femoral neck bone mass and geometry underpinning possible intervention-related changes in bone strength, secondary outcomes included HSA-derived cross-sectional area (CSA) and subperiosteal width (SPW) and DXA measures of bone mineral content (BMC) and bone area (BA). The *secondary objective* of this study was to determine the effectiveness of AS! BC for increasing DXA-derived BMC and BA at the total proximal femur, lumbar spine and total body.

6.2 *Methods*

Detailed procedures are provided in Chapter 2, and are briefly summarized here.

6.2.1 *Study Design*

This was a cluster randomized, controlled, school-based intervention trial. Ten schools from the Vancouver and Richmond School Districts were randomly assigned to control (CON, 3 schools), Level 1 intervention (4 schools) or Level 2 intervention (3 schools). The intervention arms differed in the amount of facilitation provided to teachers and not in the activity delivered to students. Thus, the two intervention arms were collapsed (INT, 7 schools) for the present analysis.

6.2.2 *Participants*

Children were recruited from grades 4 and 5 in each of the 10 schools. At baseline, 514 (47%) boys and girls (257 boys, 257 girls) aged 9-11 years and their parents provided informed consent. From the health history questionnaire completed by parents at baseline, 5 children (1 CON, 4 INT) were identified as having medical conditions that prevented participation in regular physical education or were reported to be taking medications known to affect bone metabolism. These children were excluded from the present analysis. All other children were healthy. Ethnicity classification was based on parents' or grandparents' place of birth as reported by parents in the health history questionnaire. The majority of the children were Asian (53%) with both parents or all 4 grandparents born in Hong Kong or China, India, Philippines, Vietnam, Korea or Taiwan. The remainder of the sample were Caucasian (35%) with parents born in North America or Europe and children of mixed ethnicity or other ethnic origins (12%).

6.2.3 *Intervention*

A comprehensive description of the AS! BC model is provided in Chapter 2 (Section 2.1). The required components of AS! BC are briefly summarized here.

In addition to their regular program of physical education (2, 40 minute classes per week), INT teachers provided their students with an additional 15 minutes of physical activity, 5 days a week (Classroom Action). Teachers chose from a number of different activities including skipping, dancing, playground circuits and simple resistance exercises with exercise bands. All activities required minimal equipment and could be performed in the classroom, hallway or in the school playground. Teachers were given a Classroom Action Bin that contained equipment and resources to facilitate these activities.

Within the Classroom Action program, INT teachers implemented Bounce at the Bell. Briefly, Bounce at the Bell required children to perform short bouts of high-impact jumping 3 times a day (at the morning, noon and end of day school bell), 4 days a week. During Phase I of the intervention (April – June 2003), students performed 5 two-foot landing jumps (or 10 one-foot landing jumps) at each session. During Phase II (October 2003 – May 2004) teachers were instructed to increase the number of jumps (starting from 5 per session) over each month of the school year until a maximum of 36 jumps per day was achieved.

In-school training of INT teachers (N = 48 across Phases I and II) was conducted by the AS! BC Support Team at the beginning of Phases I and II. To monitor compliance and program delivery, INT teachers completed weekly activity logs. Teachers recorded the type, frequency and duration of each activity undertaken with their class each day. For the present study the total number of minutes per week of physical activity (min/wk) delivered by INT teachers is reported. Intervention teachers also recorded the number of sessions of Bounce at the Bell and the number of jumps per session that their students performed each day.

Children at CON schools participated in their regular program of physical education which typically involved two 40-minute classes per week. Teachers at CON schools completed a modified version of the weekly activity log.

6.2.4 Measurements

Detailed procedures are provided in Chapter 2 (Methods) and are briefly summarized here. Anthropometry, questionnaire and bone data were collected at baseline (February - March 2003) and followup (May - June 2004) at the University of British Columbia Bone Health Research Laboratory. The median length of followup was 14.0 months (range = 13.8 to 14.1 months). Questionnaire data were also collected in the school at 3 additional times during the study period. A detailed study timeline is provided in Chapter 2 (Figure 2-3).

6.2.4.1 Descriptive Outcomes

Standing and sitting height were measured to the nearest 0.1 cm using a wall-mounted digital stadiometer (Seca Model 242, Hanover, MD) and body weight was measured to the nearest 0.1 kg using an electronic scale (Seca Model 840, Hanover, MD). For each variable the mean of two measures is reported. Measures of total body bone mineral free lean mass (kg) and fat mass (kg) were obtained from total body DXA scans.

Maturity status was assessed at baseline and followup using self-report Tanner staging (breast stage for girls, pubic hair stage for boys) (22). Girls' menarcheal status at baseline and followup was determined by self-report questionnaire. To estimate lower limb power, maximal height (cm) for vertical jump was measured using the Vertec™

device (Fitness Source, Concord, ON) and maximal distance (cm) for standing long jump was assessed according to standard protocol (23). A modified version of the Physical Activity Questionnaire for Children (PAQ-C) was used to assess leisure-time physical activity (24,25). A general physical activity score (*PA Score*) was calculated as an average of 10 PAQ-C items in a continuous range between 1 (low activity) and 5 (high activity) and an estimate of time (hrs/wk) spent in common sports and activities designated as loaded (impact > walking, *load time*) was generated from Item 1 of the PAQ-C. A validated food frequency questionnaire (FFQ) (26) was used to determine dietary calcium (mg/day). The PAQ-C and FFQ were administered at baseline and followup plus 3 additional times during the study period. The average across the 5 reports is presented for PA Score, load time and dietary calcium.

6.2.4.2 Primary and Secondary Outcomes

Detailed DXA and HSA acquisition and analysis procedures are provided in Chapter 2 (Sections 2.2.8.3.1 and 2.2.8.3.2) and are briefly summarized here.

6.2.4.2.1 Bone Mineral Content and Bone Area

A Hologic QDR 4500W bone densitometer (DXA, Hologic Inc., Waltham, MA, USA) was used to assess bone mineral content (BMC, g) and bone area (BA, cm^2) of the total body, total proximal femur and femoral neck subregion and lumbar spine. Three trained and qualified technicians acquired all scans in array mode and one of these technicians analyzed all scans. Scan acquisition and analysis were performed according to standardized procedures (27) and quality assurance (QA) scans were performed daily at baseline and followup. Due to a technical error in scan acquisition at baseline, proximal femur data was not available for 1 girl at baseline and lumbar spine data was not available for 1 boy at baseline.

6.2.4.2.2 Proximal Femur Bone Structure and Strength

To address the primary objective, the HSA program (Version 3.0) (28) was applied to proximal femur DXA scans to estimate the *primary outcome*, section modulus (Z, cm^3) at the femoral neck across its narrowest point (narrow-neck). This region is located proximal to the femoral neck subregion measured with DXA. Briefly, the HSA program generates a projection of the bone cross-section (bone mass profile) from a line of pixel values traversing the bone width. At the narrow neck region, bone geometric properties are averaged over five contiguous bone mass profiles, spaced 1 mm apart. Thus, the total cross-section is approximately 5 mm thick (29). Section modulus, a determinant of bone bending strength, is calculated as $Z = CSMI / d_{max}$ where the cross-sectional moment of inertia (CSMI) equals the integral of the bone mass profile weighted by the square of the distance from the centre of mass and d_{max} equals the maximum distance from the centre of mass to the outer cortical margin. The integral of the bone mass profile and the (blur corrected) width of the profile provide the *secondary HSA outcomes* of bone cross-sectional area (CSA, cm^2) and subperiosteal width (SPW, cm), respectively.

I analyzed all scans with training and supervision from Dr. Tom Beck and Lisa Semanick at Johns Hopkins University. Proximal femur scans were checked closely for positioning errors (i.e., insufficient length of the femoral

shaft, lack of internal rotation). As a result of such errors, scans from 14 INT (7 boys, 7 girls) and 12 CON (3 boys, 9 girls) participants were excluded from the present analysis.

6.2.5 *Statistical Analysis*

In this cluster randomized trial, the school was the unit of randomization and the individual was the unit of analysis. Therefore, in order to determine the effect of AS! BC on change in the primary and secondary bone outcomes it was necessary to account for the clustered design. Ideally, a multi-level model that included school as a random effect would have been used in this analysis; however, due to the relatively small number of clusters (n=10) and the large range of participants in each cluster (range: 6-40) this was not possible. Thus, the following steps were taken for the present analysis using an intent-to-treat approach. First, multivariable linear regression models were fit with change in each bone outcome as the dependent variable. Separate models were created for boys and girls due to the known difference in the tempo and timing of growth, maturation and bone mineral accrual between sexes (1,22). For boys, the following covariates were included in each model: baseline weight (to adjust for the baseline imbalance in body weight between groups), height change (to adjust for linear growth) and lean mass change (to adjust for change in estimated muscle force). Covariates were similar for girls with two exceptions: 1) baseline height was used instead of baseline weight and 2) final Tanner stage was included. Unlike for boys, there was no imbalance in baseline weight between intervention and control girls. Thus, height was used to control for girls' baseline body size. Final Tanner stage was used as a covariate for girls due to significant associations with the dependent variables noted in univariate analyses (Appendix 10). Residual plots were used to check the assumptions of normality, linearity and homoscedascity.

Second, to account for the clustered design, the standard error of the estimated intervention effect (adjusted difference in change between groups) was multiplied by the square root of the design effect (D) (or variance inflation factor) (30-33). The design effect was calculated as $D = 1 + (m - 1)*ICC$ where m = median number of boys or girls per cluster (m = 20 in the present study) and ICC = intracluster correlation coefficient (Section 2.2.9.1). There are no published reports of the ICC for HSA outcomes in school-based intervention trials. Therefore, the ICC for DXA and HSA outcomes at baseline was estimated using the standard one-way analysis of variance (ANOVA) method (34) as implemented in STATA (loneway). The ICC at baseline ranged from 0 to 0.05 (Appendix 10), and 0.05 was used as a conservative estimate of the ICC for the present analysis. Thus, $\sqrt{D} = 1.4$. The ICC for change in primary and secondary bone outcomes could not be determined from the present analysis.

An efficacy subgroup analysis was performed in order to determine the effect of teacher compliance on child-level change in primary and secondary bone outcomes. This analysis included only those children whose teacher reported providing at least 80% of the required Bounce at the Bell sessions during Phase II. This criterion also excluded those children who did not receive any intervention during Phase II (i.e., those children who moved away but returned for followup measurement).

6.3 Results

6.3.1 Participants and Compliance

The flow of schools and participants through the trial is provided in Chapter 3 (Figure 3-2). Briefly, 71 children (47 INT, 19 CON) were lost to followup. There were no significant differences in any descriptive characteristics or bone outcomes between children lost to followup and those who remained in the study. Eleven children (7 INT, 4 CON) moved to a different school (not participating in AS! BC) but returned for followup. Two boys moved to another school participating in the study; 1 moved from an INT to a CON school and 1 moved from one INT school to another. Both boys returned for followup measurements. One INT boy was excluded from the analysis because of a femur fracture sustained during Phase II (unrelated to this study). With exclusions from the HSA analysis accounted for, the present analysis includes 412 children (294 INT, 1118 CON).

Median compliance with Activity Logs was 97% (interquartile range, IQR: 89 – 100%) across CON schools and 94% (IQR: 92 – 100%) across INT schools during Phase II. Teachers at INT schools delivered approximately 60 minutes more physical activity per week than teachers at CON schools (+58.9 min/wk; 95% CI, 25.4, 92.4). Median compliance with Bounce at the Bell 74% (IQR: 50 – 89%) across INT schools. Fifteen teachers (44%) reported completing at least 80% of the required Bounce at the Bell sessions. Student attendance determined from school records averaged 96% across all schools over the course of the study.

6.3.2 Descriptives

Baseline and change in descriptive characteristics of boys and girls are presented (Table 6-1) and baseline and final Tanner stages are summarized (Table 6-2). At baseline, CON boys tended to be heavier (+2.7 kg) and have a greater fat mass (+1.8 kg) than INT boys. Control and INT boys appeared to have similar changes in body size and body composition; however, INT boys tended to have a greater improvement in long jump (7.9% vs. 5.2%) and vertical jump (16.6% vs. 9.9%) performance. The majority of CON and INT boys were prepubertal (71% and 61%, respectively) at baseline and 16-month change in Tanner stages was similar between CON and INT boys.

At baseline, body size (height, sitting height, weight) and lean mass tended to be slightly greater in INT than CON girls. Over 16-months, CON girls tended to have a greater increase in standing height (5.8% vs. 5.3%), sitting height (5.7% vs. 4.8%), weight (18.5% vs. 16.6%) and lean mass (23.2% vs. 20.3%) than INT girls, whereas INT girls tended to have a greater improvement in long jump performance than CON girls (7.6% vs. 3.4%). At baseline, the majority of CON and INT girls were early pubertal (57% and 61%, respectively) and changes in Tanner stages were similar between groups (Table 6-2). Further, the proportion of girls who were post-menarcheal at followup was similar between groups.

6.3.3 Primary Objective – Intent-to-Treat

Baseline and followup values for femoral neck bone mass, size and strength for CON and INT boys and girls and adjusted mean difference in change in bone outcomes between groups are presented in Table 6-3 (boys) and Table 6-4 (girls), respectively.

For boys, there was no significant difference in change between groups for estimated femoral neck bone strength (Z). Similarly, there was no significant difference in change between groups for femoral neck CSA, SPW, BMC or BA.

For girls, change in estimated femoral neck bone strength tended to be greater for INT girls (+0.11 mm^3; 95% CI: 0.097, 0.12) than CON girls (+0.091 mm^3; 95% CI: 0.074, 0.11). The slightly greater gain in bone strength for INT girls was associated with a trend for greater gain in CSA (+0.23 cm^2; 95% CI: 0.21, 0.25) compared with CON girls (+0.20 cm^2; 95% CI: 0.16, 0.23). Similarly, change in femoral neck BMC tended to be greater for INT girls (+0.37 g; 95% CI: 0.33, 0.40) than CON girls (+0.31 g; 95% CI: 0.25, 0.37). There was no significant difference in change between CON and INT girls for femoral neck SPW or BA.

6.3.4 *Secondary Objective – Intent-to-Treat*

Change in proximal femur BMC and BA was similar between CON and INT boys. At the lumbar spine, INT boys tended to have a greater gain in BMC (+4.3 g; 95% CI: 3.9, 4.7) than CON boys (+3.5 g; 95% CI: 2.9, 4.2), but there was no significant difference in change between groups for lumbar spine BA. Boys in the INT group also had a significantly greater increase in total body BMC (+184.1 g; 95% CI: 174.0, 194.3) compared with CON boys (+159.5 g; 95% CI: 143.3, 175.3) and this was associated with a trend for INT boys to have a greater gain in total body BA (+155.0 cm^2; 95% CI: 145.9, 164.1) compared with CON boys (+141.5 cm^2; 95% CI: 127.4, 155.7).

For girls, change in proximal femur, lumbar spine and total body BMC and BA were not significantly different between CON and INT girls.

6.3.5 *Primary Objective – Compliant Subgroup*

For boys, the subgroup analysis included 58 CON boys and 66 INT boys (Table 6-3). Results from the subgroup analysis were similar to those obtained from the intent-to-treat analysis in that change in femoral neck Z, CSA, SPW, BMC and BA were similar between CON and INT boys.

For girls, the subgroup analysis included 56 CON girls and 43 INT girls. Change in femoral neck Z was significantly greater for INT (+0.12 cm^3; 95% CI: 0.10, 0.14) than CON girls (+0.094 cm^3; 95% CI: 0.075, 0.11) (Table 6-4, Figure 6-1). Similarly, change in CSA was significantly greater for INT girls (+0.27 cm^2; 95% CI: 0.23, 0.31) than CON girls (+0.21 cm^2; 95% CI: 0.17, 0.24) and change in femoral neck BMC was greater for INT girls (+0.42 g; 95% CI: 0.36, 0.48) than CON girls (+0.32 g; 95% CI: 0.27, 0.38). Change in femoral neck SPW and BA were similar between CON and INT girls.

6.3.6 *Secondary Objective – Compliant Subgroup*

When boys in non-compliant INT classes were excluded, the magnitude of the difference in change for lumbar spine and total body BMC between INT and CON boys was larger than that observed in the intent-to-treat analysis (Table 6-3). Change in lumbar spine and total body BA and proximal femur BMC and BA was not significantly different between CON and INT boys in the subgroup analysis.

In the subgroup analysis, change in lumbar spine BMC tended to be greater for INT girls (+7.6 g; 95% CI: 6.6, 8.7) than CON girls (+ 6.6 g; 95% CI: 5.6, 7.6) (Table 6-4). Similarly, change in total body BMC tended to be greater for INT girls (+238.1 g; 95% CI: 215.1, 261.0) than CON girls (+213.1 g; 95% CI: 192.9, 233.3). There was no significant difference between CON and INT girls for change in lumbar spine and total body BA or proximal femur BMC and BA.

Table 6-1. Baseline age, baseline and final Tanner stages, ethnic distribution, menarcheal status (for girls) average physical activity and calcium outcomes and baseline and change in body size, body composition and jump performance for Control and Intervention boys and girls. Values are mean (SD) for baseline and mean (95% CI) for change (unless otherwise indicated).

	BOYS				*GIRLS*			
	Control (N = 62)		**Intervention (N = 151)**		**Control (n = 56)**		**Intervention (N = 143)**	
	Baseline	**Change (95% CI)**	**Baseline**	**Change (95% CI)**	**Baseline**	**Change (95% CI)**	**Baseline**	**Change (95% CI)**
Baseline Age (yrs)	10.3 (0.7)	-----	10.2 (0.5)	-----	10.2 (0.5)	-----	10.2 (0.6)	-----
No. Asian/Caucasian/Other	32/19/11	-----	85/52/14	-----	30/20/6	-----	79/45/19	-----
Baseline Tanner Stage (1/2/3/4/5)	43/17/2/0/0	-----	91/52/8/0/0	-----	24/29/3/0/0	-----	56/72/15/0/0	-----
Final Tanner Stage (1/2/3/4/5)	26/ 23/12/1/0	-----	48/58/38/6/1	-----	7/20/27/2/0	-----	16/62/57/8/0	-----
No. Post-menarcheal at baseline	-----	-----	-----	-----	1 (2%)	-----	6 (4%)	-----
No. Post-menarcheal at followup	-----	-----	-----	-----	8 (14%)	-----	28 (20%)	-----
Height (cm)	141.7 (6.9)	6.7 (6.3, 7.1)	141.5 (7.4)	6.9 (6.5, 7.2)	139.7 (6.7)	8.2 (7.7, 8.7)	141.0 (7.3)	7.5 (7.2, 7.9)
Sitting height (cm)	75.0 (3.5)	2.9 (2.5, 3.3)	74.2 (3.6)	2.9 (2.6, 3.2)	73.8 (3.9)	4.2 (3.8, 4.5)	74.3 (3.8)	3.5 (3.3, 3.8)
Weight (kg)	40.7 (10.2)	6.3 (5.5, 7.1)	37.4 (9.7)	5.6 (5.2, 6.0)	35.1 (8.8)	6.3 (5.6, 7.1)	36.0 (8.3)	6.0 (5.6, 6.5)
TB Lean Mass (kg)	26.8 (4.6)	4.3 (3.9, 4.8)	25.8 (3.8)	4.1 (3.8, 4.4)	20.6 (3.9)	4.8 (4.3, 5.2)	21.1 (3.7)	4.3 (4.0, 4.6)
TB Fat mass (kg)	11.8 (6.2)	1.6 (1.1, 2.2)	9.6 (6.0)	1.1 (0.7, 1.4)	9.0 (5.1)	1.1 (0.6, 1.6)	9.2 (4.9)	1.1 (0.8, 1.4)
Long Jump (cm)	132.6 (19.4)	6.4 (2.6, 10.2)	133.5 (17.2)	10.2 (7.8, 12.6)	121.1 (15.1)	3.4 (0.1, 6.7)	120.9 (14.5)	9.9 (7.4, 12.4)
Vertical Jump (cm)	28.2 (5.2)	2.4 (1.2, 3.7)	27.8 (5.7)	4.2 (3.3, 5.2)	25.0 (5.1)	3.2 (1.9, 4.6)	25.4 (4.6)	3.3 (2.5, 4.2)
Average PA score (/5)*	2.7 (0.4)	-----	2.8 (0.4)	-----	2.6 (0.3)	-----	2.6 (0.4)	-----
Average load time (hrs / week)*	6.6 (3.9)	-----	6.9 (4.2)	-----	4.7 (3.2)	-----	5.0 (3.4)	-----
Average dietary calcium (mg/day)*	930 (460)	-----	937 (432)	-----	816 (299)	-----	811 (359)	-----

SD = standard deviation; CI = confidence interval; PA = physical activity. Means, SD, CI were determined without accounting for clustering.

* Physical activity and dietary calcium variables are the average of 5 reports.

Table 6-2. Baseline and final Tanner stage for pre- and early pubertal boys and girls in Control and Intervention groups.

		BOYS		*GIRLS*	
	Baseline – Final Tanner Stage	**Control**	**Intervention**	**Control**	**Intervention**
Prepubertal	1-1	26 (60%)	48 (53%)	7 (29%)	16 (29%)
	1-2	13 (30%)	32 (35%)	12 (50%)	34 (61%)
	1-3	4 (9%)	11 (12%)	5 (21%)	6 (11%)
	Total	43 (100%)	91 (100%)	24 (100%)	56 (100%)
Early Pubertal	2-2	10 (53%)	26 (43%)	8 (25%)	28 (32%)
	2-3	6 (32%)	23 (38%)	19 (59%)	42 (48%)
	2-4	1 (5%)	3 (5%)	2 (6%)	2 (2%)
	3-3	2 (11%)	4 (7%)	3 (9%)	9 (10%)
	3-4	0	3 (5%)	0	6 (7%)
	3-5	0	1 (2%)	0	0
	Total	19 (100%)	60 (100%)	32 (100%)	87 (100%)

Table 6-3. Baseline, followup and adjusted difference in change between Intervention (INT) and Control (CON) boys for primary and secondary bone outcomes. Results are presented for both the intent-to-treat and efficacy subgroup analysis.

				Intent-to-treat (n = 62 CON, 151 INT)		***Subgroup*** (n = 58 INT, 66 INT)	
Outcome	**Group**	**Baseline Mean (SD)**	**Followup Mean (SD)**	**Difference in Change (95% CI)[a]**	***p***	**Difference in Change (95% CI)[a]**	***p***
HSA							
FN Z (cm^3)	CON	0.64 (0.13)	0.74 (0.15)	0.005 (-0.015, 0.025)	0.62	0.006 (-0.019, 0.031)	0.61
	INT	0.63 (0.13)	0.74 (0.16)				
FN CSA (cm^2)	CON	1.70 (0.24)	1.88 (0.28)	0.019 (-0.014, 0.052)	0.26	0.019 (-0.027, 0.065)	0.41
	INT	1.69 (0.26)	1.88 (0.29)				
FN SPW (cm)	CON	2.68 (0.20)	2.82 (0.20)	-0.010 (-0.043, 0.023)	0.55	-0.008 (-0.044, 0.028)	0.66
	INT	2.64 (0.21)	2.78 (0.22)				
DXA							
FN BMC (g)	CON	2.83 (0.41)	3.10 (0.48)	0.010 (-0.061, 0.081)	0.78	0.018 (-0.064, 0.100)	0.67
	INT	2.79 (0.43)	3.08 (0.48)				
FN Area (cm^2)	CON	4.10 (0.30)	4.35 (0.36)	-0.042 (-0.126, 0.043)	0.36	-0.008 (-0.104, 0.088)	0.87
	INT	4.09 (0.32)	4.28 (0.39)				
PF BMC (g)	CON	16.0 (3.0)	19.6 (3.9)	0.05 (-0.43, 0.53)	0.84	0.18 (-0.56, 0.76)	0.56
	INT	16.1 (3.4)	19.6 (4.5)				
PF Area (cm^2)	CON	22.2 (2.7)	25.7 (3.2)	-0.14 (-0.58, 0.30)	0.54	0.03 (-0.52, 0.58)	0.92
	INT	22.5 (3.3)	25.7 (4.2)				
LS BMC (g)	CON	23.6 (4.3)	27.2 (5.1)	0.77 (-0.001, 1.55)	0.05	0.96 (-0.003, 1.93)	0.05
	INT	23.1 (4.9)	27.3 (6.4)				
LS Area (cm^2)	CON	37.7 (4.4)	41.8 (5.0)	0.37 (-0.53, 1.26)	0.44	0.42 (-0.71, 1.55)	0.47
	INT	37.2 (5.1)	41.5 (5.9)				

Table 6-3 continued

				Intent-to-treat (n = 62 CON, 151 INT)		*Subgroup* (n = 58 INT, 66 INT)	
Outcome	**Group**	**Baseline Mean (SD)**	**Followup Mean (SD)**	**Difference in Change (95% CI)[a]**	***p***	**Difference in Change (95% CI)[a]**	***p***
TB BMC (g)	CON	1098.1 (178.1)	1259.9 (206.6)	24.8 (5.6, 43.8)	0.03	30.8 (7.2, 54.4)	0.01
	INT	1078.6 (193.1)	1260.3 (237.6)				
TB Area (cm^2)	CON	1276.5 (174.8)	1419.6 (192.5)	12.7 (-4.4, 29.8)	0.18	10.9 (-10.1, 31.9)	0.31
		1242.8 (187.2)	1399.7 (212.8)				

SD = standard deviation; CI = confidence interval; NN = narrow neck; Z = section modulus; CSA = cross-sectional area; SPW = subperiosteal width; FN = Femoral neck; BMC = bone mineral content; BA = bone area; PF = proximal femur; LS = lumbar spine; TB = total body.

a Adjusted for baseline weight, change in height and change in total body lean mass

Table 6-4. Baseline, followup and adjusted difference in change between Intervention (INT) and Control (CON) girls for primary and secondary bone outcomes. Results are presented for both the intent-to-treat and efficacy subgroup analysis.

