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Physical activity, musculoskeletal traits and fractures in childhood and in old men

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Physical activity, musculoskeletal traits and fractures in childhood and in old men

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DEPARTMENT OF ORTHOPEDICS AND CLINICAL SCIENCES | LUND UNIVERSITY



Physical activity, musculoskeletal traits and fractures in childhood and in old men

Felix Cronholm



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DOCTORAL DISSERTATION

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March 8, 2019 at 09:00.

Faculty opponent

Professor Jón Karlsson, Sahlgrenska akademin, Göteborgs universitet

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Title and subtitle Physical activity, musculoskeletal traits and fractures in childhood and in old men.		
Abstract <p>Background: Physical activity (PA) levels in children need to be increased. This may be done by interventions, but the activity-stat theory suggests that the total duration of PA in children is constant and cannot be altered. There are findings that PA interventions during childhood are associated with beneficial developments in various musculoskeletal traits, but such beneficial effects may attenuate over time.</p> <p>Aims: To assess whether a daily school-based PA intervention program is associated with increased duration of total PA, and when provided from before until after puberty (Tanner stage 1 to 5), with beneficial gains in musculoskeletal traits and a musculoskeletal composite score. Also, whether a composite score in old men can predict fractures, and whether the level of PA is associated with the composite score and fracture incidence.</p> <p>Methods: The Pediatric Osteoporosis Prevention (POP) study is a population-based prospective, controlled PA intervention study that includes children from four schools. In one of the schools (intervention school), we increased PA from 60 minutes/week to 200 minutes/week. The remaining three schools continued with 60 minutes/week of PA. We invited children with school start 1998-2000 and followed them from school start until the last year of compulsory school (grade 9). We evaluated duration of PA and sedentary screen-time by questionnaires, bone mass and lean mass by dual-energy X-ray absorptiometry (DXA), muscle strength by a digital dynamometer and bone mass/quality by quantitative ultrasound (QUS). To estimate the overall effect of PA on musculoskeletal development we calculated a composite score as the mean Z-score of lumbar spine bone mineral content (BMC) and bone area (BA), total body lean mass (TBLM), calcaneal speed of sound (SOS) and knee flexion muscle strength. MrOs Sweden is a population-based prospective observational study that includes elderly men. At baseline, we measured bone traits by DXA and QUS and muscle strength as hand grip strength by a handheld dynamometer. We then calculated a musculoskeletal composite score as the mean Z-score of femoral neck BMC and BA, TBLM, hand grip strength and SOS. We used the Physical Activity Scale for the Elderly (PASE) questionnaire to estimate the level of PA. We registered radiographically verified fractures during the follow-up period (median 9.6 years).</p> <p>Results: The PA intervention program was associated with higher duration of total PA in intervention compared to control children, after both three and mean seven years (both $p < 0.001$), while we found no statistically significant group differences in sedentary screen-time. From Tanner stage 1 to 5, the intervention boys and girls both gained significantly more bone mass and better musculoskeletal composite scores than their respective controls (both $p < 0.05$). In old men, a musculoskeletal composite score predicted incident fractures similar to, but not better than, a standard aBMD measurement. Level of PA was associated with both the musculoskeletal composite score and incident fractures.</p> <p>Conclusions: A school-based PA intervention program was associated with increased duration of total PA (thereby refuting the activity-stat theory), with beneficial gains in musculoskeletal traits as well as in a composite score. In old men, a musculoskeletal composite score could predict fractures and level of PA was associated with both the composite score and fracture incidence.</p>		
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Abstract

Background: Physical activity (PA) levels in children need to be increased. This may be done by interventions, but the activity-stat theory suggests that the total duration of PA in children is constant and cannot be altered. There are findings that PA interventions during childhood are associated with beneficial developments in various musculoskeletal traits, but such beneficial effects may attenuate over time.

Aims: To assess whether a daily school-based PA intervention program is associated with increased duration of total PA, and when provided from before until after puberty (Tanner stage 1 to 5), with beneficial gains in musculoskeletal traits and a musculoskeletal composite score. Also, whether a composite score in old men can predict fractures, and whether the level of PA is associated with the composite score and fracture incidence.

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Results: The PA intervention program was associated with higher duration of total PA in intervention compared to control children, after both three and mean seven years (both $p < 0.001$), while we found no statistically significant group differences in sedentary screen-time. From Tanner stage 1 to 5, the intervention boys and girls both gained significantly more bone mass and better musculoskeletal composite scores than their respective controls (both $p < 0.05$). In old men, a musculoskeletal composite score predicted incident fractures similar to, but not better than, a standard aBMD measurement. Level of PA was associated with both the musculoskeletal composite score and incident fractures.

Conclusions: A school-based PA intervention program was associated with increased duration of total PA (thereby refuting the activity-stat theory), with beneficial gains in musculoskeletal traits as well as in a composite score. In old men, a musculoskeletal composite score could predict fractures and level of PA was associated with both the composite score and fracture incidence.

List of papers

- I. **A Physical Activity Intervention Program in School is Also Accompanied by Higher Leisure-Time Physical Activity: A Prospective Controlled 3-Year Study in 194 Prepubertal Children**
(Cronholm F, Rosengren BE, Karlsson C, Karlsson MK).
Journal of Physical Activity and Health. 2017 Apr;14(4):301-307.
- II. **A comparative study found that a seven-year school-based exercise programme increased physical activity levels in both sexes**
(Cronholm F, Rosengren BE, Karlsson C, Karlsson MK).
Acta Paediatrica. 2018 Apr;107(4):701-707.
- III. **A Prospective Controlled Exercise Intervention Study from Before to After Puberty Improves Bone Mass and a Musculoskeletal Composite Score in Both Sexes**
(Cronholm F, Rosengren BE, Dencker M, Karlsson C, Karlsson MK).
Submitted to BMC Musculoskeletal Disorders.
- IV. **The Fracture Predictive Value for a Musculoskeletal Composite Score in Old Men – Data from the MrOs Sweden Study**
(Cronholm F, Rosengren BE, Nilsson J-Å, Ohlsson C, Mellström D, Ribom E, Karlsson MK).
Submitted to BMC Geriatrics.

Abbreviations

95% CI	95% confidence interval
aBMD	Areal bone mineral density
ANCOVA	Analysis of covariance
ATP	Adenosine triphosphate
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
BMU	Basic multicellular unit
BUA	Broadband ultrasound attenuation
CV	Coefficient of variation
DPA	Dual photon absorptiometry
DXA	Dual-energy X-ray absorptiometry
FRAX	Fracture Risk Assessment Tool
GH	Growth hormone
HR	Hazard ratio
HRT	Hormone replacement therapy
IGF-1	Insulin-like growth factor-1
IRR	Incidence rate ratio
MET	Metabolic equivalent of task
MRI	Magnetic resonance imaging
MrOs study	The Osteoporotic Fractures in Men study
mSv	Millisievert
Nm	Newton meter

PASE	Physical Activity Scale for the Elderly
PBM	Peak bone mass
PE	Physical education
POP study	Pediatric Osteoporosis Prevention study
pQCT	Peripheral quantitative computed tomography
PT	Peak torque
QUS	Quantitative ultrasound
RCT	Randomized controlled trial
SD	Standard deviation
SOS	Speed of sound
SPA	Single photon absorptiometry
WHO	World Health Organization

Introduction

Physical activity

Throughout history, physical activity has been an important part of human life. In the beginning of times, we needed to be physically active in order to hunt or gather food. In later times it was necessary for almost everyone to be active in order to earn a living, for instance by farming or working in factories. Today, however, physical activity is no longer a natural part of our lives. Yet we still need to be physically active and exercise in order to feel well and maintain good health. Physical activity is therefore just as important today as it was several hundred years ago (Figure 1).

Physical activity is defined by the World Health Organization (WHO) as “*any bodily movement that requires energy expenditure*” (1). Exercise is a subcategory of physical activity and includes activities that are planned, structured, repetitive and purposeful with the aim of improving or maintaining physical fitness (2). Physical activity can be performed at different intensities, usually divided into moderate and vigorous intensity. These two are expressed in terms of their metabolic equivalent of task (MET), which is the ratio of a person’s working metabolic rate relative to their resting rate. One MET is expressed as the energy cost of sitting quietly and will thus differ between people based on their fitness level (3). Moderate intensity is defined as approximately 3-6 MET and vigorous intensity is defined as >6 MET (3). Examples of moderately intense activities are brisk walking and gardening, and examples of vigorous activities are running and participating in different ball games such as football (3).



Figure 1.
The author engaged in one of his favorite physical activities in Saalbach, Austria. Photo by Lina Cronholm.

Physical activity recommendations

The WHO has presented recommendations for physical activity for three age groups: children aged 5-17 years, adults aged 18-64 years and adults aged 65 years or more (Table 1) (4). Children aged 5-17 years are recommended to participate in at least 60 minutes/day of moderate to intense physical activity together with bone- and muscle-strengthening activities at least three times/week. Adults aged 18-64 are recommended to participate in either 150 minutes/week of moderate physical activity or at least 75 minutes/week of vigorous physical activity. Activities that strengthen muscles should be undertaken at least twice a week. For adults aged 65 years or more, the recommendations are the same as for the younger adults, but with the addition of activities that enhance balance and prevent falls at least three times/week.

Table 1.

Physical activity recommendations across the lifespan according to the WHO (4).

Age group	Recommendations	
5-17 years	60 minutes/day moderate to vigorous physical activity	Bone- and muscle-strengthening activities at least 3 times/week
18-64 years	150 minutes/week of moderate or 75 minutes/week of vigorous physical activity	Muscle-strengthening activities at least 2 times/week
65 years or more	150 minutes/week of moderate or 75 minutes/week of vigorous physical activity	Muscle-strengthening activities at least 2 times/week and activities that enhance balance and prevent falls at least 3 times/week

Physical activity levels today

Globally, around 28% of adults aged 18 years or more were estimated in 2016 to be insufficiently physically active, with a more inactive lifestyle being found in high-income countries than in low-income countries (5). The problem also exists in adolescents aged 11-17 years, where only about 20% met the WHO recommendations of physical activity, and girls to a lesser extent than boys (6). The level of physical activity in society has declined during the last two decades, in both boys and girls (7), with girls being less active than boys in all ages (7-9). Children also seem to reduce their physical activity levels with increasing age (7-9), generally more in girls than boys (10).

Types of physical activity

To be able to perform physical activity, energy in the form of adenosine triphosphate (ATP) is needed. ATP can be formed either during aerobic or anaerobic metabolism (11). From a physiological view, activities are thus divided into either aerobic or anaerobic depending on which metabolic process that dominates (11). Aerobic physical activity includes activities that use large muscle groups, and ATP is formed from amino acids, carbohydrates and fatty acids during processes that require oxygen consumption (12, 13). Anaerobic physical activity includes activities of short duration and occurs when the oxygen delivery to the working muscle is insufficient. During anaerobic metabolism, the energy demand is provided from sources within the muscle itself, predominantly glycogen (11). These processes, including glycolysis and fermentation, are independent of oxygen but generate significantly less ATP than aerobic processes (12). During anaerobic work the fermentation and glycolysis cause build-up of lactic acid within the muscle, which causes pain and discomfort.

Health aspects

Physical inactivity was identified in 2010 as the fourth leading risk factor for global mortality, estimated to be directly responsible for 6% of global deaths and outranked only by hypertension, smoking and hyperglycemia (4). This is not surprising, since inactivity is associated with obesity, cardiovascular disease, type 2 diabetes, cardiovascular mortality and all-cause mortality (14-16). Historically physical inactivity has also been found to be associated with clustering of risk factors for these diseases in adults, but recent studies suggest that also children with low physical activity are at risk of clustering the same risk factors (17, 18). The associations in children could possibly be mediated by increased risk of obesity (19, 20). Pediatric obesity is today a global health problem and numbers from 2013 indicate that globally, 223.8 million children were overweight or obese, accounting for 14.2% of all children aged 5-17.9 years (21). In contrast to physical inactivity, physical activity is associated with decreased risks of developing obesity, all the diseases mentioned above, colorectal and breast cancer, and mortality (4, 16-20, 22-25).

Many studies that address these problems have focused on the relationship between physical activity and clustering of risk factors for disease. Fewer have investigated the independent effect of sedentary behavior on the risk factors or the actual diseases. Physical inactivity or sedentary behavior has been suggested to be an independent risk factor for disease, regardless of the associated physical activity level (26). Also in children it seems that sedentary behavior, just like physical inactivity, is associated with increased risk of becoming overweight (19) and clustering of risk factors for cardiovascular disease, diabetes, hypertension and hypercholesterolemia (17, 27). At the same time, it seems as if it is more important to be physically active than not being sedentary, since cardiovascular risk factors diminish along with higher levels of physical activity, independently of the time spent sedentary (28-30). In adults the inferences are less clear as some studies suggest that sedentary behavior is a cardio-metabolic risk factor regardless of accompanied time engaged in physical activity (31). It should however be noted that the evidence for the independent negative health effects from sedentary behavior is still inconclusive (32).

Physical activity interventions

One approach to increase the level of physical activity in society is by applying interventions. Also, since children in general are insufficiently physically active and therefore cluster risk factors for disease, it is desirable to promote physical activity already at young ages. This approach is supported by findings that children who are physically active seem to continue to be active also as adults (33, 34). It would

therefore be of great interest to evaluate whether children, who are exposed to physical activity interventions actually become more active and if so keep this higher activity level also beyond the termination of the intervention.

School-based interventions

For society in general the most effective intervention should ensure exposure to as many individuals as possible. A school-based approach is therefore attractive, since school is an arena where it is possible to reach all children and since they spend most continuous time there during the day. In addition, all children irrespective of socioeconomic status, geographical allocation or individual preference have to attend school, unlike, for instance, after-school leisure-time activities. With this in mind it is not surprising that experts recommend school-based physical activity interventions to alter the trend of increasing inactivity (35). However, a school-based setting is not without concerns. It has been asserted that implementing increased amounts of physical activity in school will reduce the hours spent on theoretical subjects, possibly giving negative effects on the children's academic performance. However, this does not seem to be the case as increased physical activity in school is associated with both better achievements in school and better grades (36-38). Due to this and all the above-mentioned associations between health and physical activity, and since physical activity is of low cost and with few adverse effects, and can be performed by almost everyone at least to some extent, a school-based intervention approach is most desirable.

The activity-stat theory

Some have questioned whether physical activity intervention programs in children actually do increase the total duration of physical activity. Some researchers suggest that interventions that provide extra physical activity only shift inactive hours for active hours between different periods of time. In other words, according to the theory, providing increased physical activity during school hours, thus replacing some inactive hours with active hours, would only shift the inactive hours to occur after school. The total duration of physical activity during the day would then not be altered. This controversial theory was first proposed and named during the late 1990s by Rowland as the *activity-stat theory* (39). The theory infers that physical activity in children is centrally regulated and kept at a constant level, suggesting that the duration of physical activity cannot be altered by interventions. The theory is supported by some publications (40, 41), but opposed by others (42-46). Due to these discrepancies, a detailed review article in 2013 concluded that there was not yet enough evidence to refute or accept the activity-stat theory (47).

Physical education in Sweden

Physical education (PE) is a compulsory school subject in Swedish compulsory school (Figure 2). Unlike many other European countries, the number of teaching hours in PE is not defined per school year. Instead Swedish school children are obliged to have at least 500 hours of PE scheduled during the nine compulsory school years (48). It is then up to the local municipalities to decide how to divide these hours between the different school years and up to the principals of each school to allocate the hours in the weekly schedule.

The amount of PE in schools may however be increased. Principals have an option to increase the hours of any subject by transferring some hours between subjects. The hours in the subjects Swedish, English and mathematics cannot be reduced, but the rest of the school subjects can be reduced by up to 20 percent in favor of other subjects (48). Another possibility is to increase the hours of PE without reducing hours for other subjects, by increasing the total number of hours per school week. This decision can be made by either the school or the municipality. A third option for increasing PE in school is for the children to use their selectable hours, called “student’s choice (*“elevens val”*)”, which makes up a total of 382 hours during all years of compulsory school (48). This decision is taken by the students themselves. There are thus several options to profile a school towards physical activity.

During recent decades, there has been a gradual reduction in hours of PE provided in Swedish compulsory school (49). A recent report concluded that among 31 evaluated European countries, Sweden is one of the countries providing the least hours of PE in compulsory school. Sweden is also the bottom Nordic country regarding the number of hours of PE in the national school curriculum (50).



Figure 2.
Participants in the Pediatric Osteoporosis Prevention (POP) study during a class of physical education (PE).

Sedentary behavior

In contrast to physical activity, there is no clear definition of sedentary behavior. Instead several definitions are used in the literature (51), most including duration of sitting or being in a reclining position (51). Due to changes in societal structure, a sedentary lifestyle has become a dominant part of human life (Figure 3). Some studies suggest that children spend more than 50% of their waking hours engaged in such activities (27). There are also studies that imply that the amount of time spent on sedentary activities, especially screen-time activities, has increased and continues to do so (7, 27, 52).



Figure 3.
An example of a common sedentary behavior. Photo by Lina Cronholm.

Bone

Bone is the framework of a human and is an organ with multiple roles. It allows us to move, as it provides support and attachment to our muscles. It also gives protection to vital organs. The skull bone protects the brain and the rib cage protects the chest organs. In addition, the skeleton is home to the bone marrow that is responsible for hematopoiesis, the formation of our blood cells. Finally, bone works as a storage for calcium and phosphate. The structure of bone allows it to be strong and resist bending while at the same time being light and flexible.

Bone tissue

Bone is made up of two major components, one organic and one inorganic. By weight the inorganic component makes up about 70%, the organic component stands for 20-25% and the remainder is made up of water (53). The organic component consists predominantly of type 1 collagen, other non-collagenous proteins as well as three different bone cells: osteoblasts, osteoclasts and osteocytes.

The osteoblasts are the bone-forming cells. They rest as lining cells on bone surfaces, and when they become activated, they begin to synthesize osteoid which makes up the bone matrix. The osteoclasts are the bone-resorbing cells that counteract the osteoblasts by resorbing bone matrix (54). The linkage and dependence between these two cell types is strong (55). The third cell type, the osteocyte is the most abundant bone cell that rests in the bone matrix (56). Osteocytes originate from osteoblasts which turn into osteocytes when they synthesize bone matrix and become trapped and encased within it, in spaces called lacunae (53, 54, 56). As the osteocytes are encased within lacunae, they do not have direct contact with other cells but instead communicate via dendritic processes that run in small canals called lacunar canaliculi. The function of osteocytes is not entirely clear but there is evidence to suggest that they might play a role in detecting mechanical stimuli on bone and that they are involved in bone remodeling (54, 57, 58).

