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The influence of birth weight, childhood fractures and lifestyle factors on peak bone mass in Norwegian boys and girls between 15-18 years of age *The Tromsø Study, Fit Futures*

Tore Christoffersen

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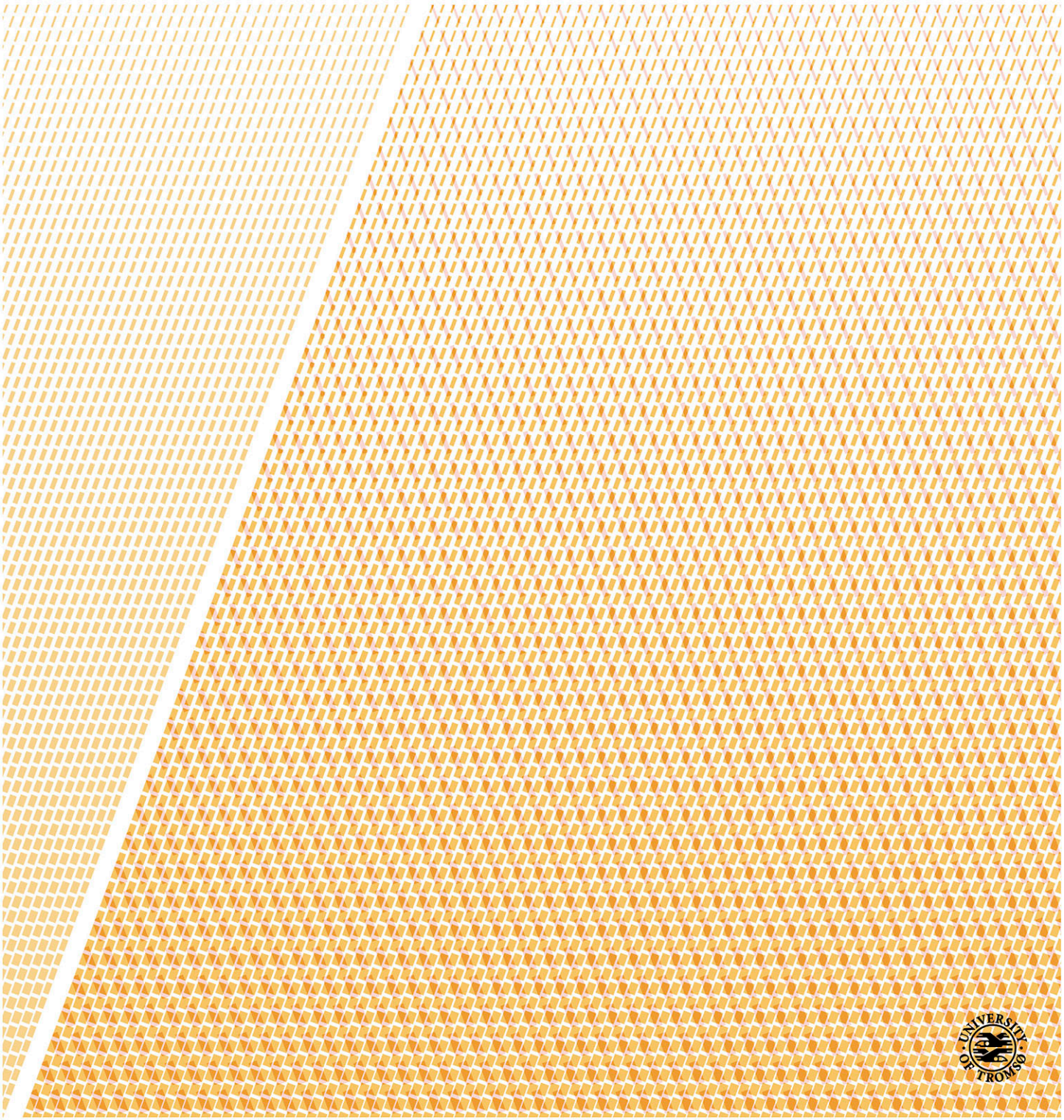

The influence of birth weight, childhood fractures and lifestyle factors on peak bone mass in Norwegian boys and girls between 15-18 years of age.

The Tromsø Study: Fit Futures

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“I was a sailor. I was born upon the tide
And with the sea I did abide.
I sailed a schooner round the Horn to Mexico
I went aloft and furled the mainsail in a blow
And when the yards broke off they said that I got killed
But I am living still.”

From “Highwayman” by Jimmy Webb

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Summary

Background: Osteoporotic fractures in the elderly constitute a major problem worldwide, and the highest incidences of hip fractures ever reported are from the Scandinavian countries including Norway. Fracture risk in old age is determined by bone mass accumulation during growth and subsequent bone loss through adult life. While traditional preventive strategies have focused on the reduction of age-related bone loss and fracture rates among the elderly, attention has recently shifted to the role of peak bone mass (PBM) on bone strength. The basis of bone strength is created during early development and growth, before the achievement and consolidation of a PBM in the second or early third decade of life. In order to optimize PBM, we need to identify modifiable predictors that influence bone mass accrual during growth and the vulnerable period of adolescence.

Objectives: The main aim of this thesis was to investigate the influence of birth parameters, childhood fractures and lifestyle factors on the accrual of bone mass levels among Norwegian adolescents.

Methods: The Tromsø Study, Fit Futures is an expansion of the population based Tromsø Study. In 2010/2011 we invited all first-year upper-secondary school students in Tromsø and surrounding municipalities to a multipurpose health survey. One thousand and thirty eight adolescents 15-18 years of age attended, 508 girls and 530 boys, providing an attendance rate of 93%. We measured hip and total body bone mineral content (BMC) (g), bone mineral density (BMD) (g/cm^2) by Dual-energy X-ray absorptiometry (DXA). Weight and height were measured and information about lifestyle was collected through clinical interviews and an electronic self-reporting questionnaire. All fractures in the cohort were retrospectively recorded from the local hospital UNN Tromsø. Information on birth parameters were collected from the Medical Birth Registry of Norway.

Results: Through childhood, fractures were registered among 35% and 31% of boys and girls, respectively, with incidence rates in correspondence with reports from other Scandinavian countries, although with a slightly more balanced male/female ratio, and an indication of vulnerability at certain stages of sexual maturation. Higher levels of physical activity (PA) in adolescence were associated with increased levels of BMD and BMC, suggesting that participation in PA is of major importance to PBM. Birth weight and length were positively associated with BMD-TB and BMC at all measured sites. However, these associations were attenuated when adjusting for change in size and lifestyle factors during adolescence. We could not confirm that childhood fracture is a marker of persistent skeletal vulnerability as the

association between a previous fracture and bone mineral outcomes appeared inconsistently across levels of physical activity and sex.

List of papers

This thesis is based on the following papers, which are referred to in the text by the Roman numerals I-IV:

Paper I

Christoffersen T, Ahmed LA, Winther A, Nilsen O-A, Furberg A-S, Grimnes G, Dennison EM, Center JR, Eisman JA, Emaus N. Fracture incidence rates in Norwegian children, The Tromsø Study, Fit Futures. *Arch Osteoporos* (2016) 11:40 Epub 2016 Dec 8

Paper II

Christoffersen T**,** Winther A, Nilsen OA, Ahmed LA, Furberg AS, Grimnes G, Dennison EM, Emaus N. Does the frequency and intensity of physical activity in adolescence have an impact on bone? The Tromsø Study, Fit Futures. *BMC Sports Sci Med Rehabil*. 2015 Nov 10;7:26.