				Intent-to-treat (n = 57 CON, 143 INT)		***Subgroup*** (n = 56 CON, 43 INT)	
Outcome	**Group**	**Baseline Mean (SD)**	**Followup Mean (SD)**	**Difference in Change (95% CI)[a]**	***p***	**Difference in Change (95% CI)[a]**	***p***
HSA							
FN Z (cm^3)	CON	0.54 (0.11)	0.64 (0.14)	0.016 (-0.004, 0.040)	0.11	0.030 (0.003, 0.057)	0.03
	INT	0.56 (0.12)	0.66 (0.15)				
FN CSA (cm^2)	CON	1.50 (0.23)	1.71 (0.29)	0.030 (-0.008, 0.068)	0.12	0.062 (0.007, 0.117)	0.03
	INT	1.55 (0.26)	1.77 (0.32)				
FN SPW (cm)	CON	2.57 (0.16)	2.67 (0.17)	0.012 (-0.021, 0.045)	0.48	0.009 (-0.032, 0.050)	0.67
	INT	2.56 (0.18)	2.67 (0.18)				
DXA							
FN BMC (g)	CON	2.51 (0.47)	2.83 (0.58)	0.057 (-0.012, 0.126)	0.10	0.100 (0.015, 0.185)	0.02
	INT	2.54 (0.42)	2.88 (0.52)				
FN Area (cm^2)	CON	3.97 (0.35)	4.16 (0.41)	0.047 (-0.030, 0.124)	0.23	0.028 (-0.068, 0.124)	0.57
	INT	3.97 (0.32)	4.19 (0.34)				
PF BMC (g)	CON	14.4 (2.9)	18.4 (4.0)	0.01 (0.49, 0.51)	0.96	0.09 (-0.54, 0.72)	0.77
	INT	15.2 (3.5)	19.0 (4.4)				
PF Area (cm^2)	CON	22.1 (3.0)	25.6 (3.4)	-0.09 (-0.57, 0.38)	0.70	-0.38 (-0.97, 0.21)	0.21
	INT	22.5 (3.2)	25.5 (3.3)				
LS BMC (g)	CON	23.3 (5.1)	29.8 (7.6)	0.72 (-0.36, 1.80)	0.19	1.05 (-0.41, 2.51)	0.16
	INT	24.1 (6.1)	30.9 (8.4)				
LS Area (cm^2)	CON	36.6 (5.0)	42.2 (6.2)	0.26 (-0.60, 1.13)	0.55	0.36 (-0.77, 1.49)	0.54
	INT	37.1 (5.4)	42.7 (6.3)				

Table 6-4 continued

Outcome	Group	Baseline Mean (SD)	Followup Mean (SD)	*Intent-to-treat* (n = 57 CON, 143 INT) Difference in Change (95% CI)[a]	*p*	*Subgroup* (n = 56 CON, 43 INT) Difference in Change (95% CI)[a]	*p*
TB BMC (g)	CON	1016.9 (189.6)	1232.2 (249.1)	9.3 (-13.5, 33.0)	0.42	25.0 (-6.6, 56.6)	0.12
	INT	1041.0 (210.3)	1254.0 (261.0)				
TB Area (cm^2)	CON	1203.4 (189.2)	1390.2 (213.0)	-1.7 (-19.2, 15.9)	0.86	5.1 (-15.8, 26.0)	0.63
	INT	1226.6 (195.5)	1398.8 (212.1)				

SD = standard deviation; CI = confidence interval; NN = narrow neck; Z = section modulus; CSA = cross-sectional area; SPW = subperiosteal width; FN = Femoral neck; BMC = bone mineral content; BA = bone area; PF = proximal femur; LS = lumbar spine; TB = total body.

a Adjusted for baseline height, change in height, change in total body lean mass and final Tanner stage.

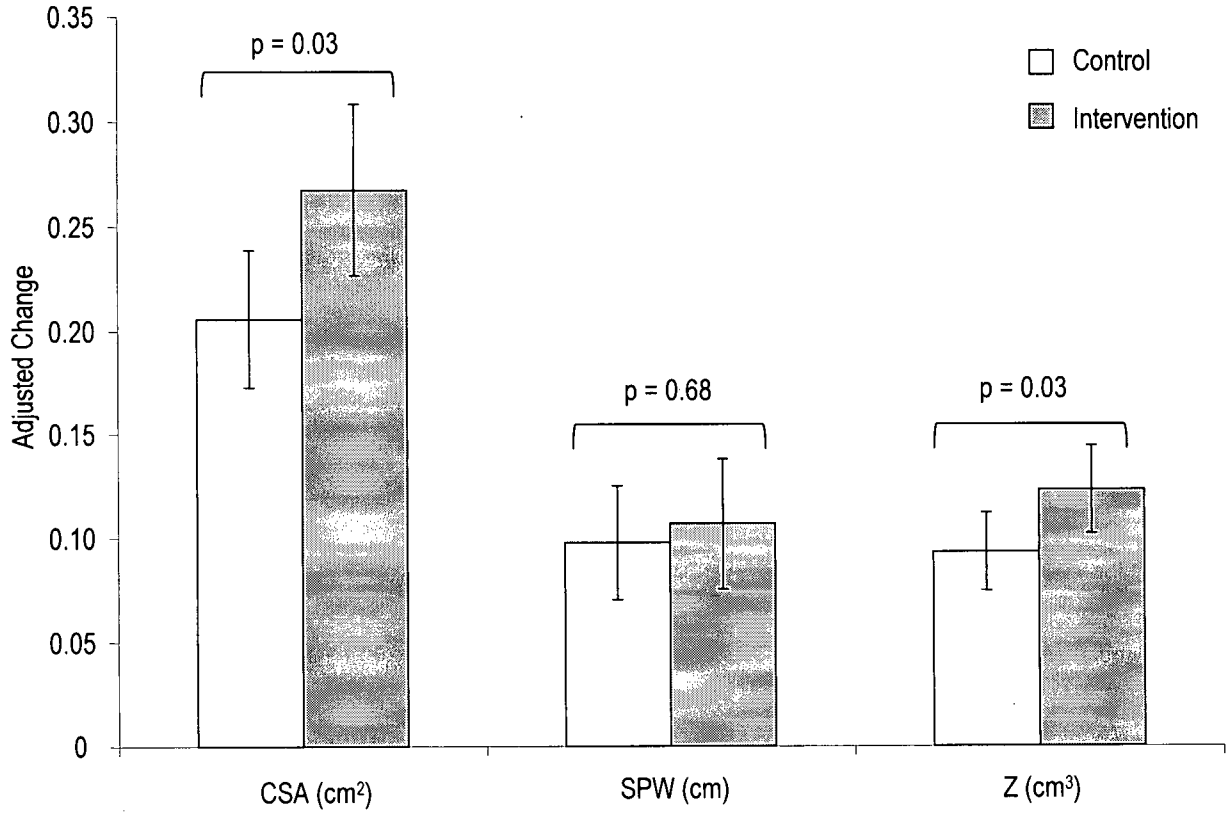

Figure 6-1. Results from the subgroup analysis showing adjusted change in femoral neck cross-sectional area (CSA), subperiosteal width (SPW) and section modulus (Z) for Control and Intervention girls. The INT group includes only those girls (n = 43) whose teacher reported at least 80% compliance with Bounce at the Bell. Bars are 95% confidence intervals and values are adjusted for baseline height, change in height, change in total body lean mass and final Tanner stage.

6.4 Discussion

Action Schools! BC (AS! BC) builds on previous school-based physical activity interventions by offering a flexible physical activity model for generalist teachers that includes a novel bone-loading program, Bounce at the Bell. These results indicate that in this cohort of pre- and early pubertal boys and girls the Classroom Action component of AS! BC was not effective for increasing femoral neck bone mass or strength. However, results from the efficacy subgroup analysis suggest that significant gains in femoral neck bone mass and strength among girls are dependent on teacher compliance with delivery of Bounce at the Bell.

Our group previously reported results from an 8-month pilot study of Bounce at the Bell in a small sample (n = 51) of pre- and early pubertal boys and girls (17). Although this study demonstrated that Bounce at the Bell could be implemented successfully within the classroom setting and could be delivered by generalist teachers, the non-randomized study design and limited power to evaluate sex-specific skeletal responses were limitations. The current investigation aimed to build on the pilot study using a cluster randomized, controlled trial. Bounce at the Bell was introduced as part of the Classroom Action program within the AS! BC physical activity model. Although intervention children participated in a range of weight-bearing activities including skipping and running, the ground reaction forces

associated with jumps in Bounce at the Bell (35) and the multi-directional nature of the jumps likely resulted in largest, and most dynamic, skeletal loads compared with other Classroom Action activities.

6.4.1 Study Design Issues

Before discussing the skeletal adaptations to the AS! BC intervention in boys and girls, it is important to highlight issues related to the study design that may influence interpretation of the findings. As discussed, in this cluster randomized trial, schools were the unit of randomization instead of individual children. This design is necessary in order to prevent contamination that would otherwise occur if intervention and control children attended the same school. However, the unit of analysis was the individual. In this situation, if the between-variance is not accounted for within the statistical analysis, the Type I error rate can be inflated (32,36). Although previous work by our group has demonstrated a negligible school effect for femoral neck and lumbar spine BMC in girls (16,37), it is not known if the same is true for HSA outcomes in both boys and girls as there are no published estimates of intraclass correlations (ICC) for Z, CSA or SPW. Thus, a conservative estimate of the ICC (0.05) was used in the present study and a variance inflation factor based on the ICC was applied to the standard error of the intervention effect obtained from linear regression analysis. An attempt was made to use a mixed linear model with school designated as a random effect; however, the model could not be fit for several of the bone outcomes. This was likely the result of the between-school variance being close to 0 as well as the small number of clusters and the range in cluster size. Because the mixed linear model was not used in this analysis, *a posteriori* estimated ICCs could not be determined.

Although the clustered design was accounted for within the statistical analysis, it is important to note that sample size was not determined with an *a priori* estimate of the ICC, which is known to have a significant impact on statistical power (30,38,39). Due to the small number of clusters and the use of a conservative estimate of the ICC, this study was likely underpowered to detect group x maturity interactions. Future school-based interventions of this type will benefit from randomizing a large number of clusters (32,34) and will aid other investigators by providing both *a priori* and *a posteriori* values for the ICC as recommended in the recent extension of the CONSORT statement for cluster randomized trials (38).

6.4.2 Skeletal Adaptations to Increased Physical Activity in Boys

Despite a significant intervention effect for change in total body BMC and a trend for an intervention effect for change in lumbar spine BMC, AS! BC did not have a significant influence on change in estimated femoral neck bone strength or bone mass at the total proximal femur or femoral neck in boys. The site-specificity is consistent with previous investigations in similarly aged (prepubertal) boys following 7-8 months of exercise intervention (7,12). In contrast, MacKelvie et al. (13) reported significantly greater changes in femoral neck bending strength as well as femoral neck BMC and BA in boys following 20-months of the HBS II intervention. This result was attributed to the longer duration of intervention and the associated change in boys' maturational status. At baseline, all HBS II boys were prepubertal and a significant proportion (77%) of intervention and control boys advanced to early puberty during

the 20-month study. Based on findings from the HBS II girls cohort, early puberty is thought to be the most opportune time during growth for exercise interventions to have a positive effect on bone mass and structure at the femoral neck (13-15,40). Thus, the more advanced maturational status of the HBS II boys was thought to have conferred a readiness for adaptation at the femoral neck (13). This hypothesis has yet to be confirmed in an intervention study with boys in two distinct maturity groups at baseline. In the present study, boys were either prepubertal (60%) or early pubertal (40%) at baseline; however, due to study design limitations discussed previously this trial was likely underpowered to detect group x maturity interaction effects. It is possible that the active intervention period (8 months) was not sufficient time for AS! BC to have a positive effect on femoral neck bone mass and strength in boys at this age and maturational status.

6.4.3 Skeletal Adaptations to Increased Physical Activity in Girls

Although the difference in change in femoral neck bending strength between intervention and control girls in the intent-to-treat cohort was small (approximately 1.6%), the intervention effect was magnified (approximately 3.3%) when only those girls whose teachers reported good compliance with Bounce at the Bell were included. The same was true for the difference in change in femoral neck bone mass (represented by CSA and BMC) between groups. These results should be interpreted with caution as subgroup analyses are subject to bias; however, they suggest that girls who participated in Bounce at the Bell at least 3 times per week during Phase II (8 months) had significantly greater gains in femoral neck bone mass and strength than control girls. In addition, the subgroup analysis indicated a trend towards greater gains in lumbar spine and total body BMC in intervention girls. These findings highlight teacher compliance as one of the challenges of implementing school-based physical activity interventions and assessing their effectiveness. Further investigation of the barriers to and facilitators of delivery of Bounce at the Bell and the AS! BC model in the classroom setting is warranted.

The changes in bone mass and strength at the femoral neck in intervention girls are smaller in magnitude than those observed following 7-months of the HBS II intervention (15). However, these findings are promising in light of the aforementioned variation in intervention delivery and the less intensive bone-loading program. Unfortunately, these data to do not provide conclusive evidence as to what geometric adaptations underpin the changes in bone bending strength. Intervention and control girls demonstrated similar periosteal expansion as indicated by the increase in subperiosteal width, although there was a very slight advantage in favour of intervention girls. Thus, it does not appear that the intervention had a significant effect on periosteal apposition at the femoral neck. However, it is important to note that resistance to bending forces at the femoral neck varies non-linearly (to the third power) with the distance of bone material from the centre of mass. As a result, even small changes in the distribution of bone material can influence bone's resistance to bending. Further, unlike the findings of Petit et al. (15) which indicated an intervention effect for endosteal expansion (reduced in intervention girls) and cortical thickness (increased in intervention girls), intervention and control girls in the present study had similar increases in endosteal diameter and cortical thickness (data not shown). A longer intervention period may be required to elucidate the surface-specific changes that occur in response to physical activity intervention in young girls. Given the limitations associated with

HSA (Section 6.4.4), future investigations may benefit from using other imaging techniques such as magnetic resonance imaging (MRI) (41) to assess the femoral neck and other regions of the proximal femur.

6.4.4 Methodological Limitations

Hip structure analysis offers a valuable tool with which bone structural parameters can be estimated; however, there are clearly limitations in attempting to assess a three-dimensional structure using two-dimensional imaging techniques. First, although precision in pediatric studies has yet to be determined, Khoo et al. (29) recently reported precision error (% CV) for HSA outcomes in elderly osteoporotic women. Precision error ranged from 2.1% for subperiosteal width to 4% for section modulus. Thus, it is possible that the small percentage differences in change between intervention and control girls for narrow neck cross-sectional area and section modulus may be explained by this measurement error.

Second, section modulus is estimated for bending in the scan plane only. This limitation is important to consider for two reasons. First, errors in positioning (i.e. femoral anteversion) may alter the location and orientation of the image plane at the narrow neck region and result in uncertainty in structural outcomes (29,42). This is of particular concern for serial measurements. In the present study, an attempt was made to minimize this source of error by having 3 trained operators acquire all scans and by standardizing positioning techniques between operators. In addition, scans were checked for positioning errors prior to HSA analysis and those with inadequate rotation were excluded. The second limitation of the single projection method is that structural changes that influence the distribution of bone mass in other planes (i.e., orthogonal to the scan plane) cannot be assessed (42).

A final limitation of HSA technology that is of issue for pediatric studies is the assumption that bone mass in the region of interest is fully mineralized. Since average tissue mineralization is clearly lower in children than adults, geometric properties are underestimated by an estimated 20% in pediatric studies (13). Although there may have been differences in mineralization density between children in intervention and control groups, the difference would likely be quite small and thus, the underestimation of geometric properties can be considered constant across children and intervention and control groups.

An additional limitation of note is that maturity status of boys and girls was determined with self-report Tanner staging. Although this method is appropriate for large field research studies, it is unable to capture the continuing process of growth or differences in the tempo and timing of maturation between individuals (22,43). Inaccuracies associated with Tanner staging may further confound investigations of possible "windows of opportunity" when the effects of physical activity intervention may be optimized. There is a need for intervention studies of longer duration that would permit alignment of individuals on biological age (age at peak height velocity). This technique has proven valuable for clarifying differences in bone mineral accrual (1,44) and estimated bone strength (3,45) between sexes and children of varying activity levels.

Finally, external validity of these findings is limited due to non-random sampling of schools and children. Participating schools were selected from a pool of volunteer schools based on their current satisfaction with school physical activity opportunities. In addition, only schools from 2 school districts were invited to participate. Although

random sampling of schools is not likely a feasible approach for this type of intervention, there is a need to evaluate the effectiveness of AS! BC in a more representative sample of schools from the Vancouver and Richmond School Districts as well as from across the province of BC. Similarly, children (and their parents) volunteered for this study and because information on non-consenting children and their families was not available it is not known if these children are representative of the general school population.

6.4.5 *Implications of the Findings*

The findings of the current investigation are encouraging for several reasons. The difference in change between groups for bone mineral accrual and bone strength are similar to those observed in previous interventions. However, the time required to implement the Classroom Action component was modest (10-15 minutes per day), the program was administered in the classroom setting by generalist teachers and neither additional gymnasium time nor modifications to the existing physical education curriculum were required. Further, the main bone loading component, Bounce at the Bell, was also administered in the classroom setting and required less than 5 minutes per day of class time. This is in contrast to previous, more intensive bone-loading interventions that have required between 10 and 90 minutes per activity session and have incorporated the exercise program into the physical education curriculum (7,9-11,14). In British Columbia, only 25% of elementary schools meet the recommended instructional time for physical education (10% of curriculum time or ~150 minutes per week) (46). On average, schools offer two 40 minutes PE classes per week and approximately 30 minutes of that time is class management (46). This is similar to results from observational studies that have reported as low as 8.6% of class time devoted to moderate to vigorous physical activity (47). Thus, contrary to traditionally held beliefs, PE, as taught currently, may not be the optimal arena for the delivery of a physical activity intervention. The AS! BC model was well-accepted by teachers and students (48) and thus, offers promise as a feasible and sustainable physical activity program for elementary schools.

Limited data from followup studies of school-based interventions suggest that gains in bone mineral accrual in intervention children are maintained 12-months after cessation of the exercise program (49,50). However, there are no long-term followup data to support the maintenance of small skeletal advantages achieved in response to intervention into adulthood. Nevertheless, if these children maintain an active lifestyle into adulthood the small, but significant, gains in bone strength and bone mineral accrual may translate into a considerable reduction in fracture risk (51).

6.4.6 *Summary*

In summary, the Classroom Action component of the AS! BC physical activity model was not effective for increasing bone mass or strength at the clinically relevant proximal femur in boys or girls. However, in light of the study design limitations, the trend for enhanced lumbar spine bone mineral accrual in boys and bone mass and bending strength at the femoral neck in girls provides promising evidence of an osteogenic effect of this novel physical activity program. Further, results from efficacy analyses highlight the importance of teacher compliance with intervention delivery. Before additional investigations into the effectiveness of AS! BC, and in particular Bounce at the

Bell, can take place there is a need for an appropriately designed trial to determine precise estimates of the ICC for DXA and HSA bone outcomes in boys and girls.

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7 Integrated Discussion

In this chapter I first provide an overview of the findings of this thesis and highlight the unique contributions of each of the three studies to the literature. I then discuss the findings of this thesis with a focus on two key areas: 1) the utility of pQCT in studies of pediatric bone and 2) the challenges of school-based interventions. In doing so, I present the limitations of the studies and highlight areas for future pediatric bone research. I close the chapter with the public health implications of this thesis and the summary and conclusions for Parts I-III.

7.1 Overview of Findings

7.1.1 Tibial Bone Strength in Pre- and Early Pubertal Children

In Part I, I presented results from the largest cross-sectional pQCT study of pre- and early pubertal children conducted to date. These data add to the current body of knowledge regarding sex differences in long bone strength during growth and highlight the need to interpret measures of estimated bone strength and cross-sectional geometry in the context of the primary mechanical challenges during growth. In addition, this study provides the first pQCT evidence of: 1) greater cortical density at the tibial shaft in pre- and early pubertal girls compared with boys of a similar maturity status and 2) ethnic differences in bone geometry and cortical density. As these findings can only be considered "hypothesis generating" there is a need to explore these relationships further in a longitudinal study in which boys and girls can be compared using a more accurate indicator of somatic maturity such as age at peak height velocity. With appropriate longitudinal data, peak velocities for growth in tibial length and muscle cross-sectional area in relation to muscle cross-sectional area, strength and power may also be determined. Multi-level modeling techniques similar to those used in recent DXA (1) and HSA (2-4) studies will prove useful in clarifying sexual dimorphism in long bone strength, cross-sectional geometry and (volumetric) density and will provide further insight into the functional model of bone development.

7.1.2 Is Action Schools! BC an Effective Means to Increase Bone Strength in Elementary School Children?

Overall, the results presented in Parts II and III are encouraging and provide support for skeletal benefits of AS! BC; however, the findings are not conclusive.Together, the pQCT, HSA and DXA results confirm what is well-accepted in the pediatric bone literature – that the skeletal response to weight-bearing activity is complex in that it is site-specific and varies between sexes and across maturational stages (5-8). Further, the maturational stage and type of loading may influence which skeletal site responds to intervention. Some authors have suggested that early puberty may offer a "window of opportunity" during which the osteogenic effects of exercise are optimized (7,9), whereas others provide evidence in support of the prepubertal years as the ideal time for intervention (6). These hypotheses are based mainly on DXA results. Due to a lack of intervention studies that have used pQCT or other 3-dimensional imaging technologies to assess the effect of physical activity intervention in boys or girls, there is insufficient evidence to determine whether there is a "window of opportunity" during growth when increased loading will lead to the greatest changes on the periosteal and endosteal surfaces and ultimately, in bone strength.

The pQCT findings in Part II of this thesis suggest that for boys, the osteogenic response to AS! BC at the tibia is greater in pre- than early puberty. However, in light of the design limitations discussed previously, this result is not conclusive and must be confirmed in future studies. It is not clear why the intervention effect was greater in prepubertal boys, but as suggested by Seeman (8) the maturity specificity may reflect the rapid growth of the appendicular skeleton that is known to occur during prepuberty (10). In contrast, the response of the axial skeleton may be favoured during puberty (8). Interestingly, the findings of Part III do not support this hypothesis. Although I was unable to identify any group x maturity interactions, the fact that intervention boys (most of whom were prepubertal at baseline) tended to accrue more lumbar spine BMC suggests that AS! BC has the potential to elicit an osteogenic response in both the appendicular and axial skeleton in boys of this age and maturational stage. Similar to the discussion of sexual dimorphism in bone strength, the relationship between maturational stage and site-specific skeletal responses to intervention can only be confirmed when children are aligned on biological age.

For girls, the lack of an intervention effect at the tibia and the trend for an intervention effect at the femoral neck is similar to the results of Heinonen et al. (11) who reported a significant intervention effect at the femoral neck and lumbar spine but no significant intervention effect at the tibial midshaft in premenarcheal girls following 9-months of a high-impact jumping program. If prepuberty is in fact the time when the appendicular skeleton is most responsive to intervention, it may be necessary in future studies to include a larger sample of girls at this maturational stage. In the case of AS! BC and in particular, Bounce at the Bell, it may also be necessary to provide additional instruction to girls in order to ensure they are performing the jumps correctly and thus achieving the maximum skeletal benefits of the jumping program.