The inorganic component of bone is primarily made up of crystalline hydroxyapatite, a mineral mainly consisting of calcium and phosphate (53). The hydroxyapatite crystals, also called bone mineral, are what makes the bone strong and together with the type 1 collagen and the other non-collagenous proteins it makes up the bone matrix. The hydroxyapatite mineral contributes to compressive strength whereas the collagen contributes to tensile strength.

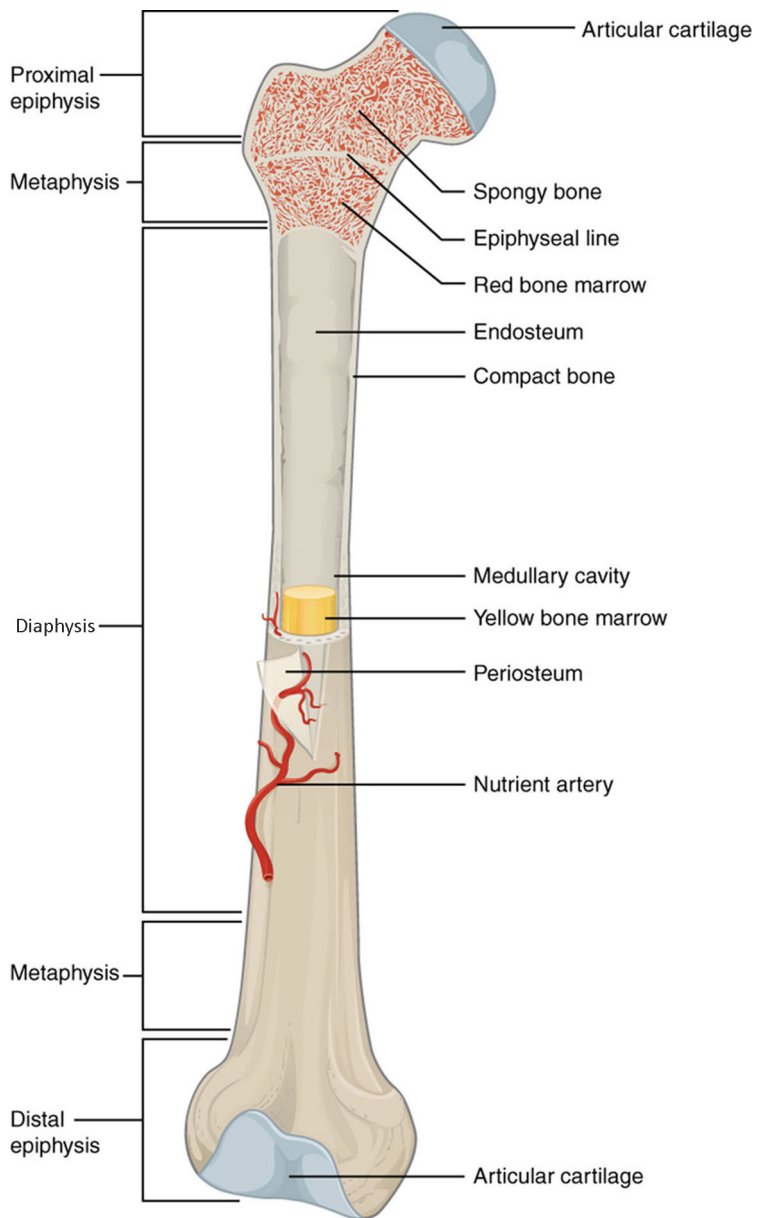


Figure 4.
The macroscopic structure of a pediatric long bone in the form of a femur (thigh bone) with remaining epiphyseal lines. Source: OpenStax College [CC BY 3.0 (<https://creativecommons.org/licenses/by/3.0/>)].

One way to divide the skeleton is into the axial and the appendicular skeleton. The axial skeleton includes the skull, the vertebrae, the pelvis and other flat-formed bones, while the appendicular skeleton includes the long bones in the extremities. The long bones can be further divided into two metaphyses, one at the proximal and one at the distal end (Figure 4). The metaphyses are then joined by a shaft-shaped part called the diaphysis. In children, longitudinal growth of long bones takes place in a plate of hyaline cartilage located in the metaphysis. This plate is referred to as the epiphyseal line or physis and can be clearly visualized on an X-ray (Figure 5). For the inexperienced eye the epiphyseal line can be mistaken for a fracture line. The part of long bones between the joint and the epiphyseal line is called the epiphysis. At the end of puberty, when longitudinal bone growth ceases, the epiphyseal lines close and can no longer be visualized on an X-ray. The expression epiphysis should then no longer be used.

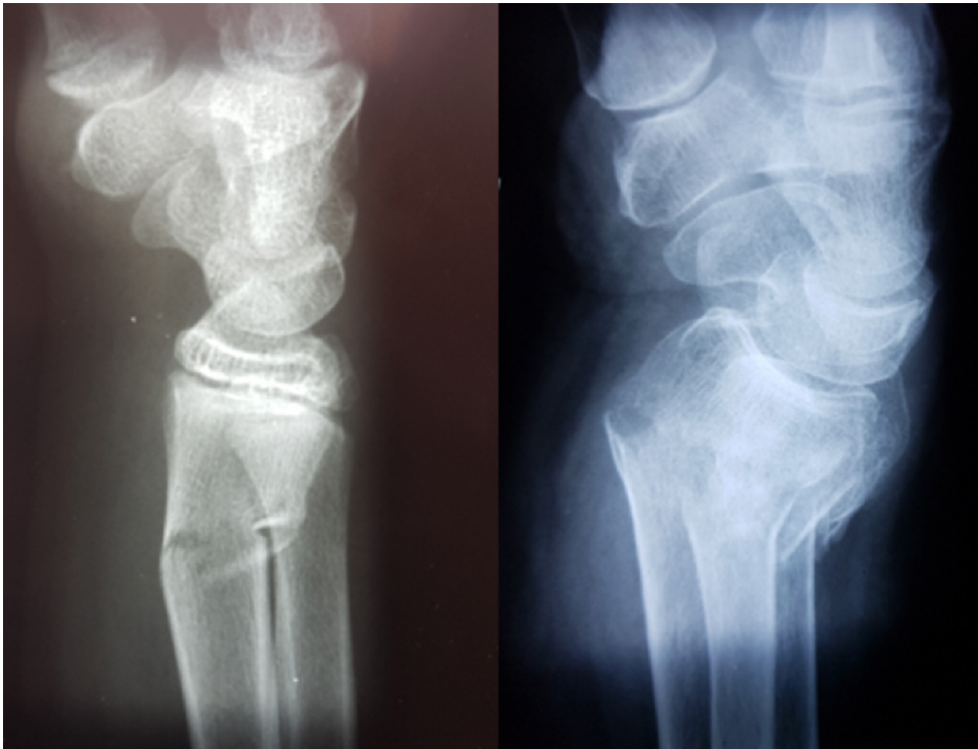


Figure 5. Two examples of distal radius fractures as seen on X-ray. One in a child (left image) and one in an adult (right image). Note the epiphyseal line that is visible on the child X-ray image distal to the fracture.

Bone can be further divided into cortical or compact bone and trabecular bone. About 80% of the skeletal mass is made up of cortical bone, while 20% is of trabecular bone. The cortical bone is compact and dense and is primarily located on the exterior parts of the skeleton and in the shaft of long bones (Figure 6). Cortical bone is arranged by multiple interconnected and tightly packed cylinder-shaped elements called osteons. The osteons in turn consist of circular arranged layers of bone matrix and encased osteocytes, called lamellae. In the center of an osteon runs a canal, called the Haversian canal, containing blood vessels. Haversian canals are also interconnected to each other by so-called Volkmann's canals which also contain blood vessels. The Volkmann's canals also have connection to the outer surface of the bone which is lined by the periosteum. The trabecular bone on the other hand has a sponge shaped structure with vertically and horizontally orientated trabeculae that are perpendicular to each other in order to withstand compressive loads. Trabecular bone is predominantly found at the end of long bones and in short and cuboid bones such as vertebrae.

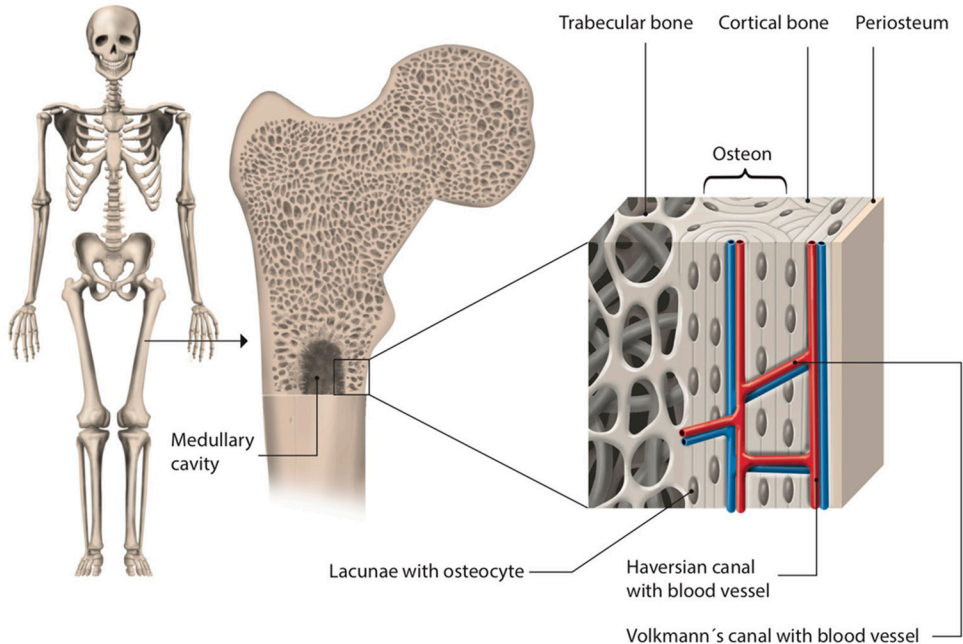


Figure 6.
The microscopic structure of a bone.

Bone remodeling and modeling

Bone does not stop to develop after puberty, even if the epiphyseal lines are closed and the longitudinal bone growth has ceased. Instead, the skeleton continues to renew during the remainder of life. This process is called bone remodeling, and occurs at a rate so that the adult skeleton is renewed every 10 years (Figure 7) (59). This process does not alter the shape of the bone, but merely exchange old damaged bone for new. Bone remodeling occurs in a so-called basic multicellular unit (BMU) which consists of osteoclasts, osteoblasts and osteocytes within a bone remodeling cavity (60). The process is divided into four phases. It begins with the recruitment and activation of osteoclasts. The second phase, called the resorption phase, occurs when the osteoclasts resorb damaged or unwanted bone in order to create a flat surface. In the third phase the osteoclasts undergo programmed cell death, apoptosis, and osteoblasts are recruited. In the fourth phase osteoblasts lay down new bone matrix which then mineralizes, and the osteoblasts eventually become encased within it as osteocytes. A full remodeling cycle lasts about 200 days in trabecular bone and 120 days in cortical bone (60, 61). Bone modeling, on the other hand, is the process of independent action of either osteoclasts or osteoblasts and is not a coupled process like bone remodeling, therefore having the possibility to alter the shape of the bone (59). The process therefore allows for growth and development of bones, also after fractures.

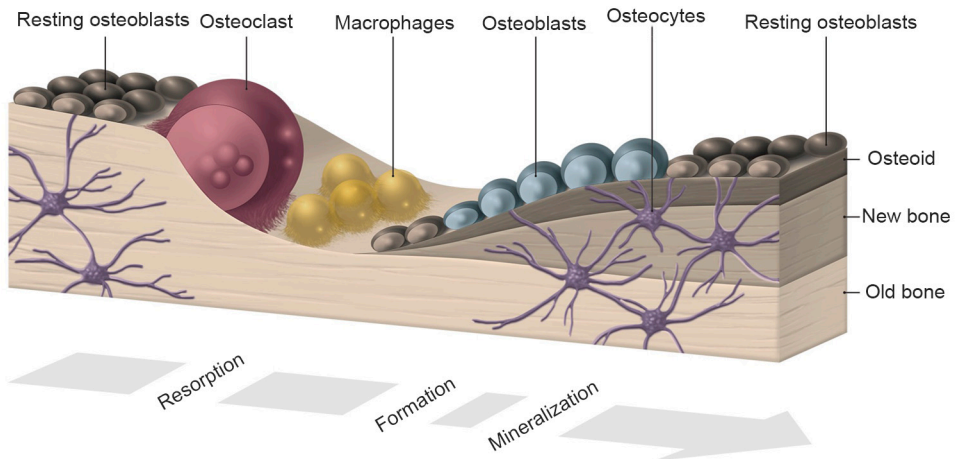


Figure 7.
The bone remodeling cycle.

Bone during growth

Human bones begin to form from mesenchymal stem cells that differentiate into either cartilage-producing chondrocytes or bone-forming osteoblasts during the prenatal period (62). The chondrocytes then begin to produce the outline of the skeleton by endochondral bone formation, which makes up the majority of the prenatal skeleton. Some lesser parts of the skull and clavicle are however formed by osteoblasts by intramembranous bone formation (62). The cartilage is then replaced by mineralized bone creating the first actual bones. Some cartilage remains in the metaphyses of long bones, where the cartilage forms the epiphyseal lines.

During childhood and adolescence, up until the end of puberty, bones grow longitudinally in the epiphyseal lines, but also appositionally, both resulting in increased bone mass. In the postnatal period up to the initiation of puberty, the hormones growth hormone (GH) and insulin-like growth factor-1 (IGF-1) stimulate bone growth (63). During puberty the levels of sex hormones, such as androgens and estrogens, increase, causing both a direct anabolic effect on bone growth and an amplification of GH and IGF-1, stimulating the pubertal growth spurt (64, 65). The bone growth during puberty is tremendous and up to 25% of the later adult bone mass is accumulated between the ages of 14 and 17 years in boys and 12 and 15 years in girls (66, 67). At the end of puberty the same sex hormones that initiated bone growth now instead induce physeal fusion and thereby terminates the longitudinal bone growth (68).

Peak bone mass

After puberty, bones continue to grow appositionally, causing bone mass to continue to increase up to a maximum level called peak bone mass (PBM). PBM is the highest bone mass value an individual attains during the course of life. It is difficult to state an exact age when PBM is reached, as it varies depending on skeletal site and sex. For instance, PBM in the hip is generally reached before the age of 20 years but PBM in the lumbar spine is sometimes not reached until the age of 40 (69-71). Heritable factors are estimated to account for 60-80% of the variability in bone mass, but there are also modifiable factors. The two primary modifiable factors are considered to be diet and physical activity (71). After an individual has reached PBM, a downward slope begins as the individual grows older (Figure 8). This downward slope is inevitable and as the bone mass gets lower the fracture risk increases (69). In women there is an accelerated rapid loss of bone mass during the first 5 to 10 years following menopause which then subsides into a more continuous loss (72, 73). The accelerated bone loss after menopause and the fact that women in general have a lower PBM than men are the main reasons why more women than men suffer fragility fractures (71, 74, 75).

However, the higher PBM an individual reaches, the older will the same individual be able to get before passing the threshold for critically low bone mass, associated with high fracture risk. Therefore, at least in theory, a higher PBM can postpone the development of osteoporosis (76).

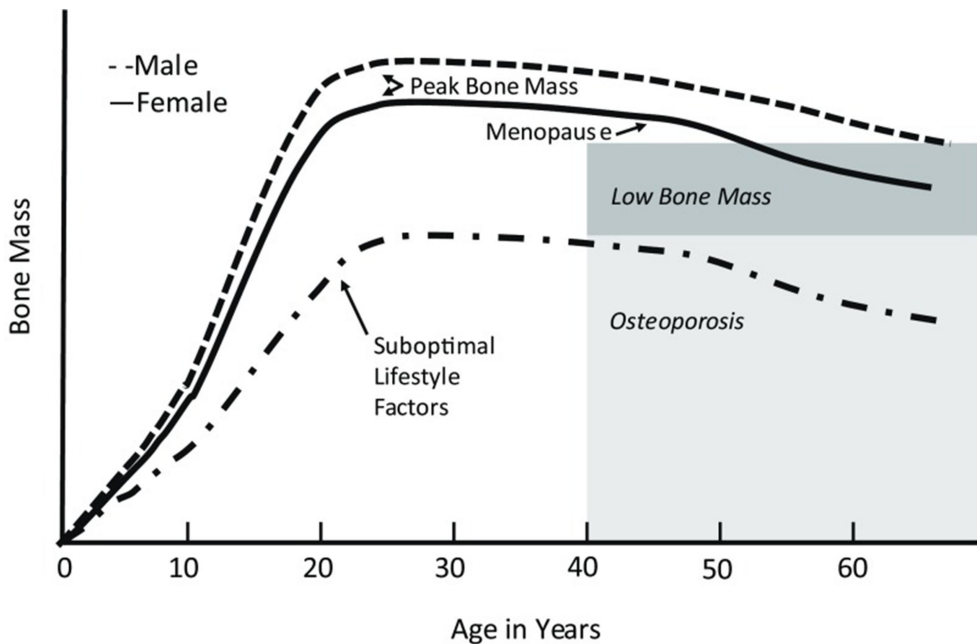


Figure 8. Bone mass across the lifespan displayed with both optimal and suboptimal lifestyle factors. Source: Weaver et al. (71).

Bone during ageing

The downward slope that begins just after PBM is reached is the result of an increased rate of bone resorption in relation to bone deposition. This process is considered as a natural part of ageing and causes the bone mass to decrease (Figure 8). Other structural changes also occur in the bone microarchitecture during ageing, such as increased cortical porosity (77).

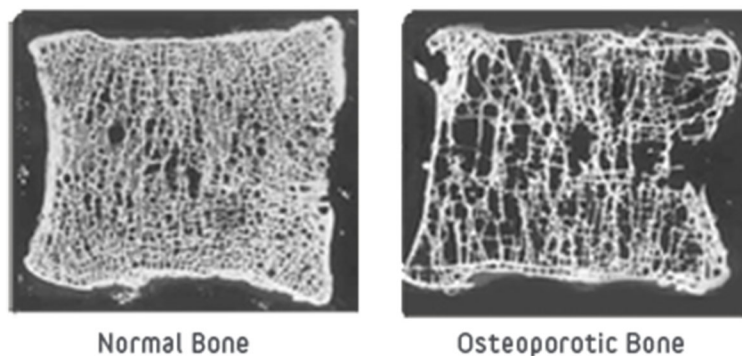


Figure 9. Comparative cross-sections of the trabecular contents in one vertebra of a healthy 37-year-old male and one vertebra of a 75-year-old woman diagnosed with osteoporosis. Source: Turner Biomechanics Laboratory [CC0].