Paper III

Christoffersen T, Ahmed LA, Daltveit AK, Dennison EM, Evensen EK, Furberg AS, Gracia-Marco L, Grimnes G, Nilsen OA, Schei B, Tell GS, Vlachopoulous D, Winther A, Emaus N. The influence of birth weight and length on bone mineral density and content in adolescence: The Tromsø Study, Fit Futures. *Arch Osteoporos* 2017 Dec;12(1):54.

Paper IV

Christoffersen T, Emaus N, Dennison EM, Furberg A-S, Gracia-Marco L, Grimnes G, Nilsen O-A, Vlachopoulos D, Winther A, Ahmed LA. The association between childhood fractures and adolescence bone outcomes: a population based study, The Tromsø Study, Fit Futures. (Submitted, under review)

Abbreviations

ANOVA: analysis of variance

aBMD: areal bone mineral density

BA: bone area

BMC: bone mineral content

BMAD: bone mineral apparent density

BMD: bone mineral density

BMD-FN: BMD femoral neck

BMD-TH: BMD total hip

BMD-TB: BMD total body

BMI: body mass index

CI: confidence interval

CV: coefficient of variation

DXA: dual-energy x-ray absorptiometry

GA: gestational age

HBSC: Health Behaviour in School children

HR-PQCT: high resolution peripheral quantitative computed tomography

LM: lean mass

MBRN: Medical Birth Registry of Norway

MRI: magnetic resonance imaging

NIPH: Norwegian Institute of Public Health

OR: Odds ratio

PA: physical activity

PAi: physical activity intensity

PBM: peak bone mass

PDS: Pubertal Development Scale

SD: standard deviation

SPSS: Statistical Package for the Social Sciences

TFF: The Tromsø study, Fit Futures

UiT: UiT The Arctic University if Norway

UNN HF: University Hospital of North Norway

WHO: World Health Organisation

Contents

1. Introduction

1.1. Background

In Norway, socioeconomic conditions have dramatically changed the last 60 years, with improved levels of prosperity, greater food availability and alteration in nutritional intake. In parallel, there is a concern that overall physical activity (PA) levels in the population has decreased, as advanced and affordable technology have reduced the demands for energy expenditure at work, in transportation and in domestic life [1]. Together with increased expectation of life, these changes have created new public health challenges [2], including the costly and widely incidence of musculoskeletal diseases and the sub group osteoporosis and its related osteoporotic fractures.

Osteoporotic fractures among the elderly constitute a major health problem. Norway has among the highest incidents of hip and forearm fractures in the world, with annual estimates of 9,000 hip fractures and 15,000 wrist fractures [3, 4]. In supplement to traditional medical treatment, there is need for optimization of preventive strategies to reduce fracture risk, lower individual suffering and economic costs for the society. This optimization includes identification of early predictors for lifelong high fracture risk, especially the recognition of modifiable life-style factors contributing to bone mass accrual before the observed age-related decline in bone mass. Determinants of the clinically important peak bone mass (PBM) observed in the second decade of life constitute the main theme of this thesis.

1.1.1. The diagnosis of osteoporosis

In 1993, the Consensus Development Conference defined Osteoporosis as “a systemic skeletal disease characterized by low bone mass and microarchitecture deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture” [5]. Later, the National Institutes of Health stated that “ Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture” [6]. The notion “bone strength” includes both measures of bone mass, often expressed as grams (g) of mineral per area (cm^2) or volume (cm^3), and bone quality. The latter incorporates bone turnover, geometry, material properties, architecture and microstructure, including micro damage accumulation [6]. Both definitions pinpoint the major clinical outcome of osteoporosis: the increased risk of fracture.

1.1.2 The burden of fractures

The consequences of osteoporotic fragility fractures are often severe, both for the individual patient and as an economic burden for the society. Although there is an increased risk of almost any type of fractures with compromised bone strength, the most common fracture sites include the hip, the spine and the distal forearm [7]. The consequences of suffering one of the major osteoporotic fractures fall in three broad groups: mortality, morbidity and costs [8].

Globally, hip fractures has been associated with around 740 000 deaths per year [9]. Men, and individuals with comorbidity and poor pre-fracture health, are more likely to die after a hip fracture [10]. Increased risk of mortality is highest immediately after the fracture, with persistent reported risk up to 10-12 years after the injury [11, 12]. Furthermore, the probability of survival after major osteoporotic fractures is significantly lower than in the general population, among both women and men [13].

Among the survivors of an osteoporotic fracture, the individual burden with respect to morbidity is considerable. All fractures lead to reduced quality of life, and may lead to life-long disability. It has been estimated that 40-79% of patients regain their function as it was after suffering a hip fracture [14]. One of ten women become functionally dependent and hip fractures attribute to a major number of nursing home admissions [15]. Although rarely responsible for institutionalization, vertebral fractures affect physical function, self-esteem, body image and mood [14]. In severe cases, vertebral fractures directly produce chronic disability through pain and major deformities [16].

The economic consequence of osteoporotic fractures is huge. Estimates propose that fractures accounts for 0.83% of non-communicable diseases globally, with notable geographical variation. In the United States, the annual cost is estimated to be about $17 billion, with an expected rise to $25 billion by 2025 [17]. Corresponding predictions in UK are estimated to be about £2 billion by 2020 [18]. A worldwide prediction from 1997 estimated the total costs of hip fractures to reach $131.5 billion by 2050 [19]. In Norway, hip fractures alone are estimated to cost 7-9 billion kroner (around $ 1 billion) every year, excluding patients admitted to nursing homes [20].

1.1.3 Geographical variation, secular trends and future predictions

Variation in epidemiology of fragility fractures, dependent of region, country and even within countries is well known [21, 22]. Scandinavia and North America have among the highest hip

fracture rates in the world [23]. Hence, the Caucasian female, settled in tempered climate have the highest risk of hip fractures. Mediterranean and Asian residents have somewhat lower risk, and the lowest risk appears in African countries. Studies have shown that countries in economic transition have increasing age-adjusted fracture rates, whilst rates in some industrialized regions seems to stagnate, and even decrease (Figure 2) [24-27] . This is the case in Norway; between 1999 and 2008, the age standardized total incidence of hip fracture decreased in both women (13.4%) and men (4.8%) [3]. However, Norwegian life expectancy is high and still rising and the population increases. Therefore, population at risk and absolute numbers of fractures are likely to rise [28].

Explanations for the originally high incidence and subsequent trends of decreasing fracture incidences in Norway and other industrialized countries are still incomplete. Several determinants, both of genetic and environmental origin influence measured bone mass and fracture risk. One area still in need of exploration is how lifestyle in the very beginning of life affects bone biology and the genetic disposition for a given Peak Bone Mass (PBM) – the highest obtained bone mass - in early adulthood.

