



LUND UNIVERSITY

The Influence of Physical Activity on Musculoskeletal Characteristics and Fracture Risk at Growth

Detter, Fredrik

2014

[Link to publication](#)

Citation for published version (APA):

Detter, F. (2014). *The Influence of Physical Activity on Musculoskeletal Characteristics and Fracture Risk at Growth*. [Doctoral Thesis (compilation), Orthopedics - Clinical and Molecular Osteoporosis Research]. Clinical and Molecular Osteoporosis Research Unit, Clinical Sciences, Malmö.

Total number of authors:

1

General rights

Unless other specific re-use rights are stated the following general rights apply:

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: <https://creativecommons.org/licenses/>

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

The Influence of Physical Activity on Musculoskeletal Characteristics and Fracture Risk at Growth

A Population-Based Prospective Controlled Exercise
Intervention Study at Growth

Fredrik Detter



LUND
UNIVERSITY

DOCTORAL DISSERTATION

by due permission of the Faculty of Medicine, Lund University, Sweden.

To be defended at the Auditorium Waldenströmssalen, Department of
Medicine, Skåne University Hospital, Malmö, 1 October 2014, 09.00.

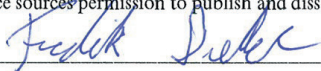
Faculty opponent

Associate Professor Diana Swolin-Eide, The Queen Silvia Children's Hospital,
Sahlgrenska University, Hospital Ostra, Gothenburg, Sweden

Organization LUND UNIVERSITY	Document name DOCTORAL DISSERTATION	
	Date of issue 20140826	
	Sponsoring organization	
Author(s) Fredrik Detter		
Title and subtitle The Influence of Physical Activity on Musculoskeletal Traits and Fracture Risk at Growth		
<p>Abstract</p> <p>Long term physical activity leads to improved musculoskeletal traits. However there are some concerns that PA may lead to more fractures. This longitudinal exercise intervention program was designed to determine the effects of intracurricular exercise on musculoskeletal traits and fracture risk.</p> <p>The amount of PA was increased from mandatory 60 min/week to 200 min/week. Fractures were registered in all children during maximum 6 years. A subgroup consisting of both controls and intervention subjects was repeatedly measured by DXA, pQCT, a computerized dynamometer and QUS.</p> <p>Children in the intervention group improved their musculoskeletal traits significantly compared to controls. The Rate ratio to sustain a fracture was not affected by the intervention.</p> <p>Therefore we can conclude that increased intracurricular exercise improves musculoskeletal traits without affecting the fracture risk.</p>		
Key words: Bone mass, BMD, BMC, Accelerometer, DXA, PQCT		
Classification system and/or index terms (if any):		
Supplementary bibliographical information:		Language English
ISSN and key title: 1652-8220		ISBN 978-91-7619-029-6
Recipient's notes	Number of pages 160	Price
	Security classification	

Distribution by (name and address) Fredrik Detter Kronborgsvägen 12 A 217 42 Malmö
I, the undersigned, being the copyright owner of the abstract of the above-mentioned dissertation, hereby grant to all reference sources permission to publish and disseminate the abstract of the above-mentioned dissertation.

Signature



Date

26/8-2014

The Influence of Physical Activity on Musculoskeletal Characteristics and Fracture Risk at Growth

A Population-Based Prospective Controlled Exercise
Intervention Study at Growth

Fredrik Deter



LUNDS
UNIVERSITET

Financial support for this study was received from ALF, Region Skane FoUU, Centre for Athletic Research, Österlund Foundation, Kock Foundation, Herman Järnhardt, Foundation, SUS Hospital Foundation.

Language revised by Alan Crozier

Copyright © Fredrik Detter

Clinical and Molecular Osteoporosis Research Unit
Department of Clinical Sciences and Orthopedics
Skåne University Hospital,
Faculty of Medicine, Lund University, Sweden

ISSN 1652-8220

ISBN 978-91-7619-029-6

Lund University, Faculty of Medicine Doctoral Dissertation Series 2014:100

Printed in Sweden by Media-Tryck, Lund University
Lund 2014



Table of Contents

Table of Contents	5
Abstract	7
Abbreviations	9
Original Papers	10
Glossary	11
Introduction	12
<i>The clinical problem – fractures</i>	12
<i>Bone mass measurements</i>	20
<i>Bone metabolic markers</i>	25
<i>Skeletal muscle</i>	26
Prediction and prevention	30
<i>Risk factors for fall, osteoporosis and fractures</i>	30
<i>Aims</i>	43
Material and methods	44
<i>Fracture registration</i>	44
<i>Measurements</i>	44
<i>Study subjects</i>	46
<i>Drop-out analysis measurements</i>	50
<i>Accelerometers</i>	51
<i>Physical activity assessed by questionnaires</i>	51
<i>Anthropometrics and maturation</i>	51
<i>Bone and Muscle Measurements</i>	51
<i>Statistical methods</i>	55
Summary of Papers	57
<i>Paper I</i>	57
<i>Paper II</i>	57
<i>Paper III</i>	58
<i>Paper IV</i>	59
General discussion	61
<i>The clinical problem</i>	61
<i>Determination of musculoskeletal traits</i>	61
Strengths and limitations	70
Conclusion	71
<i>Future Perspectives</i>	71

<i>Summary in Swedish – Populärvetenskaplig sammanfattning</i>	71
<i>Acknowledgments</i>	72
<i>References</i>	74

Abstract

Physical activity (PA) improves fitness, skeletal traits and muscle function. It is also known that PA tracks through adolescence into adulthood, so that the foundation of a healthy lifestyle may occur at an early age. Long-term PA therefore has the potential to improve peak bone mass (PBM), the highest bone mass value during life, found in young adulthood, and improve neuromuscular development. There has however been concern that a high level of PA leads to more fractures. This must be refuted before we can recommend exercise interventions within the general population. New trends in society are also of concern. Many children today have a sedentary lifestyle, and this has urged the community to initiate preventive strategies to effectively counteract the negative effects of detrimental lifestyles. School is the only arena that can reach all children, but little is known about the long-term effects of a moderate school-based PA intervention program on musculoskeletal health. For example, skeletal strength and fracture risk are both affected independently by bone mass, skeletal size and skeletal microarchitecture. Neuromuscular function and muscle strength also influence the risk of falls and fractures independently of skeletal strength. The most relevant endpoint when examining the clinical effects of PA is thus fractures, while all intervention studies but ours use a surrogate endpoint such as bone mass or muscle function. The pediatric osteoporosis intervention study (POP) study was therefore initiated to determine the fracture risk and musculoskeletal development in children in relation to increased PA in school. This

thesis outlines the outcome of 3–6 years of this program.

The POP study is a longitudinal population-based exercise intervention study where the school-based physical education (PE) in one school is increased from 1–2 lessons per week (mean 60 minutes per week) to one 40 min lesson per school day (mean 200 minutes per week) for all children with school start 1999–2009. Children in 3 schools who continued with the Swedish standard of 1–2 lessons per week during the same period served as control schools. In all these children (n=2621) we registered fractures during the study period. During the same period our research technicians annually measured musculoskeletal traits in a subsample (n=295) by dual-energy X-ray absorptiometry (DXA). We included in these measurements bone mineral content (BMC; g), bone mineral density (BMD; g/cm²), bone size (cm), total lean body mass (kg) and total fat mass (kg). In a subsample (n=223) our research physiotherapists measured muscle strength by a computerized dynamometer as isokinetic peak torque (PT) at two fixed angular velocities, 60°/second and 180°/second, in knee flexion and extension and functional performance by vertical jump height (VJH). At the last evaluation, our technicians also used peripheral computed tomography (pQCT) to assess bone mass and structural parameters of tibia and radius and quantitative ultrasound (QUS) to assess the bone mass of the calcaneus.

The risk of sustaining a fracture during the six-year period was not significantly affected by the intervention [rate ratio 1.12 (0.85, 1.46)] [mean (95% confidence interval)]. Girls in the intervention group annually improved their spine BMD, femoral neck BMC and femoral neck area more than girls in the control group (all $p < 0.05$). After 6 years with increased physical education, the intervention girls had significantly higher bone trait values than the girls in the control group, in mean 7% in total body BMC, 8% in spine BMC, 11% in femoral neck BMC, 8% in tibial cortical bone mass, 6% in tibial cortical thickness, 8% in tibial bone area, 11% in tibial resistance to torsion and 10% in calcaneus BUA (all $p < 0.05$). Boys in the intervention group annually improved their spine BMD more than boys in the control group ($p < 0.05$) but we found no significant differences in the last measurement between

boys in the intervention and the control groups. Both girls and boys in the intervention group also improved their muscle strength compared to the controls (all $p < 0.05$), registered by the PT flexion at $60^\circ/\text{second}$ in both genders and in the boys also the PT at $180^\circ/\text{second}$.

This thesis shows that a long-term PA intervention program in school in children who were prepubertal at study start improves the gain in skeletal traits and muscle strength without increasing the fracture risk. This indicates that daily school PA is one approach that improves pediatric musculoskeletal health at the population level. The program should be followed into adulthood to evaluate whether it leads to higher peak bone mass and peak muscle strength.

Abbreviations

ANCOVA	Analysis of covariance
BMC	Bone mineral content (g)
BMD	Bone mineral density (g/cm ²)
BMI	Body mass index (kg/m ²)
CI	Confidence Interval
CSA	Cross-sectional area (cm ²)
CSMI	Cross-sectional moment of inertia (cm ⁴)
CV	Coefficient of variation (%)
DPA	Dual-photon absorptiometry
DXA	Dual-energy X-ray absorptiometry
Ex	Extension
Fl	Flexion
FN	Femoral neck
HSA	Hip structural analysis
LS	Lumbar spine
MVPA	Moderate to vigorous physical activity
PA	Physical activity
PBM	Peak bone mass
PE	Physical education
POP	Pediatric Osteoporosis Prevention (study)
pQCT	Peripheral quantitative computed tomography
QUS	Quantitative ultrasound
RCT	Randomized controlled trial
RR	Rate ratio
SD	Standard deviation
SPA	Single-photon absorptiometry
SSI	Strength strain index
TB	Total body
vBMD	Volumetric bone mineral density (g/cm ³)
VJH	Vertical jump height (cm)
VPA	Vigorous physical activity
WHO	World Health Organization
Z	Section modulus (cm ³)

Original Papers

- I. **Influence of a 3-Year Exercise Intervention Program on Fracture Risk, Bone Mass and Bone Size in Prepubertal Children.**
Löfgren B, **Detter F**, Dencker M, Stenevi-Lundgren S, Nilsson J-Å, Karlsson M.
Journal of Bone and Mineral Research 2011 Aug; 26(8): 1740–7
- II. **A 3-Year school based Exercise Intervention Improves Muscle Strength – A Prospective Controlled Population-based Study in 223 Children.**
Detter F, Nilsson J-Å, Karlsson C, Dencker M, Rosengren B, Karlsson M.
Submitted BMC Musculoskeletal Disorders
- III. **A 5-Year Exercise Program in pre- and peripubertal Children improves Bone mass and Bone size without Affecting Fracture Risk**
Detter F, Rosengren B, Dencker M, Nilsson J-Å, Karlsson M.
Calcified Tissue International 2013 Apr; 92(4): 385–93
- IV. **A Six-Year Exercise Program Improves Skeletal Traits without Affecting Fracture Risk – a Prospective Controlled Study in 2 621 Children**
Detter F, Rosengren B, Dencker M, Lorentzon M, Nilsson J-Å, Karlsson M.
Journal of Bone and Mineral Research 2014 Jun; 29(6): 1325–36.

Glossary

Accuracy

How well a measured value corresponds to the true value

Concentric contraction

A contraction during shortening of the muscle

Eccentric contraction

A contraction during lengthening of the muscle

Exercise

Physical activity that is planned, structured with repetitive bodily movement performed to improve or maintain one or more components of physical fitness

Isokinetic

Movement at a constant angular velocity around the axis of rotation

Isometric contraction

A contraction during which the muscle length remains unchanged

Isotonic loading

Movement of a constant external load

Muscle endurance

The ability to exert muscle force over time

Muscle strength

The amount of force produced by muscle during a single contraction.

Peak torque

Maximum force applied around a pivot point

Physical activity

Bodily movement produced by the contraction of skeletal muscles that result in energy expenditure

Precision

The extent to which repeated measurements under the same conditions give the same results

Reliability

Refers to the consistency of measurements

Validity

The extent to which an instrument or method actually measures what it is intended to

Introduction

The clinical problem – fractures

The number of fractures in society is one of the large health care problems of today, especially the rising incidence in the old population that is associated with osteoporosis (109). The estimated number of hip fractures in 1990 was 1.7 million worldwide, and by 2050 this number is estimated to increase to over 6 million, mainly due to increased life expectancy, especially in the developing countries (109), even if recent reports indicate a decline in the age-adjusted incidence in recent decades (250). The majority of the current fracture increase occurs in Asia, but Europe is also seeing this increase (109). In Sweden, where we have among the highest incidences in the world of low-energy-related fractures in the old population, with a roughly 50% lifetime risk of sustaining a fracture related to osteoporosis in 50-year-old women, and 25% in men (148, 154). The most common fracture sites are hip, lumbar spine, distal forearm and proximal humerus.

It is important to remember, however, that it is not osteoporosis per se but the fractures related to osteoporosis that cause pain and impaired mobility for the patient. There are many other risk factors for fracture besides low bone mass, such as susceptibility to falls, low muscle strength, inferior neuromuscular function, impaired vision and treatment with long-acting benzodiazepines, all of which must be taken into account (3, 65).

The fragility fractures cause immense individual suffering, especially the hip fracture that is followed by both increased morbidity and increased mortality (6, 171, 199), but also an enormous economic burden on society (326, 327). In other words, fractures are a gigantic problem with huge consequences for both the individual patient and society (1, 5, 144). With the projected increase of elderly in the community, the challenge will grow even bigger in the future (250). Fragility fractures also contribute to more hospital bed-days in developed countries than myocardial infarction, breast cancer or prostate cancer (149, 156). Current guidelines therefore recommend further research to be performed on fracture prediction, focusing more on the multifactorial etiology of fractures and not only using the surrogate of bone mass defined by dual-energy X-ray absorptiometry (DXA) to predict the future fracture risk, but also including other endpoint variables such as fall.

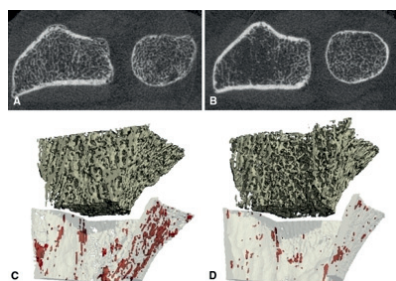
Bone tissue

The skeleton serves a variety of purposes such as support and protection for the inner organs and storage of minerals, especially calcium, it works as a lever arm for the muscles that allows body movement, and blood cells are produced within the bone marrow cavity. The skeletal system has a brilliant three-dimensional design, light yet strong and stiff but also flexible (271), a structure that optimizes body movement. Different bones also have different functions

and structure and therefore vary greatly in resistance to fracture (66).

There are two different macroscopic types of bone, cortical or compact bone and trabecular or cancellous bone. The skeleton includes 75–85% cortical and 15–25% trabecular bone. Both types include the same cell types, the same hydroxyapatite crystal and the same types of collagen, but with different organization and macroscopic morphology. The long bones of the extremities also include a marrow cavity, where the inner surface of the cortical bone adjacent to the marrow cavity is called the *endosteal* surface and the outer surface the *periosteal* surface. Cortical bone is therefore dense and strong and makes up the protective shell. Trabecular bone is hollow and consists of a network of plate- or rod-like shapes minimizing weight yet maximizing the strength of the bone (213). This network is most elegantly oriented in three dimensions determined by the loading conditions. It is primarily found in the metaphysis regions of long bones and in the vertebrae. This type of bone has a much higher surface-versus-volume ratio than in cortical bone, and bone turnover is as result much higher in trabecular than in cortical bone (12) (236).

Fig. 1. Trabecular bone of the radius. With a thin cortical shell and increased porosity in B. By courtesy of US. National Library of Medicine.



Bone is a vascularized and innervated tissue that undergoes constant remodeling and conformation to adapt to the needs of the skeleton. The hydroxyapatite molecule, $(Ca_5(PO_4)_3(OH))_2$, is a crystalline form of calcium phosphate, a structure that hardens the skeleton and serves as a building block of the skeleton. Together with the triple helix protein of collagen type 1 and several glycosaminoglycans, these structures make up the extracellular matrix surrounding the cellular component of bone. There are three different cells in the bone structure: *osteoblasts*, *osteoclasts* and *osteocytes*. The cells work coupled in units called *the basic multicellular units (BMU)*. The BMU concept was first described by an orthopedic surgeon, Harold Frost in Utah, US (103), and has since then been widely accepted. The osteoclasts are derived from progenitors of the monocyte/macrophage family of the hematopoietic stem cells, large multinucleated cells that resorb bone. The osteoblasts are derived from mesenchymal stem cells, and produce new bone (173). Bone lining cells are a form of osteoblast found on the surface of the skeleton. Finally, osteocytes are differentiated osteoblasts, which have been embedded in bone matrix during new bone formation. This type of cell makes up around 90% of all skeletal cells in adults (172), and they are connected to each other with long dendrites but also to osteoblasts and bone lining cells on the bone surface. The function of the osteocyte is not clarified, but it is believed that the cell type is mechanosensible, capable of transducing mechanical stimuli to

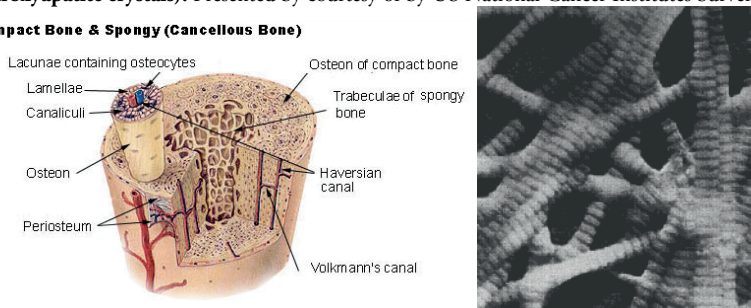
a biological response in bone (88). These cells also play key role in the autocrine and paracrine mechanisms in bone remodeling (173).

Bone matrix and osteocytes are histologically organized in onion-shaped

rings in osteons around Haversian canals, in which the canals contain blood vessels, lymphatic tissue, and sometimes nerves. In this structure there are also small cavities called lacunae in which the osteocytes lie, connected to each other by small tunnels called canaliculi (76, 173).

Figure 2. Bone tissue organized in osteons (magnified part illustrating triple helix of collagen type 1 and hydroxyapatite crystals). Presented by courtesy of by US National Cancer Institutes Surveillance.

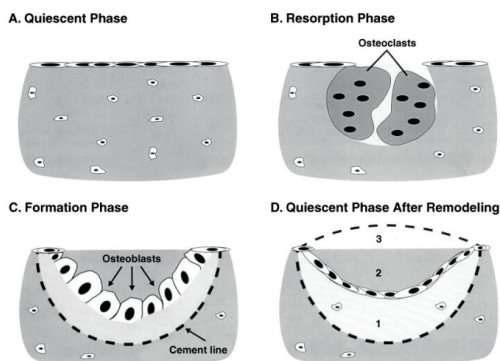
Compact Bone & Spongy (Cancellous Bone)



As the bone tissue contains living cells, it is a most active metabolic organ, and this results in two types of metabolic procedures in the skeleton, *bone modeling* when the metabolism changes the form and the size of the skeleton, and *bone remodeling*, where old bone is substituted by new fresh bone but without changing the shape and the size of the bone. The first process primarily takes place during growth, but can also be seen in

adults in response to mechanical loading or during fracture repair. The remodeling procedure is seen in adult life when bone is rebuilt by osteoblasts after removal by osteoclasts to achieve new strong bone but keeping the old shape and size of the bone (178, 271). In this remodeling cycle, approximately 10–12% of the skeleton is replaced every year (309, 310).

Figure 3. Modeling and remodeling of the skeleton. By courtesy of the National institute on Alcohol abuse and Alcoholism.



Regulation of bone metabolism

The bone metabolism is dependent on a variety of background substances and conditions, regulated by a variety of autocrine and paracrine mechanisms (173). For example, the calcium levels are of most importance for the bone-building capacity. Daily dose recommendations of calcium vary with age and gender. Generally adults of both genders need 1000 mg/day and women need to increase the daily dose to 1200 mg/day at age 50 years. All adults need 1200 mg/day after 70 years and teens need up to 1300 mg/day. Newborns and children up to 8 years need 200–800 mg/day (252, 263). Parathyroid hormone (PTH) increases the blood calcium levels by increasing the bone resorption through increased osteoclastic activity and reabsorption of calcium in the kidneys. PTH also induces enzymatic activation of vitamin D in the kidneys, which increases calcium absorption from the intestines, tubular reabsorption of

the kidneys and skeletal calcium release. (17). Over-production of PTH in the parathyroid glands thus leads to loss of calcium in the skeleton. In contrast, when calcium levels in blood are elevated, the PTH-induced bone remodeling is instantly reduced (308).

Vitamin D is essential for the calcium balance, and vitamin D induces calcium release through mechanisms mentioned above. However, it leaves the skeleton intact because of concurrent activation of osteoblasts and osteoclast, in contrast to PTH which only stimulates osteoclastic resorption (43, 131). When our skin is exposed to sunlight (ultraviolet B radiation), 7-dehydrocholesterol is converted to vitamin D. But vitamin D can also be ingested. Vitamin D deficiency has an immense effect on the skeleton, in children leading to rickets and in adults to osteomalacia (131). Besides the effects on bone, vitamin D seems to have a direct effect on skeletal muscle and neuromuscular

function and reduces the risk of falling, at least in elderly people (34). Vitamin D therefore has several different pathways for reducing fracture risk (34). Previous national and international recommendations regarding vitamin D intake were at least 400 IU/day for children and adolescents (305). Nowadays it is recommended to increase the dose to 600 IU/day at 4 years of age and 800 IU/day after 70 years (252). A serum level of less than 50 nmol/l of vitamin D (25-hydroxyvitamin D) is considered by most experts to be defined as vitamin D deficiency (131). Vitamin D deficiency is very rare in Sweden, but children with dark skin may need supplementation also after the age of two due to low sun exposure (30, 93). Finally, calcitonin is a substance that counteracts the effect of PTH, a hormone produced in the C-cells in the thyroid gland.

The skeleton during growth

Before puberty there is virtually a linear gain in bone mineral content (BMC) in both girls and boys (267). This gain is mainly regulated by growth hormone (GH) and Insulin-like Growth Factor-1 (IGF-1), which are hormones that stimulate osteoblast differentiation and proliferation (77, 78). GH and IGF-1 increase dramatically at puberty as a result of the increased levels of sex steroids (204), and the sex steroids, GH and IGF-1 all have an anabolic effect on bone and muscle tissue (204). Testosterone in boys acts centrally by increasing the GH secretion, while estrogen in girls increases GH indirectly by reduction of feedback inhibition. Testosterone also has

an anabolic effect by increasing protein synthesis (210).

Peak velocity of growth occurs earlier in girls than in boys, at a mean age of 11.8 in girls and 13.4 in boys. Peak bone mineral accrual occurs about one year later in both genders but also earlier in girls than in boys (19). The single period with the most rapid accrual of bone mineral occurs in boys at 13 to 17 years of age and in girls between 11 and 14 years (39). Approximately a quarter of the bone mineral content in adulthood is gained during the 2 years around puberty, a similar amount that is lost during the 50–60 years after peak bone mass (249). Obvious gender differences develop during puberty, mainly due to boys having a longer period of bone maturation, which results in a larger bone size and larger cortical thickness (39). This period is a “window of opportunity” to influence the skeleton by physical activity (113, 157) but also a period which can sustain detrimental effects of malnutrition (24), insufficient carbohydrate and protein intake, especially combined with menstrual dysfunction (24, 240, 269). With a general deficiency in nutrition the individual is also at risk of very low levels of calcium consumption (less than 400 mg/day) and/or vitamin D (175). This important period in bone growth is probably the result of the skeleton being maximally responsive to stimuli during periods with fast skeletal apposition (158, 237).

Peak bone mass

The skeleton accumulates bone mineral successively up to the third decade of life until it reaches a maximum of 900–1200

grams of calcium (205). Peak bone mass (PBM) is the highest bone mass value a person reaches during lifetime. PBM usually occurs in the early twenties but can vary depending on gender, type of bone, skeletal region and also on individual genetic background (124), being as early as age 17–18 years in the hip (14) and as late as age 40 in the distal forearm (10). A 10% increase in peak bone mass is predicted to delay development of osteoporosis by 13 years (128) and up to half of the variance in bone mass at age 70 is estimated to be predicted by PBM (134). Peak BMD has in fact been suggested by some to be the single most important factor in the development of osteoporosis (124, 128). Around 50–85% of the variance in peak bone mass is thought to be regulated by genetic factors (91, 239), but a variety of lifestyle factors, such as energy intake, protein intake, dietary calcium intake, level of physical activity (167, 278, 279), also contribute to PBM.

The development of osteoporosis

With aging there is a gradual loss in bone mineral and a slow periosteal expansion (10). The age-related loss in bone mass gradually leads to a weaker skeleton and an exponentially increased fracture risk (97, 120, 307). Thus, there is no specific

“fracture threshold” since the fracture risk increases exponentially with decreasing BMD (97, 120, 307). However, initially for screening purpose, the World Health Organization (WHO) in 1994 defined osteoporosis radiologically by DXA in women, although the term had existed since the 1820s (264, 320). This was an important step since low BMD is associated with increased fracture risk independent of trauma level (193), also accounting for individuals with high-energy-related fractures and children (55). Osteoporosis is defined by WHO as BMD measured by DXA in post-menopausal women with a T-score below -2.5 (2.5 standard deviations (SD) lower value than the mean value) in healthy individuals of the same gender (table 1). This should be compared with the expression Z-score that is the number of SD below or above the age-specific mean value in individuals of the same population and gender. According to WHO, however, osteoporosis is also “a systemic skeletal disorder characterized by low bone mass and micro-architectural deterioration of bone tissue” (320, 321), resulting in bone fragility and greatly increased fracture risk, which is the major clinical manifestation of the disease.

Table 1. Definition of Osteoporosis according to WHO by use of T-score (320) T-score refers to number of standard deviations (SD) below or above the mean value of young healthy individuals of the same gender

Normal bone mineral content – BMD T-score above -1 SD from the average adult value
Osteopenia – BMD T-score -1 to -2.5 SD from the average adult value
Osteoporosis – BMD T-score < -2.5 SD from the average adult value
Manifest Osteoporosis – Osteoporosis and at least one fracture related to osteoporosis

Currently the terminology is clinically applicable to post-menopausal women with BMD estimated by dual-energy X-ray absorptiometry (DXA) (3). Osteoporosis is also regarded as a progressive disease that leads to further reduced bone mass, suboptimal microarchitecture, consequently reduced bone stability and increased fracture risk. In the literature, the disease is sometimes also divided into primary postmenopausal and secondary osteoporosis, the latter term used when an underlying disease that leads to low BMD has been identified. Primary osteopenia, (BMD T-score values of -1.0 to -2.5), and primary osteoporosis are regarded as the result of low peak bone mass, an accelerated age-related bone loss or both, but without any identified underlying disease. The increased skeletal fragility that is associated with osteoporosis, together with an increased risk of falls due to neuromuscular deterioration in elderly, leads to a rapid increase in fracture incidence, the clinical consequence and problem of low BMD (35-37).

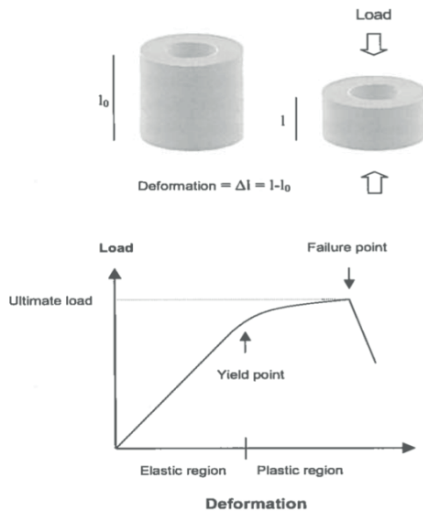
Bone strength

The term skeletal strength is not a generally accepted or defined term, but is still used in the literature (10). Bone size, skeletal geometry and architecture are other traits that contribute to the skeletal resistance to trauma independently of BMD (10, 41, 83,

84). The combined effect of all these traits is often referred to as bone strength, determining “the force required to produce mechanical failure under a specific loading condition” (29). The resistance of bone to such a mechanical failure, i.e. fractures, depends on both the material and the structural properties of bone (28, 268). Loading of the long bones is normally axial or bending compression. Compression is a shortening of the bone as an axial force acts upon it. Tension gives a lengthening of a bone, hence when a bending force acts on bone it will be compressed on one side while tension acts on the other side.

The load-displacement curve graphically describes bone strength, as the site-specific load and deformation tolerated (27). Bone strength is therefore not only the maximum load tolerated but also dependent on the elasticity of the material. Brittle bone is therefore more susceptible to fracture, as it cannot absorb as much post-yield strain as the bone of a child. The integral of the stress-strain curve, the total energy that bone can resist, therefore describes the overall toughness of bone (27). Long bones, in an adult, have intermediate properties, the fracture risk and fracture morphology are then chiefly related to trauma energy, although some studies do not show any differences between trauma levels (193).

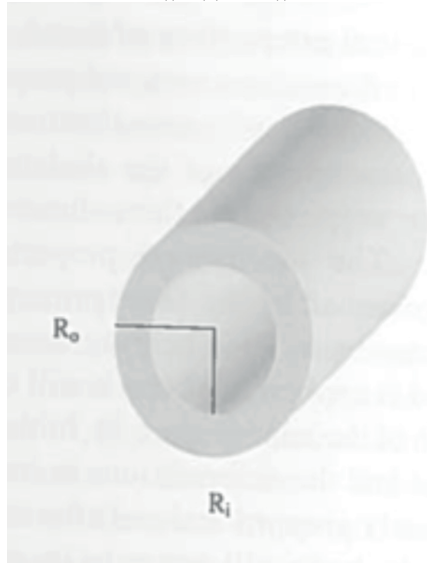
Figure 4. Stress-Strain Curve. By courtesy of Henrik Ahlborg.



The importance of the different traits is also of clinical relevance, illustrated by the fact that women with femoral neck fractures have a smaller femoral neck but normal vertebral size compared to controls, and women with spine fractures have smaller vertebrae but normal femoral neck size compared to controls without fracture at these sites (83). There are also hypotheses

that the reduction in bone mass after menopause is counteracted by an increased periosteal apposition which then partially preserves bone strength due to increased bone width (10). Whether the loss in BMD and gain in bone size after puberty are coupled or occur separately is, however, unknown (10).

Figure 5. Bone strength indices. By courtesy of Henrik Ahlborg. Cross-sectional moment of inertia $(CSMI)=(\pi/4)(R_o^4-R_i^4)$ and Section modulus $=((\pi/4)(R_o^4-R_i^4))/R_o$



Bone mass measurements

Bone mass is a general term that estimates either bone mineral content (BMC) which is the amount of mineral (g) measured within a scanned skeletal region, or bone mineral density (BMD), which is the measured mineral partially adjusted for bone size through a defined scanned area (g/cm^2). The latter measurement is also sometimes referred to as areal BMD (aBMD). This estimate is used clinically as it is a reasonable predictor of fragility fracture (295). The newer methods provide a volumetric BMD (vBMD; g/cm^3), taking length, width and depth into account, but even this is not the genuine density but only an estimate of the actual density of a bone (9, 18). In adults and in clinical practice BMD is the preferred variable, although it is important

to realize that bone mass is an unspecified term. The methods for estimating the mineralization of the bone use radiation, either ionizing or non-ionizing (67). All ionizing techniques utilize the same principle, that increased amounts of bone mineral within the beam lead to increased absorption and attenuation of the emitted radiation (67). This results in lower measured values at the detector (32). The amount of ionizing radiation that is absorbed by the bone gives a measure of the amount of mineral (mainly calcium) in the bone. New methods using X-rays as radiation source have successively been developed (table 3), but also methods using non-ionization methods such as quantitative ultrasound (QUS) and magnetic resonance imaging (MRI) have emerged.

Table 2. Interpretation of bone measurement variables

Bone size and mass	Large bone size	Normal bone size	Small bone size
High bone mass	<i>Normal BMD</i>	<i>High BMD</i>	<i>Very high BMD</i>
Normal bone mass	<i>Low BMD</i>	<i>Normal BMD</i>	<i>High BMD</i>
Low bone mass	<i>Very low BMD</i>	<i>Low BMD</i>	<i>Normal BMD</i>

In children, with a concurrent increase in bone size and mass during growth, BMC and bone size are often reported separately (33, 123). If the amount of mineral remained the same in a skeleton increasing in size, BMC would stay constant while BMD would diminish. It is only when the accrual of mineral and

the gain in size is similar that the BMD value stays constant, and only when the relative accrual of bone mineral is greater than the gain in bone size does the BMD value increase. The major limitation of BMD is thus that it has difficulties assessing the relative contribution of growth and accrual in bone mineral.

Table 3. Imaging of osteoporosis

Non-Ionizing methods	Ionizing methods	
	Gamma radiation	X-ray
Quantitative Ultrasound (QUS)	Single Photon Absorptiometry (SPA)	Single X-ray absorptiometry (SXA)
Magnetic Resonance Imaging (MRI)	Dual-Photon Absorptiometry (DPA)	Dual-Energy X-ray Absorptiometry (DXA)
		Peripheral Computed Tomography (pQCT)

Single Photon Absorptiometry (SPA)

SPA was invented in the early 1960s by Cameron and Sorensen (49), soon followed by Nilsson et al. (225, 226). The method revolutionized research in bone since it made it possible to non-invasively estimate the amount of mineral (calcium) in the bone. A disadvantage is that only appendicular skeletal parts can be measured. The radiation source is usually Iodine-125 or Americium-241. The accuracy is about 9% (220), and the precision 1–2% (226).

Dual-Photon Absorptiometry (DPA)

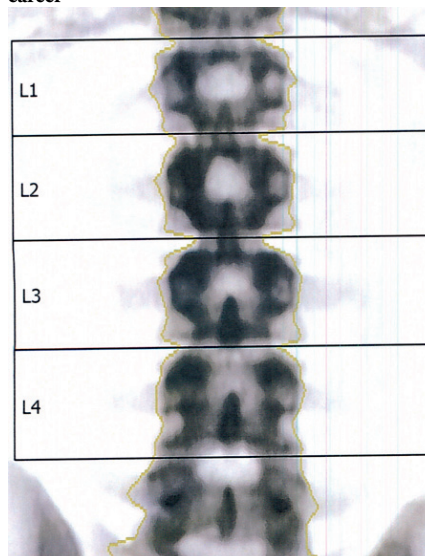
DPA is an advance on SPA, which uses two photon sources that also make it possible to measure the central parts of the body such as the spine or hip. DPA has now predominantly been replaced by DXA.

Dual-Energy X-ray absorptiometry (DXA)

DXA has been available since 1987 and the technique utilizes an X-ray generator as radiation source and a filter to send out X-rays with two distinct energy levels (180, 323). The radiation measured by the detector on the other side of the measured individual can be used to calculate bone mass. The use of DXA has replaced previous techniques, and is today considered the golden standard in clinical osteoporosis work and is also the most used method within research (32, 98). Its advantages are

the ability to measure any part of the body, no need to submerge the measured part in water as with the older SPA technique, and the relatively low radiation dose (1–8 μSv). The effective radiation dose received by the patient during a DXA measurement is low (1–8 μSv) which corresponds to 1/1000 of the yearly background radiation dose (75, 223, 232). Accuracy is about 10% (measuring a vertebra) (290). The precision of the technique is about 0.5–2% (238). The seasonal variations in bone mass detected by DXA are up to 2.5%, with lower values in the winter (211).

Figure 6. A DXA (Lunar DPX-L) scan of lumbar spine of the author at the beginning of his research career



Hip structure analysis (HSA)

HSA is an attempt to estimate three-dimensional structural bone parameters through the two-dimensional DXA hip scan (325). Cross-sectional area (CSA) is an estimation of a bone's capacity to withstand a compressive force (i.e. from an axial load). Identification of the weakest cross-section level of FN is done automatically by the HSA software. The following parameters describing hip structure are calculated, assuming the bone to be cylindrical. Cross-sectional moment of inertia (CSMI) is calculated by $(\pi/4)(R_o^4 - R_i^4)$, where R_o is the outer radius and R_i is the inner radius and gives an estimate of the resistance to a bending force of the structure. In addition it is independent of the material properties. Since strength is proportional to the fourth power of the radius, a small increase in periosteal width produces a large increase in strength. Section modulus (Z) also describes the resistance to a bending force of a tubular structure (i.e. bone). $Z = \text{CSMI} / R_o$. The correlation between

DXA-measured CSMI and direct measure on cadavers has been shown to be very high ($r^2=0.96$) (324, 325), but in reality the correlation is probably lower since limb positioning and a sometimes moving subject may influence the measurement, especially when measuring children.

Quantitative Ultrasound (QUS)

Quantitative ultrasound (QUS) has been proposed to give reliable estimates of skeletal traits and uses speed of sound (SOS; m/s), reflecting the architecture and elasticity of bone, and broadband ultrasound attenuation (BUA; dB/MHz), reflecting the density of the bone, hence no ionizing radiation is received by the patient using QUS. Although QUS is thought to reflect the elasticity and micro-architecture of the bone, the specific aspects of bone quality that are measured by the technique are not yet known (118). It is routinely measured in the calcaneus and has a 0.3–1.5% precision with a predictive value for fracture similar to DXA (287).

Figure 7. A QUS apparatus

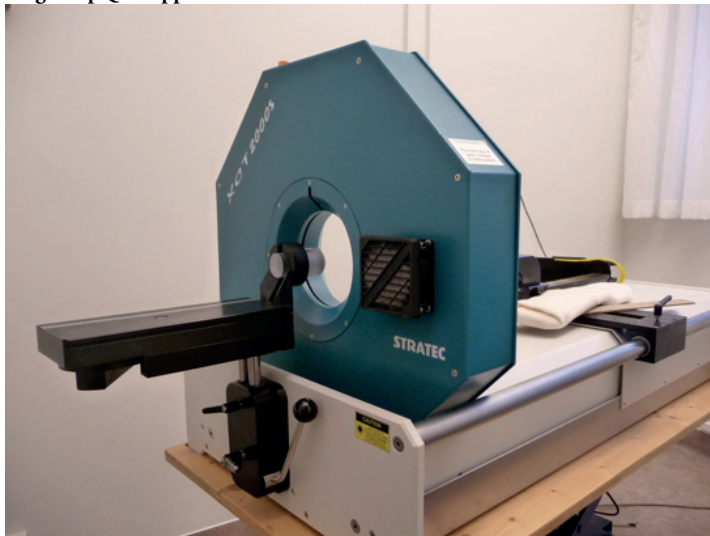


Peripheral Computed Tomography (pQCT)

Quantitative computed tomography is becoming increasingly popular in bone research. Peripheral images at the radius and tibia are commonly used, which generate an acceptable radiation dose of $\leq 10 \mu\text{Sv}$ (9, 18, 75). However, central measurements of the axial skeleton would not be acceptable in children with the current technology, as the radiation dose can be up to $250 \mu\text{Sv}$ (75). The main advantage of this technique is the ability to visualize the microarchitecture and supply a virtual three-dimensional image of the skeleton to the observer. New developments have also created high-resolution pQCT apparatus with even better resolution than the standard pQCT, so far only used within research studies and not in clinical work. There are as yet not many

well-designed longitudinal studies using the pQCT technique in children (126, 130, 147, 281, 306). PQCT-measured bone strength, Stress Strain Index (SSI), is usually expressed as a bone strength indication depending both on material quality and architecture. SSI is calculated by $\text{SSI} = \Sigma (d^2 \times A \times v\text{BMD}_{\text{vox}} / v\text{BMD}_{\text{max}}) / d_{\text{max}}$ where d is the diameter, $v\text{BMD}$ is the bone mineral density of the voxel, A is the area of the voxel, $v\text{BMD}_{\text{max}}$ and d_{max} are the maximum values of bone mineral under physiological conditions and maximal distance from the center of gravity respectively. The spatial distribution or design of bone, estimated through CSMI or section modulus, contributes more to bone strength than the $v\text{BMD}$ (59). Skeletal architecture is also subjected extra to remodeling through mechanical stimulation compared to $v\text{BMD}$ (59).

Fig.8 A pQCT apparatus



Magnetic Resonance Imaging (MRI)

This is a recently introduced method used for research purposes with an ability to depict three-dimensional structure similar to pQCT (85). This method has the great advantage of being radiation-free. The disadvantage is the high cost and unavailability. The method is currently not in use at our research department.

Bone metabolic markers

During bone metabolism, different substances are released in the blood. These can be used to estimate bone turnover and the function of the different skeletal cells. Large measurement errors, however, have been associated with such markers due to

technical and biological factors (187, 212), and the markers are therefore not routinely used in all clinics. Bone turnover markers can be classified as markers of either bone formation or resorption (Table 4). Bone formation markers are derived from osteoblast activity during bone matrix synthesis and can be enzymes released into the blood during either bone matrix synthesis (alkaline phosphatase), matrix protein (osteocalcin) or posttranslational processing products of type I collagen (53, 64). Currently one bone formation marker (s-PINP) and one marker of bone resorption (s-CTX) are recommended for use in clinical studies (304). No bone markers were used in this thesis.

Table 4. Bone turnover markers

Markers of bone metabolism	
Bone formation	Procollagen Type I N-terminal propeptide (s-PINP), Procollagen Type I C-terminal propeptide (s-PICP), Osteocalcin, bone-specific Alkaline phosphatase (s-AP)
Bone resorption	Cathepsin K, Bone sialoprotein (s-BSP), Cathepsin L, total Pyridinoline (u-PYD), free deoxypyridinoline (u-DPD), Tartrate resistant alkaline phosphatase (TRAP), C-telopeptide cross-link of type 1 collagen (CTX)

Skeletal muscle

A muscle fiber, the cell that built the muscular tissue, can contain up to thousands of thin myofibrils, which are built up by two overlapping protein filaments, actin and myosin. Contraction of skeletal muscle is mediated by the interactions between actin and myosin according to the sliding filament theory (137, 139). Each muscle fiber is innervated by a single motor neuron, but each neuron can innervate thousands of muscle fibers. The number of muscle fibers remains the same from or soon after birth, but the muscle fiber size increase 5–10 fold during growth, probably depending on the function or intensity of the work load to which the muscle is exposed (197). During activity, three types of contractions occur in muscle: concentric, eccentric and isometric contraction. Concentric contractions are characterized by shortening of the muscle, the isometric by maintained length, and the eccentric contraction that occurs during elongation of skeletal muscle. All types of contractions occur usually at the same time, in different muscle groups, during a normal motion (253).

Muscle strength

Muscle strength reflects the tension that is created when actin slide past myosin filaments within the muscle fibrils, and it is defined as “the amount of force that can be produced by a muscle in a single contraction” (253). Muscle endurance is the ability to generate muscle force over time (253).

Muscle strength is associated with age, height and/or body stature, weight, gender, and sexual maturity (73, 79) and muscle strength seems to increase in a linear fashion before puberty in both genders without any associated muscle hypertrophy (288). In other words, exercise-induced increased muscle strength early at growth seems more to be the result of optimized neuromuscular function. However, resistance training in adolescence is associated with muscular hypertrophy and hence also gains in muscle strength (288). A recent meta-analysis also stated that resistance training in children apparently enhances muscle strength and that the increment during age occurs without a boost around puberty (31). However, several other studies have reported a marked increase in the effect of training on muscle mass, in males compared to females, during late puberty, most probably due to androgen effects on protein synthesis (248). Therefore it is still controversial whether there is a “window of opportunity” to gain muscle strength in puberty.

Muscle strength is often measured by isokinetic dynamometers in knee extension and flexion, although there is still a need for further studies to determine the validity of this method in children (150). Other studies that use hand-held dynamometers measure isometric strength. Utilizing standardized weights during isotonic strength measurement is another method with high specificity (20). But the method is limited as one repetition maximum is achieved at the weakest point in the motion range (284). Isokinetic dynamometry, in contrast, measures the highest peak torque at the

strongest point during the movement around the axis of rotation. Knee extension (the quadriceps muscles) and knee flexion (the hamstring muscles) are often used to determine isokinetic strength (105).

Neuromuscular function and physical performance

Muscular function is not only dependent on muscle strength. Although associated with muscle strength, balance and neuromuscular function are also of great importance. Vertical jump height (VJH) has been used extensively to assess neuromuscular function in both children and adults, as this is an activity that includes several different aspects of performance (181, 292) (70, 201, 202, 283, 284, 312)).

Fracture risk during growth

Some reports infer that vigorous physical activity is an independent risk factor for fracture (56). There is only limited evidence for a causal relationship between increased exercise in children and fracture (56). During the first two years of an exercise intervention in children there was a doubled fracture risk, according to one study (56). However, the long-term effects may be

positive since exercise leads to improved bone health, less risk of falling and in old individuals lower fracture risk (41, 233, 285, 286, 301). Low bone mass is obviously another risk factor for fracture in children too (56, 57), and low muscle strength seems to be another (57). Fracture risk in children peaks during early puberty, possibly due to the fact that rates of bone turnover then are high with a large gain in bone size, but bone mineral accrual lags behind (23, 115, 158). During this period there is a natural increment in the fracture incidence due to transient reduction in bone strength (61, 125). But the higher fracture incidence in this period could also be the result of susceptibility to fracture at the start of puberty, due to more risk-taking behavior with increased trauma exposure. The most common fracture site in children and adolescents is the wrist and forearm (174). Interestingly, one report infers dose-response relationship between the risks of forearm or wrist fracture and time spent watching television, video or video games in children and adolescents aged 9–16 years (191). In general, age in children is associated with higher fracture risk and boys are more prone to fracture than girls (114, 174).