Osteoporosis

When the bone mass has deteriorated to a certain point an individual is categorized as being osteoporotic (Figure 9). Before the 1990s the term osteoporosis was used without a clear definition. In 1994, however, the WHO defined osteoporosis as “*a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk*” (78). The WHO also published a cut point for bone mineral density (BMD) to use for diagnosing osteoporosis. The osteoporosis cut point was set at a BMD value of -2.5 standard deviations (SDs) or lower compared to the mean BMD value of a cohort of young healthy adult Caucasian women (also referred to as a T-score of -2.5 or lower) (Table 2) (78).

Table 2.
The 1994 WHO criteria for osteoporosis (78).

Bone status	Criteria
Normal	T-score -1 SD or above
Osteopenia	T-score less than -1 but above -2.5 SD
Osteoporosis	T-score -2.5 SD or below
Severe or established osteoporosis	Osteoporosis and ≥ 1 osteoporosis-related fracture

Bone strength

Bone is one of the strongest materials in the human body. Its strength is not only dependent on the mineral density, measured as BMD, but also on other traits such as bone geometry and microarchitecture. The age-dependent decline in bone strength is much steeper than the decline in BMD, implying that other factors than bone mass contribute to bone strength and thereby also fragility during ageing (79). These factors, among others, include the orientation, thickness and connectivity of the trabeculae within trabecular bone, which deteriorates along with increasing age (80). Also cortical porosity increases with age, causing the cortical bone to become less dense and thereby weaker (81). The geometrical aspects such as size and shape are also important for bone strength (82). Bone strength is thus a complex interplay between several different factors and the somewhat simplified method of using BMD as the marker of bone strength does not take all of these into consideration.

Bone measurements

Many different aspects of bone can be measured, such as shape, size and mineralization. The probably most common one is the measurement of bone mass. However, bone mass is a broad term and generally refers to measurements of bone mineral content (BMC) and bone size. BMC is measured in grams (g) and is the amount of mineral within a specific scanned part of the skeleton such as the lumbar spine (Figure 10). Bone size is most often measured as the areal size (cm^2) of a scanned region but can also be measured as a volumetric size (cm^3). From BMC and bone size, BMD can be calculated and based on the method used for the size measurement it is either calculated as areal BMD (g/cm^2) or volumetric BMD (g/cm^3).

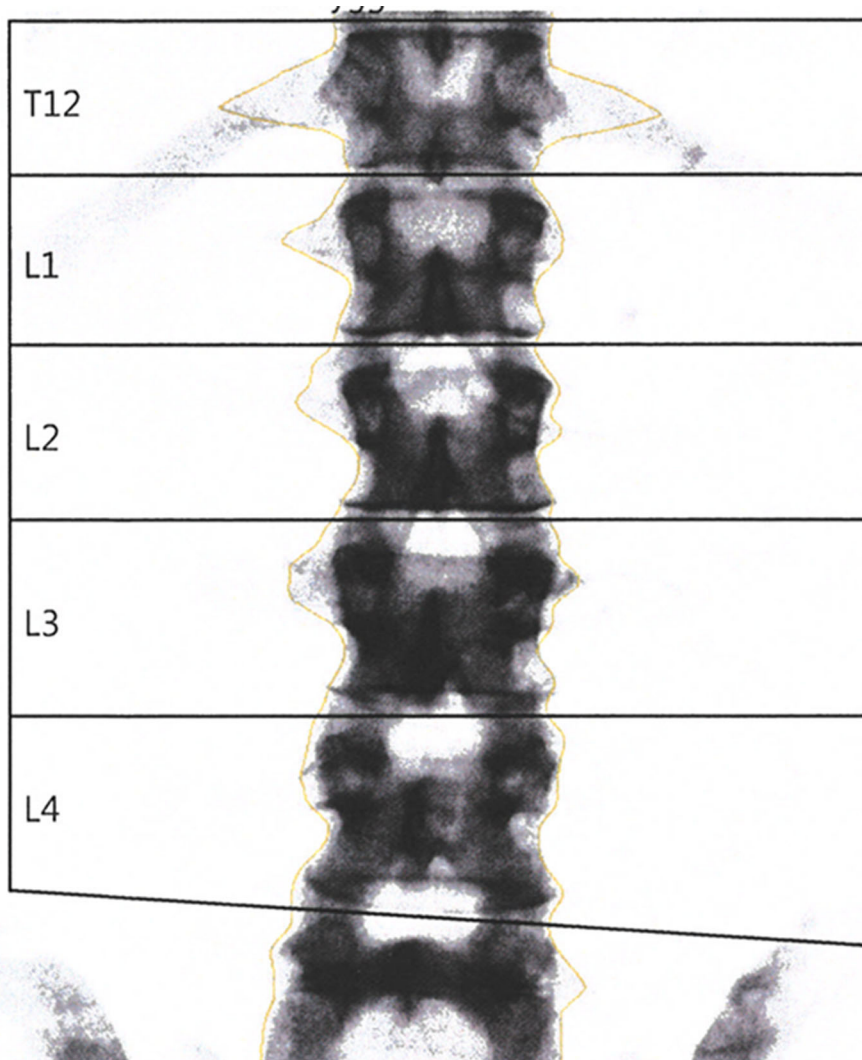


Figure 10.
DXA-scan of the author's first to fourth lumbar spine vertebrae (L1-L4) and last thoracic vertebra (Th12).

The methods used for measuring bone can be roughly divided into ionizing and non-ionizing (Table 3). Ionizing methods are based on either gamma radiation or X-ray while non-ionizing methods are based on either magnetic resonance imaging (MRI) or ultrasound technology. Previously, the most frequently used methods included the gamma radiation based single photon absorptiometry (SPA) and dual photon absorptiometry (DPA) but today the most commonly used method include the X-ray based dual-energy X-ray absorptiometry.

Table 3.
Commonly used methods for measuring bone.

Ionizing methods	Non-ionizing methods
X-ray based	
Dual-energy X-ray absorptiometry	Magnetic resonance imaging (MRI)
Peripheral computed tomography (pQCT)	Ultrasound
Gamma radiation based	
Single photon absorptiometry (SPA)	
Dual photon absorptiometry (DPA)	

Dual-energy X-ray absorptiometry

The technique of dual-energy X-ray absorptiometry (DXA) was introduced in the late 1980s when it replaced the older techniques that were isotope-based but the theory behind the technique was basically the same. A DXA apparatus (Figure 11) uses an X-ray tube as the source of photon energy that is sent through the tissues examined at two different energy levels. A detector located on the opposite side measures the reduction in energy from the transmitted X-ray beams (83). Depending on differences in density, tissues like fat and bone will reduce the energy to different extents, which is depicted in the two dimensional X-ray image obtained from a DXA measurement.

DXA is the clinical gold standard method for measuring BMD, and DXA measurements of the hip and spine can be used to predict fracture risk (84). Usually a DXA measurement is aimed at a specific part of the skeleton such as the lumbar spine or the femoral neck but also the total body can be measured. For total body measurements in children, it is recommended to exclude the head since the cranium stands for a disproportionately large part of the child's total skeleton and because the head's proportion of the body varies during growth. Not only bone can be measured; DXA also has the capability to measure body composition in the form of fat mass and lean mass. The method is convenient to use as it is easy to operate, has short scan times and exposes the scanned patient to only low doses of radiation (83). The effective radiation dose from a DXA measurement is higher in children than in adults but can still be considered to be very low. In children the effective dose varies between approximately 0.005 and 0.01 millisievert (mSv) depending on the part of the body being examined (85). This can be compared to the global average effective dose of background radiation which is estimated at 2.4 mSv per year.



Figure 11. Example of a dual-energy X-ray absorptiometry (DXA) apparatus. Source: Nick Smith photography [CC BY-SA 3.0 (<https://creativecommons.org/licenses/by-sa/3.0/>)].

Quantitative ultrasound

Quantitative ultrasound (QUS) is another method to measure bone. The usual site of measurement is the calcaneus. The measurement is usually performed by measuring through the transverse plane of the calcaneus. The outcome variables obtained are speed of sound (SOS; m/s) and broadband ultrasound attenuation (BUA; dB/MHz). The variables reflect how fast the sound waves travel through bone as well as how the sound waves are absorbed in the bone. QUS has been shown to be associated with fracture risk in the elderly and can predict fragility fractures as well as DXA (86, 87). However, the absolute majority of studies examining the fracture-predictive value of QUS have been performed in Caucasian subjects older than 60 years (88). Therefore, the inferences with fracture risk are less clear for

children, adolescents, young adults and people of other ethnicities than Caucasian. Contrary to DXA, which only reflects the quantitative aspects of bone in the form of density, QUS is thought to also reflect some aspects of quality or structure of the bone (89). This is strengthened by the fact that QUS measurements of a piece of bone in three orthogonal directions, will be significantly different from each other (90). However, exactly what part of the structural attribute of bone that is quantified by QUS remains unknown. Nevertheless, QUS is a useful method for measuring bone as it is cheap, portable, easy to use and non-ionizing.

Other methods

There are other ionizing methods for measuring bone than DXA. The most frequently used ionizing method besides DXA is peripheral quantitative computed tomography (pQCT), which can provide a three-dimensional assessment of bone density as volumetric BMD (g/cm^3) compared to areal BMD (g/cm^2) obtained by DXA (83). It can also separate trabecular bone from cortical bone thereby creating an image where the bone microarchitecture can be visualized. This adds more insight into the bone structure compared to DXA but also produces higher doses of radiation. The technique is most commonly used to measure peripheral parts of the skeleton such as the forearm or lower leg, thereby resulting in a rather low effective dose in comparison to the background radiation (85). High-resolution peripheral quantitative computed tomography (HR-pQCT) is a device that can further categorize the microstructure of both cortical and trabecular bone and thus allows more detailed imaging of, for instance, cortical porosity (91, 92). At the moment HR-pQCT is almost only used in research and not in clinical settings.

Physical activity and bone

Together with diet, physical activity is the key factor that can be influenced in order to positively affect bone development (71). Physical activity causes impact and strains to be applied on the skeleton, which in turn causes the bones to adapt to the applied mechanical loading. This was first postulated during the late 19th century by the German anatomist and surgeon Julius Wolff and named *Wolff's law*, although it was not a physical law but instead stated that tissues (including bone) adapt to the forces applied to them. Later during the 1980s, the pioneer of modern bone research, Harold M. Frost, refined *Wolff's law* into the *Mechanostat theory* (93). According to this theory, bone mass and bone structure improves following the strains applied to bone from physical activity, thereby increasing bone strength. Conversely, physical inactivity would result in decreased bone mass and bone structure, causing bone strength to be reduced. Direct external forces applied to the bone secondary to physical activity are not the only key effector for improving bone strength. This also

occurs indirectly via strains applied to bone by the muscles attached to the bones (94).

Bone strength may be improved by physical activities that are dynamic, with moderate to high load, with odd or non-repetitive load direction and with fast loads (95). The mechanical loads that saturate the anabolic capacity of bone are already achieved by short duration, and to achieve the greatest response, periods of rest between the loads are necessary (95). Physical activities that fulfill these demands are for example racket sports, ball sports and other sports that include many ground impacts such as hurdles and long jump (96), while long-distance running, swimming and cycling confer less bone anabolic response (96). It should be emphasized that an activity only exerts a local and site-specific effect on bone in the region where the strains following physical activity are applied (97).

The bone metabolic response to physical activity is markedly different across the lifespan, with the greatest effect found in the late pre- and early peri-pubertal period (97). Physical activity interventions during this period have found that children exposed to increased amounts of physical activity gain significantly higher values of BMC, bone size and BMD (98-110). The reason for the marked response during this period is probably that puberty influences rapid physiological development, where up to 25% of the adult bone mass is acquired (66). There are however problems when interpreting many of the previously published pediatric physical activity intervention studies, since many of these studies have recruited volunteers and have often been of short duration. Very few have investigated the effect of physical activity in population-based cohorts and none have followed children strictly from before until after puberty with an intervention.

The effect of physical activity on bone during adulthood is dramatically lower than that during childhood and adolescence. The positive gains in bone mass during adulthood are considered to be minimal to none, although the age-dependent bone loss to some extent can be prevented (111-113). Higher bone mass, induced by increased physical activity during childhood and adolescence, seems however to be associated with higher bone mass also during adulthood, implying that physical activity induced bone mass benefits possibly track from childhood to adulthood (114-116). This is another finding supporting the notion that physical activity interventions in childhood may be beneficial also in a long-term perspective.

Muscle

In humans as well as in all other mammals, there are three types of muscular tissues: the skeletal muscle tissue, the smooth muscle tissue and the cardiac muscle tissue. In this book we will only focus on skeletal muscle tissue, which is the only muscle tissue we can control voluntarily.

Muscle tissue

Skeletal muscle tissue accounts for approximately 40% of the total body weight and consists mainly of water and protein (117). The muscle mass depends on an interplay between protein synthesis and degradation. These processes are affected by external factors, such as dietary intake, hormones, diseases and physical activity. Muscle tissue is made up of muscle fibers, which are multinucleated cells, which in turn are arranged longitudinally in groups and surrounded by a layer of connective tissue called perimysium (Figure 12). A group of muscle fibers surrounded by a perimysium is called a fascicle. Each muscle contains multiple fascicles, which in turn are surrounded by another layer of connective tissue called epimysium. The ends of a muscle are composed of connective tissue that forms tendons, which attaches the muscle to the skeleton.

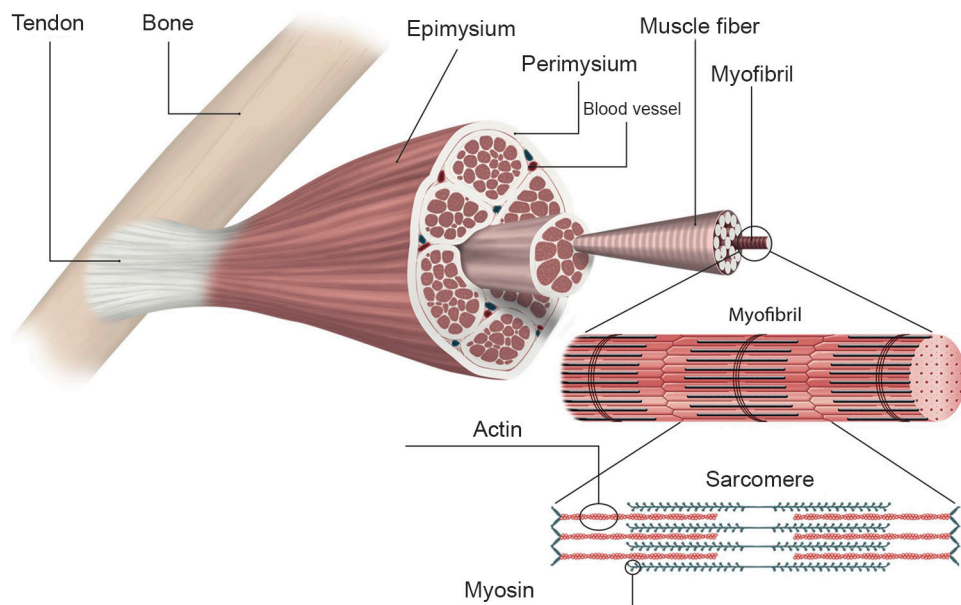


Figure 12.
The anatomy of a skeletal muscle.

Muscle fibers are to the greatest extent made up of proteins that form the element of the myofibril, which is the contractile element of the muscle (118). Myofibrils consist of elements called sarcomeres. The muscle contraction occurs when two types of filaments in the sarcomere, called myosin and actin, slide along each other thereby shortening the myofibril, which in turn shortens the muscle and causes a contraction (117, 118). The muscle fibers are divided into two main types according to their contractile speed and protein content: type I (slow twitch) and type II (fast twitch) (119, 120). Type I fibers, sometimes referred to as “red fibers”, can contract for longer periods of time but with less force, whereas type II fibers, referred to as “white fibers” can contract with greater speed and power but fatigue sooner (120).

Muscle strength

Muscle strength is the result of muscle activation, which in turn can be divided into three types: static, dynamic concentric and dynamic eccentric (Table 4) (117). In the static activation, also known as the isometric activation, muscular activation occurs without the movement of a joint or limb. In this case the muscle also maintains its

length. In the dynamic activations the activation results in movement of a joint or limb with the accompanied shortening (concentric) or lengthening (eccentric) of the muscle (117). Movements performed in artificial situations, such as research or physiotherapy, are called isokinetic as the movement velocity is constant.

Table 4.
Different types of muscle work.

Concentric contraction	Muscle contraction during shortening of a muscle
Dynamic muscle work	Muscle force developed during movement
Dynamic strength	Maximal muscle force developed during movement
Eccentric contraction	Muscle contraction during lengthening of a muscle
Endurance	Ability to perform muscle work over time
Exercise	Physical activity that is planned, structured, repeated and purposeful with the aim of improving or maintaining physical fitness
Isokinetic muscle work	Muscle work during constant movement velocity
Isometric muscle work	Muscle work during static conditions at a pre-defined position of the extremity and against constant resistance
Isotonic muscle work	Muscle work with constant loading but with varying movement velocity
Muscle function	Consists of multiple dimensions such as physical ability, strength, endurance and force
Muscle strength	Maximal force a muscle can produce during pre-defined conditions
Static muscle work	Muscle force developed without movement

During childhood gains in muscle strength are influenced by several factors such as age, sex, maturation and body size (121). Muscle strength is believed to peak sometime between the ages of 20 and 30, kept steady up until the age of 50 and then starts to decline with increasing age (122).

Neuromuscular function

Neuromuscular function is a broad term describing the complex interplay between nerve signals and muscle activation. This process occurs through nerve activation which releases neurotransmitters to the muscle fibers, thereby initiating the process of muscle contraction. The nerve, together with the innervated muscle fibers, is called a motor unit. The motor units are in charge of tuning the movement and force produced by the muscle into either maximal or submaximal work load (123), depending on the actions that are to be performed. The outcome becomes very different when performing different tasks such as lifting a heavy weight or playing piano, as these activities require different ratios between force, power and fine motor skill. Both the numbers and the function of the motor units decrease during ageing, causing loss of muscle power, speed and steadiness (123). This in turn increases the risk of falls and fractures (124, 125).