Finally, for both boys and girls, it is possible that with a longer intervention period, the osteogenic effects of AS! BC may become more apparent. Although the entire study period was 16-months long, the active intervention period lasted only 8-months. In HBS II, a second year of intervention resulted in a widened gap in the bone mineral advantage for boys and girls in favour of intervention children (12,13). It is not known if a similar gap would occur for pQCT-estimated bone strength in response to longer intervention. Considering that, on average, children in this cohort were quite active (approximately 1 hr of weight-bearing activity/day), it would also be interesting to investigate in future studies whether an intervention effect would be more apparent in low active children or in children who have low bone strength relative to body size and muscle mass. As highlighted in Part III, it will be important for future school-based trials to have an accurate estimate of the intraclass correlation coefficient (ICC) for bone outcomes to ensure adequate power for detecting such interactions or conducting subgroup analyses.

7.1.3 Bounce at the Bell – A Novel Bone-Loading Program

In addition to the use of a novel imaging technology, a unique aspect of this thesis was the bone-loading program, Bounce at the Bell, that was included as part of the AS! BC Classroom Action 15 x 5 program. Compared with previous bone-loading interventions (9,11-17), Bounce at the Bell was easily implemented in the classroom setting without additional equipment and required less than 5 minutes per day. Unfortunately, I was unable to determine if the intervention effects in Parts II and III were directly attributable to Bounce at the Bell. There are,

however, several characteristics of Bounce at the Bell that suggest this program provided a greater osteogenic stimulus than other Classroom Action activities. Bounce at the Bell was designed in accordance with the "three rules for bone adaptation to mechanical stimuli" as described by Turner (18): 1) the jumps provided dynamic loads that were short in duration, 2) the multidirectional nature of the jumps likely incurred unusual strains on the skeleton and 3) rest periods were inserted between loading bouts as this has been shown to improve mechanosensitivity of bone cells in animal models (19,20). Although the peak strain magnitude and strain rate experienced at the tibia and the proximal femur during Bounce at the Bell could not be determined in this study, results from biomechanical assessments indicate that countermovement jumps like those in Bounce at the Bell generate ground reaction forces (GRF) of up to 5 times body weight (BW) and rate of change in force of 493 BW/sec (21). Further, results from strain gauge data for the tibial midshaft in 2 adults suggest that multi-directional activity (i.e., zig-zag hopping) is associated with high principal compression, tension and shear strains and a high compression strain rate (22). In addition, compared with pattern activities such as walking and running, the angle of principal compression strain (an indicator of strain distribution) varies greatly during multi-directional activity (22).

Human strain gauge data for the femoral neck and total proximal femur are not available for the jumping activities undertaken in the current trial. However, in an adult study where compressive axial forces were measured from strain gauges inserted in a hip implant in a 47-year old man, forces were 2.5-3.0 times the GRFs (approximately 2.5 times BW) during jump take-off and 1.5 times the GRFs during jump landing (23). The greater forces were attributed to contraction of the large extensor muscles of the knee that are the source of power for take-off and of protective braking force during landing and apply a compressive force to the femoral shaft. In children, Bauer et al. (24) estimated hip joint reaction forces during drop jumping using a simple rigid body model (without the contribution of muscle forces) to be 4.7 times BW.

Together, these data provide support for the osteogenic potential of Bounce at the Bell. There remains a need for a randomized controlled trial with Bounce at the Bell as the only intervention program in order to conclusively determine its effects on the growing skeleton. Further, no controlled study with children has yet to compare the effectiveness of the various types of bone-loading programs for increasing bone mineral accrual or bone strength. Thus, it is not possible at this time to recommend one program over another. I believe, however, that Bounce at the Bell offers more promise as a sustainable bone-loading program for elementary schools compared with previous, more intensive programs given that no equipment or gym space is required and teacher burden is low.

7.2 Utility of pQCT in Pediatric Bone Research

In Parts I and II, I utilized a novel imaging technology, pQCT, to investigate a number of questions related to tibial bone strength in children. As discussed, I believe these studies will make a significant contribution to the pediatric bone literature and they also provide a solid foundation for future pQCT investigations. However, I feel it is important to acknowledge a number of issues related to pQCT technology that must be reconciled to enhance the utility of this imaging modality.

First, there is an immediate need for standardization of pQCT acquisition and analysis protocols for the assessment of pediatric bone. This includes placement of the reference line, resolution (voxel size), measurement sites, analysis modes and thresholds and outcome variables. This will permit comparisons of results across studies and will also aid in the development of normative data that may be used in both research and clinical settings. However, before standardization of such protocols can occur, the accuracy and reliability of the various acquisition and analysis protocols must be determined. Our research group investigated the reliability and accuracy of pQCT acquisition parameters for the assessment of osteoporotic bone (25,26). It will be difficult to replicate such studies with pediatric bone due to the availability of and ethical issues associated with pediatric cadaver bone. In addition, there are also ethical issues associated with *in vivo* reproducibility studies in children due to unnecessary radiation exposure. Thus, future studies of pQCT accuracy and precision should be performed with young adult cadavers and subjects that may more closely represent pediatric bone than does aged osteoporotic bone. Ultimately, it is essential that we know "what we are measuring" with pQCT so that this technology can be used to address further questions related to sexual dimorphism in bone geometry, density and strength as well as surface-specific changes that occur in response to intervention.

Second, a key concern for future longitudinal studies is the long-term reproducibility of pQCT measurements (27). In Part I, I discussed the need for a longitudinal pQCT study similar in design to the Saskatchewan Pediatric Bone Mineral Accrual Study (PBMAS) in order to clarify the timing of sexual dimorphism in appendicular bone strength. Unlike DXA measurements such as those in PBMAS, the single slice pQCT measurements will be influenced by the marked changes in the appendicular skeleton that occur during growth and vary from bone to bone. For example, approximately 60% of longitudinal growth in the tibia occurs at the proximal growth plate (28), whereas in the radius, approximately 80% of longitudinal growth occurs distally (29). Further, at regions near the growth plate, the proportions of metaphyseal to diaphyseal bone change with age which will, in turn, influence pQCT measurements of trabecular and cortical bone (27). Thus, before longitudinal pQCT studies that span pubertal growth can be carried out, there is a need to determine which sites can be measured with optimal reproducibility.

Third, although pQCT allows for separate evaluation of cortical and trabecular bone, it lacks the resolution to assess bone microstructure. Recently, a high-resolution three-dimensional pQCT (3D-pQCT) has been developed and validated for the evaluation of trabecular microstructure of the distal radius (30). Despite the increased costs and radiation associated with this technology, it may provide a valuable tool to investigate adaptations in trabecular bone architecture than underpin increases in volumetric density such as that observed in Part II of this thesis. In addition, 3D-pQCT may prove useful for evaluating regional differences in cortical density that at present can only be estimated with pQCT (31). It is important to note, however, that neither pQCT nor 3D-pQCT is able to measure the clinically relevant proximal femur and current evidence does not support the use of pQCT measurements of the peripheral for estimating proximal femur bone strength (32). In the absence of advances in pQCT technology that will permit assessment of the proximal femur, there may be utility in MRI for the evaluation of both cortical and trabecular bone at the proximal femur.

A final concern is that of pQCT measurements of muscle cross-sectional area (MCSA). Muscle CSA is used as a surrogate of muscle force and as I reported in Part I, is a significant determinant of bone strength in boys and girls. However, the relationship between MCSA and muscle force (or power) has yet to be validated in children. Further, associations between pQCT-derived MCSA and intrinsic muscular factors such as muscle fibre type and neural adaptation have not been established. This has important implications for future studies that aim to investigate the effects of physical activity on the functional muscle-bone unit. To illustrate this point, consider the large improvements in vertical and long jump performance in intervention girls and boys compared with controls that I reported in Parts II and III. These improvements were not associated with similar gains in MCSA which suggests that the AS! BC intervention may have improved muscular properties such as neural adaptation without a concomitant increase in muscle size.

Despite the aforementioned limitations and concerns associated with pQCT, this instrument provides a valuable tool to investigate bone geometry, (volumetric) density and bone strength of the peripheral skeleton. In addition, pQCT investigations provide insight into adaptations within cortical and trabecular bone compartments that cannot be assessed with conventional DXA technology. Although technological developments are needed to improve the clinical utility of pQCT for assessing future fracture risk, this should not discourage the use of pQCT in studies of the growing skeleton.

7.3 *Challenges Associated with School-Based Interventions*

In addition to the complexities associated with assessing the osteogenic effects of physical activity on the growing skeleton, Parts II and III highlighted several key issues related to study design and implementation of school-based physical activity interventions that should be considered when planning future trials in the school setting.

7.3.1 Study Design

A limitation of this study is that I did not account for the cluster design *a priori*. Although results from the HBS II intervention demonstrated a negligible school effect for DXA outcomes (12,33), this should not have precluded taking the appropriate steps to account for the cluster design in the planning stages of the present study. However, determining sample size for a cluster randomized trial requires a good estimate of the ICC (34,35) and this was not available *a priori* for our primary outcome (SSI_p). Although I provide ICC estimates for both baseline and change values for all pQCT outcomes it is likely that these estimates are not precise due to the small number of schools in the study (36). As recommended by Murray et al. (36) a pilot study should be carried out that aims to provide a valid and precise estimate of the ICC for DXA, pQCT and HSA outcomes. There is also the need to estimate the ICC for boys and girls and perhaps for different ethnicities as has been done for smoking related outcomes in adolescents (37). For cluster randomized trials, the ICC estimate is as critical as a valid and precise estimate of the variance of the primary outcome in a standard randomized trial (36).

Although the statistical approaches used in Parts II and III account for aspects of intraschool dependence which can be modeled by the ICC, they did not account for the probability that errors associated with individual

students in each *class* are related (intraclass dependence). Ideally, I would have used a three-level-model (i.e., children nested within classrooms and classrooms nested with schools) which included random factors to account for both class and school but this was not possible due to the large range in the number of students with consent in each class. Thus, if a pilot study is to be conducted for bone outcomes the ICC should be estimated at the school and classroom level.

Despite these limitations, cluster randomization is the best comparative design with which to evaluate a school-based trial as it prevents contamination that would otherwise occur if intervention and control children attended the same school (36). The statistical challenges of cluster randomized trials discussed in this thesis highlight the need for careful planning of the study design in future school-based studies.

In addition to the aforementioned issues related to cluster randomization, a design limitation of note is the method used to recruit and select schools and children for participation. The non-random sample of schools and children clearly influences the external validity of my findings. I did not have any information on those children who did not have parental consent. In particular, I was unable to distinguish between those children whose parents did not consent and those children whose parents did not receive the information letter and consent form. A better strategy for active consent in future studies may be to mail the consent package directly to each child's home with provisions for parents to return the consent forms by mail. Resources permitting, the mail-out could be followed up with a telephone call. This approach may not only increase consent rates, but would also ensure that baseline demographic information is gathered for all potential study participants.

7.3.2 Teacher Compliance

For both pQCT and HSA outcomes, the intervention effect was magnified when only those children whose teachers complied with Bounce at the Bell were included in the analysis. This finding is not surprising giving the central role of classroom teachers in this intervention. The AS! BC model was designed specifically for the generalist teacher and as such offered flexibility in how the Classroom Action requirements were met. The only exception was Bounce at the Bell which required teachers to follow a set progression plan during Phase II. There are several possible explanations for why the majority of teachers did not follow Bounce at the Bell requirements. First, because Bounce at the Bell was not the sole focus of the intervention it is possible that not enough emphasis was placed on the need for strict compliance with the program. In the HBS II intervention, the circuit program was the only intervention requirement and teachers were responsible for reporting compliance with only one activity. For AS! BC, teachers were asked to comply with the 15 x 5 component of AS! BC in addition to Bounce at the Bell and this may have been too burdensome on top of their curricular demands. Second, I relied on the AS! BC School Facilitators to provide instruction and feedback to teachers on their delivery of Bounce at the Bell. I was able to check Activity Logs on a regular basis to determine if teachers were complying with the progression component; however, I was unable to speak to teachers directly if I had concerns with their reporting. In addition, I was unable to directly observe Bounce at the Bell in the classroom which would have been helpful not only for assessing teacher compliance, but also children's performance of the jumps. However, all teachers received standardized training from the AS! BC

School Facilitators. In addition, the School Facilitators provided further instruction to teachers and students if the quality of the jumps was not satisfactory. Finally, the level of facilitation provided to teachers at Level 1 and Level 2 schools may have influenced compliance. Teachers at Level 1 schools were in contact with the School Facilitator on a weekly basis, whereas teachers at Level 2 schools were in contact with the School Facilitator for approximately 1 hour per month.

As discussed, in order to determine the effectiveness of Bounce at the Bell there remains a need for a randomized trial in which the jumping program is the only intervention. Not only would this allow us to attribute an osteogenic response to the one mode of activity, but it would also allow us to focus more attention on teacher compliance with the hope of improving program delivery and implementation. For the overall AS! BC model, the potential health benefits for children will only be achieved if teachers accept and comply with the Classroom Action program. Results from the AS! BC process evaluation identified barriers and facilitators to implementation of the AS! BC model and highlighted the importance of involving teachers in the initial planning stages (38). If the AS! BC model is to be sustainable, it is essential that teachers continue to have a central role in model development and implementation.

7.4 Public Health Implications of Action Schools! BC

" we know of no single intervention with greater promise than physical exercise to reduce the risk of virtually all chronic diseases simultaneously" (39)

In light of the results from Parts II and III, there is a need for further cluster randomized trials to determine the effectiveness of AS! BC and Bounce at the Bell for increasing bone strength in boys and girls and at what time during growth the osteogenic effects of such programs are maximized. However, I believe that given the substantial body of evidence supporting the benefits of physical activity for the growing skeleton as well as many other aspects of children's health and well-being AS! BC has the potential to have wide-scale public health impact for several reasons. First, AS! BC is unique compared with previous school-based physical activity interventions in that the focus was on changing the school environment rather than on changing individual behaviours related to physical activity or modifying the physical education curriculum. The 'active school' approach offers promise as a sustainable option in schools given the declining resources and time available for traditional physical education. In addition, by establishing physical activity as part of the school culture, AS! BC aims to increase physical activity opportunities for all students regardless of their socio-economic background or skill level. In the present study, 50% of grade 4 and 5 children participated in the evaluation; however, approximately 1400 students were exposed to AS! BC during the 16-month study. Thus, the multifactorial health benefits of physical activity can be achieved by all students.

Ultimately, the goal of AS! BC is to reduce children's risk for osteoporosis and other chronic diseases later in life. Although the long-term impact of AS! BC on the incidence of osteoporosis and related fracture will not be recognized for many years, it is known that physical activity during childhood and adolescence is associated with

decreased fracture risk (40-42). Further, there is weak, but positive, evidence that supports the tracking of physical activity behaviours from childhood to adulthood (43,44). Thus, given the alarming statistics indicating the current low level of physical activity among Canadian youth (45), it is imperative that schools, communities and governments support initiatives such as AS! BC in order to promote healthy lifestyles among children and youth.

7.5 Summary and Conclusions

7.5.1 *Part I: Bone Strength and its Determinants in Pre- and Early Pubertal Boys and Girls*

Summary (*Primary Objective*):

a) After adjusting for tibial length and muscle cross-sectional area (MCSA), tibial bone strength indices (BSI, SSI) were 5-15% greater in pre- and early pubertal boys compared with pre- and early pubertal girls. This was due largely to greater bone area (ToA, CoA) in boys.

b) At the distal tibia, total density (ToD) was 8% greater in prepubertal boys compared with prepubertal girls. There was no sex difference in ToD in early puberty.

c) At the tibial shaft, CoD was significantly greater in both pre- and early pubertal girls compared with pre- and early pubertal boys.

Summary (*Secondary Objective*):

a) After adjusting for tibial length, MCSA explained 10-16% of the variance in bone area and strength at the distal and shaft sites of the tibia in boys and girls.

b) At the distal tibia, MCSA explained a small portion of the variance in total density, whereas at the tibial shaft MCSA was not a significant determinant of cortical density in boys or girls.

c) Ethnicity was a significant determinant of CoA and CoD at the tibial shaft with Caucasian girls having greater CoA and lower CoD than Asian girls. Similarly, ethnicity was a significant determinant of CoA in boys with Caucasians having greater CoA than Asians. Ethnicity was not a significant determinant of bone strength in girls or boys.

d) Physical activity was a significant determinant of bone strength at the distal tibia in boys and girls.

Conclusions:

a) Pre- and early pubertal boys have greater bone strength at the distal tibia and tibial shaft than pre- and early pubertal girls.

b) Pre- and early pubertal girls have greater cortical density at the tibial shaft than pre- and early pubertal boys.

c) Muscle cross-sectional area is a significant determinant of tibial bone area and strength in pre- and early pubertal boys and girls, but has less influence on (volumetric) bone density.

d) In boys and girls, CoA at the tibial midshaft is greater in Caucasians than Asians. In girls, CoD is greater in Asians than Caucasians. Bone strength indices are similar between ethnicities.

e) Physical activity appears to have a stronger influence on bone strength at the distal tibia, a mainly trabecular bone site, in boys and girls.

7.5.2 *Part II: Effectiveness of a School-Based Physical Activity Intervention for Increasing Tibial Bone Strength in Boys and Girls: A 16-month Cluster Randomized Trial*

Summary (*Primary Objective*):

a) Prepubertal (Tanner stage 1) intervention boys had a significantly greater change in bone strength (BSI) at the distal tibia and tended to have a greater change in bone strength (SSI) at the tibial midshaft than prepubertal control boys. There was no significant difference in change between early pubertal intervention and control boys for bone strength at either site.

b) Change in bone strength at the distal tibia and tibial midshaft did not differ significantly between intervention and control girls.

Summary (*Secondary Objective*):

a) Prepubertal intervention boys tended to have a greater increase in bone strength in both bending planes at the tibial midshaft than prepubertal control boys.

b) Change in bone strength in the x- and y-bending planes did not differ significantly between intervention and control girls.

Conclusions:

a) The Classroom Action program of Action Schools! BC which included a simple jumping program (Bounce at the Bell) was an effective means to increase bone strength at the distal tibia in prepubertal boys, primarily through greater gains in ToD.

b) The trend for prepubertal intervention boys to have greater gains in bone strength in both the x- and y-bending planes suggests that the AS! BC intervention may increase bone strain in both the medial-lateral and anterior-posterior directions.

c) The simple, daily program of physical activity may not be a suitable means to increase tibial bone strength in pre- and early pubertal girls.

7.5.3 *Part III: Effectiveness of a School-Based Physical Activity Intervention for Increasing Femoral Neck Bone Mass and Strength in Boys and Girls*

Summary (*Primary Objective*):

a) Change in femoral neck bone mass, size and strength did not differ significantly between intervention and control boys.

b) Change in estimated femoral neck bone strength (section modulus) tended to be greater in intervention girls compared with controls; however, the difference in change between groups was only significant when girls whose teacher complied with Bounce at the Bell were included in the analysis. The trend for

greater gain in femoral neck bone strength in intervention girls was associated with a similar trend for greater gain in femoral neck CSA and BMC.

Summary (*Secondary Objective*):

a) Change in total body BMC was significantly greater in intervention than control boys and intervention boys tended to have a greater gain in lumbar spine BMC than controls. Change in total proximal femur BMC and BA did not differ significantly between intervention and control boys.
b) Changes in BMC and BA at the total proximal femur, lumbar spine and total body did not differ significantly between intervention and control girls.

Conclusions:

a) Action Schools! BC was not an effective means to increase femoral neck bone strength or bone mass in boys; however, the simple program of daily physical activity appears to have a positive effect on total body and lumbar spine bone mineral accrual in boys.
b) The osteogenic effect of AS! BC at the femoral neck in girls is dependent on teacher compliance with Bounce at the Bell. This highlights the need to identify barriers and facilitators of implementation of Bounce at the Bell in the classroom setting.

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Appendices

Appendix A: Action Schools! BC Advisory Committee Membership

Action Schools! BC Advisory Committee

Name	Title	Constituency Represented
Marion Lay	President & CEO	2010 Legacies Now
Andrew Hazlewood	Assistant Deputy Minister	BC Ministry of Health
Laurie Woodland	Acting Executive Director, Healthy Living/Chronic Disease Prevention	BC Ministry of Health
Bobbi Plecas	Lead Director, Initiatives Department	BC Ministry of Education
Heather Hoult	Director, Health Promoting Schools	BC Ministry of Education
Lori Zehr	Manager, Physical Activity/Chronic Disease Prevention/Healthy Living	BC Ministry of Health
Lee Southern	Executive Director	BC School Trustees Association
Tom Hierck	President	Principals & Vice Principals Association of BC
Shirley Wilson	External Committee Volunteer	BC Confederation of Parent Advisory Councils
Don Hutchinson	Middle School Teacher	Montgomery Middle School
Jane Hunter	Principal	RJ Tait Elementary School
Lorraine Greaves	Executive Director	BC Centre of Excellence for Women's Health
Sharon White	Policy Analyst/Sport Consultant	Ministry of Tourism, Sport and the Arts
Michelle Kilborn	Teacher & President	Physical Education BC
Dr. Ron Wilson	Physician	BCMA – Athletics & Recreation Committee
Heather McKay	Principal Investigator	University of BC, Faculty of Medicine
PJ Naylor	Associate Director of Research (Evaluation)	University of Victoria
Bryna Kopelow	Program Consultant, Manager, AS! BC	JW Sporta
Jennifer Fenton	Program Consultant, AS! BC	JW Sporta
Patti Hunter	Director, Physical Activity and Healthy Living	2010 Legacies Now
Bruce Dewar	Executive Vice President	2010 Legacies Now

Action Schools! BC Advisory Committee Continued

Name	Title	Constituency Represented
Janice Macdonald	Regional Executive Director	Dieticians of Canada, BC Region
Douglas McCall	Executive Director	Joint Consortium for School Health
Kathy Cassels	DASH/Breakfast for Learning Coordinator	The Directorate of Agencies for School Health
Marion Taylor	Consultant	2010 Legacies Now - Action Kids! BC
Karen Strange		Healthy Eating Team, Action Schools! BC
Meghan Day	Graduate Student, Dietician	Healthy Eating Team, Action Schools! BC
Jane MacCarthy	Senior Communications and Media Relations Manager	2010 Legacies Now – Sport & Recreation Now

Appendix B: Ethics Approval Form, Information Letters, Consent Form, Health History Questionnaires

The University of British Columbia
Office of Research Services and Administration
Clinical Research Ethics Board

Certificate of Expedited Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	NUMBER
McKay, H.A.	Human Kinetics	C02-0537

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT

UBC Campus

CO-INVESTIGATORS:

Khan, Karim, Family Practice; Levy Milne, Ryna, Family & Nutr Sci; Macdonald, Heather, Human Kinetics; Reed, Kate, Human Kinetics; Rhodes, Ryan, Human Kinetics; Warburton, Darren, Human Kinetics

SPONSORING AGENCIES

Provincial Health Services Authority

TITLE:

Action Schools! BC

APPROVAL DATE	TERM (YEARS)	DOCUMENTS INCLUDED IN THIS APPROVAL:
NOV 2 7 2002	1	12 November 2002, family info letter; 8 November 2002, consent forms; 18 October 2002, protocol, questionnaires

CERTIFICATION:

The documentation included for the above-named project has been reviewed by the Chair of the UBC Clinical Research Ethics Board, and the research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved by the UBC Clinical Research Ethics Board.

Approval of the Clinical Research Ethics Board by one of:
Dr. P. Loewen, Chair
Dr. A. Gagnon, Associate Chair

This Certificate of Approval is valid for the above term provided there is no change in the research study.

THE UNIVERSITY OF BRITISH COLUMBIA

School of Human Kinetics
210, War Memorial Gym
6081 University Boulevard
Vancouver, B.C. Canada V6T 1Z1

Action Schools! BC

Information for Families

In partnership with community and government organizations, a group of investigators from the University of British Columbia would like to launch a program of physical activity within elementary schools in the Richmond and Vancouver School Districts.

