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

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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

DOCTORAL DISSERTATION
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Faculty opponent
Associate Professor Diana Swolin-Eide, The Queen Silvia Children’s Hospital, Sahlgrenska University, Hospital Ostra, Gothenburg, Sweden
The Influence of Physical Activity on Musculoskeletal Traits and Fracture Risk at Growth

Abstract

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.

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.

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.

Therefore we can conclude that increased intracurricular exercise improves musculoskeletal traits without affecting the fracture risk.

Key words: Bone mass, BMD, BMC, Accelerometer, DXA, PQCT

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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
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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°/second in both genders and in the boys also the PT at 180°/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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
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<tr>
<td>BMC</td>
<td>Bone mineral content (g)</td>
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<td>BMD</td>
<td>Bone mineral density (g/cm²)</td>
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<td>BMI</td>
<td>Body mass index (kg/m²)</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CSA</td>
<td>Cross-sectional area (cm²)</td>
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<td>CSMI</td>
<td>Cross-sectional moment of inertia (cm⁴)</td>
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<td>CV</td>
<td>Coefficient of variation (%)</td>
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<td>DPA</td>
<td>Dual-photon absorptiometry</td>
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<td>DXA</td>
<td>Dual-energy X-ray absorptiometry</td>
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<td>Ex</td>
<td>Extension</td>
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<td>FI</td>
<td>Flexion</td>
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<td>FN</td>
<td>Femoral neck</td>
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<td>HSA</td>
<td>Hip structural analysis</td>
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<td>LS</td>
<td>Lumbar spine</td>
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<td>MVPA</td>
<td>Moderate to vigorous physical activity</td>
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<td>PA</td>
<td>Physical activity</td>
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<td>PBM</td>
<td>Peak bone mass</td>
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<td>PE</td>
<td>Physical education</td>
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<td>POP</td>
<td>Pediatric Osteoporosis Prevention (study)</td>
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<td>pQCT</td>
<td>Peripheral quantitative computed tomography</td>
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<td>QUS</td>
<td>Quantitative ultrasound</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<td>RR</td>
<td>Rate ratio</td>
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<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SPA</td>
<td>Single-photon absorptiometry</td>
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<tr>
<td>SSI</td>
<td>Strength strain index</td>
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<tr>
<td>TB</td>
<td>Total body</td>
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<tr>
<td>vBMD</td>
<td>Volumetric bone mineral density (g/cm³)</td>
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<td>VJH</td>
<td>Vertical jump height (cm)</td>
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<tr>
<td>VPA</td>
<td>Vigorous physical activity</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<td>Z</td>
<td>Section modulus (cm³)</td>
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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. 

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. 
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).

Bone is a vascularized and innervated tissue that undergoes constant remodeling and conformation to adapt to the needs of the skeleton. The hydroxyapatite molecule, \( \text{Ca}_3(\text{PO}_4)_3(\text{OH})_2 \), 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

![Fig. 1. Trabecular bone of the radius.](image-url)
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.

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).
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-hydoxyvitamin 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>
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<td>Normal bone mineral content – BMD T-score above –1 SD from the average adult value</td>
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<tr>
<td>Osteopenia – BMD T-score –1 to –2.5 SD from the average adult value</td>
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<tr>
<td>Osteoporosis – BMD T-score &lt; –2.5 SD from the average adult value</td>
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<tr>
<td>Manifest Osteoporosis – Osteoporosis and at least one fracture related to osteoporosis</td>
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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).
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).
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/cm²). 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/cm³), 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.
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

<table>
<thead>
<tr>
<th>Non-Ionizing methods</th>
<th>Ionizing methods</th>
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<tr>
<td>Gamma radiation</td>
<td>X-ray</td>
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<tr>
<td>Quantitative Ultrasound (QUS)</td>
<td>Single Photon Absorptiometry (SPA)</td>
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<tr>
<td>Magnetic Resonance Imaging (MRI)</td>
<td>Dual-Photon Absorptiometry (DPA)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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). \(Z=\text{CSMI divided by the outer radius}\). 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).
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 $\leq 10 \, \mu$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 $\mu$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 $SSI = \sum (d^2 \times A \times vBMD_{vox}/vBMD_{max})/d_{max}$ where $d$ is the diameter, $vBMD$ is the bone mineral density of the voxel, $A$ is the area of the voxel, $vBMD_{max}$ 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 $vBMD$ (59). Skeletal architecture is also subjected extra to remodeling through mechanical stimulation compared to $vBMD$ (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

<table>
<thead>
<tr>
<th>Markers of bone metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone formation</td>
</tr>
<tr>
<td>Procollagen Type I N-terminal propeptide (s-PINP), Procollagen Type I C-terminal propeptide (s-PICP), Osteocalcin, bone-specific Alkaline phosphatase (s-AP)</td>
</tr>
<tr>
<td>Bone resorption</td>
</tr>
<tr>
<td>Cathepsin K, Bone sialoprotein (s-BSP), Cathepsin L, total Pyrodinoline (u-PYD), free deoxypyridinoline (u-DPD), Tartrate resistant alkaline phosphatase (TRAP), C-telopeptide cross-link of type 1 collagen (CTX)</td>
</tr>
</tbody>
</table>
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 dynamometers measure isotonic strength. 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).
Figure 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

<table>
<thead>
<tr>
<th>Modifiable</th>
<th>Non-modifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedentary activity level</td>
<td>Age</td>
</tr>
<tr>
<td>Smoking</td>
<td>Family history of fracture</td>
</tr>
<tr>
<td>Medication</td>
<td>Asian or Caucasian ethnicity</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>Menarche after 15 years</td>
</tr>
<tr>
<td>Low vitamin D and calcium intake</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>Previous fracture</td>
</tr>
<tr>
<td>Use of oral glucocorticoids</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Low BMI</td>
<td></td>
</tr>
</tbody>
</table>