Physical activity and muscle

Different types of physical activity, such as aerobic and anaerobic physical activity, have different effects on muscle growth and adaptation. During aerobic activity such as running or cycling, different kinds of adaptations occur in the muscles. These include up-regulation of the number and size of mitochondria resulting in an enhanced metabolic capacity (11, 117, 126). During resistance training (Figure 13), which is considered as an anaerobic activity, the muscle adapts to be able to create a greater force. This is achieved by improving neuromuscular function and by producing muscle hypertrophy (127, 128). The hypertrophy mainly occurs by an increase in the size of individual muscle fibers (129). It is then, both in young and old age, necessary to have an adequate dietary intake (117, 130). Increased physical activity can improve muscle strength in both childhood and old age (106, 131-133).



Figure 13.
Dumbbells are commonly used during resistance training. Photo by Mikael Risedal.

Muscle measurements

Muscle measurements can be performed in different ways. Muscle strength can be measured with isokinetic dynamometers, which are dynamometers that move with a constant velocity. These devices measure peak torque (PT; Newton meter (Nm)). A common site to measure is the knee joint, where both flexion and extension can be measured. An alternative is to use handheld dynamometers that measure, for instance, hand grip strength or pinch grip strength. These devices are both smaller and cheaper, and studies have indicated that they are comparable to the isokinetic dynamometers in estimating muscle strength (134). Another way to measure muscles is to quantify muscle mass. This can be performed by using a body composition DXA scan, which separates fat and fat-free tissues and also can separate the fat-free tissue into bone and lean mass (83). Lean mass can be considered as an estimate of muscle mass.

Fractures

Fractures have troubled humans throughout the ages, having long been a threat to the limb and even life (Figure 14). Today most fractures are not life-threatening, but still associated with reduced quality of life and morbidity (135-138). Another concern is the costs that are associated with fractures and fracture treatment (135, 139, 140). This concern is particularly worrisome as fracture rates seem to be increasing. Fractures occur all through life but the fracture incidence peaks in a bimodal manner: in childhood and in old age. The forecasted increasing life expectancy and the larger proportion of elderly in the population will therefore in the future probably give rise to even more fractures and thereby even larger costs (Figures 15-17) (136, 139, 141-144).



Figure 14.
A right-sided hip fracture (seen to the left on the image) visible on an X-ray. Case courtesy of Dr Jeremy Jones, Radiopaedia.org, rID: 6383.

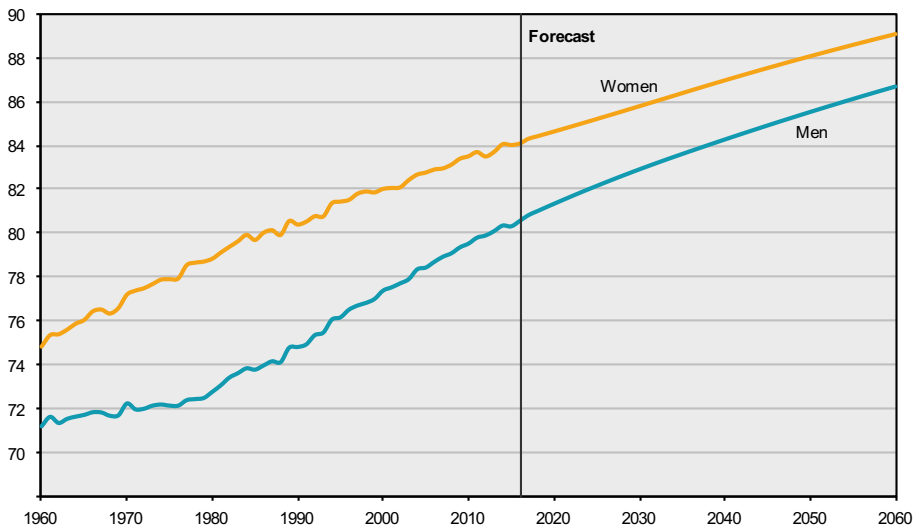


Figure 15. Life expectancy by sex 1960-2016 and forecast for 2017-2060.

Life expectancy has increased from 1960 and is predicted to continue to increase during the coming decades. Source: Statistics Sweden.

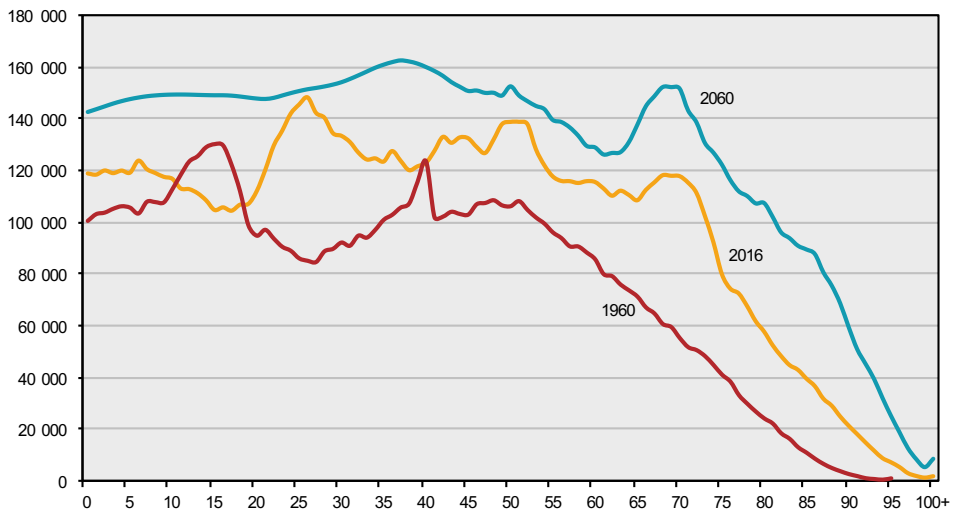


Figure 16. Population by age in 1960 and 2016 and forecast for 2060.

The elderly part of the population has increased from 1960 and is predicted to continue to increase up to 2060. Source: Statistics Sweden.

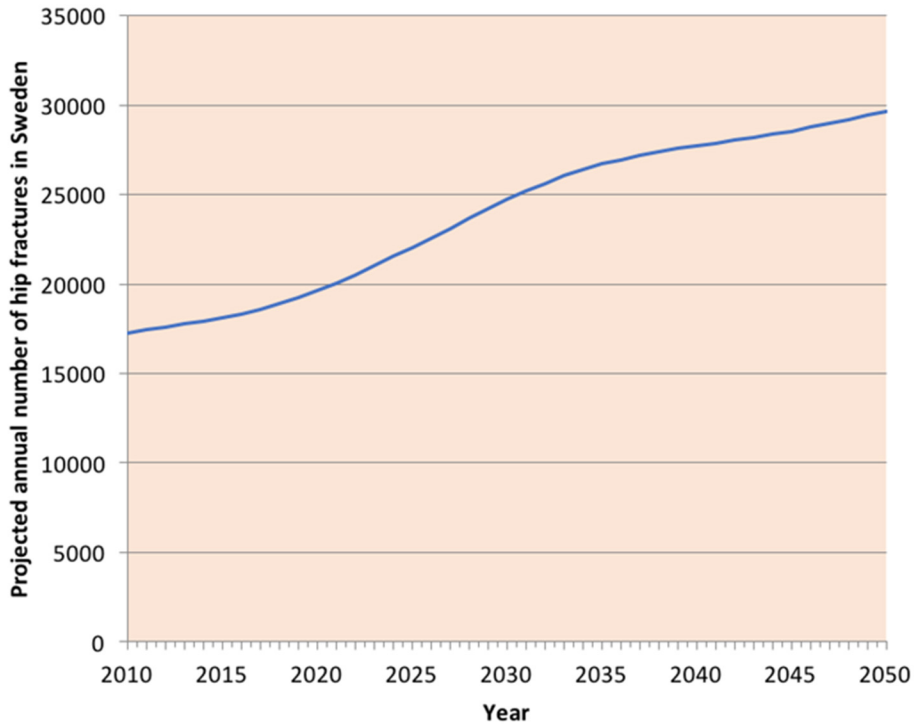


Figure 17. Projected numbers of hip fractures in Sweden for the period 2010–2050 based on the average incidence rate during the period 2002–2012 in Malmö Sweden in 5-year age strata (≥ 50 years). Adapted from: Rosengren and Karlsson (144).

Fractures in young age

Childhood fractures are a significant problem, as up to one third of all children sustain a fracture before the age of 18 years (145). In children the ligaments are stronger than the bones which is why children are more prone to incur fractures than ligament distortions compared to adults. Children also have a lower mineral content and a thicker periosteum than adults do. This sometimes results in only bending, compression or partial breaking of the bone, instead of a complete fracture, as would have happened in an adult. The peak of childhood fractures occurs during the initial phase of puberty, with a higher peak in boys than in girls (Figure 18) (145, 146). Pediatric fracture rates for the most common fracture type, the wrist fracture, have increased during recent decades (147, 148). This raises a concern as a childhood fracture causes pain and discomfort to the affected child, but also as childhood fractures are associated with low bone mass and higher fracture rate in adult life, at least for boys and men (149, 150).

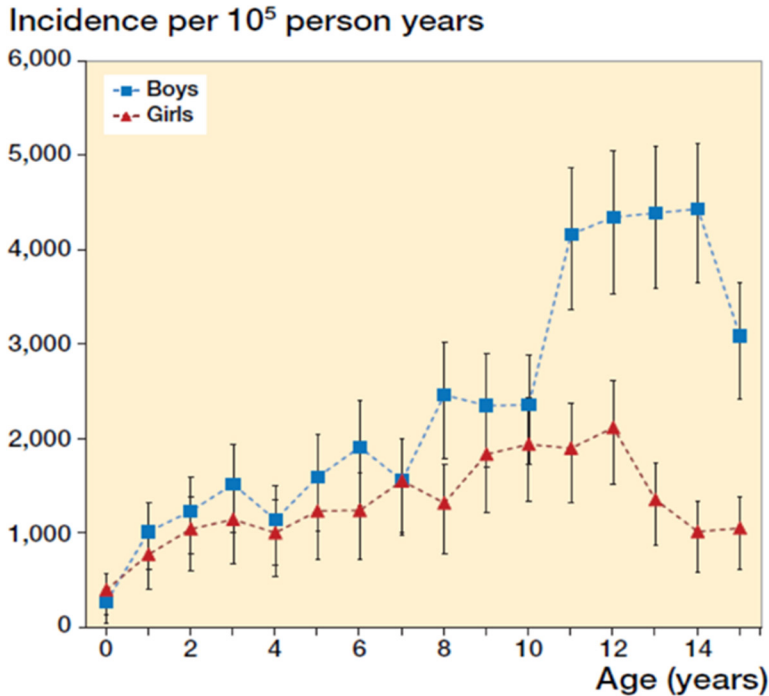


Figure 18. Sex- and age-specific fracture incidence in 1-year classes during the period 2005–2006. Data are expressed as number of fractures per 100 000 person-years, with 95% CI. Adapted from: Lempesis et al. (146).

Fractures in old age

The second rise in fracture incidence begins sometime during the sixth decade of life, earlier in women than in men, as shown already in the 1960s by the Malmö orthopedic surgeon Alffram in one of the first fracture epidemiological studies ever performed (Figure 19) (151). The most common fractures after the age of 50 are for women fractures of the wrist, hip, proximal humerus and vertebra and for men hip, hand, vertebra and rib (142). Women, from adolescence until the fifth decade of life, have lower fracture rates than men, but this gender difference is then changed around the age of 50 (142). The alteration coincides with when women enter menopause, with reduced levels of estrogen. Estrogen has an inhibitory effect on osteoclasts, thereby decreasing bone remodeling and bone resorption, and low levels of estrogen are associated with increased bone loss and thereby higher fracture risk (152). Conversely, women who receive hormone replacement therapy (HRT) have

higher BMD and lower risk for fracture than women not taking HRT (153, 154). The risks of myocardial infarction, stroke, venous thromboembolism and cancer associated with HRT nevertheless outweigh the benefits on bone (154, 155).

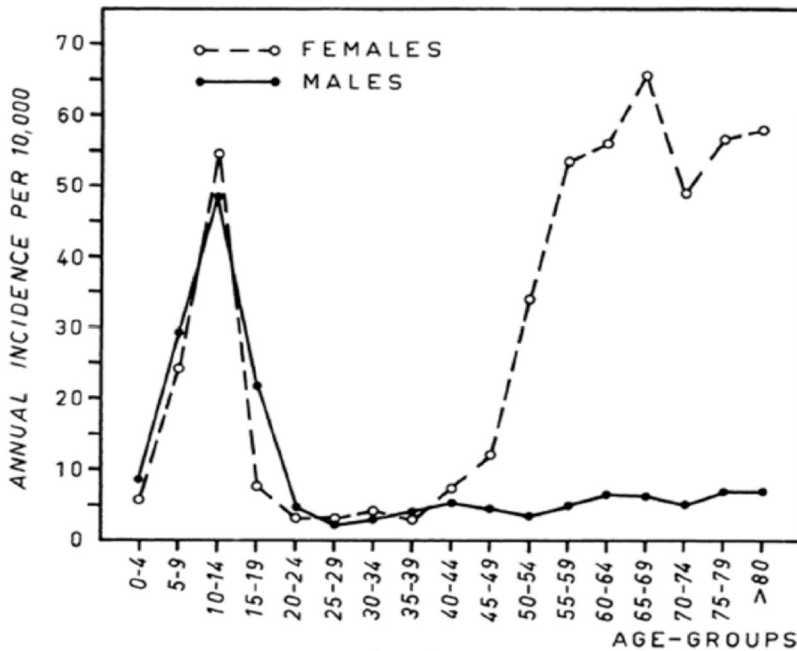


Figure 19. The incidence of distal forearm fractures in Malmö, Sweden per 10 000 person-years by age and gender 1953–1957 as described by Alffram. Source: Alffram et al. (151).

Risk factors and protective factors

Risk factors and protective factors for fracture vary during the lifespan. In this section we will focus on factors associated with fracture risk in childhood and old age, the periods when most fractures occur. Fractures in childhood usually occur after moderate- to high-energy trauma, for instance falling off the back of a horse or from a tree, while in the elderly fractures are usually the result of a low-energy trauma.

Bone mass, body composition and muscle strength

Low bone mass, in both children and elderly, is associated with increased fracture risk (156-158). Some studies in children report increased fracture risk with

increasing body weight (159), while others refute this association (160). Low body weight is associated in elderly with increased risk for several types of fractures, such as hip, spine and wrist fractures (161). The reason for a lower fracture risk in individuals with higher weight could be excess soft tissue, which works as a shock absorber in the event of a trauma, and also that higher weight is associated with higher bone mass (162, 163). However, obesity is also associated with increased risk of other types of fractures, such as ankle fractures (161). The reason for this could be that excess in weight increases the force that is applied to an ankle during a fall. The contribution of muscle function to fracture risk is debated, but low muscle strength seems to be associated with high fracture risk in childhood (164) and low lean mass (165), low muscle strength and inferior neuromuscular function with high fracture risk in the elderly (124, 125, 166).

Physical activity

The effect of physical activity on fracture risk seems to vary depending on the sort and the intensity of the activity performed. In children, physical activity seems to have a dual effect. Participation in vigorous physical activity has been shown to be associated with increased fracture risk, despite beneficial musculoskeletal gains (160), whereas participation in moderately intense physical activity is associated with a trend of declining fracture incidence (167, 168). A reason for the unclear inferences between physical activity and fractures during childhood could be that few studies are population-based and long-term. The reasons for the discrepancy is not fully understood, but physical activity in childhood increases both bone mass and muscle strength (98-106, 131), which theoretically reduces fracture risk (124, 132, 158), but some activities and intensities give more trauma, which theoretically increases fracture risk (160). In old age, physical activity is associated with a reduced risk of both fall and fracture, probably mostly mediated through improvements in neuromuscular function rather than bone mass (111-113, 132, 166).

The long-term relationship between physical activity in childhood and adolescence and fractures later in life are for obvious reasons not very well studied. Some studies, however, indicate that at least in boys and men, there could be an association between physical activity in young years and fractures in old age (169, 170). To be able to verify this, prospective and controlled long-term studies with fractures as endpoint are needed. Although causal evidence still is sparse and unclear, it still is a thrilling thought that increased physical activity during childhood possibly could prevent fractures in old age.

It is finally important to bear in mind, that many of the factors associated with fractures, such as bone mass and muscle strength, are dependent on each other.

Other factors

There are many other factors associated with fracture risk than those described above, such as pharmacological antiresorptive therapy, dietary intake, vitamin D levels, smoking, alcohol consumption, use of sedatives etc., although these factors will not be discussed further in this thesis.

Fracture risk assessments and screening for osteoporosis

To prevent fractures there is a need to identify individuals at high risk by screening. The core in this screening is based on assessing clinical risk factors and measuring BMD or neuromuscular performance. It is important to consider the BMD-independent clinical risk factors, such as age, history of previous fractures, glucocorticoid use, body weight etc., since the majority of fractures affect people who according to their BMD level do not have osteoporosis (171). Instead, the majority have osteopenia with a T-score in BMD between -1.0 and -2.5. The most frequently used tool today that use such risk factors is the Fracture Risk Assessment Tool (FRAX) (172). FRAX combines, in a composite manner, clinical risk factors with or without a measurement of BMD, in order to calculate the 10-year probability of sustaining a hip fracture or other major osteoporotic fracture. An advantage of FRAX is thus that it can be used without a BMD measurement, which is useful in regions and countries where DXA scanners are rare or impractical to use. Thus, the FRAX tool can be used both when considering which patients should undergo a DXA measurement to further assess fracture risk, and in the discussion of which patients should receive anti-fracture interventions without further examinations.

The guidelines regarding which patients should undergo a DXA measurement vary across age, gender, continents and countries. No strict global consensus recommendation exists. Some recommendations suggest that all women over the age of 65 years should undergo DXA regardless of other DXA-independent risk factors (171, 173). Some European countries, including Sweden, do not perform general DXA screenings after a certain age, but only after risk estimations, for instance with FRAX or after an incident fracture (173). For women younger than 65 years, DXA screening is usually recommended when there are specific clinical risk factors beyond low BMD (174). The recommendations for screening in men are not as consistent and vary between different expert group evaluations (171, 174).

Aims

The aims of this thesis were to evaluate:

- If a daily school-based physical activity intervention program during three years would be associated with increased durations of total physical activity, leisure-time physical activity and/or sedentary activity.
- If a daily school-based physical activity intervention program during mean seven years would be associated with increased durations of total physical activity, leisure-time physical activity and/or sedentary activity in both boys and girls.
- If a daily school-based physical activity intervention program from before (Tanner stage 1) until after (Tanner stage 5) puberty would be associated with beneficial developments in musculoskeletal traits and a musculoskeletal composite score.
- If a musculoskeletal composite score could be used to predict fractures in old men.
- If level of physical activity would be associated with a musculoskeletal composite score and fracture incidence in old men.