Fig. 9. Circle diagram of known risk factors for fractures in children

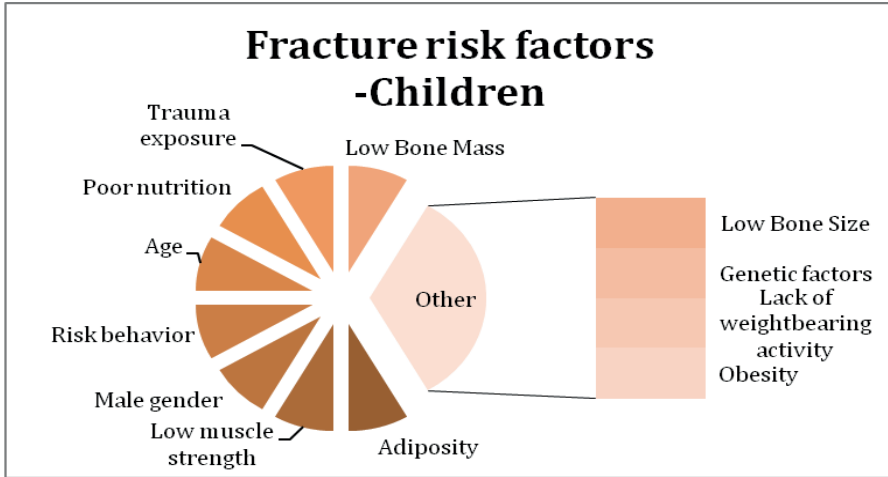
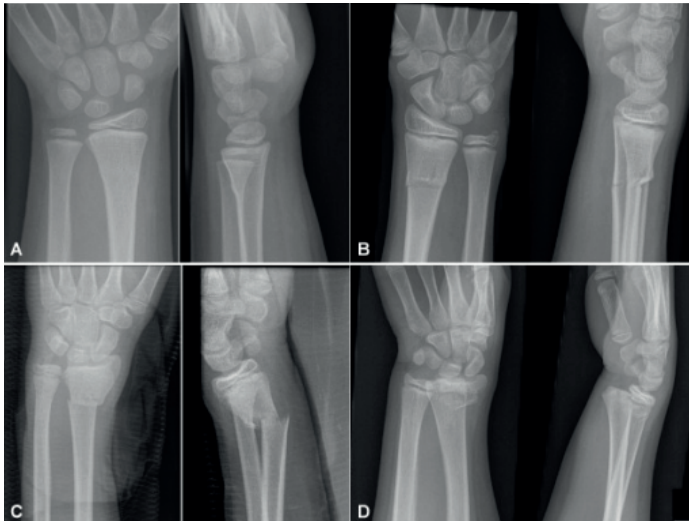


Figure 10. The most common fracture type in children is a distal radius fracture. A: Buckle fracture, B: Greenstick fracture, C: Complete fracture and D: Physeal fracture. By courtesy of US. National Library of Medicine.

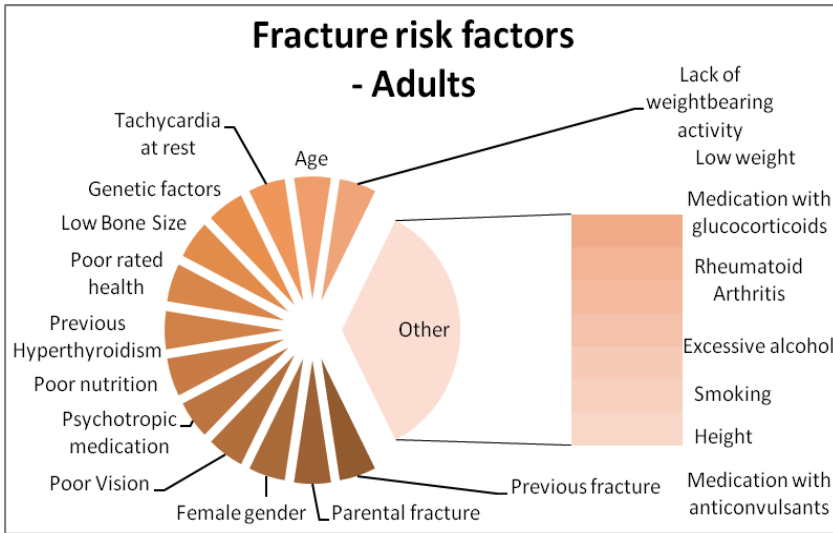


Fracture risk in the old

There is an increasing incidence of fractures with age in both genders (250). Old women also have more fractures than old men (250). The raised incidence during senescence has to a large extent been attributed to a greater prevalence of osteoporosis, although no studies have shown that the age adjusted prevalence of osteoporosis today is greater than decades ago (11). Typical fragility fractures are localized on the distal forearm, proximal humerus, hip, pelvis and vertebrae. The increased proportion of elderly in society is then of great importance since age is one of the strongest risk factors for these types of fractures. BMD or BMC are reliable tools when estimating fracture risk on a group or population level, explaining 60–70% of the

fracture risk, especially when combined with other risk factors (65). The additional risk factors for fractures are impaired vision, medication with, for instance, long-acting benzodiazepines and other psychotropic drugs, low muscle strength, poor neuromuscular function and poor balance. Perhaps the most important of these in the very old is fall risk, while BMD is a less useful predictor of fracture in the oldest (145). Physical activity, especially strength and balance training, can help prevent falls in older people (246). A recent large meta-analysis of interventions for the prevention of falls in elderly revealed that exercise programs containing strength and balance training and also Tai-Chi training effectively reduce falls and fractures in older people (111).

Fig. 11. Known risk factors for fracture in adults and elderly



Prediction and prevention

Risk factors for fall, osteoporosis and fractures

Since the level of BMD is the result of both hereditary factors and lifestyle, research has focused on finding genetic variance that explains the disease (133, 241, 278), but also on risk factors, and preferably modifiable risk factors such as low body mass, smoking, alcohol, comorbidities, inferior nutrition, physical inactivity, treatment with cortisone, low sun exposure, vitamin D deficiency and inadequate calcium consumption, all possible to modify to reduce the risk of developing

osteoporosis. But there has also been a focus on constant risk factors that together with the modifiable risk factors could be used to target individuals suitable for interventions. The most important risk factor for osteoporosis is natural aging, an unalterable risk factor that leads to an increasing risk of fracture over time independent of the level of BMD. For example, with the same BMD value the risk of sustaining fractures doubles with every 10 years of increasing age. Other similar factors are gender, ethnicity and age at menopause. Since osteoporosis is highly associated with fractures, most of these risk factors also account for fracture risk. The same accounts for fall risk – since fall risk and fracture are so closely associated, most risk factors are also the same for both these endpoints.

Figure 12. Risk factors for osteoporosis. By courtesy of the National institute on Alcohol abuse and Alcoholism

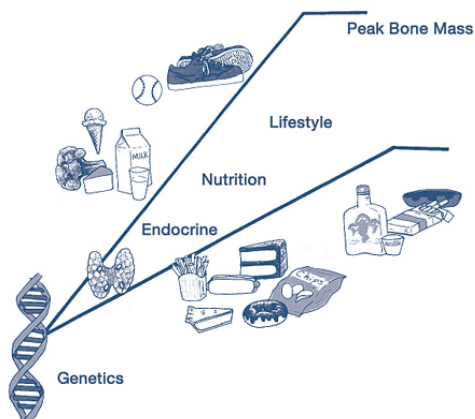


Table 5 – Risk factors for osteoporosis, falls and fractures

Risk factors for osteoporosis, fracture and fall	
Modifiable	Non-modifiable
Sedentary activity level	Age
Smoking	Family history of fracture
Medication	Asian or Caucasian ethnicity
Alcohol consumption	Menarche after 15 years
Low vitamin D and calcium intake	Pregnancy
Amenorrhea	Previous fracture
Use of oral glucocorticoids	Rheumatoid arthritis
Low BMI	

Prevention of fall, osteoporosis and fractures

A variety of regimens to prevent falls have been investigated and several have also been used with efficacy (21, 22, 45, 161, 219, 272). Therefore fall-preventive programs have been developed and several of these have been shown in randomized controlled trials (RCT) to have a fall-reductive effect (108, 189, 273-275, 319). Physical exercise that includes several training modalities, especially balance and strength training, is the only intervention program that reduces both the number of fallers and the number of falls in community dwellers. Home hazard modifications reduce the fall risk in community-living elderly but have the best effects in high risk group with the program led by occupational therapists. Vitamin D supplement in those with low levels of vitamin D, adjustment of psychotropic medication and modification of multi-pharmacy are drug-related programs that

reduce the fall risk. Anti-slip shoe devices in elderly who walk outdoors in icy conditions and multifaceted podiatry for patients with specific foot disability are interventions targeted at the lower extremity with a fall-reductive effect. First eye cataract surgery and pacemakers in patients with cardio-inhibitory carotid sinus hypersensitivity are surgical procedures with fall reductive effect. Multifactorial standardized preventive programs that include exercise components and individually designed subject-specific programs also reduce the number of falls. Fall-preventive interventions should therefore be provided in a structured approach to the elderly, especially to high-risk groups, to reduce the number of falls and fallers (48). As mentioned above, falls and osteoporosis are closely related to fracture risk. However defined, falls account for only about 15% of vertebral fractures compared to 90% of hip fractures (62).

The pathogenesis of fracture can thus be hindered by reducing the prevalence of

osteoporosis and also by enhancing fall prevention strategies. However, osteoporosis and fall risk naturally have a different relative contribution to the pathogenesis of the fracture depending on its localization. It is thus logical to focus on both aspects to prevent fractures.

Osteoporosis is screened for by DXA, the fracture risk assessment tool FRAX[®] or both in combination, to detect individuals at high risk of sustaining a fragility fracture. Many guidelines suggest that all women above 65 years should be screened for osteoporosis in order to treat osteoporotic individuals with bisphosphonates or other antiresorptive agents (216, 217, 277). Also younger individuals should be screened if they present with one or more risk factors (183). The corresponding recommended age for screening in men is above 70 years but on the contrary some researchers do not advocate screening in men at all (183, 184).

Treatment of fall risk and osteoporosis

Fall risk is reduced through daily physical activity in the elderly, which improves their musculoskeletal fitness (273, 274). In the institutional setting hip protectors significantly reduce the number of fractures (112). Bisphosphonates, a drug that inhibits bone resorption, is the primary drug used to treat osteoporosis and reduces the risk of vertebral fracture by at least 50% (155, 166, 302). The bisphosphonates mimic pyrophosphates and inhibit osteoclasts by interfering with the cellular metabolism and finally initiating apoptosis. These patients should also be given additional vitamin D3 and calcium supplement to protect against

appendicular fractures. In the elderly with contraindications for other bonemodulating therapy, however, vitamin D3 can suffice as monotherapy. Secondary drugs that could be used include intermittent administration of teriparatide, a PTH analogue, that stimulates bone growth, RANK-ligand antibody Denosumab and Selective estrogen receptor modulators (SERMs) (263).

Physical Activity

Humans, like many other animals, are built for a hunter-gatherer way of life. Our body has therefore adapted through evolution and perfected our ability to move. Inactivity is therefore, not surprisingly, associated with a variety of chronic diseases affecting the heart, the vascular system, the respiratory system and the metabolic system, including the musculoskeletal system (311). In the modern western world of today, the sedentary lifestyle of many individuals has developed out of proportion. In 2004 the World Health Organization recommended national guidelines on physical activity and also encouraged member states to implement policies and interventions (321).

Physical activity is difficult to estimate and measure with accuracy, especially in children. The most commonly used method is self-reports by questionnaires rendering only a subjective estimate of the level of PA (52, 127). The advantage is that the method is cheap and easy to administer. Objective measurement techniques include doubly labeled water (DLW), which gives a reliable estimate of energy expenditure over time, but the method is expensive and gives no information about the intensity, duration or

frequency of the activity (265). Heart rate monitors (HRM) provide potential confounders of emotional stress, body size and temperature, age and fitness (169). Pedometers provides only estimates of volume of activity (number of steps taken by the measured individual), but the technique does not provide information about the duration or intensity of the PA (296). Accelerometers are some of the newest devices, a mini-computer kept at the waist for 4–7 days and then counting the everyday activities (82, 243). This technique can also differentiate between low and high level of activities. The disadvantage is that most accelerometers count only changes in position, with the result that activities such as cycling are unregistered. Most accelerometers are not water-resistant, resulting in misclassification of water activities. Furthermore, if the individual forgets to wear the accelerometer, it will register no activity and misses that the device is not being worn. As a result the interpretation of data will be difficult in these persons.

During the last three decades, physical education (PE) has decreased in the schools from 20% to 7.5% (92). In Europe only six countries out of 28 offered at least 180 min/week of PE in school (94). Also, two thirds of the countries indicate the amount of PE in school through central education authorities (94). During the last seven years the amount of recommended PE has stabilized in most European countries (94). There is compelling evidence that PA behavior during childhood, at least moderately reflects later PA patterns during adulthood (291-293). These facts are

arguments for increased levels of PA in children.

Exercise and the skeleton – the “mechanostat” theory

Twenty-seven years ago, Dr. Harold Frost proposed the idea that the bone adapts to the mechanical stress that it is exposed to, much like a thermostat regulates temperature, hence the name mechanostat (102). Ever since Professor Bo Nilsson, former head of staff at the Department of Orthopedics in Malmö, invented one of the first devices for evaluating bone mass in the 1960s (SPA) (225) (226) and published the first paper examining the effects of exercise on bone mass in athletes in 1971 (228) (227), research in this field has flourished.

Effects of exercise on bone are age- and maturity-dependent, where the late pre- and early pubertal years (Tanner stage 2 and 3) seem to be a “window of opportunity” to influence bone through physical activity (70, 113). This notion is supported by several RCTs and non-randomized controlled exercise interventions (Table 6). The type of exercise that confers skeletal benefits is also of importance. The load should be fast, dynamic, high in magnitude, with unusual or abnormal strains and intermittent resting periods included between the sessions to produce the most pronounced skeletal response, which was first shown in animal models (176, 255, 258, 298).

This is reflected in humans by the fact that high-impact sports like weight-lifting, tennis, hockey and soccer have large effects on bone mass (182). Small effects have been observed of long-distance running (47, 129,

215, 221) whereas endurance sports without weight bearing, such as swimming or cycling, seem to give no or minimal effects on bone tissue (221). It is also well documented that the effects of exercise on bone are regional and site-specific (99, 194, 242), which is demonstrated by an elegant model of unilateral loading in racquet-sport players (158, 159), where a remarkable increase in BMC in the dominant arm compared to the unloaded non-dominant arm of the players (158). In this model the influence of exercise can be studied without risk of confounding genetic, endocrine and nutritional factors affecting bone since this study design uses the unloaded arm in the same individual as the controls (158, 222, 294).

In adults exercise effects on bone are small or moderate compared to the exercise-induced benefits seen in children and adolescents. Later studies using pQCT and MRI have confirmed the results and also on bone size and vBMD (85, 86, 259, 260). Daly et al. used MRI and the unilateral loading model examining the link between muscle size and bone parameters, testing the hypothesis that the increase in bone parameters during growth and in response to exercise is primarily mediated through muscle tissue, since muscles cause the largest

loads and strains on bone (266). However, the muscle area could only explain 12–16% of the variance in bone mass, size and bending strength in this study (74).

The question also arises whether exercise-induced benefits during growth remain into adulthood. A recent study of over 1000 young adult men using pQCT indicate that positive effects of physical activity during growth on bone geometry remain for several years sport activities have been reduced, or even discontinued (224). Also Baxter-Jones et al. presented evidence that skeletal benefits due to PA during adolescence remain into young adulthood (26), and lifetime sport participation and leisure time PA has been shown to improve bone quality, size and strength in older men (72). The outcome could be that exercise-induced skeletal benefits are retained into old ages or that exercise at growth lays the foundation for a lifelong physically active lifestyle. Both hypotheses are supported by data in the literature (291-293). This suggests that if we could implement more physical activity in the population, for example through a school-based exercise program, it would also be possible to improve various health-related aspects (25, 46, 119, 163, 164, 198, 301), and lower the incidence of fractures (168, 299, 301).

Table 6. Exercise intervention trials and their effect on skeletal traits in children.

Reference	Age and number of participants	Type of Exercise	Study duration	Effects on Bone increase in cases vs. Controls
-----------	--------------------------------	------------------	----------------	--

Tanner stage 1

Gunter et al. 2008	22 girls 34 boys 7–8 years old	20 min high-moderate impact jumps×3/week	7 months	BMC: FN
Wiebe et al. 2008	42 girls 6–10 years	50 high-moderate impact jumps×3/week	7 months	BMD: No effects
Bradney et al. 1998	38 boys 10.4±0.4	Weight bearing 30 min ×3/week	8 months	BMD: TB, LS, Legs CT: legs
MacKay et al. 2000	144 children 6.9–10.2 years	High-moderate impact 10–30 three times a week	8 months	BMD: Tr
Fuchs et al. 2001	99 children 7.6±0.2 years	High impact jumping	7 months	BMC: FN, LS BMD: LS BW: FN
Petit et al. 2002	68 children 10.0±0.6 years	High impact 10–12 min×3/week	7 months	No effects
Van Langendonck et al. 2003	42 children 8.7±0.7 years	High impact ×3/week	9 months	BMC: PF, FN
Specker et al	178 girls 3.9±0.6 years	High impact 30 min ×5/week	12 months	BMC: legs

MacKelvie et al. 2004	64 boys 10.2±0.2 years	High impact 10–12 min×3/week	20 months	BMC: FN HSA: Z
Laing et al. 2005	143 girls 10.2±0.2 years	Gymnastics min/week	60 24 months	BMC: TB, LS, PF BMD: TB, PF BA: TB, PF BMC: Tr, LS
Valdimarsson et al. 2005	103 girls 7.7±0.6 years	PE. Classes min×5/week	40 12 months	BMC: Tr, LS
Linden et al. 2006	99 girls 7.6±0.6 years	PE. Classes min×5/week	40 24 months	BMC: LS, legs BMD: TB, LS, legs BW: LS
Linden et al. 2007	138 boys 7.8±0.6 years	PE. Classes min×5/week	40 24 months	BMC: LS, legs BMD: TB, LS, legs BW: LS
Alwis et al. 2008	137 boys 7.8±0.6 years	PE. Classes min×5/week	40 24 months	BMC: LS BW: LS
Alwis et al. 2008	99 girls 7.6±0.6 years	PE. Classes min×5/week	40 24 months	No effects HSA
Hasselström et al. 2008	349 children 6.8±0.4 years	PE. Classes min×2/week	45 36 months	Girls BMC: Distal forearm BA: Distal forearm Boys: No effects
Greene et al. 2009	42 girls 6–10 years	50 high- moderate impact jumps×3/week	7 months	No effects HSA
Meyer et al. 2011	158 children 8.7±2.1 years	Extra PE classes 45 in including 10 min jumping×2/week	9 months	BMC: TB, LS, FN

Tanner 2–3 (early pubertal)

Morris et al. 1997	71 girls 8.7±2.1 years	Moderate impact min×3/week	10 30 months	BMC: TB, LS, FN, PF BMD: TB, LS, FN
Heinonen et al. 2000	58 girls 11.0±0.9 years	High impact min×2/week	20 9 months	BMC: LS, FN
MacKelvie et al. 2001	107 girls 11.0±0.9 years	High impact min×3/week	7 months 10–12	BMC: LS BMD: LS, FN
Petit et al. 2002	106 girls 10.5±0.6 years	High impact min×3/week	7 months 10–12	BMD: Tr, FN HSA: Z CT: FN
Iuliano-Burns et al. 2003	64 girls 8.8±0.1 years	Moderate impact min×3/week	9 months 20	BMC: LS, Lower leg
MacKelvie et al. 2003	75 girls 9.9±0.6 years	High impact min×3/week	20 10–12 months	BMC: FN, LS
McKay et al. 2005	122 children 10.1±0.5 years	Jumping min three times/week	3×3 8 months	BMC: PF, Tr BA: PF No effects HSA
Courteix et al. 2005	113 girls 8–13 years	Exercised mean 7.2 hrs/week vs. 1.2 hrs/week	12 months	BMD: TB, LS, FN
Macdonald et al. 2008	197 girls 213 boys 10.2±0.6 years	High impact min×5/week	15 11 months	Boys BMC: LS, TB Girls BMC: FN HSA: Z

Löfgren et al. 2011	92 girls 131 boys 7.8±0.6 years	PE classes 40 min×5/week	36 months	Boys BMC: LS BW: LS HSA: No effects Girls BMC: LS, FN BW: LS HSA: CSA
Meyer et al. 2011	133 children 11.1±0.6 years	Extra PE classes 45 in including 10 min jumping×2/week	9 months	BMC: TB, LS, FN
Löfgren et al. 2012	96 girls 125 boys 7.8±0.6 years	PE classes 40 min×5/week	48 months	Boys BMC: LS BW: FN HSA: No effects Girls BMC: TB, LS, FN, Tr BW: LS, FN HSA: CSA, Z, CSMI
Anliker et al. 2012	10 girls 12 boys	Jumping 10 min×2/week	9 months	No effects
Tanner 4–5 (late pubertal)				
Blimkie et al. 1996	36 girls 16.3±0.3 years	Weight training×3/week	7 months	No effects
Witzke et al. 2000	53 girls 14.6±0.5 years	Resistance training 30–45 min ×3/week	9 months	No effects
Heinonen et al. 2000	68 girls 13.3±0.9 years	High impact 20 min ×2/week	9 months	No effects
Nichols et al. 2001	67 girls 15.9±0.1 years	Resistance training 30–45 min ×3/week	15 months	BMD: FN

Detter et al. 2013	96 girls 125 boys 7.9±0.6 years	PE classes min×5/week	40	60 months	Boys BMD: Spine Girls BMC: FN BMD: Spine Size: FN area
Detter et al. 2014	130 girls 165 boys 7.9±0.6 years	PE classes min×5/week	40	72 months	Boys BMD: Spine Girls BMC: FN BMD: Spine Size: FN area
Sundberg et al. 2001	122 boys 104 girls 16.0±0.3 years	PE classes min×4/week	40	48 months	Boys BMC: FN, Spine BMD: FN Girls No effects
Stear et al. 2003	144 girls 17.3±0.3 years	Moderate impact min×3/week ± calcium	45	16 months	BMC: LS, TB, PF, TR
Weeks 2003	44 girls 37 boys 13.8±0.4 years	High impact jumping min×2/week	10	8 months	Girls: BMC: FN, LS Boys BMC: TB, LS, Tr QUS: BUA

Significant increase in intervention compared to controls seen in the parameters/ sites: Bone Area (BA), Bone Width (BW), Broadband ultrasound attenuation (BUA), Cross sectional area (CSA), Cross sectional moment of inertia (CSMI) Distal Forearm, Femoral Neck (FN), Hip structure analysis (HSA), Lumbar Spine (LS) Proximal Femur (PF), Total body (TB), Trochanter (Tr), Section modulus (Z).

Figure 13. Children from the POP study performing moderate exercise. By courtesy of Bjarne Løfgren.



Exercise and muscles

During aging both genders suffer from a degenerative loss of muscle mass and function, resulting in a condition named sarcopenia (261, 262). However, studies on resistance training have shown an attenuated decrease in muscle mass (95). Addition of nutrition supplements also stimulates a larger increase in muscle mass in some studies, whereas the effect is disputed in other studies (68, 235, 247, 280).

Skeletal muscle is responsive to strength training and physical activity leads to energy expenditure and hydrolysis of adenosine triphosphate (ATP) generated through several metabolic pathways (136, 138, 140). This occurs in the mitochondria of muscle cells of the slow-twitch type 1 fibers, where aerobic

metabolism of the citric acid cycle and oxidative phosphorylation predominates (143). During strenuous or very rapid activation of muscle fibers, however, there is a significant anaerobic metabolism that generates less energy and produces lactate in comparison to aerobic metabolism (207-209). The glycolytic metabolism predominates in fast-twitch type II fibers (143).

The glycolysis depends on the supply of creatine phosphorus (CK) in anaerobic conditions, whereas the aerobic metabolism chiefly depends on access to oxygen in the mitochondria (303). Availability of carbohydrates such as glycogen and plasma-glucose is necessary for the performance of prolonged strenuous exercise (58, 63).

The metabolic demands of different muscle fibers, type 1 and 2, depend on

the structure and function of the respective cells. Much like the mechanostat, muscle tissue responds to load and changes its morphology depending on fiber type and usage. However, genetics largely determines muscle fiber type its function, and conversion between the classical type I and II fibers is rare (141).

The use of muscles does not only stimulate cross-sectional growth of the muscle fibers, mitochondrial biogenesis, synthesis of oxidative enzymes, increase in GLUT4-transporter and excitation-contraction coupling improvements, but also stimulates increased recruitment of muscle units, neoangiogenesis, and coordination benefits (200).

Resistance training improves the type II fibers whereas endurance training has a greater impact on type I fibers. As previously mentioned, however, each individual has a genetic predisposition that limits adaptation and fiber conversion. Training with increasing loads, low repetition frequency and dedicated muscle building stimulates muscle cross-sectional hypertrophy. In contrast, endurance training, with multiple repetitions and less muscle loading increase mitochondrial oxidative chain capacity and muscle strength is less improved. Concurrent training can lead to less increases in muscle strength during a high frequency endurance training program(318). However there are benefits from both training modalities and the optimal exercise effect depends on the goal of the individual athlete (107, 132, 151, 234, 322).

Exercise and fractures

Movement increases the risk of falling, collision and the speed increases energy levels exponentially. In youth there is rapid growth of the appendicular skeleton initially while BMC lags behind, resulting in a relative reduction of BMD as the mineralization does not compensate enough for the increased skeletal size. In early youth when coordination is less developed and the skeleton is relatively fragile, more trauma exposure would logically lead to more fractures.

Before increased exercise within the school curriculum can be implemented, the benefits must outweigh the possibility of increased fracture risk. One previous trial has shown increased fracture incidence in children (56). Fracture risk is also increased in young exercising athletes (300, 301). In the long perspective most studies have indicated that bone mass, structure and resistance to fracture improves by exercise and that fracture risk in former athletes is lower than expected (300, 301). In other words, there is currently a debate regarding both fracture risk during periods with high activity and any possible long-term beneficial effects of PA due to residual musculoskeletal benefits.

Physical activity programs in old age have a preventive effect, independent of level of activity in young age and the primary targets include both to increase bone strength and to reduce fall risk by improving balance coordination and muscle strength (111). Other

interventions that the general practitioner can initiate in old people to reduce fracture risk are: to provide home hazard modifications; to provide vitamin D supplement in those with low levels of vitamin D; to adjust psychotropic medication and modify multi-pharmacy; to provide anti-slip shoe devices in elderly who walk outdoors in icy conditions and provide multifaceted

podiatry to patients with specific foot disability; to send individuals with bilateral cataract for first eye cataract surgery to improve vision; and to send patients with cardio-inhibitory carotid sinus hypersensitivity for pacemaker surgery to avoid sudden drops in blood pressure (111). All these measures have been shown to reduce the number of falls (48).

Aims



General

To study the effects of a school-based intra-curricular exercise intervention program on musculoskeletal traits and fracture risk in children who were prepubertal at study start.

Specific

Paper II

To evaluate the effects of increased exercise in the school curriculum for 3 years on muscle strength and neuromuscular performance in children who were prepubertal at study start.

Papers I + III–IV

To assess the effects of increased exercise in the school curriculum for 3 to 6 years on bone mass, bone structure and fracture risk in children who were prepubertal at study start.

Hypothesis

We hypothesized that 3 to 6 years with increased moderately intense PA in school in children who were prepubertal at study start would improve the annual gain in skeletal traits without affecting the fracture risk and that a 3 year with increased PA would improve muscle strength.

Material and methods

The Bunkeflo study or the Pediatric Osteoporosis Intervention (POP) study was initiated in 1999 by Professor Karlsson and Associate Professor Gärdsell. Several departments have studied this population-based cohort longitudinally, collected and followed by the Department of Orthopedics in Malmö, which primarily focused on evaluating musculoskeletal health and effects of an intra-curricular school-based exercise intervention through all the compulsory school years.

This prospective population-based controlled exercise intervention program started the implementation of 40 min of intra-curricular exercise each school day. Children in the intervention group therefore had 200 min of physical education (PE) per school day compared to the Swedish standard of a mean 60 min/week, the level also among the control subjects. The exercise included ball games, jumping, running, playing and was supervised by the original teachers and no additional funding was therefore required. The intra-curricular PE in Sweden is compulsory so all children had to participate, not only those who were particularly interested in sports. During vacation and weekend periods, no additional exercise training was provided. The study was conducted according to the Helsinki Declaration of 2000 and was approved by the Ethics

Committee of Lund University (LU 453-98; 1998-09-15). Informed written consent was obtained from parents or guardians of all participating children prior to study start.

Fracture registration

Fractures that occurred during the study period were registered in all 2621 children from school start onwards in the central radiological archives of the only hospital within the city. The radiological archives have been digitized since 2001. Fractures sustained elsewhere were classified in the radiological archives after the follow-up visit at our hospital, SUS Malmö. The methodology has been proven valid since it misses less than 3% of the fractures(152). The fracture database was regularly updated so that **papers I and III** consisted of 2395 individuals whereas **paper IV** included 2621 individuals. The increasing numbers are due to the fact that the study ran from 1999 to 2009 where all children starting the first grade gradually were included.

Measurements

The sub-cohort that was measured consisted of children from the first and second grades, invited in 1999, from the same four schools, Ängslätt, Mellanheden, Ribersborg and Fridhem, where the last three of which served as control schools. The children were repeatedly measured by Dual X-Ray Absorptiometry (DXA), a computerized dynamometer (Biodex) which evaluated

muscle strength in knee flexion and extension during the study period. Repeated assessments were also done of anthropometry and physical performance by vertical jump height test (VJH). At the last and second to last measurements

they were also invited for measurements of the radius and tibia by peripheral computed tomography (pQCT) of the tibia, radius and by Quantitative Ultrasound (QUS) of the calcaneus.

Fig. 14. Participants in the POP study during PE. By courtesy of Bjarne Löfgren



Study subjects

Paper I

At baseline, 55 of 61 girls and 84 of 89 boys in the intervention school accepted participation. One girl, 11 months younger than the rest, was excluded. At follow-up, 6 girls and 6 boys had moved out of the region or declined further participation. Two boys were excluded owing to medication that influenced bone metabolism. This left 48 girls and 76 boys for the intervention group. Sixty-four of 158 girls and 68 of 169 boys in the control group accepted participation. At follow-up, 19 girls and 12 boys had moved out of the region or declined further participation. One girl and one boy were excluded owing to medication that influenced bone metabolism. This left 44 girls and 55 boys for inclusion in the control group. All children were repeatedly measured by DXA.

Paper II

At study start we invited 65 girls and 88 boys in the intervention group. In the control group we invited 157 girls and 170 boys. Of the initially invited case subjects 61 girls and 85 boys accepted. Acceptance among controls was 64 girls and 68 boys. During the study period one girl who was only five years at study start and two boys were excluded for medical reasons in the intervention group. One control girl and one boy were also excluded for medical reasons. In the control group one girl was

excluded since she lacked a muscle measurement. In the case group 13 girls and seven boys were lost because they either moved or declined participation at baseline or follow-up. Among controls the attrition was 16 girls and 13 boys. This left a study sample of 47 girls and 76 boys in the case group. The control group consisted of 46 girls and 54 boys to be evaluated versus the case group regarding muscular development.

Paper III

At study commencement, 55 out of 61 invited girls and 84 out of 89 invited boys from the intervention school agreed to participate. One girl was excluded because she was 11 months younger than all the rest. During the five-year follow-up period, six girls and nine boys moved out of the region or declined serial measurements. Two boys were excluded due to medication known to influence bone metabolism, leaving 48 girls and 73 boys. Sixty-four out of 158 girls and 68 out of 169 boys from the control schools accepted participation. At follow-up, 15 girls and 13 boys had moved out of the region or declined serial measurements. One girl and two boys were excluded due to medication known to influence bone metabolism, and one boy adopted from Colombia was excluded as being the only Non-Caucasian, leaving 48 girls and 52 boys in the control group. All these children were repeatedly measured by DXA.

At the follow-up measurement all children in the DXA group were also

invited for follow-up measurements of volumetric bone mineral density (vBMD; g/cm^3), the structural parameters of the radius and tibia by peripheral computed tomography (pQCT). Of the children evaluated, 195 accepted this extra measurement.

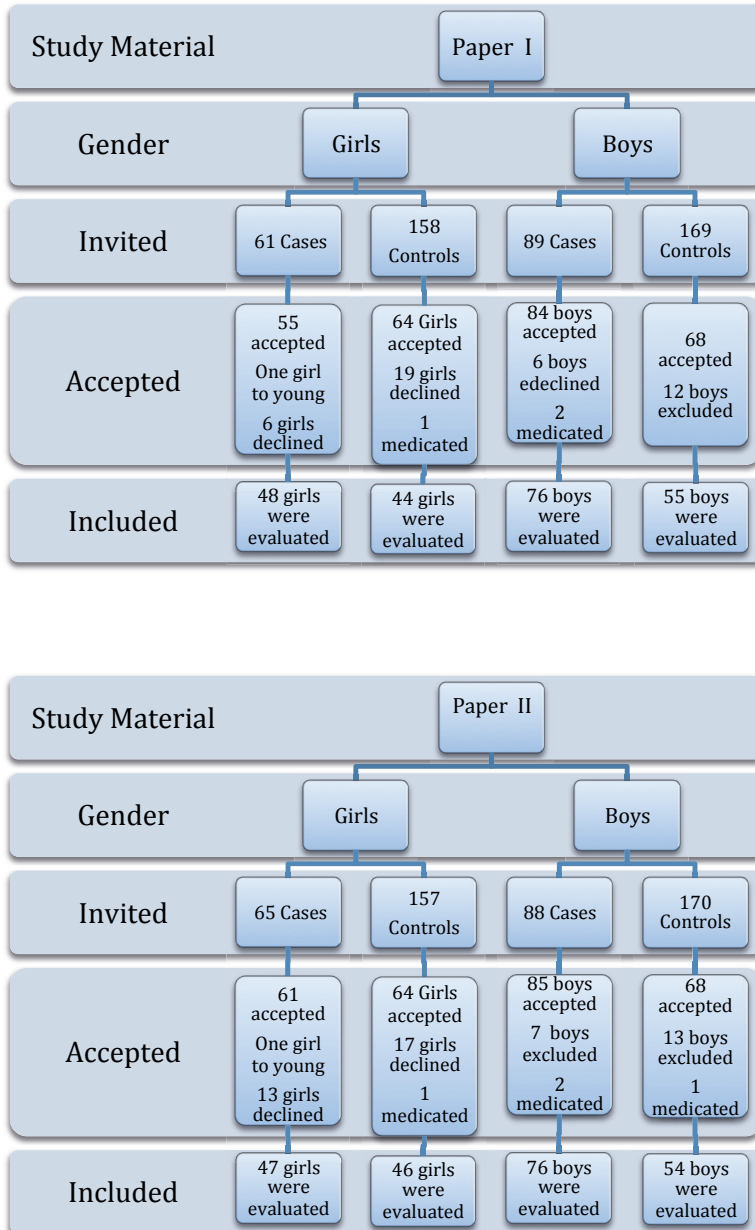
Paper IV

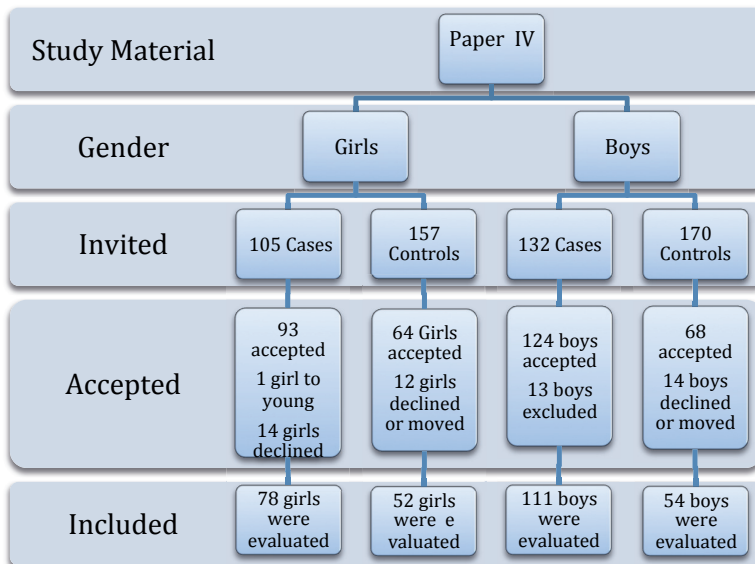
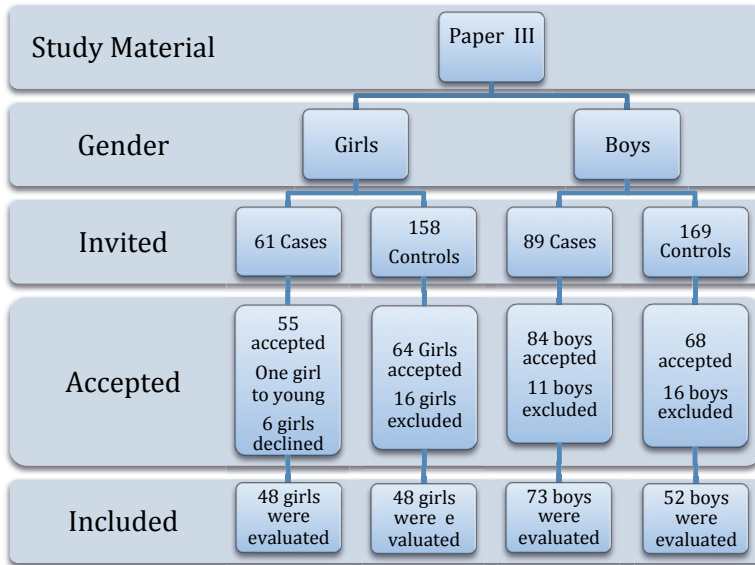
In this sub-cohort, 93 girls out of 105 and 124 boys out of 132 invited accepted participation in the intervention group and 64 girls out of 157 invited and 68 boys out of 170 invited in the control group. Measurements of anthropometry and skeletal traits were conducted at school start in all children, in the intervention school before the study start. Measurements were repeated annually, commencing after one year in eight of the intervention classes ($n=153$) and after 3 years in five classes ($n=84$) and then until study end. In the control

schools the second measurement was done after 2 years, continuing annually until study end. To be included in this report the participants had to have a baseline measurement, the sixth or the seventh measurement, at least four measurements after baseline, and they had to stay in the same school the entire study period and be without any diseases or medication known to influence bone metabolism.

These criteria rendered a drop-out of 15 girls and 13 boys in the intervention group and 12 girls and 14 boys in the control group. Our report of bone trait changes therefore includes 78 girls and 111 boys in the intervention group and 52 girls and 54 boys in the control group. As in **paper III**, we conducted pQCT ($n=221$) but now also Quantitative Ultrasound (QUS) measurements ($n=131$) in the children who accepted this extra measurement.

Fig. 15. Flow-Chart study material





Drop-out analysis measurements

Drop-out analyses in the sub-cohort that was followed revealed that there were no differences in baseline age, height, weight, body mass index (BMI), total body or regional body composition, BMC, muscle strength, or vertical jump height when comparing the children that completed the measurements and those that only attended the baseline measurement (data not shown). Furthermore, there were no differences in age, height, weight or BMI when data from the grade one compulsory school health examination were analyzed and compared to the children who participated in the baseline measurements with those who declined (185, 186, 284). This strengthens the view that the data are generalizable.

Fracture Registration

All children with school start between the years 1999 and 2009, assigned to the four participating schools in the POP study, were included in the prospective fracture registration. Since we updated the fracture cohort repeatedly and had different follow-up periods in the different papers, there were a total of 2395 children in the fracture evaluation included in **papers I and III**, whereas there were 2621 children in **paper IV**. Actually 100% of the studied population fractures were registered through the hospital archives and not through questionnaires. Less than 3% of all

fractures occurring in the studied population are expected to be treated entirely out of the hospital, predominantly by private practitioners, and might thus be missed in this registration (152). Also, about 14% of the fractures, based on previous studies, are expected to occur and initially be treated at another location (during holidays) however the majority of those fractures will then be registered at follow-up visits in Malmö (152).

All fractures in the studied population were confirmed and classified through the archives by one of the co-authors, a senior consultant in orthopedic surgery. We used the Landin classification of trauma levels (low-energy trauma, moderate trauma or high-energy trauma) (174), which has been used in several other pediatric fracture studies (54, 56).

Questionnaires

Children had to fill out an extensive non validated questionnaire regularly; it covered smoking status, alcohol use, intake of dairy products, current medication, current disease, previous medication, previous disease and also previous fracture. Also, and most importantly, the amount of organized physical activity outside school as well as within the curriculum was assessed (89). The total mean activity calculated at baseline and at follow-up is presented in our studies.

Accelerometers

This method provides an objectively measured amount of physical activity (80). Accelerometers (Model 7164 MTI; Manufacturing Technology, Inc, Fort Walton Beach, FL, USA) were used for four days in the middle of the study period. An epoch of 10 seconds was used to assess the mean amount of counts. In addition, the mean activity during every minute (6 epoches) was used to categorize PA into moderate to vigorous (MVPA) when the child had over 1000 counts per minute (cpm). When it was over 3500 cpm it was considered vigorous PA (VPA), which corresponds to over 6 metabolic equivalents (METs) whereas MVPA corresponds to only 3 METs. The most strenuous types of activities were also registered at 5000, 6000 and 10,000 cpm in order to capture the anticipated osteogenic loading (221).

Physical activity assessed by questionnaires

Duration of PA in school and organized PA during leisure time were registered through the questionnaires and the total duration of physical activity was estimated as duration of school physical education and organized leisure time activity per week and mean value during the study period was calculated (hours/week).

Anthropometrics and maturation

Height (Holtain stadiometer) and weight (Avery Berkel HL120 electric scale) were measured by standard equipment repeatedly in all children in the subgroup when wearing light clothes without shoes. Body mass index (BMI) was calculated as $\text{weight}/\text{height}^2$. Pubertal maturation was assessed by our research nurse in younger ages and self-assessed with the assistance of our research nurse if problems arose in older ages. This method has been validated by Duke et al. (87).

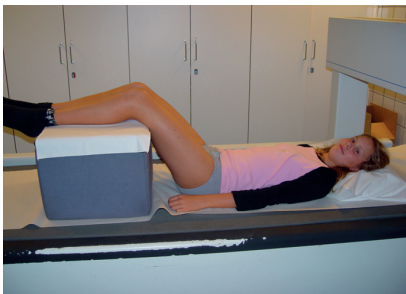
Bone and Muscle Measurements

Dual X-ray absorptiometry (DXA)

To regularly assess skeletal development, DXA (DXA; DPX-L[®] version 1.3z; Lunar Corp, Madison, WI, USA) was applied to evaluate BMC and BMD in the total body, lumbar spine and hip. From the spine scan the machine calculated BMC, BMD and size of the second to fourth lumbar vertebrae. Total body fat mass, total body lean mass, spine BMC and spine BMD was derived from the total body scan. The hip scan provided us with BMC, BMD values on the trochanter and femoral neck (FN), and also FN size. Hip structural analysis (HSA) was evaluated by the same device, from Lunar Corp, applied to the hip scan. It evaluated the femoral neck cross-sectional area (CSA, cm^2), section modulus (Z, cm^3) and cross-sectional

moment of inertia (CSMI, cm^4). Measurements that were 3 SD below or above the mean were considered biologically unlikely in the HSA analyses and excluded according to the method proposed by Beck et al. (29). The equipment was calibrated daily with the Lunar® Phantom by our research technicians who also conducted all measurements and software analyses. As we measured the precision, the coefficients of variation (CV %) were for BMC 1.4–3.8%, for bone width 1.5–2.2%, for FN CSA 2.2%, for FN Z 6.2%, for FN CSMI 6.2%, for 3 total-body fat mass 3.7% and for total-body lean mass 1.5%. The precision was assessed in 13 healthy children by duplicate measurements.

Figure 16. Girl from the POP study being measured by DXA. By courtesy of Bjarne Löfgren.



Peripheral Computed Tomography (pQCT)

Peripheral quantitative computed tomography (pQCT) (pQCT; XCT 2000; Stratec, Pforzheim, Germany) evaluated the appendicular skeletal properties in the sub-sample at the fifth

(Paper III) and sixth year (Paper IV) follow-up. A scout view determined the 4% and 38% level from the distal tibial physal plate in both extremities and 4% and 66% from the distal radius physal plate. These regions were used to measure BMC, vBMD, cortical area, cross-sectional area (CSA) and bone strength strain index with respect to torsion (polar SSI; mm^3) and bending (SSI; mm^3). These estimates have been shown to correlate well with mechanical strength in long bones of rats (100). The precision (CV %) was for tibial trabecular vBMD 1.7%, tibial cortical vBMD 0.5%, tibia cortical area 1.1%, radial trabecular vBMD 3.4%, radial cortical vBMD 1.4% and radial cortical area 4.6% estimated by double measurements in 13 children.

Quantitative Ultrasound (QUS)

At the six-year follow-up (Paper IV), right calcaneal bone traits were also measured by quantitative ultrasound (QUS) (Lunar Achilles model 1061, Lunar Corporation, Madison USA) in 133 among the children who accepted this extra measurement. QUS presents speed of sound (SOS; meters/second; m/s) and broadband ultrasound attenuation (BUA; (decibels/megahertz; dB/MHz)). Daily calibration of the machines was performed during the entire study period and measurements done according to the standard procedure. In order to get the proper position of the mid region of the calcaneus, up to two foot pads were

inserted under the foot in small children depending on foot size. Three research technicians performed all measurements. The precision (CV %) was 0.3% for SOS, and for BUA 2.2%, estimated by duplicate measurements in 13 children.

Muscle Strength

A computerized dynamometer, Biodex (Biodex System III Pro®, with Biodex advantage software) measured the strength of the quadriceps and hamstrings muscles during concentric isokinetic contractions. The children were fastened by straps, over the hip at a 85° angle flexion, thigh, shin and torso stabilizing straps over the chest. When there was space between the back and seat a cushion was placed there to fill out this space. When the child's leg was too short, a pad was likewise used to adjust the difference in leg length. The knee axis of movement was positioned at the axis of rotation of the Biodex machine. The movement measured was performed as a concentric isokinetic flexion or extension at either 60°/second (°/sec) or

180°/sec angular velocity. The knee went through a 75° range of motion from 90° flexion to 15° of flexion during extension movement and thereafter backwards to 90° during the flexion. The child would warm up with three submaximal trials before the power of each angular velocity was measured. During testing, the arms were crossed over the chest and the children were given supportive encouragement during the test to push and pull as much as they could. At the 60°/sec velocity every child did a maximum of 5 repetitions and thereafter rested for 30–60 sec and consecutively made 10 maximal contractions, both flexion and extension, at 180°/sec angular velocity. The highest value obtained for each parameter was used in our analysis and represents the force multiplied by the lever arm (Nm) corrected for gravitation.

The coefficients of variation (CV) was for PTE_x60 6.6%, for PTFI₆₀ 12.1%, for PTE_x180 12.3% and for PTFI₁₈₀ 9.1%, estimated by double measurements in 21 children.