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 don 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,
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.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age and number of participants</th>
<th>Type of Exercise</th>
<th>Study duration</th>
<th>Effects on Bone increase in cases vs. Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gunter et al. 2008</td>
<td>22 girls 34 boys 7–8 years old</td>
<td>20 min high-moderate impact jumps×3/week</td>
<td>7 months</td>
<td>BMC: FN</td>
</tr>
<tr>
<td>Wiebe et al. 2008</td>
<td>42 girls 6–10 years</td>
<td>50 high-moderate impact jumps×3/week</td>
<td>7 months</td>
<td>BMD: No effects</td>
</tr>
<tr>
<td>Bradney et al. 1998</td>
<td>38 boys 10.4±0.4</td>
<td>Weight bearing 30 min ×3/week</td>
<td>8 months</td>
<td>BMD: TB, LS, Legs CT: legs</td>
</tr>
<tr>
<td>MacKay et al. 2000</td>
<td>144 children 6.9–10.2 years</td>
<td>High-moderate impact 10–30 three times a week</td>
<td>8 months</td>
<td>BMD: Tr</td>
</tr>
<tr>
<td>Fuchs et al. 2001</td>
<td>99 children 7.6±0.2 years</td>
<td>High impact jumping</td>
<td>7 months</td>
<td>BMC: FN, LS</td>
</tr>
<tr>
<td>Petit et al. 2002</td>
<td>68 children 10.0±0.6 years</td>
<td>High impact 10–12 min×3/week</td>
<td>7 months</td>
<td>BMD: LS BW: FN</td>
</tr>
<tr>
<td>Van Langendonck et al. 2003</td>
<td>42 children 8.7±0.7 years</td>
<td>High impact ×3/week</td>
<td>9 months</td>
<td>BMC: PF, FN</td>
</tr>
<tr>
<td>Specker et al.</td>
<td>178 girls 3.9±0.6 years</td>
<td>High impact 30 min ×5/week</td>
<td>12 months</td>
<td>BMC: legs</td>
</tr>
<tr>
<td>Study</td>
<td>Gender</td>
<td>Age Mean ± SD</td>
<td>Activity Type</td>
<td>Duration (min/week)</td>
</tr>
<tr>
<td>------------------------</td>
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<td>---------------</td>
<td>---------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>MacKelvie et al. 2004</td>
<td>64 boys</td>
<td>10.2±0.2 years</td>
<td>High impact</td>
<td>10–12 min×3/week</td>
</tr>
<tr>
<td>Laing et al. 2005</td>
<td>143 girls</td>
<td>10.2±0.2 years</td>
<td>Gymnastics</td>
<td>60 min/week</td>
</tr>
<tr>
<td>Valdimarsson et al. 2005</td>
<td>103 girls</td>
<td>7.7±0.6 years</td>
<td>PE. Classes 40</td>
<td>min×5/week</td>
</tr>
<tr>
<td>Linden et al. 2006</td>
<td>99 girls</td>
<td>7.6±0.6 years</td>
<td>PE. Classes 40</td>
<td>min×5/week</td>
</tr>
<tr>
<td>Linden et al. 2007</td>
<td>138 boys</td>
<td>7.8±0.6 years</td>
<td>PE. Classes 40</td>
<td>min×5/week</td>
</tr>
<tr>
<td>Alwis et al. 2008</td>
<td>137 boys</td>
<td>7.8±0.6 years</td>
<td>PE. Classes 40</td>
<td>min×5/week</td>
</tr>
<tr>
<td>Alvis et al. 2008</td>
<td>99 girls</td>
<td>7.6±0.6 years</td>
<td>PE. Classes 40</td>
<td>min×5/week</td>
</tr>
<tr>
<td>Hasselström et al. 2008</td>
<td>349 children</td>
<td>6.8±0.4 years</td>
<td>PE. Classes 45</td>
<td>min×2/week</td>
</tr>
<tr>
<td>Greene et al. 2009</td>
<td>42 girls</td>
<td>6–10 years</td>
<td>50 high-moderate impact jumps×3/week</td>
<td>7 months</td>
</tr>
<tr>
<td>Meyer et al. 2011</td>
<td>158 children</td>
<td>8.7±2.1 years</td>
<td>Extra PE classes 45 in including 10 min jumping×2/week</td>
<td>9 months</td>
</tr>
</tbody>
</table>
### Tanner 2–3 (early pubertal)

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Age (years ± SD)</th>
<th>Impact</th>
<th>Duration (months)</th>
<th>Bone Density (BMC/BMD)</th>
<th>Additional Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morris et al. 1997</td>
<td>71 girls</td>
<td>8.7±2.1</td>
<td>Moderate impact</td>
<td>10 months</td>
<td>BMC: TB, LS, FN, PF</td>
<td>BMD: TB, LS, FN</td>
</tr>
<tr>
<td>Heinonen et al. 2000</td>
<td>58 girls</td>
<td>11.0±0.9</td>
<td>High impact 20 min×2/week</td>
<td>9 months</td>
<td>BMC: LS, FN</td>
<td></td>
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<tr>
<td>MacKelvie et al. 2001</td>
<td>107 girls</td>
<td>11.0±0.9</td>
<td>High impact 10–12 min×3/week</td>
<td>7 months</td>
<td>BMC: LS</td>
<td>BMD: LS, FN</td>
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<tr>
<td>Petit et al. 2002</td>
<td>106 girls</td>
<td>10.5±0.6</td>
<td>High impact 10–12 min×3/week</td>
<td>7 months</td>
<td>BMD: Tr, FN</td>
<td>HSA: Z CT: FN</td>
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<tr>
<td>Iuliano-Burns et al. 2003</td>
<td>64 girls</td>
<td>8.8±0.1</td>
<td>Moderate impact 20 min×3/week</td>
<td>9 months</td>
<td>BMC: LS, Lower leg</td>
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<td>MacKelvie et al. 2003</td>
<td>75 girls</td>
<td>9.9±0.6</td>
<td>High impact 10–12 min×3/week</td>
<td>20 months</td>
<td>BMC: FN, LS</td>
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<tr>
<td>McKay et al. 2005</td>
<td>122 children</td>
<td>10.1±0.5</td>
<td>Jumping 3×3 min three times/week</td>
<td>8 months</td>
<td>BMC: PF, Tr BA: PF</td>
<td>No effects HSA</td>
</tr>
<tr>
<td>Courteix et al. 2005</td>
<td>113 girls</td>
<td>8–13 years</td>
<td>Exercised mean 7.2 hrs/week vs. 1.2 hrs/week</td>
<td>12 months</td>
<td>BMD: TB, LS, FN</td>
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<td>Macdonald et al. 2008</td>
<td>197 girls</td>
<td>10.2±0.6</td>
<td>High impact 15 min×5/week</td>
<td>11 months</td>
<td>Boys BMC: LS, TB</td>
<td>Girls BMC: FN HSA: Z</td>
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<td>Study</td>
<td>Participants</td>
<td>Age</td>
<td>Training Details</td>
<td>Outcome</td>
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<tr>
<td>Löfgren et al. 2011</td>
<td>92 girls, 131 boys</td>
<td>7.8±0.6 years</td>
<td>PE classes 40 min×5/week /months Boys BMC: LS BW: LS HSA: No effects Girls BMC: LS, FN BW: LS HSA: CSA</td>
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<td>Meyer et al. 2011</td>
<td>133 children</td>
<td>11.1±0.6 years</td>
<td>Extra PE classes 45 in including 10 min jumping×2/week 9 months Boys BMC: TB, LS, FN</td>
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<td>Löfgren et al. 2012</td>
<td>96 girls, 125 boys</td>
<td>7.8±0.6 years</td>
<td>PE classes 40 min×5/week Boys BMC: LS BW: FN HSA: No effects Girls BMC: TB, LS, FN, Tr BW: LS, FN HSA: CSA, Z, CSMI</td>
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<td>Anliker et al. 2012</td>
<td>10 girls, 12 boys</td>
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<td>Jumping 10 min×2/week No effects</td>
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<td><strong>Tanner 4–5 (late pubertal)</strong></td>
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<td>Blimkie et al. 1996</td>
<td>36 girls, 16.3±0.3 years</td>
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<td>Weight training×3/week 7 months No effects</td>
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<tr>
<td>Witzke et al. 2000</td>
<td>53 girls, 14.6±0.5 years</td>
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<td>Resistance training 30–45 min ×3/week 9 months No effects</td>
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<tr>
<td>Heinonen et al. 2000</td>
<td>68 girls, 13.3±0.9 years</td>
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<td>High impact 20 min ×2/week 9 months No effects</td>
<td></td>
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<tr>
<td>Nichols et al. 2001</td>
<td>67 girls, 15.9±0.1 years</td>
<td></td>
<td>Resistance training 30–45 min ×3/week 15 months BMD: FN</td>
<td></td>
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</tbody>
</table>
Detter et al. 2013
96 girls
125 boys
7.9±0.6 years
PE classes 40 min×5/week 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 40 min×5/week 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 40 min×4/week 48 months Boys
BMC: FN, Spine Girls
BMD: FN
No effects