Our motive is based on the sad reality that many Canadian children are not active enough to achieve health benefits. We are also aware that being physically ***inactive*** is a major player in the development of a host of chronic diseases including osteoporosis, obesity, heart disease and Type II diabetes. In addition, many of the antecedents of these diseases that present in adulthood, are often rooted in childhood. Therefore, we feel there is a need to develop innovative and effective physical activity and healthy living strategies that can be implemented during childhood. As schools serve children of all ages, ethnicities and backgrounds we feel that a partnership with principals, teachers, parents and the children themselves provides the best means to introduce *Action Schools! BC.*

The Aims of the ***Action Schools! BC program***
Our overall goal is to increase physical activity levels of schools and children and to improve each individual's chronic disease risk factor profile. We have provided our vision statement below:

Action Schools! BC is a sport and physical activity initiative integrated into the fabric of our elementary schools and maintained through family and community partnerships. The ultimate aim of Action Schools! BC is to promote healthy hearts, healthy bones, healthy weight and positive self-esteem. Program development will involve children, teachers, parents and community partners. Most importantly, this initiative will allow each school to develop their own program for action. Action Schools! will lead to long term health benefits that are measurable and sustainable.

Our ultimate goal is to introduce *Action Schools! BC* to interested schools throughout the province of BC by years' end, 2004. In order to achieve that goal we wish to first pilot the program in several elementary schools in Vancouver and Richmond, beginning January, 2003.

The Action Schools! BC Program
The physical activity program will be comprised of a menu of physical activities designed, as our vision statement suggests, to promote healthy hearts, healthy bones, healthy eating, healthy weight and positive self esteem. The menu of activity choices will offer a selection of activities that span the entire school year. Clearly, for a program like this to succeed the support of parents, teachers and principals is key. Thus, we envision a partnership between the school and its larger community, our team at UBC and the Premier Sports Award program to develop a means

offerings such as "Bounce at the Bell". Menu options and the materials and resources required to implement *Action Schools! BC* activities will be provided to participating schools.

The Action Schools! BC Evaluation
In order for a program like *Action Schools! BC* to be sustained it must be affordable and effective. Although a number of physical activity programs have previously been introduced into elementary schools in Canada very few have been evaluated as to their effectiveness. Therefore, we wish to assess whether the program is sustainable, whether there are measurable changes in children's physical activity levels and whether cardiovascular and bone health risk factors and self-esteem improve over an 18-month period.

To determine if such changes occur as a result of the intervention, it is important for us to compare the *Action Schools! BC* program with regular routines of physical activity. For this reason, schools who choose to participate in the *Action Schools! BC* program will be randomly assigned to one of two groups; intervention or usual practice. Students from all schools will be evaluated according to the following procedures, however only the intervention schools will receive the *Action Schools! BC* program. At the end of the evaluation period the *Action Schools! BC* program will be offered to all schools.

> Part 1 of the evaluation is administered in the schools to grade four and five students who volunteer to participate. We will administer questionnaires to students in the classroom 4 times during the 18 month study to assess dietary intake and psychosocial well being. Three of the school visits will require 60 minutes of class time each and the remaining visit will require 30 minutes of class time to administer the questionnaires. Students in grade 6 who volunteer to participate will also complete the physical activity questionnaire.
>
> Part 2 is administered at the Vancouver General Hospital (VGH) Bone Health Research Laboratory. At the beginning and end of the study (twice over 18 months) children in grades 4 and 5 who volunteer for measurement, and with consent from parents, will travel to the Bone Health Research Laboratory at VGH. There we will assess bone health, cardiovascular health and administer the questionnaires once again. These measurement sessions will each require that participating students be out of school for approximately three hours. Detailed information for all measurement protocols is provided on the attached consent form.

At this time we would ask that you please consider your child's participation in the evaluation. We invite you to read, complete and sign the attached consent form. You may then return the forms to the school. We are extremely excited about this project! We envision that all those involved in the *Action Schools! BC* project, including students, teachers and parents, will reap the rewards of improved health.

If you have any questions please contact either Heather Macdonald at [hmacdona@interchange.ubc.ca], Josie McKay at or Heather McKay at . Thank you kindly for your attention.

Sincerely,

Dr. Heather McKay
For the *Action Schools! BC* Team

Action Schools! BC
Consent Form for Families

Investigators:
Heather McKay PhD, Karim Khan MD PhD, Darren Warburton PhD, Ryan Rhodes PhD, Kate Reed MSc, Heather Macdonald BSc.

Your child's school is currently involved in the *Action Schools! BC* program. Your child may soon be participating in a variety of activities targeted towards healthy bones, healthy hearts, healthy weight and positive self-esteem. In order to measure the success of *Action Schools! BC* we wish to evaluate children from grades 4 and 5 according to the following procedures. Please read the following with your child, and if you or your child have any questions, please do not hesitate to contact us. If you and your child wish to participate in the evaluation, you will find a consent form attached to this document that both you and your child can sign and return to your child's teacher.

Procedures:

Your child's participation in the *Action Schools! BC* Program evaluation will involve two testing sessions (approximately 3 hours each, including transportation time), one in January of this year and one in June 2004, at the Vancouver General Hospital, Bone Health Research Lab. The lab is located at the VGH Research Pavilion - 5th Floor, 828 West 10th Avenue, Vancouver. The children will be transported from the school via mini–van in groups of 5 – 6 and supervised en route by the *Action Schools! BC* chaperone, in addition to the driver. Parents will be sent a notification 24 hours prior to the dates for these visits.

Each session will include the following procedures:

1. Measures of height, sitting height, weight, calf, waist and hip girth will be taken. In addition your child will be asked to complete questionnaires that will assess their physical activity, calcium intake and physical maturity. A trained study staff person will discuss the importance of these assessments with the children. A brief health history questionnaire and a 24-hour food intake questionnaire will be sent home to be completed by a parent or guardian and returned to the University in a self-addressed stamped envelope.

2. Your child's whole body, hip and spine bone status will be evaluated using a bone densitometer. This procedure is painless and routinely used in modern medical practice. It requires only that the child lie still on the padded measurement table for about 15 minutes. We will also assess changes in bone structure at the tibia using a peripheral computerized tomography system. This procedure is performed while the child is sitting with one leg extended and takes approximately 10 minutes. Although the bone measurements are X-ray based, the total patient effective dose per session will be approximately 10 millirem. This is less than you receive on an airplane flight across the country. A trained operator will perform all the bone measurements.

3. Cardiovascular fitness will be assessed by means of a shuttle run test. Children run at a set pace, that steadily increases in speed, until they can no longer keep up. This will take up to 15 minutes. Blood pressure will also be measured using a cuff and a sphygmomanometer. All of these procedures have been performed extensively with children and are harmless.

Benefits:

If you and your child choose to participate in the *Action Schools! BC* program evaluation, you and your child will learn more about how physical activity can contribute to improved bone and cardiovascular health. It is our hope that through this program, your child will achieve the many health benefits that accompany an active lifestyle. You and your child will receive results of the bone measurements and cardiovascular fitness at the end of the study, along with a summary of the findings.

Rights and Welfare of the Individual:

You have the right to refuse your child's participation in this program evaluation. It is understood that you are free to withdraw your child from any or all parts of the program at any time without penalty. If your child's teacher chooses to stop participating in the *Action Schools BC!* program we would like to still involve your child in the evaluation process. Your child's identity will remain confidential as all individual records and results will be analyzed and referred to by number code only. Files are kept in the Vancouver General Hospital, Bone Health Research Lab. The lab remains locked and only those directly involved in the study (namely, the *Action Schools! BC* Research Evaluation Team) will have access to your child's records and results. Your child will not be referred to by name in any program reports or research papers. Your child's individual results will remain confidential as they will not be discussed with anyone outside the research team.

Please be assured that you may ask questions at any time. We will be glad to discuss your child's results with you and your child when they have become available and we welcome your comments and suggestions. Should you have any concerns about this program or wish further information please contact Dr. Heather McKay, Heather Macdonald, or Josie McKay, . If you have any concerns about your child's rights or treatment as a research subject, you may contact the Director, Office of Research Services at the University of British Columbia at

Consent Form for Participation

Parent's Consent Statement:

I, _____ (please print the name of one or both parents) understand the purpose and procedures of this evaluation as described and I voluntarily agree to allow my child, _____, to participate in the *Action Schools! BC* Program evaluation (height, weight, physical activity / nutrition / maturity questionnaires, bone measurements, cardiovascular fitness, blood pressure)

I understand that at any time during the *Action Schools! BC Program* evaluation 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 program.

_____	_____
Signature of Parent/Guardian	Date
_____	_____
Signature of Witness	Date
_____	_____
Signature of Investigator	Date

Child's Statement:

I understand the purpose and procedures of this program as described and I voluntarily agree to participate. I understand that at any time during the program, 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 these procedures.

_____	_____
Signature of Child	Date

Consent Form for Travel

I hereby authorize the School of Human Kinetics, as agent of the University of British Columbia, to arrange transportation of my child to and from the Vancouver General Hospital, Bone Health Research Laboratory located at the Vancouver General Hospital - Research Pavilion - 5th Floor, 828 West 10th Avenue, Vancouver, British Columbia.

_____

Child 1 – First and last name – please print

_____

Child 2 – First and last name – please print

_____

Name of parent, guardian or individual – please print

_____

Signature

_____

Date

Please return this form to your child's teacher.

Thank you!

Health History Questionnaire

Please take the time to answer the following questions about your child's health. This questionnaire is voluntary and you are free to leave any questions unanswered. Please be assured that all information will remain strictly confidential and will only be available to the researchers. If you have any questions regarding the contents of this questionnaire, please contact Heather Macdonald , Josie McKay , or Dr. Heather McKay at the University of British Columbia. You can also email any questions to _____ Please return this questionnaire to us in the self-addressed, stamped envelope provided. Thank you for your participation in this part of the Action Schools! BC Program.

REGARDING YOU (mother or father of child participating in Action Schools! BC):

1.0 Where were you born?
Mother: _____ Father: _____

1.1 Where were **your parents** born?
Maternal Mother: _____ Maternal Father: _____
Paternal Mother: _____ Paternal Father: _____

1.2 How long has your family lived in North America? Years: _____ Months: _____

1.3 Where did your family live before moving to North America? _____

1.4 How would you classify your family ethnically? (i.e., Caucasian-Canadian, Japanese-Canadian, etc.)
_____

1.5 If you wish to have your child's results sent home at the end of the study, please provide us with the following contact information.

Mailing Address _____

Phone Number _____ **Email** _____

REGARDING YOUR CHILD:

Child's name: _____ Age: _____ Birth Date (d/m/y) _____

Child's birthweight _____ (grams or lbs/ozs)

2.0 **Nutrition History:**

2.1 Who prepares your child's meals (i.e., mother, father, grandmother, nanny) _____

2.2 Does your child drink milk every day?
_____YES: if **yes:**
How many cups per day? _____
Has your child always drank milk every day (after being weaned from breast or bottle)?
yes _____ no _____
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)

2.3 Is your child on a special diet? _____ Yes _____ No
If **yes:** _____ vegetarian
_____ low sodium
_____ low cholesterol
_____other
Please specify: _____

3.0 **Medical History and Status:**

3.1 Has your child ever been 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) _____

3.2 Is your child currently taking any medications? _____ Yes _____ No
If **yes**, what medication(s) is your child taking? _____
What are these medication(s) for? _____

3.3 Has your family doctor ever said that your child has a heart condition and that he/she should only do physical activity recommended by a doctor? _____Yes _____No

3.4 Does your child complain of chest pain when they are doing physical activity?
_____Yes _____No

3.5 In the past month, has your child complained of chest pain when they were not doing any physical activity?
_____Yes _____No

3.6 Does your child have a bone or joint problem that could be made worse by a change in their physical activity? _____Yes _____No

3.7 Does your child lose their balance because of dizziness or do they ever lose consciousness?
_____Yes _____No

3.8 Do you know of any other reason why your child should not participate in physical activity?
_____Yes _____No

4.0 **Bone History:**

4.1 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

4.2 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

4.3 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

4.4 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. _____

5.0 **Physical Activity:**

5.1 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

ID: _____

Checked by: _____

Updated Health History Questionnaire: Spring 2004

1. Are you right handed or left handed? O Right O Left

2. Has your diet changed over the past year? O Yes O No

   If **yes:** _____ vegetarian
   _____ dairy-free
   _____ low sodium
   _____ low cholesterol
   _____ other (Please specify: _____)

3. Do you drink milk every day? O Yes O No

   If **yes:** How many cups per day? _____

4. Do you currently take any medications? O Yes O No

   If **yes**, what medication(s) are you taking? _____

5. Did you break any bones during the past year (March 2003 – present)? O Yes O No

   If **yes**, what bone(s), when (month), and for how long was the bone in a cast? (indicate R or L, and upper or lower arm/leg). **For example: right radius (or lower arm), July 2003, 6 weeks.**

   _____
   _____
   _____

   How did you break the bone(s)? (check one)
   a. ___ fell while running;
   b. ___ fell while walking/standing;
   c. ___ contact during sports* (i.e., to person, equipment, ground (includes snowboarding/ skateboarding));
      *indicate sport (i.e., soccer) _____
   d. ___ fell from height (i.e., playground equipment, bike, tree, stairs);
   e. ___ trauma in car/skidoo/boat accident;
   f. _____ other (specify)

6. Prior to the past year, have you **EVER** broken a bone(s)? O Yes O No

   If **yes, for each fracture,** indicate: Bone, R or L, upper or lower for arm/leg, year/month, length of casting, and how fracture occurred using categories (a-f) from previous question:
   For example: right radius (lower arm), March 1999, 6 weeks, (d).
   Fracture 1: _____
   Fracture 2: _____
   Fracture 3: _____

7. Were you sick for longer than one month during the past year? O Yes O No

   If **yes**, what did you have? _____

8. Were you hospitalized during the past year? O Yes O No

   If **yes**, for how long? _____

9. Has any member of your family been diagnosed with osteoporosis during the past year? O Yes O No

   If **yes**, who? _____

10. Has any member of your family been diagnosed with cardiovascular disease or stroke during the past year? O Yes O No

    If **yes**, who? _____

Appendix C: Action Inventory, School Health Inventory, Action Plan Worksheet

Baseline Action Inventory Form

Complete Only Once

Use this inventory to record current physical activities occurring in your school and classroom program.

When completed, please send this form to Action Schools! BC: fax ; submit online, email info@actionschoolsbc.ca

Action Schools! BC

School and SD#: _____

Completed by: _____ Date completed: _____

Action Zones	Baseline Action	When do these activities generally occur?
	Describe current physical activities taking place	*Indicate the months or dates*
School Environment		
List may include: *workshops, equipment, resources,* *food services, health policies* *facilities – indoor/outdoor*		
Scheduled Physical Education		
# of min/week *List PE themes per month*		
Classroom Action		
# of min/week *List type of activities*		
Family and Community		
List may include: *community sport/programs* *family participation* *community presentations*		
Extra-curricular		
List may include: *before/recess/lunch/after* *clubs, teams*		
School Spirit		
List may include: *school-wide mass physical activities* *active fundraisers*		

School:_____
SD#: _____
Inventory Takers:_____

Action Schools! BC SCHOOL HEALTH INVENTORY

This School Health Inventory is a tool to help school Action Teams assess the school environment to identify areas of improvement to incorporate into the Action Plan!. Each question includes a rating scale that corresponds to the scoring table at the end of the inventory.

The Inventory is a required component of the pilot, and should be completed prior to the creation of the school Action Plan!, and as part of the year-end report. Please contact the AS! BC Support Team at 604-738-2468 or info@actionschoolsbc.ca with any questions or concerns.

1. SCHOOL HEALTH POLICIES AND SCHOOL ENVIRONMENT

1.1 Representative committee for school health programs

Does the school have a representative* committee that meets at least twice a year and oversees school health policies and programs concerning physical activity, healthy eating, and tobacco prevention and cessation?

3 = Yes, there is a representative committee that meets at least twice a year and oversees school health policies and programs.
2 = There is a committee, but it is not representative; **or** it does not address physical activity, healthy eating, and tobacco prevention and cessation policies and programs; **or** it meets less than twice a year.
1 = There is no committee for school health programs, but there are plans to establish one.
0 = There is no committee for school health programs, and there are no plans to establish one.

* *Representative means that it includes relevant members of the school community, such as students, school staff (e.g. teachers, administrators, food services and custodial staff), families, community practitioners (e.g. recreation programmers, public health nurses, counselors), and community volunteers (e.g. coaches).*

1.2 Written health policies

a) Does the school or district have written school health policies that commit the school to the following? (check all that apply)
- ☐ Providing a broad range of competitive and noncompetitive physical activities that help students develop the skills needed to participate in lifetime physical activity.
- ☐ Providing foods that are low in fat, sodium, and added sugars wherever food is available inside the school (in the case of schools with cafeterias, this would also apply to food being served in the cafeteria).
- ☐ Providing a 100% tobacco-free environment 24 hours a day.

3 = Yes, for all of the above.
2 = Yes, but for only two of the above.
1 = Yes, but for only one of the above.
0 = No, neither the school nor district have policies on any of the above.

b) Does the school have written policies about helmet and safety equipment for cyclists and those commuting to school with 'small wheel vehicles' (e.g. rollerblades, skateboards, scooters)?

3= Yes, the school has both helmet and safety equipment policies.
2= The school has policies about helmet and safety equipment for only one of the above.
1= There are no written policies about helmet or safety equipment, but there are plans to develop them in the future.
0= No, there are no written policies about helmet or safety equipment, and there are no plans to develop them in the future.

1.3 Recess

Are students provided with at least 20 minutes of recess* during each school day, and do teachers or recess monitors encourage students to be active?

3 = Yes, students are provided with at least 20 minutes of recess each day, and are encouraged to be active.
2 = Recess is provided for at least 20 minutes each day, but neither teachers nor recess monitors encourage students to be active.
1 = Recess is provided each day, but for less that 20 minutes; **or** it is provided on some days, but not on all days.
0 = Recess is not provided on any day.

* *Recess is an opportunity for unstructured physical activity, and should complement rather than substitute for physical education.*

1.4 Adequate physical activity facilities

Are physical activity facilities adequate in the following ways? (check all that apply)
- ☐ Both indoor and outdoor facilities are available for physical education, classroom physical activity, and extracurricular physical activity programs.
- ☐ Physical education classes do not have to be canceled due to weather extremes (rain, high or low temperatures, etc.).
- ☐ In physical education classes, all students can be physically active without overcrowding or safety risks.
- ☐ For extracurricular activities, all interested students can sign-up and participate without overcrowding or safety risks.

3 = Yes, physical activity facilities are adequate in all four ways described above.
2 = Physical activity facilities are adequate in three of the ways described above.
1 = Physical activity facilities are adequate in only one or two of the ways described above.

0 = Physical activities facilities are adequate in none of the ways described above.

1.5 Access to physical activity facilities outside school hours

Can all students use the school's indoor and outdoor physical activity facilities outside school hours*?

3 = Yes, students can use the school's indoor and outdoor physical activity facilities outside school hours.
2 = Indoor or outdoor facilities are available, but not both.
1 = Indoor or outdoor facilities are available, but the hours of availability are limited.
0 = No, students can not use the school's indoor and outdoor physical activity facilities outside school hours.

* *Outside school hours means before and after school, evenings, weekends, and school vacations.*

1.6 Access to facilities and programs that promote safe, active transportation to and from school

Does the School have the following facilities and programs that promote safe, active transportation to and from school? (check all that apply)
☐ A 'car-free zone' to provide safe walking areas.
☐ Adequate* facilities available to lock bicycles and small wheel vehicles like skateboards and scooters.
☐ A 'walk-to school' program involving teachers and families.
☐ Programs promoting the use of helmets and safety gear for those who use active transportation to school (bicycles and 'small wheel vehicles).

3 = Yes, the school has three or more of the above.
2 = Yes, two of the above.
1 = Yes, one of the above.
0 = No, none of the above.

* *Adequate means that most of the time (80% +) there are spaces available for students to lock up active transportation equipment.*

1.7 Fund-raising efforts promote physical activity

Do school fund-raising efforts promote physical activity (e.g. fun runs, family walks, programs like Jump Rope for Heart)?

Please list the school's physically active fund-raisers:

_____

_____

3 = Yes, all of the school's fund-raising efforts promote physical activity in some form.
2 = Some of the school's fund-raising efforts promote physical activity in some form.
1 = The school's fund-raising efforts do not involve or promote physical activity, but there are plans to change in the future.
0 = The school's fund-raising efforts do not involve or promote physical activity, and there are not plans to change in the future.

1.8 Fund-raising efforts support healthy eating

Do school fund-raising efforts support healthy eating through the sale of non-food items or foods that are low in fat, sodium, and added sugars (for example, fruits, vegetables, pretzels, or air-popped popcorn) instead of foods that are high in fat, sodium, and added sugars (for example, candy)?

3 = Yes, fund-raising efforts support healthy eating through the sale of non-food items or foods low in sodium, and added sugars.
2 = Fund-raising efforts rarely support health eating.
1 = Fund-raising efforts typically include the sale of foods high in fat, sodium and added sugars, but there are plans to change this practice.
0 = Fund-raising efforts typically include the sale of foods high in fat, sodium and added sugars, and there are no plans to change this practice.

1.9 Access to healthy foods

Does the school promote the sale and distribution of healthy foods* and discourage the sale and distribution of foods of minimal and low nutritive value** throughout the school grounds until after the end of the last lunch period?

3 = Yes, the school promotes the sale and distribution of healthy foods and discourages the sale and distribution of foods of minimal and low nutritive value.
2 = The school prohibits the sale and distribution of foods of minimal nutritional value and other foods of low nutritive value throughout the school grounds, but only during meal service hours.
1 = No, but there are plans to do so.
0 = No, and there are no plans to do so.

* *Healthy foods are low in fat, sodium, and added sugars (for example, fruits, vegetables, pretzels, air-popped popcorn).*
** *Foods of minimal nutritional value include carbonated soft drinks, chewing gum and certain candies. Foods of low nutritive value provide most calories in the form of fat and/or sugars but contain few vitamin or minerals. Examples include candy, fried chips and juice drinks.*

1.10 Staff orientation to school health policies

Are staff oriented to (verbal and/or written orientation) and given copies of the policies on physical activity, healthy eating, and tobacco prevention and cessation that relate to their job responsibilities?

3 = Yes, staff are oriented to and given policies about these topics as they relate to their job responsibilities.
2 = Staff are oriented to or given copies of the above policies, but not both.
1 = No, but there are plans to do so.
0 = No, and there are no plans to do so.

1.11 Communication of school health policies

Does the school communicate its policies on physical activity, healthy eating, and tobacco prevention and cessation to students, staff, families and visitors in each of the following ways? (check all that apply)

- ☐ 'Tobacco-free school' signs
- ☐ Student handbook
- ☐ Staff handbook
- ☐ Family handbook and/or newsletters
- ☐ Staff orientation and meetings
- ☐ Student orientation
- ☐ Announcements at school events
- ☐ Community meetings
- ☐ Contracts with outside vendors and organizations that rent school facilities
- ☐ Other methods? _____

3 = Yes, 8-10 of the ways are used to communicate school policy.
2 = 4-7 of the ways are used to communicate school policy.
1 = 1-3 of the ways are used to communicate school policy.
0 = School policy is not communicated to students, staff, families or visitors.

2. PHYSICAL EDUCATION AND OTHER PHYSICAL ACTIVITY PROGRAMS

2.1 150 minutes of physical education per week (IRP guidelines)

Do all intermediate grade students receive physical education* for at least 150 minutes per week throughout the school year, spread over at least three days?

3 = Yes, intermediate grade students receive 150 minutes of physical education per week spread over at least three days each week throughout the school year.
2 = Students receive 90-149 minutes of physical education over at least three days each week throughout the school year.
1 = Students receive 90+ minutes of physical education on one or two days each week throughout the school year.
0 = Students receive fewer than 90 minutes of physical education per week.

* *Physical education refers to scheduled instruction-based physical education classes.*

2.2 Equitable distribution of gym time

Do all intermediate grade classes receive equal amounts of gym time?

3 = Yes, all intermediate grade classes receive equal amounts of gym time.
0 = No, all intermediate grade classes do not receive equal amounts of gym time.

2.3 Student preparation for physical education (adequate time in clean, safe changing facilities)

Do students have adequate time in clean, safe changing facilities to change before and after physical education class?

2 = Yes, students have adequate time to change, and the changing facilities are clean and safe.
1 = Students have only one of the above.
0 = Students do not change for physical education.

2.4 Assessment of satisfaction with physical education

Is information collected from students about their satisfaction/enjoyment and participation in physical education?