Figure 17. The Biodex machine



Vertical Jump Height (VJH)

Neuromuscular function was assessed by a vertical jump on an electronic mat, which registered time in the air (“Time it”; Eleiko Sport*, Halmstad, Sweden) and thereafter calculated the height in centimeters. During this movement several joints are used, such as ankle,

knee, hip and depending on the setting sometime the arms. Also, several different muscles are activated. Maximal jumps are done from a standing position after the participants have jumped onto the mat. Every child does three jumps and the highest is recorded (cm). The CV % was 5.9% estimated by double measurements in 21 children.

Fig 18. VJH performed on the “Time it” electronic mat. By courtesy of Bjarne Löfgren



Statistical methods

All calculations were performed using Statistica (Statwin, 2005) (**Papers I+IV**) and Statistical Package for the Social Sciences (SPSS, Version 20–22) (**Papers II–IV**). Data are presented as Means \pm SD or Means with 95% Confidence Interval (CI). Rate ratio was used for fracture risk assuming Poisson distribution.

Paper I

Lifestyle factors were compared using cross-tabulation with either Chi-2 or Fisher's exact test. Tanner stage between groups was compared using the Mann-Whitney U test at both baseline and follow-up. Two-tailed Student's t-test was applied to compare group differences in parametrics at baseline. Annual changes were calculated as delta values (Follow-up value – Baseline value / Follow-up time). Annual changes were compared using Analysis of Covariance (ANCOVA) with group difference in final Tanner stage as covariate. The amount of physical activity was used to categorize children into tertiles. Subsequently the group differences in bone mineral accrual depending on the respective amount of physical activity, dose-response, was analyzed by Analysis of Variance (ANOVA). Fracture risk was calculated as a rate ratio assuming a Poisson distribution. Survival function curves were done using Kaplan-Meier statistics.

Paper II

The lifestyle factors were compared in the same way as in **paper I** and **III–IV**. Two-tailed Student's t-test was used to compare baseline differences and ANCOVA to adjust for differences in baseline age. The annual changes were calculated using delta values as in **paper I**. In the first model comparing group differences, Two-tailed student's t-test was used. In the second model ANCOVA was used with adjustment for baseline age, final Tanner stage, annual change in height and baseline parameter value.

Paper III

Lifestyle factors, baseline values and fracture data was compared as previously mentioned in **Paper I**. In this paper, however, linear regression analysis was performed on the six measurements of bone parameters, resulting in a slope. The slope was used to compare annual changes between groups by the two-tailed Student's T-test. At follow-up Peripheral Computed Tomography (pQCT) was applied at the radius and tibia. This cross-sectional data was also evaluated with Student's T-test in order to evaluate group differences at follow-up.

Paper IV

The lifestyle factors and fracture evaluation were calculated in the same way as in **papers I–II** and **IV**. Baseline differences were presented in two different models, first adjusted for baseline age and secondly adjusted for

baseline age, height and weight. The annual changes, in bone parameters evaluated by linear regression slopes, were in this paper compared by ANCOVA presented in three models with different covariates. Model 1 compared means adjusting for final age. Model 2 adjusted for age at follow-up, final Tanner stage and height at follow-up. Model 3 additionally adjusted for weight at follow-up compared to the second model.

Summary of Papers

Paper I

Introduction: The aim of this study was to determine the effects of a longitudinal three-year exercise intervention trial on skeletal traits, hip structure and fracture risk in prepubertal children.

Subjects: We assessed fracture risk in 2395 children. In 76 intervention boys and 48 girls as well as 55 boys and 44 girls who served as controls, DXA examinations was done at study start and in the third year.

Methods: The school-based exercise hours were increased from 40 min to 200 min/week. Fractures were registered from the radiological archives in all children in the intervention and control schools. In a subcohort, we used DXA to measure bone mineral content (BMC), bone mineral density (BMD) and bone size of the lumbar spine and hip. Hip strength was assessed by special software that calculated values for resistance to bending forces, cross-sectional moment of inertia (CSMI) and section modulus (Z).

Results: The risk of sustaining a fracture was not increased after commencement of increased PA (rate ratio 1.08 (0.71, 1.62)) (mean (95% CI)). The annual accrual of BMC in the lumbar spine was greater in intervention children (boys $p < 0.001$, girls $p < 0.001$), as was third lumbar vertebrae bone size (in both

genders $p < 0.05$), The femoral neck CSA annual gain was larger in girls in the intervention group ($p < 0.05$) as was FN BMC ($p < 0.05$).

Discussion: Strengths of the study include the prospective population-based study design and the thorough drop-out analysis. Limitations include the lack of randomization and larger drop-out frequency in control group.

Conclusion: A three-year exercise intervention program in prepubertal children improves bone mass and size without affecting the fracture risk.

Paper II

Introduction: Evidence suggests that strength training in children is associated with beneficial muscle strength. However, there is less information in the literature regarding the effects in prepubertal children of a population-based exercise intervention program on muscle function. Previous short-term studies have shown beneficial effects after two years. The aim of this study was to evaluate the effects of a three-year exercise intervention program on muscle development and body composition.

Subjects: The cohort which was measured consisted of 47 girls and 76 boys in the intervention group and 46 girls and 54 boys in the control group.

Methods: This longitudinal controlled exercise intervention study assessed isokinetic concentric flexion and extension of the knee joint measured by a computerized dynamometer at study start and follow-up. Two velocities were

used during the testing, 60°/second and 180°/second. Delta values were used to calculate annual changes. Group differences were evaluated by ANCOVA.

Results: Both girls and boys improved their annual gain in muscle strength of the hamstring muscles during flexion at 60°/second (all $p < 0.05$).

Discussion: The improved gain in muscle strength could lead to positive health effects including reduced fracture risk due to better neuromuscular function. A high level of evidence and a design that reaches all children is a major strength of this study. Other strengths include the population-based design and the moderately intense intervention so all children could participate. One limitation include lack of individual randomization.

Conclusion: Increased exercise during a three-year period in children who were prepubertal at study start, brings benefits in the annual gain in muscle strength.

Paper III

Introduction: Most pediatric exercise intervention studies that evaluate the skeletal effects of exercise include volunteers, use specific training programs and have short follow-up periods. It is known that bone mass and bone size affect bone strength and subsequent fracture risk. However, there are studies that have coupled intense exercise to increased fracture risk. We assessed the risk of sustaining fractures and the possibility of achieving skeletal benefits

at growth during a 5-year exercise intervention trial where the intervention group had five mandatory gym classes every week.

Subjects: We registered fractures in 2395 children. We measured bone mass and size repeatedly by DXA in a subcohort consisting of 48 girls and 73 boys in the intervention group and 48 girls and 52 boys in the control group.

Methods: Fractures were registered in the radiological archives and classified by trauma mechanism. A questionnaire evaluated lifestyle factors. The intra-curricular exercise was increased from 60 min/week to 200 min/week in the intervention group. The control group continued with 60 min/week. Anthropometry was measured by standard equipment and skeletal development by DXA. Peripheral computed tomography (pQCT) measured the appendicular skeleton at the radius and tibia at follow-up.

Results: The rate ratio of sustaining a fracture in the intervention group was 1.08 (0.79, 1.47) (mean (95% CI)). The annual gain in spine BMD was greater in children in the intervention than in the control group (girls $p < 0.001$, boys $p = 0.01$). Girls in the intervention group had also larger annual gain in the femoral neck BMC ($p = 0.02$) and FN area ($p = 0.03$) and at follow-up more cortical BMC of the tibia ($p = 0.03$), cortical area ($p = 0.02$), larger total cross-sectional area of the radius ($p = 0.04$) and larger stress strain index (SSIX) in both

the tibia ($p=0.04$) and radius ($p=0.02$) than control girls.

Discussion: This study shows that our inferences in the previous papers with a shorter follow-up period remain with a longer duration of the intervention. In other words, the skeletal benefits remain with an increased PA period but without causing changes in fracture risk. Study strengths include the long follow-up, implementation of linear regression slopes that use all measurements instead of using delta values, and also the inclusion of pQCT measurements at follow-up.

Conclusion: A five-year exercise intervention program improves skeletal traits without increasing the risk of fracture.

Paper IV

Introduction: There are few exercise intervention trials that focus on the long-term effects of a moderately intense intra-curricular exercise program on fracture risk and skeletal development. This study examined whether previously reported benefits on the skeleton were retained with extension of the program into the peripubertal period without affecting fracture risk.

Subjects: In 2621 children in the study cohort we registered fractures in the radiological archives. In a subcohort that included 78 girls and 111 boys in the intervention and 52 girls and 54 boys in the control group we followed skeletal traits by repeated measurements.

Methods: We registered fractures and classified them according to trauma level and localization in the radiographic archives. We used DXA measurements of the total body, spine and the hip for repeated evaluations of bone mass and bone size during the study period, in most individuals with annual measurements. Slopes were calculated for annual changes by using all measurements. Bone mass and bone structure at follow-up were measured by DXA, pQCT and QUS and then compared between the groups. Questionnaires evaluated lifestyle factors. Group differences in annual bone mass, bone size changes, group differences in bone traits at study start and follow-up were compared by ANCOVA, adjusting for potential confounders.

Results: The rate ratio for fracture risk in the intervention group was 1.12 (0.85, 1.46) (mean 95% CI). Girls in the intervention group had higher annual accrual in spine BMD, femoral neck BMC and femoral neck area than girls in the control group (all $p<0.05$) while boys in the intervention group had higher annual gain in spine BMD than boys in the control group ($p<0.05$). At follow-up, girls in the intervention group had mean 8% larger tibial cortical BMC, 8% larger tibial cortical area and 6% larger tibial cross-sectional area (all $p<0.05$). Girls in the intervention group also had mean 11% higher femoral neck BMC, 8% higher femoral neck BMD, 8% higher spine BMC and 4% higher spine BMD than girls in the control group.

Discussion: This is currently the longest pediatric prospective controlled exercise intervention study on skeletal traits in the literature. The study infers that the skeletal benefits reported with PA with shorter intervention periods are retained with extension of the program. The benefits are more obviously seen in girls than in boys. The findings support the view that intracurricular PA in children may improve peak bone mass.

Conclusion: Long-term exposure to increased moderately intense PA in children who were prepubertal at study start improves the annual gain in skeletal traits, also when most children have reached puberty, without increasing the fracture risk.

General discussion

The clinical problem

Strategies to prevent osteoporosis and fractures need to be implemented in society, since the increasing numbers of fragility fractures must be reversed. These strategies must both reduce the economic burden on society and minimize individual suffering. At present we predominantly address osteoporosis by targeting individuals with manifest osteoporosis or osteopenia, with or without fractures, using pharmacologic treatments (60, 170) or trying to reduce other risk factors for fractures in high-risk individuals [172,177]. These treatments are excellent and have been shown in multiple RCTs to reduce the future fracture risk (110, 214). Even better would, however, be to intervene before osteoporosis or the first fracture occurs, for example by improving two of the most important modifiable risk factors for fractures, bone mass and muscle strength (10, 65). This should be done in those who are in greatest need or even better, in all individuals in the community. Physical activity (PA) may be a strategy to reach these benefits.

Determination of musculoskeletal traits

Although genetic factors contribute to 60–80% of the variance in bone mass (8, 96, 160, 239, 241, 245, 278), there are various lifestyle factors that could modify the path of bone mass changes and fracture risk by aging. Reduction of

smoking habits, of alcohol consumption, optimizing the diet and increasing the level of PA are all factors that could improve bone mass. This could be achieved by either reducing the age-related bone loss or by improving the accrual of bone mass and gain in bone size at growth. The growth period may actually be the most important period in life to influence the skeleton, since growth is highly variable, compared to the more constant and more stable bone attrition after PBM (134). The estimations that 50% of the bone mass at age 70 is predicted by PBM (134) and that 60% of the mature skeletal traits are dependent on the variance before puberty (190) support this view.

An increase in the level of PA at growth would thus hypothetically be one of the most available modifiable lifestyle factors that could influence the BMD level and PBM in the population. But PA may also be beneficial for the development of muscle strength and neuromuscular function, other traits that determine who will fall and incur a fracture (106, 117, 254, 313). Improvements in these traits would thus be important, since beneficial muscle function would lead to fewer falls, less trauma and fewer fractures. If exercise also improves bone strength, a more trauma-resistant skeleton will not fracture even in the event of a fall. That is, PA ought to reduce the number of fractures if we could achieve these benefits through a change in the PA habits of children. This is what my thesis and **papers I–IV** are about.

Physical activity and musculoskeletal traits

It is imperative to understand that the influence PA may have on bone mass and muscle strength compared to heredity is small (91, 239, 241). In addition, as shown in **papers I–IV**, compared to the absolute gain in bone mass, muscle size and muscle strength that occur at growth, the effect that could be gained by extra PA is small over time. In studies of monozygotic and dizygotic twins, genetic factors have been shown to determine 50–85% of the variance in bone traits depending on the studied site (44, 91, 239), where hip and distal forearm seemed to be sites where BMD was genetically determined to a lesser extent than lumbar spine (241). Some 30–50% of the variance in muscle strength is determined by the genome, but the genetic proportion seems to decrease with advancing age due to the lifelong influence of a variety of lifestyle factors. In other words, the genetic proportion contributes to more of the variance in the traits of the child than in the old individual. In contrast to heredity, PA contributes to a smaller proportion, 5–7%, of the variance in bone mass in the hip and spine (206, 314). Environmental factors, such as PA, also contributes to the variance in muscle strength. The influence depends on localization and as much as 54 % in leg extensor strength and 70 % in hand grip strength is affected by the environment(16). But if PA at growth could be a strategy to reduce the adult

fracture risk, then PA-related musculoskeletal benefits at growth must be retained long-term. Now there is growing evidence that this could be the case (71, 224, 229, 299, 301) but whether muscle strength and bone strength follow the same long term path remains to be evaluated(282).

Today it must be regarded as proven that PA confers musculoskeletal benefits (71, 224, 229, 299, 301). One question then arises: could a PA intervention program in children that includes all individuals, not only those with interest and special skills in exercise, and on such low level that all could participate, improve the general level of bone and muscle strength in the general population?

In **papers I–IV** and in this thesis we evaluated such a program in children who were prepubertal at study start. We therefore purposely did not design a specific exercise program known to be most beneficial for gaining muscle and bone. Such a program would include load that is fast, dynamic, high in magnitude, with unusual or abnormal strains, being intermittent and with a short duration of loads, with resting periods included between the loading session in order to produce the most pronounced musculoskeletal response (176, 177, 255, 258, 297). But our program was intended to improve not only the skeleton and the muscles, but also general health and school performance (80, 81, 92, 121, 122), being simple so that it could be implemented with no extra resources and

at low cost. Such a program could then target the entire pediatric population in one area and be started in any school with no extra resources. By including a variety of activities we wanted to reduce the risk of drop-outs, something that often occurs among children if conducting only few repeated activities. Finally, by varying the activities we would hopefully lay the foundation for a lifelong healthy lifestyle (158), a view supported by previous publications showing that the level of PA in adulthood is founded in childhood (293).

Skeletal measurements

In **papers I–IV** we therefore wanted to follow the musculoskeletal development in children with different PA levels from school start and at growth. But there are great challenges in conducting bone mass measurements at growth. The gold standard of bone mass measurements today is dual-energy X-ray absorptiometry (DXA). DXA has several advantages. The technique includes a low radiation dose (one DXA measurement approximately equals the radiation dose received during a transatlantic flight from Copenhagen to New York i.e. 1–8 micro Sievert (μSv)) (4) and is relatively accessible. It is also the most commonly used scanning method and the one used in clinical work, also in children, when assessing bone mass. Bone mineral content (BMC; g) at growth is considered to be a more reliable measure than bone mineral density (BMD; g/cm^2), since BMD is affected by the body size and since body

size changes at growth (244). The International Society of Clinical Densitometry (ISCD) has therefore recommended the presentation of BMC and bone size separately in children (33). In contrast, BMD is the value most used when presenting bone mass in adults. Yet neither BMC nor BMD provide a true measure of bone mineral content in relation to a volume, since DXA is not a three-dimensional scanning technique. BMC estimates the total amount of mineral within the beam of the scanned region and BMD the total amount of mineral related to the scanned area of the bone, not the scanned volume. BMD is therefore sometimes referred to as areal BMD (aBMD). Increase in bone size, as seen at growth, with exactly the same amount of bone mineral would thus produce a decrease in the BMD value, erroneously leading to the conclusion that the child is losing bone mineral (while the child instead is actually gaining in size). We also know that the accrual of bone mineral and the gain in bone size actually do not follow the same pattern, especially at puberty (40), which causes problems when trying to understand what actually happens with the skeleton if there are BMD changes. In **papers I, III and IV**, however, we report both BMC and BMD values, since BMD, in spite of the problem discussed above, is often reported in the clinical setting and since several of our reviewers actually suggested that we should also include BMD values when we initially only provided the BMC and bone size values.

Furthermore, because DXA is designed to measure bone mineral, not skeletal structure, it limits the value of the HSA method because of the minor spatial resolution, compared to new techniques such as pQCT and MRI, the detection of bone dimensions are difficult (13, 14). Also a small measurement error results in a large difference in CSMI since this calculation uses the fourth power of the size measurement. Therefore limb positioning, in particular anteversion of the hip, and inaccuracies during the manual placement of the region of interest (ROI) may result in substantial errors. Due to this we used the method recommended by Beck et al., which excludes biologically unlikely values when the HSA technique is utilized in children (29). However, as the importance of bone structure for bone strength has gradually gained more and more interest, we still added the HSA method, as one of the first attempts to include the bone structure in the discussion, even if only being estimated on a two-dimensional DXA scan (42, 270). With the development of newer three-dimensional scanning methods, however, the interest in the HSA technique has gradually diminished.

Another discussion that has been conducted is which skeleton region to scan and use in pediatric studies. Some researchers have recommended total body, lumbar spine, hip or distal forearm as being the gold standard (33), while others have recommended the use of total body minus the head (TBLH) since

the proportion of the head is larger in young than in old children and in adults (33), and since the head is a non-loaded skeletal region (162). In spite of these concerns, the hip and the spine are the most commonly clinical used pediatric regions today.

Novel scanning techniques have also been launched. One such technique is peripheral quantified computed tomography (pQCT) and recently the high-resolution PQCT technique. This technique can give information about the density and three-dimensional properties of bone. But it is important to realize that this method too is only an estimate of the true density, since pQCT, for example, does not take the amount of intra-cortical porosity into account. The method was not available at study start, but as the method provides additional information on the skeleton, we added this in **paper III and IV**, to include cross-sectional evaluation of the cohorts at the study end.

Muscle measurements

There are challenges when conducting muscle measurements at growth since a number of factors then influence the gain in muscle strength. Increased muscle size at growth does not account for the entire gain in muscle strength, even though there seems to be a linear gain in muscle volume until puberty in both boys and girls (195, 196). The cross-sectional muscle area is thus not the sole determinant of muscle torque (153). Developmental alterations in the

contractile mechanism and neural influences are also important. Age, body size, evaluated region, genetic and activity-related influences are also reported to exert important independent influences on strength performance, even though many of these factors are interrelated and may influence strength through common or shared variance (38). The development of muscle strength during the course of childhood is thus multifactorial (253).

It is therefore debated how to estimate the trait in children. We chose to use muscle strength tests, with the knowledge that the registration is highly dependent on the cooperation of the child and that this can vary substantially day from day, especially in young children, depending on motivation. As this is a standardized muscle strength test, however, we used it in **paper II**. VHJ is also highly dependent on maturation and the cooperation of the child. This especially accounts for younger children and is the reason why, as in the HSA study in **paper I**, we excluded biologically unlikely values in the muscle evaluation paper by a method described in the literature (29).

Fracture ascertainment

We ascertained fractures in **papers I, III and IV** in the radiographic archives of our hospital and through the computerized regional radiographic archive of Region Skåne. Fractures that occurred outside the region are usually classified during a follow-up visit in the home clinic. That is, in **papers I, III and**

IV we included only objectively verified fractures. This is a strength since other studies have shown that when only using patient-reported fracture data, there could be an overestimation of 10% to an underestimation of 30% of the actual fracture incidence, based on recall bias (51, 135, 142, 146). The ascertainment method has also been used extensively at our center in epidemiological studies for decades (188). Previous validation studies have shown that less than 3% of all fractures are missed by this classification system due to treatment outside our hospital (146, 152). We also identified trauma mechanism through a manual review of charts, referrals and reports. We defined slight trauma as falls in the same level or low-energy playing and sporting injuries, moderate trauma as falls from more than the same level up to 3 meters or traffic accidents that did not include motor vehicles, and severe trauma as falls from more than 3 meters or traffic accidents that included motor vehicles (174). This is a non-validated classification, but we used it since it has been advocated in several other studies for five decades, and by utilizing the same classification in **papers I, III and IV** we were able to compare our data with the previous reports in the literature (90, 174).

Physical activity measurements

Since this thesis and **papers I–IV** evaluate the musculoskeletal effects of PA in children, a definition of physical activity is in place. There has been ongoing discussion about the expression PA, but one of the most commonly used

definitions is “*any bodily movement produced by the contraction of skeletal muscles that results in energy expenditure*” (50). There is also ongoing discussion of how to register the amount of PA in children and whether an intervention really can increase the total level of PA (317). There are studies that infer the level of PA to be constant in children, which is referred to as “*the activity stat*” theory (316). This says that if you increase the level of PA in one way or another, these children perform less during other periods. In other words, by increasing the level of PA in school they would be less active during spare time, so that the total amount of PA would be unchanged (317). Our intervention program would then be useless in respect of the most important measure, the total amount of PA.

It is difficult to test the “*the activity stat*” hypothesis because of the known difficulty of estimating the level of PA in children (52). Some studies suggest that questionnaires do not give reliable estimations in children under the age of 10–12 years (52, 127). In order to minimize the risk of errors, the children answered the questionnaires in **papers I–IV** together with their parents. But also the use of objective measurements of PA is problematic (179). Accelerometer data in **papers I–IV** were only collected during a very short period in comparison to the total study duration, four days compared to a study period of up to 6 years in **paper IV**. The same problem is seen in virtually all studies using

accelerometers. Other accelerometer weaknesses include the inability to measure some activities such as cycling, since our accelerometers only captured changes in body level and swimming, since the accelerometers are not waterproof. Finally, we could not separate complete resting from the accelerometers not being worn. Due to this, erroneous PA data could also be provided by the accelerometers.

The available accelerometer data in **papers I–IV** imply that children in the intervention group had higher amount of the most intense recorded activities (>10,000 cpm). But these data must be interpreted with caution since these high intensity levels were only recorded a couple of minutes each day. The findings should anyways be noted, since it is the high-impact activities in short bursts that best influence bone tissue (176, 177, 256, 257). Another most interesting finding is that all children in **papers I–IV** had a general high level of PA, well above the current international recommendations of over 60 min MVPA per day (2). This indicates that the children, regardless of whether they are in the intervention or the control group, may obtain PA-induced benefits in cardiorespiratory, cardiovascular and metabolic traits, benefits reached by an extended duration of low to moderately intense training (311). That different types of PA are of different importance for different traits is part of the reason general guidelines regarding PA in children are difficult to establish (288).

The influence of PA on musculoskeletal growth

As shown in **papers I–IV**, it is possible to improve the gain in musculoskeletal traits in both girls and boys by introducing a moderately intense school-based general PA program. Our study design also shows that this can be done within the ordinary school resources. The only demand is that there is interest and willingness among the principals, the teachers, the parents and the children. The data in **papers I, III and IV** indicate that the beneficial skeletal effects of the PA intervention program were more obvious in girls than in boys. The gender discrepancy also seems to include benefits in skeletal structure, as captured by the pQCT data in **paper IV**. The reason could be that more girls than boys in **papers I, III and IV** had reached puberty, thus being closer or within their peak bone mineral accrual and peak bone width gain, since the PA-induced effects on the skeleton are most effective in Tanner stages 2 and 3(192). These Tanner stages correspond to the late pre-early peripubertal period (158). Girls in **papers I, III and IV** also had lower participation in organized sports activities outside school than the boys. This results in school PA contributing to a larger proportion of the total PA in girls than in boys, the intervention thus being of greater importance in girls than in boys. Another possible explanation is that there could be gender differences in the response to PA at growth.

It must also be discussed whether PA could increase PBM. A high PBM would

induce a great reserve capacity when the age-related bone attrition starts. Starting from a higher level of BMD in young years would hypothetically reduce the risk of developing osteoporosis in old age. In addition, if they adopted a physically active lifestyle at growth, these individuals would be more prone to continue with an active lifestyle in adulthood (293), then maintaining a strong skeleton in relation to others (301). As regards this, we must highlight that in **paper IV** we followed the effect of PA in respect of skeletal traits for a maximum of 6 years and in **paper II** muscle strength for 3 years. Yet it is unknown whether these benefits remain with our program until peak values. The data are promising but the cohort must be followed until young adulthood before we can draw inferences with stronger evidence in respect of PBM effects. Since there is now growing evidence in the literature that musculoskeletal gains through PA at growth persist in a longer perspective (72, 224, 230, 299, 301), the data in **papers I–IV** is most promising.

In **paper II** we showed that our program conferred beneficial neuromuscular effects in both genders. Improved muscular strength also reduces the fracture risk (117, 165), and simple muscle strength tests, such as hand grip strength test, have been shown to predict the risk of fall and fracture risk in adulthood (251). It also seems as if the intervention primarily influenced muscle strength through neurological adaptations, since the inferences in **paper II** remained after adjustment for

annual gain in leg lean mass and since there were no group differences in the gain in lean mass. This finding is supported in the literature (101, 104), suggesting that neural optimization is the primary way PA increases muscle strength before puberty (69). The group-by-gender analysis in **paper II** also suggest that there were no gender difference in the muscle strength response to the intervention. The findings of a less advantageous response in VHJ in girls might be to the fact that intervention girls were heavier than controls.

One unexpected finding, as shown in **papers I–IV**, was the higher gain in fat mass in the intervention girls than in the control group, since most studies infer high PA to be associated with low fat mass (218). We have no plausible explanation for this finding. One explanation might be an increased need of energy due to the extra PA in school, afterwards followed by excessive food intake. But, as we did not find a dose response relation between hours of PA and the annual gain in fat mass in **papers I–IV**, this indicate that the finding may be due to chance. Furthermore, as shown in **paper IV**, the disappearance of the group difference in fat gain in girls with a longer duration of the intervention supports this view.

The influence of PA on fracture risk

In **papers I** and **III** and **IV** we were able to refute the hypothesis that increased

levels of PA lead to more fractures. The finding of similar fracture incidence, as in previously published pediatric fracture studies (61, 174), indicates that our data are representative and therefore can be generalized to the entire population. The most common fracture site was the distal forearm followed by hand fractures, also consistent with previous publications regarding childhood fracture epidemiology (61, 174). The constant trend of a gender difference (although not statistically significant in **papers I** and **III** and **IV**) with boys having more fractures than girls, is also consistent with the literature (61, 174). Due to the power problem, however, as in most studies with prospective fracture risk evaluation, in **paper IV** we could only state that there was at least no 46% higher or 15% lower fracture incidence in the intervention group. Extended fracture epidemiological studies with more participants and a longer follow-up period must therefore be conducted before we can reach a final verdict.

It is also debated whether a high level of PA in young years actually decreases the fracture risk in the long term (276). At present, several studies have been published which infer that a high level in young years is associated with low fracture risk in later adulthood (72, 231, 233, 301). These inferences are based on studies with a lower level of evidence within the evidence-based hierarchy, but as there are no prospective long-term studies evaluating the question, we have to rely on the data that exist. These data

are promising, indicating a lower fracture risk in those with high levels of PA in young years. There are also reports indicating that there is a decreased fracture risk in senescence due to residual PA-induced bone mass benefits that are retained also after the active training career (301). According to large observational studies, a 1 SD higher BMD would induce a halved fracture risk (7, 10, 203).

Strengths and limitations

Paper IV includes the longest prospective population-based controlled exercise intervention program in children that studies the effects on the skeleton and **paper II** on the muscles. **Papers I and III and IV** include not only surrogate endpoint variables for the clinical problem, but also the actual clinical problem, fractures. Another advantage is that the fractures were objectively verified and ascertained by X-ray verification and medical reports instead of using self-reports as in most other similar studies (146) (152). Another advantage is the focus on not only the skeletal effects of PA but also on muscle strength and neuromuscular performance, which probably plays an underestimated role in fracture prevention (145). The inclusion of both pQCT and QUS in addition to DXA provides additional information, predominantly as regards bone structure. The use of individual linear regression slopes calculated by use of all individuals' data when estimating the annual changes in **papers III and IV**, compared to using delta values as in most published studies, is a more robust statistical method.

The limitations include the lack of individual randomization and that the study is not a double-blinded trial. However, this type of study could not be designed to be double blinded. Randomization was also practically

impossible to initiate due to the resistance of the teachers, pupils and the parents. The practical schoolwork would not have been possible to conduct if children in the same class had had different school curricula for such a long period. The lower participation rate in the control schools than in the intervention school in all **papers I–IV** could also lead to problems such as including self-selection bias at baseline. Our drop-out analyses in **papers I–IV** refute this risk. It would also have been advantageous to have accelerometer data already at study start and with annual measurements conducted. This could not be done due to lack of resources. A more thorough evaluation of the type of leisure time sports participation, also including non-organized PA, would have provided additional important information.

Conclusion

Increasing the amount of school PA from approximately 60 min/week to 40 min every day (200 min/week) in children who were prepubertal at study start is a possible strategy to improve skeletal traits and muscle strength at population level without increasing fracture risk. The collectively enhanced musculoskeletal health achieved by this program therefore has the potential to reduce fracture risk in the future. With available data, politicians and decision makers ought to consider implementing increased PA in all Swedish schools in order to improve the musculoskeletal health of the growing population.

Future Perspectives

There is compelling evidence that the PA intervention should be initiated before or in early puberty and that ongoing persistent PA leads to a variety of health benefits. A moderately intense PA program in childhood provides enough osteogenic stimulus to boost bone accrual and bone structure. The POP cohort must however be followed further longitudinally in order to evaluate whether the program really influences PBM in both genders. However, a six-year exercise intervention trial is a leap forward in the field that provides new knowledge in the respect that a school-based PA program has long-term effects when continued into puberty. Future studies should also include pQCT, preferably high-resolution pQCT, in the longitudinal measurements to give a

more reliable and accurate assessment of the structural and geometrical effects. The fracture epidemiology should also be extended to include more participants for a longer duration, to be able to state with high power if fracture risk is influenced or not.

Summary in Swedish – Populärvetenskaplig sammanfattning

Fysisk aktivitet har sedan länge sammankopplats med stark benstomme och stark muskulatur. Andra studier visar att hög fysisk aktivitet möjligen ger upphov till fler olyckor och frakturer. Man vet inte heller om ökad idrott i en oselektade grupp med barn, inkluderande även de som inte gillar idrott, kan påverka skelettet och muskulaturen positivt. Bunkeflostudien, eller som den kallas på engelska ”The Pediatric Osteoporosis Prevention (POP) Study”, är en studie där en grupp barn fick daglig fysisk aktivitet i skolan medan en annan grupp fick fortsätta med 1–2 lektionstimmar per vecka. I olika studier utvärderar vi sedan effekten av daglig skolgymnastik på frakturrisik och utvecklingen av skelett och muskulatur. Barnen var vid studiens inledning 6–9 år och ingen hade då kommit in i puberteten. På Ängsslättskolan i Bunkeflostrand, en förort till Malmö, ökades mängden idrott och hälsa i skolan från 60 minuter i veckan till en daglig lektion på 40 minuter (totalt 200 minuter i veckan). I tre närliggande kontrollskolor fortsatte man med svensk standard på 1–2 lektionstimmar per

vecka (60 minuter per vecka) Antalet frakturer registrerades via röntgenarkivet i Malmö hos alla deltagande 2621 barn under utvärderingsperioden som respektive rapport studerade (de olika delstudierna i avhandlingen hade uppföljningstider mellan 3 och 6 år). I en subgrupp mättes bentäthet, benstorlek, benstruktur, muskelstyrka och hoppförmåga med regelbundna intervall (hos de flesta med ett års mellanrum). Benmassa mättes återkommande med lågdosröntgen (DXA-teknik) och efter 5 och 6 år dessutom med datortomografi av underarm och underben samt efter 6 år med ultraljud av hälbenet. Muskelstyrka mättes som maximal knäböjnings- och maximal knästräckningsförmåga samt som förmågan att hoppa högt på stället under en 3-årsperiod.

I artikel I, III och IV visar vi att ökad fysisk aktivitet inom ramen för ämnet idrott och hälsa under en upp till 6-årsperiod förbättrar inlagringen av benmassa hos både flickor och pojkar utan att påverka frakturrisken. Flickorna erhöll dessutom en gynnsam utveckling av benets storlek och skelettstruktur. I artikel II visar vi att 3 år med samma program medförde i båda könen en gynnsam utveckling av den muskulära styrkan hos både pojkar och flickor.

Ökad skolgymnastik förefaller således vara en strategi som kan förbättra utvecklingen av skelett och muskelstyrka utan att öka frakturförekomsten. Vi hoppas nu att dessa gynnsamma förändringar under tillväxten leder till ett

starkare skelett och bättre muskulatur även i vuxenlivet, något som andra publicerade studier stödjer, och med det färre frakturer. Med den nya kunskap som dessa studier ger oss har vi nu underlag att rekommendera att skolan bör erbjuda daglig schemalagd fysisk aktivitet.

Acknowledgments

I would first like to thank my family, my girlfriend Manuela, my co-workers and all the friends who all have helped me with invaluable support, both professional and personal, in the course of my work. You all have my greatest respect and devotion, and I am so thankful for all the input and help I have received with the things that came up along the way in life. This includes keeping me on track when I needed it and supporting me when logistics and other matters did not turn out as I wanted on my path during the Ph.D. period. The work on this thesis began when I was still a medical student in Copenhagen, dreaming of becoming a doctor, perhaps an orthopedic surgeon. At that time I was satisfied just to become a doctor but I saw the opportunity to write a thesis, having been an athlete most of my life, only as a bonus with the chance of a thorough examination to learn more about the beneficial effects of physical activity. When now looking at this retrospectively, I realize that the reason of writing this thesis was a way to fill the void of not being a competitive athlete any more. Professor Karlsson recruited

me at our Saturday sessions at the floorball arena at the Malmö Bellevue station, then further into the research department as a summer research student and then into a research register position. With enthusiasm and a tremendous work ethic, which implied great leadership skills from the very beginning, we managed to “walk the line”. The project was simple but contained an original idea – could daily school physical education during the compulsory school years provide better health and improved school performance? When I attended the research group, the project had been running since 1999 and data had been reported from the first years of the intervention. Professor Karlsson inspired me to pursue the research education and provide the skills in the statistical field, computer software and critical evaluation of the research of other authors, to continue to report the outcome of the project with long-term follow-up data. Without this guidance and help during the journey I would not have been able to write this thesis. My co-supervisor Dr. Rosengren also had a great influence in this endeavor. You have refined the work I have drafted and provided invaluable input, and the precision of your comments can never be overestimated.

But I would also like to express my sincerest thanks to everyone for all the help during the work with this thesis. To Per Gärdsell and Christian Linden, two colleagues who were involved in the planning and the initiation of the study. Christian was also, together with Örnulfur Valdimarsson, the first who

presented their thesis with data from the POP cohort. Susanne Jönsson, Christina Nilsson, Eva-Lena Forsberg, Karin Kristensson and Gunnel Nilsson have helped me with the measurements. Susanna Stenevi-Lundgren and Karin Ringsberg have been responsible for the muscle measurements and Magnus Dencker for the accelerometer measurements. Lise-Lott Hägg and Lisa Quensel have helped me with the data management. Jan-Åke Nilsson has provided invaluable statistical help. Anette Rafsted, Åsa Almgren and Carin Holmberg have been very important in keeping track of all the study participants, collecting fracture data, giving logistic support and practical advice. My co-authors Bjarne Löfgren, Magnus Dencker, Susanna Stenevi-Lundgren, Caroline Karlsson and Mattias Lorentzon have all contributed different skills in the publications.

But I wish also, and maybe most importantly, to express my gratitude to the children who took part in this study with a fantastic sense of duty, and all the parents and teachers at the schools who have supported the study through all the years. Finally, I would like to acknowledge my Alma Mater, the University of Copenhagen, for excellent medical education, Lund University for comparably commendable research education and the country of Denmark for implementing school-based intra-curricular activity as a means to improve bone health. I look forward to the day when Sweden will also adopt this model in all schools.

References

1. Interventions on Diet and Physical Activity: What Works: Summary Report. WHO Guidelines Approved by the Guidelines Review Committee. Geneva 2009.
2. Pacific Physical Activity Guidelines for Adults: Framework for Accelerating the Communication of Physical Activity Guidelines. WHO Guidelines Approved by the Guidelines Review Committee. Geneva 2008.
3. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. World Health Organization technical report series. 1994;843:1-129. PubMed PMID: 7941614.
4. Guidelines for school and community programs to promote lifelong physical activity among young people. National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and prevention. The Journal of school health. 1997 Aug;67(6):202-19. PubMed PMID: 9285866.
5. Physical inactivity a leading cause of disease and disability, warns WHO. Journal of advanced nursing. 2002 Sep;39(6):518. PubMed PMID: 12365404.
6. Abrahamsen B, van Staa T, Ariely R, Olson M, Cooper C. Excess mortality following hip fracture: a systematic epidemiological review. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2009 Oct;20(10):1633-50. PubMed PMID: 19421703.
7. Abrahamsen B, Vestergaard P, Rud B, Barenholdt O, Jensen JE, Nielsen SP, et al. Ten-year absolute risk of osteoporotic fractures according to BMD T score at menopause: the Danish Osteoporosis Prevention Study. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2006 May;21(5):796-800. PubMed PMID: 16734396.
8. Ackert-Bicknell CL, Hibbs MA. The need for mouse models in osteoporosis genetics research. BoneKEy reports. 2012;1:98. PubMed PMID: 23951485. Pubmed Central PMCID: 3727715.
9. Adams JE. Quantitative computed tomography. European journal of radiology. 2009 Sep;71(3):415-24. PubMed PMID: 19682815.
10. Ahlborg HG, Johnell O, Turner CH, Rannevik G, Karlsson MK. Bone loss and bone size after menopause. The New England journal of medicine. 2003 Jul 24;349(4):327-34. PubMed PMID: 12878739.
11. Ahlborg HG, Rosengren BE, Jarvinen TL, Rogmark C, Nilsson JA, Sernbo I, et al. Prevalence of osteoporosis and incidence of hip fracture in women--secular trends over 30 years. BMC musculoskeletal disorders. 2010;11:48. PubMed PMID: 20222965. Pubmed Central PMCID: 2842231.
12. Akesson K. Biochemical markers of bone turnover. A review. Acta

- orthopaedica Scandinavica. 1995 Aug;66(4):376-86. PubMed PMID: 7676832.
13. Alwis G, Linden C, Stenevi-Lundgren S, Ahlborg HG, Dencker M, Besjakov J, et al. A school-curriculum-based exercise intervention program for two years in pre-pubertal girls does not influence hip structure. *Dynamic medicine : DM*. 2008;7:8. PubMed PMID: 18442381. Pubmed Central PMCID: 2397397.
14. Alwis G, Rosengren B, Stenevi-Lundgren S, Duppe H, Sernbo I, Karlsson MK. Normative dual energy X-ray absorptiometry data in Swedish children and adolescents. *Acta paediatrica*. 2010 Jul;99(7):1091-9. PubMed PMID: 20178508.
15. Anliker E, Dick C, Rawer R, Toigo M. Effects of jumping exercise on maximum ground reaction force and bone in 8- to 12-year-old boys and girls: a 9-month randomized controlled trial. *Journal of musculoskeletal & neuronal interactions*. 2012 Jun;12(2):56-67. PubMed PMID: 22647278.
16. Arden NK, Spector TD. Genetic influences on muscle strength, lean body mass, and bone mineral density: a twin study. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 1997 Dec;12(12):2076-81. PubMed PMID: 9421240.
17. Arnaud CD. Role of dietary calcium in osteoporosis. *Advances in internal medicine*. 1990;35:93-106. PubMed PMID: 2405603.
18. Ashby RL, Ward KA, Roberts SA, Edwards L, Mughal MZ, Adams JE. A reference database for the Stratec XCT-2000 peripheral quantitative computed tomography (pQCT) scanner in healthy children and young adults aged 6-19 years. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2009 Aug;20(8):1337-46. PubMed PMID: 19066709.
19. Bailey DA, McKay HA, Mirwald RL, Crocker PR, Faulkner RA. A six-year longitudinal study of the relationship of physical activity to bone mineral accrual in growing children: the university of Saskatchewan bone mineral accrual study. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 1999 Oct;14(10):1672-9. PubMed PMID: 10491214.
20. Baker D, Wilson G, Carlyon B. Generality versus specificity: a comparison of dynamic and isometric measures of strength and speed-strength. *European journal of applied physiology and occupational physiology*. 1994;68(4):350-5. PubMed PMID: 8055895.
21. Ballard JE, McFarland C, Wallace LS, Holiday DB, Roberson G. The effect of 15 weeks of exercise on balance, leg strength, and reduction in falls in 40 women aged 65 to 89 years. *Journal of the American Medical Women's Association*. 2004 Fall;59(4):255-61. PubMed PMID: 16845754.
22. Barnett A, Smith B, Lord SR, Williams M, Baumand A. Community-based group exercise improves balance and reduces falls in at-risk older people: a randomised controlled trial. *Age and ageing*. 2003

- Jul;32(4):407-14. PubMed PMID: 12851185.
23. Bass S, Pearce G, Bradney M, Hendrich E, Delmas PD, Harding A, et al. Exercise before puberty may confer residual benefits in bone density in adulthood: studies in active prepubertal and retired female gymnasts. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 1998 Mar;13(3):500-7. PubMed PMID: 9525351.
24. Bass SL, Eser P, Daly R. The effect of exercise and nutrition on the mechanostat. *Journal of musculoskeletal & neuronal interactions*. 2005 Jul-Sep;5(3):239-54. PubMed PMID: 16172515.
25. Batty GD, Lee IM. Physical activity and coronary heart disease. *Bmj*. 2004 May 8;328(7448):1089-90. PubMed PMID: 15130959. Pubmed Central PMCID: 406310.
26. Baxter-Jones AD, Eisenmann JC, Mirwald RL, Faulkner RA, Bailey DA. The influence of physical activity on lean mass accrual during adolescence: a longitudinal analysis. *Journal of applied physiology (Bethesda, Md : 1985)*. 2008 Aug;105(2):734-41. PubMed PMID: 18467546.
27. Beaupied H, Lespessailles E, Benhamou CL. Evaluation of macrostructural bone biomechanics. *Joint, bone, spine : revue du rhumatisme*. 2007 May;74(3):233-9. PubMed PMID: 17382570.
28. Beck BR, Snow CM. Bone health across the lifespan--exercising our options. *Exercise and sport sciences reviews*. 2003 Jul;31(3):117-22. PubMed PMID: 12882476.
29. Beck TJ, Oreskovic TL, Stone KL, Ruff CB, Ensrud K, Nevitt MC, et al. Structural adaptation to changing skeletal load in the progression toward hip fragility: the study of osteoporotic fractures. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2001 Jun;16(6):1108-19. PubMed PMID: 11393788.
30. Becker W. [Vitamin deficiency is very rare in Sweden. Vitamin D supplementation to children for prevention of rickets]. *Lakartidningen*. 1997 Aug 27;94(35):2936, 9-40. PubMed PMID: 9312607. Vitaminbrist mycket ovanligt i Sverige. D-vitamin till barn för att undvika rakit.
31. Behringer M, Vom Heede A, Yue Z, Mester J. Effects of resistance training in children and adolescents: a meta-analysis. *Pediatrics*. 2010 Nov;126(5):e1199-210. PubMed PMID: 20974785.
32. Berger A. Bone mineral density scans. *Bmj*. 2002 Aug 31;325(7362):484. PubMed PMID: 12202332. Pubmed Central PMCID: 1124002.
33. Bianchi ML, Baim S, Bishop NJ, Gordon CM, Hans DB, Langman CB, et al. Official positions of the International Society for Clinical Densitometry (ISCD) on DXA evaluation in children and adolescents. *Pediatric nephrology*. 2010 Jan;25(1):37-47. PubMed PMID: 19603190.
34. Bischoff-Ferrari HA, Dawson-Hughes B, Stachelin HB, Orav JE, Stuck AE, Theiler R, et al. Fall

- prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *Bmj*. 2009;339:b3692. PubMed PMID: 19797342. Pubmed Central PMCID: 2755728.
35. Bleibler F, Benzinger P, Lehnert T, Becker C, König HH. [Cost of fractures in German hospitals--what role does osteoporosis play?]. *Gesundheitswesen*. 2014 Mar;76(3):163-8. PubMed PMID: 23709102. Frakturkosten im deutschen Krankenhaussektor--Welche Rolle spielt die Osteoporose?
36. Bleibler F, Konnopka A, Benzinger P, Rapp K, König HH. The health burden and costs of incident fractures attributable to osteoporosis from 2010 to 2050 in Germany--a demographic simulation model. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2013 Mar;24(3):835-47. PubMed PMID: 22797490.
37. Bleibler F, Rapp K, Jaensch A, Becker C, König HH. Expected lifetime numbers and costs of fractures in postmenopausal women with and without osteoporosis in Germany: a discrete event simulation model. *BMC health services research*. 2014 Jun 30;14(1):284. PubMed PMID: 24981316.
38. Blimkie CJ. Age- and sex-associated variation in strength during childhood. Anthropometric, morphologic, neurological, biomechanical, endocrinologic, genetic and physical activity correlates. *Perspectives in exercise science and sports medicine* 1989;99-163.
39. Bonjour JP, Theintz G, Buchs B, Slosman D, Rizzoli R. Critical years and stages of puberty for spinal and femoral bone mass accumulation during adolescence. *The Journal of clinical endocrinology and metabolism*. 1991 Sep;73(3):555-63. PubMed PMID: 1874933.
40. Bonjour JP, Theintz G, Law F, Slosman D, Rizzoli R. Peak bone mass. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 1994;4 Suppl 1:7-13. PubMed PMID: 8081064.
41. Boreham CA, McKay HA. Physical activity in childhood and bone health. *British journal of sports medicine*. 2011 Sep;45(11):877-9. PubMed PMID: 21807670.
42. Bouxsein ML, Seeman E. Quantifying the material and structural determinants of bone strength. *Best practice & research Clinical rheumatology*. 2009 Dec;23(6):741-53. PubMed PMID: 19945686.
43. Bringhurst FRD, Marie B.; Krane, Stephen M.; Kronenberg, Henry M. . "Bone and Mineral Metabolism in Health and Disease", chapter 346 in Fauci, Anthony S.; Braunwald, E.; Kasper, D. L.; Hauser, S. L.; Longo D. L.; Jameson, J. L.; Loscalzo, J. *Harrison's Principles of Internal Medicine*, 17th edition. 2008.
44. Brown LB, Streeten EA, Shapiro JR, McBride D, Shuldiner AR, Peyser PA, et al. Genetic and environmental influences on bone mineral density in pre- and postmenopausal women. *Osteoporosis international : a journal established as result of cooperation between the*