Stear et al. 2003
144 girls
17.3±0.3 years
Moderate impact 45 min×3/week 16 months ± calcium Girls
BMC: LS, TB, PF, TR

Weeks 2003
44 girls
37 boys
13.8±0.4 years
High impact jumping 10 min×2/week 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).
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).
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 digitilized 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 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

#### Study Material

<table>
<thead>
<tr>
<th>Gender</th>
<th>Paper I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girls</td>
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<tr>
<td>Invited</td>
<td>61 Cases</td>
</tr>
<tr>
<td></td>
<td>158 Controls</td>
</tr>
<tr>
<td></td>
<td>89 Cases</td>
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<td></td>
<td>169 Controls</td>
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<tr>
<td>Accepted</td>
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<tr>
<td></td>
<td>55 accepted One girl to young 6 girls declined</td>
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<tr>
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<td>64 Girls accepted 19 girls declined 1 medicated</td>
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<td></td>
<td>84 boys accepted 6 boys declined 2 medicated</td>
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<td>68 accepted 12 boys excluded</td>
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<tr>
<td>Included</td>
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<td></td>
<td>48 girls were evaluated</td>
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<td>44 girls were evaluated</td>
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<td>76 boys were evaluated</td>
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<td>55 boys were evaluated</td>
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#### Study Material

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<td>76 boys were evaluated</td>
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<tr>
<td></td>
<td>54 boys were evaluated</td>
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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 weight/height². 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, cm²), section modulus (Z, cm³) 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 physeal plate in both extremities and 4% and 66% from the distal radius physeal 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 PTEx60 6.6%, for PTFl60 12.1%, for PTEx180 12.3% and for PTFl180 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 ± 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 repeated 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 intracurricular 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/cm²), 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
“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 möjlichen ger upphov till fler olyckor och frakturer. Man vet inte heller om ökad idrott i en oselekttrade 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 lektionstimmer per vecka. J olika studier utvärderar vi sedan effekten av daglig skolgymnastik på frakturrisk och utvecklingen av skelett och muskulatur. Barnen var vid studiens inledning 6–9 år och ingen hade då kommit in i puberteten. På Ångslättsskolan i Bunkfloostrand, 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 lektionstimmer 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 uppföljningsperioder 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 hälbden. 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 benmassa hos både flickor och pojkar.

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

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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 before¹⁹⁻²¹ 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,¹⁵⁻¹⁸ so also when we have reported the short-term data in the Malmö Prospective Pediatric Osteoporosis Prevention (POP) Study cohort,¹⁶⁻¹⁸ 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 adults²⁰ and children²¹⁻²³ is associated with fractures, there is no causal relationship. Athletes, despite high

ORIGINAL ARTICLE

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bone mass, also have a high fracture risk owing to more exposure to trauma, and the fracture risk is also high in physically active children. 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.

**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. 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. 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. Fewer than 3% of fractures in the target population were missed when this system was used. The classification system is well validated and has been used in epidemiologic studies for decades, and the system was described in detail previously.

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. 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.

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. Self-assessed Tanner stage estimated pubertal maturity was measured. 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. The widths of the third lumbar vertebra and the femoral neck were evaluated on the lumbar spine and hip scans. The hip structural analysis (HSA) software, provided by Lunar Corp. was applied to the hip scan, evaluating femoral neck cross-sectional area (CSA, cm²), section modulus (Z, cm³), and cross-sectional moment of inertia (CSMI, cm⁴). Values 3 SD above or below the mean were excluded as being biologically unlikely in accordance with Beck and colleagues. 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).
Boys
Girls
All individuals

osteogenic activities. (13, 14) and 10,000 cpm also was included in order to capture the most Fracture Epidemiology in Children in the Exercise Intervention Group and the Control Group

Table 1.

<table>
<thead>
<tr>
<th>Participants (n)</th>
<th>Fractures (n)</th>
<th>Person-years</th>
<th>Fractures/1000 person-years [mean (95% CI)]</th>
<th>Rate ratio [mean (95% CI)]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All individuals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention group</td>
<td>808</td>
<td>37</td>
<td>2129</td>
<td>17.4 (12.2, 23.9)</td>
</tr>
<tr>
<td>Control group</td>
<td>1587</td>
<td>71</td>
<td>4430</td>
<td>16.0 (12.5, 20.2)</td>
</tr>
<tr>
<td><strong>Girls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention group</td>
<td>362</td>
<td>12</td>
<td>935</td>
<td>12.8 (6.6, 22.4)</td>
</tr>
<tr>
<td>Control group</td>
<td>780</td>
<td>33</td>
<td>2187</td>
<td>15.1 (10.4, 21.2)</td>
</tr>
<tr>
<td><strong>Boys</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention group</td>
<td>446</td>
<td>25</td>
<td>1194</td>
<td>20.9 (13.6, 30.9)</td>
</tr>
<tr>
<td>Control group</td>
<td>807</td>
<td>38</td>
<td>2243</td>
<td>16.9 (12.0, 23.3)</td>
</tr>
</tbody>
</table>

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

Results

There were 108 fractures during the study period (57 forearm, 20 hand, 14 humerus, 2ibia, 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
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. 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. 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 and children. This study also supports published studies with shorter durations such as the previous POP reports and studies with a similar follow-up period but with bone mass only evaluated by a peripheral DEXA device. 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. 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, even if performed only for a short duration each day (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. 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. 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. 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 and adults owing to a higher exposure to trauma. 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. 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.