Hypotheses

Paper I

A three-year daily school-based physical activity intervention program would be associated with increased duration of total physical activity but not with a decreased duration of leisure-time physical activity or an increased duration of sedentary activity, thereby refuting the activity-stat theory.

Paper II

A mean seven-year daily school-based physical activity intervention program would, in both boys and girls, be associated with increased duration of total physical activity without being associated with a decreased duration of leisure-time physical activity or an increased duration of sedentary activity.

Paper III

A daily school-based physical activity intervention program, initiated before and lasting throughout puberty, would be associated with beneficial musculoskeletal developments in children of both sexes, also detectable in a musculoskeletal composite score.

Paper IV

A musculoskeletal composite score would predict fractures in old men superior to a single measurement of femoral neck aBMD and level of physical activity would be associated with the composite score and fracture incidence.

Materials and methods

The Pediatric Osteoporosis Prevention (POP) study

The Pediatric Osteoporosis Prevention (POP) study was initiated in 1999 in the city of Malmö, Sweden. The study is a prospective and controlled population-based intervention study, and examines the effect of daily school-based physical activity, provided as daily classes of PE. The study included one intervention school (Ängslättsskolan) and three control schools (Mellanhedsskolan, Fridhemsskolan and Ribersborgsskolan). All four schools were located in the same geographical area in the southwest part of Malmö and the children had similar socioeconomic background. All schools were government-funded and the children were allocated to the respective schools according to their residential addresses. Before the initiation of the study, all four schools followed the standard national school curriculum of PE of 60 minutes/week. Children with school start 1998-1999 in the intervention school, and 1999-2000 in the control schools, were initially invited to participate in the scientific study. In the year 2000, an additional group of children from the intervention school were invited. The inclusion of participants in the papers in this thesis varies and will be further specified in detail below. The children in the intervention school with school start 1998-1999 were assessed at baseline and then each year up until last year of compulsory school (grade 9). The children in the control schools with school start 1999-2000 were assessed at baseline and then annually from the second year following baseline up until the last year of compulsory school. For the additional group of children invited in the year 2000 in the intervention school, assessments were performed at baseline and then annually from the fourth year following baseline up until last year of compulsory school.

The intervention program

The intervention program consisted of increased duration of school-based PE in the intervention school. The extra PE was provided as daily classes of 40 minutes, all school days during the nine compulsory school years. No extra PE was provided during weekends or school holidays. The extra classes consisted of a variety of different activities, used in the Swedish PE curriculum, such as running, jumping, climbing, playing ball games and dancing and the intervention did not contain any

pre-specified activities. The activities took place both indoors and outdoors and were held and supervised by the children's regular teachers. PE is a mandatory school subject in Sweden and therefore all children had to participate in the extra PE although participation in the scientific study was voluntary. Apart from the extra PE classes, all children in the intervention school followed the same national school curriculum as all other Swedish compulsory schools.

The control schools continued with the standard PE of 60 minutes/week, provided in 1-2 lessons per week, and included activities according to the national school curriculum.

Inclusion of participants

Initially we invited children with school start 1998-1999 in the intervention school, and 1999-2000 in the control schools to participate. In the intervention school we invited a total of 89 boys and 61 girls and in the control schools we invited 170 boys and 157 girls. Of the children in the intervention school, 84 boys and 56 girls accepted participation while in the control schools, 68 boys and 64 girls agreed to participate. After the first study year, we invited another 43 boys and 44 girls with school start in the year 2000 in the intervention school. Of these children, 39 boys and 38 girls agreed to participate.

Paper I

In this study, we included children with school start 1998-1999 in the intervention school and 1999-2000 in the control schools who had participated in the baseline assessment and in the two- and three-year follow-up visits. These predefined inclusion criteria rendered a study cohort of 66 boys and 40 girls in the intervention group and 50 boys and 38 girls in the control group (Figure 20).

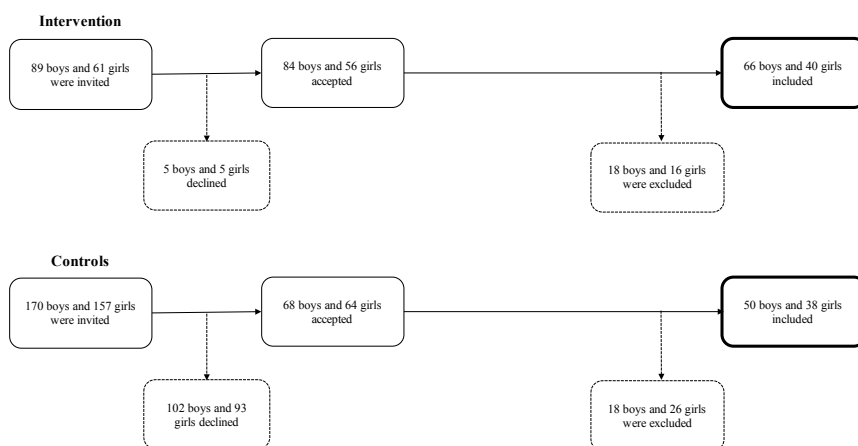


Figure 20.
Flowchart of participants in Paper I.

Paper II

In this study, we included children with school start 1998-2000 in the intervention school and 1999-2000 in the control schools who had participated in the baseline assessment and in any measurement during the last three years of the compulsory school period. We primarily included assessments from the last year. If the last year follow-up was missing we included assessments from the second last follow-up and if this also was missing, the third last follow-up. Moreover, two children in the intervention group were excluded due to disease. These predefined inclusion criteria rendered a study cohort of 89 boys and 63 girls in the intervention group and 38 boys and 38 girls in the control group (Figure 21).

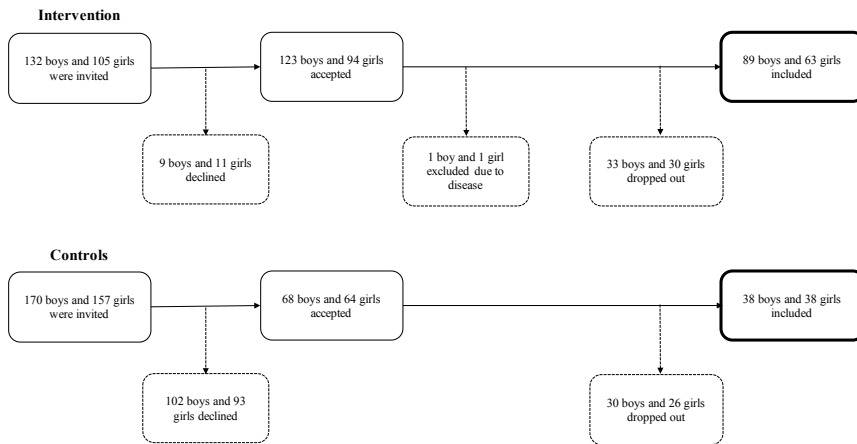


Figure 21.
Flowchart of participants in Paper II.

Paper III

In this study, we followed children with school start 1998-2000 in the intervention school and 1999-2000 in the control schools who at baseline were in Tanner stage 1 and also had a valid measurement in Tanner stage 5. We excluded 4 boys and 2 girls in the intervention group and 1 girl in the control group due to disease or medication. This rendered an inclusion of 63 boys and 34 girls in the intervention group and 26 boys and 17 girls in the control group (Figure 22).

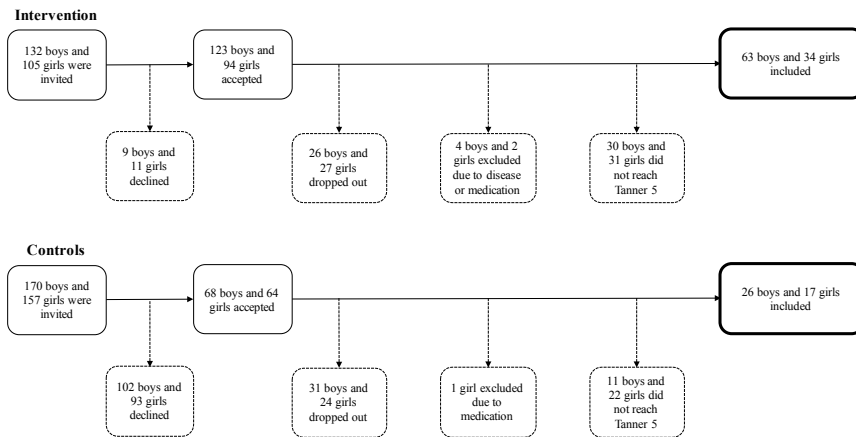


Figure 22.
Flowchart of participants in Paper III.

Assessments

Questionnaire

Prior to each assessment, all included children were provided with a questionnaire. The non-validated questionnaire, which has been used in a number of pediatric studies (102-104, 175, 176), was sent by mail to the home address of each child and then completed with help from a parent or guardian, and also checked by the research staff during the follow-up visit. The questionnaire covered a broad range of questions regarding different aspects of lifestyle, medical conditions, medication use and dietary intake. Specific questions on physical activity and sedentary time were included. We asked the children to specify the duration of organized leisure-time physical activity that they performed (Appendix) separately for summer and winter seasons, as the children can be expected to participate in different activities in different seasons, and we then used an annual mean duration. We defined organized leisure-time physical activity as activities performed in a sports club or sports association (Appendix). The principals of the schools provided us with the amount of school-based PE and we then calculated and defined total physical activity as the sum of organized leisure-time physical activity and school-based PE. Thus, we did not include any unorganized activities such as playing or transportations to and from school. According to the literature, organized leisure-time physical activity is associated with total physical activity (177). In addition, we have performed a post-hoc analysis where we, on group level, compared quartiles of duration of total physical activity estimated by the questionnaire, with physical activity measured by accelerometer during the second year of intervention following baseline. We then found associations between duration of physical activity estimated by the questionnaire and general physical activity estimated as average accelerometer counts per minute (CPM) ($p < 0.001$), moderate physical activity estimated as average number of minutes per day > 3500 CPM ($p < 0.001$) as well as vigorous physical activity estimated as average number of minutes per day > 6000 CPM ($p = 0.002$). In addition to the durations of physical activity, we also asked the children to, in the questionnaire, estimate the time they spent in front of screens, such as television and/or computer and used this as an estimate of sedentary time.

Anthropometry and pubertal status

We assessed weight (kg) using a digital scale (Avery Berkel HL120) and height (cm) using a Holtain Stadiometer. Body mass index (BMI; kg/m^2) was calculated as weight divided by height squared. Pubertal maturation status was estimated according to the Tanner scale (178, 179). At baseline a research nurse assessed Tanner stage and at the follow-up evaluations self-assessment was used. Self-assessment of pubertal stage has been found to correspond well with objective assessments by a physician or nurse (180). During the self-assessment, girls were

presented with images of breasts and pubic hair growth and boys with images of genitalia and pubic hair growth for the different stages of the Tanner scale. The children were then asked to decide what stage they identified themselves within. We did not provide any guidelines on how to decide a definite Tanner stage if the children chose different stages in the two different image scales (breast/pubic hair growth for girls and genitalia/pubic hair growth for boys). The possible errors this could render would however have been the same in both the intervention and control groups, thus we decided that we still could use the data in our studies.

Bone mass and body composition

We used dual-energy X-ray absorptiometry (DXA, DPX-L[®] version 1.3z, Lunar Corporation, Madison, WI, USA) to measure bone mass and body composition (Figure 23). We measured bone mineral content (BMC; g) and areal bone mineral density (aBMD; g/cm²) for total body less head, left side femoral neck and first to fourth lumbar spine vertebrae. We also measured bone area (cm²) for left side femoral neck and lumbar spine. Body composition was estimated as total body lean mass (kg). Our research nurses performed all DXA measurements and the software analyses. The DXA machine was calibrated regularly during the study period with a Lunar Phantom. We used pediatric software for children with a body weight less than 35 kg. The coefficients of variation (CV) were estimated by dual scans in 13 children aged 7-15 years, and were accordingly 1.4-5.2% depending on site for BMC, 1.5% for bone area and 2.4-2.6% depending on site for aBMD.

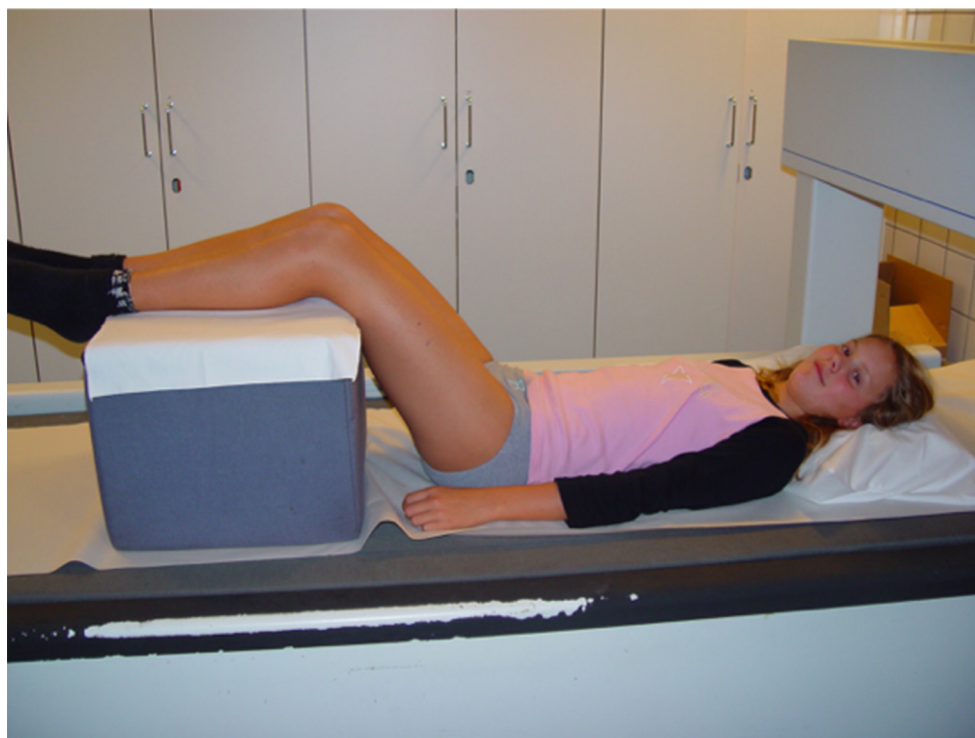


Figure 23.
A child from the POP study being measured in the Malmö DXA apparatus.

We used quantitative ultrasound (QUS, Lunar Achilles model 1061[®], Lunar Corporation, Madison, WI, USA) to measure the calcaneus. This device measures speed of sound (SOS; m/s) and broadband ultrasound attenuation (BUA; dB/MHz) and these estimates also reflect some degree of bone quality (90). All measurements were performed by our research nurses who also calibrated the device on a regular basis. The CV was calculated in the same manner as for DXA and was accordingly 0.2% for SOS and 6.7% for BUA.

Muscle strength

We used a computerized dynamometer (Biodex System III Pro[®]) to assess muscle strength as concentric isokinetic peak torque (PT; Nm) in the right knee joint. The device measured both flexion and extension at two different speeds: 60 and 180 degrees per second ($^{\circ}/s$). The participant was seated in the device and secured with three belts over the upper torso, thigh and pelvis (Figure 24). Pads were used if needed to position the knee joint properly in the machine. The participant was then instructed to perform five repeated movements of flexion and extension at the speed of $60^{\circ}/s$. After 30 seconds of rest another five repeated movements of flexion and

extension were performed at the speed of 180°/s. This provided us with four different endpoint measurements: PT flexion 180°/s, PT extension 180°/s, PT flexion 60°/s and PT extension 60°/s. The movements always started with the right knee in 90 degrees (°) flexion and ended with the knee in 15° flexion. The muscle strength tests were performed by an experienced physiotherapist. We used the highest obtained value of each endpoint in our statistical analyses. The CV, estimated for each endpoint by repeated measurements of 21 children aged 7-15 years, were 6.6% for PT extension 60°/s, 12.1% for PT flexion 60°/s, 12.3% for PT extension 180°/s and 9.1% for PT flexion 180°/s.



Figure 24.
A child from the POP study being measured in the computerized dynamometer (Biodex System III Pro®).

Fractures

We identified fractures among the included children by repeatedly searching the regional radiographic database. Fractures that occurred outside the region (Region Skåne) were registered at follow-up visits at the orthopedic department in Malmö. This method of evaluating incident fractures has been validated in previous studies (142, 181). From the charts and referrals we were able to categorize the trauma mechanism of the fractures according to the Landin classification as high-energy, moderate-energy or low-energy (182).

Dropout analyses

In **Papers I-III**, we performed dropout analyses to assess some aspect of potential selection bias. In **Paper I**, the analysis was performed by comparing the baseline measurements between those children who attended both the baseline visit and the two- and three-year follow-up visits to those who attended baseline but not both follow-up visits. In **Papers II and III**, the analyses were performed by comparing the baseline measurements of children who attended both the baseline visit and the follow-up visit to those who dropped out following the baseline visit. The analyses revealed no statistically significant differences as shown in Tables 5-7.

Paper I

Table 5.

Dropout analysis for **Paper I** comparing baseline variables between those who attended baseline and both follow-up visits (study population) and those who did not attend both follow-up visits (dropouts). Data are presented as numbers (n), means (SDs) and means (95% confidence intervals).

	Study population (n=194)	Dropouts (n=78)	P value
Age (years)	7.8 (0.6)	7.8 (0.6)	0.78
Height (cm)	129.3 (7.0)	128.9 (5.8)	0.63
Weight (kg)	27.9 (5.7)	27.7 (5.1)	0.86
BMI (kg/m ²)	16.5 (2.4)	16.6 (2.2)	0.86
Total physical activity (hours/week)	4.9 (4.5, 5.4)	4.6 (3.9, 5.2)	0.44
Leisure-time physical activity (hours/week)	2.7 (2.4, 3.1)	2.8 (2.2, 3.4)	0.93
Screen-time (hours/day)	1.7 (1.6, 1.8)	1.7 (1.5, 1.9)	0.90

Paper II

Table 6.

Dropout analysis for **Paper II** comparing baseline variables between those who attended both baseline and follow-up (study population) and those who only attended baseline (dropouts). Data are presented as numbers (n), means (SDs) and means (95% confidence intervals).