- European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2005 Dec;16(12):1849-56. PubMed PMID: 15997421. Pubmed Central PMCID: 4049290.
45. Buchner DM, Cress ME, Wagner EH, de Lateur BJ, Price R, Abrass IB. The Seattle FICSIT/Movelt study: the effect of exercise on gait and balance in older adults. *Journal of the American Geriatrics Society*. 1993 Mar;41(3):321-5. PubMed PMID: 8440857.
46. Buttazzoni C, Rosengren BE, Tveit M, Landin L, Nilsson JA, Karlsson MK. A pediatric bone mass scan has poor ability to predict adult bone mass: a 28-year prospective study in 214 children. *Calcified tissue international*. 2014 Feb;94(2):232-9. PubMed PMID: 24101230.
47. Callreus M, McGuigan F, Ringsberg K, Akesson K. Self-reported recreational exercise combining regularity and impact is necessary to maximize bone mineral density in young adult women: a population-based study of 1,061 women 25 years of age. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2012 Oct;23(10):2517-26. PubMed PMID: 22246601.
48. Cameron ID, Gillespie LD, Robertson MC, Murray GR, Hill KD, Cumming RG, et al. Interventions for preventing falls in older people in care facilities and hospitals. *Cochrane database of systematic reviews*. 2012;12:CD005465. PubMed PMID: 23235623.
49. Cameron JR, Sorenson J. Measurement of Bone Mineral in Vivo: An Improved Method. *Science*. 1963 Oct 11;142(3589):230-2. PubMed PMID: 14057368.
50. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public health reports*. 1985 Mar-Apr;100(2):126-31. PubMed PMID: 3920711. Pubmed Central PMCID: 1424733.
51. Chen Z, Kooperberg C, Pettinger MB, Bassford T, Cauley JA, LaCroix AZ, et al. Validity of self-report for fractures among a multiethnic cohort of postmenopausal women: results from the Women's Health Initiative observational study and clinical trials. *Menopause (New York, NY)*. 2004 May-Jun;11(3):264-74. PubMed PMID: 15167305.
52. Chinapaw MJ, Mokkink LB, van Poppel MN, van Mechelen W, Terwee CB. Physical activity questionnaires for youth: a systematic review of measurement properties. *Sports medicine*. 2010 Jul 1;40(7):539-63. PubMed PMID: 20545380.
53. Civitelli R, Armamento-Villareal R, Napoli N. Bone turnover markers: understanding their value in clinical trials and clinical practice. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2009 Jun;20(6):843-51. PubMed PMID: 19190842.
54. Clark BJ, Hamilton DA, Whishaw IQ. Motor activity (exploration) and formation of home

- bases in mice (C57BL/6) influenced by visual and tactile cues: modification of movement distribution, distance, location, and speed. *Physiology & behavior*. 2006 Apr 15;87(4):805-16. PubMed PMID: 16530235.
55. Clark EM, Ness AR, Tobias JH. Bone fragility contributes to the risk of fracture in children, even after moderate and severe trauma. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2008 Feb;23(2):173-9. PubMed PMID: 17922615. Pubmed Central PMCID: 2742712.
56. Clark EM, Ness AR, Tobias JH. Vigorous physical activity increases fracture risk in children irrespective of bone mass: a prospective study of the independent risk factors for fractures in healthy children. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2008 Jul;23(7):1012-22. PubMed PMID: 18570539. Pubmed Central PMCID: 2742075.
57. Clark EM, Tobias JH, Murray L, Boreham C. Children with low muscle strength are at an increased risk of fracture with exposure to exercise. *Journal of musculoskeletal & neuronal interactions*. 2011 Jun;11(2):196-202. PubMed PMID: 21625056.
58. Coggan AR, Coyle EF. Carbohydrate ingestion during prolonged exercise: effects on metabolism and performance. *Exercise and sport sciences reviews*. 1991;19:1-40. PubMed PMID: 1936083.
59. Cointry GR, Ferretti JL, Reina PS, Nociolino LM, Rittweger J, Capozza RF. The pQCT 'Bone Strength Indices' (BSIs, SSI). Relative mechanical impact and diagnostic value of the indicators of bone tissue and design quality employed in their calculation in healthy men and pre- and post-menopausal women. *Journal of musculoskeletal & neuronal interactions*. 2014 Mar;14(1):29-40. PubMed PMID: 24583538.
60. Compston J, Bowring C, Cooper A, Cooper C, Davies C, Francis R, et al. Diagnosis and management of osteoporosis in postmenopausal women and older men in the UK: National Osteoporosis Guideline Group (NOGG) update 2013. *Maturitas*. 2013 Aug;75(4):392-6. PubMed PMID: 23810490.
61. Cooper C, Dennison EM, Leufkens HG, Bishop N, van Staa TP. Epidemiology of childhood fractures in Britain: a study using the general practice research database. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2004 Dec;19(12):1976-81. PubMed PMID: 15537440.
62. Coutinho ES, Fletcher A, Bloch KV, Rodrigues LC. Risk factors for falls with severe fracture in elderly people living in a middle-income country: a case control study. *BMC geriatrics*. 2008;8:21. PubMed PMID: 18727832. Pubmed Central PMCID: 2532993.
63. Coyle EF, Coggan AR, Hemmert MK, Ivy JL. Muscle glycogen utilization during prolonged strenuous exercise when fed carbohydrate. *Journal of applied physiology*. 1986 Jul;61(1):165-72. PubMed PMID: 3525502.
64. Cremers S, Garnero P. Biochemical markers of bone turnover in the clinical development of drugs for

- osteoporosis and metastatic bone disease: potential uses and pitfalls. *Drugs*. 2006;66(16):2031-58. PubMed PMID: 17112299.
65. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *The New England journal of medicine*. 1995 Mar 23;332(12):767-73. PubMed PMID: 7862179.
66. Currey JD. How well are bones designed to resist fracture? *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2003 Apr;18(4):591-8. PubMed PMID: 12674319.
67. Curry T. *Christensens Physics of Diagnostic Radiology*. 1990 (fourth edition).
68. Cuthbertson D, Smith K, Babraj J, Leese G, Waddell T, Atherton P, et al. Anabolic signaling deficits underlie amino acid resistance of wasting, aging muscle. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology*. 2005 Mar;19(3):422-4. PubMed PMID: 15596483.
69. Dahab KS, McCambridge TM. Strength training in children and adolescents: raising the bar for young athletes? *Sports health*. 2009 May;1(3):223-6. PubMed PMID: 23015875. Pubmed Central PMCID: 3445252.
70. Daly RM. The effect of exercise on bone mass and structural geometry during growth. *Medicine and sport science*. 2007;51:33-49. PubMed PMID: 17505118.
71. Daly RM, Bass S, Nowson C. Long-term effects of calcium-vitamin-D3-fortified milk on bone geometry and strength in older men. *Bone*. 2006 Oct;39(4):946-53. PubMed PMID: 16725396.
72. Daly RM, Bass SL. Lifetime sport and leisure activity participation is associated with greater bone size, quality and strength in older men. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2006;17(8):1258-67. PubMed PMID: 16680498.
73. Daly RM, Rosengren BE, Alwis G, Ahlborg HG, Sernbo I, Karlsson MK. Gender specific age-related changes in bone density, muscle strength and functional performance in the elderly: a 10 year prospective population-based study. *BMC geriatrics*. 2013 Jul 6;13(1):71. PubMed PMID: 23829776. Pubmed Central PMCID: 3716823.
74. Daly RM, Saxon L, Turner CH, Robling AG, Bass SL. The relationship between muscle size and bone geometry during growth and in response to exercise. *Bone*. 2004 Feb;34(2):281-7. PubMed PMID: 14962806.
75. Damilakis J, Adams JE, Guglielmi G, Link TM. Radiation exposure in X-ray-based imaging techniques used in osteoporosis. *European radiology*. 2010 Nov;20(11):2707-14. PubMed PMID: 20559834. Pubmed Central PMCID: 2948153.
76. Datta HK, Ng WF, Walker JA, Tuck SP, Varanasi SS. The

- cell biology of bone metabolism. *Journal of clinical pathology*. 2008 May;61(5):577-87. PubMed PMID: 18441154.
77. Davies HM, Watson KM. Third metacarpal bone laterality asymmetry and midshaft dimensions in Thoroughbred racehorses. *Australian veterinary journal*. 2005 Apr;83(4):224-6. PubMed PMID: 15907042.
78. Davies JH, Evans BA, Gregory JW. Bone mass acquisition in healthy children. *Archives of disease in childhood*. 2005 Apr;90(4):373-8. PubMed PMID: 15781927. Pubmed Central PMCID: 1720329.
79. De Ste Croix M, Deighan M, Armstrong N. Assessment and interpretation of isokinetic muscle strength during growth and maturation. *Sports medicine*. 2003;33(10):727-43. PubMed PMID: 12895130.
80. Dencker M, Andersen LB. Accelerometer-measured daily physical activity related to aerobic fitness in children and adolescents. *Journal of sports sciences*. 2011 Jun;29(9):887-95. PubMed PMID: 21604226.
81. Dencker M, Thorsson O, Karlsson MK, Linden C, Eiberg S, Wollmer P, et al. Daily physical activity related to body fat in children aged 8-11 years. *The Journal of pediatrics*. 2006 Jul;149(1):38-42. PubMed PMID: 16860124.
82. Dencker M, Thorsson O, Karlsson MK, Linden C, Svensson J, Wollmer P, et al. Daily physical activity in Swedish children aged 8-11 years. *Scandinavian journal of medicine & science in sports*. 2006 Aug;16(4):252-7. PubMed PMID: 16895530.
83. Duan Y, Parfitt A, Seeman E. Vertebral bone mass, size, and volumetric density in women with spinal fractures. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 1999 Oct;14(10):1796-802. PubMed PMID: 10491228.
84. Duan Y, Turner CH, Kim BT, Seeman E. Sexual dimorphism in vertebral fragility is more the result of gender differences in age-related bone gain than bone loss. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2001 Dec;16(12):2267-75. PubMed PMID: 11760841.
85. Ducher G, Daly RM, Bass SL. Effects of repetitive loading on bone mass and geometry in young male tennis players: a quantitative study using MRI. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2009 Oct;24(10):1686-92. PubMed PMID: 19419304.
86. Ducher G, Turner AI, Kukuljan S, Pantano KJ, Carlson JL, Williams NI, et al. Obstacles in the optimization of bone health outcomes in the female athlete triad. *Sports medicine*. 2011 Jul 1;41(7):587-607. PubMed PMID: 21688870.
87. Duke PM, Litt IF, Gross RT. Adolescents' self-assessment of sexual maturation. *Pediatrics*. 1980 Dec;66(6):918-20. PubMed PMID: 7454482.
88. Duncan RL, Turner CH. Mechanotransduction and the functional response of bone to mechanical strain. *Calcified tissue international*. 1995 Nov;57(5):344-58. PubMed PMID: 8564797.
89. Duppe H, Gardsell P, Johnell O, Nilsson BE, Ringsberg K. Bone mineral density, muscle strength

- and physical activity. A population-based study of 332 subjects aged 15-42 years. *Acta orthopaedica Scandinavica*. 1997 Apr;68(2):97-103. PubMed PMID: 9174442.
90. Edwards P. Avhandling - Fracture of the shaft of the tibia. 492 consecutive cases in adults. Importance of soft tissue injury. 1965.
91. Eisman JA. Genetics of osteoporosis. *Endocrine reviews*. 1999 Dec;20(6):788-804. PubMed PMID: 10605626.
92. Ericsson I. Motorik, koncentrationsförmåga och skolprestationer (Ericsson 2003). Malmö Högskola. 2003.
93. Eriksson S, Strandvik B. [Vitamin D status in healthy children in Sweden still satisfactory. Changed supplementation and new knowledge motivation for further studies]. *Lakartidningen*. 2010 Oct 13-19;107(41):2474-7. PubMed PMID: 21137563. Vitamin D-status hos friska barn i Sverige annu tillfredsställande. Andrad supplementering och ny kunskap motiverar dock ytterligare studier.
94. European Commission E, Eurodyce. *Physical Education and Sport at School in Europe*. 2013.
95. Evans WJ. Reversing sarcopenia: how weight training can build strength and vitality. *Geriatrics*. 1996 May;51(5):46-7, 51-3; quiz 4. PubMed PMID: 8621102.
96. Farber CR. Systems genetics: a novel approach to dissect the genetic basis of osteoporosis. *Current osteoporosis reports*. 2012 Sep;10(3):228-35. PubMed PMID: 22802146. Pubmed Central PMCID: 3422742.
97. Faulkner KG. Bone matters: are density increases necessary to reduce fracture risk? *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2000 Feb;15(2):183-7. PubMed PMID: 10703919.
98. Faulkner KG, McClung MR. Quality control of DXA instruments in multicenter trials. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 1995;5(4):218-27. PubMed PMID: 7492859.
99. Feldman S, Capozza RF, Mortarino PA, Reina PS, Ferretti JL, Rittweger J, et al. Site and sex effects on tibia structure in distance runners and untrained people. *Medicine and science in sports and exercise*. 2012 Aug;44(8):1580-8. PubMed PMID: 22330024.
100. Ferretti JL, Capozza RF, Zanchetta JR. Mechanical validation of a tomographic (pQCT) index for noninvasive estimation of rat femur bending strength. *Bone*. 1996 Feb;18(2):97-102. PubMed PMID: 8833202.
101. Folland JP, Williams AG. The adaptations to strength training : morphological and neurological contributions to increased strength. *Sports medicine*. 2007;37(2):145-68. PubMed PMID: 17241104.
102. Frost HM. Bone "mass" and the "mechanostat": a proposal. *The Anatomical record*. 1987 Sep;219(1):1-9. PubMed PMID: 3688455.
103. Frost HM. Tetracycline-based histological analysis of bone

- remodeling. *Calcified tissue research*. 1969;3(3):211-37. PubMed PMID: 4894738.
104. Gabriel DA, Kamen G, Frost G. Neural adaptations to resistive exercise: mechanisms and recommendations for training practices. *Sports medicine*. 2006;36(2):133-49. PubMed PMID: 16464122.
105. Gaines JM, Talbot LA. Isokinetic strength testing in research and practice. *Biological research for nursing*. 1999 Jul;1(1):57-64. PubMed PMID: 11225298.
106. Ganz DA, Bao Y, Shekelle PG, Rubenstein LZ. Will my patient fall? *JAMA : the journal of the American Medical Association*. 2007 Jan 3;297(1):77-86. PubMed PMID: 17200478.
107. Garcia-Pallares J, Izquierdo M. Strategies to optimize concurrent training of strength and aerobic fitness for rowing and canoeing. *Sports medicine*. 2011 Apr 1;41(4):329-43. PubMed PMID: 21425890.
108. Gardner MM, Robertson MC, Campbell AJ. Exercise in preventing falls and fall related injuries in older people: a review of randomised controlled trials. *British journal of sports medicine*. 2000 Feb;34(1):7-17. PubMed PMID: 10690444. Pubmed Central PMCID: 1724164.
109. Genant HK, Cooper C, Poor G, Reid I, Ehrlich G, Kanis J, et al. Interim report and recommendations of the World Health Organization Task-Force for Osteoporosis. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 1999;10(4):259-64. PubMed PMID: 10692972.
110. Geusens P. Bisphosphonates for postmenopausal osteoporosis: determining duration of treatment. *Current osteoporosis reports*. 2009 Mar;7(1):12-7. PubMed PMID: 19239824.
111. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al. Interventions for preventing falls in older people living in the community. *Cochrane database of systematic reviews*. 2012;9:CD007146. PubMed PMID: 22972103.
112. Gillespie WJ, Gillespie LD, Parker MJ. Hip protectors for preventing hip fractures in older people. *Cochrane database of systematic reviews*. 2010 (10):CD001255. PubMed PMID: 20927724.
113. Going SB, Farr JN. Exercise and Bone Macro-architecture: Is Childhood a Window of Opportunity for Osteoporosis Prevention? *International journal of body composition research*. 2010 Dec;8:1-9. PubMed PMID: 24478595. Pubmed Central PMCID: 3903297.
114. Goulding A. Risk factors for fractures in normally active children and adolescents. *Medicine and sport science*. 2007;51:102-20. PubMed PMID: 17505122.
115. Goulding A, Grant AM, Williams SM. Bone and body composition of children and adolescents with repeated forearm fractures. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2005 Dec;20(12):2090-6. PubMed PMID: 16294262.
116. Greene DA, Wiebe PN, Naughton GA. Influence of drop-

- landing exercises on bone geometry and biomechanical properties in prepubertal girls: a randomized controlled study. *Calcified tissue international*. 2009 Aug;85(2):94-103. PubMed PMID: 19458887.
117. Gregg EW, Pereira MA, Caspersen CJ. Physical activity, falls, and fractures among older adults: a review of the epidemiologic evidence. *Journal of the American Geriatrics Society*. 2000 Aug;48(8):883-93. PubMed PMID: 10968291.
118. Guglielmi G, Adams J, Link TM. Quantitative ultrasound in the assessment of skeletal status. *European radiology*. 2009 Aug;19(8):1837-48. PubMed PMID: 19259681.
119. Guidelines. Physical activity guidelines for Americans. *The Oklahoma nurse*. 2008 Dec-2009 Feb;53(4):25. PubMed PMID: 19090067.
120. Guise TA. Bone loss and fracture risk associated with cancer therapy. *The oncologist*. 2006 Nov-Dec;11(10):1121-31. PubMed PMID: 17110632.
121. Gustafsson P, Holmstrom E, Besjakov J, Karlsson MK. ADHD symptoms and maturity - a follow-up study in school children. *Acta paediatrica*. 2010 Oct;99(10):1536-9. PubMed PMID: 20456272.
122. Gustafsson P, Thernlund G, Besjakov J, Karlsson MK, Ericsson I, Svedin CG. ADHD symptoms and maturity--a study in primary school children. *Acta paediatrica*. 2008 Feb;97(2):233-8. PubMed PMID: 18177440.
123. Heaney RP. BMD: the problem. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2005 Sep;16(9):1013-5. PubMed PMID: 15776218.
124. Heaney RP, Abrams S, Dawson-Hughes B, Looker A, Marcus R, Matkovic V, et al. Peak bone mass. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2000;11(12):985-1009. PubMed PMID: 11256898.
125. Hedstrom EM, Svensson O, Bergstrom U, Michno P. Epidemiology of fractures in children and adolescents. *Acta orthopaedica*. 2010 Feb;81(1):148-53. PubMed PMID: 20175744. Pubmed Central PMCID: 2856220.
126. Heinonen A, Sievanen H, Kannus P, Oja P, Pasanen M, Vuori I. High-impact exercise and bones of growing girls: a 9-month controlled trial. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2000;11(12):1010-7. PubMed PMID: 11256891.
127. Helmerhorst HJ, Brage S, Warren J, Besson H, Ekelund U. A systematic review of reliability and objective criterion-related validity of physical activity questionnaires. *The international journal of behavioral nutrition and physical activity*. 2012;9:103. PubMed PMID: 22938557. Pubmed Central PMCID: 3492158.
128. Hernandez CJ, Beaupre GS, Carter DR. A theoretical analysis of

- the relative influences of peak BMD, age-related bone loss and menopause on the development of osteoporosis. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2003 Oct;14(10):843-7. PubMed PMID: 12904837.
129. Hetland ML, Haarbo J, Christiansen C. Low bone mass and high bone turnover in male long distance runners. *The Journal of clinical endocrinology and metabolism*. 1993 Sep;77(3):770-5. PubMed PMID: 8370698.
130. Hind K, Burrows M. Weight-bearing exercise and bone mineral accrual in children and adolescents: a review of controlled trials. *Bone*. 2007 Jan;40(1):14-27. PubMed PMID: 16956802.
131. Holick MF. Vitamin D deficiency. *The New England journal of medicine*. 2007 Jul 19;357(3):266-81. PubMed PMID: 17634462.
132. Holloszy JO, Coyle EF. Adaptations of skeletal muscle to endurance exercise and their metabolic consequences. *Journal of applied physiology: respiratory, environmental and exercise physiology*. 1984 Apr;56(4):831-8. PubMed PMID: 6373687.
133. Howard GM, Nguyen TV, Harris M, Kelly PJ, Eisman JA. Genetic and environmental contributions to the association between quantitative ultrasound and bone mineral density measurements: a twin study. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 1998 Aug;13(8):1318-27. PubMed PMID: 9718201.
134. Hui SL, Slemenda CW, Johnston CC, Jr. The contribution of bone loss to postmenopausal osteoporosis. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 1990 Oct;1(1):30-4. PubMed PMID: 2133638.
135. Hundrup YA, Hoidrup S, Obel EB, Rasmussen NK. The validity of self-reported fractures among Danish female nurses: comparison with fractures registered in the Danish National Hospital Register. *Scandinavian journal of public health*. 2004;32(2):136-43. PubMed PMID: 15255503.
136. Huxley AF. Muscle structure and theories of contraction. *Progress in biophysics and biophysical chemistry*. 1957;7:255-318. PubMed PMID: 13485191.
137. Huxley AF. Muscular contraction. *The Journal of physiology*. 1974 Nov;243(1):1-43. PubMed PMID: 4449057. Pubmed Central PMCID: 1330687.
138. Huxley AF, Niedergerke R. Measurement of the striations of isolated muscle fibres with the interference microscope. *The Journal of physiology*. 1958 Dec 30;144(3):403-25. PubMed PMID: 13621405. Pubmed Central PMCID: 1356787.
139. Huxley AF, Simmons RM. Proposed mechanism of force generation in striated muscle. *Nature*. 1971 Oct 22;233(5321):533-8. PubMed PMID: 4939977.
140. Huxley HE, Hanson J. Quantitative studies on the structure of cross-striated myofibrils. I. Investigations

- by interference microscopy. *Biochimica et biophysica acta*. 1957 Feb;23(2):229-49. PubMed PMID: 13412718.
141. Ingalls CP. Nature vs. nurture: can exercise really alter fiber type composition in human skeletal muscle? *Journal of applied physiology*. 2004 Nov;97(5):1591-2. PubMed PMID: 15475545.
142. Ivers RQ, Cumming RG, Mitchell P, Peduto AJ. The accuracy of self-reported fractures in older people. *Journal of clinical epidemiology*. 2002 May;55(5):452-7. PubMed PMID: 12007547.
143. Jacobs RA, Diaz V, Soldini L, Haider T, Thomassen M, Nordsborg NB, et al. Fast-twitch glycolytic skeletal muscle is predisposed to age-induced impairments in mitochondrial function. *The journals of gerontology Series A, Biological sciences and medical sciences*. 2013 Sep;68(9):1010-22. PubMed PMID: 23371970.
144. Janssen I. Health care costs of physical inactivity in Canadian adults. *Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme*. 2012 Aug;37(4):803-6. PubMed PMID: 22667697.
145. Jarvinen TL, Sievanen H, Khan KM, Heinonen A, Kannus P. Shifting the focus in fracture prevention from osteoporosis to falls. *Bmj*. 2008 Jan 19;336(7636):124-6. PubMed PMID: 18202065. Pubmed Central PMCID: 2206310.
146. Joakimsen RM, Fonnebo V, Sogaard AJ, Tollan A, Stormer J, Magnus JH. The Tromso study: registration of fractures, how good are self-reports, a computerized radiographic register and a discharge register? *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2001 Dec;12(12):1001-5. PubMed PMID: 11846324.
147. Johannsen N, Binkley T, Englert V, Neiderauer G, Specker B. Bone response to jumping is site-specific in children: a randomized trial. *Bone*. 2003 Oct;33(4):533-9. PubMed PMID: 14555256.
148. Johnell O, Kanis J. Epidemiology of osteoporotic fractures. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2005 Mar;16 Suppl 2:S3-7. PubMed PMID: 15365697.
149. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2006 Dec;17(12):1726-33. PubMed PMID: 16983459.
150. Jones, Stratton G. Muscle function assessment in children. *Acta paediatrica*. 2000 Jul;89(7):753-61. PubMed PMID: 10943949.
151. Jones TE, Baar K, Ojuka E, Chen M, Holloszy JO. Exercise induces an increase in muscle UCP3 as a component of the increase in mitochondrial biogenesis. *American journal of physiology Endocrinology and*

- metabolism. 2003 Jan;284(1):E96-101. PubMed PMID: 12388129.
152. Jonsson B, Gardsell P, Johnell O, Redlund-Johnell I, Sernbo I. Remembering fractures: fracture registration and proband recall in southern Sweden. *Journal of epidemiology and community health.* 1994 Oct;48(5):489-90. PubMed PMID: 7964361. Pubmed Central PMCID: 1060014.
153. Kanehisa H, Ikegawa S, Tsunoda N, Fukunaga T. Strength and cross-sectional areas of reciprocal muscle groups in the upper arm and thigh during adolescence. *International journal of sports medicine.* 1995 Jan;16(1):54-60. PubMed PMID: 7713632.
154. Kanis JA. An update on the diagnosis of osteoporosis. *Current rheumatology reports.* 2000 Feb;2(1):62-6. PubMed PMID: 11123041.
155. Kanis JA, Adams J, Borgstrom F, Cooper C, Jonsson B, Preedy D, et al. The cost-effectiveness of alendronate in the management of osteoporosis. *Bone.* 2008 Jan;42(1):4-15. PubMed PMID: 18156107.
156. Kanis JA, Delmas P, Burckhardt P, Cooper C, Torgerson D. Guidelines for diagnosis and management of osteoporosis. *The European Foundation for Osteoporosis and Bone Disease. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* 1997;7(4):390-406. PubMed PMID: 9373575.
157. Kanis JA, Johnell O, Oden A, Sembo I, Redlund-Johnell I, Dawson A, et al. Long-term risk of osteoporotic fracture in Malmo. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* 2000;11(8):669-74. PubMed PMID: 11095169.
158. Kannus P, Haapasalo H, Sankelo M, Sievanen H, Pasanen M, Heinonen A, et al. Effect of starting age of physical activity on bone mass in the dominant arm of tennis and squash players. *Annals of internal medicine.* 1995 Jul 1;123(1):27-31. PubMed PMID: 7762910.
159. Kannus P, Jarvinen M, Sievanen H, Oja P, Vuori I. Osteoporosis in men with a history of tibial fracture. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* 1994 Mar;9(3):423-9. PubMed PMID: 8191937.
160. Karasik D, Cohen-Zinder M. Osteoporosis genetics: year 2011 in review. *BoneKEy reports.* 2012;1:114. PubMed PMID: 23951496. Pubmed Central PMCID: 3727733.
161. Karinkanta S, Piirtola M, Sievanen H, Uusi-Rasi K, Kannus P. Physical therapy approaches to reduce fall and fracture risk among older adults. *Nature reviews Endocrinology.* 2010 Jul;6(7):396-407. PubMed PMID: 20517287.
162. Karlsson M. [Exercise increases bone mass in children but only insignificantly in adults]. *Lakartidningen.* 2002 Aug 29;99(35):3400-5. PubMed PMID: 12362763. Traning okar benmassan hos barn men bara obetydligt hos vuxna.
163. Karlsson MK, Linden C, Karlsson C, Johnell O, Obrant K, Seeman E. Exercise during growth and bone mineral density and fractures in old

- age. *Lancet*. 2000 Feb 5;355(9202):469-70. PubMed PMID: 10841134.
164. Karlsson MK, Nordqvist A, Karlsson C. Physical activity increases bone mass during growth. *Food & nutrition research*. 2008;52. PubMed PMID: 19109652. Pubmed Central PMCID: 2596740.
165. Karlsson MK, Nordqvist A, Karlsson C. Physical activity, muscle function, falls and fractures. *Food & nutrition research*. 2008;52. PubMed PMID: 19158939. Pubmed Central PMCID: 2615636.
166. Karpf DB, Shapiro DR, Seeman E, Ensrud KE, Johnston CC, Jr., Adami S, et al. Prevention of nonvertebral fractures by alendronate. A meta-analysis. Alendronate Osteoporosis Treatment Study Groups. *JAMA : the journal of the American Medical Association*. 1997 Apr 9;277(14):1159-64. PubMed PMID: 9087473.
167. Kelly PJ, Eisman JA, Sambrook PN. Interaction of genetic and environmental influences on peak bone density. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 1990 Oct;1(1):56-60. PubMed PMID: 2133642.
168. Kettunen JA, Impivaara O, Kujala UM, Linna M, Maki J, Raty H, et al. Hip fractures and femoral bone mineral density in male former elite athletes. *Bone*. 2010 Feb;46(2):330-5. PubMed PMID: 19836005.
169. Keytel LR, Goedecke JH, Noakes TD, Hiiloskorpi H, Laukkanen R, van der Merwe L, et al. Prediction of energy expenditure from heart rate monitoring during submaximal exercise. *Journal of sports sciences*. 2005 Mar;23(3):289-97. PubMed PMID: 15966347.
170. Kling JM, Clarke BL, Sandhu NP. Osteoporosis prevention, screening, and treatment: a review. *Journal of women's health*. 2014 Jul;23(7):563-72. PubMed PMID: 24766381. Pubmed Central PMCID: 4089021.
171. Klop C, Welsing PM, Cooper C, Harvey NC, Elders PJ, Bijlsma JW, et al. Mortality in British hip fracture patients, 2000-2010: A population-based retrospective cohort study. *Bone*. 2014 Jun 14. PubMed PMID: 24933345.
172. Knothe Tate ML, Adamson JR, Tami AE, Bauer TW. The osteocyte. *The international journal of biochemistry & cell biology*. 2004 Jan;36(1):1-8. PubMed PMID: 14592527.
173. Kular J, Tickner J, Chim SM, Xu J. An overview of the regulation of bone remodelling at the cellular level. *Clinical biochemistry*. 2012 Aug;45(12):863-73. PubMed PMID: 22465238.
174. Landin LA. Fracture patterns in children. Analysis of 8,682 fractures with special reference to incidence, etiology and secular changes in a Swedish urban population 1950-1979. *Acta orthopaedica Scandinavica Supplementum*. 1983;202:1-109. PubMed PMID: 6574687.
175. Lanou AJ, Berkow SE, Barnard ND. Calcium, dairy products, and bone health in children and young adults: a reevaluation of the evidence. *Pediatrics*. 2005 Mar;115(3):736-43. PubMed PMID: 15741380.

176. Lanyon LE. Control of bone architecture by functional load bearing. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 1992 Dec;7 Suppl 2:S369-75. PubMed PMID: 1485545.
177. Lanyon LE. Functional strain as a determinant for bone remodeling. *Calcified tissue international*. 1984;36 Suppl 1:S56-61. PubMed PMID: 6430523.
178. Lanyon LE. Osteocytes, strain detection, bone modeling and remodeling. *Calcified tissue international*. 1993;53 Suppl 1:S102-6; discussion S6-7. PubMed PMID: 8275362.
179. LaPorte RE, Montoye HJ, Caspersen CJ. Assessment of physical activity in epidemiologic research: problems and prospects. *Public health reports*. 1985 Mar-Apr;100(2):131-46. PubMed PMID: 3920712. Pubmed Central PMCID: 1424723.
180. Laskey MA. Dual-energy X-ray absorptiometry and body composition. *Nutrition*. 1996 Jan;12(1):45-51. PubMed PMID: 8838836.
181. Lees A, Vanrenterghem J, De Clercq D. The maximal and submaximal vertical jump: implications for strength and conditioning. *Journal of strength and conditioning research / National Strength & Conditioning Association*. 2004 Nov;18(4):787-91. PubMed PMID: 15574084.
182. Leigey D, Irrgang J, Francis K, Cohen P, Wright V. Participation in high-impact sports predicts bone mineral density in senior olympic athletes. *Sports health*. 2009 Nov;1(6):508-13. PubMed PMID: 23015914. Pubmed Central PMCID: 3445153.
183. Lim LS, Hoeksema LJ, Sherin K, Committee APP. Screening for osteoporosis in the adult U.S. population: ACPM position statement on preventive practice. *American journal of preventive medicine*. 2009 Apr;36(4):366-75. PubMed PMID: 19285200.
184. Lim SY, Lim JH, Nguyen D, Okamura R, Amiri HM, Calmes M, et al. Screening for osteoporosis in men aged 70 years and older in a primary care setting in the United States. *American journal of men's health*. 2013 Jul;7(4):350-4. PubMed PMID: 23440083.
185. Linden C, Ahlborg HG, Besjakov J, Gardsell P, Karlsson MK. A school curriculum-based exercise program increases bone mineral accrual and bone size in prepubertal girls: two-year data from the pediatric osteoporosis prevention (POP) study. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2006 Jun;21(6):829-35. PubMed PMID: 16753013. Epub 2006/06/07. eng.
186. Linden C, Alwis G, Ahlborg H, Gardsell P, Valdimarsson O, Stenevi-Lundgren S, et al. Exercise, bone mass and bone size in prepubertal boys: one-year data from the pediatric osteoporosis prevention study. *Scandinavian journal of medicine & science in sports*. 2007 Aug;17(4):340-7. PubMed PMID: 16774651. Epub 2006/06/16. eng.
187. Lindsay R. Clinical utility of biochemical markers. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for*

- Osteoporosis and the National Osteoporosis Foundation of the USA. 1999;9 Suppl 2:S29-32. PubMed PMID: 10525723.
188. Lofgren B, Dencker M, Nilsson JA, Karlsson MK. A 4-year exercise program in children increases bone mass without increasing fracture risk. *Pediatrics*. 2012 Jun;129(6):e1468-76. PubMed PMID: 22641757. Epub 2012/05/30. eng.
189. Lord SR, Ward JA, Williams P, Strudwick M. The effect of a 12-month exercise trial on balance, strength, and falls in older women: a randomized controlled trial. *Journal of the American Geriatrics Society*. 1995 Nov;43(11):1198-206. PubMed PMID: 7594152.
190. Loro ML, Sayre J, Roe TF, Goran MI, Kaufman FR, Gilsanz V. Early identification of children predisposed to low peak bone mass and osteoporosis later in life. *The Journal of clinical endocrinology and metabolism*. 2000 Oct;85(10):3908-18. PubMed PMID: 11061556.
191. Ma D, Jones G. Television, computer, and video viewing; physical activity; and upper limb fracture risk in children: a population-based case control study. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2003 Nov;18(11):1970-7. PubMed PMID: 14606509.
192. MacKelvie KJ, Khan KM, McKay HA. Is there a critical period for bone response to weight-bearing exercise in children and adolescents? a systematic review. *British journal of sports medicine*. 2002 Aug;36(4):250-7; discussion 7. PubMed PMID: 12145113. Pubmed Central PMCID: 1724536.
193. Mackey DC, Lui LY, Cawthon PM, Bauer DC, Nevitt MC, Cauley JA, et al. High-trauma fractures and low bone mineral density in older women and men. *JAMA : the journal of the American Medical Association*. 2007 Nov 28;298(20):2381-8. PubMed PMID: 18042915.
194. Magnusson HI, Linden C, Obrant KJ, Johnell O, Karlsson MK. Bone mass changes in weight-loaded and unloaded skeletal regions following a fracture of the hip. *Calcified tissue international*. 2001 Aug;69(2):78-83. PubMed PMID: 11683427.
195. Malina R. Growth of Muscle Tissue and Muscle Mass. Human Growth, Chapter in Human Growth: Postnatal growth by Frank Falkner. 1978.
196. Malina RM. Adolescent changes in size, build, composition and performance. *Human biology*. 1974 Feb;46(1):117-31. PubMed PMID: 4426587.
197. Malina RM, Eisenmann JC, Cumming SP, Ribeiro B, Aroso J. Maturity-associated variation in the growth and functional capacities of youth football (soccer) players 13-15 years. *European journal of applied physiology*. 2004 May;91(5-6):555-62. PubMed PMID: 14648128.
198. Marcus BH, Williams DM, Dubbert PM, Sallis JF, King AC, Yancey AK, et al. Physical activity intervention studies: what we know and what we need to know: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity);

- Council on Cardiovascular Disease in the Young; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research. *Circulation*. 2006 Dec 12;114(24):2739-52. PubMed PMID: 17145995.
199. Margetts B. WHO global strategy on diet, physical activity and health. Editorial. *Public health nutrition*. 2004 May;7(3):361-3. PubMed PMID: 15153266.
200. Marini M. The Exercised Skeletal Muscle: A review. *European Translational Myology - Myology reviews*. 2010.
201. Markovic G. Does plyometric training improve vertical jump height? A meta-analytical review. *British journal of sports medicine*. 2007 Jun;41(6):349-55; discussion 55. PubMed PMID: 17347316. Pubmed Central PMCID: 2465309.
202. Markovic G, Jaric S. Positive and negative loading and mechanical output in maximum vertical jumping. *Medicine and science in sports and exercise*. 2007 Oct;39(10):1757-64. PubMed PMID: 17909403.
203. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *Bmj*. 1996 May 18;312(7041):1254-9. PubMed PMID: 8634613. Pubmed Central PMCID: 2351094.
204. Mauras N, Rogol AD, Haymond MW, Veldhuis JD. Sex steroids, growth hormone, insulin-like growth factor-1: neuroendocrine and metabolic regulation in puberty. *Hormone research*. 1996;45(1-2):74-80. PubMed PMID: 8742123.
205. Mazess RB, Cameron JR. Skeletal growth in school children: maturation and bone mass. *American journal of physical anthropology*. 1971 Nov;35(3):399-407. PubMed PMID: 4332709.
206. McGuigan FE, Murray L, Gallagher A, Davey-Smith G, Neville CE, Van't Hof R, et al. Genetic and environmental determinants of peak bone mass in young men and women. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2002 Jul;17(7):1273-9. PubMed PMID: 12096841.
207. Medbo JI. [Anaerobic capacity--theoretical basis and methods for practical testing]. *Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raeke*. 1993 Feb 20;113(5):591-4. PubMed PMID: 8465318. Anaerob kapasitet--teoretisk grunnlag og metoder for praktisk testing.
208. Medbo JI. Is the maximal accumulated oxygen deficit an adequate measure of the anaerobic capacity? *Canadian journal of applied physiology = Revue canadienne de physiologie appliquee*. 1996 Oct;21(5):370-83; discussion 84-8. PubMed PMID: 8905188.
209. Medbo JI, Mohn AC, Tabata I, Bahr R, Vaage O, Sejersted OM. Anaerobic capacity determined by maximal accumulated O2 deficit. *Journal of applied physiology*. 1988 Jan;64(1):50-60. PubMed PMID: 3356666.
210. Meinhardt UJ, Ho KK. Modulation of growth hormone action by sex steroids. *Clinical endocrinology*. 2006 Oct;65(4):413-22. PubMed PMID: 16984231.
211. Melin A, Wilske J, Ringertz H, Saaf M. Seasonal variations in serum levels of 25-hydroxyvitamin D and parathyroid hormone but no

- detectable change in femoral neck bone density in an older population with regular outdoor exposure. *Journal of the American Geriatrics Society*. 2001 Sep;49(9):1190-6. PubMed PMID: 11559378.
212. Miller PD, Baran DT, Bilezikian JP, Greenspan SL, Lindsay R, Riggs BL, et al. Practical clinical application of biochemical markers of bone turnover: Consensus of an expert panel. *Journal of clinical densitometry : the official journal of the International Society for Clinical Densitometry*. 1999 Fall;2(3):323-42. PubMed PMID: 10548827.
213. Mosekilde L, Mosekilde L, Danielsen CC. Biomechanical competence of vertebral trabecular bone in relation to ash density and age in normal individuals. *Bone*. 1987;8(2):79-85. PubMed PMID: 3593611.
214. Mulder JE, Kolatkar NS, LeBoff MS. Drug insight: Existing and emerging therapies for osteoporosis. *Nature clinical practice Endocrinology & metabolism*. 2006 Dec;2(12):670-80. PubMed PMID: 17143314.
215. Mussolino ME, Looker AC, Orwoll ES. Jogging and bone mineral density in men: results from NHANES III. *American journal of public health*. 2001 Jul;91(7):1056-9. PubMed PMID: 11441731. Pubmed Central PMCID: 1446719.
216. Nelson HD, Haney EM, Dana T, Bougatsos C, Chou R. Screening for osteoporosis: an update for the U.S. Preventive Services Task Force. *Annals of internal medicine*. 2010 Jul 20;153(2):99-111. PubMed PMID: 20621892.
217. Nelson HD, Helfand M, Woolf SH, Allan JD. Screening for postmenopausal osteoporosis: a review of the evidence for the U.S. Preventive Services Task Force. *Annals of internal medicine*. 2002 Sep 17;137(6):529-41. PubMed PMID: 12230356.
218. Ness AR, Leary SD, Mattocks C, Blair SN, Reilly JJ, Wells J, et al. Objectively measured physical activity and fat mass in a large cohort of children. *PLoS medicine*. 2007 Mar;4(3):e97. PubMed PMID: 17388663. Pubmed Central PMCID: 1831734.
219. Neyens JC, van Haastregt JC, Dijcks BP, Martens M, van den Heuvel WJ, de Witte LP, et al. Effectiveness and implementation aspects of interventions for preventing falls in elderly people in long-term care facilities: a systematic review of RCTs. *Journal of the American Medical Directors Association*. 2011 Jul;12(6):410-25. PubMed PMID: 21450201.
220. Nielsen AP, Morris KG, Murdock R, Bruno FP, Cobb FR. Linear relationship between the distribution of thallium-201 and blood flow in ischemic and nonischemic myocardium during exercise. *Circulation*. 1980 Apr;61(4):797-801. PubMed PMID: 7357723.
221. Nikander R, Sievanen H, Heinonen A, Kannus P. Femoral neck structure in adult female athletes subjected to different loading modalities. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2005 Mar;20(3):520-8. PubMed PMID: 15746998.
222. Nikander R, Sievanen H, Uusi-Rasi K, Heinonen A, Kannus P. Loading modalities and bone structures at nonweight-bearing upper extremity

- and weight-bearing lower extremity: a pQCT study of adult female athletes. *Bone*. 2006 Oct;39(4):886-94. PubMed PMID: 16731064.
223. Nilas L, Hassager C, Christiansen C. Long-term precision of dual photon absorptiometry in the lumbar spine in clinical settings. *Bone and mineral*. 1988 Mar;3(4):305-15. PubMed PMID: 3228615.
224. Nilsson A, Anderssen SA, Andersen LB, Froberg K, Riddoch C, Sardinha LB, et al. Between- and within-day variability in physical activity and inactivity in 9- and 15-year-old European children. *Scandinavian journal of medicine & science in sports*. 2009 Feb;19(1):10-8. PubMed PMID: 18248534.
225. Nilsson BE. Post-traumatic osteopenia. A quantitative study of the bone mineral mass in the femur following fracture of the tibia in man using americium-241 as a photon source. *Acta orthopaedica Scandinavica*. 1966;37:Suppl 91:1-55. PubMed PMID: 5960756.
226. Nilsson BE, Johnell O, Petersson C. In vivo bone-mineral measurement. How and why--a review. *Acta orthopaedica Scandinavica*. 1990 Jun;61(3):275-81. PubMed PMID: 2196756.
227. Nilsson BE, Westlin NE. [Apparatus for bone density determination in vivo]. *Nordisk medicin*. 1971 Sep 16;86(37):1089-90. PubMed PMID: 5127540. En apparat for bentathetsmatning in vivo.
228. Nilsson BE, Westlin NE. Bone density in athletes. *Clinical orthopaedics and related research*. 1971;77:179-82. PubMed PMID: 5140447.
229. Nilsson GM, Jonsson K, Ekdahl CS, Eneroth M. Effects of a training program after surgically treated ankle fracture: a prospective randomised controlled trial. *BMC musculoskeletal disorders*. 2009;10:118. PubMed PMID: 19781053. Pubmed Central PMCID: 2760502.
230. Nilsson M, Ohlsson C, Eriksson AL, Frandin K, Karlsson M, Ljunggren O, et al. Competitive physical activity early in life is associated with bone mineral density in elderly Swedish men. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2008 Nov;19(11):1557-66. PubMed PMID: 18373050.
231. Nilsson M, Ohlsson C, Oden A, Mellstrom D, Lorentzon M. Increased physical activity is associated with enhanced development of peak bone mass in men: a five-year longitudinal study. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2012 May;27(5):1206-14. PubMed PMID: 22247082. Pubmed Central PMCID: 3415622.
232. Njeh CF, Fuerst T, Hans D, Blake GM, Genant HK. Radiation exposure in bone mineral density assessment. *Applied radiation and isotopes : including data, instrumentation and methods for use in agriculture, industry and medicine*. 1999 Jan;50(1):215-36. PubMed PMID: 10028639.
233. Nordstrom A, Olsson T, Nordstrom P. Bone gained from physical activity and lost through detraining: a longitudinal study in young males.

- Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2005 Jul;16(7):835-41. PubMed PMID: 15517188.
234. Ohira Y, Cartier LJ, Chen M, Holloszy JO. Induction of an increase in mitochondrial matrix enzymes in muscle of iron-deficient rats. *The American journal of physiology*. 1987 Nov;253(5 Pt 1):C639-44. PubMed PMID: 3479908.
235. Paddon-Jones D, Rasmussen BB. Dietary protein recommendations and the prevention of sarcopenia. *Current opinion in clinical nutrition and metabolic care*. 2009 Jan;12(1):86-90. PubMed PMID: 19057193. Pubmed Central PMCID: 2760315.
236. Parfitt AM. High bone turnover is intrinsically harmful: two paths to a similar conclusion. The Parfitt view. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2002 Aug;17(8):1558-9; author reply 60. PubMed PMID: 12162510.
237. Parfitt AM. Misconceptions (2): turnover is always higher in cancellous than in cortical bone. *Bone*. 2002 Jun;30(6):807-9. PubMed PMID: 12052445.
238. Patel R, Blake GM, Rymer J, Fogelman I. Long-term precision of DXA scanning assessed over seven years in forty postmenopausal women. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2000;11(1):68-75. PubMed PMID: 10663361.
239. Peacock M, Turner CH, Econs MJ, Foroud T. Genetics of osteoporosis. *Endocrine reviews*. 2002 Jun;23(3):303-26. PubMed PMID: 12050122.
240. Pearce G, Bass S, Young N, Formica C, Seeman E. Does weight-bearing exercise protect against the effects of exercise-induced oligomenorrhea on bone density? *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 1996;6(6):448-52. PubMed PMID: 9116390.
241. Pocock NA, Eisman JA, Hopper JL, Yeates MG, Sambrook PN, Eberl S. Genetic determinants of bone mass in adults. A twin study. *The Journal of clinical investigation*. 1987 Sep;80(3):706-10. PubMed PMID: 3624485. Pubmed Central PMCID: 442294.
242. Polidoulis I, Beyene J, Cheung AM. The effect of exercise on pQCT parameters of bone structure and strength in postmenopausal women--a systematic review and meta-analysis of randomized controlled trials. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2012 Jan;23(1):39-51. PubMed PMID: 21811864.
243. Puyau MR, Adolph AL, Vohra FA, Butte NF. Validation and calibration of physical activity monitors

- in children. *Obesity research*. 2002 Mar;10(3):150-7. PubMed PMID: 11886937.
244. Remer T, Boye KR, Manz F. Long-term increase in bone mass through high calcium intake before puberty. *Lancet*. 2002 Jun 8;359(9322):2037-8; author reply 8. PubMed PMID: 12076578.
245. Richards JB, Zheng HF, Spector TD. Genetics of osteoporosis from genome-wide association studies: advances and challenges. *Nature reviews Genetics*. 2012 Aug;13(8):576-88. PubMed PMID: 22805710.
246. Robertson MC, Campbell AJ, Gardner MM, Devlin N. Preventing injuries in older people by preventing falls: a meta-analysis of individual-level data. *Journal of the American Geriatrics Society*. 2002 May;50(5):905-11. PubMed PMID: 12028179.
247. Robinson S, Cooper C, Aihie Sayer A. Nutrition and sarcopenia: a review of the evidence and implications for preventive strategies. *Journal of aging research*. 2012;2012:510801. PubMed PMID: 22506112. Pubmed Central PMCID: 3312288.
248. Rogol AD, Clark PA, Roemmich JN. Growth and pubertal development in children and adolescents: effects of diet and physical activity. *The American journal of clinical nutrition*. 2000 Aug;72(2 Suppl):521S-8S. PubMed PMID: 10919954.
249. Rosen C. The aging skeleton. 1999.
250. Rosengren BE, Karlsson MK. The annual number of hip fractures in Sweden will double from year 2002 to 2050. *Acta orthopaedica*. 2014 Jun;85(3):234-7. PubMed PMID: 24786906.
251. Rosengren BE, Ribom EL, Nilsson JA, Mallmin H, Ljunggren O, Ohlsson C, et al. Inferior physical performance test results of 10,998 men in the MrOS Study is associated with high fracture risk. *Age and ageing*. 2012 May;41(3):339-44. PubMed PMID: 22314696. Pubmed Central PMCID: 3335372.
252. Ross AC TC, Yaktine AL, et al., editors. . *Dietary Reference Intakes for Calcium and Vitamin D*. Washington (DC): National Academies Press (US); 2011. Available from: Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium; .
253. Rowland TW. Developmental exercise physiology. 1996:215-30.
254. Rubenstein LZ. Falls in older people: epidemiology, risk factors and strategies for prevention. *Age and ageing*. 2006 Sep;35 Suppl 2:ii37-ii41. PubMed PMID: 16926202.
255. Rubin CT, Lanyon LE. Dynamic strain similarity in vertebrates; an alternative to allometric limb bone scaling. *Journal of theoretical biology*. 1984 Mar 21;107(2):321-7. PubMed PMID: 6717041.
256. Rubin CT, Lanyon LE. Kappa Delta Award paper. Osteoregulatory nature of mechanical stimuli: function as a determinant for adaptive remodeling in bone. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society*. 1987;5(2):300-10. PubMed PMID: 3572599.
257. Rubin CT, Lanyon LE. Regulation of bone formation by applied dynamic loads. *The Journal of bone and joint surgery American volume*. 1984

- Mar;66(3):397-402. PubMed PMID: 6699056.
258. Rubin CT, Lanyon LE. Regulation of bone mass by mechanical strain magnitude. *Calcified tissue international*. 1985 Jul;37(4):411-7. PubMed PMID: 3930039.
259. Sanchis-Moysi J, Dorado C, Olmedillas H, Serrano-Sanchez JA, Calbet JA. Bone and lean mass inter-arm asymmetries in young male tennis players depend on training frequency. *European journal of applied physiology*. 2010 Sep;110(1):83-90. PubMed PMID: 20401491.
260. Sanchis-Moysi J, Dorado C, Olmedillas H, Serrano-Sanchez JA, Calbet JA. Bone mass in prepubertal tennis players. *International journal of sports medicine*. 2010 Jun;31(6):416-20. PubMed PMID: 20301044.
261. Sayer AA. Sarcopenia. *Bmj*. 2010;341:c4097. PubMed PMID: 20699307.
262. Sayer AA, Robinson SM, Patel HP, Shavlakadze T, Cooper C, Grounds MD. New horizons in the pathogenesis, diagnosis and management of sarcopenia. *Age and ageing*. 2013 Mar;42(2):145-50. PubMed PMID: 23315797. Pubmed Central PMCID: 3575121.
263. SBU. Osteoporos prevention, diagnostik och behandling. Statens beredning för medicinsk utvärdering. 2003;1.
264. Schapira D, Schapira C. Osteoporosis: the evolution of a scientific term. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 1992 Jul;2(4):164-7. PubMed PMID: 1611220.
265. Schoeller DA, van Santen E. Measurement of energy expenditure in humans by doubly labeled water method. *Journal of applied physiology: respiratory, environmental and exercise physiology*. 1982 Oct;53(4):955-9. PubMed PMID: 6759491.
266. Schoenau E, Frost HM. The "muscle-bone unit" in children and adolescents. *Calcified tissue international*. 2002 May;70(5):405-7. PubMed PMID: 11960207.
267. Seeman E. Bone quality. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2003 Sep;14 Suppl 5:S3-7. PubMed PMID: 14504698.
268. Seeman E. Bone quality: the material and structural basis of bone strength. *Journal of bone and mineral metabolism*. 2008;26(1):1-8. PubMed PMID: 18095057.
269. Seeman E. Estrogen therapy and variable-resistance weight training. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 1992 Jun;7(6):709-11. PubMed PMID: 1414489.
270. Seeman E. An exercise in geometry. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2002 Mar;17(3):373-80. PubMed PMID: 11874229.
271. Seeman E. Structural basis of growth-related gain and age-related loss of bone strength. *Rheumatology*. 2008 Jul;47 Suppl 4:iv2-

8. PubMed PMID: 18556646. Pubmed Central PMCID: 2427165.
272. Sherrington C, Whitney JC, Lord SR, Herbert RD, Cumming RG, Close JC. Effective exercise for the prevention of falls: a systematic review and meta-analysis. *Journal of the American Geriatrics Society*. 2008 Dec;56(12):2234-43. PubMed PMID: 19093923.
273. Shumway-Cook A, Baldwin M, Polissar NL, Gruber W. Predicting the probability for falls in community-dwelling older adults. *Physical therapy*. 1997 Aug;77(8):812-9. PubMed PMID: 9256869.
274. Shumway-Cook A, Ciol MA, Hoffman J, Dudgeon BJ, Yorkston K, Chan L. Falls in the Medicare population: incidence, associated factors, and impact on health care. *Physical therapy*. 2009 Apr;89(4):324-32. PubMed PMID: 19228831. Pubmed Central PMCID: 2664994.
275. Shumway-Cook A, Gruber W, Baldwin M, Liao S. The effect of multidimensional exercises on balance, mobility, and fall risk in community-dwelling older adults. *Physical therapy*. 1997 Jan;77(1):46-57. PubMed PMID: 8996463.
276. Sievanen H, McKay H, Heinonen A, Bailey D, Khan K. The Achilles heel of exercise. *Lancet*. 2000 May 27;355(9218):1909; author reply 11. PubMed PMID: 10866465.
277. Siris ES, Baim S, Nattiv A. Primary care use of FRAX: absolute fracture risk assessment in postmenopausal women and older men. *Postgraduate medicine*. 2010 Jan;122(1):82-90. PubMed PMID: 20107292.
278. Slemenda CW, Christian JC, Williams CJ, Norton JA, Johnston CC, Jr. Genetic determinants of bone mass in adult women: a reevaluation of the twin model and the potential importance of gene interaction on heritability estimates. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 1991 Jun;6(6):561-7. PubMed PMID: 1887818.
279. Slemenda CW, Miller JZ, Hui SL, Reister TK, Johnston CC, Jr. Role of physical activity in the development of skeletal mass in children. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 1991 Nov;6(11):1227-33. PubMed PMID: 1805545.
280. Smith A. Sarcopenia, malnutrition and nutrient density in older people. *Post reproductive health*. 2014 Mar 13;20(1):19-21. PubMed PMID: 24879776.
281. Specker B, Binkley T. Randomized trial of physical activity and calcium supplementation on bone mineral content in 3- to 5-year-old children. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2003 May;18(5):885-92. PubMed PMID: 12733728.
282. Staron RS, Leonardi MJ, Karapondo DL, Malicky ES, Falkel JE, Hagerman FC, et al. Strength and skeletal muscle adaptations in heavy-resistance-trained women after detraining and retraining. *Journal of applied physiology*. 1991 Feb;70(2):631-40. PubMed PMID: 1827108.
283. Stenevi-Lundgren S, Daly RM, Karlsson MK. A school-based exercise intervention program increases muscle strength in prepubertal boys. *International journal of pediatrics*.

- 2010;2010:307063. PubMed PMID: 20652076. Pubmed Central PMCID: 2905710.
284. Stenevi-Lundgren S, Daly RM, Linden C, Gardsell P, Karlsson MK. Effects of a daily school based physical activity intervention program on muscle development in prepubertal girls. *European journal of applied physiology.* 2009 Mar;105(4):533-41. PubMed PMID: 19018558.
285. Stenhagen M, Ekstrom H, Nordell E, Elmstahl S. Falls in the general elderly population: a 3- and 6-year prospective study of risk factors using data from the longitudinal population study 'Good ageing in Skane'. *BMC geriatrics.* 2013;13:81. PubMed PMID: 23919320. Pubmed Central PMCID: 3750524.
286. Stenhagen M, Nordell E, Elmstahl S. Falls in elderly people: a multifactorial analysis of risk markers using data from the Swedish general population study 'Good ageing in Skane'. *Aging clinical and experimental research.* 2013 Apr;25(1):59-67. PubMed PMID: 23740634.
287. Stewart A, Porter RW, Primrose WR, Walker LG, Reid DM. Cervical and trochanteric hip fractures: bone mass and other parameters. *Clinical rheumatology.* 1999;18(3):201-6. PubMed PMID: 11206344.
288. Strong WB, Malina RM, Blimkie CJ, Daniels SR, Dishman RK, Gutin B, et al. Evidence based physical activity for school-age youth. *The Journal of pediatrics.* 2005 Jun;146(6):732-7. PubMed PMID: 15973308.
289. Sundberg M, Gardsell P, Johnell O, Karlsson MK, Ornstein E, Sandstedt B, et al. Peripubertal moderate exercise increases bone mass in boys but not in girls: a population-based intervention study. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* 2001;12(3):230-8. PubMed PMID: 11315242.
290. Svendsen OL, Hassager C, Skodt V, Christiansen C. Impact of soft tissue on in vivo accuracy of bone mineral measurements in the spine, hip, and forearm: a human cadaver study. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* 1995 Jun;10(6):868-73. PubMed PMID: 7572310.
291. Tammelin T. A review of longitudinal studies on youth predictors of adulthood physical activity. *International journal of adolescent medicine and health.* 2005 Jan-Mar;17(1):3-12. PubMed PMID: 15900807.
292. Taylor WC, Blair SN, Cummings SS, Wun CC, Malina RM. Childhood and adolescent physical activity patterns and adult physical activity. *Medicine and science in sports and exercise.* 1999 Jan;31(1):118-23. PubMed PMID: 9927019.
293. Telama R, Yang X, Viikari J, Valimaki I, Wanne O, Raitakari O. Physical activity from childhood to adulthood: a 21-year tracking study. *American journal of preventive medicine.* 2005 Apr;28(3):267-73. PubMed PMID: 15766614.
294. Tenforde AS, Fredericson M. Influence of sports participation on

- bone health in the young athlete: a review of the literature. *PM & R : the journal of injury, function, and rehabilitation*. 2011 Sep;3(9):861-7. PubMed PMID: 21944303.
295. Tremollieres FA, Pouilles JM, Drewniak N, Laparra J, Ribot CA, Dargent-Molina P. Fracture risk prediction using BMD and clinical risk factors in early postmenopausal women: sensitivity of the WHO FRAX tool. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2010 May;25(5):1002-9. PubMed PMID: 20200927. Pubmed Central PMCID: 3112173.
296. Tudor-Locke C, Williams JE, Reis JP, Pluto D. Utility of pedometers for assessing physical activity: construct validity. *Sports medicine*. 2004;34(5):281-91. PubMed PMID: 15107007.
297. Turner CH. Functional determinants of bone structure: beyond Wolff's law of bone transformation. *Bone*. 1992;13(6):403-9. PubMed PMID: 1476817.
298. Turner JG, Gilchrist NL, Ayling EM, Hassall AJ, Hooke EA, Sadler WA. Factors affecting bone mineral density in high school girls. *The New Zealand medical journal*. 1992 Mar 25;105(930):95-6. PubMed PMID: 1553121.
299. Tveit M, Rosengren BE, Nilsson JA, Ahlborg HG, Karlsson MK. Bone mass following physical activity in young years: a mean 39-year prospective controlled study in men. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2013 Apr;24(4):1389-97. PubMed PMID: 22806559.
300. Tveit M, Rosengren BE, Nilsson JA, Karlsson MK. Former male elite athletes have a higher prevalence of osteoarthritis and arthroplasty in the hip and knee than expected. *The American journal of sports medicine*. 2012 Mar;40(3):527-33. PubMed PMID: 22130474.
301. Tveit M, Rosengren BE, Nyquist F, Nilsson JA, Karlsson MK. Former male elite athletes have lower incidence of fragility fractures than expected. *Medicine and science in sports and exercise*. 2013 Mar;45(3):405-10. PubMed PMID: 23034643.
302. Uusi-Rasi K, Kannus P, Cheng S, Sievanen H, Pasanen M, Heinonen A, et al. Effect of alendronate and exercise on bone and physical performance of postmenopausal women: a randomized controlled trial. *Bone*. 2003 Jul;33(1):132-43. PubMed PMID: 12919708.
303. Van Waarde A, Van den Thillart G, Erkelens C, Addink A, Lugtenburg J. Functional coupling of glycolysis and phosphocreatine utilization in anoxic fish muscle. An in vivo ³¹P NMR study. *The Journal of biological chemistry*. 1990 Jan 15;265(2):914-23. PubMed PMID: 2295625.
304. Vasikaran SD, Cooper C, Kanis JA. Recommendations for bone marker standards in osteoporosis: what, why and where to now? *Annals of clinical biochemistry*. 2011 Mar;48(Pt 2):91-2. PubMed PMID: 21406559.
305. Wagner CL, Taylor SN, Hollis BW. Does vitamin D make the world go 'round'? *Breastfeeding medicine : the official journal of the Academy of Breastfeeding Medicine*.

- 2008 Dec;3(4):239-50. PubMed PMID: 19086827. Pubmed Central PMCID: 2981372.
306. Wang QJ, Suominen H, Nicholson PH, Zou LC, Alen M, Koistinen A, et al. Influence of physical activity and maturation status on bone mass and geometry in early pubertal girls. *Scandinavian journal of medicine & science in sports*. 2005 Apr;15(2):100-6. PubMed PMID: 15773864.
307. Wasnich RD. Perspective on fracture risk and phalangeal bone mineral density. *Journal of clinical densitometry : the official journal of the International Society for Clinical Densitometry*. 1998 Fall;1(3):259-68. PubMed PMID: 15304897.
308. Wastney ME, Martin BR, Peacock M, Smith D, Jiang XY, Jackman LA, et al. Changes in calcium kinetics in adolescent girls induced by high calcium intake. *The Journal of clinical endocrinology and metabolism*. 2000 Dec;85(12):4470-5. PubMed PMID: 11134095.
309. Watts NB. Clinical utility of biochemical markers of bone remodeling. *Clinical chemistry*. 1999 Aug;45(8 Pt 2):1359-68. PubMed PMID: 10430819.
310. Watts NB. Understanding the Bone Mass Measurement Act. *Journal of clinical densitometry : the official journal of the International Society for Clinical Densitometry*. 1999 Fall;2(3):211-7. PubMed PMID: 10548816.
311. Waxman A, World Health A. WHO global strategy on diet, physical activity and health. *Food and nutrition bulletin*. 2004 Sep;25(3):292-302. PubMed PMID: 15460274.
312. Weeks BK, Beck BR. Twice-weekly, in-school jumping improves lean mass, particularly in adolescent boys. *Pediatric obesity*. 2012 Jun;7(3):196-204. PubMed PMID: 22434783.
313. Wehren LE. The epidemiology of osteoporosis and fractures in geriatric medicine. *Clinics in geriatric medicine*. 2003 May;19(2):245-58. PubMed PMID: 12916284.
314. Welten DC, Kemper HC, Post GB, Van Mechelen W, Twisk J, Lips P, et al. Weight-bearing activity during youth is a more important factor for peak bone mass than calcium intake. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 1994 Jul;9(7):1089-96. PubMed PMID: 7942156.
315. Wiebe PN, Blimkie CJ, Farpour-Lambert N, Briody J, Marsh D, Kemp A, et al. Effects of single-leg drop-landing exercise from different heights on skeletal adaptations in prepubertal girls: a randomized controlled study. *Pediatric exercise science*. 2008 May;20(2):211-28. PubMed PMID: 18579901.
316. Wilkin TJ, Mallam KM, Metcalf BS, Jeffery AN, Voss LD. Variation in physical activity lies with the child, not his environment: evidence for an 'activitystat' in young children (EarlyBird 16). *Int J Obes (Lond)*. 2006 Jul;30(7):1050-5. PubMed PMID: 16801942.
317. Wilkin TJ, Metcalf BS. Testing the activitystat hypothesis. *Preventive medicine*. 2012 Feb;54(2):177; author reply 8-9. PubMed PMID: 22172661.

318. Wilson JM, Marin PJ, Rhea MR, Wilson SM, Loenneke JP, Anderson JC. Concurrent training: a meta-analysis examining interference of aerobic and resistance exercises. *Journal of strength and conditioning research / National Strength & Conditioning Association*. 2012 Aug;26(8):2293-307. PubMed PMID: 22002517.
319. Wolfson L, Whipple R, Derby C, Judge J, King M, Amerman P, et al. Balance and strength training in older adults: intervention gains and Tai Chi maintenance. *Journal of the American Geriatrics Society*. 1996 May;44(5):498-506. PubMed PMID: 8617896.
320. World Health Organization WHO. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. *World Health Organization technical report series*. 1994;843:1-129. PubMed PMID: 7941614.
321. World Health Organization WHO. WHO Scientific Group on the assessment of Osteoporosis at primary health care level. 2004.
322. Wright DC, Han DH, Garcia-Roves PM, Geiger PC, Jones TE, Holloszy JO. Exercise-induced mitochondrial biogenesis begins before the increase in muscle PGC-1alpha expression. *The Journal of biological chemistry*. 2007 Jan 5;282(1):194-9. PubMed PMID: 17099248.
323. Wu T. *Hologic Bone Densitometry and the Evolution of DXA*. 2012.
324. Yoshikawa H, Rettig WJ, Lane JM, Takaoka K, Alderman E, Rup B, et al. Immunohistochemical detection of bone morphogenetic proteins in bone and soft-tissue sarcomas. *Cancer*. 1994 Aug 1;74(3):842-7. PubMed PMID: 8039112.
325. Yoshikawa H, Takaoka K. [Bone remodelling and its regulators]. *Nihon rinsho Japanese journal of clinical medicine*. 1994 Sep;52(9):2262-7. PubMed PMID: 7967065.
326. Zethraeus N, Gerdtham UG. Estimating the costs of hip fracture and potential savings. *International journal of technology assessment in health care*. 1998 Spring;14(2):255-67. PubMed PMID: 9611901.
327. Zethraeus N, Stromberg L, Jonsson B, Svensson O, Ohlen G. The cost of a hip fracture. Estimates for 1,709 patients in Sweden. *Acta orthopaedica Scandinavica*. 1997 Feb;68(1):13-7. PubMed PMID: 9057561.

Paper I

Influence of a 3-Year Exercise Intervention Program on Fracture Risk, Bone Mass, and Bone Size in Prepubertal Children

Bjarne Löfgren,¹ Fredrik Detter,¹ Magnus Dencker,² Susanna Stenevi-Lundgren,¹ Jan-Åke Nilsson,¹ and Magnus K Karlsson¹

¹Clinical and Molecular Osteoporosis Research Unit, Department of Orthopaedics, Lund University, Skane University Hospital, Malmö, Sweden

²Department of Clinical Physiology, Clinical Sciences, Lund University, Skane University Hospital, Malmö, Sweden

ABSTRACT

Published prospective pediatric exercise intervention studies are short term and use skeletal traits as surrogate endpoints for fractures, whereas other reports infer exercise to be associated with more trauma and fractures. This prospective, controlled exercise intervention study therefore followed both skeletal traits and fracture risk for 36 months. Fractures were registered in children aged 7 to 9 years; there were 446 boys and 362 girls in the intervention group (2129 person-years) and 807 boys and 780 girls in the control group (4430 person-years). The intervention included school physical education of 40 minutes per day for 3 years. The control children achieved the Swedish standard of 60 minutes per week. In a subsample of 76 boys and 48 girls in the intervention group and 55 boys and 44 girls in the control group, bone mineral content (BMC, g) and bone width (cm) were followed in the lumbar spine and hip by dual-energy X-ray absorptiometry (DXA). The rate ratio (RR) for fractures was 1.08 (0.71, 1.62) [mean (95% confidence interval)]. In the DXA-measured children, there were no group differences at baseline in age, anthropometrics, or bone traits. The mean annual gain in the intervention group in lumbar spine BMC was 0.9 SD higher in girls and 0.8 SD higher in boys (both $p < .001$) and in third lumbar vertebra width 0.4 SD higher in girls and 0.3 SD higher in boys (both $p < .05$) than in control children. It is concluded that a moderately intense 3-year exercise program in 7- to 9-year-old children increases bone mass and possibly also bone size without increasing fracture risk. © 2011 American Society for Bone and Mineral Research.

KEY WORDS: BMC; BONE SIZE; CHILDREN; EXERCISE; FRACTURE

Introduction

High physical activity produces beneficial skeletal effects,⁽¹⁾ as does moderate activity, during growth.^(2–12) Osteogenic loads include fast dynamic loads with high magnitude and high frequency, whereas long duration of activities is less important.^(13,14) Furthermore, 50% of the variance in bone mass at age 70 is estimated to be predicted by peak bone mass.⁽¹⁵⁾ Low bone mass in the elderly is also associated with a high fracture incidence,⁽¹⁶⁾ so physical activity during growth potentially could be used as intervention against osteoporosis and fragility fractures in old age.

The timing of the load is also important. The pre- and early peripubertal years are the most advantageous period because mechanical load preferentially affects bone surfaces with fast apposition.^(17,18) Intervention studies support this view

when reporting that similar physical activity confers benefit before^(2–12,18) but not after puberty.^(18,19) However, these reports use bone traits as surrogate endpoint variables for fractures, and most studies include volunteers and use specific programs designed to be osteogenic. Moreover, all but three of the studies have durations of 12 months or less. And even if the short-term results of exercise intervention programs in children suggest that exercise may improve the accrual in bone mineral content (BMC) and bone structure,^(2–11,18) so also when we have reported the short-term data in the Malmö Prospective Pediatric Osteoporosis Prevention (POP) Study cohort,^(8–11) it is still debated whether an exercise intervention program confers long-term benefits.⁽¹²⁾ Furthermore, fracture risk is never evaluated as an endpoint variable, but this ought to be done because even if low bone mass in both adults⁽²⁰⁾ and children^(21–23) is associated with fractures, there is no causal relationship. Athletes, despite high

Received in original form August 30, 2010; revised form January 25, 2011; accepted February 18, 2011. Published online March 4, 2011.

Address correspondence to: Bjarne Löfgren, MD, Department of Orthopaedics, Skane University Hospital, SE-205 02 Malmö, Sweden.

E-mail: bjarne.lofgren@med.lu.se

Journal of Bone and Mineral Research, Vol. 26, No. 8, August 2011, pp 1740–1747

DOI: 10.1002/jbmr.381

© 2011 American Society for Bone and Mineral Research

bone mass, also have a high fracture risk owing to more exposure to trauma,^(24,25) and the fracture risk is also high in physically active children.^(21,26) Thus, before physical activity can be recommended, it must be shown that the intervention does not increase fracture risk. This moderately intense 3-year exercise intervention study that evaluated changes both in skeletal traits and in fracture incidence therefore was initiated. We hypothesized that the intervention would lead not only to a higher duration of physical activity but also to more of the most intense activities and then maybe also to an increased incidence of fractures because Clark and colleagues have shown that vigorous physical activity is associated with high fracture risk.^(22,26)

Material and Methods

The Malmö Prospective Pediatric Osteoporosis Prevention (POP) Study is a prospective, controlled exercise intervention study following skeletal traits and fracture incidence in 7- to 9-year-old children described previously in detail.⁽⁸⁻¹¹⁾ Four elementary schools in the same neighborhood that were government funded, with the children allocated to the school based on their residential address and with a standard physical education curriculum, were invited. The schools accepted. One school that instantly accepted was invited to be the intervention school, even though it had to change its physical education curriculum. The study design was acceptable because reports have shown low between-school variability in anthropometrics, bone mass, and lifestyle before any intervention is provided.⁽⁵⁾ The intervention consisted of 200 minutes per week of school physical education provided 5 days a week. The control children achieved the Swedish standard 60 minutes per week provided in one or two lessons per week. The regular class teachers led the lessons, which included standard educational activities such as ball games, running, jumping, and climbing. In our school system, all primary school teachers are educated to lead physical education classes. No specially educated teachers were used in the intervention. Compliance with the program was not specifically evaluated, but a low compliance in school physical education would lead to a missing grade in the subject at the end of primary school for that pupil, and no children had a missing grade.

Fractures were registered prospectively in 446 boys and 362 girls in the intervention group and 807 boys and 780 girls in the control group for the 3-year study period. Since our city has only one hospital, fracture patients usually attended the emergency clinic for treatment, where the fracture is also classified. The fracture data were obtained from the files at the Department of Radiology, and all fractures, independent of trauma energy, were included. If a fracture was sustained elsewhere, the patients were referred to our hospital for follow-up, where the fractures likewise were classified.⁽²⁷⁾ Fewer than 3% of fractures in the target population were missed when this system was used.⁽²⁷⁾ The classification system is well validated and has been used in epidemiologic studies for decades, and the system was described in detail previously.⁽²⁷⁾

Children within the target population, with school start in the next 2 years, were invited for measurements of anthropometric

and skeletal traits. Measurements were done before intervention and then annually in the same month for a period of 3 years.^(8,10) Those with diseases or medication known to influence bone metabolism were excluded. At baseline, 55 of 61 girls and 84 of 89 boys in the intervention school accepted participation. One girl, 11 months younger than the rest, was excluded. At follow-up, 6 girls and 6 boys had moved out of the region or declined further participation. Two boys were excluded owing to medication that influenced bone metabolism. This left 48 girls with a baseline mean age of 7.7 ± 0.6 years (range 6.5 to 8.7 years) and 76 boys with a mean age of 7.8 ± 0.6 years (range 6.7 to 8.7 years) for the intervention group. Sixty-four of 158 girls and 68 of 169 boys in the controls group accepted participation. At follow-up, 19 girls and 12 boys had moved out of the region or declined further participation. One girl and one boy were excluded owing to medication that influenced bone metabolism. This left 44 girls with a baseline mean age of 7.9 ± 0.6 years (range 6.8 to 8.9 years) and 55 boys with a mean age of 8.0 ± 0.6 years (range 6.7 to 8.9 years) for inclusion in the control group. The risk of selection bias seems to be minor because there were no differences in anthropometric or skeletal traits between children within the different schools before the intervention or between children who participated throughout the study and the dropouts.^(8,10) Also, when data from the grade one compulsory school health examination were analyzed, no differences in height, weight, or body mass index (BMI) were found between the children who participated and those who refused.^(9,11)

Questionnaires given at each measurement evaluated numerous lifestyle factors such as smoking, nutritional habits, diseases, medication, and physical activity, with the total duration of physical activity estimated as duration of school physical education plus organized leisure time activity per week. The mean activity for the study period was calculated.⁽⁸⁻¹¹⁾ Self-assessed Tanner stage estimated pubertal maturity.⁽²⁸⁾ Measurements were performed annually for 3 years. Body weight and height were measured by standard equipment. Bone mineral content (BMC, g) was measured by dual-energy X-ray absorptiometry (DXA; DPX-L Version 1.3z; Lunar Corp., Madison, WI, USA) in the total body, lumbar spine, left femoral neck, and trochanter.⁽⁸⁻¹¹⁾ The widths of the third lumbar vertebra and the femoral neck were evaluated on the lumbar spine and hip scans.^(8,10) The hip structural analysis (HSA) software, provided by Lunar Corp. was applied to the hip scan,^(9,11) evaluating femoral neck cross-sectional area (CSA, cm^2), section modulus (Z , cm^3), and cross-sectional moment of inertia (CSMI, cm^4). Values 3 SD above or below the mean were excluded as being biologically unlikely in accordance with Beck and colleagues.⁽²⁹⁾ This resulted in the exclusion of 25 HSA analyses. Total-body fat mass and total-body lean mass were estimated from the total-body scans. The equipment was calibrated daily with the Lunar phantom, and our technicians also did all measurements and software analyses. The coefficients of variation, evaluated by duplicate measurements in 13 healthy children, were BMC 1.4% to 3.8%, bone width 1.5% to 2.2%, FN CSA 2.2%, FN Z 6.2%, FN CSMI 6.2%, total-body fat mass 3.7%, and total-body lean mass 1.5%.

Physical activity was measured objectively by accelerometers (Model 7164 MTI; Manufacturing Technology, Inc., Fort Walton

Beach, FL, USA) after 2 years. The accelerometer measurements have been described in detail in the previously published 2-year outcome of the POP Study.^(9,11) In summary, measurements were performed for four consecutive days.⁽¹¹⁾ Accelerometer data were averaged over a period called an *epoch*, representing 10 seconds. Mean activity was estimated as the total accelerometer counts per minute of monitoring (counts/min or cpm), moderate to vigorous physical activity (MVPA) as time spent above 3 metabolic equivalents (METs), and vigorous physical activity (VPA) as time spent above 6 METs. Cutoff points used for all children were more than 1000 cpm for MVPA and more than 3500 cpm for VPA.^(9,11) Physical activity above 5000, 6000, and 10,000 cpm also was included in order to capture the most osteogenic activities.^(13,14)

Informed written consent was obtained from parents or guardians of the participants, and the Ethics Committee of Lund University (LU 453-98; 1998-09-15) approved the study. Data are presented as mean \pm SD or mean with 95% confidence interval (95% CI). All comparisons, with the exception of the fracture evaluation, which in addition was evaluated in all children as one group, were performed gender-specifically. Baseline group differences for parametric values were tested by Student's *t* test, and differences in nonparametric values as lifestyle factors were evaluated with Fisher's exact test. The Mann-Whitney *U* test was used to compare group differences in Tanner stage at follow-up. The annual changes in all parameters were calculated as delta values and group difference in annual changes by ANCOVA with adjustment for Tanner stage at follow-up. The accuracy of the models was checked by studying the residuals with a Shapiro-Wilks test, which revealed that the normality assumptions for all models were fulfilled. The mean group difference, expressed in SD, was calculated as the mean annual changes in the intervention group minus the mean annual changes in the control group divided by the SD for the annual changes in the control group. The mean physical activity in hours per week over the 3-year study period was calculated from the questionnaires. All children then were divided into tertiles according to questionnaire-estimated physical activity to test any dose-response relationship, and the tertile differences then were tested by ANOVA. Spearman correlation was used to analyze the associations between the tertiles in Tanner stage at follow-up. Fracture risk with 95% CI was

estimated by Poisson distribution, and $p < .05$ was regarded as a statistically significant difference.

Results

There were 108 fractures during the study period (57 forearm, 20 hand, 14 humerus, 2 tibia, 4 clavicle, 5 ankle, 4 foot, 1 spine, and 1 pelvis). In the intervention group there were 37 fractures (17.4 events/1000 person-years) and in the control group there were 71 fractures (16.0 events/1000 person-years), leading to a rate ratio (RR) of 1.08 (95% CI 0.71, 1.62), with no gender difference (Table 1, Fig. 1).

In the DXA-measured children, the only difference in lifestyle, anthropometrics, and skeletal traits was a higher duration of physical activity in the intervention groups (Tables 2 and 3). At baseline, all children were in Tanner stage 1. At follow-up, more boys in the control group than in the intervention group were at a higher Tanner stage (Table 2). The accelerometer data showed that both girls and boys in the intervention group were exposed to more of the most intense activities than children in the control group (Table 2).

The mean annual gain in the intervention girls was 0.9 SD higher in lumbar spine BMC ($p < .001$), 0.5 SD higher in femoral neck BMC ($p < .05$), 0.4 SD higher in third lumbar vertebra width ($p < .05$), and 0.5 SD higher in femoral neck cross-sectional area ($p < .05$) than in the control girls (Table 3). The mean annual gain in the intervention boys was 0.8 SD higher in lumbar spine BMC ($p < .001$) and 0.3 SD higher in third lumbar vertebra width ($p < .05$) than in the control boys (Table 3). The group differences between children in the intervention and control groups in both boys and girls remained after adjusting for annual changes in weight and height and Tanner stage at follow-up, except that the group difference in the third lumbar vertebra width changed from $p = .04$ to $p = .06$ in both genders (data not shown).

Finally, all the boys and all the girls were mixed in two separate cohorts and within each gender divided into tertiles. No differences between the tertiles were seen in anthropometric outcomes. In girls, there were no differences between tertiles in maturity outcome. At follow-up, more boys in the lowest tertile than in the two higher tertiles were at a higher Tanner stage ($p < .001$). The outcomes when comparing the tertiles remained

Table 1. Fracture Epidemiology in Children in the Exercise Intervention Group and the Control Group

	Participants (n)	Fractures (n)	Person-years	Fractures/1000 person-years [mean (95% CI)]	Rate ratio [mean (95% CI)]
All individuals					
Intervention group	808	37	2129	17.4 (12.2, 23.9)	1.08 (0.71, 1.62)
Control group	1587	71	4430	16.0 (12.5, 20.2)	
Girls					
Intervention group	362	12	935	12.8 (6.6, 22.4)	0.85 (0.40, 1.68)
Control group	780	33	2187	15.1 (10.4, 21.2)	
Boys					
Intervention group	446	25	1194	20.9 (13.6, 30.9)	1.24 (0.72, 2.08)
Control group	807	38	2243	16.9 (12.0, 23.3)	

Note: Data are presented as numbers, years, and means with 95% confidence intervals (95% CIs).

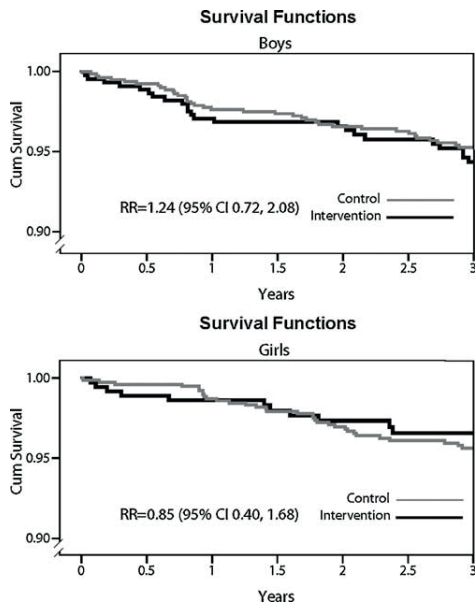


Fig. 1. Fracture incidence in girls and boys in the intervention and control groups.

in both boys and girls after adjusting for annual changes in weight and height and Tanner stage at follow-up. The analyses revealed a dose-response effect between questionnaire-evaluated weekly duration of physical activity and annual gain in BMC such that with each higher tertile of physical activity, there was a higher gain in BMC, reaching significance in lumbar spine BMC in girls ($p = .012$) and boys ($p = .002$; Fig. 2).

Discussion

This study should not be viewed as an additional study that evaluates whether osteogenic training in children improves bone mass and bone size because this has already been shown in most elegant intervention studies.⁽²⁻⁷⁾ The study instead adds knowledge when reporting that a moderately intense general exercise intervention program in the peri- to pubertal years also could be initiated to improve at least the level of bone mass and possibly also structure and in both genders. However, we must be aware that a statistically significant difference is not the same as a difference in biologic significance. That is, a statistically significant group difference in bone mass may not be transferred to a difference in fracture risk, as possibly suggested by the fracture data in this study. However, finding an exercise-induced bone mass effect in these early prepubertal children must be regarded as most promising because it is generally accepted that exercise exerts even greater effects on bone mass in the late prepubertal and early pubertal periods.^(17,18) Therefore, it is of

most importance also to follow these children into the pubertal period.

Most important, the intervention could be performed without increasing the fracture incidence suggested to occur with a high level of physical activity in both adults^(24,25) and children.^(21,26) This study also supports published studies with shorter durations such as the previous POP reports⁽⁸⁻¹¹⁾ and studies with a similar follow-up period but with bone mass only evaluated by a peripheral DXA device.⁽¹²⁾ This study indicates that exercise-induced benefits seem to remain into puberty, which increases the probability that the intervention may lead to improved peak bone mass.⁽³⁰⁾ The intervention also seemed to be associated with more general physical activity, at least in subjective estimation (Table 2). But it is also of interest to note that the intervention was associated with more of the most intense activities, activities known to be osteogenic,^(13,14) even if performed only for a short duration each day^(13,14,31) (Table 2).

The finding that the intervention possibly may influence bone size as well is of special interest because bone size contributes to bone strength independent of bone mass.⁽³²⁻³⁴⁾ This is of clinical relevance because women with spine fractures have smaller lumbar spine vertebrae but normal femoral neck size, whereas women with hip fractures have smaller femoral neck size but normal vertebral body size compared with nonfractured control individuals.⁽³³⁾ The gender differences in exercise response could be due to girls being more advanced in pubertal maturation than boys because it is generally believed that the late pre- and early peripubertal period is the period with the most obvious beneficial skeletal response to exercise.⁽²⁻¹²⁾ Another possible explanation is that boys in general were able to withstand a higher duration of physical activity than girls; that is, the extra school physical education contributed less to the total physical activity in boys than in girls.

The reported dose-response effects in the gain in BMC also strengthen the view that there really is a causal relationship between duration of exercise and gain in bone mass (Fig. 2).

Finally, high physical activity has been reported to be associated with increased fracture risk in both children⁽²¹⁾ and adults⁽²⁴⁾ owing to a higher exposure to trauma.⁽²¹⁾ Even if exercise leads to higher bone mass and fewer fragility fractures in old age, the lifetime fracture risk then would be similar or even higher in physically active individuals than in lifelong sedentary individuals.^(24,25) Before exercise intervention programs are recommended, therefore, we must be sure that the intervention does not confer more fractures. This study refutes this hypothesis, at least with the power to conclude that in the intervention group there was no fracture reduction of more than 29% or increase of more than 62%. Also, the contradictory hypothesis, that higher BMC found in physically active children would result in fewer fractures, was refuted. This is not surprising because even if they have low BMC for that age, most children are beyond the level of BMC referred to as the *fracture threshold*.^(22,26)

Study limitations include the power problem when using fracture as the endpoint. Despite including 2395 children in the fracture evaluation, by existing data, we could only conclude statistically that there was at least no fracture reduction of more

Table 2. Lifestyle Factors at Baseline and Follow-Up and Accelerometer Data Collected After 2 Years in the Subsample of Children Who Were Selected for Measurements

	Girls			Boys		
	Intervention group (n = 48)	Control group (n = 44)	p Value	Intervention group (n = 76)	Control group (n = 55)	p Value
Lifestyle factors at baseline						
Excluding dairy products	0 (0%)	0 (0%)	1.0	0 (0%)	0 (0%)	1.0
Drinking coffee	0 (0%)	0 (0%)	1.0	2 (3%)	0 (0%)	.2
Smoking	0 (0%)	0 (0%)	1.0	0 (0%)	0 (0%)	1.0
Alcohol	0 (0%)	0 (0%)	1.0	0 (0%)	0 (0%)	1.0
Tried to lose weight	1 (2%)	0 (0%)	.3	1 (1%)	0 (0%)	.4
Current disease	3 (7%)	1 (2%)	.3	7 (9%)	3(6%)	.4
Ongoing medication	5 (11%)	2 (5%)	.3	10 (13%)	4 (7%)	.3
Earlier medication	4 (9%)	2 (5%)	.5	3 (4%)	5 (9%)	.2
Fractures	6 (13%)	5 (12%)	.8	6 (8%)	6 (11%)	.6
Tanner stage 1/2/3/4/5	48/0/0/0/0	44/0/0/0/0	1.0	76/0/0/0/0	55/0/0/0/0	1.0
Organized physical activity (h/wk)						
School curriculum	3.3	1.0	<.001	3.3	1.0	<.001
Outside the school	0.7 (0.7)	1.3 (1.7)	<.03	1.7 (1.6)	1.3 (1.3)	.2
Total physical activity	4.0 (0.7)	2.3 (1.7)	<.001	5.0 (1.6)	2.3 (1.3)	<.001
Accelerometer data after 2 years						
Numbers	(n = 41)	(n = 40)		(n = 72)	(n = 55)	
Recording time per day (h/d)	11.8 (1.4)	12.0 (1.3)	.5	11.7 (1.3)	12.7 (1.4)	.02
Mean activity (min/d)	644 (192)	590 (121)	.1	770 (267)	728 (211)	.3
>3 METS (min/d)	193 (47)	185 (37)	.4	211 (55)	209 (45)	.8
>6 METS (min/d)	34 (15)	35 (13)	.8	44 (21)	48 (19)	.2
>5000 mean cpm (min/d)	17.9 (9.9)	16.8 (8.5)	.6	23 (13)	24 (13)	.6
>6000 mean cpm (min/d)	12.5 (7.6)	10.5 (6.2)	.2	16 (10)	15 (9)	.7
>10000 mean cpm (min/d)	2.6 (2.5)	1.0 (1.2)	<.001	4 (3)	2 (3)	.01
Lifestyle factors at follow-up						
	(n = 47)	(n = 44)		(n = 75)	(n = 53)	
Excluding dairy products	0 (0%)	0 (0%)	1.0	0 (0%)	0 (0%)	1.0
Drinking coffee	0 (0%)	2 (5%)	.1	4 (6%)	1 (2%)	.3
Smoking	0 (0%)	0 (0%)	1.0	0 (0%)	0 (0%)	1.0
Alcohol	0 (0%)	0 (0%)	1.0	0 (0%)	0 (0%)	1.0
Tried to lose weight	0 (0%)	0 (0%)	1.0	4 (6%)	1 (2%)	.3
Current disease	4 (9%)	4 (10%)	.9	4 (6%)	2 (4%)	.6
Ongoing medication	7 (16%)	1 (2%)	.06	12 (17%)	5 (9%)	.2
Earlier medication	5 (11%)	2 (5%)	.3	9 (13%)	6 (11%)	.8
Fractures	7 (16%)	8 (19%)	.7	12 (17%)	11 (20%)	.7
Tanner stage 1/2/3/4/5	11/24/9/3/0	10/18/14/2/0	.5	64/11/0/0/0	11/27/14/1/0	<.001
Menarche	4 (9%)	1 (2%)	.2	—	—	—
Organized physical activity (h/wk)						
School curriculum	3.3	1.5	<.001	3.3	1.5	<.001
Outside the school	2.1 (2.0)	2.6 (2.4)	.2	3.0 (3.2)	2.7 (2.5)	.5
Total physical activity	5.4 (2.0)	4.1 (2.4)	<.01	6.3 (3.2)	4.2 (2.5)	<.001

Note: The baseline measurements were performed just before the intervention was initiated and then annually for 3 years, with the last measurement performed when the intervention was still ongoing. Questionnaire-evaluated duration of organized physical activity was estimated as hours per week. Accelerometer-measured levels of physical activity were presented as minutes per day above 3 or 6 metabolic equivalents (METs) or above 6000 or 10,000 counts per minute (cpm). Data are presented as number of children with proportion (%) or as mean (SD). Group comparison between nonparametric data was done by Fisher's exact test and between parametric data by Student's *t* test between means. The Mann-Whitney *U* test was used to compare group differences in Tanner stage at follow-up.

than 29% and no fracture increase of more than 62%. An individual randomization also had been advantageous. It also would have been advantageous to have had the bone structure estimated by 3D techniques such as computed tomography. In

girls, we found a significantly larger annual gain in CSA in the intervention group than in the control group. However, no such group differences were found in the mechanical calculations *Z* or CSMI. This highlight the problem of using a 2D imaging

Table 3. Baseline Data and Annual Changes in the Subsample of Girls and Boys Who Were Chosen for Measurements, Presented as Absolute Values, Evaluating the Effect of 3 Years of Exercise Intervention in Anthropometry, Bone Mineral Parameters, Bone Size, and Hip Structure Analysis (HSA) in the Exercise Intervention Group and the Control Group

	Girls					
	Baseline			Annual changes		
	Intervention group (n = 48)	Control group (n = 44)	p Value	Intervention group (n = 48)	Control group (n = 44)	p Value
Age	7.7 (7.5, 7.8)	7.9 (7.7, 8.1)	0.10	—	—	
Anthropometrics						
Weight (kg)	27.9 (26.3, 29.6)	27.6 (25.9, 29.3)	0.79	4.2 (3.7, 4.7)	3.7 (3.2, 4.1)	0.12
Height (cm)	128.3 (126.7, 129.8)	129.6 (127.2, 132.0)	0.33	6.2 (5.9, 6.5)	6.1 (5.7, 6.4)	0.57
Lean mass (kg)	19.9 (19.2, 20.6)	20.4 (19.5, 21.2)	0.39	2.4 (2.2, 2.7)	2.3 (2.1, 2.5)	0.10
Fat mass (kg)	5.5 (4.3, 6.7)	5.3 (4.3, 6.4)	0.83	1.7 (1.4, 2.0)	1.0 (0.7, 1.3)	<0.001
Bone mineral content (BMC, g)						
Total body	942.7 (898.4, 987.1)	944.1 (887.3, 1000.9)	0.97	166.6 (147.7, 185.4)	152.2 (135.9, 168.4)	0.09
Lumbar spine	29.4 (27.2, 31.6)	30.0 (28.0, 32.0)	0.69	10.9 (9.2, 12.6)	7.7 (6.6, 8.8)	<0.001
Femoral neck	2.6 (2.4, 2.8)	2.7 (2.5, 2.9)	0.58	0.41 (0.33, 0.49)	0.29 (0.22, 0.29)	<0.05
Bone width (cm)						
Third lumbar vertebra	2.9 (2.8, 2.9)	2.9 (2.8, 3.0)	0.18	0.13 (0.11, 0.15)	0.11 (0.09, 0.13)	<0.05
Femoral neck	2.4 (2.4, 2.5)	2.5 (2.4, 2.6)	0.28	0.15 (0.12, 0.18)	0.12 (0.09, 0.15)	0.16
HSA	(n = 40)	(n = 41)		(n = 40)	(n = 41)	
CSA (cm ²)	0.91 (0.86, 0.95)	0.90 (0.85, 0.95)	0.65	0.11 (0.09, 0.13)	0.09 (0.07, 0.10)	<0.05
Z (cm ³)	0.28 (0.26, 0.30)	0.28 (0.26, 0.30)	0.84	0.05 (0.05, 0.06)	0.05 (0.04, 0.05)	0.16
CSMI (cm ⁴)	0.34 (0.31, 0.37)	0.35 (0.32, 0.39)	0.79	0.09 (0.07, 0.11)	0.07 (0.06, 0.09)	0.08
	Boys					
	Baseline			Annual changes		
	Intervention group (n = 76)	Control group (n = 55)	p Value	Intervention group (n = 76)	Control group (n = 55)	p Value
Age	7.8 (7.7, 7.9)	7.9 (7.8, 8.1)	0.18	—	—	
Anthropometrics						
Weight (kg)	28.4 (27.1, 29.7)	27.6 (26.1, 29.1)	0.41	3.6 (3.2, 3.9)	3.7 (3.4, 4.0)	0.47
Height (cm)	129.4 (127.9, 130.9)	130.0 (128.1, 131.8)	0.64	5.5 (5.4, 5.7)	5.6 (5.4, 5.8)	0.51
Lean mass (kg)	21.8 (21.1, 22.5)	21.9 (21.0, 22.7)	0.98	2.2 (2.1, 2.3)	2.3 (2.2, 2.5)	0.63
Fat mass (kg)	4.1 (3.3, 5.0)	3.7 (3.0, 4.4)	0.41	1.3 (1.0, 1.6)	1.1 (0.9, 1.3)	0.22
Bone mineral content (BMC, g)						
Total body	1001.5 (958.0, 1045.0)	983.4 (932.6, 1034.2)	0.59	148.6 (139.2, 157.9)	150.7 (141.4, 160.0)	0.13
Lumbar spine	32.1 (30.0, 34.2)	31.4 (29.5, 33.3)	0.65	8.9 (8.2, 9.6)	7.1 (6.6, 7.7)	<0.001
Femoral neck	3.0 (2.8, 3.1)	2.8 (2.6, 3.0)	0.33	0.32 (0.28, 0.37)	0.28 (0.23, 0.32)	0.98
Bone width (cm)						
Third lumbar vertebra	3.1 (3.0, 3.1)	3.1 (3.0, 3.2)	0.30	0.11 (0.10, 0.12)	0.09 (0.07, 0.11)	<0.05
Femoral neck	2.5 (2.4, 2.5)	2.5 (2.4, 2.5)	0.57	0.13 (0.11, 0.15)	0.11 (0.09, 0.13)	0.84
HSA	(n = 65)	(n = 52)		(n = 65)	(n = 52)	
CSA (cm ²)	1.01 (0.96, 1.05)	0.99 (0.94, 1.04)	0.60	0.09 (0.08, 0.11)	0.08 (0.07, 0.10)	0.34
Z (cm ³)	0.32 (0.30, 0.35)	0.31 (0.29, 0.34)	0.54	0.05 (0.04, 0.06)	0.05 (0.04, 0.05)	0.27
CSMI (cm ⁴)	0.41 (0.38, 0.45)	0.39 (0.36, 0.43)	0.47	0.09 (0.08, 0.10)	0.08 (0.07, 0.09)	0.36

Note: Eight HSA analyses were excluded in the intervention girls, 6 with scans above or below 3 SD and 2 with missing baseline scan, and 3 HSA analyses were excluded in the control girls, 2 with scans above or below 3 SD and 1 with missing baseline scan. Eleven HSA analyses were excluded in the intervention boys, 8 with scans above or below 3 SD, 1 with missing baseline scan, and 2 with technical errors, and 3 HSA analyses were excluded in the control boys, all with scans above or below 3 SD. Data are presented as means (95% CI). Group comparisons are done by ANCOVA adjusted for Tanner stage at follow-up.