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
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 highlights the problem of using a 2D imaging

<table>
<thead>
<tr>
<th>Lifestyle factors at baseline</th>
<th>Intervention group (n = 48)</th>
<th>Control group (n = 44)</th>
<th>p Value</th>
<th>Intervention group (n = 76)</th>
<th>Control group (n = 55)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excluding dairy products</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1.0</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Drinking coffee</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1.0</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Smoking</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1.0</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Alcohol</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1.0</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Tried to lose weight</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>.3</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>.4</td>
</tr>
<tr>
<td>Current disease</td>
<td>3 (7%)</td>
<td>1 (2%)</td>
<td>.3</td>
<td>7 (9%)</td>
<td>3 (6%)</td>
<td>.4</td>
</tr>
<tr>
<td>Ongoing medication</td>
<td>5 (11%)</td>
<td>2 (5%)</td>
<td>.3</td>
<td>10 (13%)</td>
<td>4 (7%)</td>
<td>.3</td>
</tr>
<tr>
<td>Earlier medication</td>
<td>4 (9%)</td>
<td>2 (5%)</td>
<td>.5</td>
<td>3 (4%)</td>
<td>5 (9%)</td>
<td>.2</td>
</tr>
<tr>
<td>Fractures</td>
<td>6 (13%)</td>
<td>5 (12%)</td>
<td>.8</td>
<td>6 (8%)</td>
<td>6 (11%)</td>
<td>.6</td>
</tr>
<tr>
<td>Tanner stage 1/2/3/4/5</td>
<td>48/0/0/0/0</td>
<td>44/0/0/0/0</td>
<td>1.0</td>
<td>76/0/0/0/0</td>
<td>55/0/0/0/0</td>
<td>1.0</td>
</tr>
<tr>
<td>Organized physical activity (h/wk)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>School curriculum</td>
<td>3.3</td>
<td>1.0</td>
<td>&lt;.001</td>
<td>3.3</td>
<td>1.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Outside the school</td>
<td>0.7 (0.7)</td>
<td>1.3 (1.7)</td>
<td>&lt;.03</td>
<td>1.7 (1.6)</td>
<td>1.3 (1.3)</td>
<td>.2</td>
</tr>
<tr>
<td>Total physical activity</td>
<td>4.0 (0.7)</td>
<td>2.3 (1.7)</td>
<td>&lt;.001</td>
<td>5.0 (1.6)</td>
<td>2.3 (1.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Accelerometer data after 2 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numbers</td>
<td>(n = 41)</td>
<td>(n = 40)</td>
<td></td>
<td>(n = 72)</td>
<td>(n = 55)</td>
<td></td>
</tr>
<tr>
<td>Recording time per day (h/d)</td>
<td>11.8 (1.4)</td>
<td>12.0 (1.3)</td>
<td>.5</td>
<td>11.7 (1.3)</td>
<td>12.7 (1.4)</td>
<td>.02</td>
</tr>
<tr>
<td>Mean activity (min/d)</td>
<td>644 (192)</td>
<td>590 (121)</td>
<td>.1</td>
<td>770 (267)</td>
<td>728 (211)</td>
<td>.3</td>
</tr>
<tr>
<td>&gt;3 METS (min/d)</td>
<td>193 (47)</td>
<td>185 (37)</td>
<td>.4</td>
<td>211 (55)</td>
<td>209 (45)</td>
<td>.8</td>
</tr>
<tr>
<td>&gt;6 METS (min/d)</td>
<td>34 (15)</td>
<td>35 (13)</td>
<td>.8</td>
<td>44 (21)</td>
<td>48 (19)</td>
<td>.2</td>
</tr>
<tr>
<td>&gt;5000 mean cpm (min/d)</td>
<td>17.9 (9.9)</td>
<td>16.8 (8.5)</td>
<td>.6</td>
<td>23 (13)</td>
<td>24 (13)</td>
<td>.6</td>
</tr>
<tr>
<td>&gt;6000 mean cpm (min/d)</td>
<td>12.5 (7.6)</td>
<td>10.5 (6.2)</td>
<td>.2</td>
<td>16 (10)</td>
<td>15 (9)</td>
<td>.7</td>
</tr>
<tr>
<td>&gt;10000 mean cpm (min/d)</td>
<td>2.6 (2.5)</td>
<td>1.0 (1.2)</td>
<td>&lt;.001</td>
<td>4 (3)</td>
<td>2 (3)</td>
<td>.01</td>
</tr>
</tbody>
</table>

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.
<table>
<thead>
<tr>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Girls</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Anthropometrics</strong></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>Lean mass (kg)</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
</tr>
<tr>
<td>Bone mineral content (BMC, g)</td>
</tr>
<tr>
<td>Total body</td>
</tr>
<tr>
<td>Lumbar spine</td>
</tr>
<tr>
<td>Femoral neck</td>
</tr>
<tr>
<td><strong>Boys</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Anthropometrics</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>Lean mass (kg)</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
</tr>
<tr>
<td>Bone mineral content (BMC, g)</td>
</tr>
<tr>
<td>Total body</td>
</tr>
<tr>
<td>Lumbar spine</td>
</tr>
<tr>
<td>Femoral neck</td>
</tr>
<tr>
<td>Bone width (cm)</td>
</tr>
<tr>
<td>Third lumbar vertebra</td>
</tr>
<tr>
<td>Femoral neck</td>
</tr>
<tr>
<td>HSA</td>
</tr>
<tr>
<td>CSA (cm²)</td>
</tr>
<tr>
<td>Z (cm³)</td>
</tr>
<tr>
<td>CSMI (cm⁴)</td>
</tr>
</tbody>
</table>

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.
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


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

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/cm²) and bone area (mm²) 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/cm³) 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/cm², 0.005–0.019) and boys (difference 0.01 g/cm², 0.001–0.008) in the intervention group. Intervention girls also had higher gain in femoral neck area (difference 0.04 mm², 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 mm², 2.4–31.3), and larger radial cross-sectional area (difference 11.0 mm², 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 endpoint 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,
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 (POPP) 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 POPP study, where incidence 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 6.5–7.7) and 73 boys with a mean age of 7.8 ± 0.6 years (range 6.7–8.7). Forty-six 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%.
At the 5-year follow-up, bone mineral content (BMC), volumetric bone mineral density (vBMD, grams per centimeter cubed), and structural parameters of the tibia and radius were also measured by peripheral quantitative computed tomography (pQCT, XCT 2000, Stratec, Pforzheim, Germany) in the 195 children who accepted this new measurement. A scout view determined the 4 and 38 % level from the distal tibial physeal plate in both extremities and 4 and 66 % from the distal radius physeal plate. These regions were used to measure BMC, vBMD, cortical area, cross-sectional area (CSA), and bone strength strain index regions were used to measure BMC, vBMD, cortical area, cross-sectional area (CSA), and bone strength strain index with respect to torsion (polar SSI, millimeters cubed). These estimates have previously been shown to correlate with vBMD 3.4 %, tibial cortical vBMD 1.4 %, and radial vBMD 0.5 %, tibial cortical area 1.1 %, radial trabecular vBMD 3.4 %, radial cortical vBMD 1.4 %, and radial cortical area 4.6 %.

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

Accelerometric data were averaged over a period called an “epoch,” representing 10 s. Mean activity was defined as the total accelerometer counts per minute (cpm) of monitoring, 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 >1,000 cpm for MVPA and >3,500 cpm for VPA [20]. Activity above 5000, 6000, and 10,000 cpm was also registered in order to capture the most intense activities, known to be highly osteogenic [11, 12].