1.2 Bone biology

1.2.1. Bone as a tissue

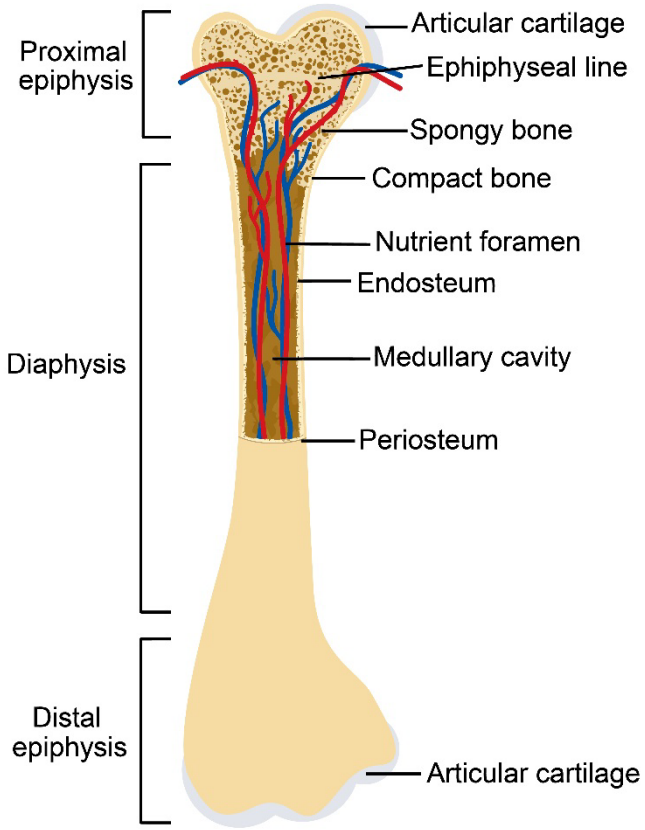
One of the major marks that distinguish vertebrates from invertebrates is the formation of a skeletal system. In mammals, the skeletal system main composites are cartilage and bone (figure 1). Ossification and bone remodeling serves to build bone into specialized connective tissue. The skeletal system, together with cartilage, has three primary functions: metabolic, mechanical and protective. The metabolic function includes production of blood cells in the red bone marrow, storage of triglycerides in the yellow bone marrow, and maintenance of mineral homeostasis by being a reservoir for minerals throughout its components. Important minerals such as phosphate and calcium are continuously loaded and released within the bone, dependent on physiological requirements [29]. The mechanical function incorporates origins and attachments of the muscular system that make bones and muscles work together as a lever. As muscles use energy to contract, antagonistic pairs create movement in bones around joints to perform locomotion. The protective function belongs primarily to the axial skeleton, including the skull, the vertebral column and the ribs, which protect essential tissues like the central nervous system, heart, lung and other intestines from external damage [29].

Bone consists of extracellular matrix with minerals, collagen, water, non-collagenous proteins and lipids, which per se have both mechanical and metabolic functions. The internal architecture of bone depends on position and function, and bone tissue is categorized as two main types; cortical (compact) and trabecular (cancellous) bone. Both are made of the same cells and matrix, but have structural divergence and serve separate functions.

Cortical bone is compact and comprise 80-90 % of the total skeleton. It is typically found in the shafts of long bones in the appendicular sites of the skeletal system, and on the surfaces of flat bones [30]. The strong, stiff and dense properties of cortical bone serve the function of weigh bearing and levers, and as storage and releaser of calcium. It is composed of concentric lamellae surrounding central canals forming osteons. Inside these Haversian systems blood vessels, lymphatic vessels, nerves and connective tissue run parallel with the long axis of the bone, connected with surface vessels through perforating canals [31]. An outer membrane, the periosteum, covers the cortical surface. A corresponding inner structure, the endosteum, makes a membrane towards the marrow cavity [30].

Trabecular or spongy bone comprises 15-20 % of the skeleton. Trabecular plates and rods, averaging 50 to 400 mm in thickness [30], form a honeycomb-like structure, less dense, less stiff, but with greater surface area than cortical bone. It is common at the proximal and distal ends of long bones and in the interior of vertebrae. Trabecular osteons, or packets, are semilunar, approximately 35 mm thick and composed by concentric lamellae. The spongy bone is important for energy absorption and transmissions of loading due to its architecture and mechanical properties. In the vertebral body, the trabecular bone carries approximately 75 % of the load [32], while the high portion of plates and rods near major joints are responsible for managing loading during locomotion [33].

Figure 1. Bone structure.



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1.2.2. Bone cells

In order to accomplish the metabolic, mechanical and protective functions, the skeletal system has evolved into a highly changeable and flexible tissue. Bone endures continuous growth, modeling and remodeling through life. In addition to the osteogenic cells, three main types of specialized bone cells are responsible for the repeated adaptation to physiological demands and mechanical forces.

The osteoblasts are responsible for synthesizing and building bone matrix. Pluripotent self-regenerating stem cells (mesenchymal stem cells, MSC) situated in bone marrow, muscles, and fat hold the property of differentiation to several tissues, including bone. What lineage the MSC follow is dependent of a variety of cytokines that, together with hormones and mechanical signals, initiate and regulate cascades of lineage specific sets of transcription factors [34]. However, MSCs devoted to a phenotype may change because of environmental stimuli during proliferation and end up as a different phenotype [30]. For a MSC to become an osteoblast, the lineage is dependent of the Wnt/β-catenin pathway, with associated proteins [35]. Multitudes of findings have emphasized the significance of this canonical pathway, including embryonic

skeletal patterning, fetal skeletal development and adult skeletal remodeling [30, 34, 35]. The mature osteoblast, characterized by large nuclei, extended Golgi structure and considerable endoplasmic reticulum, secrete type I collagen and associated proteins on the formation sites. An active, mature osteoblast also stimulates osteoclast differentiation by cytokines secretion [34]. The final process or termination of the osteoblast cell lineage includes differentiation into bone lining cells that make the trabecular endosteum and the periosteum on mineralized surfaces. Other osteoblasts are buried in the extracellular matrix and differentiate into osteocytes. This heterogeneity of groups in the cells may explain the variety of microarchitecture throughout the skeleton and differences in diseases depending on anatomical sites [30].

The osteoclast is the only cell known to break down, or resorb the extracellular matrix. Differentiation of osteoclasts comes from the monocyte-macrophage family. Precursors of this family are found in a variety of tissues, but there is consensus that most osteoclasts derive from bone marrow macrophages [30, 36]. Osteoclast genesis is dependent of two cytokines, namely receptor activator of nuclear factor-κB ligand (RANKL) and macrophage-colony stimulating factor (M-CSF). Both cytokines comes from marrow stromal cells and osteoblasts and occur as membrane bound, secreted from activated T-cells, or in soluble forms [36]. Once mature, the osteoclast connects to peptides in the bone matrix via membrane receptors. Binding to the matrix, the cell polarizes and the surface in contact with bone develops a ruffled border, protected by an actin ring and creating a sealing zone around the attachment with the matrix. The osteoclast secretes hydrogen ions that acidify underlying compartments and thus dissolve the mineralization of matrix, followed by digestion of proteinaceous, mainly type I collagen matrix through the release of cathepsin K and other proteases [36].