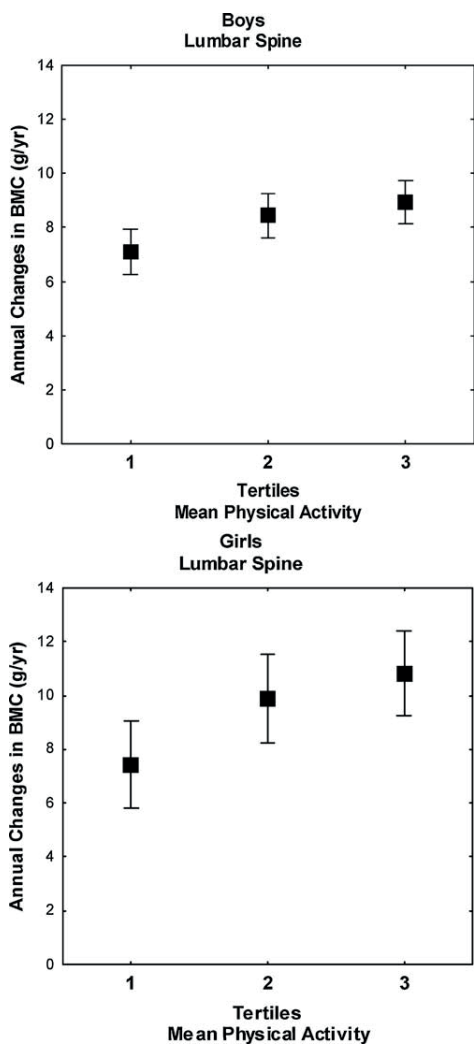


Fig. 2. Annual changes in lumbar spine bone mineral content (BMC) in girls and boys divided into tertiles according to weekly duration of physical activity. Data are provided as means with 95% confidence intervals. Tertile comparisons are done by ANCOVA adjusted for Tanner stage at follow-up. Girls: $p = .012$; boys: $p = .002$.

technique in an attempt to estimate the 3D structure of the femoral neck.

In conclusion, this study infers that a general, moderately intense school-based exercise intervention program for 3 years in prepubertal children leads to improved bone mass and possibly also bone size without increasing fracture risk. Daily

moderate physical activity ought to be initiated in prepubertal school children and then continue into puberty as a preventive strategy to improve bone strength.

Disclosures

All the authors state that they have no conflicts of interest.

Acknowledgments

We thank the teachers and students for their help with this study. Financial support for this study was provided by the Swedish Research Council (K2007-53X-14080-07-3), the Centre for Athletic Research (160/07), the Osterlund Foundation, the Kock Foundation, and the Region Skane Foundation.

References

- Hind K, Burrows M. Weight-bearing exercise and bone mineral accrual in children and adolescents: a review of controlled trials. *Bone*. 2007;40:14–27.
- Bradney M, Pearce G, Naughton G, et al. Moderate exercise during growth in prepubertal boys: changes in bone mass, size, volumetric density, and bone strength: a controlled prospective study [see comments]. *J Bone Miner Res*. 1998;13:1814–1821.
- McKay HA, Petit MA, Schutz RW, Prior JC, Barr SI, Khan KM. Augmented trochanteric bone mineral density after modified physical education classes: a randomized school-based exercise intervention study in prepubescent and early pubescent children [see comments]. *J Pediatr*. 2000;136:156–162.
- Petit MA, McKay HA, MacKelvie KJ, Heinonen A, Khan KM, Beck TJ. A randomized school-based jumping intervention confers site and maturity-specific benefits on bone structural properties in girls: a hip structural analysis study. *J Bone Miner Res*. 2002;17:363–372.
- MacKelvie KJ, Khan KM, Petit MA, Janssen PA, McKay HA. A school-based exercise intervention elicits substantial bone health benefits: a 2-year randomized controlled trial in girls. *Pediatrics*. 2003;112:e447.
- MacKelvie KJ, Petit MA, Khan KM, Beck TJ, McKay HA. Bone mass and structure are enhanced following a 2-year randomized controlled trial of exercise in prepubertal boys. *Bone*. 2004;34:755–764.
- Laing EM, Wilson AR, Modlesky CM, O'Connor PJ, Hall DB, Lewis RD. Initial years of recreational artistic gymnastics training improves lumbar spine bone mineral accrual in 4- to 8-year-old females. *J Bone Miner Res*. 2005;20:509–519.
- Linden C, Alwis G, Ahlberg H, et al. Exercise, bone mass and bone size in prepubertal boys: one-year data from the pediatric osteoporosis prevention study. *Scand J Med Sci Sports*. 2007;17:340–347.
- Linden C, Ahlberg HG, Besjakov J, Gardsell P, Karlsson MK. A school curriculum-based exercise program increases bone mineral accrual and bone size in prepubertal girls: two-year data from the pediatric osteoporosis prevention (POP) study. *J Bone Miner Res*. 2006;21:829–835.
- Valdimarsson O, Linden C, Johnell O, Gardsell P, Karlsson MK. Daily physical education in the school curriculum in prepubertal girls during 1 year is followed by an increase in bone mineral accrual and bone width—data from the prospective controlled Malmo pediatric osteoporosis prevention study. *Calcif Tissue Int*. 2006;78:65–71.
- Alwis G, Linden C, Ahlberg HG, Dencker M, Gardsell P, Karlsson MK. A 2-year school-based exercise programme in pre-pubertal boys induces skeletal benefits in lumbar spine. *Acta Paediatr*. 2008;97:1564–1571.

12. Hasselstrom HA, Karlsson MK, Hansen SE, Gronfeldt V, Froberg K, Andersen LB. A 3-year physical activity intervention program increases the gain in bone mineral and bone width in prepubertal girls but not boys: the prospective copenhagen school child interventions study (CoSCIS). *Calcif Tissue Int.* 2008;83:243–250.
13. Lanyon LE. Control of bone architecture by functional load bearing. *J Bone Miner Res.* 1992;7 (Suppl 2): S369–375.
14. Rubin CT, Lanyon LE. Regulation of bone formation by applied dynamic loads. *J Bone Joint Surg [Am].* 1984;66:397–402.
15. Hui SL, Slemenda CW, Johnston CC Jr. The contribution of bone loss to postmenopausal osteoporosis. *Osteoporos Int.* 1990;1:30–34.
16. Melton LJd, Atkinson EJ, O'Fallon WM, Wahner HW, Riggs BL. Long-term fracture prediction by bone mineral assessed at different skeletal sites. *J Bone Miner Res.* 1993;8:1227–1233.
17. Ruff CB, Walker A, Trinkaus E. Postcranial robusticity in Homo. III: Ontogeny. *Am J Phys Anthropol.* 1994;93:35–54.
18. Kannus P, Haapasalo H, Sankelo M, et al. Effect of starting age of physical activity on bone mass in the dominant arm of tennis and squash players. *Ann Intern Med.* 1995;123:27–31.
19. Blimkie CJ, Rice S, Webber CE, Martin J, Levy D, Gordon CL. Effects of resistance training on bone mineral content and density in adolescent females. *Can J Physiol Pharmacol.* 1996;74:1025–1033.
20. Johnell O, Gullberg B, Kanis JA, et al. Risk factors for hip fracture in European women: the MEDOS Study. *Mediterranean Osteoporosis Study.* *J Bone Miner Res.* 1995;10:1802–1815.
21. Clark EM, Ness AR, Tobias JH. Bone fragility contributes to the risk of fracture in children, even after moderate and severe trauma. *J Bone Miner Res.* 2008;23:173–179.
22. Clark EM, Tobias JH, Ness AR. Association between bone density and fractures in children: a systematic review and meta-analysis. *Pediatrics.* 2006;117:e291–297.
23. Jones G, Boon P. Which bone mass measures discriminate adolescents who have fractured from those who have not? *Osteoporos Int.* 2008;19:251–255.
24. Karlsson MK, Linden C, Karlsson C, Johnell O, Obrant K, Seeman E. Exercise during growth and bone mineral density and fractures in old age. *Lancet.* 2000;355:469–470.
25. Nordstrom A, Karlsson C, Nyquist F, Olsson T, Nordstrom P, Karlsson M. Bone loss and fracture risk after reduced physical activity. *J Bone Miner Res.* 2005;20:202–207.
26. Clark EM, Ness AR, Tobias JH. Vigorous physical activity increases fracture risk in children irrespective of bone mass: a prospective study of the independent risk factors for fractures in healthy children. *J Bone Miner Res.* 2008;23:1012–1022.
27. Jonsson B, Gardsell P, Johnell O, Redlund-Johnell I, Sernbo I. Remembering fractures: fracture registration and proband recall in southern Sweden. *J Epidemiol Community Health.* 1994;48:489–490.
28. Duke PM, Litt IF, Gross RT. Adolescents' self-assessment of sexual maturation. *Pediatrics.* 1980;66:918–920.
29. Beck TJ, Oreskovic TL, Stone KL, et al. Structural adaptation to changing skeletal load in the progression toward hip fragility: the study of osteoporotic fractures. *J Bone Miner Res.* 2001;16:1108–1119.
30. Mora S, Gilsanz V. Establishment of peak bone mass. *Endocrinol Metab Clin North Am.* 2003;32:39–63.
31. Karlsson MK, Magnusson H, Karlsson C, Seeman E. The duration of exercise as a regulator of bone mass. *Bone.* 2001;28:128–132.
32. Ahlborg HG, Johnell O, Turner CH, Rannevik G, Karlsson MK. Bone loss and bone size after menopause. *N Engl J Med.* 2003;349:327–334.
33. Duan Y, Parfitt A, Seeman E. Vertebral bone mass, size, and volumetric density in women with spinal fractures. *J Bone Miner Res.* 1999;14: 1796–1802.
34. Duan Y, Seeman E, Turner CH. The biomechanical basis of vertebral body fragility in men and women. *J Bone Miner Res.* 2001;16:2276–2283.

Paper II

Paper III

A 5-Year Exercise Program in Pre- and Peripubertal Children Improves Bone Mass and Bone Size Without Affecting Fracture Risk

Fredrik T. L. Detter · Björn E. Rosengren · Magnus Dencker · J.-Å. Nilsson · Magnus K. Karlsson

Received: 17 September 2012 / Accepted: 8 December 2012
© Springer Science+Business Media New York 2013

Abstract We studied the effect in children of an exercise intervention program on fracture rates and skeletal traits. Fractures were registered for 5 years in a population-based prospective controlled exercise intervention study that included children aged 6–9 years at study start, 446 boys and 362 girls in the intervention group and 807 boys and 780 girls in the control group. Intervention subjects received 40 min/school day of physical education and controls, 60 min/week. In 73 boys and 48 girls in the intervention group and 52 boys and 48 girls in the control group, bone mineral density (BMD, g/cm^2) and bone area (mm^2) were followed annually by dual-energy X-ray absorptiometry, after which annual changes were calculated. At follow-up we also assessed trabecular and cortical volumetric BMD (g/cm^3) and bone structure by peripheral computed tomography in the tibia and radius. There were 20.0 fractures/1,000 person-years in the intervention group and 18.5 fractures/1,000 person-years in the control group, resulting in a rate ratio of 1.08 (0.79–1.47) (mean and 95 % CI). The gain in spine BMD was higher in both girls (difference 0.01 g/cm^2 , 0.005–0.019) and boys (difference 0.01 g/cm^2 , 0.001–0.008) in the intervention group. Intervention girls also had higher gain in femoral neck area

(difference 0.04 mm^2 , 0.005–0.083) and at follow-up larger tibial bone mineral content (difference 0.18 g, 0.015–0.35), larger tibial cortical area (difference 17 mm^2 , 2.4–31.3), and larger radial cross-sectional area (difference 11.0 mm^2 , 0.63–21.40). As increased exercise improves bone mass and in girls bone size without affecting fracture risk, society ought to encourage exercise during growth.

Keywords Bone mineral content · Bone size · Children · Controlled · Exercise · Fracture · Prospective

A high level of physical activity induces anabolic skeletal effects, as does moderate activity during growth [1–10]. The most osteogenic activities include fast novel dynamic loads with high magnitude and high frequency, whereas endurance activities seem to be less effective [11, 12]. Physical activity during growth is also associated with high peak bone mass, and half of the variance in bone mass at age 70 is estimated to be predicted by peak bone mass [13]. As low bone mass in advanced age is associated with high fracture risk, exercise during growth could possibly be used as a preventive measure for osteoporosis and fragility fractures [14].

The pre- and early peripubertal years are ideal for exercise if the aim is to improve skeletal strength as mechanical load preferentially affects surfaces of the skeleton undergoing fast apposition [15]. This notion is supported by intervention studies showing that the same type of exercise mediates benefit before puberty but with no or only minor effects after puberty [1–6, 8–11]. Most such intervention studies have used bone mass as the end-point variable, included volunteers, and utilized specific training programs designed to be osteogenic; and none has so far exceeded 36 months [5, 6, 9, 11, 16]. Furthermore,

The authors have stated that they have no conflict of interest.

F. T. L. Detter (✉) · B. E. Rosengren · J.-Å. Nilsson · M. K. Karlsson
Clinical and Molecular Osteoporosis Research Unit, Department of Clinical Sciences and Orthopedics, Skåne University Hospital, Lund University, SE-205 02 Malmö, Sweden
e-mail: fredrik.detter@med.lu.se

M. Dencker
Department of Clinical Physiology, Skåne University Hospital, SE-205 02 Malmö, Sweden

there is no consensus as to whether skeletal benefits gained by moderately intense intervention are retained in the long term. Most importantly, bone mass is only a surrogate end point for the clinically relevant entity, fractures, and even if low bone mass in both adults and children is associated with high fracture risk [13, 17], there is no causal relationship. For example, fracture incidence is higher in athletes with higher than average bone mass and in children with high physical activity levels [18]. The aim of this prospective controlled study was therefore to evaluate whether the benefits in bone mass reported in previous intervention studies with shorter duration could be gained and retained also with a moderately intense general exercise intervention program in a population-based cohort of children in the long term, without increasing fracture risk.

Materials and Methods

The Malmö Pediatric Osteoporosis Prevention (POP) study is a population-based, prospective, controlled, exercise intervention study following skeletal development and fracture incidence in 6- to 9-year-old children; the protocol was described in detail previously [7–9]. In summary, four neighboring government-funded elementary schools, with the children allocated to their school depending on residential address and with a standard curriculum of physical education, accepted participation. One school was chosen as the intervention school. Low between-school variability was reported in lifestyle, anthropometrics, and bone parameters before intervention was initiated [5]. The intervention constituted of daily physical education at school (in total 200 min per week), in contrast to the controls, who continued with the Swedish standard of 60 min given in one or two lessons per week. All physical education lessons were led by the ordinary teachers and included general moderately intense activities such as ball games, running, jumping, climbing, and playing.

The POP study, where incident fractures are continuously registered, includes 446 boys and 362 girls in the intervention group and 807 boys and 780 girls in the control group. In the city of Malmö there is only one hospital, and virtually all fracture patients attend the hospital. Since all referrals, reports, and radiographs have been saved in the hospital for more than a century, it is possible to identify and verify all fractures. This registration system has been shown to be reliable and advantageous compared to proband recall [19]. Previous evaluations have reported that fewer than 3 % of all fractures are missed by this system [19].

From each of the control and intervention groups, a randomly selected subsample was also invited for repeated measurements of anthropometrics and skeletal traits. The measurements started just before the intervention was

initiated and were then repeated annually in the same month for a period of 5 years [7, 9]. Children with diseases or medication known to influence bone metabolism were excluded. At baseline, 55 out of 61 invited girls and 84 out of 89 invited boys from the intervention school agreed to participate. One girl was excluded as she was 11 months younger than all the rest. During the 5-year follow-up period, six girls and nine boys moved out of the region or declined serial measurements. Two boys were excluded due to medication known to influence bone metabolism, leaving 48 girls with a baseline mean age of 7.7 ± 0.6 (SD) years (range 6.5–8.7) and 73 boys with a mean age of 7.8 ± 0.6 years (range 6.7–8.7). Sixty-four out of 158 girls and 68 out of 169 boys from the control schools accepted participation. At follow-up, 15 girls and 13 boys had moved out of the region or declined serial measurements. One girl and two boys were excluded due to medication known to influence bone metabolism, and one boy adopted from Colombia was excluded as being the only non-Caucasian, leaving 48 girls with a baseline mean age of 7.9 ± 0.6 years (range 6.8–8.9) and 52 boys with a mean age of 8.0 ± 0.6 years (range 6.7–8.9) in the control group. Anthropometrics and bone traits were similar when children from the different schools were compared before the intervention was initiated, and there were no differences in these traits at baseline between the children who participated throughout the study and those who did not [7, 9]. Furthermore, based on data from the grade-one compulsory school health examination, there were no differences in height, weight, or body mass index (kilograms per meter squared) between the children who accepted participation at baseline and those who declined [20].

Lifestyle factors were evaluated by a questionnaire at baseline and at follow-up. Total duration of physical activity was estimated as the sum of school physical education and mean organized leisure time activity per week [7–10]. The questionnaires were filled out with help from a parent, guardian, or member of the research staff. Pubertal maturity was determined by self-assessment of Tanner staging [21]. Body weight and body height were measured by standard equipment. Bone mineral density (BMD, grams per centimeter squared) was measured by dual-energy X-ray absorptiometry (DXA; DPX-L version 1.3z; Lunar, Madison, WI) in the total body, lumbar spine, and hip [7–10]. The femoral neck (FN) area was estimated at the hip scan [7–10] and total-body fat mass and total-body lean mass, at the total body scan. Our research technicians calibrated the machine daily with a Lunar[®] phantom and performed all measurements and software analyses. The coefficients of variation (CV %), evaluated by duplicate measurements in 13 healthy children, were for BMD 1.4–3.8 %, FN area 2.2 %, total-body fat mass 3.7 %, and total-body lean mass 1.5 %.

168 At the 5-year follow-up, bone mineral content (BMC),
 169 volumetric bone mineral density (vBMD, grams per cen-
 170 timeter cubed), and structural parameters of the tibia and
 171 radius were also measured by peripheral quantitative com-
 172 puted tomography (pQCT, XCT 2000, Stratec, Pforzheim,
 173 Germany) in the 195 children who accepted this new
 174 measurement. A scout view determined the 4 and 38 %
 175 level from the distal tibial physal plate in both extremities
 176 and 4 and 66 % from the distal radius physal plate. These
 177 regions were used to measure BMC, vBMD, cortical area,
 178 cross-sectional area (CSA), and bone strength strain index
 179 with respect to torsion (polar SSI, millimeters cubed).
 180 These estimates have previously been shown to correlate
 181 very well with mechanical strength in the long bones of rats
 182 [22]. Using measured data and standard pQCT software,
 183 we also calculated the strength stability index (SSIX), an
 184 index that takes both the geometrical properties (section
 185 modulus) and the material properties (cortical volumetric
 186 density) of the bone into account. Daily calibration of the
 187 apparatus was done with a standard phantom. The CV %
 188 values for tibial trabecular were vBMD 1.7 %, tibial cortical
 189 vBMD 0.5 %, tibia cortical area 1.1 %, radial tra-
 190 becular vBMD 3.4 %, radial cortical vBMD 1.4 %, and
 191 radial cortical area 4.6 %.

192 Two years after study start, physical activity was mea-
 193 sured by accelerometer (model 7164 MTI, Manufacturing
 194 Technology, Fort Walton Beach, FL) during 4 consecutive
 195 days; the methodology was described in detail previously
 196 [20].

197 Accelerometric data were averaged over a period called an
 198 “epoch,” representing 10 s. Mean activity was defined as
 199 the total accelerometer counts per minute (cpm) of
 200 monitoring, moderate-to-vigorous physical activity
 201 (MVPA) as time spent above three metabolic equivalents
 202 (METs), and vigorous physical activity (VPA) as time
 203 spent above six METs. Cut-off points used for all children
 204 were >1,000 cpm for MVPA and >3,500 cpm for VPA
 205 [20]. Activity above 5000, 6000, and 10,000 cpm was also

206 registered in order to capture the most intense activities,
 207 known to be highly osteogenic [11, 12].

208 Informed written consent was obtained from the parents
 209 or guardians of the participants, and the study was
 210 approved by the Ethics Committee of our university. Data
 211 are presented as means ± standard deviation (SD) or as
 212 means with 95 % confidence intervals (95 % CI). Gender-
 213 specific baseline group differences were tested by Student’s
 214 *t* test and Fisher’s exact test. The mean annual changes of
 215 all parameters were calculated using linear regression
 216 slopes for each individual. Group comparison of annual
 217 changes was done by independent Student’s *t* test. Fracture
 218 risk with 95 % CI was estimated by Poisson distribution.
 219 *P* < 0.05 was regarded as a statistically significant differ-
 220 ence. A post hoc calculation revealed that, with this sample
 221 size and using observed SDs, we had 80 % power to detect
 222 a difference in change in spine BMD of 0.010 units for girls
 223 and 0.005 units for boys, with a significance level of 5 %.

224 **Results**

225 During the 5-year study period there were in total 188
 226 fractures (Table 1), with the distribution of fractures shown
 227 in Table 2. In the intervention group there were 63 frac-
 228 tures (20.0 events/1,000 person-years) and in the control
 229 group, 125 (18.5 events/1,000 person-years), leading to a
 230 rate ratio (RR) of 1.08 (0.79–1.47). When a gender-specific
 231 evaluation was conducted, no difference in fracture inci-
 232 dence was found between the intervention and control
 233 groups (Table 1; Fig. 1).

234 In the children who were followed by repeated mea-
 235 surements, the only difference in anthropometrics, bone
 236 parameters, and lifestyle was a higher duration of physical
 237 activity in the intervention group (Tables 3, 4). The
 238 accelerometric data showed that girls and boys in the
 239 intervention group had more intense activities than children
 240 in the control group (Table 3).

Table 1 Fracture epidemiology in children in the exercise intervention group and the control group. Data presented as numbers, years, and means with 95 % confidence interval (95 % CI)

	Participants (n)	Fractures (n)	Person-years (years)	Fractures/10,000 person-years (95 % CI)	Risk ratio (95 % CI)
Both genders					
Cases	808	63	3,152	20.0 (15.4, 25.6.)	1.08 (0.79, 1.47)
Controls	1,587	125	6,761	18.5 (15.4, 22.0)	
Girls					
Cases	362	23	1,382	16.6 (10.6, 25.0)	1.03 (0.60, 1.69)
Controls	780	54	3,330	16.2 (12.2, 21.2)	
Boys					
Cases	446	40	1,770	22.6 (16.1, 30.8)	1.09 (0.72, 1.62)
Controls	807	71	3,431	20.7 (16.6, 26.1)	

Table 2 Distribution of fracture sites and trauma types reported in girls and boys who sustained fractures: number with proportion (%) in brackets

	Cases (n = 808)	Controls (n = 1,587)
Girls		
Distal forearm	10 (43.5)	26 (48.1)
Proximal humerus	1 (4.3)	2 (3.7)
Other upper extremity fracture	8 (34.8)	21 (38.9)
Vertebra	0	0
Pelvis	0	0
Ribs	0	0
Hip	0	0
Tibial condyle	0	0
Other lower extremity fracture	4 (17.4)	5 (9.3)
Other fractures	0	0
Total fractures	23	54
Type of trauma		
Severe trauma	0	0
Moderate trauma	11 (47.8)	19 (35.2)
Slight trauma	11 (47.8)	28 (51.9)
No information	1 (4.3)	8 (12.9)
Boys		
Distal forearm	20 (50)	27 (38.0)
Proximal humerus	3 (7.5)	3 (4.2)
Other upper extremity fracture	11 (27.5)	28 (39.4)
Vertebra	0	1 (1.4)
Pelvis	0	1 (1.4)
Ribs	0	0
Hip	0	0
Tibial condyle	0	0
Other lower extremity fracture	5 (12.5)	6 (8.5)
Other fractures	1 (2.5)	5 (7.0)
Total number of fractures	40	71
Type of trauma		
Severe trauma	0	3 (4.2)
Moderate trauma	15 (37.5)	28 (39.4)
Slight trauma	21 (52.5)	33 (46.5)
No information	4 (10.0)	7 (9.9)

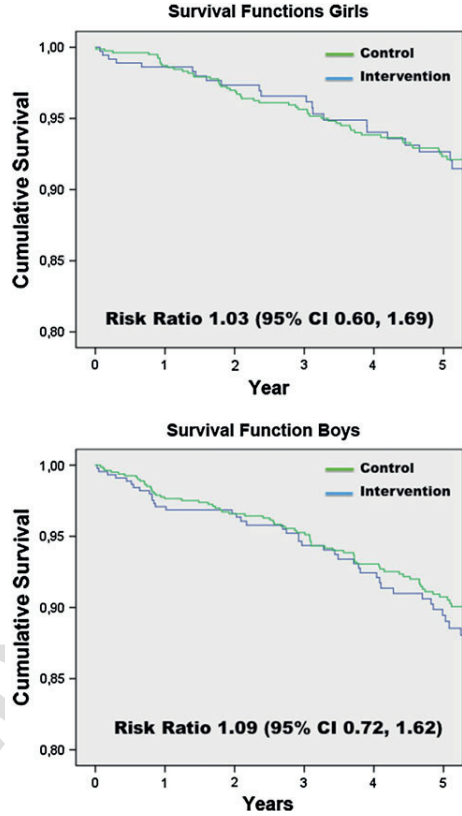


Fig. 1 Fracture risk in girls and boys presented as Kaplan–Meier survival curves with mean risk ratio and 95 % confidence interval (95 % CI) estimated by Poisson distribution

241 The mean annual gain in spine BMD (difference
 242 0.01 g/cm², 0.01–0.02), FN BMC (difference 0.07 g,
 243 0.009–0.013), and FN area (difference 0.04 mm²,
 244 0.01–0.08) was larger in girls in the intervention group than
 245 in the control group (Table 4). Girls in the intervention
 246 group also had a larger tibial cortical BMC at follow-up
 247 (difference 0.18 g, 0.02–0.35), larger tibial cortical area
 248 (difference 17 mm², 2.4–31.3), and larger radial CSA
 249 (difference 11.0 mm², 0.6–21.4) than girls in the control
 250 group, resulting in a larger SSIX in both the tibial diaphysis

(difference 61.8, 3.3–120.3) and the radial diaphysis (dif-
 252 ference 14.8, 2.8–26.9) (Table 5).

The mean annual gain in spine BMD was larger in boys
 253 in the intervention group than in the control group (dif-
 254 ference 0.005 g/cm², 0.001–0.008) (Table 4). Results from
 255 pQCT measurements were similar between boys in the
 256 intervention and control groups (Table 5).
 257

Discussion

258
 259 This study should not be misinterpreted as just another
 260 study confirming that osteogenic training in motivated
 261 children improves bone mass. This is already known. Our
 262 study instead adds information when reporting that an
 263

Table 3 Lifestyle factors at baseline and follow-up and accelerometric data collected after 2 years in the subsample of children randomized for measurements

	Girls			Boys		
	Cases (n = 48)	Controls (n = 48)	P	Cases (n = 73)	Controls (n = 52)	P
Lifestyle factors at baseline						
Excluding dairy products	0	0	1.0	0	0	1.0
Drinking coffee	0	0	1.0	2	0	0.3
Smoking	0	0	1.0	0	0	1.0
Alcohol	0	0	1.0	0	0	1.0
Tried to lose weight	1	0	0.5	0	0	1.0
Current disease	3	3	0.7	7	3	0.3
Ongoing medication	5	2	0.2	10	4	0.2
Previous medication	4	2	0.3	3	5	0.2
Previous Fractures	6	7	0.5	6	5	0.5
Tanner stage 1/2/3/4/5	48/0/0/0/0	48/0/0/0/0	1.0	73/0/0/0/0	52/0/0/0/0	1.0
Organized physical activity (hours/week)						
School curriculum	3.3	1.0	<0.001	3.3	1.0	<0.001
Outside school	0.6 (0.6)	1.1 (1.5)	<0.005	1.7 (1.6)	1.5 (1.3)	0.4
Total physical activity	3.9 (0.6)	2.1 (1.5)	<0.001	5.0 (1.6)	2.5 (1.3)	<0.001
Accelerometric data at 2-year follow-up						
Numbers	(n = 46)	(n = 42)		(n = 66)	(n = 48)	
Recording time (hours/day)	11.7 (1.4)	11.9 (1.3)	0.5	11.7 (1.3)	12.2 (1.4)	0.05
Mean activity (cpm)	649 (186)	597 (115)	0.1	763 (272)	737 (209)	0.6
>3 METS (minutes/day)	195 (46)	187 (35)	0.3	210 (56)	209 (45)	0.9
>6 METS (minutes/day)	34 (15)	35 (12)	0.8	44 (22)	49 (20)	0.2
>6,000 mean cpm (minutes/day)	12.2 (7.3)	10.4 (6.2)	0.2	16 (10)	16 (10)	0.9
>10,000 mean cpm (minutes/day)	2.4 (2.5)	1.0 (1.2)	<0.001	3.6 (3.6)	2.3 (3.0)	0.01
Lifestyle factors at 5-year follow-up						
Smoking	0	0	1.0	0	0	1.0
Alcohol	1	1	0.75	1	0	0.58
Tanner stage 1/2/3/4/5 (%)	5/14/28/39/14	0/12/46/37/5	0.47	3/26/43/25/3	12/12/31/33/12	0.21
Menarche	26	27	1.0	–	–	–
Physical activity at 5-year follow-up (hours/week)						
School curriculum	3.3	1.0	<0.001	3.3	1.0	<0.001
Outside school	4.9 (4.0)	5.0 (3.3)	0.94	6.4 (4.5)	5.4 (3.5)	0.22
Total physical activity	8.2 (4.0)	6.0 (3.3)	0.05	9.7 (4.5)	6.4 (3.5)	<0.001

Baseline estimations were collected just after initiation of the study and then annually for 5 years. Questionnaire-evaluated duration of organized physical activity was estimated as mean hours per week. Accelerometer-measured level of physical activity is presented as minutes per day above three or six metabolic equivalents (METs) or above 6,000 or 10,000 counts per minutes (cpm). Data are presented as number of children with proportion (%) or as mean with standard deviation (SD). Statistically significant differences are highlighted in bold

263 extended, moderately intense general exercise intervention
 264 program in the pre- to pubertal years improves bone mass
 265 and in girls also skeletal architecture, benefits that are
 266 retained in the long term. The structural benefits are
 267 probably of clinical relevance as individuals with spine
 268 fractures have smaller lumbar vertebrae but normal FN
 269 size, while individuals with hip fractures have normal
 270 vertebral body size but smaller FN size than nonfractured
 271 controls [23] and as bone structure is associated with

fracture risk, independently of bone mass [23–25]. The
 current study is also the longest intervention study evalu-
 ating skeletal traits and corroborates that the beneficial
 exercise-induced effects in shorter interventions [2–6,
 8–11] remain also with extended interventions. These
 inferences support the view that interventions with physical
 activity during growth could improve peak bone mass.

The similar fracture risks in the intervention and control
 groups are also important data as reports have suggested a

272
 273
 274
 275
 276
 277
 278
 279
 280

Table 4 Baseline data and annual changes in the subsample of girls and boys randomized for measurements, presented as mean absolute values, evaluating the effects of 5 years of exercise intervention on annual changes in anthropometry, bone mineral parameters, bone size, and hip structure analysis in the exercise intervention group and the control group: means (95 % CI)

	Baseline		<i>P</i>	Average annual changes		
	Cases (<i>n</i> = 48)	Controls (<i>n</i> = 48)		Cases (<i>n</i> = 48)	Controls (<i>n</i> = 48)	<i>P</i>
<i>Girls</i>						
Age	7.7 (7.5, 7.8)	7.9 (7.7, 8.1)	0.08	–	–	
Anthropometrics						
Weight (kg)	27.8 (26.2, 29.5)	27.4 (25.7, 29.0)	0.63	4.5 (4.1, 5.0)	3.9 (3.6, 4.3)	0.02
Height (cm)	128.3 (126.7, 129.9)	129.2 (126.8, 131.6)	0.57	6.2 (5.9, 6.4)	6.2 (5.9, 6.7)	0.93
Lean mass (kg)	19.9 (19.2, 20.6)	20.2 (19.4, 21.0)	0.54	2.8 (2.6, 3.0)	2.7 (2.5, 2.9)	0.50
Fat mass (kg)	5.5 (4.3, 6.6)	5.2 (4.2, 6.2)	0.73	1.5 (1.2, 1.8)	1.1 (0.9, 1.3)	0.01
BMC (g)						
Total body	943.6 (899.4, 987.8)	931.8 (877.9, 985.7)	0.73	185.8 (164.6, 207.1)	179.6 (164.8, 194.5)	0.63
Spine	85.1 (79.6, 90.6)	79.2 (73.6, 84.8)	0.84	21.3 (18.6, 24.0)	20.7 (18.6, 22.9)	0.74
Femoral neck	2.6 (2.4, 2.8)	2.7 (2.5, 2.9)	0.60	0.36 (0.32, 0.40)	0.29 (0.25, 0.33)	0.02
BMD (g/cm ²)						
Total body	0.84 (0.83, 0.86)	0.84 (0.82, 0.85)	0.17	0.035 (0.031, 0.039)	0.031 (0.028, 0.033)	0.05
Spine	0.68 (0.66, 0.69)	0.70 (0.68, 0.72)	0.05	0.045 (0.038, 0.050)	0.032 (0.029, 0.036)	<0.001
Femoral neck	0.72 (0.70, 0.75)	0.71 (0.69, 0.74)	0.63	0.044 (0.039, 0.049)	0.038 (0.033, 0.044)	0.13
Bone size (cm ² or cm)						
Femoral neck area	3.6 (3.4, 3.7)	3.7 (3.5, 3.8)	0.78	0.21 (0.18, 0.24)	0.17 (0.14, 0.20)	0.03
L3 width	2.9 (2.8, 2.9)	2.9 (2.8, 3.0)	0.18	1.27 (1.15, 1.39)	1.15 (1.04, 1.27)	0.16
<hr/>						
	Baseline		<i>P</i>	Average annual changes		
	Cases (<i>n</i> = 73)	Controls (<i>n</i> = 52)		Cases (<i>n</i> = 73)	Controls (<i>n</i> = 52)	<i>P</i>
<i>Boys</i>						
Age	7.8 (7.7, 7.9)	8.0 (7.8, 8.1)	0.11	–	–	
Anthropometrics						
Weight (kg)	28.2 (27.0, 29.5)	27.4 (26.0, 28.8)	0.37	4.1 (3.7, 4.4)	3.9 (3.6, 4.3)	0.54
Height (cm)	129.3 (127.8, 130.8)	129.8 (128.0, 131.6)	0.68	5.7 (5.5, 5.9)	5.9 (5.7, 6.2)	0.20
Lean mass (kg)	21.8 (21.1, 22.5)	21.8 (21.0, 22.6)	0.95	2.7 (2.5, 2.9)	2.9 (2.7, 3.1)	0.34
Fat mass (kg)	4.0 (3.2, 4.8)	3.5 (2.8, 4.1)	0.30	1.1 (0.9, 1.4)	0.9 (0.7, 1.2)	0.28
BMC (g)						
Total body	996.2 (952.6, 1,039.8)	989.5 (941.9, 1,037.1)	0.84	165.3 (153.5, 177.2)	169.0 (157.2, 180.9)	0.67
Spine	88.7 (83.6, 93.8)	84.2 (79.4, 89.0)	0.76	15.3 (14.0, 16.7)	16.0 (14.6, 17.3)	0.50
Femoral neck	2.9 (2.8, 3.1)	2.8 (2.7, 3.0)	0.28	0.26 (0.24, 0.29)	0.28 (0.24, 0.31)	0.74
BMD (g/cm ²)						
Total body	0.85 (0.84, 0.86)	0.85 (0.83, 0.86)	0.55	0.026 (0.024, 0.028)	0.026 (0.024, 0.028)	0.69
Spine	0.68 (0.67, 0.70)	0.69 (0.67, 0.71)	0.58	0.028 (0.025, 0.030)	0.023 (0.021, 0.025)	0.01
Femoral neck	0.79 (0.78, 0.81)	0.78 (0.75, 0.82)	0.09	0.026 (0.021, 0.030)	0.028 (0.023, 0.033)	0.45
Bone size (cm ² or cm)						
Femoral neck area	3.7 (3.6, 3.8)	3.6 (3.5, 3.7)	0.33	0.19 (0.17, 0.21)	0.19 (0.16, 0.21)	0.91
L3 width	3.1 (3.0, 3.1)	3.1 (3.0, 3.2)	0.30	0.98 (0.87, 1.08)	1.02 (0.92, 1.14)	0.52

Statistically significant changes are marked in bold

281 high incidence of fractures following high levels of physical activity also in children [18, 26–28]. Before an exercise intervention program can be generally recommended, it must be shown not to result in more fractures. The results

of our study contradict any significant increment or decrement in fracture risk by intervention. However, the power of the inference restricts us to conclude that there was at least no fracture reduction of more than 21 % or any

285
286
287
288

Table 5 Cross-sectional pQCT data for girls (*n* = 84) and boys (*n* = 111) randomized for measurements, presented as mean absolute values, evaluating the effect of an exercise intervention on bone mineral parameters and bone size for the exercise intervention group and the control group: means (95 % CI)

	Girls		<i>P</i>	Boys		<i>P</i>
	Cases (<i>n</i> = 45)	Controls (<i>n</i> = 39)		Cases (<i>n</i> = 67)	Controls (<i>n</i> = 44)	
Tibia trabecular (4 %)						
Trabecular vBMD (mg/cm ³)	216 (208, 224)	213 (202, 223)	0.62	211 (204, 218)	217 (208, 225)	0.32
Tibia cortical (38 %)						
Cortical BMC (g)	2.8 (2.7, 2.9)	2.6 (2.5, 2.7)	0.03	2.8 (2.7, 2.9)	2.9 (2.8, 3.0)	0.47
Cortical vBMD (mg/cm ³)	1,059 (1,047, 1,072)	1,056 (1,047, 1,066)	0.72	1,011 (1,001, 1,021)	1,016 (1,007, 1,026)	0.50
Cortical area (mm ²)	236 (225, 245)	219 (208, 229)	0.02	246 (236, 257)	252 (241, 262)	0.49
Total CSA (mm ²)	356 (342, 370)	339 (325, 353)	0.09	372 (359, 387)	382 (366, 398)	0.41
Polar SSI (cm ³)	1,135 (1,055, 1,216)	1,050 (977, 1,124)	0.13	1,194 (1,126, 1,261)	1,222 (1,142, 1,303)	0.59
SSIX	618 (575, 662)	557 (518, 595)	0.04	651 (612, 690)	652 (611, 694)	0.97
Radius trabecular (4 %)						
Trabecular vBMD 4 % (mg/mm ³)	180 (168, 191)	179 (166, 192)	0.96	184 (177, 192)	192 (183, 202)	0.96
Radius cortical (66 %)						
Cortical BMC (g)	0.8 (0.7, 0.8)	0.7 (0.7, 0.8)	0.11	0.8 (0.7, 0.8)	0.8 (0.7, 0.8)	0.55
Cortical vBMD (mg/mm ³)	1,020 (1,007, 1,032)	1,020 (1,007, 1,032)	0.99	987 (977, 997)	998 (986, 1,010)	0.19
Cortical area (mm ²)	59.3 (56.1, 62.5)	56.9 (53.5, 60.3)	0.86	58.4 (55.2, 61.6)	57.9 (54.5, 61.4)	0.30
Total CSA 66 % (mm ²)	130 (122, 139)	119 (113, 125)	0.04	140 (133, 147)	133 (124, 142)	0.20
Polar SSI (cm ³)	228 (209, 247)	201 (108, 215)	0.11	241 (225, 258)	227 (207, 247)	0.26
SSIX	121 (62.7, 204)	106 (62.8, 154)	0.02	125 (65.3, 238)	122 (56.6, 222)	0.57

Statistically significant differences are highlighted in bold

289 increase of more than 47 % in the intervention group
 290 compared to the control group. However, the contradictory
 291 hypothesis that high bone mass in children would result in
 292 fewer fractures was also refuted [29].

293 Our data show that general moderately intense physical
 294 activities may influence skeletal growth. Some previous
 295 studies have suggested that lower levels of physical
 296 activity, low-impact sports, and endurance sports may have
 297 no or only a minor effect on bone mass, especially when
 298 these types of exercises are practiced for long durations
 299 [30–32]. Some authors have therefore advocated the use of
 300 specifically designed osteogenic programs with high
 301 intensity [30–32]. This could be problematic as an inter-
 302 vention must be at a suitable general level and with a
 303 variety of activities in order to facilitate the participation of
 304 all children if the program is to be launched as a strategy to
 305 improve bone strength at the population level. However,
 306 our study shows that such an intervention program can be
 307 used without losing the osteogenic effect, a view supported
 308 by the accelerometric data in this report, which show a
 309 higher duration of high-impact activities in the intervention
 310 than in the control group.

311 This report also indicates that girls gain more obvious
 312 skeletal benefits than boys from the intervention. This
 313 could be due to boys in general having higher leisure-time
 314 activities than girls, a view also supported by our study

(Table 3). As a consequence, the extra physical education
 in school contributed to a smaller proportion of the total
 duration of physical activity in boys than in girls. Since the
 skeletal response to exercise is greater in the late pre- and
 early peripubertal period than in younger years [15], the
 more advanced pubertal maturation in girls than in boys of
 similar age is another possible explanation.

The greater annual gain in fat mass in the intervention
 girls compared with the controls was an unexpected find-
 ing. However, there are studies supporting our findings
 [7, 9, 33, 34]. The reason for the higher gain in fat in the
 intervention group is unclear but could be associated with
 increased food intake with more exercise. Although we did
 not assess dietary habits, previous studies have speculated
 that the increased gain in fat is most likely the result of
 other influences besides physical activity as there has been
 no dose–response effect between level of physical activity
 and gain in fat mass [33]. The finding may also be the
 result of chance.