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

### Results

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

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

<table>
<thead>
<tr>
<th>Participants (n)</th>
<th>Fractures (n)</th>
<th>Person-years (years)</th>
<th>Fractures/10,000 person-years (95 % CI)</th>
<th>Risk ratio (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Both genders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases 808</td>
<td>63</td>
<td>3,152</td>
<td>20.0 (15.4, 25.6)</td>
<td>1.08 (0.79, 1.47)</td>
</tr>
<tr>
<td>Controls 1,587</td>
<td>125</td>
<td>6,761</td>
<td>18.5 (15.4, 22.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Girls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases 362</td>
<td>23</td>
<td>1,382</td>
<td>16.6 (10.6, 25.0)</td>
<td>1.03 (0.60, 1.69)</td>
</tr>
<tr>
<td>Controls 780</td>
<td>54</td>
<td>3,330</td>
<td>16.2 (12.2, 21.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Boys</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases 446</td>
<td>40</td>
<td>1,770</td>
<td>22.6 (16.1, 30.8)</td>
<td>1.09 (0.72, 1.62)</td>
</tr>
<tr>
<td>Controls 807</td>
<td>71</td>
<td>3,431</td>
<td>20.7 (16.6, 26.1)</td>
<td></td>
</tr>
</tbody>
</table>
The mean annual gain in spine BMD (difference 0.01 g/cm², 0.01–0.02), FN BMC (difference 0.07 g, 0.009–0.013), and FN area (difference 0.04 mm², 0.01–0.08) was larger in girls in the intervention group than in the control group (Table 4). Girls in the intervention group also had a larger tibial cortical BMC at follow-up (difference 0.18 g, 0.02–0.35), larger tibial cortical area (difference 17 mm², 2.4–31.3), and larger radial CSA (difference 11.0 mm², 0.6–21.4) than girls in the control group, resulting in a larger SSIX in both the tibial diaphysis (difference 61.8, 3.3–120.3) and the radial diaphysis (difference 14.8, 2.8–26.9) (Table 5).

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

**Discussion**

This study should not be misinterpreted as just another study confirming that osteogenic training in motivated children improves bone mass. This is already known. Our study instead adds information when reporting that an...
extended, moderately intense general exercise intervention program in the pre- to pubertal years improves bone mass and in girls also skeletal architecture, benefits that are retained in the long term. The structural benefits are probably of clinical relevance as individuals with spine fractures have smaller lumbar vertebrae but normal FN size, while individuals with hip fractures have normal vertebral body size but smaller FN size than nonfractured 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 evaluating 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

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

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

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.
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

<table>
<thead>
<tr>
<th>Table 4</th>
<th>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)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Girls</strong></td>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td></td>
<td>Cases (n = 48)</td>
</tr>
<tr>
<td>Age</td>
<td>7.7 (7.5, 7.8)</td>
</tr>
<tr>
<td>Anthropometrics</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>27.8 (26.2, 29.5)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>128.3 (126.7, 129.9)</td>
</tr>
<tr>
<td>Lean mass (kg)</td>
<td>19.9 (19.2, 20.6)</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>5.5 (4.3, 6.6)</td>
</tr>
<tr>
<td>BMC (g)</td>
<td></td>
</tr>
<tr>
<td>Total body</td>
<td>943.6 (899.4, 987.8)</td>
</tr>
<tr>
<td>Spine</td>
<td>85.1 (79.6, 90.6)</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>2.6 (2.4, 2.8)</td>
</tr>
<tr>
<td>Bone size (cm² or cm)</td>
<td></td>
</tr>
<tr>
<td>Femoral neck area</td>
<td>3.6 (3.4, 3.7)</td>
</tr>
<tr>
<td>L3 width</td>
<td>2.9 (2.8, 2.9)</td>
</tr>
</tbody>
</table>

| **Boys** | **Baseline** | **Average annual changes** |
| | Cases (n = 73) | Controls (n = 52) | P | Cases (n = 73) | Controls (n = 52) | P |
| 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 |
| Bone size (cm² 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
Some authors have therefore advocated the use of no or only a minor effect on bone mass, especially when activity, low-impact sports, and endurance sports may have studies suggested that lower levels of physical activities may influence skeletal growth. Some previous our data show that general moderately intense physical activities may influence skeletal growth. Some previous studies have suggested that lower levels of physical activity, low-impact sports, and endurance sports may have no or only a minor effect on bone mass, especially when these types of exercises are practiced for long durations [30–32]. Some authors have therefore advocated the use of specifically designed osteogenic programs with high intensity [30–32]. This could be problematic as an intervention must be at a suitable general level and with a variety of activities in order to facilitate the participation of all children if the program is to be launched as a strategy to improve bone strength at the population level. However, our study shows that such an intervention program can be used without losing the osteogenic effect, a view supported by the accelerometric data in this report, which show a higher duration of high-impact activities in the intervention than in the control group.

This report also indicates that girls gain more obvious skeletal benefits than boys from the intervention. This could be due to boys in general having higher leisure-time 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 finding. 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

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### 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)