3 = Yes, information about student satisfaction/enjoyment and participation is collected several times each year.
2 = Information is collected annually.
1 = Information is collected less than annually.
0 = No, information about student satisfaction/enjoyment and participation in physical education is not collected.

2.5 Promotion of community based physical activity

Does the physical education program use three or more promotional methods* to promote student participation in a variety of community-based physical activity**?

3 = Yes, the physical education program uses three or more promotional methods to promote student participation in a variety of community based physical activity.
2 = The physical education program promotes participation in a variety of community physical activity options, but through only one or two methods.
1 = The physical education program promotes only one or two types of community based physical activity.
0 = The program does not promote participation in community based physical activity.

* *Promotional methods (check all that apply):*

- ☐ *Class discussions*
- ☐ *Bulletin boards*
- ☐ *Public address announcements*
- ☐ *Take-home flyers*
- ☐ *Homework assignments*
- ☐ *Newsletter articles*
- ☐ *Other:* _____

** *Examples of community based physical activity include clubs, teams, recreational classes, special events, and use of playgrounds, parks, bike paths, etc.*

3. SCHOOL HEALTH SERVICES

Many school health service positions/budgets have been cut recently. Is this the case in your school? What specific programs and/or positions have been removed? Have any alternatives been explored to continue school health services in the absence of government funding?

- ☐ Our school health service positions/budgets have not been cut.
- ☐ Our school health service positions/budget have been cut (please provide additional information below).
- ☐ Our school does not have a health service position/budget.

Positions and/or budgets removed:

_____

_____

_____

Alternatives explored:

_____

_____

_____

3.1 Physical activity promotion

Does the school nurse* or other health service practitioner** promote physical activity to students and their families through the following methods? (check all that apply)

☐ Distribution of educational materials
☐ Individual advice
☐ Small group discussions
☐ Presentations
☐ Other: _____

3 = Yes, physical activity is promoted through three or more of the methods listed above.
2 = Physical activity is promoted through two of the methods.
1 = Physical activity is promoted through one method.
0 = Physical activity is not promoted through any of these methods; **or** the school does not have a school nurse or other health service practitioner.

* *School nurse means a licensed nurse employed by the school or district.*
** *Other health service practitioner refers to a health professional who provides service to the school on either a contracted or a volunteer basis.*

3.2 Healthy eating promotion

Does the school nurse or other health service practitioner promote healthy eating to students and their families through the following methods? (check all that apply)

☐ Distribution of educational materials
☐ Individual advice
☐ Small group discussions
☐ Presentations
☐ Other: _____

3 = Yes, healthy eating is promoted through three or more of the methods listed above.
2 = Healthy eating is promoted through two of the methods.
1 = Healthy eating is promoted through one method.
0 = Healthy eating is not promoted through any of these methods; **or** the school does not have a school nurse or other health service practitioner.

4. HEALTH PROMOTION FOR STAFF

4.1 Staff physical activity/fitness programs

Does the school or district offer* staff members physical activity/fitness programs** that are accessible and free or low-cost?

3 = Yes, the school or district offers staff members physical activity or fitness programs that are accessible and free or low-cost.
2 = The school or district offers accessible physical activity/fitness programs, but the programs are not low-cost.
1 = The school or district offers physical activity/fitness programs, but the programs are not low-cost and not accessible.
0 = The school or district does not offer physical activity/fitness programs.

* *Offer means that the school or district has a special arrangement for staff to participate in physical activity/fitness programs either on-site or off-site through a community program.*
** *Physical activity/fitness programs include classes, workshops, facilities and special events.*

4.2 Staff healthy eating programs

Does the school or district offer* staff members healthy eating programs that are accessible and free or low-cost?

3 = Yes, the school or district offers staff members healthy eating programs that are accessible and free or low-cost.
2 = The school or district offers accessible healthy eating programs, but the programs are not low-cost.
1 = The school or district offers healthy eating programs, but the programs are not low-cost and not accessible.
0 = The school or district does not offer healthy eating programs.

* *Offer means that the school or district has a special arrangement for staff to participate in physical activity/fitness programs either on-site or off-site through a community program.*

4.3 Staff participation in health promotion programs

Does the school or district promote and encourage* staff participation in health promotion programs?

3 = Yes, the school or district promotes and encourages staff participation in health promotion programs with three or more of the methods listed below.
2 = The school or district promotes and encourages staff participation in health promotion programs with two of the methods.
1 = The school or district promotes and encourages staff participation in health promotion programs with only one method.
0 = No, the school or district does not promote or encourage staff participation in health promotion programs.

* *Participation promotion methods: (check all that apply)*
☐ *Information at orientation for new staff*

- ☐ *Information included with pay cheque*
- ☐ *Flyers posted on school walls*
- ☐ *Letters mailed directly to staff*
- ☐ *Announcements at staff meeting*
- ☐ *Articles in school/staff newsletter*
- ☐ *Incentive/reward programs*
- ☐ *Public recognition*
- ☐ *Other methods:* _____

4.4 Staff access to facilities that promote physical activity

Does the school have bike racks, changing facilities and shower facilities for staff who choose to actively commute to work or exercise at the school during breaks?

3 = The school has all of the above facilities.
2 = The school has two of the above facilities.
1 = The school has one of the above facilities.
0 = There are no facilities available to the staff.

5. FAMILY AND COMMUNITY INVOLVEMENT

5.1 Family education

Does the school provide families with opportunities to learn about physical activity, healthy eating, and tobacco prevention and cessation, through educational materials* sent home and involvement in school-sponsored activities**?

3 = Yes, the school provides families with opportunities to learn about physical activity, healthy eating, and tobacco prevention and cessation through educational materials sent home and involvement in school-sponsored activities.
2 = The school provides many opportunities to learn about only two of the three topics.
1 = The school provides few opportunities; **or** provides many opportunities to learn about only one of the three topics.
0 = The school does not provide families with opportunities to learn about physical activity, healthy eating, or tobacco prevention and cessation.

* *Examples of educational materials include brochures, newsletter articles, introductions to curricula, and homework assignments that require family participation.*
** *Examples of school-sponsored activities include parent/teacher meetings, health fairs, food tastings, international meals, field days, walkathons, and fun runs.*

5.2 Student and family involvement in planning meals

Note: Only for those schools with breakfast/hot lunch programs

Are students and families involved* in planning school meals?

3 = Yes, students and parents are involved with planning school meals.
2 = Students or parents are involved, but not both.
1 = Neither are involved, but there are plans to involve one or both groups.
0 = Neither are involved, and there are no plans to involve them.

* *Examples of being involved include giving menu and recipe suggestions, identifying food preferences, and participating in taste-testing activities.*

5.3 Family and community involvement in programs

Do families and community members help plan and implement* school physical activity and/or healthy eating programs?

3 = Yes, family and community members help in all three areas.
2 = Family and community members help in two of the three areas.
1 = Family and community members help in one of the three areas.
0 = No, family and community members do not help plan and implement school physical activity and/or healthy eating programs.

* *Examples of family and community involvement: (check all that apply)*
  - ☐ *Volunteering to help in the classroom, cafeteria, or with special events;*
  - ☐ *Serving on a school planning committee for physical activity or healthy eating programs;*
  - ☐ *Designing or conducting a needs assessment or program evaluation.*

5.4 Community access to school facilities

Do community practitioners have access to indoor and outdoor school facilities* outside school hours** to participate in or conduct health promotion programs***?

3 = Yes, community practitioners have access to school facilities.
2 = Yes, but the hours of access are somewhat limited.
1 = Yes, but the hours of access are quite limited; **or** there is access to indoor or outdoor facilities but not both.
0 = Community practitioners do not have access to either indoor or outdoor school facilities.

* *Examples of school facilities include classrooms, gymnasiums, and outdoor areas.*
** *Outside school hours means before and after school, in the evening, on weekends, and during school vacations.*
*** *Examples of health promotion programs include physical activity, healthy eating and/or tobacco prevention and cessation programs.*

How To Use this AS! BC Planner

Use this Planner to record your school's Action Plan including Goal Statements and Actions for each of the six Action Zones. Once this has been completed, the teachers can use the school's completed Action Plan along with this plan to incorporate their own Action Plans.

Refer to the descriptions to clarify instructions within each of the six school Action Zones or refer to the AS! BC Handbook.

Once the planners are complete, send them our way!

Action Schools! BC Support Team at info@actionschoolsbc.ca or

1 School Environment

"pick 1 do 1" – recommends the AS! Action Team to "pick 1 Action Idea!" (from the list) that supports the Goal Statement and "do 1" within the months indicated on the Action Plan! Many examples are provided in the AS! BC Handbook or the school and teacher may choose others based on their own resources and planning.

2 Scheduled Physical Education

"pick 2 do 2" – recommends the classroom or physical education teacher to "pick 2 PE Themes" and within each of those themes, "pick 2 activities" (from the list). If the physical education program has already been planned, then this component may be already be achieved without any changes required.

"required" – requires the classroom or physical education teacher to implement the Action Idea!: SportFit (AS! BC Handbook).

3 Classroom Action

"required" – requires the classroom teacher to implement the Action Idea!: AS! BC Pedometer Program (Appendix D).

"required" – requires the classroom teacher to implement the Action Idea!: AS! BC Classroom Action 15 x 5 (Appendix D).

"required" – requires the classroom teacher to implement the Action Idea!: AS! BC 5-TODAY Nutrition Program (Appendix D).

4 Family & Community

"pick 2 do 2" – recommends the teacher to "pick 2 Action Ideas!" (from the list) and "do 2" within the months indicated on the Action Plan!

5 Extra-curricular

"pick 1 do 1" – recommends the Action Team to "pick 1 Action Idea!" (from the list) and "do 1" within the months indicated on the Action Plan! This Action Idea! should reach out to any non-active target group within the school population. Refer to the AS! BC Handbook.

6 School Spirit

"pick 1 do 1" – recommends the Action Team to "pick 1 Action Idea!" (from the list) that supports the Goal Statement and "do 1" (within the months indicated on the Action Plan!). Examples are provided, however, the school may choose something that complements the program based on their own resources and planning.

AS! BC Pilot

Action Plan! with Required Elements

September to December 2003

Action Schools! BC

School/SD#: _____

Teacher: _____

Grade: _____ Division: _____

Date: _____

Pilot requirements	Goal Statements (see Handbook for details)	Actions (see Handbook for details)	September	October	November	December
1 School Environment						
pick 1 do 1						
2 Scheduled Physical Education						
	achieve curriculum outcomes (150min/wk)	PE (enter scheduled times)				
pick 2 do 2	*achieve curriculum outcomes*	PE Themes (enter class program)	Fitness Playground Games	Fitness Outdoor Action 1	Dance Indoor Games 1	Dance
required	*to motivate students to increase their personal fitness*	SportFit Challenge		x		
3 Classroom Action						
required	*motivate children to increase their physical activity*	AS! BC Pedometer Program				
required	*provide 15 min/day of physical activity (heart, bones, self)*	AS! BC Action 15x5	x	x	x	x
required	*provide nutrition education/challenge and 2 activities*	AS! BC 5-TODAY				
4 Family & Community						
pick 2 do 2	*Increase family and community physical activity experiences*	Activities/Presentations/Special Projects				
5 Extra-Curricular						
pick 1 do 1	*e.g. maintain an intra/inter school sport programs*	cross-country running	x	x		
		soccer	x			
		volleyball		x	x	x
6 School Spirit						
pick 1 do 1	*increase school wide physical activity opportunities*					

PE Themes:
Fitness
Fitness Circuits (in/outdoors)
Run/Walk/Wheel for Fun
SportFit

Playground Games
Ball & Scoop
Skipping
Tag Games
Tarmac Games

Outdoor Action 1
Flag Football
Frisbee/disc
Inter-lacrosse
Soccer sports

Indoor Games 1
Bounceball
Netball
Team Handball
Volleyball

Dance
Canadian Favourites
Multicultural/Folk
Hip Hop/Funk/Jazz
Line/Party

Community Activities:
skating, swimming, bowling, bicycling, skiing, curling, showshoeing, golfing, martial arts, yoga, hiking, canoeing, rock climbing, in-line

Community Presentations
Esteem Team Speaker
Multicultural Dances/Sport
Wheelchair Sports Demos
Other Physical Activity Demos

Special Projects:
Walk to School Program
Family Dance/Activity Night
Student/Parent Cooking Classes
School/Community Garden

School Spirit:
Terry Fox Run
Fun Theme Days
Walk to School Day
WinterActive

Appendix D: The Action Schools! BC Manual - Classroom Action 15 x 5, Classroom Action Bin, Bounce at the Bell

AS! Bc Pilot 2003-2004

Action Schools! Bc

AS! Bc Action is X s

only 15 minutes a day – take an AS! Bc energy break!

Health Targets	Physical Activities	Action Ideas!	AS! BC Recommended Resources *(Find In Action Pages!, or Contact AS! BC Support Team)*
	• Bounce-at-the-Bell	• 3 times a day 4 times a week **REQUIRED**	1 AS! BC Bounce-at-the-Bell (Appendix D)
	• Skipping	• indoor or outdoor	1 Jump 2b Fit (video, manual, music cd) 2 Heart Healthy Kids 3 Awesome Asphalt Activities
	• Classroom Workouts	• schedule an "Energy Break" everyday with these energizing classroom videos	1 Energy Blasts Video 2 Classroom Workout Video 3 Kardio Funk for Kids Video 4 Latin Explosion/Funk music cd
	• Chair Aerobics	• take '5' at the desk moving to popular tunes and sequences	1 Ever Active...Everywhere
	• Timed Running • Power Walking • Kilometre Clubs	• keep track of distance or time – motivate the kids with goal setting	1 AS! BC Sneaker Club Ideas Book 2 Not Just Another Games Book 3 Ever Active...Everywhere
	• Tag • Playground Games • Ball, Paddle and Scoop Games	• tag and playground games are active and easy to modify • watch the students do it on their own during recess and lunch!	1 You're It...Tag, Tag and More Tag 2 Awesome Asphalt Activities 3 Gator Ball 4 Scoopball 5 Hand, Paddle and Racquet-Type Games
	• Playground Fitness	• Fall and Spring • anytime, everyday for 5 or 10 minutes	1 Ready-To-Use PE Activities for Grades 5-6 2 AS! BC Fitness Circuit (Appendix D) 3 Station Games
	• Head-to-Toe Warm-Up - stretching	• create active living habits by doing it daily – alternate leaders	1 p.s.a.p. Head-To-Toe Poster 2 Heart Healthy Kids: Daily In-Class Physical Activities for K-6 3 Ready-to-Use PE Activities for Grades 5-6
	• Muscle Fitness - Exercising with Bands - Hand Grippers	• get into a routine and build muscle fitness safely and easily – mix up the program and alternate leaders	1 Exercising with Bands Teacher's Resource (Appendix D) 2 Get a Grip (Appendix D) 3 Jump 2b Fit music cd
	• Juggling - coordination	• use scarves, bean bags, rings, balloons	1 Ready-to-Use PE Activities for Grades 5-6 2 Ever Active...Everywhere

AS! BC Support Team – 1.800.565.7727 – www.actionschoolsbc.ca – psap@jwsporta.ca

...providing more opportunities for more children to be more physically active more often

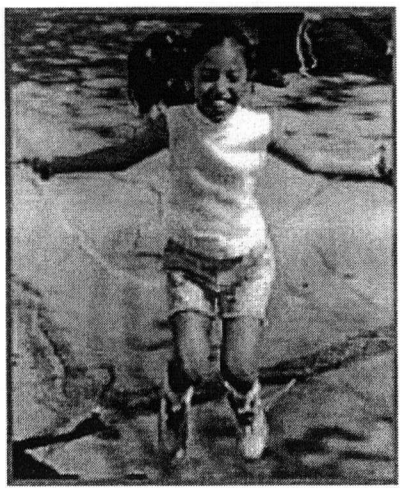
Figure 1. Action Schools! BC Classroom Action Bin. The standard resources in the Action Bin for Level 1 and 2 Intervention schools included the following:

- 1 class set of skipping ropes
- Playground balls
- Exercise bands
- Strength grippers
- Teaching resources (e.g. Action Pages!, Great Gator Games Book among others)
- Playground chalk
- Energy Blasts Video/DVD
- Fit Kids Workout Video/DVD
- Jump 2bFit (video/manual/CD)
- Action Schools! BC Head-to-Toe Stretch Poster

Action Schools! Bc

Action Schools! BC

Bounce-at-the-Bell Program



Part of the Classroom Action 15 x 5

Provided by: UBC Evaluation Team
Principal Investigator: Dr. Heather McKay

...providing more opportunities for more children to be more physically active more often

Bounce-at-the-Bell Program

What is Bounce-at-the-Bell?

Bounce-at-the-Bell is a physical activity program in which children do a series of jumps everyday contributing to the Healthy Bones outcome of Action Schools! BC.

Why should our class do Bounce-at-the-Bell?

Many children regularly receive the physical benefits of running, but less frequently experience the benefits of extra loads on their skeletons through jumping. The Bounce-at-the-Bell program is designed to help children build strong skeletons during their formative years and reduce the risk of osteoporotic fractures later in life. Initial results from a previous research project indicated positive benefits from an 8-month, school based jumping program.

How and when should our class bounce?

Included in this resource are descriptions and diagrams of four different types of jumps suitable for Bounce-at-the-Bell. Use these jumps to meet your daily jumping goals as part of your Classroom Action 15 x 5 (see Appendix D).

Tip: Your class may choose to jump at the morning, recess and lunch bells, although there is no set formula. Make a class-jumping schedule to match your teaching schedule and have fun jumping!

How many times should we bounce per session?

The AS! BC pilot requires that students follow the progression chart provided for the months of October to May. Initially your students will begin with 5 jumps, 3 times per day, 4 days per week. Each month another jump will be added to the session so that in May your students have reached 36 jumps per day.

What should our class do after we bounce?

At the end of each day they jump, ask the children to record the date and the number of bells (times) they jumped. Children can record this information in their school agendas. After each weekly session of Bounce-at-the-Bell, record when your class jumped in the AS! BC Weekly Activity Log as part of your Classroom Action 15 x 5.

How does Bounce-at-the-Bell fit into the AS! BC pilot?

Students who participate in the AS! BC pilot will have their bone density measured at Vancouver General Hospital twice during the 18-month pilot. These measurements will assess the bone status, and growth, and also physical performance in jumping tasks. The goal is to explore the relationship between physical activity interventions, such as Bounce-at-the-Bell, and calcium nutrition in the prevention of osteoperosis.

AS! BC Pilot 2003-2004

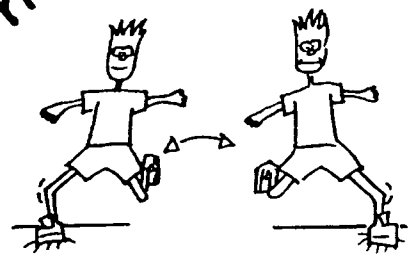
Action Tips for Bounce-at-the-Bell:

1. Jump 5 times, 3 times a day, 4 times a week!
2. Add 1 jump each month according to the Bounce-at-the-Bell Progression chart.
3. Please choose 1 of the 4 jumping options – research does not tolerate deviations.
4. If your students are doing single-leg landings (such as Disco Dancer and Terrific Triathlete) then the number of jumps must be doubled in order to achieve the correct total of landings per leg (see chart).
5. When recording Bounce-at-the-Bell in your Weekly Activity Log, please record the number of jumping sessions under "Frequency" and the number of jumps per session under "Duration". If your class chooses to be creative and do a variation of the jumps, please note this under "Comments".

Month	# of two-foot landing jumps (Jumping Jack Flash or Leapin' Lizards at each bell	# of one-foot landing jumps (Terrific Triathlete or Disco Dancer) at each bell	# jumping sessions per day	Total # of jumps per leg
October	5	10 (5 per leg)	3	15
November	6	12 (6 per leg)	3	18
December	7	14 (7per leg)	3	21
January	8	16 (8 per leg)	3	24
February	9	18 (9 per leg)	3	27
March	10	20 (10 per leg)	3	30
April	11	22 (11 per leg)	3	33
May	12	24 (12 per leg)	3	36

...providing more opportunities for more children to be more physically active more often

Terrific Triathletes



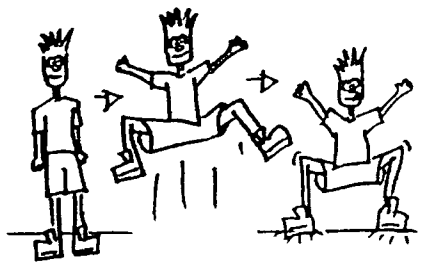
Starting Position:
- Stand with feet shoulder width apart

Action:
- Jump from side to side with full power
- Swing arms in rollerblading style

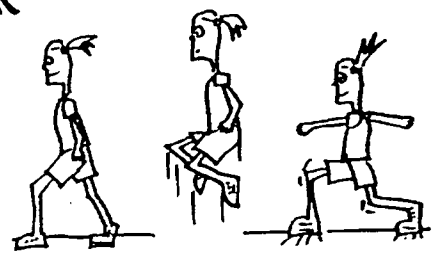
Jumping Jack Flash

Starting Position:
- Stand with feet together

Action:
- Jump with knees together, bringing them up as high as possible
- Bring arms over head and clap



Leapin' Lizards



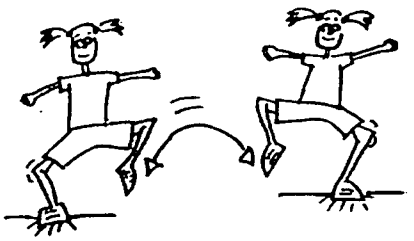
Starting Position:
- Stand with legs together
- Hands at side

Action:
- Jump into tuck position
- Land in scissor step with legs bent

Disco Dancers

Starting Position:
- Stand with one leg up and bent

Action:
- Jump from leg on floor to other leg
- Repeat on initial standing leg
- Get "air"!!



Appendix E: Activity Logs

Action Schools! BC

AS! BC Weekly Activity Log

send to info@actionschoolsbc.ca

School/SD#: INTERVENTION (LEVEL 1/2)

Teacher: _____

Grade: _____ Division: _____

Week of: _____

MONDAY	FREQ	DUR	TUESDAY	FREQ	DUR	WEDNESDAY	FREQ	DUR	THURSDAY	FREQ	DUR	FRIDAY	FREQ	DUR
Scheduled PE:			**Scheduled PE:**			**Scheduled PE:**			**Scheduled PE:**			**Scheduled PE:**		
Classroom Action:			**Classroom Action:**			**Classroom Action:**			**Classroom Action:**			**Classroom Action:**		
☐ B@Bell			☐ B@Bell			☐ B@Bell			☐ B@Bell			☐ B@Bell		
☐ Skipping			☐ Skipping			☐ Skipping			☐ Skipping			☐ Skipping		
☐ Classroom Workout			☐ Classroom Workout			☐ Classroom Workout			☐ Classroom Workout			☐ Classroom Workout		
☐ Energy Blasts			☐ Energy Blasts			☐ Energy Blasts			☐ Energy Blasts			☐ Energy Blasts		
☐ Timed Running			☐ Timed Running			☐ Timed Running			☐ Timed Running			☐ Timed Running		
☐ Playground Fitness			☐ Playground Fitness			☐ Playground Fitness			☐ Playground Fitness			☐ Playground Fitness		
☐ Grippers			☐ Grippers			☐ Grippers			☐ Grippers			☐ Grippers		
☐ Exercise Bands			☐ Exercise Bands			☐ Exercise Bands			☐ Exercise Bands			☐ Exercise Bands		
☐ Head to Toe W-Up			☐ Head to Toe W-Up			☐ Head to Toe W-Up			☐ Head to Toe W-Up			☐ Head to Toe W-Up		
☐ Tag			☐ Tag			☐ Tag			☐ Tag			☐ Tag		
☐ Playground Games			☐ Playground Games			☐ Playground Games			☐ Playground Games			☐ Playground Games		
☐ 5-TODAY Nutrition			☐ 5-TODAY Nutrition			☐ 5-TODAY Nutrition			☐ 5-TODAY Nutrition			☐ 5-TODAY Nutrition		
OTHER ZONES			**OTHER ZONES**			**OTHER ZONES**			**OTHER ZONES**			**OTHER ZONES**		

COMMENTS:

Action Schools! BC

AS! BC
Weekly Activity Log

Use this form to record physical education programming and daily class physical activities. See "How To" on reverse for more information about how to complete the log correctly.