The strengths of the study include the presentation of
 data with a high level of evidence in the evidence-based
 system. The similar anthropometric characteristics in
 children who did or did not participate in the study and
 children in the intervention and control groups at baseline
 gives further corroboration that our inferences could be
 generalized. The use of accelerometers is also an advantage

315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340

341 compared to subjective estimates of the level of physical
 342 activity. The inclusion of not only bone mass but also bone
 343 structure and incident fractures is another advantage.
 344 Limitations include the power problem. Despite including
 345 2,395 children having a 5-year follow-up, we could not
 346 capture small group differences in fracture incidence; and
 347 our data, based on the 95 % CI, only let us state that there
 348 was no fracture reduction of more than 21 % and no
 349 fracture increase of more than 47 % in the intervention
 350 group. Individual randomization would also have been
 351 preferable to the school-based grouping used, but, as pre-
 352 viously discussed, it would have been impossible to
 353 achieve in practice because of resistance from parents,
 354 pupils, and teachers [2, 18, 19, 26]. The participation rate
 355 for the controls randomized for measurements was lower
 356 than that for the intervention school. However, as our
 357 dropout analyses revealed no group differences at baseline,
 358 the risk of selection bias must be regarded as minor. Also,
 359 it would have been preferable to have longitudinal pQCT
 360 data to evaluate changes in bone structure and not only to
 361 rely on DXA-derived data for bone size. It would have
 362 been advantageous too if we had been able to report frac-
 363 tures that had occurred during physical education classes in
 364 school separately and fractures during other activities
 365 separately, data not possible to find in the referrals or
 366 reports. Finally, when we gathered the accelerometric data
 367 we had only access to an apparatus that could capture
 368 4 days in a row. It would have been advantageous to use
 369 modern accelerometers that could capture a period of up to
 370 a month and have measurements performed on several
 371 different occasions during the 5-year study period. It would
 372 also have been advantageous if we had had information
 373 about play activities and extraprotocol physical activity on
 374 a voluntary basis.

375 In conclusion, this study shows that a general, moder-
 376 ately intense, school-based exercise intervention program
 377 in prepubertal children with 5 years' duration improves
 378 bone mass and in girls also skeletal architecture without
 379 increasing fracture risk. We are therefore of the opinion
 380 that daily moderate physical activity ought to be introduced
 381 to prepubertal children from school start.

382 **Acknowledgement** We thank the teachers and students for partic-
 383 ipating in the study. Financial support for this study was received
 384 from ALF, the Centre for Athletic Research, the Osterlund Founda-
 385 tion, the Kock Foundation, and the Region Skåne Foundation.

386 References

- 387 1. Hind K, Burrows M (2007) Weight-bearing exercise and bone
 388 mineral accrual in children and adolescents: a review of con-
 389 trolled trials. *Bone* 40(1):14–27
- 390 2. Bradney M, Pearce G, Naughton G, Sullivan C, Bass S, Beck T,
 391 Carlson J, Seeman E (1998) Moderate exercise during growth in

- prepubertal boys: changes in bone mass, size, volumetric density,
 and bone strength: a controlled prospective study. *J Bone Miner
 Res* 13(12):1814–1821
3. McKay HA, Petit MA, Schutz RW, Prior JC, Barr SI, Khan KM
 (2000) Augmented trochanteric bone mineral density after mod-
 ified physical education classes: a randomized school-based
 exercise intervention study in prepubescent and early pubescent
 children. *J Pediatr* 136(2):156–162
 4. Petit MA, McKay HA, MacKelvie KJ, Heinonen A, Khan KM,
 Beck TJ (2002) A randomized school-based jumping intervention
 confers site and maturity-specific benefits on bone structural
 properties in girls: a hip structural analysis study. *J Bone Miner
 Res* 17(3):363–372
 5. MacKelvie KJ, Khan KM, Petit MA, Janssen PA, McKay HA
 (2003) A school-based exercise intervention elicits substantial
 bone health benefits: a 2-year randomized controlled trial in girls.
Pediatrics 112(6 Pt 1):e447
 6. MacKelvie KJ, Petit MA, Khan KM, Beck TJ, McKay HA (2004)
 Bone mass and structure are enhanced following a 2-year ran-
 domized controlled trial of exercise in prepubertal boys. *Bone*
 34(4):755–764
 7. Linden C, Alwis G, Ahlberg H, Gardsell P, Valdimarsson O,
 Stenevi-Lundgren S, Besjakov J, Karlsson MK (2007) Exercise,
 bone mass and bone size in prepubertal boys: one-year data from
 the pediatric osteoporosis prevention study. *Scand J Med Sci
 Sports* 17(4):340–347
 8. Linden C, Ahlberg HG, Besjakov J, Gardsell P, Karlsson MK
 (2006) A school curriculum-based exercise program increases
 bone mineral accrual and bone size in prepubertal girls: two-year
 data from the Pediatric Osteoporosis Prevention (POP) study.
J Bone Miner Res 21(6):829–835
 9. Valdimarsson O, Linden C, Johnell O, Gardsell P, Karlsson MK
 (2006) Daily physical education in the school curriculum in
 prepubertal girls during 1 year is followed by an increase in bone
 mineral accrual and bone width—data from the prospective
 controlled Malmo Pediatric Osteoporosis Prevention study. *Calcif
 Tissue Int* 78(2):65–71
 10. Alwis G, Linden C, Ahlberg HG, Dencker M, Gardsell P, Kar-
 lsson MK (2008) A 2-year school-based exercise programme in
 pre-pubertal boys induces skeletal benefits in lumbar spine. *Acta
 Paediatr* 97(11):1564–1571
 11. Lanyon LE (1992) Control of bone architecture by functional
 load bearing. *J Bone Miner Res* 7(Suppl 2):S369–S375
 12. Rubin CT, Lanyon LE (1984) Regulation of bone formation by
 applied dynamic loads. *J Bone Joint Surg Am* 66(3):397–402
 13. Hui SL, Slemenda CW, Johnston CC Jr (1990) The contribution
 of bone loss to postmenopausal osteoporosis. *Osteoporos Int*
 1(1):30–34
 14. Melton LJ 3rd, Atkinson EJ, O'Fallon WM, Wahner HW, Riggs BL
 (1993) Long-term fracture prediction by bone mineral assessed at
 different skeletal sites. *J Bone Miner Res* 8(10):1227–1233
 15. Kannus P, Haapasalo H, Sankelo M, Sievanen H, Pasanen M,
 Heinonen A, Oja P, Vuori I (1995) Effect of starting age of
 physical activity on bone mass in the dominant arm of tennis and
 squash players. *Ann Intern Med* 123(1):27–31
 16. Hasselstrom HA, Karlsson MK, Hansen SE, Gronfeldt V, Froberg
 K, Andersen LB (2008) A 3-year physical activity intervention
 program increases the gain in bone mineral and bone width in
 prepubertal girls but not boys: the prospective Copenhagen
 School Child Interventions Study (CoSCIS). *Calcif Tissue Int*
 83(4):243–250
 17. Johnell O, Gullberg B, Kanis JA, Allander E, Elffors L, Dequeker
 J, Dilsen G, Gennari C, LopesVaz A, Lyritis G et al (1995) Risk
 factors for hip fracture in European women: the MEDOS Study.
 Mediterranean Osteoporosis Study. *J Bone Miner Res*
 10(11):1802–1815

458 18. Clark EM, Ness AR, Tobias JH (2008) Vigorous physical activity
459 increases fracture risk in children irrespective of bone mass: a
460 prospective study of the independent risk factors for fractures in
461 healthy children. *J Bone Miner Res* 23(7):1012–1022
462 19. Jonsson B, Gardsell P, Johnell O, Redlund-Johnell I, Sembo I
463 (1994) Remembering fractures: fracture registration and proband
464 recall in southern Sweden. *J Epidemiol Community Health*
465 48(5):489–490
466 20. Dencker M, Thorsson O, Karlsson MK, Linden C, Eiberg S,
467 Wollmer P, Andersen LB (2006) Daily physical activity related to
468 body fat in children aged 8–11 years. *J Pediatr* 149(1):38–42
469 21. Duke PM, Litt IF, Gross RT (1980) Adolescents' self-assessment
470 of sexual maturation. *Pediatrics* 66(6):918–920
471 22. Ferretti JL, Capozza RF, Zanchetta JR (1996) Mechanical vali-
472 dation of a tomographic (pQCT) index for noninvasive estimation
473 of rat femur bending strength. *Bone* 18(2):97–102
474 23. Duan Y, Parfitt A, Seeman E (1999) Vertebral bone mass, size,
475 and volumetric density in women with spinal fractures. *J Bone*
476 *Miner Res* 14(10):1796–1802
477 24. Duan Y, Seeman E, Turner CH (2001) The biomechanical basis
478 of vertebral body fragility in men and women. *J Bone Miner Res*
479 16(12):2276–2283
480 25. Ahlborg HG, Johnell O, Turner CH, Rannevik G, Karlsson MK
481 (2003) Bone loss and bone size after menopause. *N Engl J Med*
482 349(4):327–334
483 26. Clark EM, Ness AR, Tobias JH (2008) Bone fragility contributes
484 to the risk of fracture in children, even after moderate and severe
485 trauma. *J Bone Miner Res* 23(2):173–179

27. Karlsson MK, Linden C, Karlsson C, Johnell O, Obrant K,
486 Seeman E (2000) Exercise during growth and bone mineral
487 density and fractures in old age. *Lancet* 355(9202):469–470
488 28. Nordstrom A, Karlsson C, Nyquist F, Olsson T, Nordstrom P,
489 Karlsson M (2005) Bone loss and fracture risk after reduced
490 physical activity. *J Bone Miner Res* 20(2):202–207
491 29. Manias K, McCabe D, Bishop N (2006) Fractures and recurrent
492 fractures in children; varying effects of environmental factors as
493 well as bone size and mass. *Bone* 39(3):652–657
494 30. Guadalupe-Grau A, Fuentes T, Guerra B, Calbet JA (2009)
495 Exercise and bone mass in adults. *Sports Med* 39(6):439–468
496 31. Heinonen A, Oja P, Kannus P, Sievanen H, Haapasalo H,
497 Manttari A, Vuori I (1995) Bone mineral density in female ath-
498 letes representing sports with different loading characteristics of
499 the skeleton. *Bone* 17(3):197–203
500 32. Nikander R, Sievanen H, Heinonen A, Kannus P (2005) Femoral
501 neck structure in adult female athletes subjected to different
502 loading modalities. *J Bone Miner Res* 20(3):520–528
503 33. Stenevi-Lundgren S, Daly RM, Linden C, Gardsell P, Karlsson
504 MK (2009) Effects of a daily school based physical activity
505 intervention program on muscle development in prepubertal girls.
506 *Eur J Appl Physiol* 105(4):533–541
507 34. Treuth MS, Hunter GR, Figueroa-Colon R, Goran MI (1998)
508 Effects of strength training on intra-abdominal adipose tissue in
509 obese prepubertal girls. *Med Sci Sports Exerc* 30(12):1738–1743
510 511

Paper IV

A 6-Year Exercise Program Improves Skeletal Traits Without Affecting Fracture Risk: A Prospective Controlled Study in 2621 Children

Fredrik Detter,¹ Björn E Rosengren,¹ Magnus Dencker,² Mattias Lorentzon,³ Jan-Åke Nilsson,¹ and Magnus K Karlsson¹

¹Clinical and Molecular Osteoporosis Research Unit, Department of Clinical Sciences and Orthopedics, Lund University, and Skåne University Hospital, Malmö, Sweden

²Department of Clinical Physiology, Skåne University Hospital, Malmö, Sweden

³Gothenburg University, Sahlgrenska University Hospital, Gothenburg, Sweden

ABSTRACT

Most pediatric exercise intervention studies that evaluate the effect on skeletal traits include volunteers and follow bone mass for less than 3 years. We present a population-based 6-year controlled exercise intervention study in children with bone structure and incident fractures as endpoints. Fractures were registered in 417 girls and 500 boys in the intervention group (3969 person-years) and 835 girls and 869 boys in the control group (8245 person-years), all aged 6 to 9 years at study start, during the 6-year study period. Children in the intervention group had 40 minutes daily school physical education (PE) and the control group 60 minutes per week. In a subcohort with 78 girls and 111 boys in the intervention group and 52 girls and 54 boys in the control group, bone mineral density (BMD; g/cm³) and bone area (mm²) were measured repeatedly by dual-energy X-ray absorptiometry (DXA). Peripheral quantitative computed tomography (pQCT) measured bone mass and bone structure at follow-up. There were 21.7 low and moderate energy-related fractures per 1000 person-years in the intervention group and 19.3 fractures in the control group, leading to a rate ratio (RR) of 1.12 (0.85, 1.46). Girls in the intervention group, compared with girls in the control group, had 0.009 g/cm² (0.003, 0.015) larger gain annually in spine BMD, 0.07 g (0.014, 0.123) larger gain in femoral neck bone mineral content (BMC), and 4.1 mm² (0.5, 7.8) larger gain in femoral neck area, and at follow-up 24.1 g (7.6, 40.6) higher tibial cortical BMC (g) and 23.9 mm² (5.27, 42.6) larger tibial cross-sectional area. Boys with daily PE had 0.006 g/cm² (0.002, 0.010) larger gain annually in spine BMD than control boys but at follow-up no higher pQCT values than boys in the control group. Daily PE for 6 years in at study start 6- to 9-year-olds improves bone mass and bone size in girls and bone mass in boys, without affecting the fracture risk. © 2014 American Society for Bone and Mineral Research.

KEY WORDS: BONE MINERAL CONTENT (BMC); BONE SIZE; BOYS; CHILDREN; CONTROLLED; EXERCISE; FRACTURE; GIRLS; GROWTH; PHYSICAL ACTIVITY; PROSPECTIVE; BONE MINERAL DENSITY (BMD); pQCT

Introduction

Physical activity at an intense level is associated with high bone mass and large bone size.⁽¹⁻⁵⁾ This is of clinical relevance because skeletal integrity depends on both bone mass and skeletal geometry.⁽¹⁾ Short-term pediatric exercise intervention studies corroborate that skeletal benefits can be reached even with moderate levels of exercise.⁽⁶⁻¹²⁾ The type of activity with the greatest possibility to induce these effects include loading with great magnitude and high frequency that is dynamic and rapid, with different directions and with resting periods included between the loading sessions.^(13,14) In contrast, the duration of the load is of minor importance.^(13,14) Mechanical load seems also to preferentially affect surfaces that are undergoing fast apposition,^(3,15) a notion supported by studies

inferring that the late pre- and early peripubertal period are the periods with the greatest osteogenic response.⁽¹⁶⁾ Exercise during these periods ought to have a possibility to enhance peak bone mass (PBM),⁽²⁾ which is of clinical importance because high bone mineral density (BMD) is associated with low fracture risk^(1,2,17-19) and half of the variance in BMD at age 70 years seems to be predicted by PBM.⁽¹⁷⁾ Physical activity during growth may, therefore, have the potential to reduce the burden of fractures in old age.^(2,20-23)

However, most published exercise intervention studies have included volunteers, used specific osteogenic training programs, only evaluated bone mass, and been short term.^(9,10,24-35) Only one study had an intervention longer than 36 months.⁽⁸⁾ Furthermore, there is no consensus as to whether moderately intense interventions on a population-based level, without

Received in original form August 27, 2013; revised form December 18, 2013; accepted January 1, 2014. Accepted manuscript online January 6, 2014.

Address correspondence to: Fredrik Detter, MD, Department of Orthopedics, Skåne University Hospital, SE - 205 02 Malmö, Sweden.

E-mail: fredrik.detter@med.lu.se

For a Commentary on this article, please see Gordon (J Bone Miner Res. 2014;29:1322-1324. DOI: 10.1002/jbmr.2264)

Journal of Bone and Mineral Research, Vol. 29, No. 6, June 2014, pp 1325-1336

DOI: 10.1002/jbmr.2168

© 2014 American Society for Bone and Mineral Research

specific osteogenic programs, reach the same effects or whether the reported short-term effects are retained with extension of the program. This should be evaluated because children, especially girls, in general are known to reduce their level of physical activity in puberty,⁽³⁶⁾ and girls, therefore, ought to hypothetically achieve more benefits in this period from an exercise program than boys because the program would then contribute to a greater extent to the total amount of physical activity in the girls than in the boys. It should also be evaluated whether the intervention induces a greater level of activity that is osteogenic because there are reports indicating that the level of physical activity in children could not be changed by interventions.^(37,38) Finally, there are reports suggesting that a high level of physical activity is associated with a high fracture risk.⁽³⁹⁾ Before an exercise intervention program could be recommended, then, it must be clarified that it does not increase the fracture risk.

The aim of this study was, therefore, to evaluate of the effects of a 6-year moderately intense general exercise intervention program in a population-based cohort of children reaching puberty. We aimed to assess whether the intervention resulted in a higher total level of physical activity known to be osteogenic and to determine whether the program influenced fracture risk, accrual of bone mass, and gain in bone size. We hypothesized that in children reaching puberty, (i) a general intervention program confers a higher total level of physical activity including the most osteogenic activities, (ii) an exercise intervention program improves the accrual of bone mass and gain in bone size, (iii) the benefits are more obvious in girls than in boys, and (iv) the intervention would not induce more fractures.

Materials and Methods

The Malmö Pediatric Osteoporosis Prevention (POP) Study is a population-based, prospective, controlled exercise intervention study of fracture incidence and skeletal development in 6- to 9-year-old children in the city of Malmö, Sweden. The protocol has been described previously in detail,^(6-8,12,40) but in summary, four neighboring elementary schools located in a middle-class area with a homogenous socioeconomic status, all government-funded with the compulsory Swedish standard curriculum, all with the same physical education curriculum, and all with the children allocated to the school according to their residential address, were invited to participate in the study at baseline. The four schools were quite similar in size. None of the invited schools declined participation. The cohort could, therefore, be regarded as a cluster of convenience, the schools being the clusters and the convenience being that they are all from the same neighborhood. We then offered one of the schools to participate as the intervention school; that is, no strict randomization was done. The school accepted, even if they had to modify their curriculum by increasing the amount of physical educational classes. Thus, we did not choose a school with an already high level of physical activity as the intervention school.

The intervention school increased the amount of physical activity within the school curriculum from the Swedish standard of 60 minutes/week provided in one or two lessons to one physical education (PE) class of 40 minutes every school day, resulting in a total amount of 200 minutes/week. The nonspecific intervention included a variety of activities used in the general PE, such as ball games, jumping, running, and playing activities with the children supervised by the usual teachers. The choice of one intervention school was regarded as adequate because

previous reports have shown low between-school variability in lifestyle, anthropometrics, and bone parameters.⁽²⁸⁾

In the target population, which included 417 girls and 500 boys in the intervention group and 835 girls and 869 boys in the control group, we registered all incident fractures that were sustained during the 6-year period through the radiological archives of our hospital and from the computerized radiological archive that includes all radiographs taken in southern Sweden. Because there is only one emergency hospital in the city, virtually all patients attend this emergency department when sustaining a fracture. If a fracture was sustained outside of the region, the children were referred to our clinic for a follow-up evaluation, a visit when the fracture was registered. All referrals, radiographs, and reports have been saved in the archives for more than a century and can, therefore, be verified,⁽⁴¹⁾ a system known to miss less than 3% of all sustained fractures.⁽⁴¹⁾ Because the target population was evaluated through the archives and registers without specifically involving the children with questionnaires, this cohort included all children with no dropouts. The fracture trauma level was assessed according to the journals, referrals, and reports as being low-, moderate-, or high-energy related, as proposed by Landin and colleagues.⁽⁴²⁾ Low-energy trauma corresponded to kicks, falls from low heights on a soft surface, and playing injuries; moderate-energy trauma as a fall from low heights on a nonresilient surface, falling in stairs, bicycling accidents, and falls from swings and slides; and high-energy trauma as falls greater than 3 meters and traffic accidents that included motor vehicles. The children who moved or died during the study period were followed from baseline until this date.

From the target population, we invited a subsample in both the intervention and the control group for repeated measurements of anthropometrics and skeletal traits. In the intervention group, we invited all with school start during 3 consecutive years and in the control group all with school start during 2 consecutive years. Because all pupils were allocated to the schools according to their residential address and by including all children who started schools during the reported period, we achieved a population-based cohort also for the subsample that was included in the bone mass measurements. In this subcohort, 93 girls of 105 and 124 boys of 132 invited accepted participation in the intervention group and 64 girls of 157 invited and 68 boys of 170 invited in the control group accepted. Measurements of anthropometry and skeletal traits were conducted at school start in all children, in the intervention school just before the intervention was initiated. Measurements were repeated annually starting after 1 year in eight of the intervention classes ($n = 153$) and after 3 years in five classes ($n = 84$) until study end. In the control schools, the second measurement was done after 2 years, continuing annually until study end. To be included in this report, the participants had to have a baseline measurement, the sixth or the seventh measurement, at least four later measurements, and they had to stay in the same school the entire study period and be without any diseases or medication known to influence bone metabolism. This rendered a dropout of 15 girls and 13 boys in the intervention group and 12 girls and 14 boys in the control group. Our report of bone trait changes, therefore, includes 78 girls aged 7.5 ± 0.5 years (mean \pm SD) and 111 boys aged 7.6 ± 0.6 years in the intervention group and 52 girls aged 7.9 ± 0.6 years and 54 boys aged 8.0 ± 0.6 years in the control group (Table 3).

Body weight and body height were measured by standard equipment.^(6,7,12) Bone mineral content (BMC; g) and BMD (g/cm^2) were measured by the same dual-energy X-ray

absorptiometry apparatus (DXA; DPX-L version 1.3z, Lunar, Madison, WI, USA) during the entire study period in total body, lumbar spine, and hip. The femoral neck (FN) area was measured from the hip scan, the area of lumbar vertebrae 1 to 4 (L₁ to L₄) from the lumbar spine scan and total body fat mass and total body lean mass from the total body scan. The research technicians calibrated the machine daily with a Lunar phantom and performed all measurements and software analyses. The coefficients of variation (CV%), evaluated by duplicate measurements in 13 healthy children, was for BMD 1.4–3.8%, BMC 1.3–3.2%, FN area 2.2%, total body fat mass 3.7%, and total body lean mass 1.5%. There was no long-term drift of the equipment.

Dropout analyses in the measured children revealed that anthropometrics and bone traits did not differ when children from the different schools were compared before the intervention was initiated, nor were there any differences in these traits at baseline between children who participated throughout the study and those who did not.^(7,12) Furthermore, based on data from the grade one compulsory school health examination that includes all Swedish children, there were no differences in height, weight, or body mass index (BMI; kg/m²) between children who participated at baseline and those who declined.⁽⁴³⁾

At follow-up, all of the DXA-followed children were invited to also participate in a measurement of BMC, volumetric bone mineral density (vBMD; g/cm³), and structural parameters of the tibia and radius by peripheral quantitative computed tomography (pQCT; XCT 2000, Stratec, Pforzheim, Germany). A total of 221 children accepted this extra measurement. A scout view determined the 4% and 38% level from the distal tibial physal plate in both extremities and 4% and 66% from the distal radius physal plate. These regions were used to measure BMC, vBMD, cortical area, cross-sectional area (CSA), and bone strength strain index with respect to torsion (polar SSI; mm³). These estimates have been shown to correlate with mechanical strength in long bones.^(44,45) Daily calibration of the apparatus was done with a standard phantom. The CV%, evaluated by duplicate measurements in 13 healthy children, was for tibial trabecular vBMD 1.7%, tibial cortical vBMD 0.5%, tibial cortical area 1.1%, radial trabecular vBMD 3.4%, radial cortical vBMD 1.4%, and radial cortical area 4.6%.

At the 6-year follow-up, right calcaneal bone traits were also measured by quantitative ultrasound (QUS; Achilles model 1061, Lunar) in 133 of the children. QUS presents speed of sound (SOS; meters/second [m/s]) and broadband attenuation (BUA; decibels/megahertz [dB/MHz]). Daily calibration of the machines was done during the entire study period and measurements performed according to the standard procedure provided by the manufacturer. To get the proper position of the mid region of the calcaneus, one or two foot pads were inserted under the foot in small children depending on foot size. Pads were used after visual inspection by the research nurse but without having any defined weight limit for using the pads. All measurements and analyses were performed by three research technicians. The CV, evaluated by duplicate measurements in 13 healthy children aged 7 to 15 years, was 0.3% for SOS and 2.2% for BUA.

In the subcohort where bone traits were measured by DXA (*n* = 295), we offered all children the chance to have their physical activity objectively measured by accelerometers (model 7164 MTI; Manufacturing Technology Inc., Fort Walton Beach, FL, USA) twice, each period spanning 4 consecutive days. In the 248 children who accepted participation, these measurements were undertaken 2 and 4 years after study start, the methodology described in detail previously.⁽⁴³⁾ Accelerometer data were

averaged over a period called an epoch, representing 10 seconds. Mean activity was defined as the total accelerometer counts per minute of monitoring (counts/min [cpm]), moderate-to-vigorous physical activity (MVPA) as time spent above three metabolic equivalents (METs), and vigorous physical activity (VPA) as time spent above six METs. Cut-off points used for all children were >1000 cpm for MVPA and >3500 cpm for VPA.⁽⁴³⁾ Activity greater than 5000, 6000, and 10,000 cpm was also registered to capture the most intense activities, known to be most osteogenic.^(13,14) We then calculated the mean value of the two measurements, and in those who only attended one measurement, we used that single evaluation. We then excluded all measurements greater than and less than 3 standard deviations (SD) (*n* = 10), leaving 238 individuals with accelerometer measurements in this report.

A nonvalidated questionnaire evaluated lifestyle factors at each measurement with special reference to the amount of physical activity within and outside school. The total duration of physical exercise was calculated as the sum of school physical education and organized leisure time activity. We then calculated the mean value for total duration of physical activity during the 6-year study period.^(6–8,12,40,46) The questionnaires were filled out with help from a parent, guardian, and member of the research staff. Pubertal maturity was determined by self-assessment of Tanner staging.⁽⁴⁷⁾

Informed written consent was obtained from the parents or guardians of the participant. The study was approved by the Ethics Committee of Lund University and conducted according to the Declaration of Helsinki. All calculations were performed using IBM SPSS Statistics standard edition version 20 (IBM Corp., Armonk, NY, USA). Data are presented as means ± SD or as means with 95% confidence intervals (95% CI). Baseline sex-specific group differences were tested by chi-square test, Fisher's exact test, and ANCOVA adjusted for age at baseline. The annual changes were calculated using linear regression slopes for each individual, after which mean slope value for each trait was calculated. Group comparison of the baseline values was then tested by ANCOVA adjusted for age, weight, and height and annual changes adjusted for age and Tanner stage at follow-up and annual changes in height and weight. Mann-Whitney's U-test test was used to test for group differences in pubertal maturation. Fracture risk, expressed as a rate ratio (RR) with 95% CI, was estimated by Poisson distribution after excluding the high-energy-related fractures (*n* = 4). A *p* value of <0.05 was considered as a statistically significant difference. A post hoc power calculation revealed that with 80% power and a significance level of 5% in girls, we could detect a difference in annual change in spine BMD of 0.008 units and in boys of 0.005 units.

Results

Fracture epidemiology is reported in Table 1 and fracture distribution in Table 2. During the study period, 245 low- or moderate-energy-related and 4 high-energy-related fractures occurred in the 2621 children, the majority occurring in the distal forearm (Table 2). In the intervention group, there were 21.7 low- or moderate-energy-related fractures/1000 person-years and in the control group 19.3 fractures/1000 person-years, leading to a rate ratio of 1.12 (95% CI 0.85, 1.46). In the sex-specific evaluation, there were no group differences (Table 1, Fig. 1 and Fig. 2). In the subsample that was allocated to bone mass measurements

Table 1. Fracture Epidemiology in Children in the Exercise Intervention Group and the Control Group

	Participants (n)	Fractures (n)	Person-years (years)	Fractures/1000 person-years (95% CI)	Risk ratio (95% CI)
Both sexes					
Cases	917	86	3969	21.67 (17.33, 26.76)	1.12 (0.85, 1.46)
Controls	1704	159	8245	19.28 (16.40, 22.53)	
Girls					
Cases	417	33	1752	18.84 (12.97, 26.45)	1.18 (0.75, 1.80)
Controls	835	65	4068	15.98 (12.33, 20.37)	
Boys					
Cases	500	53	2217	23.91 (17.91, 31.27)	1.06 (0.74, 1.49)
Controls	869	94	4177	22.50 (18.19, 27.54)	

among the 189 individuals in the intervention group, there were 12 individuals with fractures, and among the 107 individuals in the control group, 4 individuals with fractures, but because of the small sample size, we only report these data as descriptive.

In the subcohort of children who were followed by repeated measurements, there were no group difference in anthropometrics, bone parameters, or lifestyle before study start (Table 3). After the intervention was initiated, children in the training school had a longer duration of physical activity (Table 4).

During the study period, girls in the intervention group compared with girls in the control group had a higher annual accrual of femoral neck BMC with a mean difference of 0.07 g (0.014, 0.123), spine BMD with a mean difference of 0.009 g/cm² (0.003, 0.015), and a larger gain in femoral neck area with a mean difference of 0.041 cm² (0.005, 0.078) (Table 5 and Fig. 2). Girls in the intervention group compared with girls in the control group also had a higher tibial cortical BMC at follow-up, with a mean difference of 24.1 g (7.6, 40.6), a larger tibial cortical area with a mean difference of 21.2 mm² (6.5, 36.0), and a larger tibial CSA with a mean difference of 23.9 mm² (5.27, 42.6) (Table 6). This

resulted in a larger tibial diaphysis polar SSI in the intervention girls (mean difference of 140.2 [43.3, 237.1]). The differences in bone mass between girls in the intervention and control groups were registered at follow-up by all three scanning methods, DXA, pQCT, and QUS, with a mean group difference of around 0.5 SD in the DXA evaluation (Table 7).

Boys in the intervention group compared with boys in the control group had a higher annual accrual of spine BMD with a mean difference of 0.006 g/cm² (0.002, 0.010) (Table 5 and Fig. 3). No other group differences in annual changes were registered in the boys, and there was no difference at follow-up in bone mass between boys in the intervention and control groups, whether evaluated by DXA, pQCT, or QUS (Tables 6 and 7).

Questionnaire data showed that girls and boys in the intervention group had a longer weekly duration of physical activity than girls and boys in the control group, and the accelerometer data showed that girls and boys in the intervention group had more intense activities than girls and boys in the control group (Table 4). Boys in both the intervention and control groups also had a higher weekly duration of physical

Table 2. Sex-Specific Distribution of the Total 249 Fractures That Occurred During the Study Period and Related Type of Trauma

	Girls		Boys	
	Cases (n = 417) No. (%)	Controls (n = 835) No. (%)	Cases (n = 500) No. (%)	Controls (n = 869) No. (%)
Fracture distribution				
Distal forearm	14 (42.4)	30 (40.6)	24 (45.3)	39 (39.8)
Proximal humerus	2 (6.1)	4 (6.2)	4 (7.4)	2 (2.0)
Other upper extremity	11 (33.3)	24 (36.9)	18 (34.0)	36 (36.7)
Vertebra	0	0	0	1 (1.0)
Pelvis	0	0	0	1 (1.0)
Ribs	0	0	0	0
Hip	0	1 (1.5)	0	0
Tibial condyle	1 (3.0)	0	0	2 (2.0)
Other lower extremity	5 (15.2)	6 (9.2)	7 (13.2)	11 (11.2)
Other fractures	0	0	0	6 (6.1)
Total number	33	65	53	98
Type of trauma				
High-energy related	0	0	0	4 (4.1)
Moderate-energy related	15 (45.5)	22 (33.8)	19 (35.8)	37 (37.8)
Low-energy related	16 (48.5)	35 (53.8)	28 (52.8)	49 (20.0)
No information	2 (6.0)	8 (12.4)	6 (11.4)	8 (8.1)

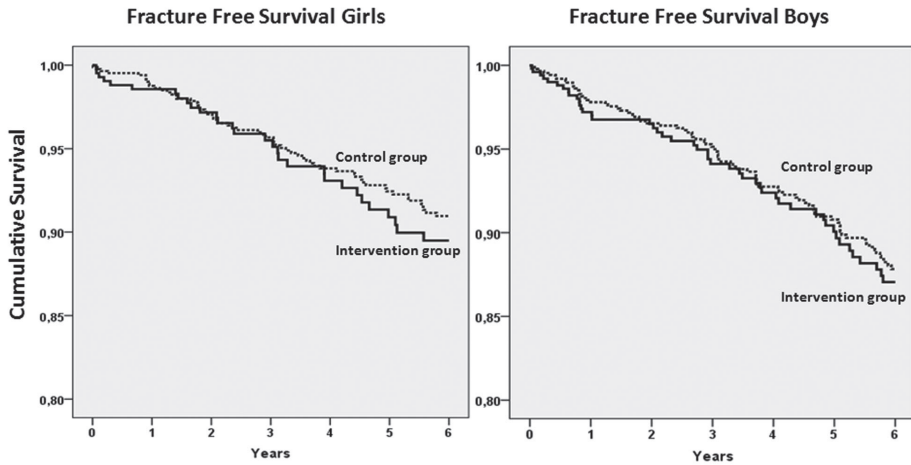


Fig. 1. Fracture risk in boys and girls presented as Kaplan-Meier Survival curves with mean risk ratio with 95% confidence interval (95% CI) estimated by Poisson distribution. The fractures resulting from high-energy-related trauma ($n = 4$) were excluded from these analyses.

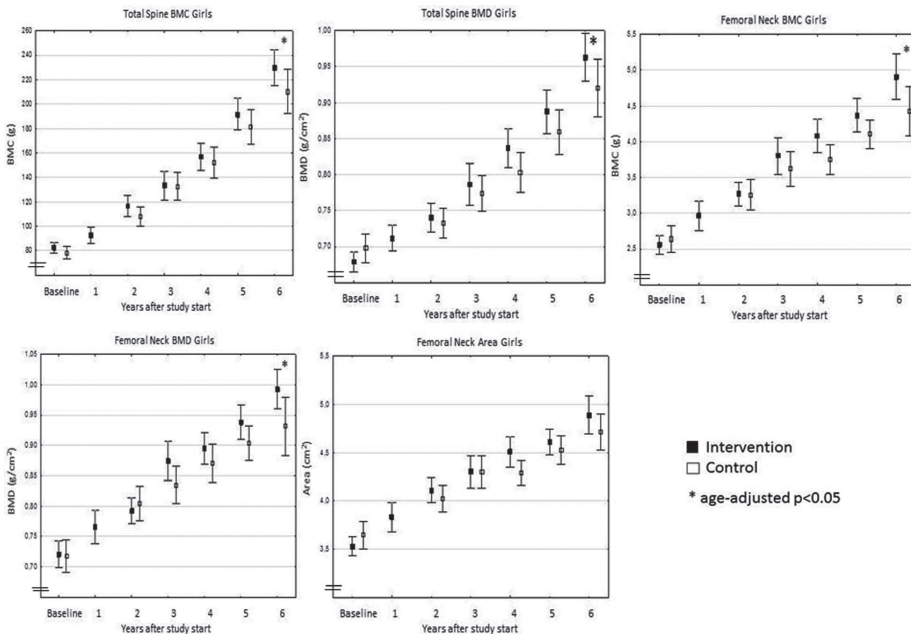


Fig. 2. Bone mineral content (BMC; g), bone mineral density (BMD; g/cm²), and bone area (cm²) shown in girls at the seven different measurements. Data are shown as means with error bars representing the 95% confidence intervals. The second measurement was in the controls done first after 2 years of the study period.

Table 3. Baseline and Follow-up Data in the Subsample of Girls and Boys (*n* = 295) Who Were Measured, Presented as Numbers and Proportion (%) or as Mean With Standard Deviation (SD)

	Girls			Boys		
	Cases (<i>n</i> = 78)	Controls (<i>n</i> = 52)	<i>p</i> Value	Cases (<i>n</i> = 111)	Controls (<i>n</i> = 54)	<i>p</i> Value
Baseline						
Age (years)	7.5 (0.5)	7.9 (0.6)	< 0.001	7.6 (0.6)	8.0 (0.6)	< 0.001
Weight (kg)	27.1 (5.2)	27.4 (5.6)	0.72	27.9 (5.8)	27.7 (4.8)	0.86
Height (cm)	127.5 (7.1)	129.3 (7.9)	0.17	128.5 (6.4)	129.9 (6.2)	0.19
Lifestyle factors						
Excluding dairy products	0	0	1.0	1 (1%)	1 (2%)	0.54
Drinking coffee	3 (4%)	1 (2%)	0.56	4 (4%)	0	0.16
Smoking	0	0	1.0	0	0	1.0
Alcohol	0	0	1.0	0	0	1.0
Tried to lose weight	1 (1%)	0	1.0	1 (1%)	0	1.0
Current disease	8 (10%)	3 (6%)	0.40	14 (13%)	4 (7%)	0.31
Ongoing medication	8 (10%)	2 (4%)	0.31	18 (16%)	5 (9%)	0.22
Previous medication	6 (8%)	2 (4%)	0.48	6 (5%)	6 (11%)	0.21
Previous fracture	6 (8%)	7 (14%)	0.25	8 (7%)	6 (11%)	0.41
Tanner stage 1/2/3/4/5	78/0/0/0/0	52/0/0/0/0	1.0	111/0/0/0/0	54/0/0/0/0	1.0
Follow-up (after 6 years)						
Age (years)	13.5 (0.5)	13.8 (0.7)	< 0.03	13.6 (0.6)	14.0 (0.7)	< 0.01
Weight (kg)	54.7 (11.3)	51.1 (10.2)	0.12	55.0 (13.8)	55.6 (11.1)	0.84
Height (cm)	165.5 (9.4)	167.7 (9.1)	0.23	162.9 (7.4)	161.9 (8.3)	0.55
Lifestyle factors						
Smoking	0	0	1.0	1 (1%)	0	0.74
Alcohol	1 (2%)	0	0.64	2 (2%)	1 (3%)	0.60
Tanner stage 1/2/3/4/5 (%)	0/6/23/45/26	0/0/26/43/31	0.49	0/4/28/44/24	3/3/15/46/33	0.21
Menarche	43 (66%)	22 (65%)	0.89	—	—	—

Statistically significant differences are highlighted in bold.

Table 4. Baseline and Follow-up Physical Activity Data and Mean Accelerometer Data From Two Evaluations After 2 and 4 Years in the Subsample of Girls and Boys Who Were Measured

	Girls			Boys		
	Cases (<i>n</i> = 78)	Controls (<i>n</i> = 52)	<i>p</i> Value	Cases (<i>n</i> = 111)	Controls (<i>n</i> = 54)	<i>p</i> Value
Baseline						
Organized physical activity before study start (hours/week)						
Total physical activity	1.8 (0.8)	2.3 (1.6)	0.06	2.7 (1.7)	2.5 (1.4)	0.41
Organized physical activity after study start (hours/week)						
School curriculum	3.3	1.0	< 0.001	3.3	1.0	< 0.001
Outside school	0.8 (0.8)	1.3 (1.6)	0.06	1.7 (1.7)	1.5 (1.4)	0.41
Total physical activity	4.1 (0.8)	2.3 (1.6)	< 0.001	5.0 (1.7)	2.5 (1.4)	< 0.001
Follow-up (after 6 years)						
Organized physical activity (hours/week)						
School curriculum	3.3	1.0	< 0.001	3.3	1.0	< 0.001
Outside school	3.3 (2.9)	2.5 (2.5)	0.23	3.9 (4.4)	2.9 (2.3)	0.23
Total physical activity	6.6 (2.9)	3.5 (2.5)	< 0.001	7.2 (4.4)	3.9 (2.3)	< 0.001
Mean accelerometer data of measurements done 2 and 4 years after study start						
	(<i>n</i> = 56)	(<i>n</i> = 44)		(<i>n</i> = 73)	(<i>n</i> = 52)	
Recording time per day (hours/day)	12.4 (1.5)	11.8 (1.1)	0.04	12.1 (1.4)	12.3 (1.3)	0.34
Mean activity (counts/min)	605.0 (142.1)	605.2 (149.1)	0.99	711.8 (220.9)	699.2 (177.4)	0.74
>3 METS (min/day)	185.9 (38.1)	177.3 (30.4)	0.23	202.2 (46.0)	199.0 (41.1)	0.69
>6 METS (min/day)	34.1 (12.7)	36.1 (11.1)	0.41	42.7 (17.8)	48.2 (16.7)	0.08
>6000 mean counts/min (cpm) (min/day)	10.6 (5.5)	10.4 (5.6)	0.85	13.4 (8.2)	14.1 (7.3)	0.64
>10,000 mean counts/min (cpm) (min/day)	2.0 (1.7)	1.3 (1.2)	0.02	2.9 (2.5)	2.0 (1.9)	0.04

Questionnaire-evaluated duration of organized physical activity was estimated as mean hours per week. Accelerometer-measured level of physical activity is presented as minutes per day above 3 or 6 metabolic equivalents (METs) or above 6000 or 10,000 counts per minute (cpm). Data are presented as means with standard deviation (SD).

Comparing intervention subjects with controls for respective sex. Statistically significant differences are highlighted in bold.

Table 5. Baseline Data and Annual Changes in the Subsample of Girls and Boys Who Were Measured, Presented as Mean Absolute Values, Evaluating the Effects of 6 Years of Exercise Intervention in Anthropometry, Bone Mineral Parameters, and Bone Size in the Exercise Intervention Group and the Control Group

	Baseline			Between-group differences baseline			Annual changes			Between-group differences annual changes			
	Cases (n = 78)	Controls (n = 52)		Mean difference (95% CI)	P-Value	P ₂ -Value	Cases (n = 78)	Controls (n = 52)		Mean difference (95% CI)	P ₃ Value	P ₄ Value	P ₅ Value
Girls													
Anthropometry (kg)													
Lean mass	19.67 (2.32)	20.25 (2.70)		0.10 (-0.8, 0.9)	0.88	0.60	2.77 (0.57)	2.76 (0.57)		0.052 (-0.16, 0.26)	0.63	0.38	0.71
Fat mass	5.15 (3.44)	5.05 (3.30)		0.10 (-1.2, 1.4)	0.89	0.56	1.60 (0.91)	1.20 (0.67)		0.34 (0.004, 0.65)	0.03	0.04	0.60
BMD (g/cm²)													
Total Body	0.84 (0.05)	0.84 (0.05)		0.010 (-0.01, 0.03)	0.25	0.29	0.036 (0.01)	0.033 (0.01)		0.004 (-0.001, 0.01)	0.08	0.05	0.37
Femoral neck	0.76 (0.10)	0.74 (0.11)		0.025 (-0.01, 0.06)	0.17	0.66	0.044 (0.02)	0.038 (0.02)		0.01 (-0.001, 0.01)	0.13	0.10	0.27
Total spine	0.68 (0.06)	0.70 (0.07)		-0.01 (-0.03, 0.01)	0.40	0.15	0.044 (0.02)	0.037 (0.01)		0.01 (0.003, 0.02)	0.03	0.001	< 0.01
BMC (g)													
Total body	922 (157.5)	932 (178.6)		36.7 (-21, 95)	0.21	0.12	199.3 (57.0)	190.1 (53.9)		13.76 (-6.9, 34)	0.19	0.11	0.77
Femoral neck	2.73 (0.61)	2.68 (0.60)		0.14 (-0.06, 0.3)	0.16	0.79	0.37 (0.159)	0.30 (0.126)		0.07 (0.01, 0.12)	0.02	0.008	< 0.05
Total spine	82.62 (18.7)	78.8 (18.4)		8.1 (1.4, 15)	0.02	0.001	23.1 (8.04)	22.2 (7.56)		1.7 (-1.2, 4.6)	0.25	0.16	0.78
Bone size (cm²)													
FN area	3.58 (0.42)	3.59 (0.43)		0.06 (-0.08, 0.2)	0.41	0.82	0.21 (0.10)	0.18 (0.09)		0.04 (0.01, 0.08)	0.03	0.02	0.05
L ₁ to L ₄ area	27.5 (3.13)	28.0 (3.89)		0.56 (-0.6, 1.7)	0.35	0.57	3.10 (0.81)	2.97 (0.72)		0.21 (-0.07, 0.50)	0.14	0.04	0.23
Boys													
Anthropometry (kg)													
Lean mass	21.51 (2.92)	21.85 (2.84)		0.52 (-0.33, 1.38)	0.23	0.98	3.03 (0.93)	3.18 (0.87)		0.055 (-0.23, 0.342)	0.71	0.43	0.70
Fat mass	4.12 (3.61)	3.55 (2.19)		0.96 (-0.11, 2.0)	0.08	0.91	1.18 (1.16)	0.94 (0.72)		0.236 (-0.117, 0.59)	0.19	0.09	0.26
BMD (g/cm²)													
Total body	0.85 (0.05)	0.85 (0.05)		0.01 (-0.003, 0.03)	0.11	0.36	0.027 (0.010)	0.028 (0.008)		0.0003 (-0.03, 0.03)	0.84	0.71	0.30
Femoral neck	0.76 (0.10)	0.76 (0.12)		0.026 (-0.01, 0.06)	0.17	0.19	0.034 (0.054)	0.029 (0.021)		0.002 (-0.014, 0.02)	0.81	0.74	0.81
Total spine	0.68 (0.06)	0.69 (0.06)		0.001 (-0.02, 0.02)	0.91	0.25	0.030 (0.013)	0.026 (0.011)		0.006 (0.002, 0.01)	0.006	< 0.001	< 0.01
BMC (g)													
Total body	979.1 (180)	989.0 (168)		46.0 (-47.6, 96.8)	0.08	0.27	179.8 (57.4)	183.3 (51.8)		7.88 (-9.95, 25.7)	0.38	0.21	0.70
Femoral neck	2.73 (0.59)	2.80 (0.62)		0.10 (-0.10, 0.31)	0.32	0.38	0.314 (0.16)	0.295 (0.14)		0.03 (-0.02, 0.08)	0.25	0.22	0.42
Total spine	85.93 (21.5)	84.44 (17.8)		6.89 (0.76, 13.0)	0.03	0.08	17.68 (7.02)	17.85 (6.26)		1.10 (-1.15, 3.26)	0.35	0.15	1.0
Bone size (cm²)													
FN area	3.59 (0.43)	3.67 (0.42)		0.011 (-0.14, 0.16)	0.88	0.82	0.22 (0.136)	0.20 (0.09)		0.027 (-0.015, 0.07)	0.20	0.11	0.24
L ₁ to L ₄ area	29.1 (3.4)	29.8 (3.3)		-0.015 (-1.1, 1.1)	0.98	0.30	2.70 (0.85)	2.92 (0.93)		-0.061 (-0.35, 0.23)	0.68	0.78	0.37

Data are presented as means (SD), adjusted mean differences with 95% CI. P values are presented in five different models adjusted for differences in age at baseline (P₁); adjusted for age, height, and weight at baseline (P₂); adjusted for age at follow-up (P₃); adjusted for age and Tanner at follow-up and annual changes in height and weight (P₄); and adjusted for age, Tanner at follow-up, and annual changes in height and weight (P₅). Statistically significant changes are highlighted in bold.