Osteoblastic cells are, through an unknown mechanism, destined to one out of three terminations: to undergo apoptosis, become lining cells or differentiate into osteocytes [37]. ***The osteocytes*** are buried in lacunae throughout the mineralized matrix and form a cellular network where cells communicate with each other through dendritic processes. The embedded cells represent approximately 95% of bone cells in the adult skeletal system, a quantity notable larger than osteoblasts (4%) and osteoclasts (1-2%) [37]. In addition to internal communication, the dendritic processes, networking through a lacuna-canaliculi system, also radiate towards the bone surface, blood vessels and into the bone marrow. The well-known and probably major function of this system is mechanosensation with responding signals of resorption or formation. Mechanical bending, stretching and compression of bone tissue alter fluid flow and shear stress

within blood vessels, bone marrow and the canaliculi system, which again initiates adequate osteocyte response. In the postnatal and adult skeletal system influenced by gravity, bone formation adapts to loading rates as bone is added where loading is increased and removed in the case of decreased loading or inactivity. A more recent discovery is the role of osteocytes in phosphate hemostasis, hence it can also defined as a endocrine gland [37].

1.2.3 Bone modeling and remodeling

Bone faces a diversity of demands, both with respect to structure and metabolism dependent of age, use and environment throughout life. In order to accomplish its functions as an organ, bone tissue undergoes continuous change and rebuilding. This process of removal of bone matrix by the osteoclasts (bone resorption) and formation of new bone by the osteoblasts (bone formation) is known as bone remodeling. Bone remodeling is the biological phenomenon that prevent accumulation of old bone, maintain calcium homeostasis and rebuild bone architecture as response to micro-damage and altered mechanical loads.

Osteoclasts and osteoblasts are responsible for the actions of bone remodeling in basic multicellular units (BMU). Although biological correspondent, BMU morphological organization differ between cortical and trabecular tissue. During one cycle in cortical tissue, BMUs dig tunnels in the loading direction by the bone resorption properties of a few osteoclasts followed by thousands of osteoblastic tunnel-fillers [38, 39]. In trabecular bone, where the surface to volume ratio is larger, osteoclasts makes trenches 40-60 μm deep at the surface, again followed by osteoblast repairing the pits. However, the remodeling cycle in both cortical and trabecular bone undergoes the same sequence with different identified phases [40]. During the first phase, mononuclear pre-osteoclasts migrate to the bone surface where they form multinuclear cells and initiate resorption. After completing the resorption, a reversal phase starts by the appearance of mononuclear cells that prepare the surface for osteoblasts and provide signals facilitating pre-osteoblastic migration and differentiation. The next phase includes the formation of bone (osteoid) by the team of arriving osteoblasts. Chronological separated from the matrix formation, mineralization finalizes the remodeling cycle, followed by a prolonged quiescent period before a new cycle is initiated [40]. This way, coupling remove and replace packets of bone exposed to micro-damage or susceptible for failing to meet structural demands.

1.3 Bone growth and development

1.3.1 Fetal bone development

During embryogenesis, chondrocytes and osteoblasts, respectively, build the mesoderm-derived tissues of cartilage and bone, and are responsible for a major function in the fetus: very rapid growth. In the first trimester of gestation, approximately 8 weeks after fertilization, patterning of the skeletal system is mainly determined [41]. The first signs of skeletal development is the aggregation of mesenchymal progenitor cells to what becomes anatomical locations [42]. Various cell linages provide various cells to different parts of the embryo. This localization of differentiated skeletal elements are responsible for ossification mechanisms and properties, such as size and shape of the bone. Attained very early in the embryonic growth, this position identity prepares mesenchymal condensation and the next step of skeletal growth [42]. One important matter during the fetal development is ossification of bone. Ossification centers appear sequential throughout the embryonic stages, and include osteoblast differentiation, matrix production, mineralization and vasculogenesis [43]. At the same time, ossification is closely coupled with bone resorption to maintain the bone shape. Hence, the phenomenon of bone remodeling starts early in fetal life, and already at 16-20 weeks of gestation, bone remodeling is prominent. The skeletal system is ready for rapid development, and indeed, between 16 and 41 weeks of gestation, femur elongation rate is 0.35 mm daily on average [44]. The fetus is in need of huge portions of proteins and minerals for the rapid growth. Active transport across the placenta transfers substances and during the third trimester, it is estimated that more than 150 g of calcium and 70 g phosphorus per kilogram of fetus body weight are delivered this way [45]. The mechanisms responsible for the transport of calcium from mother to fetus are not fully understood, and the phosphorous transport is even less well known. However, parathyroid hormone related peptide (PTHrP), produced by the placenta, umbilical cord, fetus and breast tissue, is recognized as the hormone responsible for active transportation of minerals [46]. In contrast, fetus serum contain low levels of parathyroid hormone (PTH) and vitamin D, hormones known to be hallmarks of adult mineral homeostasis [47]. Moreover, the findings of growth hormone and cortisol as predictors for birth weight support the hypothesis that environmental stimuli of the fetus may adjust skeletal sensitivity to these hormones in later life [48].

1.3.2. Neonatal bone development

At birth, several changes to the mechanisms responsible for skeletal growth occurs. The rapid rate of skeletal growth continues but removal of the placenta requires new sources of building blocks and altered tools for utilizing them. In contrast to the mechanical influences in utero, where movement is mostly resistance against the amniotic fluid, the neonatal is exposed to gravity with progressively increased loco-motional requirements. During gestation, calcium levels are higher in the fetus than in its mother's serum [41]. At birth, the calcium levels decrease towards a base level and the newborn becomes reliant on intestinal calcium absorption. Parathyroid Hormone (PTH) and vitamin D conduct the mineral homeostasis and indeed PTH levels increase fast in newborns [41]. In case of maternal vitamin D deficiency or diabetes, premature birth, infants small for gestational age and with vitamin D deficiency, the fast mineralization of bone in infancy make the newborn susceptible for hypocalcemia. Another, more extrinsic influence that affect bone development during the very early period of life is maternal nutritional status under gestation. In pregnant rats, diets with low protein content have resulted in decreases bone area (BA) and bone mineral content (BMC) in adult offspring [49]. In addition, undernutrition in utero may modify the genetic programming of adult bone mineral density (BMD) and bone size [50] and seasonal variation or residence in regions with restricted sun exposure may influence BMC, probably because of reduction of maternal vitamin D levels [51].

1.3.3 Sex differences in skeletal development

The greatest difference between males and females with respect to skeletal development and bone morphology, occur in connection with puberty. Females may hold a smaller skeleton at birth and have 1-2 years shorter pre-pubertal growth because of earlier onset of puberty compared to males [52]. Although bone length development before puberty seem equal, some studies have pointed to wider bones among males than females [53], probably due to exposure to sex hormones, whilst others demonstrate no differences [54]. At puberty, the appendicular growth rate slows down and the axial growth rate accelerates. Growth in stature changes from approximately two times greater rate in advantage of appendicular growth during childhood, through a balanced rate during the first two years of puberty, reaching a greater rate in advantage of axial growth in late puberty [52]. In boys, periosteal apposition and endosteal resorption increase bone width and expand inner cavity, respectively, during puberty. As the apposition is higher, cortical thickness increase, probably because of higher levels of androgens in pubertal

boys [55]. In girls, the net effect of decelerated periosteal apposition and stable cavity construct a smaller bone with respect to size, yet with similar cortical thickness, compared to boys [52].