When completed, please send this log our way!
AS! BC Support Team:
email info@actionschoolsbc.ca

School: USUAL PRACTICE (CONTROL)
SD#: _____
Teacher: _____
Grade: _____
Division: _____
Week of: _____

Day of Week	# of Students	Physical Activity*	Frequency	Duration	Comments
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					

Appendix F: Questionnaires

ID: _____

Action Schools! BC
Personal Data Form – Winter 2003

NAME:_____ TODAY'S DATE:_____

AGE:_____ BIRTHDATE:_____ GENDER: (circle one) MALE FEMALE

SCHOOL:_____ GRADE:_____ TEACHER:_____

ADDRESS: _____ CITY: _____

POSTAL CODE: _____ PHONE NUMBER: _____

MOTHER'S NAME: _____ FATHER'S NAME: _____

DO YOU HAVE A COMPUTER AT HOME? (circle one) YES NO DO YOU USE EMAIL? (circle one) YES NO

EMAIL ADDRESS_____

DURING THIS SCHOOL YEAR:

DID YOU BREAK ANY BONES? (circle one) (YES / NO) WHICH BONE(S)? _____

HOW LONG WAS IT IN A CAST? _____

WERE YOU SICK FOR GREATER THAN A MONTH? ((circle one) YES / NO)

WHAT DID YOU HAVE?_____

WERE YOU IN THE HOSPITAL? (circle one) YES / NO) FOR HOW LONG? _____

ANTHROPOMETRY, JUMPS, pQCT and DXA:

MEASURERS: Anthro:_____ Jumps: _____

HEIGHT:	_____	_____	_____
WEIGHT:	_____	_____	_____
SITTING HEIGHT:	_____	_____	_____
CALF GIRTH:	_____	_____	_____
LONG JUMP:	_____	_____	_____

VERTICAL JUMP: - Jump-standing difference

SH 1_____	SH 2_____	SH 3_____
Jump1_____	Jump 2____	Jump 3____

pQCT: _____ DXA: _____

Name: _____

ID: _____
Checked by: _____

Action Schools! BC
Physical Activity Questionnaire

We would like to know about the physical activity you have done in the last 7 days. This includes sports or dance that make you sweat or make your legs feel tired, or games that make you huff and puff, like tag, skipping, running, and climbing.

Remember:

A. There are no right or wrong answers – this is not a test.

B.. Please answer all questions as honestly and accurately as you can – this is very important.

---

1. PHYSICAL ACTIVITY IN YOUR **SPARE TIME (this does not include P.E classes)**.
Have you done any of the following activities in the **past 7 days**? If yes, how many times and for how long?
(Remember, **recess is 15 minutes long, and lunch is usually ½ an hour** (30 minutes)).

Tick only one circle per row	No	1-2	3-4	5-6	7 or more times	time per session
Skipping	O	O	O	O	O	_____
Four Square	O	O	O	O	O	_____
Creative Playground	O	O	O	O	O	_____
Tag	O	O	O	O	O	_____
Walking for exercise	O	O	O	O	O	_____
Bicycling	O	O	O	O	O	_____
Jogging or running	O	O	O	O	O	_____
Swimming	O	O	O	O	O	_____
Baseball, softball	O	O	O	O	O	_____
Dance	O	O	O	O	O	_____
Football	O	O	O	O	O	_____
Badminton	O	O	O	O	O	_____
Skateboarding/Scooter	O	O	O	O	O	_____
Soccer	O	O	O	O	O	_____
Street Hockey	O	O	O	O	O	_____
Volleyball	O	O	O	O	O	_____
Floor Hockey	O	O	O	O	O	_____
Basketball	O	O	O	O	O	_____
Ice skating	O	O	O	O	O	_____
Cross-country skiing	O	O	O	O	O	_____
Ice hockey/ringette	O	O	O	O	O	_____
Martial Arts	O	O	O	O	O	_____
Gymnastics	O	O	O	O	O	_____
Rollerblading	O	O	O	O	O	_____
Skiing/Snowboarding	O	O	O	O	O	_____
Other: _____	O	O	O	O	O	_____

2. In the last 7 days, during your **PHYSICAL EDUCATION (PE) CLASSES**, how often were you very active (playing hard, running, jumping and throwing)? Check only one.

- O I don't do PE
- O Hardly ever
- O Sometimes
- O Quite often
- O Always

3. In the last 7 days, what did you do most of the time at **RECESS?** Check only one.

- O Sat down (talking, reading, doing school work)
- O Stood around or walked around.
- O Ran or played a little bit.
- O Ran around and played quite a bit.
- O Ran and played hard most of the time.

4. In the last 7 days, what did you normally do **AT LUNCH** (besides eating lunch)? Check only one.

- O Sat down (talking, reading, doing school work)
- O Stood around or walked around.
- O Ran or played a little bit.
- O Ran around and played quite a bit.
- O Ran and played hard most of the time.

5. In the last 7 days, on how many days **RIGHT AFTER SCHOOL**, did you do sports, dance, or play games in which you were very active? Check only one.

- O None.
- O 1 time last week.
- O 2 or 3 times.
- O 4 times last week.
- O 5 times last week.

6. In the last 7 days, on how many **EVENINGS** did you do sports, dance, or play games in which you were very active? Check only one.

- O None.
- O 1 time last week.
- O 2 - 3 times.
- O 4 - 5 times last week.
- O 6 - 7 times last week.

7. How many times did you do sports, dance, or play games in which you were very active **LAST WEEKEND?** Check only one.

- O None.
- O 1 time.
- O 2 - 3 times.
- O 4 - 5 times.
- O 6 or more times.

8. Which **ONE** of the following five statements describes you best for the last 7 days? Read all 5 before deciding on the one answer that describes you.

- O All or most of my free time was spent doing things that involved **little physical effort** (e.g. watching TV, homework, playing computer games, Nintendo).
- O **I sometimes (1-2 times last week) did physical things** in my free time (e.g. played sports went running, swimming, bike riding, did aerobics).
- O **I often (3-4 times last week) did physical things** in my free time.
- O **I quite often (5-6 times last week) did physical things** in my free time.
- O **I very often (7 or more times last week) did physical things** in my free time.

9. How many hours per day did you watch television or play video games (Playstation, X-Box) or computer games last week? (each show is usually a half hour or 30 minutes). Check only one.

- O I watched/played less than 1 hour or have no TV (or no video/computer games).
- O I watched/played more than 1 hour but less than 2.
- O I watched/played more than 2 hours but less than 3.
- O I watched/played more than 3 hours but less than 4.
- O I watched/played more than 4 hours.

10. Were you sick last week, or did anything prevent you from doing your normal physical activities?

- O Yes
- O No

If yes, what prevented you?_____

11. Mark how often you did physical activity (like playing sports, games, doing dance or any other physical activity) for each day last week (this includes P.E, lunch, recess, after school, evenings, spare time, etc). **Circle the days that you had P.E. during the last week.**

	None	Little Bit	Medium	Often	Very Often
Monday	O	O	O	O	O
Tuesday	O	O	O	O	O
Wednesday	O	O	O	O	O
Thursday	O	O	O	O	O
Friday	O	O	O	O	O
Saturday	O	O	O	O	O
Sunday	O	O	O	O	O

12. Do you participate in **organized sport** (soccer, dance, karate etc.) outside of school?

- O Yes
- O No

13. Do you participate in other **organized activities** (music lessons, Chinese school tutoring, girl guides, boy scouts) outside of school?

- O Yes
- O No

14. If you do participate in organized sport or other activities, how many nights during the week do you do these sports and/or activities? (If you have swimming lessons on 2 nights of the week, check the circle beside "2" and write swimming lessons on the line. You can have more than one activity on a line).

SPORTS	OTHER ACTIVITIES
O 1 _____	O 1 _____
O 2 _____	O 2 _____
O 3 _____	O 3 _____
O 4 _____	O 4 _____
O 5 _____	O 5 _____
O 6 _____	O 6 _____
O 7 _____	O 7 _____

15. During the last 7 days, on how many days did you **travel to school by car or by bus?**

- O None.
- O 1 time last week.
- O 2 or 3 times.
- O 4 times last week.
- O 5 times last week.

16. During the last 7 days, on how many days did you **travel home from school by car or by bus?**

- O None.
- O 1 time last week.
- O 2 or 3 times.
- O 4 times last week.
- O 5 times last week.

17. During the last 7 days, on how many days did you **walk or bike to school?**

- O None.
- O 1 time last week.
- O 2 or 3 times.
- O 4 times last week.
- O 5 times last week.

18. During the last 7 days, on how many days did you **walk or bike home from school?**

- O None.
- O 1 time last week.
- O 2 or 3 times.
- O 4 times last week.
- O 5 times last week.

19. If you walk to and from school, how long does it take you? _____minutes

20. If you bike to and from school, how long does it take you? _____minutes

THANK YOU!

ID:
Checked by:

Food Frequency Questionnaire

Name:_____ 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				

	Per day	Per week	Per month	Don't eat
Yogurt, small (174 ml) carton or equivalent				
Canned salmon or sardines with bones, ½ small can				
Soft drink, 1 can or large glass				
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!

Action Schools! BC

Self Assessment of Maturity Status: Boys

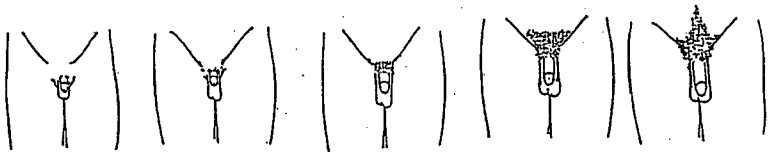
As you keep growing over the next few years, you will see changes in your body. These changes happen at different ages for different children, and you may already be seeing some changes, others may have already gone through some changes. Sometimes it is important to know how a person is growing without 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.

Action Schools! BC - Winter 2003 Name:

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

1 _____ 2 _____ 3 _____ 4 _____ 5 _____



1	2	3	4	5
There is no pubic hair at all.	There is a small amount of long, lightly coloured hair. This hair may be straight or a little curly.	There is hair that is darker, curlier and thinly spread out to cover a somewhat larger area than in stage 2.	The hair is thicker and more spread out, covering a larger area than in stage 3.	The hair now is widely spread and covering a large area, like that of an adult male.

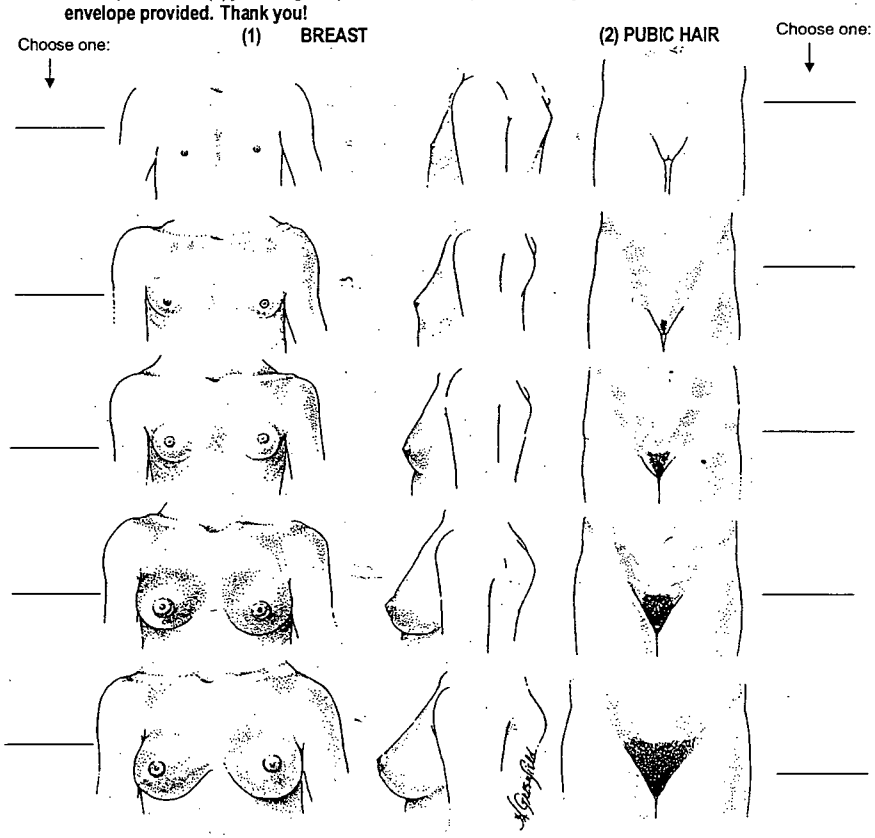
Action Schools! BC

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.

Action Schools! BC - Winter 2003 Name: _____

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!



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

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

THANK YOU.

Appendix G: Results for Study Participants

Action Schools! BC 2003 - 2004

Results for:

Table 1

	Test Date	Age	Height (cm)	Weight (kg)	Long Jump (cm)	Vertical Jump (cm)	Calcium (mg/day)	Physical Activity Score	Steps per Day (Pedometer)
Winter 2003	February 27	10.6	144.8	32.0	146.1	34.3	797	2.8	
Spring 2004	April 22	11.8	150.6	35.4	210.4	34.3	1106	2.5	16086

Table 2

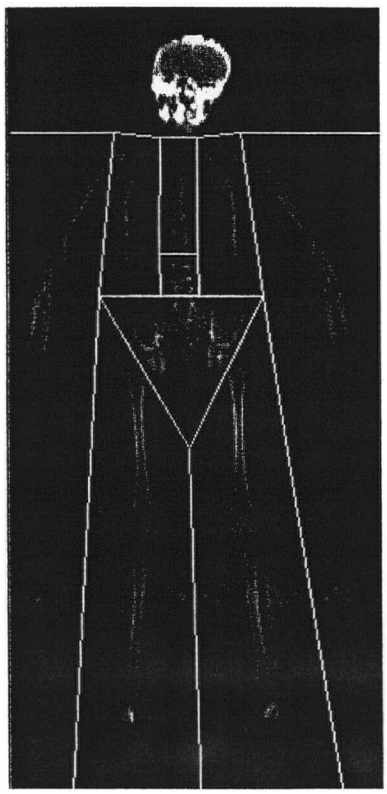
Boys' Averages

	Winter 2003	Spring 2004
Number of Subjects	258	226
Average Age	10.2	11.4 yrs
Average Height	141.3	148.1 cm
Average Weight	38.0	44.0 cm
Average Long Jump	132.7	141.4 cm
Average Vertical Jump	27.7	31.3 cm
Average Calcium	947	884 mg/day
Average Physical Activity	2.6	2.8
Average Steps per Day	10808	10964

Table 1 shows some of your physical changes that we assessed during last year's measurements. Table 2 shows the averages for a large population of healthy children of the same age and sex. There is tremendous variation in the rate and timing of children's growth at this age. Be assured that for a measurement to fall outside of average is not unusual and may simply indicate that you are either an early or a late maturing person. If your growth spurt begins early, your height would be above the average. If you have not yet started your growth spurt, your height would be below the average.

The physical activity score is from a questionnaire that measured moderate to vigorous activity in the past 7 days. Physical activity is scored on a 1 to 5 scale where 1 represents a low activity level and 5 a high activity level. If you were sick or missed participating in your normal activities at the time of the assessment, the value might be low. Pedometers were worn for an average of 4 days at both testing sessions. If you do not have a value for one of the testing sessions, you may have been away when the pedometers were given out. Children at this age are recommended to take between 10,000 and 12,000 steps per day. Calcium intake averaged 892 mg/day across all children at Winter 2003 testing and 822 mg/day at Spring 2004 testing. The daily recommended intake for 11 - 13 year old children is 1300 mg/day.

Action Schools! BC 2003 - 2004



	Your total body bone mass (grams)	Boys' Averages	
Winter 2003	1066	Winter 2003	1080
Spring 2004	1205	Spring 2004	1256

This image of your skeleton is from the DXA scan that was performed in our laboratory. From this scan we were able to measure the amount of bone in your skeleton, which is your total body bone mass. The numbers below the image show the changes in your skeleton that we assessed during last year's measurements and the averages for children of the same age and sex. Again, there is tremendous variation in skeletal development in this age group of children and this variation is closely related to changes in body size (height).

Thank you very much for being an Action Schools! BC participant! You are an important part of our research team. If you have any questions regarding your results please contact Connie Waterman at
or Dr. Heather McKay at

Appendix H: Intervention Delivery

1.1 Weekly Activity Logs

Teachers at intervention and control schools were asked to complete weekly Activity Logs for the duration of the study period. Since Phase I was only 3 months in duration and was also subject to a seasonal effect (April – June), compliance during Phase I will not be considered for the purpose of this thesis.

During Phase II, the maximum number of weeks for which Activity Logs could be submitted was 32. Teachers began logging their weekly activities during the week of September 29 – October 3, 2003 and ended logging at the end of the week of May 25 - 28, 2003. The weeks of December 22 – 26, December 29, 2003 – January 2, 2004 and March 15 – 19, 2004 were not included because schools were on Christmas holidays and Spring Break.

Median compliance with Activity Logs was 97% [interquartile range (IQR): 89 – 100%] across control schools and 94% (IQR: 92 – 100%) across intervention schools (Table 1). One intervention teacher chose not to participate in AS! BC; however, those children in her class with consent returned for followup. The difference between intervention and control schools for minutes of physical activity delivered was determined using a mixed linear model (group = fixed effect; school = random effect). After accounting for clustering, teachers at intervention schools delivered approximately 60 minutes more physical activity per week than teachers at control schools (+58.9 min/wk; 95% CI: 25.4 to 92.4) (Table 1, Figure 1). The intraclass correlation coefficient (ICC) for minutes delivered was 0.18. A summary of the types of activities reported by teachers at control and intervention schools is presented (Figure 2).

Table 1. Number of Activity Logs submitted and average minutes of physical activity delivered by teachers at Control (CON) and Intervention (INT) schools during Phase I (April – June 2003) and Phase II (October 2003 – May 2004). The number of students with consent in each class is provided. Intervention schools 1-4 are Level 1 and 5-7 are Level 2.

	PHASE I				*PHASE II*			
School	**Teacher ID**	**Number of Logs**	**Minutes per week Mean (range)**	**Number of students**	**Teacher ID**	**Number of Logs (%)**	**Minutes per week Mean (range)**	**Number of students**
CON - 1	1	7	84.3 (40.0 – 120.0)	12	58	32 (100)	95.2 (40.0 – 310.0)	6
	2	9	158.9 (40.0 – 280.0)	7	59	32 (100)	87.9 (40.0 – 310.0)	4
	3	9	125.3 (60.0 – 250.0)	5	60	32 (100)	106.3 (40.0 – 260.0)	4
					61	31 (97)	78.9 (30.0 – 255.0)	4
CON - 2	17	9	235.0 (70.0 – 360.0)	8	76	32 (100)	70.2 (35.0 – 150.0)	7
	18	7	311.6 (155.0 – 480.0)	18	77	24 (75)	99.0(40.0 – 335.0)	8
	19	5	259.0 (40.0 – 730.0)	4	78	31 (97)	100.5 (40.0 – 330.0)	10
	20	10	151.5 (45.0 – 400.0)	7	79	17 (53)	74.4 (0.0 – 170.0)	6
	21	11	145.9 (40.0 – 350.0)	16	80	27 (84)	69.1 (20.0 – 160.0)	14
CON - 3	22	8	140.0 (90.0 – 260.0)	6	81	24 (75)	86.5 (40.0 – 130.0)	12
	23	6	175.0 (80.0 – 270.0)	8	82	31 (97)	87.1 (40.0 – 380.0)	8
	24	4	162.5 (120.0 – 250.0)	14	83	29 (91)	85.5 (40.0 – 170.0)	13
	25	7	117.1 (40.0 – 200.0)	24	84	31 (97)	119.2 (15.0 – 305.0)	12
	26	8	117.5 (30.0 – 180.0)	22	85	32 (100)	105.3 (40.0 – 250.0)	5
	27	8	139.4 (40.0 – 245.0)	4	86	31 (97)	88.1 (40.0 – 200.0)	12
					87	32 (100)	97.5 (40.0 – 300.0)	2

Table 1 Continued	*PHASE I*				*PHASE II*			
School	**Teacher ID**	**Weeks with logs**	**Minutes per week**	**Number of students**	**Teacher ID**	**Weeks with logs (%)**	**Minutes per week**	**Number of students**
INT - 1	4	12	236.7 (150.0 – 345.0)	9	62	32 (100)	156.7 (95.0 – 230.0)	12
	5	12	158.8 (60.0 – 255.0)	20	63	32 (100)	243.8 (100.0 – 425.0)	18
	54	11	117.5 (60.0 – 240.0)	8				
INT - 2	12	8	226.9 (90.0 – 420.0)	15	71	32 (100)	205.5 (120.0 – 322.5)	7
	13	3	168.3 (165.0 – 170.0)	11	72	31 (97)	180.6 (120.0 – 300.0)	11
	14	4	260.0 (205.0 – 365.0)	17	73	31 (97)	150.8 (60.0 – 235.0)	8
	15	5	169.8 (120.0 – 234.0)	8	74	25 (78)	140.4 (0.0 – 370.0)	13
					75	30 (94)	124.7 (40.0 – 280.0)	6
INT - 3	35	6	120.0 (85.0 – 195.0)	7	93	32 (100)	118.1 (30.0 – 280.0)	3
	36	8	239.5 (139.0 – 390.0)	12	95	32 (100)	114.8 (50.0 – 300.0)	3
	38	9	241.0 (85.0 – 405.0)	11	96	32 (100)	111.9 (35.0 – 370.0)	3
	51	6	148.3 (55.0 – 310.0)	6	97	30 (94)	121.3 (35.0 – 310.0)	7
					98	28 (88)	107.1 (45.0 – 235.0)	9
					99	32 (100)	91.1 (30.0 – 220.0)	6
INT - 4	47	4	186.8 (110.0 – 315.0)	15	105	32 (100)	239.7 (0 – 472.5)	6
	48	9	67.5 (37.5 – 215.0)	14	106	28 (88)	138.4 (30.0 – 270.0)	20
	49	9	237.2 (125.0 – 570.0)	16	107	30 (94)	131.1 (45.0 – 215.0)	15
	50	7	142.2 (46.0 – 274.0)	19	108	32 (100)	189.4 (80.0 – 295.0)	11
					109	32 (100)	104.6 (32.5 – 257.5)	7

Table 1 Continued	*PHASE I*				*PHASE II*			
School	**Teacher ID**	**Weeks with logs**	**Minutes per week**	**Number of students**	**Teacher ID**	**Weeks with logs (%)**	**Minutes per week**	**Number of students**
INT - 5	6	2	80	7	65	0 (0)	0	10
	7	9	159.0 (70.0 – 311.3)	8	66	28 (88)	129.2 (45.0 – 265.0)	8
	8	9	225.4 (12.0 – 1350.0)	10	67	29 (91)	141.4 (75.0 – 247.5)	8
	11	9	120.9 (40.0 – 275.0)	9	68	30 (94)	113.9 (40.0 – 220.0)	6
	10	0	0	13	69	28 (88)	160.6 (85.0 – 270.0)	3
					70	30 (94)	149.1 (90.0 – 270.0)	5
INT - 6	29	10	227.0 (100.0 – 450.0)	5	88	25 (78)	99.8 (40.0 – 247.5)	4
	30	12	217.9 (118.0 – 339.0)	23	89	30 (94)	146.8 (45.0 – 305.0)	18
	32	10	157.6 (86.0 – 255.0)	18	90	32 (100)	150.1 (82.5 – 282.5)	18
	33	10	175.0 (70.0 – 280.0)	23	91	30 (94)	116.7 (40.0 – 230.0)	20
	53	10	215.0 (110.0 – 400.0)	25	92	32 (100)	117.3 (40.0 – 235.0)	20
INT - 7	44	8	233.1 (120.0 – 415.0)	16	100	30 (94)	152.7 (42.5 – 335.0)	4
	45	8	195.5 (130.0 – 462.0)	14	101	28 (88)	129.3 (10.0 – 220.0)	5
					102	30 (94)	150.6 (23.5 – 235.0)	7
					103	32 (100)	137.7 (23.5 – 255.0)	7
					104	32 (100)	165.8 (80.0 – 300.0)	4

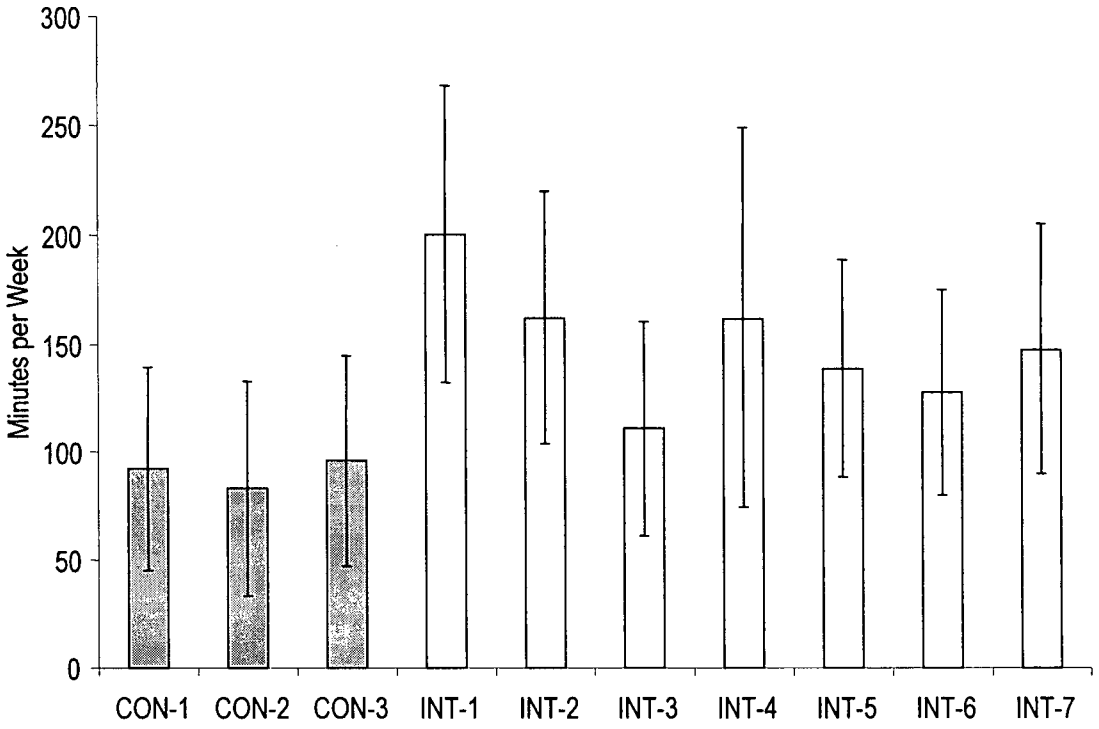


Figure 1. Mean number of minutes per week of physical activity as reported in Activity Logs by teachers at Control (CON) and Intervention (INT) schools during Phase II. Bars represent standard deviation.