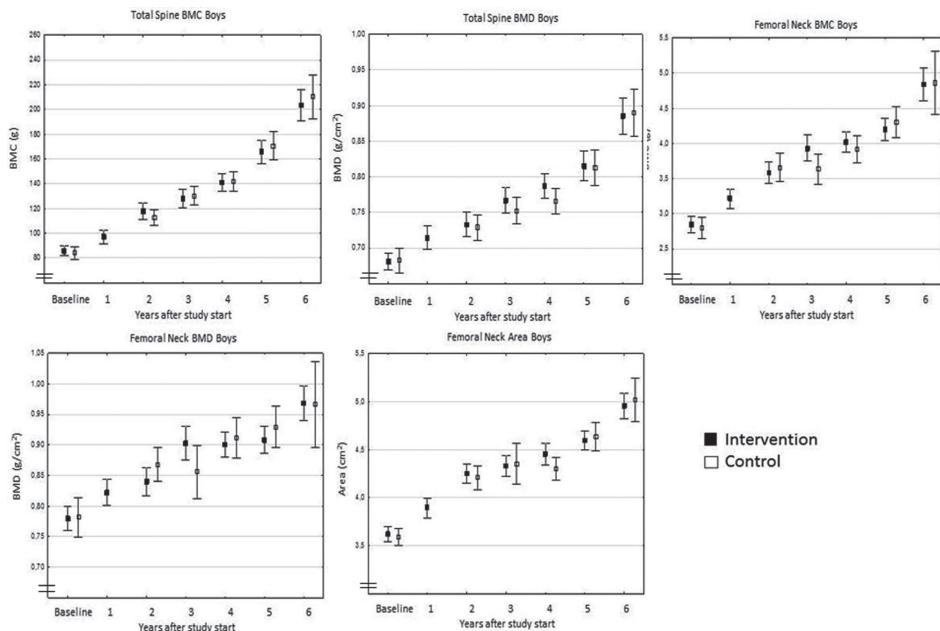


Fig. 3. Bone mineral content (BMC; g), bone mineral density (BMD; g/cm²), and bone area (cm²) shown in boys at the seven different measurements. Data are shown as means with error bars representing the 95% confidence intervals. The second measurement was in the controls done first after 2 years of the study period.

activity than girls in the intervention and control groups, and the accelerometer data that boys in both the intervention and control groups had more intense activities than girls in the respective group (Table 4).

Discussion

This study confirms that skeletal benefits that have previously been found with this program in a shorter perspective^(7,8,12) actually are retained with extension of the program into puberty, with more obvious benefits found in girls than boys, and that the program does not cause more fractures. The improved BMD by 0.5 SD in the girls at follow-up would, according to observational studies, confer a 25% lower fracture incidence,⁽⁴⁸⁾ a difference of clinical significance.

Our data suggest that not only bone mass but also bone structure can be influenced by moderate activity. This is of clinical relevance because bone structure is important for mechanical strength, and it has been shown that a large skeleton has a greater resistance to trauma than a smaller skeleton and that bone size is associated with fracture independently of bone mass.⁽⁴⁹⁾ For example, individuals with spine fractures have in general smaller lumbar vertebrae but normal femoral neck size, whereas individuals with hip fractures

in general have normal vertebral body size but smaller femoral neck size than nonfractured controls.^(50,51) In other words, bone size seems to be important not only in the mechanical calculations but actually also in clinical terms.

However, before an intervention program can be recommended, it must be clear that it does not confer adverse effects. The similar fracture risks in the intervention and control groups, also in the sex-specific evaluation, indicate that it seems not associated with a higher fracture risk. This is important knowledge because earlier reports have inferred that a high level of physical activity in children is associated with high fracture risk.^(39,52)

Our study shows that girls have a lower level of physical activity than boys in the late pre- and peripubertal period and that an intervention program actually increases the duration of physical activity in both groups. In addition to this, both girls and boys, as shown by the accelerometer data, achieved more intense activities than children in the control group.

The data also show that a general moderately intense physical activity intervention program may influence the cross-sectional enlargement of the bone (Table 6). Some studies have suggested that a lower level of physical activity, low-impact sports, and endurance sports may have no effect on bone mass.^(3,53,54) Some authors have, therefore, advocated the absolute need for specifically osteogenic programs with high intensity to achieve skeletal benefits.^(3,4,53) This could be problematic because an

Table 6. Cross-sectional pQCT Data for Girls (n = 100) and Boys (n = 121) and QUS Data for Girls (n = 61) and Boys (n = 72) in the Subsample of Girls and Boys Who Were Measured by These Techniques at Follow-up, Presented as Mean Absolute Values for the Exercise Intervention Group and the Control Group

	Girls				Boys				Mean difference 95% CI	P ₁ Value	P ₂ Value	P ₃ Value
	Cases (n = 67)	Controls (n = 33)	Mean difference (95% CI)	P ₁ Value	P ₂ Value	P ₃ Value	Cases (n = 89)	Controls (n = 32)				
Peripheral quantitative computed tomography (pQCT)												
Tibia trabecular 4%												
Trabecular vBMD (mg/cm ³)	217.7 (34.1)	213.2 (32.5)	2.62 (-12.0, 17.3)	0.52	0.57	0.63	209.6 (25.8)	218 (32.6)	-8.65 (-20.8, 3.44)	0.15	0.13	0.11
Tibia cortical 38%												
Cortical vBMD (mg/cm ³)	1075.8 (30.6)	1075.6 (28.0)	5.7 (-6.3, 17.6)	0.35	0.94	0.90	1022 (38.9)	1028 (31.7)	-0.13 (-15.6, 15.3)	0.99	0.97	0.94
Cortical BMC (g)	262.4 (39.2)	242.4 (37.3)	24.1 (7.6, 40.6)	0.005	0.08	0.11	266 (45.20)	281 (42.5)	-5.6 (-23.6, 12.3)	0.53	0.52	0.36
Cortical area (mm ²)	243.7 (34.5)	225.2 (33.0)	21.2 (6.5, 36.0)	0.005	0.08	0.12	260.4 (42.5)	273.8 (41.7)	-5.7 (-23.1, 11.7)	0.51	0.49	0.35
Cortical thickness (mm)	4.57 (0.51)	4.32 (0.53)	0.29 (-0.07, 0.51)	0.01	0.13	0.17	4.67 (0.62)	4.82 (0.60)	-0.05 (-0.31, 0.20)	0.69	0.66	0.52
Total area (CSA) (mm ²)	365.0 (44.6)	343.3 (38.4)	23.9 (5.3, 42.6)	0.01	0.13	0.20	395.9 (58.0)	413.7 (57.5)	-8.0 (-32.0, 15.9)	0.51	0.54	0.45
Polar SI (cm ⁻¹)	1220 (233.1)	1100 (205.7)	140.2 (43.3, 237)	0.005	0.08	0.12	1291 (274.3)	1397 (267.2)	-165.9 (165.9, 56.8)	0.33	0.30	0.21
Radius trabecular 4%												
Trabecular vBMD (mg/cm ³)	177.9 (30.22)	175.5 (35.6)	-0.48 (-14.3, 13)	0.95	0.97	0.93	191.0 (32.9)	194.5 (30.4)	-1.2 (-15.2, 12.7)	0.86	0.75	0.71
Radius cortical 66%												
Cortical vBMD (mg/cm ³)	1034.4 (40.0)	1038.3 (43.0)	3.4 (-13.2, 20.1)	0.69	0.66	0.78	993.7 (38.2)	1000 (37.8)	-3.5 (-20.0, 12.9)	0.67	0.62	0.62
Cortical BMC (g)	65.4 (12.5)	64.2 (12.3)	3.0 (-2.2, 8.2)	0.26	0.83	0.99	63.3 (14.6)	68.0 (16.2)	-1.1 (-7.1, 5.0)	0.73	0.37	0.28
Cortical area (mm ²)	63.0 (10.9)	61.5 (10.1)	2.8 (-1.7, 7.3)	0.23	0.70	0.91	63.5 (13.9)	67.8 (15.3)	-0.8 (-6.5, 4.9)	0.78	0.39	0.29
Cortical thickness (mm)	1.84 (0.32)	1.88 (0.36)	-0.01 (-0.2, 0.1)	0.92	0.13	0.15	1.7 (0.38)	1.9 (0.43)	-0.08 (-0.24, 0.08)	0.33	0.13	0.10
Total area (CSA) (mm ²)	131.0 (27.6)	121.8 (18.6)	10.0 (-0.91, 21)	0.07	0.07	0.10	146.4 (30.0)	145.4 (29.4)	6.8 (-5.5, 19.0)	0.27	0.31	0.33
Polar SI (cm ⁻¹)	204.6 (57.1)	194.1 (41.1)	16.0 (-6.2, 38.3)	0.16	0.33	0.50	214.0 (60.4)	224.9 (68.7)	3.3 (-22.0, 28.6)	0.80	0.94	0.85
Quantitative ultrasound (QUS)												
SOS	1594.9 (41.1)	1594.9 (38.6)	-2.7 (-25.2, 19.8)	0.81	0.74	0.58	1580 (29.0)	1587 (39.3)	-14.5 (-33.0, 4.0)	0.12	0.10	0.08
BUA	114.3 (19.2)	103.8 (14.2)	10.5 (0.99, 19.9)	0.03	0.07	0.15	107.1 (12.2)	104.4 (16.7)	3.8 (4.2, 11.7)	0.35	0.39	0.47

Data are presented as means (SD) or mean differences with 95% CI. P values are presented in three different models adjusted for differences in age at follow-up (P₁), age, Tanner stage, and height at follow-up (P₂), and age, Tanner stage, height, and weight at follow-up (P₃). Statistically significant differences are highlighted in bold.

Table 7. Cross-sectional DXA Data for Children (n = 100) and Boys (n = 127) in the Subsample of Girls and Boys Who Were Measured, Presented as Mean Absolute Values, Evaluating the Effect of an Exercise Intervention in Bone Mineral Parameters and Bone Size for the Exercise Intervention Group and the Control Group

	Girls				Boys				Mean difference 95% CI	P ₁ Value	P ₂ Value	P ₃ Value
	Cases (n = 65)		Controls (n = 33)		Cases (n = 94)		Controls (n = 33)					
	Mean difference (95% CI)	P ₁ Value	P ₂ Value	P ₃ Value	Mean difference (95% CI)	P ₁ Value	P ₂ Value	P ₃ Value				
Anthropometry												
Lean mass	36.2 (4.2)	35.1 (4.7)	1.6 (-0.23, 3.4)	0.09	0.22	0.42	41.4 (7.8)	43.3 (6.9)	0.2 (-2.6, 2.9)	0.90	0.98	0.53
Fat mass	15.5 (8.0)	13.2 (6.8)	2.3 (-0.9, 5.6)	0.16	0.19	0.45	10.8 (8.7)	9.8 (5.5)	1.2 (-2.1, 4.5)	0.49	0.44	0.89
BMD (g/cm³)												
Total body	1.1 (0.09)	1.03 (0.09)	0.04 (0.001, 0.08)	0.04	0.08	0.16	1.02 (0.09)	1.04 (0.09)	0.002 (-0.03, 0.04)	0.93	0.98	0.57
Femoral neck	1.0 (0.13)	0.93 (0.14)	0.07 (0.008, 0.12)	0.03	0.07	0.15	0.97 (0.14)	0.97 (0.20)	0.025 (-0.04, 0.09)	0.42	0.43	0.55
Total spine	0.96 (0.13)	0.92 (0.12)	0.05 (0.001, 0.11)	0.045	0.07	0.14	0.88 (0.13)	0.89 (0.09)	0.015 (-0.03, 0.06)	0.52	0.48	0.84
BMC (g)												
Total body	2157 (429.9)	2020 (427.2)	191.3 (12.7, 369.9)	0.04	0.06	0.11	2144 (496.7)	2241 (454)	22.2 (-159.4, 203.8)	0.81	0.85	0.65
Femoral neck	4.9 (1.2)	4.43 (1.01)	0.54 (0.04, 1.04)	0.04	0.06	0.15	4.84 (1.13)	4.87 (1.26)	0.20 (-0.25, 0.66)	0.38	0.34	0.49
Total spine	228.3 (57.1)	210.6 (52.5)	25.2 (2.1, 48.2)	0.03	0.03	0.06	203.3 (60.1)	210.1 (50.7)	6.1 (-15.9, 28.0)	0.58	0.51	0.86
Bone size (cm²)												
FN area	4.9 (0.8)	4.7 (0.5)	0.23 (-0.06, 0.5)	0.12	0.14	0.33	4.96 (0.64)	5.02 (0.64)	0.07 (-0.18, 0.32)	0.59	0.54	0.76
L ₁ to L ₄ area	46.6 (6.1)	45.1 (5.6)	2.6 (0.2, 5.0)	0.03	0.05	0.10	47.2 (7.9)	49.2 (7.5)	-0.03 (-2.94, 2.9)	0.98	0.82	0.63

Data are presented as means (SD), mean differences with 95% CI. *p* values are presented in three different models adjusted for differences in age at follow-up (P₁); age, Tanner stage, and height at follow-up (P₂); and age, Tanner stage, height, and weight at follow-up (P₃). Statistically significant differences are highlighted in bold.

intervention must be at an acceptable level so that it not attract only the most interested and the most skilled participants. The activity ought also to include a variety of activities because monotonous repeated programs with few variations are often associated with a high dropout rate.⁽⁵³⁾ These aspects must be taken into account if the aim is to facilitate the participation of all children in the program. Our program indicates that a moderately intense training program could be launched with reaching skeletal benefits, as the program, even though moderate in design, could possibly, as being indicated by the accelerometer data, be followed by more of the high-impact activities known to be osteogenic.^(13,56)

The program also conferred more benefits on girls than on boys, in that girls reached benefits in all measured traits and in different skeletal regions. Sex differences in skeletal response to exercise are intriguing and they have not been completely explained.⁽¹¹⁾ In our study, one explanation could be that the girls were more maturationally advanced than the boys because the skeletal response to exercise is greatest in the late pre- and early peripubertal period.⁽¹⁶⁾ However, when adjusted for maturation (Tanner stage) and annual changes in height and weight, the group differences remained, indicating that factors beyond pubertal maturation influenced the sex-specific data. One such possible explanation could be that boys had more leisure-time activity than girls, with the result that the intervention contributed a greater proportion of the total amount of physical activity in the girls than in the boys. This hypothesis is supported by our data, which suggest that girls have a lower level of physical activity than boys and that the intervention program actually induced a higher level of physical activity.

The finding of a greater annual gain in fat mass in the intervention girls than controls girls has been reported in other studies.^(7,12,57,58) The reason for the larger fat gain in the intervention group, also after adjusting for the confounders, is unclear but could possibly be associated with an increased food intake concomitantly with an increment in exercise. Although we did not assess dietary habits in detail, previous studies have speculated that the increment in fat gain is most likely the result of other influences beyond physical activity, as there has been no dose-response relationship between level of physical activity and gain in fat mass.⁽⁵⁷⁾

Strengths of this study include a study design with a high level of evidence. The baseline similarities between both children who did and did not participate in the study and between children in the intervention and control groups indicate representative samples with low risk for selection bias at inclusion. The similarity between participants and dropouts further supports this view. The evaluation of not only bone mass but also bone size and incident fracture is another strength, as is the use of the more modern technique pQCT, giving us the possibility to estimate bone structure as well. Limitations include the power problem when evaluating fracture risk. This study found a 12% higher fracture risk in the intervention group, but because of the power problem, we cannot state that this increase was statistically different from what was expected. Actually, the only statement we could make is that there was at least no fracture reduction of 15% or more and no fracture increase of 46% or more in the intervention group (based on the 95% CI). However, given the low total number of fractures during the study period, it could be questioned if a 12% increase in fracture risk would be clinically relevant. Individual randomization would also have been preferable, but all schools refused to participate in such a study design because of practical problems with the schedule. The

lower participation rate in the control schools than in the intervention school could also influence the data, even if our dropout analyses oppose this view. It would also have been preferable to have longitudinal pQCT data but the pQCT apparatus was not available at baseline. There was no possibility to find data in the referrals on whether fractures had occurred during physical education classes. It would also have been advantageous if we had had information about play activities and extra-protocol physical activity on a voluntary basis as well as an extended food questionnaire. The lack of physical performance and motor skills measurements is also a shortcoming.

In conclusion, this study shows that a general moderately intense school-based exercise intervention program in prepubertal children with 6-year duration improves bone mass and in girls also skeletal architecture without increasing the fracture risk. We, therefore, believe that a daily moderate physical activity program ought to be implemented from school start in all children.

Disclosures

All authors have completed the Unified Competing Interest form at http://www.icmje.org/col_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 6 years; and no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgments

Financial support for this study was received from ALF, the Centre for Athletic Research, the Osterlund Foundation, the Kock Foundation, and the Region Skåne Foundation.

We thank Lise-Lott Hägg for her data managing expertise and Per Gärdåll for his help during the initiation of the study.

Authors' roles: MK designed the study and was responsible for data collection. Accelerometer data were collected and analyzed by MD. ML analyzed and validated the data from the pQCT measurements. FD and JÅN analyzed group differences in lifestyle, DXA, and pQCT variables, the linear regression slopes, and Poisson distributions. FD drafted the manuscript and transferred calculated data to the manuscript. FD, BR, and MK finalized the manuscript. All authors read and approved the final manuscript.

References

- Boreham CA, McKay HA. Physical activity in childhood and bone health. *Br J Sports Med.* 2011;45(11):877–9.
- Gunter KB, Almstedt HC, Janz KF. Physical activity in childhood may be the key to optimizing lifespan skeletal health. *Exerc Sport Sci Rev.* 2012;40(1):13–21.
- Heinonen A, Oja P, Kannus P, et al. Bone mineral density in female athletes representing sports with different loading characteristics of the skeleton. *Bone.* 1995;17(3):197–203.
- Nikander R, Sievanen H, Heinonen A, Daly RM, Uusi-Rasi K, Kannus P. Targeted exercise against osteoporosis: a systematic review and meta-analysis for optimising bone strength throughout life. *BMC Med.* 2010;8:47.
- Nilsson M, Ohlsson C, Oden A, Mellstrom D, Lorentzon M. Increased physical activity is associated with enhanced development of peak

bone mass in men: a five-year longitudinal study. *J Bone Miner Res.* 2012;27(5):1206–4.

- Linden C, Ahlborg HG, Besjakov J, Gardsell P, Karlsson MK. A school curriculum-based exercise program increases bone mineral accrual and bone size in prepubertal girls: two-year data from the pediatric osteoporosis prevention (POP) study. *J Bone Miner Res.* 2006;21(6):829–35.
- Linden C, Alwis G, Ahlborg H, et al. Exercise, bone mass and bone size in prepubertal boys: one-year data from the pediatric osteoporosis prevention study. *Scand J Med Sci Sports.* 2007;17(4):340–7.
- Lofgren B, Dencker M, Nilsson JA, Karlsson MK. A 4-year exercise program in children increases bone mass without increasing fracture risk. *Pediatrics.* 2012;129(6):e1468–76.
- MacKelvie KJ, Petit MA, Khan KM, Beck TJ, McKay HA. Bone mass and structure are enhanced following a 2-year randomized controlled trial of exercise in prepubertal boys. *Bone.* 2004;34(4):755–64.
- McKay HA, MacLean L, Petit M, et al. "Bounce at the Bell": a novel program of short bouts of exercise improves proximal femur bone mass in early pubertal children. *Br J Sports Med.* 2005;39(8):521–6.
- Petit MA, McKay HA, MacKelvie KJ, Heinonen A, Khan KM, Beck TJ. A randomized school-based jumping intervention confers site and maturity-specific benefits on bone structural properties in girls: a hip structural analysis study. *J Bone Miner Res.* 2002;17(3):363–72.
- Valdimarsson O, Linden C, Johnell O, Gardsell P, Karlsson MK. Daily physical education in the school curriculum in prepubertal girls during 1 year is followed by an increase in bone mineral accrual and bone width—data from the prospective controlled Malmo pediatric osteoporosis prevention study. *Calcif Tissue Int.* 2006;78(2):65–71.
- Lanyon LE. Control of bone architecture by functional load bearing. *J Bone Miner Res.* 1992;7(Suppl 2):S369–75.
- Rubin CT, Lanyon LE. Regulation of bone formation by applied dynamic loads. *J Bone Joint Surg Am.* 1984;66(3):397–402.
- Hughes JM, Petit MA. Biological underpinnings of Frost's mechanostat thresholds: the important role of osteocytes. *J Musculoskelet Neuronal Interact.* 2010;10(2):128–35.
- Kannus P, Haapasalo H, Sankelo M, et al. Effect of starting age of physical activity on bone mass in the dominant arm of tennis and squash players. *Ann Intern Med.* 1995;123(1):27–31.
- Hui SL, Slemenda CW, Johnston CC Jr. The contribution of bone loss to postmenopausal osteoporosis. *Osteoporos Int.* 1990;1(1):30–4.
- Johnell O, Gullberg B, Kanis JA, et al. Risk factors for hip fracture in European women: the MEDOS Study. *Mediterranean Osteoporosis Study.* *J Bone Miner Res.* 1995;10(11):1802–15.
- Siris ES, Baim S, Nattiv A. Primary care use of FRAX: absolute fracture risk assessment in postmenopausal women and older men. *Postgrad Med.* 2010;122(11):82–90.
- McNamara A, Gunter K. The influence of participation in Better Bones and Balance on skeletal health: evaluation of a community-based exercise program to reduce fall and fracture risk. *Osteoporos Int.* 2012;23(6):1813–22.
- Nordstrom A, Olsson T, Nordstrom P. Bone gained from physical activity and lost through detraining: a longitudinal study in young males. *Osteoporos Int.* 2005;16(7):835–41.
- Tveit M, Rosengren BE, Nilsson JA, Ahlborg HG, Karlsson MK. Bone mass following physical activity in young years: a mean 39-year prospective controlled study in men. *Osteoporos Int.* 2013;24(4):1389–97.
- Tveit M, Rosengren BE, Nyquist F, Nilsson JA, Karlsson MK. Former male elite athletes have lower incidence of fragility fractures than expected. *Med Sci Sports Exerc.* 2013;45(3):405–10.
- Bradley M, Pearce G, Naughton G, et al. Moderate exercise during growth in prepubertal boys: changes in bone mass, size, volumetric density, and bone strength: a controlled prospective study. *J Bone Miner Res.* 1998;13(12):1814–21.
- Fuchs RK, Bauer JJ, Snow CM. Jumping improves hip and lumbar spine bone mass in prepubescent children: a randomized controlled trial. *J Bone Miner Res.* 2001;16(1):148–56.
- Heinonen A, Sievanen H, Kannus P, Oja P, Pasanen M, Vuori I. High-impact exercise and bones of growing girls: a 9-month controlled trial. *Osteoporos Int.* 2000;11(12):1010–7.

27. Laing EM, Wilson AR, Modlesky CM, O'Connor PJ, Hall DB, Lewis RD. Initial years of recreational artistic gymnastics training improves lumbar spine bone mineral accrual in 4- to 8-year-old females. *J Bone Miner Res.* 2005;20(3):509-19.
28. MacKelvie KJ, Khan KM, Petit MA, Janssen PA, McKay HA. A school-based exercise intervention elicits substantial bone health benefits: a 2-year randomized controlled trial in girls. *Pediatrics.* 2003;112(6 Pt 1):e447.
29. McKay HA, Petit MA, Schutz RW, Prior JC, Barr SI, Khan KM. Augmented trochanteric bone mineral density after modified physical education classes: a randomized school-based exercise intervention study in prepubescent and early pubescent children. *J Pediatr.* 2000;136(2):156-62.
30. Morris FL, Naughton GA, Gibbs JL, Carlson JS, Wark JD. Prospective ten-month exercise intervention in premenarcheal girls: positive effects on bone and lean mass. *J Bone Miner Res.* 1997;12(9):1453-62.
31. Nichols DL, Sanborn CF, Love AM. Resistance training and bone mineral density in adolescent females. *J Pediatr.* 2001;139(4):494-500.
32. Specker B, Binkley T. Randomized trial of physical activity and calcium supplementation on bone mineral content in 3- to 5-year-old children. *J Bone Miner Res.* 2003;18(5):885-92.
33. Van Langendonck L, Claessens AL, Vlietinck R, Derom C, Beunen G. Influence of weight-bearing exercises on bone acquisition in prepubertal monozygotic female twins: a randomized controlled prospective study. *Calcif Tissue Int.* 2003;72(6):666-74.
34. Weeks BK, Young CM, Beck BR. Eight months of regular in-school jumping improves indices of bone strength in adolescent boys and girls: the POWER PE study. *J Bone Miner Res.* 2008;23(7):1002-11.
35. Wiebe PN, Blimkie CJ, Farpour-Lambert N, et al. Effects of single-leg drop-landing exercise from different heights on skeletal adaptations in prepubertal girls: a randomized controlled study. *Pediatr Exerc Sci.* 2008;20(2):211-28.
36. Knuth AG, Bielemann RM, Silva SG, et al. [Public knowledge on the role of physical activity in the prevention and treatment of diabetes and hypertension: a population-based study in southern Brazil]. *Cadernos de Saude Publica.* 2009;25(3):513-20.
37. Fremeaux AE, Mallam KM, Metcalf BS, Hosking J, Voss LD, Wilkin TJ. The impact of school-time activity on total physical activity: the activitystat hypothesis (EarlyBird 46). *Int J Obes (Lond).* 2011;35(10):1277-83.
38. Wilkin TJ, Metcalf BS. Testing the activitystat hypothesis. *Prev Med.* 2012;54(2):177; author reply 8-9.
39. Clark EM, Ness AR, Tobias JH. Vigorous physical activity increases fracture risk in children irrespective of bone mass: a prospective study of the independent risk factors for fractures in healthy children. *J Bone Miner Res.* 2008;23(7):1012-22.
40. Dettler FT, Rosengren BE, Dencker M, Nilsson JA, Karlsson MK. A 5-year exercise program in pre- and peripubertal children improves bone mass and bone size without affecting fracture risk. *Calcif Tissue Int.* 2013;92(4):385-93.
41. Jonsson B, Gardsell P, Johnell O, Redlund-Johnell I, Sernbo I. Remembering fractures: fracture registration and proband recall in southern Sweden. *J Epidemiol Community Health.* 1994;48(5):489-90.
42. Landin LA. Fracture patterns in children. Analysis of 8,682 fractures with special reference to incidence, etiology and secular changes in a Swedish urban population 1950-1979. *Acta Orthop Scand Suppl.* 1983;202:1-109.
43. Dencker M, Thorsson O, Karlsson MK, et al. Daily physical activity in Swedish children aged 8-11 years. *Scand J Med Sci Sports.* 2006;16(4):252-7.
44. Ferretti JL, Capozza RF, Zanchetta JR. Mechanical validation of a tomographic (pQCT) index for noninvasive estimation of rat femur bending strength. *Bone.* 1996;18(2):97-102.
45. Ashby RL, Ward KA, Roberts SA, Edwards L, Mughal MZ, Adams JE. A reference database for the Stratec XCT-2000 peripheral quantitative computed tomography (pQCT) scanner in healthy children and young adults aged 6-19 years. *Osteoporos Int.* 2009;20(8):1337-46.
46. Alwis G, Linden C, Stenevi-Lundgren S, et al. A school-curriculum-based exercise intervention program for two years in pre-pubertal girls does not influence hip structure. *Dyn Med.* 2008;7:8.
47. Duke PM, Litt IF, Gross RT. Adolescents' self-assessment of sexual maturation. *Pediatrics.* 1980;66(6):918-20.
48. Cummings SR, Marcus R, Palermo L, Ensrud KE, Genant HK. Does estimating volumetric bone density of the femoral neck improve the prediction of hip fracture? A prospective study. *Study of Osteoporotic Fractures Research Group.* *J Bone Miner Res.* 1994;9(9):1429-32.
49. Ahlborg HG, Johnell O, Turner CH, Rannevik G, Karlsson MK. Bone loss and bone size after menopause. *N Engl J Med.* 2003;349(4):327-34.
50. Duan Y, Parfitt A, Seeman E. Vertebral bone mass, size, and volumetric density in women with spinal fractures. *J Bone Miner Res.* 1999;14(10):1796-802.
51. Duan Y, Turner CH, Kim BT, Seeman E. Sexual dimorphism in vertebral fragility is more the result of gender differences in age-related bone gain than bone loss. *J Bone Miner Res.* 2001;16(12):2267-75.
52. Ma D, Jones G. Television, computer, and video viewing; physical activity; and upper limb fracture risk in children: a population-based case control study. *J Bone Miner Res.* 2003;18(11):1970-7.
53. Guadalupe-Grau A, Fuentes T, Guerra B, Calbet JA. Exercise and bone mass in adults. *Sports Med.* 2009;39(6):439-68.
54. Nikander R, Sievanen H, Heinonen A, Kannus P. Femoral neck structure in adult female athletes subjected to different loading modalities. *J Bone Miner Res.* 2005;20(3):520-8.
55. Marcus BH, Williams DM, Dubbert PM, et al. Physical activity intervention studies: what we know and what we need to know: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity); Council on Cardiovascular Disease in the Young; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research. *Circulation.* 2006;114(24):2739-52.
56. Rubin CT, Lanyon LE. Kappa Delta Award paper. Osteoregulatory nature of mechanical stimuli: function as a determinant for adaptive remodeling in bone. *J Orthop Res.* 1987;5(2):300-10.
57. Stenevi-Lundgren S, Daly RM, Linden C, Gardsell P, Karlsson MK. Effects of a daily school based physical activity intervention program on muscle development in prepubertal girls. *Eur J Appl Physiol.* 2009;105(4):533-41.
58. Treuth MS, Figueroa-Colon R, Hunter GR, Weinsier RL, Butte NF, Goran MI. Energy expenditure and physical fitness in overweight vs non-overweight prepubertal girls. *Int J Obes Relat Metab Disord.* 1998;22(5):440-7.

Editorial for Paper IV

Run, Jump, and Be Merry: How Much Exercise Is Needed for Building Young Bones?

Catherine M Gordon

Divisions of Adolescent Medicine and Endocrinology, Hasbro Children's Hospital and Alpert Medical School of Brown University, Providence RI, USA

Regular weight-bearing physical activity is essential for the development of a strong and healthy skeleton. This concept is of particular importance during childhood and adolescence, because over half of peak bone mass is accrued during the teenage years, accompanying the development of secondary sexual characteristics and the pubertal growth spurt.⁽¹⁾ The skeletal loading associated with exercise has also been shown in both animal and human models to augment bone size and strength, thus facilitating the development of a structurally optimized skeleton,⁽²⁻⁴⁾ and data from clinical trials support the skeletal benefits of exercise, particularly during periods of growth.⁽⁵⁻⁷⁾ However, the exercise prescription that yields optimal bone accrual and skeletal strength for the pediatric skeleton is unknown. Thus, the article of Detter and colleagues⁽⁸⁾ in this issue of the *Journal of Bone and Mineral Research* is timely and of high interest.

The study of Detter and colleagues⁽⁸⁾ was elegantly designed, using data from a prospective, population-based, controlled exercise intervention study with incident fractures, and bone mass and structure as outcomes. The Malmö Pediatric Osteoporosis Prevention (POP) Study captured data from 417 girls and 500 boys in their intervention group and 835 girls and 869 boys in the control group, each age 6 to 9 years at study entry. The children were enrolled in four neighboring elementary schools in Sweden, from a middle-class socioeconomic status, and each school was government funded, necessitating use of a compulsory standard Swedish physical education curriculum. Although representing a convenience sample, these aspects of the study are noteworthy because there was less variability at baseline with respect to physical activity. The four schools were also similar in size, which is important given how the treatment was assigned in the current exercise intervention trial. One of the four schools was offered to participate as the intervention school, with the other three serving as controls. Fracture incidence was assessed in all participants. Importantly, a sophisticated surveillance system was employed with all fractures verified radiographically. Fractures during the 6-year period were registered in radiological archives from the hospital and a computerized database that included all radiographs obtained in southern Sweden. As there was only one emergency hospital in the city, virtually all fractures were captured, a unique system that has been previously shown to miss less than 3% of all sustained

fractures.⁽⁹⁾ This feature of the study is a remarkable one, because fracture verification can be tedious and time-consuming, with efforts often yielding inaccurate data. In a study of children, documentation of fractures is critically important because the International Society for Clinical Densitometry (ICSD) and the American Society for Bone and Mineral Research (ASBMR) recently convened international experts for the second Pediatric Position Development Conference and deemed that in a child or adolescent, the diagnosis of osteoporosis cannot be established "without clinical evidence of skeletal fragility."⁽¹⁰⁾

In addition to fracture data, anthropometric and skeletal traits were obtained in a subset of participants. Multiple skeletal assessment tools were employed to assess bone density, and skeletal geometry and strength before and after a 6-year physical activity intervention: a 40-minute session every school day (200 minutes/week) versus the Swedish standard of 60 minutes/week provided in one to two classes per week. The intervention included ball games, jumping, running, and other play. This is a noteworthy feature of the study because the authors tested a feasible and sustainable intervention, including activities and games that children generally enjoy. Seventy-eight girls and 111 boys were in the intervention group, and 52 girls and 54 boys were in the control group. All underwent dual-energy X-ray absorptiometry (DXA) measures (hip, spine, whole body) at baseline and annually; 221 adolescents underwent radial and tibial peripheral quantitative computed tomography (pQCT) measurements at the study's conclusion; 133 underwent quantitative ultrasound (QUS) calcaneal measures at the 6-year follow-up visit; and 248 agreed to wear an accelerometer for 4 consecutive days, 2 and 4 years after study initiation, to verify reported physical activity.

In addition to strengths, there are limitations of this study that merit discussion. DXA was the tool used to obtain measures of bone mass, which can be confounded by bone size, relevant to note in a study of growing children.⁽¹¹⁾ Additionally, DXA provides little information about bone strength, and no information on bone geometry or microarchitecture which are informative outcomes to consider in determining fracture risk. Another assessment tool, pQCT, was employed, but only at the study's conclusion, which provided information on bone structure, geometry, and volumetric bone mineral density (BMD). Although the authors acknowledge that it was not possible, valuable

Address correspondence to: Catherine M Gordon, MD, MSc, Division of Adolescent Medicine, Hasbro Children's Hospital, 593 Eddy Street, Providence, RI 02903, USA. E-mail: catherine_gordon@brown.edu

This is a Commentary on Detter et al. (*J Bone Miner Res.* 2014;29:1325-1336. DOI: 10.1002/jbmr.2168).

Journal of Bone and Mineral Research, Vol. 29, No. 6, June 2014, pp 1322-1324

DOI: 10.1002/jbmr.2264

© 2014 American Society for Bone and Mineral Research

information would have been afforded by an evaluation of changes in bone structure and geometry after the intervention, as captured by pQCT. At the 6-year follow-up visit, right calcaneal bone traits were also measured by QUS. This modality has been used in pediatrics much less frequently than in adults, because there is continued debate as to which skeletal properties are captured by QUS. Finally, high-resolution pQCT (HR-pQCT) measurements were not obtained in this trial, and would be needed to explore whether bone geometry or microarchitecture changes in children who have engaged in weight-bearing exercise are sustained as peak bone mass is approached.

Children in this study were assessed during a "critical window" for bone health, with all participants entering the protocol during elementary school. The skeleton appears to be highly impressionable during late childhood and early adolescence, and thus, more sensitive to an exercise intervention when initiated during this period. This "sensitivity" may relate to skeletal loads introduced to surfaces undergoing fast apposition,^(11,12) a critical concept to consider during adolescence because over half of bone accrual occurs during the teenage years.⁽¹⁾ The current results, including an intervention initiated during late childhood and skeletal benefits noted 6 years later, illustrate this point. An important clinical take-home message is that any osteogenic intervention begun during these formative years has the potential to enhance peak bone mass. Perhaps most importantly, exercise initiated when an individual is young may augment bone size and strength more dramatically than bone mass, and these ultimate changes in skeletal dimensions and strength may confer long-term benefits for bone health.⁽²⁻⁴⁾

Sexually dimorphic results were seen in the current study by Detter and colleagues.⁽⁸⁾ Among girls in the intervention group, a higher annual bone accrual rate was observed in femoral neck bone mineral content (BMC), spine BMD, and a larger gain noted in the femoral neck area. A higher tibial cortical BMC was also seen at follow-up, as well as larger tibial cross-sectional area and polar strength strain index (SSI). In fact, there was evidence of skeletal benefit in the girls on measures from all three bone assessment tools employed. In boys from the intervention group, only a higher annual accrual rate was seen in spine BMD. No differences were observed in the boys on either pQCT or QUS assessments. Per the rigorous design of the study, sexually dimorphic differences were also seen in the both the axial versus appendicular skeleton. However, some of the findings may have been due to the reduced physical activity levels in the female participants at baseline as opposed to intrinsic differences between gender groups. Because of lower physical activity levels, the female participants were exposed to greater differences between their habitual and the new loading associated with the intervention, with the differential potentially being a strong predictor of the magnitude of bone adaptation. Nonetheless, the article leaves the reader considering the possibility that the female skeleton may be more receptive to the effects of weight-bearing activity, especially when initiated during prepubertal and peripubertal years.

What is novel about the study of Detter and colleagues?⁽⁸⁾ First, many previous studies that have explored the response of the pediatric skeleton to exercise have used a cross-sectional design and documented solely measures of bone density, without considering bone size or skeletal strength. The current study examined youth over age 6 years, allowing for repeated measures of multiple bone traits. Most studies have only used DXA, with its inherent limitations, as mentioned, in growing children. The current study used not only DXA, but also pQCT and

QUS to afford measures of the appendicular skeleton, which is important because children typically fracture extremity bones versus the axial skeleton. There is current consensus that bone strength is the most informative variable to follow to capture skeletal health.⁽¹³⁾ Those studies that have employed tools which afford three-dimensional measures of bone density (eg, volumetric BMD from pQCT) and estimated strength parameters (such as polar SSI derived from pQCT) are regarded as more valuable assessment tools. On a structural level, intense physical activity has also been shown to be associated with high bone mass and larger bone size.^(14,15) Importantly, both in mice and humans, it has been shown that the maintenance of bone size, but not mass, is sustained following cessation of exercise.^(2,3) Thus, the most important benefits of exercise may be conferred through changes in bone size. The longitudinal design of the current study afforded some insight into whether exercise during adolescence garners skeletal benefits. However, further observation would have been needed to determine whether the changes were sustained after stopping the intervention.

With any exercise intervention, risks and benefits must be assessed, especially with regard to fracture risk. Safety endpoints included documented fractures over the 6-year study period, and efficacy endpoints, the change in bone mass accrual and gains in bone size. Why would one consider the safety of a running and jumping routine in children and young adolescents? Khosla and colleagues⁽¹⁶⁾ have shown that that the young adolescent skeleton is particularly vulnerable to fracture during periods of rapid growth, including the early years of puberty, prior to completion of bone accrual and consolidation. The same investigative group used HR-pQCT to explain the microarchitectural basis for the observation of increased fracture frequency among young adolescents.⁽¹⁷⁾ The fractures observed in the current study, with the highest percentage occurring at the distal forearm, replicate findings from other studies of children and adolescents.^(18,19) Whereas the title and take-home message of the current article is that a 6-year exercise program improves skeletal traits without affecting fracture risk, each point in this paragraph is important to consider.⁽⁸⁾

Are there public health implications that stem from the data of Detter and colleagues?⁽⁸⁾ The investigators were clever in the design of their intervention as they chose activities that children generally enjoy as part of routine play (ie, running and jumping). Thus, the current intervention is one that could be widely adopted by healthy children and adolescents on a population level. Likely more than adults, a child must be engaged to remain compliant with any type of physical intervention. Among contemporary youth, there are concerning trends of inactivity.⁽²⁰⁾ There are also disturbing trends within school systems, with fewer funds being allocated toward physical education classes compared to other activities, with inherent threats to optimal bone accretion and other aspects of health. Additionally, the authors highlight the point that girls tend to reduce their level of activity during puberty.⁽²¹⁾ In fact, the authors hypothesized that they would identify more robust benefits from an exercise program among the girls whom they studied (versus boys), a finding that bore out. At baseline, school-age girls in the current study were documented to be less physically active than their male peers, which in itself merits reflection regarding accompanying negative health ramifications. Public health efforts should particularly target girls in campaigns to encourage school children and teenagers to become more physically active.

In summary, considering which exercise regimen provides the optimal osteogenic stimulus for bone is a question of high interest and fervent investigation in the skeletal health field. Although the study of Detter and colleagues⁽⁸⁾ focused on growing children, the data are likely to be of interest to pediatric bone clinicians and investigators, as well as those whose focus is the adult skeleton. The amount of bone accrued by skeletal maturity is the primary contributor to peak bone mass, which, in turn, is a major determinant of osteoporosis and fractures later in life.^(1,10) Physical activity introduced during growth has the potential to reduce the burden of fractures during the elderly years.⁽¹⁵⁾ In fact, some experts consider osteoporosis to be a “pediatric disease” given that the underpinnings of this disease appear to occur during early to late adolescence. Paraphrasing the charge in the book of Ecclesiastes to “eat, drink, and be merry,”⁽²²⁾ the study by Detter and colleagues⁽⁸⁾ provides data to suggest that children should run and jump, as well! For growing children and adolescents, endorsement of this practice appears to be safe and may eventually lead to optimized peak bone mass, augmented bone size, and gains in skeletal strength, which in turn, may lower their future risk of osteoporosis and fractures as adults.

Disclosures

The author states that she has no conflicts of interest.

Acknowledgments

The author's work is supported by a grant from the National Institutes of Health, National Institute of Arthritis and Musculoskeletal and Skin Diseases (R01 AR060829).

References

- Ma NS, Gordon CM. Pediatric osteoporosis: where are we now? *J Pediatr*. 2012 Dec;161(6):983–90.
- Warden SJ, Galley MR, Hurd AL, et al. Cortical and trabecular bone benefits of mechanical loading are maintained long-term in mice independent of ovariectomy. *J Bone Miner Res*. 2014 May;29(5):1131–40.
- Warden SJ, Mantila Roosa SM, Kersh ME, et al. Physical activity when young provides lifelong benefits to cortical bone size, strength in men. *Proc Natl Acad Sci U S A*. 2014 Apr 8;111(14):5337–42.
- Nilsson M, Sundh D, Ohlsson C, Karlsson M, Mellström D, Lorentzon M. Exercise during growth and young adulthood is independently associated with cortical bone size and strength in old Swedish men. *J Bone Miner Res*. Forthcoming. Epub. 2014 Mar 2. DOI: 10.1002/jbmr.2212.
- Linden C, Ahlborg HG, Besjakov J, Gardsell P, Karlsson MK. A school curriculum-based exercise program increase bone mineral accrual and bone size in prepubertal girls: two-year-data from the pediatric osteoporosis prevention (POP) study. *J Bone Miner Res*. 2006 Jun;21(6):829–35.
- MacKelvie KJ, Petit MA, Khan KM, Beck TJ, McKay HA. Bone mass and structure are enhanced following a 2-year randomized controlled trial of exercise in prepubertal boys. *Bone*. 2004 Apr;34(4):755–64.
- McKay HA, MacLean L, Petit M, et al. “Bounce at the Bell”: a novel program of short bouts of exercise improves proximal femur bone mass in early pubertal children. *Br J Sports Med*. 2005 Aug;39(8):521–6.
- Detter F, Rosengren BE, Dencker M, Lorentzon M, Nilsson JA, Karlsson MK. A six-year exercise program improves skeletal traits without affecting fracture risk—a prospective controlled study in 2621 children. *J Bone Miner Res*. 2014;29(6):1325–1336.
- Jonsson B, Gardsell P, Johnell O, Redlund-Johnell I, Sernbo I. Remembering fractures: fracture registration and proband recall in southern Sweden. *J Epidemiol Community Health*. 1994 Oct;48(5):489–90.
- Crabtree NJ, Arabi A, Bachrach LK, et al. Dual energy X-ray absorptiometry interpretation and reporting in children and adolescents: the revised 2013 ISCD pediatric official positions. *J Clin Densitom*. 2014 Apr-Jun;17(2):225–42.
- Heinonen A, Oja P, Kannus P, et al. Bone mineral density in female athletes representing sports with different loading characteristics of the skeleton. *Bone*. 1995 Sep;17(3):197–203.
- Hughes JM, Petit MA. Biological underpinnings of Frost's mechanostat thresholds; the important role of osteocytes. *J Musculoskelet Neuronal Interact*. 2010 Jun;10(2):128–35.
- Davison KS, Siminoski K, Adachi JD, et al. Bone strength: the whole is greater than the sum of its parts. *Semin Arthritis Rheum*. 2006 Aug;36(1):22–31.
- Boreham CA, McKay HA. Physical activity in childhood and bone health. *Br J Sports Med*. 2011 Sep;45(11):877–9.
- Gunter KB, Almstedt HC, Janz KF. Physical activity in childhood may be the key to optimizing lifespan bone health. *Exerc Sport Sci Rev*. 2012 Jan;40(1):13–21.
- Khosla S, Melton LJ 3rd, Dekutoski MB, Achenbach SJ, Oberg AL, Riggs BL. Incidence of childhood distal forearm fractures over 30 years: a population-based study. *JAMA*. 2003 Sep 17;290(11):1479–85.
- Kirmani S, Christen D, van Lenthe GH, et al. Bone structure at the distal radius during growth. *J Bone Miner Res*. 2009 Jun;24(6):1033–42.
- Goulding A, Jones IE, Taylor RW, Manning PJ, Williams SM. More broken bones: a 4-year double cohort study of young girls with and without distal forearm fractures. *J Bone Miner Res*. 2000 Oct 15;15(10):2011–8.
- Goulding A, Grant AM, Williams SM. Bone and body composition of children and adolescents with repeated forearm fractures. *J Bone Miner Res*. 2005 Dec;20(12):2090–6.
- Myer GD, Faigenbaum AD, Straciolini A, et al. Exercise deficit disorder in youth: a paradigm shift toward disease prevention and comprehensive care. *Curr Sports Med Rep*. 2013 Jul-Aug;12(4):248–55.
- Knuth AG, Bielemann RM, Silva SG, et al. [Public knowledge on the role of physical activity in the prevention and treatment of diabetes and hypertension: a population-based study in southern Brazil]. *Cad Saude Publica*. 2009 Mar;25(3):513–20. Portuguese.
- Ecclesiastes. 8:15 (King James Version).