1.4. Determinants of peak bone mass and adult bone health

In childhood and adolescence, the skeleton continues its rapid growth in length and thickness. The appendicular and axial regions contribute with different rates at different times to the final stature result. During this period of bone development, cellular mechanisms and activity favor net bone formation, which on the diaphyseal side of the epiphyseal plate drive growth in length, while thickness development is due to bone formation on the periosteal surface. Simultaneously, bone resorption on the endosteal surface increases the medullary cavity [52]. At the end of skeletal maturity, osteoclastic bone resorption and osteoblastic bone formation becomes balanced, a final stature or height is achieved and the maximal amount of bone tissue consolidates. This plateau, which occur at the end of the second or early in the third decade of life, is defined as the peak bone mass (PBM) [56]. Although 70-80% of population variance in PBM can be explained by genetics [57, 58], the variation in bone mass and properties accomplished during growth is probably more crucial for fracture risk in adulthood, than individual variation in bone loss over years [52, 59]. Thus, identification of modifiable determinants to exalt the genetic potential is of major concern.

1.4.1 Birth weight and length

Described in previous section 1.3, during pregnancy the skeletal system develop rapidly, with great demands of sufficient nutrition, mainly proteins and minerals. Population studies based on birth records have demonstrated that undernutrition during this critical phase, leading to low birth weight, enhanced the risk of several diseases including coronary heart disease, diabetes and hypercholesterolemia [60]. This phenomenon is known as fetal programming, based on the hypothesis of Barker [61] and describes alterations in tissue structure and function because of “memories” of environmental stimuli during early development. In many years, Rickets has demonstrated that malnutrition during development also have consequences with respect to the skeletal system [62]. However, the realization connected to fetal programming is the early nutritional role on diseases later in life. Evidence that fetal programming, with birth weight as a proxy, contribute to the risk of bone health is continuously accumulating [63]. Based on the same rationale, birth length represents a proxy for environmental stimuli during the fetal period. Moreover, several studies suggest that birth length is more important in predicting adult height and that birth length and birth weight independently predict final adult stature both in term and

pre-term infants, yet weaker in the latter [64]. Nevertheless, there is still a need to confirm the role of fetal programming on bone mineral accrual taking into account life-style factors after birth.

1.4.2 Physical activity and exercise

The level of evidence for a beneficial effect of PA and exercise on bone mass and density during growth is high [65]. PA is defined as body movement by muscle contraction leading to energy expenditure above resting levels [66], while exercise is planned, organized, repeated and targeted physical activity for increasing or preserving components of fitness or health outcomes, such as bone strength [66]. In animal studies, increased bone loading through reaction force impact and muscle forces induce deformation or strains on whole bone [67, 68]. As elaborated above, osteocytes sense the strain and transduce mechanical loading into biological signals, regulating the activity of osteoclasts and osteoblasts. Hence, bone adapts to changes in physical activity levels and exercise, or other miscellaneous alterations in mechanical loading (e.g. change in body weight and microgravity). To achieve a notable osteogenic effect, the mechanical loading must exceed an individual given and bone site-specific threshold set by habitual activity, maturation, sex and other factors. Therefore, the same mechanical loading may produce different responses with respect to bone mass and structure, i.e. a habitual inactive person may benefit more from low strains than an already vigorous active person [65, 69]. The growing bone has greater susceptibility for adequately response to changed mechanical loading compared to adult bone [70-77] and escalating evidence suggest that pre- and early puberty are the most advantageous time periods [73, 74].

However, knowledge about quantification of PA dimensions (duration, frequency, intensity, type and timing) in order to maximize the genetic potential for bone mass (and strength) accumulation is still incomplete. Isometric loading and exercise where ground reaction forces are low (e.g. swimming and cycling) yield a minimum of bone formation response, and mechanical loading applied at low strain rates or held at constant rates over time give lower adaptive responses than rapid applied, high strains [78-81]. In the case of the latter, few cycles give notable response with a fast saturation, thus long duration of high strain fail to yield additional effect [80, 82, 83]. In addition, due to the recovery of cell sensitivity during inactivity, exercise may induce a greater osteogenic effect if rest periods separate bouts of strains [84].

Early cross-sectional and retrospective studies suggested that the effect of childhood and adolescent exercise on bone were lost during adulthood [85-87]. Other longitudinal investigations, starting in childhood, reported effects on BMC up to 8 years after the exercise intervention [88-90]. Therefore, PA and exercise during pre- and pubertal ages may have a modest effect on adult bone mass and thus a marginal effect on prevention of osteoporotic fractures in older ages. On the other side, the large proportion of active bone formatting cells during growth, which respond well to mechanical loading, do not only lead to changes in BMD and BMC. Skeletal response to exercise also induces changes to geometry, structural properties and material traits, showed through variation in bone size between the active and inactive arm in tennis players [74, 91]. This indicates how periosteal apposition shapes a structure dependent on mechanical loading during growth, and how site specific (in terms of anterior-posterior vs lateral-medial) periosteal apposition optimizes bone strength with a minimum of bone mass [52]. A modest retention of bone mass from childhood through adolescence to adulthood probably correspond to a significantly higher preservation of bone strength through architecture and geometry. Taken together, approaches to identify the optimal dimensions and timing of physical activity as determinant of PBM and peak bone strength, can elicit improved data on preventive strategies for later osteoporotic fractures.

1.4.3 Body composition and nutrition

In adults, body weight is the greatest single determinant of bone mass variability and adjusted for stature it explains approximately 50% of the variance at a population level [58]. Among youths, body mass index (BMI) is positively associated with bone mass, and weight stability or maintenance is recognized as protective with respect to future fracture risk [92-95]. There are some indications that the positive association between BMI and BMD/BMC at some point reaches a threshold and a further increase in BMI gives limited, if any, profit [96, 97]. Moreover, lean mass is likely to be responsible for the positive association between BMI and bone mineral parameters, and structural strength [96, 98-101]. A considerable threat to the interpretation of lean mass as a predictor for PBM lies in the complexity of strong heritability for both lean mass and bone, with 69 - 88% covariance between lean mass and BMD due to additive genetic components, dependent of skeletal site [65]. The role of fat mass in the achievement of PBM is more controversial, yet made highly current due to the rising burden of childhood obesity in industrialized regions. Increased body weight due to adiposity may enhance mechanical loading of bone, yet depending on the source of adipose tissue, metabolic effects may be deleterious or anabolic with respect to bone [65, 92].

The key micronutrients widely accepted as important for bone health are calcium and vitamin D. In the former, findings in observational and intervention studies reveal discrepancy, but a recent systematic review described the evidence of a beneficial effect of calcium on bone as strong, based on results from multitude of randomized controlled trials (RCT) [65]. The 1,000 g of calcium in the adult body is mainly (99%) located in the bone mineral matrix as hydroxyapatite and serve as a source to numerous calcium dependent biological systems, as a key factor in the weight-bearing properties of bone, and as maintenance of blood ionized calcium [102]. Low levels of calcium in growing individuals have been shown to limit bone accumulation [103] and to be associated with childhood fractures in both sexes [104, 105]. However, in the case of calcium intake above requirements, any additional beneficial effect is unlikely; hence, calcium can be considered a threshold nutrient [65]. Adequate intestinal calcium absorption depend on sufficient vitamin D levels, which is mainly synthesized through solar or UVB irradiation to the skin. The level of evidence for benefits of vitamin D on bone accrual is set to moderate based on well-conducted RCTs [65]. However, among children in general and especially in late adolescence, vitamin D deficiency is common [106-110] and studies with low baseline levels of serum vitamin D showed significant effects on BMC and BMD [111, 112]. With respect to micronutrients other than calcium and vitamin D, several have been postulated to have an effect on bone, including magnesium, fluoride, vitamin C, vitamin K, zinc, iron, sodium and phosphorus. The overall evidence for effects on bone among these are still inadequate and need further investigation [65].