<table>
<thead>
<tr>
<th></th>
<th>Girls Cases (n = 45)</th>
<th>Controls (n = 39)</th>
<th>P</th>
<th>Boys Cases (n = 67)</th>
<th>Controls (n = 44)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tibia trabecular (4 %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trabecular vBMD (mg/cm³)</td>
<td>216 (208, 224)</td>
<td>213 (202, 223)</td>
<td>0.62</td>
<td>211 (204, 218)</td>
<td>217 (208, 225)</td>
<td>0.32</td>
</tr>
<tr>
<td>Tibia cortical (38 %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical BMC (g)</td>
<td>2.8 (2.7, 2.9)</td>
<td>2.6 (2.5, 2.7)</td>
<td>0.03</td>
<td>2.8 (2.7, 2.9)</td>
<td>2.9 (2.8, 3.0)</td>
<td>0.47</td>
</tr>
<tr>
<td>Cortical vBMD (mg/cm³)</td>
<td>1.059 (1.047, 1.072)</td>
<td>1.056 (1.047, 1.066)</td>
<td>0.72</td>
<td>1.011 (1.001, 1.021)</td>
<td>1.016 (1.007, 1.026)</td>
<td>0.50</td>
</tr>
<tr>
<td>Cortical area (mm²)</td>
<td>236 (225, 245)</td>
<td>219 (208, 229)</td>
<td>0.02</td>
<td>246 (236, 257)</td>
<td>252 (241, 262)</td>
<td>0.49</td>
</tr>
<tr>
<td>Total CSA (mm³)</td>
<td>356 (342, 370)</td>
<td>339 (325, 353)</td>
<td>0.09</td>
<td>372 (359, 387)</td>
<td>382 (366, 398)</td>
<td>0.41</td>
</tr>
<tr>
<td>Polar SSI (cm³)</td>
<td>1.135 (1.055, 1.216)</td>
<td>1.050 (0.977, 1.124)</td>
<td>0.13</td>
<td>1.194 (1.126, 1.261)</td>
<td>1.222 (1.142, 1.303)</td>
<td>0.59</td>
</tr>
<tr>
<td>SSIX</td>
<td>618 (575, 662)</td>
<td>557 (518, 595)</td>
<td>0.04</td>
<td>651 (612, 690)</td>
<td>652 (611, 694)</td>
<td>0.97</td>
</tr>
<tr>
<td>Radius trabecular (4 %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trabecular vBMD 4 % (mg/mm³)</td>
<td>180 (168, 191)</td>
<td>179 (166, 192)</td>
<td>0.96</td>
<td>184 (177, 192)</td>
<td>192 (183, 202)</td>
<td>0.96</td>
</tr>
<tr>
<td>Radius cortical (66 %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical BMC (g)</td>
<td>0.8 (0.7, 0.8)</td>
<td>0.7 (0.7, 0.8)</td>
<td>0.11</td>
<td>0.8 (0.7, 0.8)</td>
<td>0.8 (0.7, 0.8)</td>
<td>0.55</td>
</tr>
<tr>
<td>Cortical vBMD (mg/mm³)</td>
<td>1.020 (1.007, 1.032)</td>
<td>1.020 (1.007, 1.032)</td>
<td>0.99</td>
<td>987 (977, 997)</td>
<td>998 (986, 1,010)</td>
<td>0.19</td>
</tr>
<tr>
<td>Cortical area (mm²)</td>
<td>59.3 (56.1, 62.5)</td>
<td>56.9 (53.5, 60.3)</td>
<td>0.86</td>
<td>58.4 (55.2, 61.6)</td>
<td>57.9 (54.5, 61.4)</td>
<td>0.30</td>
</tr>
<tr>
<td>Total CSA 66 % (mm³)</td>
<td>130 (122, 139)</td>
<td>119 (113, 125)</td>
<td>0.04</td>
<td>140 (133, 147)</td>
<td>133 (124, 142)</td>
<td>0.20</td>
</tr>
<tr>
<td>Polar SSI (cm³)</td>
<td>228 (209, 247)</td>
<td>201 (108, 215)</td>
<td>0.11</td>
<td>241 (225, 258)</td>
<td>227 (207, 247)</td>
<td>0.26</td>
</tr>
<tr>
<td>SSIX</td>
<td>121 (62.7, 204)</td>
<td>106 (62.8, 154)</td>
<td>0.02</td>
<td>125 (65.3, 238)</td>
<td>122 (56.6, 222)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Statistically significant differences are highlighted in bold.
We are therefore of the opinion that the risk of selection bias must be regarded as minor. Also, it would have been preferable to the school-based grouping used, but, as previously discussed, it would have been impossible to achieve in practice because of resistance from parents, pupils, and teachers [2, 18, 19, 26]. The participation rate for the controls randomized for measurements was lower than that for the intervention school. However, as our dropout analyses revealed no group differences at baseline, the risk of selection bias must be regarded as minor. Also, it would have been preferable to have longitudinal pQCT data to evaluate changes in bone structure and not only to rely on DXA-derived data for bone size. It would have been advantageous too if we had been able to report fractures that had occurred during physical education classes in school separately and fractures during other activities separately, data not possible to find in the referrals or reports. Finally, when we gathered the accelerometric data we had only access to an apparatus that could capture 4 days in a row. It would have been advantageous to use modern accelerometers that could capture a period of up to a month and have measurements performed on several different occasions during the 5-year study period. It would also have been advantageous if we had had information about play activities and extraprotocol physical activity on a voluntary basis.

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

Acknowledgement We thank the teachers and students for participating in the study. 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.

References


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

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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/cm2) 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.1–3 This is of clinical relevance because skeletal integrity depends on both bone mass and skeletal geometry.4 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.11,14 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,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),17 which is of clinical importance because high bone mineral density (BMD) is associated with low fracture risk.12,17–19 and half of the variance in BMD at age 70 years seems to be predicted by PBM.19 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.5,10,24–30 Only one study had an intervention longer than 36 months.30 Furthermore, there is no consensus as to whether moderately intense interventions on a population-based level, without...
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,(15,16) and girls, therefore, ought to hypotheti-
cally 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 intervention.(37,38)
Finally, there are reports suggesting that a high level of physical
activity is associated with a high fracture risk; (19) 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,(6,8,11,40) put 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
decided 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
level 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 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. Low-energy trauma
coresponded 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 slider; 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 measure-
ments 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 annu-
ally 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 measure-
ments, 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 ± 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/
cm²) 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. Further, 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. 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 physeal plate in both extremities and 4% and 66% from the distal radius physeal 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; mm²). These estimates have been shown to correlate with mechanical strength in long bones. Daily calibration of the apparatus was done with a standard phantom. The CV%, evaluated by duplicate measurements in 13 healthy children, was for 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 MTL; 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. 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. The activity greater than 5000, 6000, and 10,000 cpm was also captured to register the most intense activities, known to be most osteogenic. 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 4000 cpm.

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. 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.

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

<table>
<thead>
<tr>
<th>Participants (n)</th>
<th>Fractures (n)</th>
<th>Person-years (years)</th>
<th>Fractures/1000 person-years (95% CI)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both sexes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>917</td>
<td>86</td>
<td>3969</td>
<td>21.67 (17.33, 26.76)</td>
</tr>
<tr>
<td>Controls</td>
<td>1704</td>
<td>159</td>
<td>8245</td>
<td>19.28 (16.40, 22.53)</td>
</tr>
<tr>
<td>Girls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>417</td>
<td>33</td>
<td>1752</td>
<td>18.84 (12.97, 26.45)</td>
</tr>
<tr>
<td>Controls</td>
<td>835</td>
<td>65</td>
<td>4068</td>
<td>15.98 (12.33, 20.37)</td>
</tr>
<tr>
<td>Boys</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>500</td>
<td>53</td>
<td>2217</td>
<td>23.91 (17.91, 31.27)</td>
</tr>
<tr>
<td>Controls</td>
<td>869</td>
<td>94</td>
<td>4177</td>
<td>22.50 (18.19, 27.54)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Fracture distribution</th>
<th>Girls (n = 417)</th>
<th>Controls (n = 835)</th>
<th>Boys (n = 500)</th>
<th>Controls (n = 869)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>No. (%)</td>
<td>Controls</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Distal forearm</td>
<td>14</td>
<td>(42.4)</td>
<td>30</td>
<td>(40.6)</td>
</tr>
<tr>
<td>Proximal humerus</td>
<td>2</td>
<td>(6.1)</td>
<td>4</td>
<td>(6.2)</td>
</tr>
<tr>
<td>Other upper extremity</td>
<td>11</td>
<td>(33.3)</td>
<td>24</td>
<td>(36.9)</td>
</tr>
<tr>
<td>Vertebral</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Pelvis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Ribs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Hip</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tibial condyle</td>
<td>1</td>
<td>(3.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other lower extremity</td>
<td>5</td>
<td>(15.2)</td>
<td>6</td>
<td>(9.2)</td>
</tr>
<tr>
<td>Other fractures</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total number</td>
<td>33</td>
<td>65</td>
<td>53</td>
<td>98</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of trauma</th>
<th>Girls (n = 417)</th>
<th>Controls (n = 835)</th>
<th>Boys (n = 500)</th>
<th>Controls (n = 869)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-energy related</td>
<td>15</td>
<td>(45.5)</td>
<td>22</td>
<td>(33.8)</td>
</tr>
<tr>
<td>Moderate-energy related</td>
<td>16</td>
<td>(48.5)</td>
<td>35</td>
<td>(53.8)</td>
</tr>
<tr>
<td>Low-energy related</td>
<td>2</td>
<td>(6.0)</td>
<td>8</td>
<td>(12.4)</td>
</tr>
<tr>
<td>No information</td>
<td>2</td>
<td>(6.0)</td>
<td>8</td>
<td>(12.4)</td>
</tr>
</tbody>
</table>
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/cm$^2$), and bone area (cm$^2$) 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)