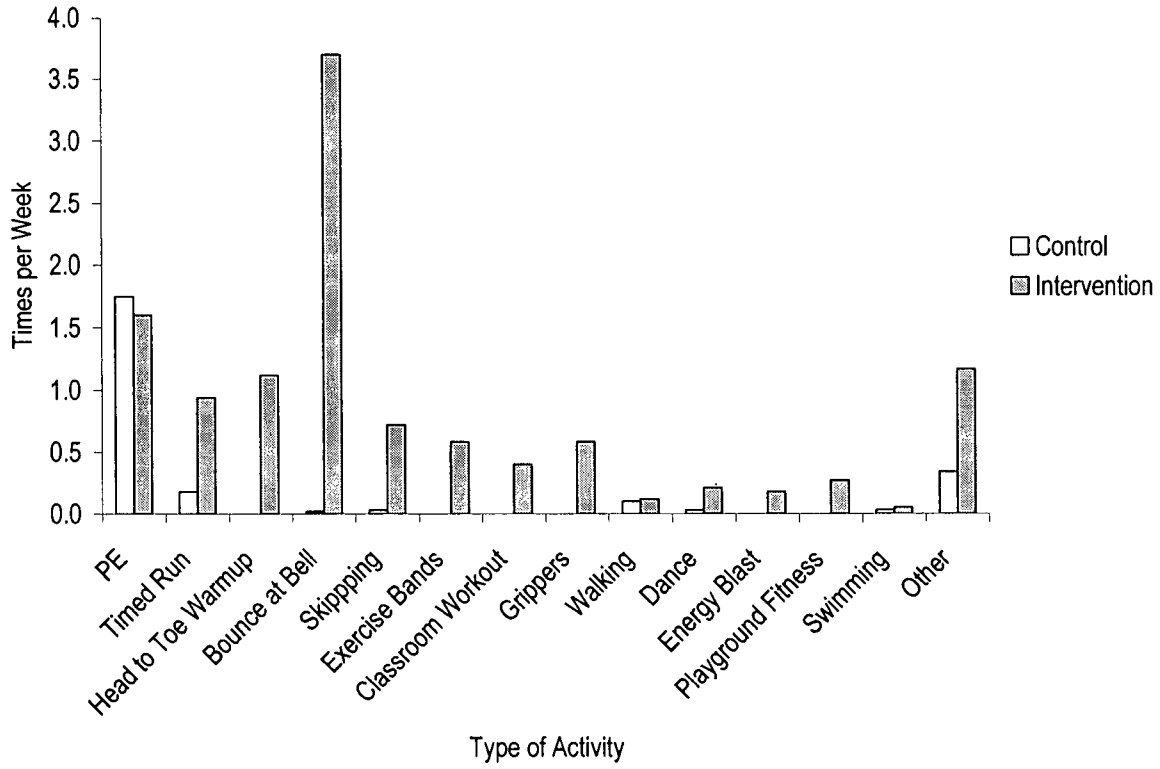


Figure 2. Average frequency of activities performed in Control and Intervention schools during Phase II.

1.2 Bounce at the Bell

Delivery of Bounce at the Bell across intervention schools during Phase II is summarized in Table 2 and Figure 3. Compliance was assessed according to four criteria: 1) *weeks with Bounce at the Bell* (maximum = 32), 2) *number of days with Bounce at the Bell* (4 days/week for 32 weeks = 128 days), 3) *number of sessions of Bounce at the Bell* (3 times/day, 4 days/week for 32 weeks = 384 sessions) and 4) *number of jumps* (3 times/day, 4 times/week, progressing from 5 jumps per session to 12 jumps per session over the 8 month period = 3264 jumps). Median compliance for each of these criteria was as follows:

- Criteria 1 (weeks): median = 94% (IQR: 82 to 97)
- Criteria 2 (days): median = 100% (IQR: 81 to 107)
- Criteria 3 (sessions): median = 74% (IQR: 50 to 89)
- Criteria 4 (jumps): median = 94% (IQR: 78 to 106).

For the purposes of the analysis in Parts II and III of this thesis, I report compliance according to criteria 3 (number of sessions). Compliance with Bounce at the Bell sessions across intervention schools is illustrated in Figure 3 and the distribution of intervention teachers according to percentage compliance is illustrated in Figure 4.

Table 2. Compliance with Bounce at the Bell (B@B) across intervention (INT) schools. Values presented as total and percent (%) of maximum.

School	Teacher ID	Weeks with logs (%)[a]	Weeks with B@B (%)[b]	Days with B@B (%)[c]	Sessions of B@B (%)[d]	Total Jumps (%)[e]
INT - 1	62	32 (100)	27 (84)	112 (88)	336 (88)	3471 (106)
	63	32 (100)	31 (97)	143 (112)	429 (112)	4257 (130)
INT - 2	71	32 (100)	32 (100)	148 (116)	378 (98)	3300 (101)
	72	31 (97)	31 (97)	145 (113)	349 (91)	3039 (93)
	73	31 (97)	20 (63)	81 (63)	184 (48)	1884 (58)
	74	25 (78)	22 (69)	94 (73)	258 (67)	3058 (94)
	75	30 (94)	30 (94)	139 (106)	399 (104)	3462 (106)
INT - 3	93	32 (100)	16 (50)	34 (27)	34 (9)	636 (19)
	95	32 (100)	31 (97)	128 (100)	347 (90)	3314 (102)
	96	32 (100)	32 (100)	103 (80)	227 (59)	1229 (38)
	97	30 (94)	30 (94)	124 (97)	310 (81)	2738 (84)
	98	28 (88)	25 (78)	77 (60)	212 (55)	2184 (67)
	99	32 (100)	26 (81)	115 (90)	335 (87)	3295 (101)
INT - 4	105	32 (100)	32 (100)	133 (104)	427 (111)	7212 (221)
	106	28 (88)	21 (66)	67 (52)	123 (32)	1419 (43)
	107	30 (94)	30 (94)	131 (102)	322 (84)	3065 (94)
	108	32 (100)	32 (100)	145 (113)	373 (97)	4014 (123)
	109	32 (100)	31 (97)	114 (89)	254 (66)	2644 (81)
INT - 5	65	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	66	28 (88)	28 (88)	104 (81)	284 (74)	2735 (84)
	67	29 (91)	29 (91)	135 (105)	283 (74)	2702 (83)
	68	30 (94)	30 (94)	132 (103)	328 (85)	3328 (102)
	69	28 (88)	28 (88)	129 (101)	322 (84)	3055 (94)
	70	30 (94)	30 (94)	136 (106)	376 (98)	3079 (94)
INT - 6	88	25 (78)	25 (78)	103 (80)	165 (43)	2113 (65)
	89	30 (94)	29 (91)	108 (84)	108 (28)	2720 (83)
	90	32 (100)	32 (100)	137 (107)	137 (36)	3462 (106)
	91	30 (94)	29 (91)	80 (63)	80 (21)	2118 (65)
	92	32 (100)	0 (0)	0 (0)	0 (0)	0 (0)
INT - 7	100	30 (94)	30 (94)	132 (103)	337 (88)	3480 (107)
	101	28 (88)	28 (88)	105 (82)	116 (30)	2531 (78)
	102	30 (94)	30 (94)	137 (107)	234 (61)	4747 (145)
	103	32 (100)	32 (100)	130 (102)	211 (55)	2091 (64)
	104	32 (100)	30 (94)	111 (87)	223 (58)	3727 (114)

Maximum for: a = 32 weeks; b = 32 weeks; c = 128 days; d = 384 sessions; e = 3264 jumps

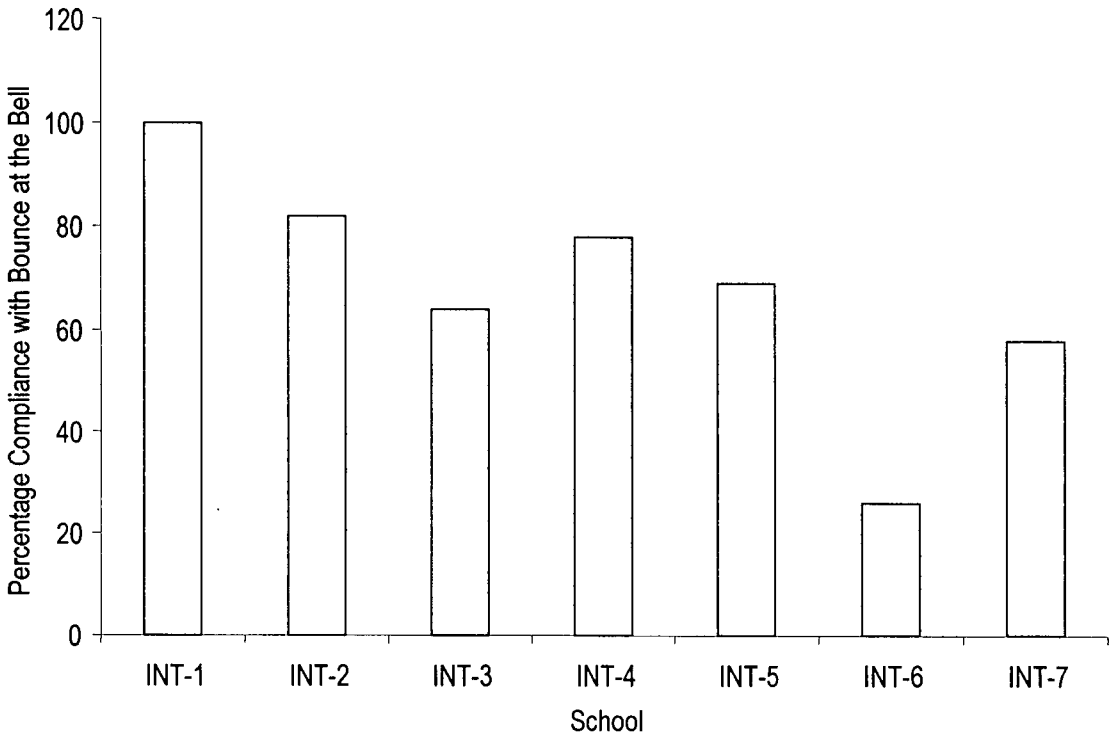


Figure 3. Mean percentage compliance with sessions of Bounce at the Bell during Phase II across Intervention (INT) schools.

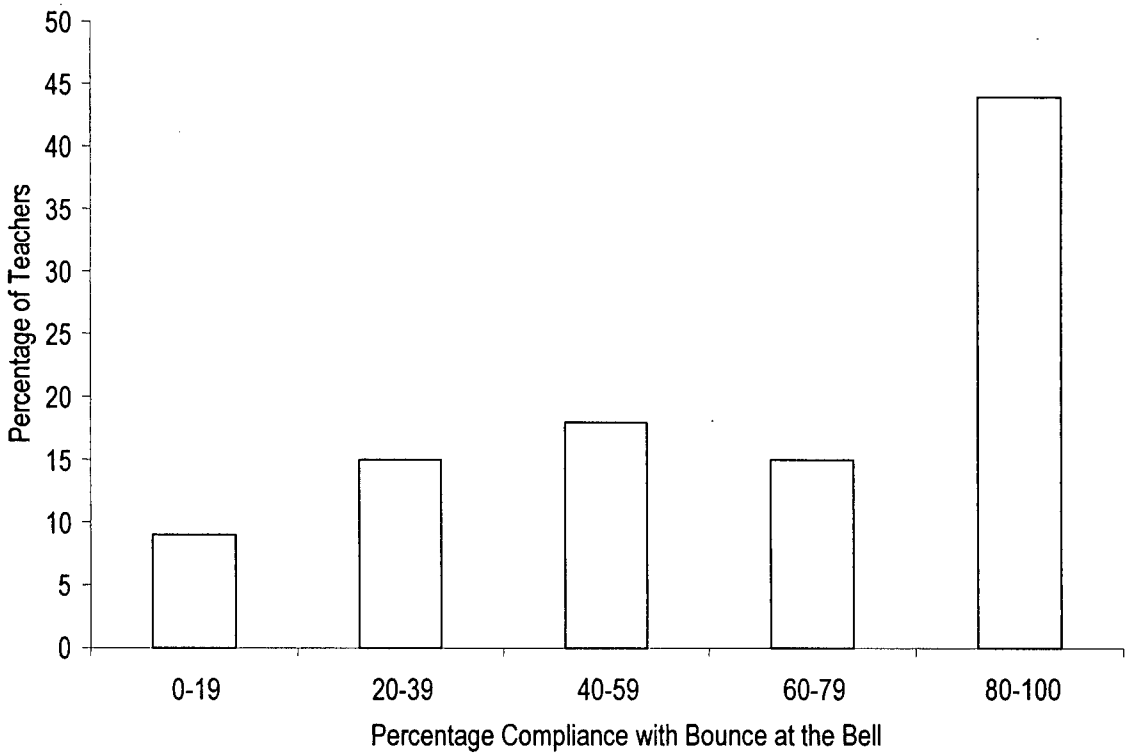


Figure 4. Distribution of Intervention teachers according to percentage compliance with Bounce at the Bell sessions during Phase II.

Appendix I: Additional Data for Chapter 5

Table 1. BOYS: Pearson correlations of age, anthropometric variables (and their changes), change in jump performance, physical activity and dietary calcium with 16-month *change* in total bone area (ToA), total bone mineral density (ToD) and bone strength index (BSI) at the distal tibia (8% site) and cortical bone area (CoA), cortical density (CoD), polar strength strain index (SSI_p) and strength strain index in the x- and y-bending planes (SSI_x, SSI_y) at the tibial midshaft (50% site) for boys (n = 211). Bivariate correlations with Tanner stage were determined using Spearman's rank correlation.

	Distal tibia			**Midshaft**					
	ToA	ToD	BSI	ToA	CoA	CoD	SSI_p	SSI_x	SSI_y
Age	0.14*	0.11	0.19**	0.26**	0.23**	-0.14*	0.27**	0.26**	0.25**
Baseline Tanner Stage	0.15*	0.03	0.12	0.14*	0.16*	-0.21**	0.14*	0.11	0.06
Final Tanner Stage	0.30**	-0.08	0.10	0.23**	0.19**	-0.26**	0.24**	0.23**	0.12
Baseline Height	0.30**	0.05	0.19*	0.42**	0.36**	-0.12	0.53**	0.51**	0.43**
Height Change	0.50**	0.07	0.33**	0.54**	0.52**	-0.21**	0.49**	0.48**	0.39**
Baseline Tibia Length	0.33**	0.01	0.18**	0.39**	0.36**	-0.12	0.51**	0.49**	0.41**
Tibia Length Change	0.12	0.12	0.10	0.46**	0.30**	-0.07	0.42**	0.43**	0.28**
Baseline Weight	0.21**	0.003	0.13	0.27**	0.25**	-0.07	0.42**	0.38**	0.42**
Weight Change	0.33**	0.09	0.26**	0.40**	0.33**	-0.11	0.38**	0.35**	0.30**
Baseline MCSA	0.21**	-0.07	0.07	0.27**	0.21**	-0.02	0.32**	0.32**	0.37**
MCSA Change	0.46**	0.14	0.42**	0.41**	0.42**	-0.19**	0.39**	0.39**	0.29**
Baseline ToA (8%)	0.24**	0.10	0.12	0.38**	0.29**	-0.05	0.46**	0.46**	0.41**
Baseline ToD	0.009	-0.19*	0.13	-0.04	0.02	-0.03	-0.05	-0.05	0.05
Baseline BSI	0.16*	-0.11	0.19**	0.23**	0.21**	-0.05	0.27**	0.27**	0.33**
Baseline ToA (50%)	0.28**	0.02	0.19**	0.41**	0.33**	-0.04	0.53**	0.53**	0.47**

Note: Correlations do not account for clustering
* $p < 0.05$; ** $p < 0.01$

Table 1 continued	ToA	ToD	BSI	ToA	CoA	CoD	SSI_p	SSI_x	SSI_y
Baseline CoA	0.24**	0.02	0.22**	0.42**	0.35**	-0.02	0.53**	0.53**	0.48**
Baseline CoD	0.08	-0.11	-0.06	-0.18**	-0.11	-0.15*	-0.14*	-0.14*	-0.06
Baseline SSI_p	0.28**	-0.02	0.17*	0.41**	0.32**	-0.07	0.51**	0.49**	0.44**
Baseline SSI_x	0.27**	-0.001	0.18*	0.42**	0.33**	-0.05	0.54**	0.51**	0.46**
Baseline SSI_y	0.27**	-0.03	0.16*	0.36**	0.28**	-0.06	0.46**	0.42**	0.36**
Long Jump Change	0.05	0.07	0.10	0.09	0.16*	-0.04	0.14*	0.09	0.15*
Vertical Jump Change	-0.02	0.03	0.08	0.10	0.12	0.04	0.10	0.05	0.12
Avg PA Score	0.07	0.03	0.13	0.04	0.12	-0.08	0.11	0.03	0.09
Avg Load Time	0.12	-0.05	0.09	0.02	0.08	-0.07	0.08	0.007	0.11
Avg Dietary Calcium	0.09	-0.004	0.08	0.04	0.12	-0.16*	0.05	0.001	0.03

Note: Correlations do not account for clustering
* $p < 0.05$; ** $p < 0.01$

Table 2. GIRLS: Pearson correlations of age, anthropometric variables (and their changes), change in jump performance, physical activity and dietary calcium with 16-month *change* in total bone area (ToA), total bone mineral density (ToD) and bone strength index (BSI) at the distal tibia (8% site) and cortical bone area (CoA), cortical density (CoD), polar strength strain index (SSI_p) and strength strain index in the x- and y-bending planes (SSI_x, SSI_y) at the tibial midshaft (50% site) for girls (n = 202). Bivariate correlations with Tanner stage were determined using Spearman's rank correlation.

	Distal tibia			**Midshaft**					
	ToA	ToD	BSI	ToA	CoA	CoD	SSI_p	SSI_x	SSI_y
Baseline Age	-0.11	0.24**	0.24**	-0.10	0.03	0.19**	0.04	0.06	0.07
Baseline Tanner Stage	-0.03	0.34**	0.39**	0.05	0.23**	0.23**	0.30**	0.30**	0.29**
Final Tanner Stage	-0.09	0.44**	0.47**	0.09	0.25**	0.25**	0.31**	0.30**	0.28**
Baseline Height	-0.15*	0.40**	0.42**	-0.05	0.16*	0.46**	0.35**	0.32**	0.25**
Height Change	0.58**	-0.06	0.24**	0.63**	0.65**	-0.24*	0.53**	0.50**	0.50**
Baseline Tibia Length	-0.07	0.33**	0.40**	0.02	0.20**	0.38**	0.33**	0.34**	0.23**
Tibia Length Change	0.41**	-0.29**	-0.14	0.50**	0.33**	-0.42**	0.29**	0.27**	0.28**
Baseline Weight	-0.09	0.36**	0.46**	-0.02	0.22**	0.30**	0.38**	0.41**	0.27**
Weight Change	0.39**	0.21**	0.44**	0.43**	0.52**	-0.03	0.44**	0.40**	0.40**
Baseline MCSA	-0.13	0.40**	0.47**	0.07	0.25**	0.33**	0.40**	0.42**	0.29**
MCSA Change	0.44**	0.29**	0.54**	0.46**	0.57**	-0.03	0.49**	0.50**	0.41**
Baseline ToA (8%)	0.02	0.21**	0.26**	0.06	0.20**	0.29**	0.38**	0.33**	0.35**
Baseline ToD	-0.08	0.06	0.31**	0.04	0.11	0.003	0.11	0.13	0.09
Baseline BSI	-0.07	0.18**	0.45**	0.05	0.20*	0.18*	0.31**	0.29**	0.29**
Baseline ToA (50%)	-0.05	0.35**	0.47**	0.07	0.17*	0.31**	0.46**	0.45**	0.38**

Note: Correlations do not account for clustering
* $p < 0.05$; ** $p < 0.01$

Table 2 continued	ToA	ToD Δ	BSI	ToA Δ	CoA	CoD	SSI_p	SSI_x	SSI_y
Baseline CoA	0.07	0.36**	0.51*	0.08	0.19**	0.34**	0.45**	0.47**	0.37**
Baseline CoD	-0.17*	-0.03	-0.12	-0.24**	-0.19**	-0.22**	-0.30**	-0.31**	-0.30**
Baseline SSIp	-0.09	0.36**	0.48**	0.16*	0.17*	0.22**	0.40**	0.39**	0.34**
Baseline SSIx	-0.09	0.36**	0.47**	0.16*	0.17*	0.22**	0.39	0.40**	0.32**
Baseline SSIy	-0.10	0.34**	0.45**	0.16*	0.16*	0.21**	0.40	0.39**	0.32**
Long Jump Change	0.10	0.04	0.09	0.07	0.14	0.03	0.15*	0.19*	0.10
Vertical Jump Change	0.03	0.16*	0.17*	0.11	0.18**	-0.03	0.14*	0.18*	0.15*
Avg PA Score	0.14	-0.05	0.07	0.18*	0.09	-0.04	0.13	0.08	0.10
Avg Load Time	0.16*	0.02	0.19**	0.16*	0.21**	-0.02	0.18*	0.14*	0.20**
Avg Dietary Calcium	0.003	-0.01	0.03	0.003	0.009	0.07	0.06	0.03	0.09

Note: Correlations do not account for clustering
* $p < 0.05$; ** $p < 0.01$

Table 3. BOYS & GIRLS: Intraclass correlation coefficients (ICC) and 95% confidence intervals (CI) for *baseline* total bone cross-sectional area (ToA), total bone mineral density (ToD) and bone strength index (BSI) at the distal tibia and total bone cross-sectional area (ToA), cortical area (CoA), cortical density (CoD), polar strength strain index (SSI_p) and the bending strength strain indices (SSI_x, SSI_y) for boys and girls.