	Study population (n=228)	Dropouts (n=119)	P value
Age (years)	7.7 (0.6)	7.7 (0.6)	0.53
Height (cm)	128.8 (6.7)	127.8 (6.9)	0.19
Weight (kg)	27.7 (5.3)	27.3 (6.0)	0.52
BMI (kg/m ²)	16.6 (2.3)	16.6 (2.6)	0.99
Total physical activity (hours/week)	5.2 (4.8, 5.6)	4.8 (4.2, 5.5)	0.37
Leisure-time physical activity (hours/week)	2.7 (2.3, 3.1)	2.9 (2.3, 3.4)	0.71
Screen-time (hours/week)	12.1 (11.4, 12.9)	11.7 (10.4, 12.9)	0.56

Paper III

Table 7.

Dropout analysis for **Paper III** comparing baseline variables between those who attended both baseline and follow-up (study population) and those who only attended baseline (dropouts). Data are presented as numbers (n) and means (SDs).

	Study population (n=140)	Dropouts (n=108)	P value
Age (years)	7.7 (0.6)	7.8 (0.6)	0.33
Height (cm)	129.3 (6.1)	129.5 (6.5)	0.79
Weight (kg)	28.4 (5.3)	27.9 (5.9)	0.51
BMI (kg/m ²)	16.9 (2.4)	16.5 (2.4)	0.23
Lean mass (kg)	21.3 (2.8)	21.2 (3.0)	0.62
BMC total body less head (g)	993.4 (172.6)	969.6 (182.8)	0.31
BMC lumbar spine (g)	20.0 (4.4)	19.2 (4.1)	0.19
BMC femoral neck (g)	2.8 (0.5)	2.8 (0.7)	0.77
aBMD total body less head (g/cm ²)	0.85 (0.05)	0.84 (0.05)	0.12
aBMD lumbar spine (g/cm ²)	0.68 (0.10)	0.66 (0.08)	0.19
aBMD femoral neck (g/cm ²)	0.77 (0.11)	0.76 (0.11)	0.89
Bone area lumbar spine (cm ²)	29.2 (3.5)	28.9 (3.9)	0.51
Bone area femoral neck (cm ²)	3.6 (0.3)	3.7 (0.6)	0.61
QUS SOS (m/s)	1530.2 (20.9)	1528.7 (19.6)	0.62
QUS BUA (dB/MHz)	96.2 (9.4)	95.6 (10.9)	0.70
PTextension60°/s (Nm)	43.8 (10.7)	44.0 (11.7)	0.85
PTflexion60°/s (Nm)	23.6 (6.4)	23.4 (6.5)	0.85
PTextension180°/s (Nm)	35.6 (8.3)	35.8 (8.3)	0.86
PTflexion180°/s (Nm)	21.5 (6.0)	21.0 (5.8)	0.49

The Osteoporotic Fractures in Men (MrOs) Sweden study

The Osteoporotic Fractures in Men (MrOs) Sweden study is a prospective population-based multicenter observational study with the primary aim of studying risk factors for osteoporosis and fractures. It includes 3014 elderly men who were aged between 69 and 81 years at study start. The participants were recruited randomly from the Swedish national population register and the inclusion criteria consisted of the men being community-dwelling and able to walk without assistance. The included participants (attendance rate = 45%) were assessed at three hospitals in the cities of Gothenburg (n=1010), Malmö (n=1005) and Uppsala (n=999) from October 2001 until December 2004.

Study period follow-up

The participants were followed prospectively from inclusion and baseline assessment until the date of first fracture, death, relocation or 31 December 2013. The median follow-up time was 9.6 years. During the follow-up period a total of 1237 of the initial 3014 men died or moved.

Assessments

Questionnaire

All participants filled out a detailed questionnaire that included questions on lifestyle, highest completed educational level, falls during the past 12 months and their medical history.

Physical Activity Scale for the Elderly (PASE)

Physical activity level and activities of daily living were assessed by the Physical Activity Scale for the Elderly (PASE) questionnaire. This is a validated self-reported questionnaire that contains 12 different questions regarding physical activity and functional level in the elderly (183). The different questions are weighted and then the results are summarized into a total score, the PASE-score. This score ranges from 0 to 400 or more (although the maximum score limit is set at 400). A higher score indicates a higher level of physical activity. In **Paper IV** we accepted a maximum of two missing answers (of the total 12) and missing values were then replaced by imputation of the mean score for all participants for the respective questions.

Anthropometry

A Harpenden Stadiometer (Holtain Ltd, Crymych, UK) and an electric scale were used to measure height (cm) and weight (kg). We calculated BMI (kg/m^2) as weight divided by height squared.

Bone mass and body composition

DXA with femoral neck software was used to measure BMC (g), aBMD (g/cm^2) and bone area (cm^2) in the femoral neck (Figure 25). We primarily used the measurement from the right side but if this was missing we used the left side. We used total body software to measure total body lean mass (kg). In Gothenburg we used a Hologic DXA Hologic QDR 4500/A-Delphi (Hologic Inc., Bedford, MA, USA) and in Malmö and Uppsala we used a Lunar Prodigy DXA (GE Lunar Corporation, Madison, WI, USA). Our research technicians regularly performed calibrations of the machines.

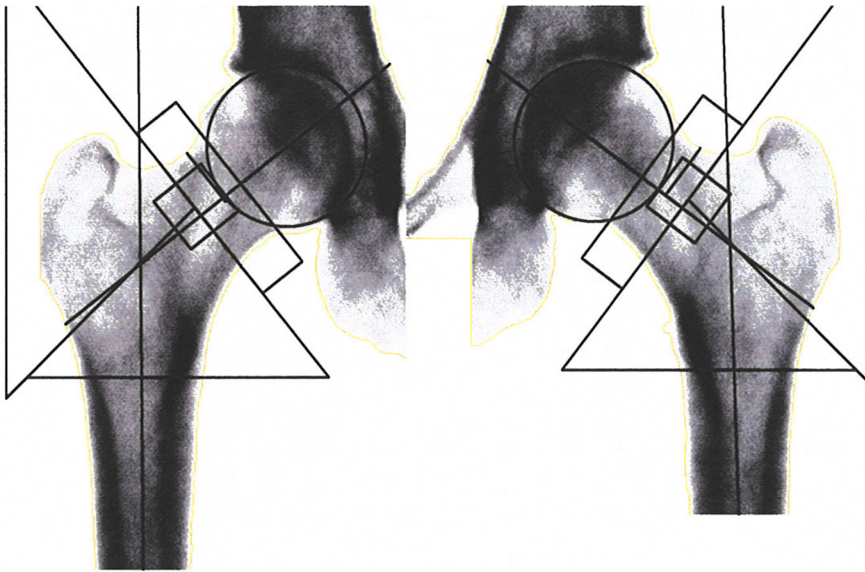


Figure 25.
DXA-scan of the author's right and left hip joints performed with the Malmö DXA machine.

We used QUS (Hologic Sahara, Waltham, MA, USA) to estimate SOS (m/s) and BUA (dB/MHz) in the left calcaneus. These measurements, as mentioned previously, reflect some degree of bone quality (90).

Muscle strength

Muscle strength was estimated as hand grip strength with a hydraulic handheld dynamometer (Jamar[®] 5030J1, Jackson, MI, USA) with adjustable handgrip. The participant was seated in a chair with the arm resting on a table and with the dynamometer gripped in an upright position. We measured two attempts on each hand and used the best of all four measurements in the analyses. We did not measure hand grip strength if a participant had undergone surgery in the hand or arm during the past three months.

Fractures

We identified fractures during the follow-up period from the digital radiographic archives in Gothenburg, Malmö and Uppsala, thus only objectively verified fractures are included in the analyses. We registered the first observed fracture and if a participant sustained multiple fractures on the same occasion only one fracture was included and registered. Therefore, the expression fracture incidence corresponds to individuals with at least one fracture.

Statistical analyses

Papers I-III

We used IBM SPSS Statistics® version 22 for **Paper I** and version 23 for **Papers II-III**. Categorical data are presented as absolute numbers (n) and proportions (%). We present non-skewed data as means with SDs. For comparisons of group differences, we used Chi-squared test, Fischer's exact test, Mann-Whitney U test or Student's t-test. Normality was tested by Shapiro-Wilks test and equal variances by Levene's test. We regarded $p < 0.05$ as a statistically significant difference.

Paper I

In **Paper I** we present skewed data as medians with interquartile range. We present group differences in durations of physical activity and sedentary time as mean differences with 95% confidence intervals (95% CI) derived by bootstrapping 1000 samples. Analysis of covariance (ANCOVA) was used to adjust for covariates age at each year and Tanner stage at the three-year follow-up.

Paper II

In **Paper II** we present skewed data as means with 95% CI since the sample means were normally distributed. Group differences in durations of physical activity and sedentary time are presented as mean differences with 95% CI derived by bootstrapping 10000 samples. We used ANCOVA to adjust for the baseline trait value in the study period change analyses.

Paper III

In **Paper III** we estimated fracture incidence as number of fractures/1000 person-years. We used five traits that reflect musculoskeletal health (lumbar spine BMC and bone area, total body lean mass, calcaneal SOS and muscle strength as knee flexion PT) and calculated a musculoskeletal composite score. We first calculated sex-specific Z-scores for all five traits for each individual (number of SDs above or below the age predicted mean value) and then used the mean Z-score as a composite score. If an individual missed one or two traits we calculated a composite score from the remaining Z-scores. Study period changes were calculated as the difference between the follow-up value and the baseline value. We used ANCOVA adjusted for age at follow-up and baseline trait value (for composite score only baseline trait value) when estimating group differences in the study period changes (from Tanner 1 to 5). Spearman's correlation test was used for correlating average duration of physical activity during the study period with composite score change.

Paper IV

For all statistical analyses in this study we used IBM SPSS Statistics® version 25. Data are presented as absolute numbers (n) with proportions (%) or SDs. We created a musculoskeletal composite score, which included five traits that have previously been reported to be associated with fracture risk: femoral neck BMC, femoral neck bone area, total body lean mass, calcaneal SOS and hand grip strength. For each individual we first calculated Z-scores (number of SDs above or below the age-predicted mean value) for each trait by a linear regression model with age versus included trait. We then used the mean Z-score of the five traits as a composite score. If a participant had missing values for one or two traits we calculated a composite score from the remaining four or three traits. We used DXA machines from two different manufacturers, and thus to be able to compare individuals who were measured by different machines, all traits were transferred to Z-scores within each city cohort (Gothenburg, Malmö and Uppsala). In contrast to the composite score described for the POP study above, the composite score in this study used hand grip strength instead of knee flexion strength as an estimator of muscle strength. We used a Cox proportional hazards model to analyze associations between single musculoskeletal traits, a musculoskeletal composite score, level of physical activity (measured as PASE-score) and incident fractures during the follow-up period. Hazard ratios (HR) are presented with 95% CI for fracture, for a +1 SD change in the musculoskeletal traits, composite score and PASE-score. We also used a linear regression model for estimating the association of level of physical activity (PASE-score) on the various musculoskeletal traits and composite score. We considered $p < 0.05$ statistically significant.

Ethics

The POP study was approved by the ethics committee of Lund University (LU 453-98, LU 368-99) and was registered as a clinical trial (ClinicalTrials.gov. NCT 00633828). The MrOs Sweden study was approved by the ethics committees at Lund, Gothenburg and Uppsala Universities (LU 693/00, Gbg M 014-1, UPS 01-057). Both studies were carried out in accordance with the Declaration of Helsinki and all participants (for the POP study also parents/guardians) gave written informed consent before study start. All patient information was anonymized and data are only reported on group level. There are no moments or examinations in either study that can cause pain or discomfort to the participants and the radiation doses from the DXA measurements are low. If we found any pathologic results during the assessments, the individual was referred to their regular physician for further evaluation and treatment according to current guidelines and treatment protocols.

The intervention program in the POP study was provided to all children at the intervention school (Ängslättskolan), thus it was not voluntary to participate in the extra PE classes since PE in Swedish compulsory school is a compulsory school subject. It was however voluntary to participate in the scientific study and measurements. All included children and their parents/guardians received information about the study. The intervention itself only consisted of increased PE and all children still followed the national school curriculum. The fact that all children had to take part in the extra PE could of course potentially cause discomfort to children who do not like to participate in extra physical activity. However, all activities were carried out at a moderately intense level so that all children had the possibility to take part at their own level. In addition, 93% of the participating children regarded, at study start, PE as being fun, also indicating minimal discomfort from the intervention. Finally, physical activity is associated with numerous positive effects on health, which we argue exceeds the possible risk of discomfort in children who do not like to participate in the extra PE.

The MrOs Sweden study did not include any intervention but only a baseline assessment with physical measurements and a questionnaire. Since no intervention was provided and since these participants were all adults, the possible ethical dilemmas are less than for the POP study. The assessments, just as for the children in the POP study, did not cause any pain or discomfort, although since the participants were elderly men, some might have found the assessments exhausting. The benefits were that individuals with pathological findings could be referred to further examination and treatment.

Summary of papers

Paper I

Introduction: Children of today seem to reduce their levels of physical activity (PA) which could increase the risk of disease. It would therefore be beneficial to increase, with intervention, PA. However, the activity-stat theory states that the total duration of PA in children is constant and cannot be altered by interventions.

Methods: We used a school-based approach and increased the duration of physical education (PE) to 200 minutes/week in one school, the intervention school. Three control schools continued with 60 minutes/week PE. The extra PE was provided to the intervention children throughout compulsory school. We used a questionnaire to evaluate the duration of organized leisure-time PA and the principals provided us with duration of school PE. We then calculated a duration of total PA (sum of organized leisure-time PA and school PE) and also registered duration of sedentary time, estimated as time spent in front of screens, through the questionnaire. These assessments were done at baseline and after two and three years of intervention. Data are presented as mean differences with 95% CI adjusted for age at each year and also Tanner stage at the third-year follow-up.

Participants: We assessed the durations of total PA, leisure-time PA and sedentary time in 66 boys and 40 girls in the intervention cohort and 50 boys and 38 girls in the control cohort.

Results: There were no statistically significant group differences in duration of PA or sedentary time between intervention and control children before intervention start. Two years after intervention start the intervention children had higher durations of both total PA (mean difference boys 4.2 (3.0, 5.6) hours/week and girls 3.4 (2.4, 4.4) hours/week) and organized leisure-time PA (mean difference boys 2.2 (1.0, 3.6) hours/week and girls 1.4 (0.3, 2.5) hours/week). Three years after intervention start the duration of total PA was still significantly higher in the intervention children than in control children (mean difference boys 4.2 (2.4, 6.2) hours/week and girls 2.5 (0.9, 3.9) hours/week). Organized leisure-time PA was significantly higher in the intervention boys compared to their controls (mean difference 2.3 (0.5, 4.4) hours/week) but not in the girls (mean difference 0.5 (-0.1,

2.0) hours/week). There were no statistically significant group differences in sedentary time during the follow-up period.

Conclusions: A school-based PA intervention program, applied for three years in pre-pubertal children, is associated with higher durations of total PA and organized leisure-time PA, without being associated with significant group differences in sedentary time activities. These results oppose the activity-stat theory and suggest that the intervention program might lead to a more physically active lifestyle.

Paper II

Introduction: Physical activity (PA) levels seem to be decreasing globally which is problematic since low PA is a risk factor for disease and death. We therefore assessed whether a school-based PA intervention program would be associated with higher duration of total PA in children in a long-term perspective.

Methods: We increased the amount of physical education (PE) in one school, from 60 minutes/week to 200 minutes/week, provided as daily classes of 40 minutes. We also recruited children from three control schools. These children continued with the regular amount of 60 minutes/week PE. The children were 6-9 years old at baseline. We assessed the duration of organized leisure-time PA, total PA and sedentary time (defined as time spent in front of TV and/or computer) with a questionnaire at baseline and after mean five and mean seven years of intervention. Data are presented as mean differences with 95% CI.

Participants: We included children who had attended the baseline assessment and also an assessment during any of the last three intervention years. We primarily included data from the last year of intervention, and if this was missing we used data from the second last or third last year. This rendered an inclusion of 152 children (89 boys and 63 girls) in the intervention group and 76 children (38 boys and 38 girls) in the control group.

Results: Before intervention start the durations of PA and sedentary time were similar between intervention and control groups (all $p > 0.05$). The intervention group then had a higher duration of total PA compared to controls after both mean five and mean seven years of intervention (all $p < 0.001$). These results remained also in the sex-specific analyses (p-values varying from < 0.001 to 0.03). There were no statistically significant group differences in organized leisure-time PA (p-values varying from 0.08 to 0.77) or sedentary time (p-values varying from 0.31 to 0.91), apart from the intervention girls at the mean seven-year evaluation having a significantly higher duration of sedentary time than their controls (mean difference 3.7 (1.0, 6.4) hours/week).

Conclusions: A school-based PA intervention program was associated with higher duration of PA in children of both sexes with up to mean seven years of intervention, this without being associated with a compensatory increase in sedentary time. These findings oppose the activity-stat theory and also suggest that school-based PA interventions could be a strategy for increasing and maintaining higher durations of PA in children.

Paper III

Introduction: Regular physical activity (PA) in children is associated with high bone mass, beneficial muscle strength and a trend of declining fracture incidence. However, the effects seem to attenuate over time and children often reduce their PA-levels during puberty. We conducted a prospective study to assess whether a school-based PA intervention program from before until after puberty (Tanner stage 1 to 5) would induce beneficial gains in musculoskeletal traits and a musculoskeletal composite score that may explain the trend of declining fracture incidence.

Methods: We followed 63 boys and 34 girls who were exposed to an intervention program consisting of daily classes of physical education (PE) of 40 minutes (total 200 minutes/week). We also followed 26 boys and 17 girls who maintained PE of 60 minutes/week. All children were followed from Tanner stage 1 (mean age 8 years) to Tanner stage 5 (mean age 15 years). At Tanner stage 1 and 5 we measured bone mineral content (BMC; g), bone area (BA; cm²) and total body lean mass (kg) with DXA, calcaneal speed of sound (SOS; m/s) by quantitative ultrasound and knee muscle strength peak torque (PT; Nm) by a computerized dynamometer. To estimate the overall effect of PA on musculoskeletal development we calculated a musculoskeletal composite score, as the mean Z-score of the above mentioned five traits.

Participants: We included children who had attended the baseline assessment when in Tanner stage 1, and a follow-up assessment when in Tanner stage 5. We excluded 4 boys and 2 girls from the intervention cohort and 1 girl from the control cohort due to disease or medication that could affect bone or muscle growth.