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

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

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

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

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Between-group differences baseline</th>
<th>Annual changes</th>
<th>Between-group differences annual changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=78)</td>
<td>(n=52)</td>
<td>p1Value</td>
<td>p1Value</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=78</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(n=52)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean difference (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lean mass</td>
<td>19.67 (2.32)</td>
<td>20.25 (2.70)</td>
<td>0.10 (−0.8, 0.9)</td>
</tr>
<tr>
<td></td>
<td>Fat mass</td>
<td>5.15 (3.44)</td>
<td>5.05 (3.30)</td>
<td>0.10 (−1.2, 1.4)</td>
</tr>
<tr>
<td></td>
<td>BMD (g/cm²)</td>
<td>0.84 (0.05)</td>
<td>0.84 (0.05)</td>
<td>0.00 (−0.01, 0.01)</td>
</tr>
<tr>
<td></td>
<td>Total Body</td>
<td>0.68 (0.06)</td>
<td>0.60 (0.07)</td>
<td>0.00 (−0.03, 0.01)</td>
</tr>
<tr>
<td></td>
<td>Femoral neck</td>
<td>0.76 (0.10)</td>
<td>0.74 (0.11)</td>
<td>0.02 (−0.01, 0.006)</td>
</tr>
<tr>
<td></td>
<td>Total spine</td>
<td>0.68 (0.06)</td>
<td>0.70 (0.07)</td>
<td>0.00 (−0.03, 0.01)</td>
</tr>
<tr>
<td></td>
<td>BMC (g)</td>
<td>922 (157.5)</td>
<td>932 (178.6)</td>
<td>0.00 (−0.01, 0.01)</td>
</tr>
<tr>
<td></td>
<td>Total body</td>
<td>21.51 (2.92)</td>
<td>21.85 (2.84)</td>
<td>0.52 (−0.33, 1.38)</td>
</tr>
<tr>
<td></td>
<td>Femoral neck</td>
<td>2.73 (0.61)</td>
<td>2.68 (0.60)</td>
<td>0.01 (−0.06, 0.3)</td>
</tr>
<tr>
<td></td>
<td>Total spine</td>
<td>82.62 (18.7)</td>
<td>78.8 (18.4)</td>
<td>0.02 (0.00, 0.001)</td>
</tr>
<tr>
<td></td>
<td>Bone size (cm²)</td>
<td>3.58 (0.42)</td>
<td>3.59 (0.43)</td>
<td>0.00 (−0.06, 0.02)</td>
</tr>
<tr>
<td></td>
<td>FN area</td>
<td>27.5 (3.13)</td>
<td>28.0 (3.89)</td>
<td>0.56 (−0.6, 1.7)</td>
</tr>
<tr>
<td></td>
<td>L1 to L4 area</td>
<td>29.1 (3.4)</td>
<td>29.8 (3.3)</td>
<td>0.01 (−0.01, 0.02)</td>
</tr>
</tbody>
</table>

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 (P4); and adjusted for age, Tanner at follow-up, and annual changes in height and weight (P5). Statistically significant changes are highlighted in bold.
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.\(^{46,51}\) 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.\(^{3,5,54}\) 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.