1.4.4 Tobacco and alcohol

In adulthood, smoking predisposes bone loss following several pathophysiological mechanisms and includes all anatomical sites through both BMD-dependent and BMD-independent factors. Dose and duration influence the magnitude of adverse effects, and studies have observed a reversible effect following cessation [113]. In adolescents, association between tobacco use and BMD-levels are contradictory [58, 114, 115], probably because of heterogeneity in smoking habits and difficulties in controlling confounding factors.

Likewise, among adults, alcohol consumption is likely to suppress bone formation and studies showed an association between excessive alcohol consumption and reduced BMD [58]. On the other side, a meta-analysis concluded that moderate alcohol consumption may have a beneficial effect on bone mineral outcome [116] . Nevertheless, the association between alcohol and bone mineral accrual in adolescence is unclear [58, 114].

1.4.5 Fractures during growth

Childhood fractures are common [117-119]. The incidence of childhood fractures peaks in late childhood and early adolescence with critical periods between 10-12 years of age in girls and between 12-14 years of age in boys [117]. This corresponds to the time of pubertal growth spurt where linear growth peak ahead of bone mass, resulting in reduced bone strength. Some sites (e.g. the distal metaphysis of distal radius) are more susceptible to the phenomenon that longitudinal growth outpaces bone formation on trabecular surfaces arriving from the growth plate, leading to transitory porosity [120-122]. And indeed, distal forearm fractures are the most common fracture in early adolescence [123]. However, in late puberty longitudinal bone growth is markedly decreased, while bone formation continue at cortical and trabecular surfaces. Studies suggest that low areal BMD independently increases the risk for sustaining a fracture throughout childhood in both sexes [124, 125]. In some studies, girls that experience a forearm fracture during childhood fail to reach the BMC levels observed in peers without fractures [126, 127], which together with tracking and heritability of BMC indicate that these fractures are markers of a persistent bone fragility. Other factors associated with fractures during growth includes previous fractures, high body weight and physical inactivity [124, 128]. Whether the beneficial effect of physical activity on bone surpass the increased risk of fracture due to injury exposure, is still to be elucidated.

1.4.6 Measuring bone tissue

Dual energy x-ray absorptiometry (DXA) is the most common method of measuring bone mineral parameters (Figure 2) [129]. The method has been considered a good and feasible surrogate measure of bone strength due to very low ionizing radiation doses and provision of precise results, and its measure of bone mineral content (BMC) divided by scanned area to provide bone mineral density (BMD) predicts 60-70% of bone strength variability [130].

Figure 2. Measurement of bone mineral density using dual energy x-ray absorptiometry (DXA).

The main rationale for DXA examinations is the documented relationship between BMD and the probability of fracture [131, 132], and the reference values based on DXA measurements that define the diagnosis criteria for osteoporosis. Although several non-invasive three-dimensional techniques have been developed for both clinical and research utilization, including quantitative computed tomography (QCT), high resolution QCT (HR-pQCT) and magnetic resonance imaging (MRI), their advantages with robust geometric and volumetric bone density quantification has not outdistanced the feasibility and precision of DXA.

2.0 RATIONALE AND AIMS

Osteoporotic fractures in the elderly causes serious negative health effects and constitute a major economic burden globally [8]. Norway have among the highest incidents of hip and forearm fractures reported, with a prognostic increase in numbers of fractures because of an ageing population [3, 28]. Measured BMD levels in the adult population is a suitable surrogate measure of bone strength with a strong relationship to fracture risk [130]. In elderly, BMD is a function of amount bone gained during development and growth and the amount lost during ageing [121, 133]. Traditionally, treatment and preventive strategies have put emphasis on the latter together aiming to reduce fracture severity and frequency among the elderly. However, the contribution of bone tissue present at the end of skeletal maturation and consolidation at the end of skeletal growth is probably more important than individual variation in bone loss over years with respect to fracture risk [52, 59]. In addition, modifiable lifestyle factors like exercise and nutrition may influence skeletal morphology and bone mineral accrual when enacted during childhood and adolescence compared to late life stages [52, 134]. The Tromsø Study – Fit Futures provided an opportunity to analyze associations between birth anthropometry, fracture rates in childhood, lifestyle factors and bone health at the beginning of adult life. The main objective of the present PhD-project was to explore determinants at birth, childhood and adolescence that may predict the accrual of PBM. Sex differences were explored and the following specific issues, each presented as one paper each, have been addressed:

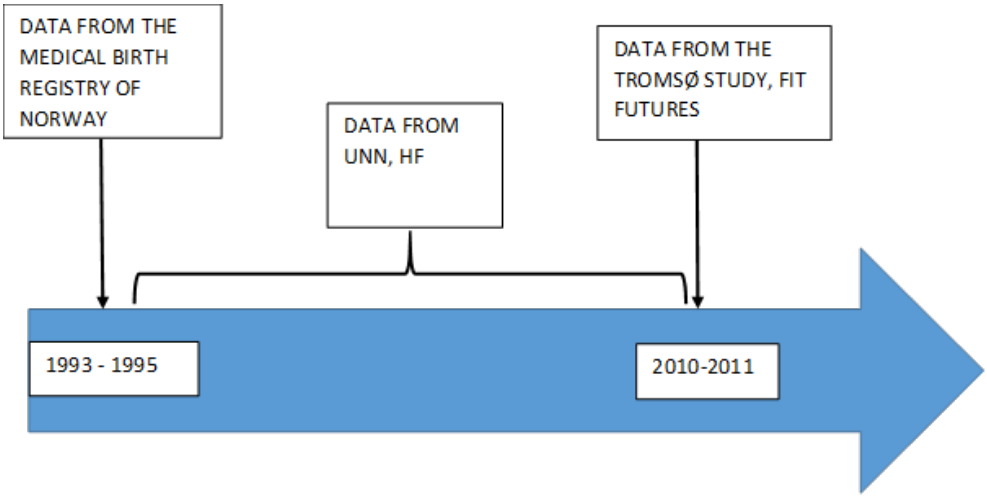
1. Fracture rates during childhood in a Norwegian adolescence cohort.
2. Associations between different dimensions of physical activity and BMD/BMC in girls and boys 15-18 years of age.
3. Association between birth weight/birth length, and BMD/BMC in girls and boys 15-18 years of age.
4. Association between childhood fractures and BMD/BMC in girls and boys 15-18 years of age, stratified by levels of physical activity.

3.0 MATERIALS AND METHODS

3.1. Study population: The Tromsø Study – Fit Futures

The Tromsø study is a population-based study with repeated health surveys conducted in the municipality of Tromsø [135, 136]. The study comprises seven surveys initiated in 1974 with repeated appearances in 1979-80, 1986-87, 1994-95, 2001-02, 2007-08 and 2015-16. Total birth cohorts in the municipality born between 1925 and 1966 together with random samples of inhabitants are invited and the attendance rate has ranged from 65% to 77%. The Fit Futures study is an expansion of the Tromsø Study inviting birth cohorts mainly from 1993- 1994 in collaboration between the University Hospital of North Norway (UNN HF), UiT The Arctic University of Norway and the Norwegian Institute of Public Health (NIPH). The Fit Futures study was established for collection of health data from an age group scarcely represented in the initial population-based survey. An overall objective for the 13 research groups represented in the initial phase of Fit Futures was the investigation of adolescence health and health behavior. The project groups share data from clinical examinations, measurements, interviews and questionnaires and this data collection builds a fundament for a multipurpose longitudinal health survey. For the present thesis, we applied and were granted access to measurements of bone mineral parameters, body composition, height and weight. Moreover, we had access to information about pubertal status and physical activity from questionnaires, and past medical history collected through clinical interviews. The data were linked with birth anthropometrics of the cohort collected from the Medical Birth Registry of Norway (MBRN) and registered fractures from the x-ray reports in the medical journals at the UNN HF.