Results: Intervention boys gained higher lumbar spine BMC ($p=0.02$) and BA ($p=0.03$) and PT ($p=0.008$) compared to controls. Intervention girls gained higher lumbar spine BMC ($p=0.003$) and BA ($p=0.03$) as well as calcaneal SOS ($p=0.003$) compared to controls. Both intervention boys and girls gained better composite scores than their respective controls (both $p=0.02$).

Conclusions: A school-based PA intervention program provided from Tanner stage 1 to 5 is associated with significant improvements in some (but not all) measured musculoskeletal traits and also in a musculoskeletal composite score.

Paper IV

Introduction: Fractures affect 50% of women and 25% of men after the age of 50 and result in individual suffering and enormous healthcare costs. Thus, detection of individuals at high risk of fracture is necessary. We assessed whether level of physical activity (PA) and a musculoskeletal composite score could be used for fracture prediction and if they had a better predictive value than areal bone mineral density (aBMD).

Methods: We included 3014 men between the ages of 69 and 81 years, from the prospective and population-based observational study MrOs Sweden. We used DXA to measure femoral neck bone mineral content (BMC; g), bone area (BA; cm²), aBMD (g/cm²) and also total body lean mass (TBLM; kg). In addition, we measured calcaneal speed of sound (SOS; m/s) by quantitative ultrasound and hand grip strength (kg) by an adjustable handheld dynamometer. We calculated a composite score as the mean Z-score of the five musculoskeletal traits above. PA was assessed with the Physical Activity Scale for the Elderly (PASE) questionnaire. The participants were followed from inclusion until date of first fracture, death or relocation (median follow-up time 9.6 years). During the follow-up period we registered incident fractures by reviewing the digital X-ray archives of the regional study center hospitals. Data are presented as hazard ratio (HR) with 95% CI or linear regression beta coefficients (B) with 95% CI.

Participants: The participants were randomly selected from the Swedish national population register and then invited for study participation (the attendance rate was 45%). To be included they had to be community-dwelling and able to walk without assistance.

Results: A +1 standard deviation (SD) higher musculoskeletal composite score was associated with an incident fracture HR of 0.61 (0.54, 0.69), which was similar to aBMD (HR = 0.62 (0.57, 0.67)). A +1 SD higher PASE-score was associated with both a higher composite score (B = 0.09 (0.07, 0.12)) and a lower fracture incidence (HR = 0.83 (0.76, 0.90)).

Conclusions: The composite score was equally useful for fracture prediction as femoral neck aBMD and also low level of PA could predict fractures in old men.

General discussion

Physical activity

In **Papers I and II** we found that a daily school-based physical activity intervention program was associated with increased duration of total physical activity and this without being associated with increased duration of sedentary time activity (estimated as screen-time activity). These findings are of great importance since high levels of physical activity are associated with numerous health benefits such as decreased risk for obesity, cardiovascular disease, diabetes and some cancer forms (4, 16-20, 22-25). Inactivity may also be an independent risk factor for disease, irrespective of the accompanying level of physical activity during non-sedentary hours (26). The findings are also important as the inactivity levels in children and adolescents today are far too high (5, 184). For example, a publication from the Public Health Agency of Sweden (*"Folkhälsomyndigheten"*) in 2019 reported that only 9-15% of Swedish children and adolescents aged 13-15 years reached the recommended level of 60 minutes/day of physical activity (185). This worrying inactivity trend is also reflected in the adult population and an association study implies a possible tracking of inactivity from childhood to adulthood (186). The exposure time to inactivity and its related risk factors thus becomes longer, which relates well to the WHO statement that physical inactivity is one of the top risk factors for death globally (4). With this in mind, every attempt to increase physical activity in society has to be considered most important.

During the first two to three years of our intervention, when most children were pre- to early peri-pubertal, there were indications that the children in the intervention group also increased the duration of organized leisure-time physical activity more than the children in the control group (**Paper I**). This led us to speculate that the intervention program made the children adapt to a more physically active lifestyle. However, after mean seven years of intervention (**Paper II**), the organized leisure-time physical activity was similar in the intervention and control children. We speculate that this could be linked to the fact that many children in **Paper II** had approached the later stages of puberty, or had passed through it. Previous studies have reported that children generally reduce their amount of physical activity as they grow older and enter puberty (7-9). However, even though the effect on leisure-time physical activity seemed to be attenuated over time, both the short- and the long-

term data oppose the activity-stat theory (that the total duration of physical activity in children is pre-set and constant). In **Paper I** and **Paper II** we found no relative increase in the duration of sedentary time activity and/or reduction in the duration of leisure-time physical activity in the intervention group compared to the control group. Today most other studies also refute the activity-stat theory (42-46). We acknowledge that we found a higher duration of sedentary time in the intervention girls than in the controls in **Paper II**. The intervention girls then spent 3.7 (1.0, 6.4) (mean difference (95% CI)) hours/week more in front of screens than the control girls at the mean seven-year follow-up and they also had increased their screen-time activity by 3.5 (0.9, 6.2) (mean difference (95% CI)) hours/week more during the follow-up period than the controls. We speculate however that these two findings could have been due to chance, as we found no corresponding differences in boys (**Papers I and II**), or in girls in the short-term study (**Paper I**). Moreover, the duration of total physical activity was statistically significantly higher in the intervention girls compared to controls in both studies (**Papers I and II**), also speaking against the occurrence of compensation and thus opposing the activity-stat theory. We must however highlight that our studies only evaluate organized physical activity as well as screen-time activity and we acknowledge that there are other forms of physical activity and sedentary activity not captured in our studies, that could have been altered in compensation to the intervention.

In this thesis, in **Papers I and II** we have only assessed the effect on physical activity and sedentary time with the intervention still ongoing. It might however be even more interesting to examine what happens with the duration of physical activity after termination of the intervention and even later, when the children enter adulthood. Some studies suggest that there is an association between high durations of physical activity in childhood and high durations of physical activity in adulthood (33, 34). If this proves to be accurate, one could speculate that by increasing physical activity in children, for example through an intervention program, we could also increase the duration of physical activity in adulthood and thereby hopefully also reduce the burden of disease and reduce health care costs.

For our intervention program, we used a school-based setting, where we theoretically could reach all children. There are however some concerns with this type of setting. Firstly, there is a hypothetical risk that other school subjects must be reduced in order to keep the total school week within the maximum allowed school hours, possibly with the consequence of inferior results in other subjects. This was not the case however, as all children followed the national school curriculum and thus received sufficient hours of all compulsory school subjects. Even better, we also found that the intervention program in boys was associated with an improvement in academic achievements (38). No such effect was seen in girls (38) and we speculate that this was because the girls already had high academic performance before the intervention started, with less scope for further

improvement. In summary, these findings speak strongly against any academic disadvantage of receiving the intervention program.

Another concern about implementing the intervention program was that it would result in increased costs for school and society. We oppose this too, since the extra physical activity in our study was provided, organized and supervised by the children's regular teachers without any extra funding. Yet another concern is that increased physical activity in children could result in more injuries and fractures due to falls and other trauma. A previous pediatric study found an association between increased vigorous physical activity and high fracture risk (160). We argue that this is not the case with this intervention program of moderate physical activity, as we actually have found a trend of declining relative fracture incidence by each year of intervention. It should however be noted that during the first year of intervention we found a higher relative fracture incidence in the intervention group compared to the control group (167, 168).

An interesting finding in **Paper II**, although not included as a primary aim, was the lower proportion of children with overweight or obesity at follow-up compared to baseline. We must then clarify that we used BMI at or above the 85th percentile, according to the WHO growth reference, of the sex-specific mean age value (187) as the limit for overweight or obesity. Another way of relating BMI to overweight status in children is to use the iso-BMI system, which is commonly used in Sweden, and also adjusts the BMI value for age and sex (188). When we analyzed the number of children classified as overweight according to iso-BMI, that is with iso-BMI 25, the proportion of overweight boys in the intervention group was only 15% at follow-up compared to 21% at study start. This should be compared with 8% at baseline and 14% at follow-up in the control boys, raising the hypothesis that the intervention program could possibly have a weight-reducing effect in boys (Appendix, Table 8). Why the proportion of boys with iso-BMI 25 at baseline was higher in the intervention group than in the control group is unclear and not possible to evaluate further in our study design. Furthermore, in the girls, the proportion of children with iso-BMI 25 was lower at follow-up in both the intervention and the control groups, thereby not supporting a hypothesis of a weight-reducing effect of our intervention program in girls (Appendix, Table 8). We must clarify that these data should only be regarded as descriptive data, where no comparative statistical analyses should be used, as such comparisons were not preplanned. The gender discrepancy also raises the question of whether the finding of a potential weight-reducing effect in boys occurred by chance.

Single musculoskeletal traits

When assessing the effect of physical activity on musculoskeletal development during childhood it is, once more, important to bear in mind the influence of puberty. A great part of bone accrual takes place during this period. Up to 25% of the peak adult bone mass is acquired during the years 14 to 17 in boys and 12 to 15 in girls (66, 67). The skeleton also seems to be most responsive to physical activity during pre-puberty and the initial early phase of puberty (97). Therefore, it could be argued that physical activity interventions, with the aim of improving bone growth in children, should be initiated before the onset of puberty. Whether or not the same accounts for muscular development is less clear.

Previous pediatric studies have shown an association between regular physical activity and beneficial gains in various musculoskeletal traits (106, 131, 189, 190). However, the initial beneficial effects seem to attenuate over time as the children grow older, especially in boys (106, 131). These studies, however, have possibly been confounded by growth as the children have been in different pubertal stages at follow-up. During puberty children generally reduce their level of physical activity (7-9), which may influence musculoskeletal development. In **Paper III** we therefore designed a study that followed children from pre-puberty (Tanner stage 1) to post-puberty (Tanner stage 5), in order to reduce the confounding effect of including children with different pubertal maturation. Instead we wanted to assess the possible effects of increased physical activity from before to after puberty. We then found statistically significant gains in various musculoskeletal traits in children of both sexes, contrary to the previous publications where the children were in different pubertal stages at follow-up and where statistically significant bone benefits were only found in girls (106, 131). Data in **Paper III** therefore highlight the importance of following children all the way over puberty before drawing inferences as to whether a physical activity intervention program potentially may influence PBM and adult neuromuscular function. The statistically significantly higher gains in the musculoskeletal traits in the intervention girls resulted in them having significantly higher values at follow-up in femoral neck BMC, aBMD and bone area, in lumbar spine aBMD and in the QUS measurements BUA and SOS, compared to the control girls (Appendix, Table 10). Even if there were also statistically significant higher gains in some of the musculoskeletal traits in the intervention boys compared to the controls, there were no statistically significant group differences at follow-up (Appendix, Table 9).

The findings that physical activity is associated with beneficial musculoskeletal gains are of great importance since such benefits are associated with low fracture risk. Bone mass as well as bone size, bone quality and muscle strength are all factors that are associated with fracture risk (88, 106, 114, 124, 132, 158, 168, 191). In addition, the positive association between increased physical activity and increased

gains in bone mass during childhood could possibly be favorable later in adulthood as well. Although bone mass during childhood is mainly influenced by genetic factors, as much as 20-40% of the adult PBM can be altered by external factors, where physical activity probably is one of the most important (71). Also, about 50% of the variance in bone mass at the age of 70 could be explained by the bone mass at the age of 50 and PBM (71, 192). With this in mind, we speculate that reaching a higher PBM means that an individual will begin the downward age-related bone mass loss from a higher level, and accordingly reach the levels for osteopenia and osteoporosis later in life. Theoretical analyses support this by estimating that a 10% increase in PBM could postpone the development of osteoporosis by 13 years (76). If these theoretical calculations are true, the implications of our findings are obvious both for the individual in terms of reduced fracture-related pain and impairment, and for society as a result of reduced costs for fracture treatment and rehabilitation.

Evaluation of bone mass is often used as a surrogate endpoint for the clinically relevant endpoint fractures. Although bone mass probably can be altered by increased physical activity in childhood and thereby possibly also influence fracture risk, children seldom suffer fractures due to low bone mass but rather due to falls and other trauma (182, 193). Therefore, it seems probable that factors that reduce the risk of fall and/or trauma also reduce the number of fractures. One such factor may be muscle strength (194). In **Paper III** we found beneficial gains in muscle strength only in boys but not in girls. The reason for this is unclear but we speculate that boys during their leisure-time engage in strength training such as gym training to a higher degree than girls. Furthermore, as the statistically significantly higher gain in muscle strength was not accompanied by a corresponding gain in total body lean mass, we speculate that factors beyond muscle growth, such as neural adaptation, may contribute to the higher functional muscle strength (195). As we only measured muscle strength as knee flexion and extension we cannot draw any inferences as to whether the intervention program also had effects on other muscle groups.

A musculoskeletal composite score

In many studies the effect of physical activity is estimated by single bone mass or single muscle strength measurements (98-109, 111-113, 131-133). However, to what extent physical activity influences these traits as well as the relative contribution of the traits to fracture risk in children is unclear. We therefore speculated that a musculoskeletal composite score, combining different musculoskeletal traits, could be a better estimate for both the total musculoskeletal effect of physical activity and fracture risk, than single traits. In **Paper III** we found an association between increased duration of physical activity and the composite score, as both boys and girls in the intervention group gained significantly better composite scores than their respective controls. Thus, the score also seems positively associated with duration of physical activity. In a previous study we have reported an inverse correlation between the number of years with the intervention and fracture incidence rate ratio (IRR) (comparing intervention and control group) (106). However, beneficial gains were not found in all individual musculoskeletal traits in the intervention group during the same period (106). Consequently, if we had only used one or a few of these individual traits as surrogate endpoints, we might erroneously have concluded that the physical activity intervention program was not associated with musculoskeletal benefits. We therefore speculate that the composite score, by including several different traits that contribute to fracture risk, could be a better estimate for the potential physical activity-induced fracture-reducing effect. We must state that, due to low statistical power in **Paper III**, we were unable to test whether the composite score actually was associated with reduced fracture risk in children. This was however later verified in old men in **Paper IV**.

Also in adults, other traits than bone mass influence the fracture risk. Previous studies have found associations between high fracture risk and low lean mass (165), low muscle strength and poor neuromuscular function (124, 125, 166). Bone quality, as estimated by QUS, may also be predictive of fractures in adults (88). Thus, in adults too, the use of a single trait to estimate the musculoskeletal effect of physical activity in relation to fractures may lead to erroneous conclusions. Whereas bone mass seems to increase in response to physical activity in children (106, 131, 189, 190) there is no similar gain-effect in adults (although physical activity to some extent seems to slow the age-dependent bone mass loss) (111-113). Physical activity can however improve muscle strength and neuromuscular function also in elderly (132, 133). As shown in **Paper IV**, a musculoskeletal composite score could thus also facilitate the quantification of the musculoskeletal effects of physical activity in adults, or at least in old men.

Fractures

Some studies have inferred that increased vigorous physical activity in children increases the risk of fracture (160). In previous studies on the POP cohort, we have refuted this as the intervention program with increased moderate physical activity was not associated with increased risk of fracture, but instead a trend of gradually lower relative fracture incidence with each year of intervention (apart from the first year where we found a higher relative fracture incidence in the intervention group compared to the control group) (167, 168). These studies, however, could not provide a full explanation for the decreasing fracture incidence in the children who received the extra physical activity, since the musculoskeletal gains in boys were attenuated over time (106). We now speculate that the summarized musculoskeletal composite score could perhaps better capture the effect of the increased physical activity as we found beneficial gains in both boys and girls in **Paper III**, and thereby also possibly provide a better explanatory base for the lower relative fracture incidence in children of both sexes (168). It seems reasonable to think that fracture predictions in children would improve by including other traits than just bone mass. The use of a composite score for pediatric risk evaluations for disease is not a new approach and has already been used for cardiovascular disease (196, 197), but to our knowledge not for pediatric fracture evaluation. In contrast, in adults such scores are already used in the clinical setting, such as the FRAX tool for fracture probability assessment for hip fracture or other major osteoporotic fractures (172). It would be of great interest to use our musculoskeletal composite score for pediatric fracture risk assessments but due to the small cohort in **Paper III** and the risk of conducting a statistical type II error, we instead performed this analysis in old men in **Paper IV**.

We then found, as shown in Figure 26, that a musculoskeletal composite score could predict fractures in old men but not superior to the gold standard fracture predictor, femoral neck aBMD. Therefore, it seems as if a composite score, at least in old men, has limited use for fracture prediction, since it is more complicated and requires additional measurements compared to DXA alone. In addition, the aim in **Paper III** was to develop a composite score and to evaluate whether this score could possibly capture the summarized fracture-sparing effect of increased physical activity more accurately than a single trait measurement, in children of both sexes. In **Paper IV** our aim was to test the score versus the clinically relevant endpoint, fractures, and not to launch it as an alternative score to FRAX. Since we now found that the score could predict fractures, at least in old men, it also seems more probable that it is not only a hypothetically interesting fracture predictive score, but actually also a clinically relevant score.

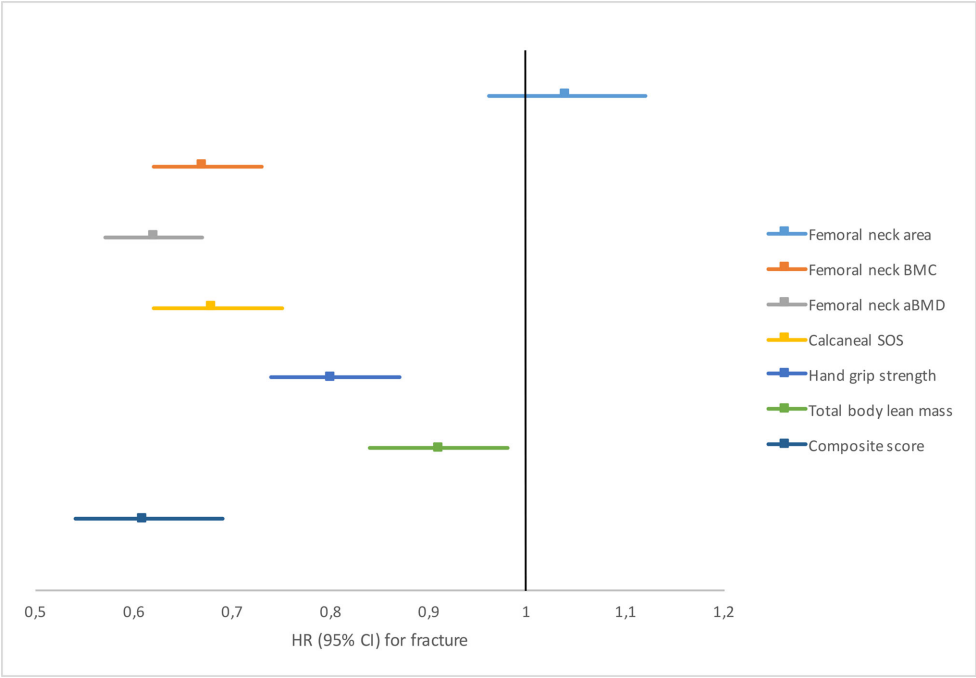


Figure 26. Hazard ratio (HR) with 95% CI for fracture for +1 SD change in musculoskeletal traits and a composite score in old men.