		BOYS		***GIRLS***	
Site	**Outcome**	**ICC**	**CI**	**ICC**	**CI**
Distal	ToA	0.005	(0 - 0.06)	0	(0 - 0.05)
	ToD	0.008	(0 - 0.06)	0.01	(0 - 0.07)
	BSI	0	(0 - 0.05)	0	(0 - 0.05)
Midshaft	ToA	0.002	(0 - 0.05)	0	(0 - 0.05)
	CoA	0.01	(0 - 0.07)	0.005	(0 - 0.06)
	CoD	0	(0 - 0.05)	0.02	(0 - 0.09)
	SSI_p	0	(0 - 0.05)	0	(0 - 0.05)
	SSI_x	0.009	(0 - 0.06)	0	(0 - 0.05)
	SSI_y	0	(0 - 0.04)	0	(0 - 0.05)

Appendix J: Additional Data for Chapter 6

Table 1. BOYS: Pearson correlations of age, anthropometric variables (and their changes), vertical and long jump performance (and their changes), physical activity and dietary calcium with 16-month change (Δ) bone mineral content (BMC) and bone area (BA) of the total body (TB), proximal femur (PF) and lumbar spine (LS) and narrow neck (NN) cross-sectional area (CSA), subperiosteal width (SPW) and section modulus (Z) for boys (n = 213). Correlations with baseline and final Tanner stage are Spearman's rank correlation.

	TB BMC Δ	TB Area Δ	PF BMC Δ	PF Area Δ	LS BMC Δ	LS Area Δ	FN BMC Δ	FN Area Δ	NN CSA Δ	NN SPW Δ	NN Z Δ
Baseline age	0.27**	0.16*	0.42**	0.41**	0.29**	0.15*	0.20**	0.13	0.21**	0.11	0.23**
Baseline Tanner Stage	0.13	0.14*	0.12	0.07	0.12	0.06	0.07	0.03	0.10	-0.06	0.14*
Final Tanner Stage	0.25**	0.22**	0.22**	0.20**	0.19**	0.09	0.19**	0.18**	0.13	0.03	0.20**
Baseline height	0.53**	0.39**	0.49**	0.44**	0.38**	0.25**	0.28**	0.17*	0.29**	0.06	0.36**
Height Δ	0.66**	0.66**	0.69**	0.71**	0.63**	0.58**	0.50**	0.36**	0.53**	0.36**	0.51**
Baseline Sit Height	0.49**	0.36**	0.47**	0.40**	0.35**	0.23**	0.21**	0.11	0.24**	0.05	0.30**
Sit Height Δ	0.44**	0.49**	0.47**	0.50**	0.47**	0.43**	0.36**	0.25**	0.37**	0.29**	0.38**
Baseline Leg Length	0.48**	0.37**	0.43**	0.40**	0.33**	0.22**	0.29**	0.20**	0.27**	0.08	0.36**
Leg Length Δ	0.47**	0.42**	0.48**	0.48**	0.41**	0.36**	0.33**	0.24**	0.36**	0.20**	0.32**
Baseline Weight	0.39**	0.27**	0.44**	0.32**	0.34**	0.21**	0.21**	0.07	0.24**	0.02	0.28**
Weight Δ	0.46**	0.57**	0.34**	0.27**	0.25**	0.17*	0.37**	0.21**	0.37**	0.26**	0.37**
Baseline Lean Mass	0.52**	0.34**	0.53**	0.41**	0.42**	0.26**	0.29**	0.13	0.31**	0.02	0.37**
Lean Mass Δ	0.71**	0.65**	0.74**	0.65**	0.70**	0.56**	0.53**	0.27**	0.60**	0.32**	0.56**
Baseline Fat Mass	0.25**	0.17*	0.32**	0.21**	0.24**	0.15*	0.14*	0.02	0.16*	0.02	0.18**
Fat Mass Δ	-0.04	0.18**	-0.25**	-0.26**	-0.33**	-0.30**	-0.01	0.02	-0.06	0.07	-0.03
Baseline Long Jump	0.02	-0.04	0.007	0.01	0.004	-0.02	0.03	0.05	0.04	-0.06	0.04

Note: Correlations do not account for clustering
* $p < 0.05$; ** $p < 0.01$

Table 1 continued	TB BMC Δ	TB Area Δ	PF BMC Δ	PF Area Δ	LS BMC Δ	LS Area Δ	FN BMC Δ	FN Area Δ	NN CSA Δ	NN SPW Δ	NN Z Δ
Long Jump Δ	0.08	-0.04	0.04	0.001	0.14*	0.17*	0.09	0.001	0.12	0.04	0.04
Baseline Vertical Jump	0.11	-0.02	0.12	0.08	0.12	0.08	0.13	0.06	0.12	-0.02	0.11
Vertical Jump Δ	0.10	0.09	0.12	0.14*	0.07	0.08	0.09	0.03	0.10	-0.03	0.04
Avg PA Score	0.08	-0.03	0.12	-0.01	0.12	0.05	0.17*	0.03	0.18*	-0.03	0.17*
Avg Load Time	0.09	-0.03	0.11	0.004	0.16	0.14	0.14	0.04	0.12	-0.07	0.13
Avg Dietary Calcium	0.13	0.02	0.07	0.01	-0.009	-0.06	0.08	0.05	-0.001	-0.08	0.09
Baseline TB BMC	0.46**	0.24**	0.50**	0.37**	0.37**	0.18**	0.25**	0.11	0.26**	0.03	0.35**
Baseline TB Area	0.47**	0.26**	0.51**	0.40**	0.39**	0.22**	0.27**	0.12	0.28**	0.04	0.35**
Baseline PF BMC	0.48**	0.24**	0.41**	0.23**	0.32**	0.14*	0.25**	0.11	0.25**	-0.01	0.35**
Baseline PF Area	0.50**	0.32**	0.42**	0.31**	0.35**	0.19**	0.28**	0.15*	0.27**	0.02	0.33**
Baseline LS BMC	0.42**	0.22**	0.40**	0.26**	0.28**	0.07	0.25**	0.13	0.27**	-0.04	0.33**
Baseline LS Area	0.42**	0.25**	0.41**	0.32**	0.27**	0.03	0.23**	0.15*	0.24**	0.01	0.30**
Baseline FN BMC	0.33**	0.13	0.33**	0.19**	0.24**	0.11	0.06	-0.03	0.12	-0.09	0.25**
Baseline FN Area	0.41**	0.30**	0.37**	0.34**	0.28**	0.20*	0.09	0.03	0.17*	-0.04	0.27**
Baseline NN CSA	0.33**	0.13	0.35**	0.21**	0.25**	0.12	0.15*	0.06	0.12	-0.09	0.25**
Baseline NN SPW	0.42**	0.32**	0.37**	0.36**	0.30**	0.21**	0.21**	0.22**	0.17*	-0.10	0.28**
Baseline NN Z	0.38**	0.17*	0.40**	0.28**	0.30**	0.16*	0.19**	0.10	0.16*	-0.06	0.24**

Note: Correlations do not account for clustering
* $p < 0.05$; ** $p < 0.01$

Table 2. BOYS: Pearson correlations of baseline and change (Δ) in anthropometric variables, body composition, long and vertical jump performance and 16-month average scores for physical activity score (PA Score), load time and dietary calcium (calc). Correlations with baseline and final Tanner stage are Spearman's rank correlations.

	Height Δ	Sit Height Δ	Leg Length Δ	Tib Length Δ	Weight Δ	MCSA Δ	Lean Mass Δ	Fat Mass Δ	Long Jump Δ	Vertical Jump Δ	Avg PA Score	Avg Load Time	Avg Calc
Baseline age	0.27**	0.14*	0.24**	0.16*	0.09	0.18*	0.33**	-0.21**	-0.01	0.06	0.05	0.13	0.02
Baseline Tanner Stage	0.08	0.03	0.07	0.07	0.05	0.11	0.17*	-0.09	-0.006	-0.15*	0.11	0.09	0.14*
Final Tanner Stage	0.22**	0.14*	0.18**	0.20**	0.12	0.14	0.25**	-0.11	-0.04	-0.03	0.11	0.09	0.12
Baseline height	0.29**	0.12	0.29**	0.26**	0.34**	0.21**	0.44**	0.01	0.05	-0.11	0.13	0.16*	0.13
Height Δ	-----	0.75**	0.63**	0.56**	0.41**	0.68**	0.79**	-0.21**	0.02	0.18*	-0.02	0.009	-0.04
Baseline Sit Height	0.24**	0.05	0.30**	0.18**	0.32**	0.20**	0.42**	0.02	0.02	-0.13	0.09	0.08	0.10
Sit Height Δ	0.75**	------	-0.05	0.36**	0.36**	0.52**	0.58**	-0.09	-0.07	0.03	-0.06	0.004	-0.05
Baseline Leg Length	0.29**	0.17*	0.24**	0.27**	0.30**	0.19**	0.39**	0.02	0.05	-0.09	0.14*	0.19**	0.13
Leg Length Δ	0.63**	-0.05	------	0.43**	0.19**	0.41**	0.50**	-0.20**	0.12	0.23**	0.05	0.007	-0.003
Baseline Tibia Length	0.29**	0.14	0.28**	0.17*	0.36**	0.20**	0.43**	0.05	0.05	-0.11	0.15*	0.21**	0.11
Tibia Length Δ	0.56**	0.36**	0.43**	------	0.20**	0.42**	0.46**	-0.18*	0.05	0.10	0.06	0.001	-0.03
Baseline Weight	0.16*	0.04	0.19**	0.06	0.43**	0.17*	0.43**	0.16*	-0.01	-0.16*	0.04	0.08	0.01
Weight Δ	0.41**	0.36**	0.19**	0.20**	------	0.60**	0.65**	0.71**	-0.09	-0.11	-0.04	-0.03	-0.08
Baseline MCSA	0.14	0.05	0.15*	0.04	0.35**	0.16*	0.37**	0.09	-0.03	-0.05	0.04	0.06	-0.002
MCSA Δ	0.68**	0.52**	0.41**	0.42**	0.60**	------	0.80**	0.06	0.03	0.11	-0.08	-0.02	-0.10
Baseline Lean Mass	0.23**	0.10	0.23**	0.11	0.43**	0.17*	0.47**	0.10	0.02	-0.09	0.10	0.13	0.09
Lean Mass Δ	0.79**	0.58**	0.50**	0.46**	0.65**	0.80**	------	-0.05	0.004	0.08	0.03	0.08	-0.03

Table 2 continued	Height Δ	Sit Height Δ	Leg Length Δ	Tib Length Δ	Weight Δ	MCSA Δ	Lean Mass Δ	Fat Mass Δ	Long Jump Δ	Vertical Jump Δ	Avg PA Score	Avg Load Time	Avg Calc
Baseline Fat Mass	0.09	-0.005	0.14	0.02	0.38**	0.16*	0.35**	0.18**	-0.03	-0.19**	-0.01	0.03	-0.05
Fat Mass Δ	-0.21**	-0.09	-0.20**	-0.18*	0.71**	0.06	-0.05	------	-0.14**	-0.22**	-0.06	-0.08	-0.06
Baseline Long Jump	0.03	0.08	-0.04	-0.11	-0.18**	-0.12	-0.05	-0.19**	-0.20**	0.08	0.02	0.04	0.19**
Long Jump Δ	0.02	-0.07	0.12	0.05	-0.09	0.03	0.004	-0.14*	------	0.11	0.08	0.14*	-0.16*
Baseline Vertical Jump	0.06	0.06	0.02	0.04	-0.13	-0.05	0.05	-0.22**	0.09	-0.26**	0.11	0.15*	0.13
Vertical Jump Δ	0.18*	0.03	0.23**	0.10	-0.11	0.11	0.08	-0.22**	0.11	------	0.08	0.04	0.07
Avg PA Score	-0.02	-0.06	0.05	0.06	-0.04	-0.08	0.03	-0.06	0.08	0.08	------	0.72**	0.33**
Avg Load Time	0.009	0.004	0.007	0.001	-0.03	-0.02	0.08	-0.08	0.14*	0.04	0.72**	------	0.20**
Avg Dietary Calcium	-0.04	-0.05	-0.003	-0.03	-0.08	-0.10	-0.03	-0.06	-0.16*	0.07	0.33**	0.20**	------

Note: Correlations do not account for clustering
* $p < 0.05$; ** $p < 0.01$

Table 3. GIRLS: Pearson correlations of age, anthropometric variables (and their changes), vertical and long jump performance (and their changes), physical activity and dietary calcium with 16-month change (Δ) in bone mineral content (BMC) and bone area (BA) of the total body (TB), proximal femur (PF) and lumbar spine (LS) and narrow neck (NN) cross-sectional area (CSA), subperiosteal width (SPW) and section modulus (Z) for girls (n = 199). Correlations with baseline and final Tanner stage are Spearman's rank correlation.

	TB BMC Δ	TB Area Δ	PF BMC Δ	PF Area Δ	LS BMC Δ	LS Area Δ	FN BMC Δ	FN Area Δ	NN CSA Δ	NN SPW Δ	NN Z Δ
Baseline age	0.30**	0.13	0.27**	0.01	0.32**	0.19**	0.12	0.02	0.17**	-0.10	0.18*
Baseline Tanner Stage	0.47**	0.24**	0.34**	-0.01	0.51**	0.40**	0.30**	0.18**	0.26**	-0.12	0.25**
Final Tanner Stage	0.50**	0.27**	0.42**	0.05	0.53**	0.41**	0.32**	0.10	0.36**	-0.08	0.32**
Baseline height	0.51**	0.23**	0.46**	0.11	0.47**	0.28**	0.33**	0.12	0.37**	-0.08	0.39**
Height Change	0.49**	0.66**	0.53**	0.47**	0.43**	0.53**	0.43**	0.23**	0.43**	0.24**	0.39**
Baseline Sit Height	0.46**	0.19**	0.41**	0.08	0.48**	0.28**	0.30**	0.12	0.35**	-0.07	0.37**
Sit Height Δ	0.47**	0.57**	0.47**	0.38**	0.42**	0.50**	0.36**	0.14*	0.37**	0.20**	0.34**
Baseline Leg Length	0.46**	0.23**	0.43**	0.11	0.38**	0.23**	0.30**	0.10	0.33**	-0.07	0.34**
Leg Length Δ	0.21*	0.34**	0.28**	0.27**	0.17*	0.22**	0.24**	0.19**	0.23**	0.15*	0.21**
Baseline Weight	0.51**	0.19*	0.44**	0.05	0.47**	0.28**	0.42**	0.16*	0.38**	-0.19**	0.35**
Weight Δ	0.52**	0.56**	0.47**	0.19*	0.37**	0.29**	0.50**	0.18*	0.50**	0.07	0.45**
Baseline Lean Mass	0.57**	0.23**	0.49**	0.08	0.56**	0.36**	0.40**	0.14*	0.42**	-0.11	0.41**
Lean Mass Δ	0.65**	0.68**	0.67**	0.38**	0.57**	0.52**	0.62**	0.25**	0.62**	0.16*	0.56**
Baseline Fat Mass	0.36**	0.11	0.32**	0.02	0.33**	0.17*	0.35**	0.15	0.28**	-0.24**	0.24**
Fat Mass Δ	0.07	0.19**	-0.001	-0.08	-0.09	-0.14	0.09	0.008	0.07	-0.04	0.06
Baseline Long Jump	0.10	0.02	0.14	0.02	0.05	0.02	0.02	-0.06	0.08	0.05	0.11

Note: Correlations do not account for clustering
* $p < 0.05$; ** $p < 0.01$

Table 3 Continued	TB BMC Δ	TB Area Δ	PF BMC Δ	PF Area Δ	LS BMC Δ	LS Area Δ	FN BMC Δ	FN Area Δ	NN CSA Δ	NN SPW Δ	NN Z Δ
Long Jump Δ	0.11	0.13	0.03	0.01	0.15*	0.14*	0.10	0.05	0.13	0.23**	0.08
Baseline Vertical Jump	0.14	0.11	0.14*	0.06	0.15*	0.16*	0.12	0.10	0.15*	0.08	0.15*
Vertical Jump Δ	0.17*	0.13*	0.18*	0.04	0.21**	0.14*	0.14	-0.04	0.19**	0.06	0.20**
Avg PA Score	0.05	0.07	0.08	0.02	-0.05	-0.02	-0.01	-0.06	-0.04	-0.07	-0.04
Avg Load Time	0.18*	0.11	0.19**	0.003	0.14*	0.07	0.11	-0.06	0.14	-0.10	0.12
Avg Dietary Calcium	0.02	-0.002	0.11	0.08	-0.08	-0.13	0.03	0.004	0.03	0.08	0.07
Baseline TB BMC	0.50**	0.13	0.44**	-0.01	0.52**	0.26**	0.43**	0.14	0.41**	-0.17*	0.42**
Baseline TB Area	0.54**	0.16*	0.47**	0.04	0.54**	0.29**	0.42**	0.15	0.41**	-0.17*	0.40**
Baseline PF BMC	0.52**	0.16*	0.40**	-0.09	0.50**	0.28**	0.35**	0.07	0.39**	-0.16*	0.40**
Baseline PF Area	0.50**	0.28**	0.37**	-0.02	0.48**	0.31**	0.25**	0.08	0.33**	-0.08	0.32**
Baseline LS BMC	0.41**	0.06	0.35**	-0.02	0.44**	0.15*	0.28**	0.09	0.33**	-0.14	0.35**
Baseline LS Area	0.37**	0.08	0.33**	0.02	0.40**	0.13	0.24**	0.09	0.28**	-0.12	0.30**
Baseline FN BMC	0.47**	0.14*	0.43**	-0.006	0.43**	0.21**	0.33**	0.02	0.38**	-0.17*	0.38**
Baseline FN Area	0.32**	0.18*	0.32**	0.10	0.29**	0.14*	0.14*	-0.07	0.24**	-0.03	0.25**
Baseline NN CSA	0.48**	0.14	0.42**	-0.05	0.43**	0.22**	0.37**	0.09	0.34**	-0.26**	0.33**
Baseline NN SPW	0.34**	0.24**	0.28**	0.07	0.25**	0.14*	0.17*	0.14	0.12	-0.27**	0.12
Baseline NN Z	0.46**	0.16*	0.40**	-0.03	0.37**	0.17*	0.34**	0.10	0.29**	-0.28**	0.26**

Note: Correlations do not account for clustering
* $p < 0.05$; ** $p < 0.01$

Table 4. GIRLS: Pearson correlations of baseline and change (Δ) in anthropometric variables, body composition, long and vertical jump performance and 16-month average scores for physical activity score (PA Score), load time and dietary calcium (calc). Correlations with baseline and final Tanner stage are Spearman's rank correlations.

	Height Δ	Sit Height Δ	Leg Length Δ	Tibia Length Δ	Weight Δ	MCSA Δ	Lean Mass Δ	Fat Mass Δ	Long Jump Δ	Vertical Jump Δ	Avg PA Score	Avg Load Time	Avg Calc
Baseline age	0.06	0.13	-0.04	-0.11	0.15*	0.14	0.17*	-0.02	0.03	0.09	-0.13	0.04	-0.03
Baseline Tanner Stage	0.12	0.15*	-0.01	-0.06	0.25**	0.23**	0.29**	-0.02	0.001	-0.06	-0.09	0.10	-0.11
Final Tanner Stage	0.17**	0.24**	-0.06	-0.13	0.33**	0.30**	0.32**	0.007	-0.06	-0.002	-0.03	0.17*	-0.06
Baseline height	0.01	0.08	-0.07	-0.23**	0.22**	0.13	0.23**	0.002	-0.06	0.08	0.04	0.21**	0.08
Height Δ	-----	0.72**	0.68**	0.48**	0.39**	0.58**	0.72**	-0.14	0.15*	0.15*	0.10	0.15*	0.06
Baseline Sit Height	-0.01	0.03	-0.03	-0.29**	0.22**	0.14	0.22**	0.002	-0.04	0.10	-0.007	0.09	0.03
Sit Height Δ	0.72**	-----	-0.02	0.28**	0.44**	0.55**	0.59**	0.05	0.06	0.17*	0.05	0.03	0.05
Baseline Leg Length	0.03	0.11	-0.07	-0.15*	0.19**	0.10	0.20**	0.005	-0.06	0.06	0.07	0.24**	0.12
Leg Length Δ	0.68**	-0.02	-----	0.42**	0.09	0.27**	0.41**	-0.22**	0.17*	0.05	0.07	0.11	0.03
Baseline Tibia Length	0.04	0.06	-0.10	-0.25**	0.23**	0.15*	0.36**	0.01	-0.006	0.09	0.07	0.24**	0.06
Tibia Length Δ	0.48**	0.28**	0.42**	-----	0.18*	0.21**	0.18*	0.02	0.30**	-0.03	0.20**	0.10	0.13
Baseline Weight	-0.01	0.06	-0.06	-0.27**	0.30**	0.20**	0.26**	0.08	-0.08	0.09	-0.005	0.15*	-0.06
Weight Δ	0.39**	0.44**	0.09	0.18*	-----	0.72**	0.71**	0.74**	0.07	0.04	0.04	0.08	0.01
Baseline MCSA	0.07	0.17*	-0.08	-0.22**	0.24**	0.26**	0.41**	-0.06	0.03	0.09	0.02	0.08	-0.06
MCSA Δ	0.58**	0.55**	0.27**	0.21**	0.72**	------	0.79**	0.26**	0.12	0.17*	0.11	0.13	-0.03
Baseline Lean Mass	-0.004	0.10	-0.10	-0.21**	0.28**	0.26**	0.23**	0.06	-0.04	0.09	0.02	0.15*	0.02

Table 4 continued	Height Δ	Sit Height Δ	Leg Length Δ	Tibia Length Δ	Weight Δ	MCSA Δ	Lean Mass Δ	Fat Mass Δ	Long Jump Δ	Vertical Jump Δ	Avg PA Score	Avg Load Time	Avg Calc
Lean Mass Δ	0.72**	0.59**	0.41**	0.18*	0.71**	0.79**	-----	0.12	0.14	0.18**	0.09	0.20**	0.04
Baseline Fat Mass	-0.01	0.02	-0.03	-0.18*	0.28**	0.17*	0.22**	0.09	-0.08	0.10	0.006	0.13	-0.09
Fat Mass Δ	-0.14	0.05	-0.22**	0.02	0.74**	0.26**	0.12	------	-0.10	-0.16*	-0.04	-0.10	-0.03
Baseline Long Jump	0.02	0.12	-0.11	-0.20**	-0.03	-0.003	0.03	-0.05	-0.22**	0.11	0.12	0.16*	0.22**
Long Jump Δ	0.15*	0.06	0.17*	0.30**	0.07	0.12	0.14	-0.10	0.03	0.15*	0.05	-0.03	-0.10
Baseline Vertical Jump	0.08	0.07	0.05	-0.03	0.04	0.09	0.12	-0.08	0.04	-0.21**	0.01	0.10	0.04
Vertical Jump Δ	0.15*	0.17*	0.05	-0.03	0.04	0.17**	0.18**	-0.16*	0.15*	------	0.03	0.004	-0.02
Avg PA Score	0.10	0.05	-0.07	0.20**	0.04	0.11	0.09	-0.04	0.05	0.03	------	0.50**	0.32**
Avg Load Time	0..15*	0.03	0.11	0.10	0.08	0.13	0.20**	-0.10	-0.03	0.004	0.50**	------	0.18*
Avg Dietary Calcium	0.06	0.05	0.03	0.13	0.01	-0.03	0.04	-0.03	-0.10	-0.02	0.32**	0.18*	------

Note: Correlations do not account for clustering
* $p < 0.05$; ** $p < 0.01$

Table 5. BOYS & GIRLS: Intraclass correlation coefficients (ICC) and 95% confidence intervals (CI) for *baseline* bone mineral content (BMC) and bone area (BA) of the total body, lumbar spine, proximal femur and femoral neck and cross-sectional area (CSA), subperiosteal width (SPW) and section modulus (Z) of the narrow neck for boys and girls.

		BOYS		***GIRLS***	
Site	**Outcome**	**ICC**	**CI**	**ICC**	**CI**
Total body	BMC	0.006	(0 - 0.05)	0	(0 - 0.04)
	Area	0.002	(0 - 0.05)	0	(0 - 0.04)
Lumbar spine	BMC	0.03	(0 - 0.10)	0	(0 - 0.05)
	Area	0.05	(0 - 0.13)	0	(0 - 0.05)
Proximal femur	BMC	0.02	(0 - 0.08)	0	(0 - 0.04)
	Area	0	(0 - 0.04)	0	(0 - 0.04)
Femoral neck	BMC	0.03	(0 - 0.09)	0	(0 - 0.04)
	Area	0	(0 - 0.04)	0	(0 - 0.04)
Narrow neck	CSA	0.04	(0 - 0.12)	0	(0 - 0.05)
	SPW	0	(0 - 0.05)	0	(0 - 0.05)
	Z	0.01	(0 to 0.07)	0.008	(0 to 0.06)