Figure 3. Design of the study in the present thesis.



In 2010/2011, all first year upper-secondary school students (n=1,117) in the municipalities of Tromsø and Balsfjord were invited to the Fit Futures Study. The invitation included eight schools and covered both the city of Tromsø and the more sparsely inhabited neighboring municipalities. In total 1,038 (approximately 93%) adolescents attended the survey, of which most of them were aged 15-18 years and born in 1993-1995. In the present thesis, we included participants younger than 18 years of age, n = 961. Through a clinical interview, research technicians asked each participants about past medical history, including possible pregnancy and use of medication. Furthermore, each individual filled out a self-administered electronic questionnaire incorporating information on pubertal status and life-style factors like physical activity, use of tobacco and alcohol consumption.

3.2 Compliance with ethical guidelines.

The Regional Committee of Medical and Health Research Ethics and the Norwegian Data Protection Authority approved the Fit Futures study (reference numbers 2011/1702/REK nord and 2009/1282, respectively). In addition, The Regional Committee of Medical and Health Research approved linking the Fit Future data with MBRN and x-rays files at the UNN HF (reference number 2013/1466/REK nord). Participants aged 16 years or older signed informed consents according to the Declaration of Helsinki [137] and the Norwegian Health Research Act [138] when arriving at the study site. Younger participants brought written permission from parents or guardians according to guidelines from the Norwegian Patients' Rights Act [139].

3.3 Measurements

3.3.1 Measurements of bone mineral density and bone mineral content

Bone mineral density (BMD) in g/cm^2 and bone mineral content (BMC) in g were measured by Dual-energy X-ray Absorptiometry (DXA) by a GE Lunar Prodigy device (Lunar Corporation, Madison, Wisconsin, USA) and analyzed by enCORE pediatric software version 13.4. [140]. Anatomical sites of interest were femoral neck (FN), total hip (TH) and total body (TB). Moreover, the device also provided measurements of body composition including total body lean mass (g), used as an adjustment variable in the present thesis, and total body fat mass (g). Experienced research technicians at the UNN HF calibrated the device through daily phantom measurements and executed all scans according to the protocol defined by the manufacturer. All scans were performed on the same device and no densitometer drift was detected. The technicians reviewed, and if necessary, reanalyzed all captured scans. A quality control excluded ten scans due to artefacts.

3.3.2 Anthropometric measurements

Research technicians measured participant's height and weight on a Jenix DS-102 stadiometer (Dong Sahn Jenix co Ltd, Seoul, Korea), an automatic electronic scale. Height were measured to the nearest 0.1 cm and weight were measured with a precision of 0.1.kg. BMI was calculated as weight (kg) divided by squared height (m^2).

3.4. Assessment of exposure variables

3.4.1 Assessment of birth parameters

The MBRN is a national health registry, managed by NIPH. It includes information about all pregnancies (after week 12) and births in Norway, notified by approved maternity units. A standardized notification form covers data of personal identification of child and parents, maternal health before and during pregnancy, complications during pregnancy and birth and birth anthropometrics [141]. The purpose and task of the MBRN is to monitor information and achieve knowledge about maternal and child health and to use this knowledge for surveillance, research, management of health services and administration and assemble statistics.

The present project applied the MBRN for data on child anthropometrics i.e. weight, length, and head circumference at birth in addition to variables on maternal health and descriptions of gestation. Data was retrieved, prepared and anonymized using a code system by a MBRN case consultant before it was merged with the Fit Futures data through serial numbers by an information technology consultant at UiT The Arctic University of Norway. The variables applied in paper III was birth length (cm), birth weight (g) and gestation age (weeks).

3.4.2 Fracture registration

UNN HF, situated in Tromsø, is a secondary care university hospital also serving as the primary care center for residents of Tromsø and surrounding municipalities. UNN HF is the only public hospital in the catchment area of the Fit Futures participants, and provide easy access to free of charge services for pediatric injuries. Thus, the radiology department performs and archives virtually all x-rays for possible fractures. Fractures initially treated outside the region are also likely to be retrieved as follow-up and controls are usually referred to UNN HF. Exceptions from registration in the radiology archives at UNN HF includes injuries with possible fractures never radiographically examined and injuries examined at local private hospitals.

All available radiographic examinations of Fit Futures participants were searched to identify injuries compatible with fracture. The inspection included events from date of birth to the date

of DXA measurements. In the case of radiologically verified fractures, we collected information on the exact anatomical location, examination date, possible pathologic (tumor or metastasis) and body side. Inclusion criterion for fracture was a radiological confirmation as stated by radiologist on duty at the time of treatment. In the case of multiple fractures, every fracture was recorded as a separate event with following exceptions: fractures of radius and ulna on the same forearm, tibia and fibula on the same leg, multiple vertebral, skull, toes or fingers, which all were recorded as one event. Re-fractures were recorded as separate event only if the fracture lines were confirmed united before a new injury. We excluded diagnoses with missing fracture codes, questioned in follow-up records or solely stated by clinical findings. The fracture registration followed previously validated protocols as discussed in chapter 5.4.3 [142, 143].

3.4.3 Assessment of physical activity

The Fit Futures participants answered several questions about life style behavior and perceived health status in a self-administered electronic questionnaire at the study site. With respect to physical activity and exercise, the present thesis utilized components of the Health Behavior in School-aged Children (HBSC) questionnaire [144]. The self-reported levels of physical activity and exercise included questions about frequency, duration and intensity (Table 1). The explorations of physical activity levels were further categorized throughout several questions [145]. First the participants were asked the question *"Are you actively doing sports or physical activity outside school hours?"* dividing them in groups of active ("yes") or inactive ("no"). Physical activity frequencies were determined *by "if you are actively doing sports or physical activity outside school, how many days a week are you active?"* and initially categorized into "never" (1 or no), "less than once a week" (2), "1 day a week" (3),"2 to 3 days a week" (4), "4 to 6 days a week" (5) and "almost every day" (6). Answers of perceived intensity of physical activity was initially categorized in 5 groups, namely: not hard at all (1), a bit hard (2), quite hard (3), very hard (4) and extremely hard (5). The answers on physical activity frequencies were recoded into three possible groups. For this question, the answers (1) and (2) were coded as, (3) and (4) as moderate, and (5) and (6) as highly. The answers on perceived intensity were divided into not hard ("no") and (1 -2), quite hard (3) and hard (4-5). In paper IV, we changed the category labels to low, moderate and vigorous with respect to physical activity intensity.

Table 1. Questions regarding physical activity in the Tromsø Study, Fit Futures.