Strengths and limitations

Papers I-III

Strengths

The strengths of these studies are the population-based inclusion of participants from the invited schools, the prospective and controlled study design and the long follow-up period. In many previous pediatric physical activity intervention studies, the included participants, in contrast to our study, have consisted of volunteers, which increases the risk of selection bias. Another strength is that in **Paper III** we followed children from before until after puberty and thus can assess the associations between musculoskeletal traits and the physical activity intervention beyond the pubertal development. To our knowledge this has not previously been done.

Limitations

The principal limitation of these papers is the lack of a randomized study design. This was considered at the planning of the POP study, but was refused by the parents and teachers as being practically impossible. Instead we had to assign the children to the respective groups according to their school allocation. For this reason, we must state that in **Papers I-III** we can only make associations and not draw any conclusions about causality between the intervention program and the outcome variables physical activity, bone mass, muscle strength and composite score. Theoretically it could be other factors than the intervention program, both within and outside the schools, that we cannot control for, that affect the outcome variables. Once again, however, the aim was not to evaluate whether increased physical activity would induce bone mass benefits since this is already known. Instead we wanted to evaluate whether a population-based physical activity intervention program would be associated with musculoskeletal benefits.

The acceptance rate for study participation was markedly lower in the control group (40%) than the intervention group (92%) and as the study proceeded the dropout rates were rather high (around 30%). These are also important limitations as they can increase the risk of selection bias. We do argue, however, that this risk seems low, as the compulsory 1st grade health examinations did not reveal any statistically significant group differences (or any great absolute differences) between the

children who accepted study participation and those who declined. Furthermore, there were no statistically significant group differences (or great absolute differences) in the dropout analyses comparing the dropouts with those who remained in the study (Tables 5-7).

Other limitations are that we used questionnaires to assess the durations of organized leisure-time physical activity and screen-time activity. We are aware of the limitations of this method, including both recall bias and the non-validated questionnaire. However, according to the literature there is an association between organized leisure-time physical activity and total physical activity (177). Also, according to the post-hoc analysis performed on our material, we found on group level, an association between physical activity estimated by the questionnaire and physical activity estimated by accelerometer (see Materials and methods section). We defined total physical activity as the sum of organized leisure-time physical activity and school-based physical activity, thus we did not account for other non-organized physical activity during leisure-time, which is another limitation.

Also we do not know with what intensity the children performed the physical activities neither during school PE nor during leisure-time. We only included screen-time activity as a measure of sedentary time and consequently cannot control for other sedentary behaviors that do not include screens. We tried to address these shortcomings by using objective measurements of physical activity and sedentary time with accelerometers. However, when this study began in 1999, the available devices could only capture data from a few days which does not necessarily reflect the amount of physical activity during a year. Another limitation is that the use of smartphones or tablets was not included in the questionnaire, although during the study years, the use of these devices probably was not as wide spread as today.

We used the Tanner scale for pubertal staging and this was done by our research nurse at baseline and through self-assessment from pictures of pubic hair growth (for both boys and girls), genitalia (boys) and breast stage (girls) at the follow-up visits. We did not provide any guidelines on what stage to choose if there were discrepancies between pubic hair growth stage and genitalia (boys) or breast stage (girls). This, together with the fact that some girls by definition do not reach Tanner 5 breast stage until after giving birth to their first child, are other limitations of these assessments that should be mentioned. Although some studies suggest that self-assessment of pubertal status is an acceptable method, we are aware of the potential lack of validity in these assessments. However, we argue that the potential errors of the pubertal stage assessments would have been equal in the two groups (intervention and control).

Due to low statistical power, we were unable to evaluate the clinically relevant endpoint fractures in **Paper III**. This would have been advantageous as we then might have been able to associate the musculoskeletal composite score with

fractures in children too and not only in old men, as in **Paper IV**. In the children, we only measured muscle strength in the lower extremity as knee flexion and extension, thus we cannot say whether the intervention also had effects on other muscle groups. In addition, we are unable to examine whether the gains in muscle strength in boys were due to peripheral muscle hypertrophy or due to central or peripheral neural adaptation, since we did not measure lean mass in single muscle groups but only estimated total body lean mass. It is known that lean mass is only a rough estimate of muscle mass, as this trait includes all soft tissues except fat.

Finally, since we only included Caucasian children from a socioeconomic middle-class area we are only able to draw inferences regarding this group of children. Ideally, we would have included children with other ethnicities and from other socioeconomic areas to assess whether the intervention was associated with beneficial effects in these settings as well.

Paper IV

Strengths

The primary strengths of this paper are the large sample size and the population-based study design. The well-defined study cohort and the long follow-up period should also be considered as strengths. The inclusion of objectively verified fractures, the evaluation of both bone and muscle traits and the thorough evaluation of level of physical activity with the validated PASE questionnaire are further strengths.

Limitations

The participation rate of 45% is a limitation and could imply a risk of selection bias. The men in the study were all elderly and it is possible that the frailest and sickest men declined participation as the baseline visit, with assessment of various musculoskeletal traits, may have been perceived as exhausting. There is also a possibility of recall bias when the participants estimated their level of physical activity through the PASE questionnaire. The cohort only included elderly men of whom almost all were Caucasian. It would have been advantageous to also include men of other ethnicities, and to evaluate the composite score in women.

Conclusions

The general conclusions of this thesis are that:

A school-based physical activity intervention program with daily classes of 40 minutes (total weekly duration 200 minutes), applied for up to mean seven years in children, is associated with increased duration of total physical activity in both boys and girls, and not associated with increased duration of sedentary time. Our results refute the activity-stat theory.

The intervention program was also associated with increased duration of organized leisure-time physical activity during the first three years in boys and the first two years in girls, but not after mean seven years in any of the sexes.

When the intervention program was applied from before until after puberty (Tanner stage 1 to 5) it was associated, in both boys and girls, with beneficial developments in musculoskeletal traits as well as in a musculoskeletal composite score.

An intervention program of daily school-based physical activity in children may be a method to increase the duration of physical activity and improve musculoskeletal health.

Level of physical activity was, in old men, associated with a musculoskeletal composite score, and the composite score predicted fractures similar to femoral neck aBMD. Low level of physical activity also predicted fractures. Physical activity might therefore be used, not only in children but also in old men, as a fracture-preventive strategy.

Future perspectives

Future studies are necessary to evaluate the duration of physical activity after termination of the intervention program, especially if the intervention participants continue to have a higher duration of physical activity than their controls. It would also be of great interest to compare clinically relevant measures of health, such as obesity, diabetes, hypertension, hypercholesterolemia, fractures as well as sick leave, between the intervention and control groups, and to relate the mean duration of physical activity during growth with these end points.

In addition, future studies should investigate whether the gains in musculoskeletal traits and the composite score will be maintained also after termination of the intervention program, especially if the intervention children reach a higher PBM than the control children. The POP cohort should therefore be followed through the course of life with repeated measurements. In about 50 to 60 years from now we might have data with higher evidence than today, based on a prospective and controlled physical activity intervention study, whether a school-based physical activity intervention program in young years can influence fracture risk in old age or not.

The results and conclusions drawn from the POP cohort (**Papers I-III**) should also be verified by other studies and in other settings to see if our inferences could be generalized to other pediatric cohorts. It would thus be advantageous to include schools from other socioeconomic areas and to include children of other ethnicities. Future studies should also, if possible, include objective measurements of physical activity to increase the validity of the estimations. Today, with the technical advances during recent years, accelerometers could be used over a much longer continuous time period. A higher attendance rate could possibly be reached if the duration of physical activity is assessed through smartphone applications, as a majority of children today carry these devices during most of the day and as most smartphones have a built-in accelerometer.

Future studies should also estimate the predictive value of the composite score for fractures in men with other ethnic backgrounds and in women. Even if the composite score in old men was associated with level of physical activity and predicted fractures, perhaps the most interesting study would be to perform a randomized controlled trial (RCT) with a long follow-up period, to assess whether physical activity actually could be used for fracture prevention in the elderly.

Errata

Paper I

In the methods section, third paragraph: *All children who started school during 2 consecutive years, in any of the 4 schools* should read: *All children who started school during 3 consecutive years, in the 4 schools.*

The figure legend of Figure 1 should read: *Flowchart describing the process of recruitment, measurement and assessment and inclusion for analysis for study participants.*

In the heading of Table 2 the duration of school-based physical activity should read *hours/week* instead of *hours/day*.

Summary in Swedish – Populärvetenskaplig sammanfattning

Allmän bakgrund

Att vara regelbundet fysiskt aktiv är viktigt för hälsan, både för barn och vuxna. Regelbunden fysisk aktivitet associeras exempelvis med lägre risk för att insjukna i de stora folksjukdomarna hjärt-kärlsjukdom och diabetes, men även lägre risk för att drabbas av Alzheimers sjukdom samt vissa cancerformer så som tjocktarmscancer. Fysisk aktivitet medför även starkare skelett, i form av högre benmassa, och starkare muskler. Då både benmassa och muskelstyrka är av betydelse för frakturrisken så skulle ökad fysisk aktivitet teoretiskt sett kunna medföra en minskad risk för att drabbas av frakturer, det vill säga fungera som frakturprofylax. Detta skulle i sin tur kunna resultera i stora vinster, dels för den enskilda individen då frakturer orsakar stort lidande i form av smärta och nedsatt rörelseförmåga, men även för samhället, då frakturer tar stora kostnader i anspråk för hälso- och sjukvården samt för övrig omsorgsverksamhet.

Genom att öka mängden skolidrott skulle man potentiellt kunna stärka upp barns skelett i form av ökad benmassa, samt muskler i form av ökad muskelstyrka. På så vis skulle man både på kort och lång sikt möjligen kunna minska risken att drabbas av frakturer. Dessa tankar stöds av tidigare studier som har visat att det finns ett samband mellan hög benmassa i unga år och hög benmassa i vuxenlivet. De fördelar man då erhållit i unga år i form av ett starkt skelett (hög benmassa) skulle då alltså kunna minska risken för frakturer även i högre åldrar. Frakturrisken beror dock inte enbart på skelettets hållfasthet mätt som benmassa, utan även på andra faktorer så som muskelstyrka, muskelmassa samt skelettstruktur, och fysisk aktivitet kan påverka alla dessa faktorer. Således, för att bättre kunna påvisa den frakturskyddande effekten av fysisk aktivitet skulle man istället för att använda en enstaka mätning av benmassa, kunna använda en summerad riskpoäng för frakturer, en så kallad *composite score* där man utöver benmassa också väger in muskelstyrka, muskelmassa och ett mått på skelettstruktur. En *composite score* är alltså en poäng där man kombinerar och väger in flera olika parametrar för att bättre kunna uppskatta en risk. De används idag ofta vid uppskattning av risk för hjärtinfarkt där man då kombinerar riskfaktorer så som högt blodtryck, höga blodfetter och rökning.

Liknande *composite scores* används också vid uppskattning av frakturnrisk för vuxna men det finns idag inga motsvarande som används för barn.

Innan man kan rekommendera införandet av ökad skolidrott i den svenska grundskolan måste man kunna visa att det finns ett samband mellan ökad skolidrott och ökad fysisk aktivitet. Vissa forskare menar att så inte är fallet, med hänvisning till den så kallade *activity-stat-teorin*. Denna teori hävdar att den totala mängden fysisk aktivitet hos barn är konstant och därför inte kan påverkas med interventioner, i form av exempelvis ökad skolidrott.

Övergripande syfte

Avhandlingens övergripande syfte är att studera: (I) Hur en intervention med daglig skolidrott, på kort och lång sikt, påverkar barns fysiska aktivitetsnivå. (II) Om utvecklingen av benmassa, muskelstyrka och en *composite score* från före till efter puberteten, kan påverkas om vi inför daglig skolidrott. (III) Om en *composite score*, hos äldre män, kan förutsäga risken att drabbas av en fraktur och i så fall om den är bättre på detta än vad bara en enkel mätning av individens benmassa är. (IV) Om fysisk aktivitetsnivå hos äldre män är associerad med en *composite score* och med risken att drabbas av en fraktur.

Hypoteser

Ökad skolidrott är associerad med ökad mängd fysisk aktivitet. Ökad skolidrott från före till efter puberteten är associerad med en gynnsam utveckling av benmassa, muskelstyrka och en *composite score*. En *composite score* kan förutsäga risken att drabbas av en fraktur bättre än bara en enkel mätning av individens benmassa, och fysisk aktivitetsnivå hos äldre män är associerad till både en *composite score* och risken att drabbas av en fraktur.

Bunkefloprojektet

Bunkefloprojektet (på engelska The Pediatric Osteoporosis Prevention (POP) study) startade år 1999 i Bunkeflostrand strax utanför Malmö. Studien inkluderade fyra grundskolor: Ängslättsskolan som blev interventionsskola och tre så kallade kontrollskolor (Mellanhedsskolan, Fridhemsskolan och Ribersborgsskolan). I interventionsskolan infördes daglig skolidrott på schemat, totalt 200 minuter per vecka (40 minuter per skoldag). De tre kontrollskolorna fortsatte med 1-2 lektioner per vecka (genomsnitt 60 minuter per vecka). Vi bjöd in alla barn med skolstart åren 1998-2000 i de fyra skolorna för att delta i studien och av totalt 564 inbjudna barn valde 349 att delta. Barnen i interventionsskolan hade sedan den dagliga skolidrotten under hela grundskoletiden. Deltagarna i de fyra skolorna utvärderades årligen upp till och med nionde klass. Vi skattade, med hjälp av ett frågeformulär, mängden fysisk aktivitet och mängden stillasittande tid framför dator och/eller TV,

och via vår forskningsavdelning mättes benmassa, muskelstyrka, muskelmassa och skelettstruktur.

MrOs Sweden

MrOs Sweden är en studie som utfördes i tre svenska städer: Malmö, Göteborg och Uppsala. Vid starten inkluderades 3014 män i åldrarna 69-81 år. Männen utvärderades vid studiestarten genom mätningar av benmassa, muskelstyrka, muskelmassa och skelettstruktur. Livsstil och fysisk aktivitetsnivå utvärderades med hjälp av ett frågeformulär. Därefter följde vi männen i upp till tio år från studiestarten (till och med 31 december 2013) eller till dess att de flyttade eller dog. Under denna uppföljningstid samlade vi in information i form av röntgenverifierade frakturer.

Resultat

Barnen med daglig skolidrott hade, såväl efter tre och i medeltal sju års intervention, högre mängd fysisk aktivitet jämfört med de barn som endast hade 1-2 lektioner skolidrott per vecka. Vi fann ingen gruppskillnad (interventionsskola jämfört med kontrollskolor) i mängden stillasittande tid. Utvecklingen av benmassa och en *composite score* från före till efter puberteten var hos både pojkar och flickor, som haft daglig skolidrott, bättre än hos de som haft 1-2 lektioner skolidrott per vecka. Hos pojkarna med daglig skolidrott fann vi även en gynnsam utveckling av muskelstyrka i jämförelse med de pojkar som bara haft 1-2 lektioner skolidrott per vecka. Bland de äldre männen fann vi att en *composite score* till viss del kunde förutsäga risken att drabbas av en fraktur, dock inte bättre än en enkel mätning av individens benmassa. De äldre människors fysiska aktivitetsnivå var associerad till deras *composite score* och även till risken att drabbas av en fraktur.

Slutsatser

Daglig skolidrott hos barn är associerad med ökad mängd fysisk aktivitet. Detta fynd motsäger den så kallade *activity-stat-teorin*. Daglig skolidrott är också associerad med en gynnsam utveckling av benmassa, muskelstyrka (bara hos pojkar) och en *composite score* hos både pojkar och flickor, i förhållande till 1-2 lektioner skolidrott per vecka. En *composite score* kan hos äldre män förutsäga risken att drabbas av en fraktur, dock inte bättre än en vad enkel mätning av individens benmassa kan. Fysisk aktivitetsnivå hos äldre män är associerad till både en *composite score* samt risken att drabbas av en fraktur.

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Appendix

Extract from the POP study questionnaire (questions 93-96 and question 108) which were used to estimate durations of physical activity and sedentary time. Questions provided in the original language Swedish:

93. Tränar Du i en idrottsklubb/ar under vinterhalvåret?

Nej Ja

94. Om Ja, Idrott 1: _____tim/vecka

Idrott 2: _____tim/vecka

Idrott 3: _____tim/vecka

95. Tränar Du i en idrottsklubb/ar under sommarhalvåret?

Nej Ja

96. Om Ja, Idrott 1: _____tim/vecka

Idrott 2: _____tim/vecka

Idrott 3: _____tim/vecka

108. Hur många tim/dygn tillbringar Du framför TV, TV-spel eller dator?

_____tim

Additional post-hoc analysis on overweight status in Paper II:

Table 8.

Children included in Paper II who are classified as overweight (iso-BMI 25) at baseline and at last follow-up according to the iso-BMI system as defined by Cole et al. (188). Data are presented as numbers (n) and proportions (%).

	Boys		Girls	
	Intervention (n=89)	Control (n=38)	Intervention (n=62)	Control (n=38)
Iso-BMI 25 at baseline n (%)	19 (21%)	3 (8%)	18 (29%)	4 (11%)
Iso-BMI 25 at follow-up n (%)	12 (15%)	5 (14%)	12 (19%)	3 (8%)



Regular physical activity is associated with numerous health benefits, but the children and adolescents of today are far too inactive. This could, in the long-term perspective, increase the risk of both disease and death, and strategies that increase physical activity are therefore needed.

In addition to reduced risk for disease and death, regular physical activity is also associated with a beneficial musculoskeletal development and reduced fracture risk.

This thesis explores how a school-based physical activity intervention program can affect the duration of total physical activity and musculoskeletal growth in children and also how physical activity is related to musculoskeletal health and fracture risk in old men.

Felix Cronholm was born 1991 in Malmö. He studied medicine at Lund University and is currently working as a Medical Doctor at Skåne University Hospital. He began his doctoral studies during the last year of medical school and the results from these studies are presented in this thesis.

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