<table>
<thead>
<tr>
<th></th>
<th>Girls (n=67)</th>
<th>Controls (n=33)</th>
<th>Mean difference (95% CI)</th>
<th>$p_1$ Value</th>
<th>$p_2$ Value</th>
<th>$p_3$ Value</th>
<th>Boys (n=89)</th>
<th>Controls (n=32)</th>
<th>Mean difference (95% CI)</th>
<th>$p_1$ Value</th>
<th>$p_2$ Value</th>
<th>$p_3$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peripheral quantitative computed tomography (pQCT)</strong></td>
<td></td>
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<tr>
<td>Tibia trabecular 4%</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Trabecular vBMD (mg/cm³)</td>
<td>217.7 (34.1)</td>
<td>213.2 (32.5)</td>
<td>2.62 (-12.0, 17.3)</td>
<td>0.52</td>
<td>0.57</td>
<td>0.63</td>
<td>209.6 (25.8)</td>
<td>218 (32.6)</td>
<td>-8.65 (-20.8, 3.44)</td>
<td>0.15</td>
<td>0.13</td>
<td>0.11</td>
</tr>
<tr>
<td>Tibia cortical 38%</td>
<td></td>
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</tr>
<tr>
<td>Cortical vBMD (mg/cm³)</td>
<td>1075.8 (30.6)</td>
<td>1075.6 (28.0)</td>
<td>0.08 (-14.3, 13.7)</td>
<td>0.95</td>
<td>0.97</td>
<td>0.93</td>
<td>993.7 (38.2)</td>
<td>1000 (37.8)</td>
<td>-3.5 (-20.0, 12.9)</td>
<td>0.67</td>
<td>0.62</td>
<td>0.62</td>
</tr>
<tr>
<td>Cortical BMC (g)</td>
<td>262.4 (39.2)</td>
<td>242.4 (37.3)</td>
<td>2.1 (17.6, 46.0)</td>
<td>0.12</td>
<td>0.11</td>
<td>0.10</td>
<td>266 (45.20)</td>
<td>278 (42.5)</td>
<td>-5.6 (-23.6, 12.3)</td>
<td>0.53</td>
<td>0.52</td>
<td>0.36</td>
</tr>
<tr>
<td>Cortical area (mm²)</td>
<td>243.7 (34.5)</td>
<td>225.2 (33.0)</td>
<td>1.8 (6.5, 36.0)</td>
<td>0.01</td>
<td>0.02</td>
<td>0.01</td>
<td>260.4 (42.5)</td>
<td>273.8 (41.7)</td>
<td>-3.5 (-23.1, 11.7)</td>
<td>0.51</td>
<td>0.49</td>
<td>0.35</td>
</tr>
<tr>
<td>Cortical thickness (mm)</td>
<td>4.57 (0.51)</td>
<td>4.32 (0.53)</td>
<td>0.29 (-0.07, 0.51)</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>4.67 (0.62)</td>
<td>4.82 (0.60)</td>
<td>-0.05 (-0.31, 0.20)</td>
<td>0.69</td>
<td>0.66</td>
<td>0.52</td>
</tr>
<tr>
<td>Total area (CSA) (mm²)</td>
<td>1220 (233.1)</td>
<td>1100 (205.7)</td>
<td>1.0 (43.3, 237)</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>1291 (274.3)</td>
<td>1397 (267.2)</td>
<td>-165.9 (165.9, 56.8)</td>
<td>0.33</td>
<td>0.30</td>
<td>0.21</td>
</tr>
<tr>
<td>Radius trabecular 4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Trabecular vBMD (mg/cm³)</td>
<td>177.9 (30.22)</td>
<td>175.5 (35.6)</td>
<td>-0.48 (-14.3, 13)</td>
<td>0.95</td>
<td>0.97</td>
<td>0.93</td>
<td>191.0 (38.2)</td>
<td>194.5 (30.4)</td>
<td>-1.2 (-15.2, 12.7)</td>
<td>0.86</td>
<td>0.75</td>
<td>0.71</td>
</tr>
<tr>
<td>Radius cortical 66%</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cortical vBMD (mg/cm³)</td>
<td>1034.4 (40.0)</td>
<td>1038.3 (43.0)</td>
<td>0.06 (-13.2, 20.1)</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>993.7 (38.2)</td>
<td>1000 (37.8)</td>
<td>-3.5 (-20.0, 12.9)</td>
<td>0.67</td>
<td>0.62</td>
<td>0.62</td>
</tr>
<tr>
<td>Cortical BMC (g)</td>
<td>65.4 (12.5)</td>
<td>64.2 (12.3)</td>
<td>0.2 (2.2, 8.2)</td>
<td>0.01</td>
<td>0.1</td>
<td>0.1</td>
<td>63.3 (14.6)</td>
<td>68.0 (16.2)</td>
<td>-1.1 (-7.1, 5.0)</td>
<td>0.73</td>
<td>0.37</td>
<td>0.28</td>
</tr>
<tr>
<td>Cortical area (mm²)</td>
<td>63.0 (10.9)</td>
<td>61.5 (10.1)</td>
<td>0.2 (1.7, 7.3)</td>
<td>0.02</td>
<td>0.1</td>
<td>0.1</td>
<td>63.5 (13.9)</td>
<td>67.8 (15.3)</td>
<td>-0.8 (-6.5, 4.9)</td>
<td>0.78</td>
<td>0.39</td>
<td>0.29</td>
</tr>
<tr>
<td>Cortical thickness (mm)</td>
<td>1.84 (0.32)</td>
<td>1.88 (0.36)</td>
<td>-0.01 (-0.2, 0.1)</td>
<td>0.19</td>
<td>0.19</td>
<td>0.19</td>
<td>1.7 (0.38)</td>
<td>1.9 (0.42)</td>
<td>-0.04 (-0.20, 0.16)</td>
<td>0.33</td>
<td>0.13</td>
<td>0.10</td>
</tr>
<tr>
<td>Total area (CSA) (mm²)</td>
<td>131.0 (27.6)</td>
<td>121.8 (18.6)</td>
<td>0.0 (0.91, 21)</td>
<td>0.07</td>
<td>0.07</td>
<td>0.07</td>
<td>146.4 (30.0)</td>
<td>154.5 (29.4)</td>
<td>6.8 (-5.5, 19.0)</td>
<td>0.25</td>
<td>0.31</td>
<td>0.33</td>
</tr>
<tr>
<td>Polar SSI (cm²)</td>
<td>204.6 (57.1)</td>
<td>194.1 (41.1)</td>
<td>10.0 (-6.2, 38.3)</td>
<td>0.16</td>
<td>0.17</td>
<td>0.17</td>
<td>214.0 (60.4)</td>
<td>224.9 (68.7)</td>
<td>3.3 (-22.0, 28.6)</td>
<td>0.80</td>
<td>0.94</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>Quantitative ultrasound (QUS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOS</td>
<td>1594.9 (41.1)</td>
<td>1594.9 (38.6)</td>
<td>-2.7 (-25.2, 19.8)</td>
<td>0.81</td>
<td>0.74</td>
<td>0.58</td>
<td>1580 (29.0)</td>
<td>1587 (39.3)</td>
<td>-1.45 (-33.0, 4.0)</td>
<td>0.12</td>
<td>0.10</td>
<td>0.08</td>
</tr>
<tr>
<td>BUA</td>
<td>114.3 (19.2)</td>
<td>103.8 (14.2)</td>
<td>10.5 (99.9, 19.9)</td>
<td>0.03</td>
<td>0.07</td>
<td>0.15</td>
<td>107.1 (12.2)</td>
<td>104.4 (16.7)</td>
<td>3.8 (42.4, 11.7)</td>
<td>0.35</td>
<td>0.39</td>
<td>0.47</td>
</tr>
</tbody>
</table>

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 DEXA 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.

<table>
<thead>
<tr>
<th>Case/Control</th>
<th>Mean difference (95% CI)</th>
<th>p Value</th>
<th>p Value</th>
<th>p Value</th>
<th>p Value</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean mass</td>
<td>1.6 (–0.23, 3.4)</td>
<td>0.22</td>
<td>0.19</td>
<td>0.18</td>
<td>0.19</td>
<td>0.19</td>
</tr>
<tr>
<td>BMD (g/cm²)</td>
<td>0.04 (0.0001, 0.07)</td>
<td>0.004</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>Total body</td>
<td>0.05 (0.0001, 0.09)</td>
<td>0.005</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>BMC (g)</td>
<td>0.05 (0.0001, 0.09)</td>
<td>0.005</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>0.15 (0.013)</td>
<td>0.15</td>
<td>0.14</td>
<td>0.14</td>
<td>0.14</td>
<td>0.14</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>0.05 (0.0001, 0.11)</td>
<td>0.005</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>Total spine</td>
<td>0.03 (0.012)</td>
<td>0.03</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>EN area</td>
<td>0.12 (0.056, 0.18)</td>
<td>0.12</td>
<td>0.14</td>
<td>0.14</td>
<td>0.14</td>
<td>0.14</td>
</tr>
<tr>
<td>L1 to L2 area</td>
<td>0.03 (0.02, 0.05)</td>
<td>0.03</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
</tr>
</tbody>
</table>

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 have not been completely explained. 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. 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. 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 mass 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. 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 protocol 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. 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.
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/coi_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.

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Authors’ roles: MK designed the study and was responsible for data collection. Accelerometer data were collected and analyzed by MD. MD 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 finalized the manuscript. All authors read and approved the final manuscript.

References

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

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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. 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, and data from clinical trials support the skeletal benefits of exercise, particularly during periods of growth. 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 in this issue of the Journal of Bone and Mineral Research is timely and of high interest.

The study of Detter and colleagues 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 Malmo 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. 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.”

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. 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...
children undergoing fast apposition,(11,12) a critical issue during late childhood and early adolescence, and thus, the skeleton appears to be highly impressionable during adolescence because over half of bone accrual occurs during the teenage years. The current concept to consider during adolescence because over half of bone accrual occurs during the teenage years. 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. 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. 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. 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 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 have shown 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. 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. 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. Are there public health implications that stem from the data of Detter and colleagues? 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. 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. 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’s0 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.5,13 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’s0 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.

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22. Ecclesiastes, 8:15 (King James Version).