Question	Answer options
Are you actively doing sports or physical activity (e.g. skateboarding, football, dancing, running) outside school hours?	□ Yes □ No
If you are actively doing sports or physical activity outside school, how many days a week are you active?	□ Never □ Less than once a week □ 1 day a week □ 2 to 3 days a week □ 4 to 6 days a week □ Almost every day
If you are actively doing sports or physical activity outside school, how many hours a week are you active?	□ None □ About half an hour □ About 1 to 1.5 hours □ About 2 to 3 hours □ About 4 to 6 hours □ 7 hours or more
If you are actively doing sports or physical activity outside school, how hard do you find the sports you are doing?	□ Not hard at all □ A bit hard □ Quite hard □ Very hard □ Extremely hard

3.4.4 Assessment of pubertal status

The self-administered electronic questionnaire included questions on pubertal status for both sexes. In girls, questions about if and at what age they had their first menstruation indicated pubertal status. In boys, the questionnaires included Pubertal Development Scale (PDS) as a method to capture secondary sexual characteristics (Table 2). Answers on the latter were categorized into “Completed”, “Underway” or “Barely started”. In the case of menarche age in girls, responses were categorized in “Early”, “Intermediate” or “Late”. In paper I, the answers from girls given on a continuous scale were re-coded into a five-stage scale based on literature describing time from onset of puberty to time of menarche [146-148]. This scale was initiated with stage 1 more than 2 years before first menstrual period. Stage 2 was defined from 1 to 2

years before menarche, followed by yearly steps for stages 3 and 4. One year or more after menarche was included in the final stage 5. Based on the timing of male puberty and pubic hair development [148], stage 1 was set by more than 1 year before the report of pubic hair. Stage 2 included the year before and after pubic hair onset, followed by yearly increments for stage 3 and 4. The final stage was defined as more than three years after pubic hair development.

Table 2. Questions regarding pubertal status in the Tromsø Study, Fit Futures.

Sex	Question	Answer Options
Girls	Have you started menstruating?	□ Yes □ No
	Girls: if you have started menstruating, how old were you when you had your first menstrual period? Years	Continuous scale
Boys	Boys: Would you say that your growth in height,	□ Have not begun □ Barely started □ Underway □ Completed
	Boys: Would you say that your body hair growth,	□ Have not begun □ Barely started □ Underway □ Completed
	Boys: Have you noticed a deepening of your voice?	□ Have not begun □ Barely started □ Underway □ Completed
	Boys: Have you begun to grow hair on your face?	□ Have not begun □ Barely started □ Underway □ Completed
	Boys: have you got or started to get pubic hair?	□ Yes □ No

	Boys: how old were you when you started to get pubic hair?	Continuous scale

3.4.5 Assessment of covariates

The extensive electronic questionnaire incorporated a multitude of questions concerning lifestyle factors. In addition, the study technicians performed clinical interviews asking about medical history, including possible pregnancy and subjects' present use of medication. In paper I, questions on smoking allowed three possible answers: daily, sometimes or never. Alcohol consumption allowed answers of drinking frequency rated from 1 (never) to 5 (four or more times per week). Answers were categorized into never, up to once per month or twice or more per month. We dichotomized past medical history and use of medication known to influence bone or not according to the Lunar reference manual. In girls, hormonal contraceptives were used categorical as "no hormonal contraceptive", "estrogen and progestin" or "progestin only".

3.6 Statistical analyses

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) (Chicago, IL, USA), versions 22-24. P-values <0.05 were considered statistically significant and all tests were two-sided and stratified by sex. Descriptive characteristics of the cohort were presented as mean and standard deviation (SD) in the case of continuous variables, and numbers and percentages in the case of categorical variables. Overall, we explored group differences using Independent samples t-test, Pearson's Chi-squared test, or ANOVA with Bonferroni correction where applicable, and analyzed correlations between variables with Pearson's r correlation coefficient. We controlled for normal distribution, linearity, homogeneity of variance and potential outliers in regression models by analyses of residuals. In general, missing values in exposure, outcome or confounders excluded subjects from regression analyses.

In paper I, we estimated age- and sex- specific incidence rates by dividing numbers of new fractures during the time interval by the sum of total person-years of observation. The rates were multiplied to present incidence rates per 10,000 persons-year in line with comparable literature.

In paper II, we used independent samples t-test to examine discrepancy in BMD and BMC between the physically inactive and active participants, and Spearman's correlation coefficient to describe correlation between the ordinal categorical groups. For assessment of BMD and BMC differences according to levels of PA we used ANOVA after controlling for homogeneity between groups. In the case of violation of this assumption, we used Games-Howell procedure, elsewhere Bonferroni post hoc test for multiple comparisons within the group were used. Based on the different covariates contribution in simple regression analyses and biological plausibility for effect on bone mineral parameters, we built two different models in the multivariate regression analyses. When relevant, odds ratio were estimated by logistic regression.

In paper III we used a multiple regression modeling to investigate fetal predictors of bone development according to a suggestion form Lucas et al [149]. By the use of four models, we related birth size and outcome, controlled for change in size and potential centile crossing and finally separated prediction importance of birth and youth anthropometrics. All models were adjusted for age, pubertal status, gestational age and PA. Standardized β coefficients and 95% confidence intervals were reported.

In paper IV, the participants were categorized according to the history of fractures, fracture localization and repeated fractures from paper I. Because of large variation in groups and hence violation to the assumption of equal variance, we tested for differences in BMD/BMC, and a calculated BMAD between the groups using independent samples t-test. We repeated this procedure with participants stratified by levels of physical activity, before regression modeling with fracture status as main exposure.

4. Results – summary of papers

4.1 Paper I

Several studies have suggested that suffering a childhood fracture increases the risk of fracture in adult age. Therefore, knowledge of childhood fracture rates are of public health importance.

The aim of this study was to describe the incidence rates and patterns by sex, age, anatomic sites and sexual maturation in the study cohort, and to compare it to previous reports. We registered 316 fractures in 253 individuals. Among boys, 35% had experienced a fracture between birth and bone scanning, with corresponding figures of 31% among girls. The overall annual fracture incidence rate was 204 per 10,000 persons-year under the age of 18 and 205 under the age of 16. Forearm- (24%) and phalanges- fractures were the most common sites and the majority of fractures involved the upper extremities. Plotted against sexual maturation, fractured peaked at stage 3 in girls and stage 2 in boys and similar trends were observed in the case of subsequent fractures.

We concluded that fractures during childhood in Northern Norway corresponds with observations in Scandinavia, with a slightly higher proportion among girls compared to other reports. The study indicates a vulnerability at certain stages of sexual maturation. Both bone vulnerability per se and other puberty-related changes may be responsible for these findings.

4.2. Paper II

The beneficial effect of PA on bone is well documented, and especially among athletic subjects performing sports with planned repetitive programs, the evidence is strong. However, in a population with great variance of activities structure and time spent, we know comparably less about the association between physical activity dimensions and bone mineral density and content.

The aim of paper II was to elucidate the association between self- reported PA and BMD/BMC. Moreover, we aimed to describe the relationship between quantities in frequency

and intensity, and BMD/BMC levels in the cohort. The active adolescents had a significantly higher BMD and BMC at all sites ($p < 0.001$), except for BMC total body in girls, compared to inactive participants. In multiple linear regression analyses, increased PA frequency was positively associated with BMD at all sites in girls. Girls reporting themselves as highly active had BMD levels 0.093 g/cm^2, 0.090 g/cm^2 and 0.046 g/cm^2 higher ($p < 0.001$) at femoral neck, total hip and total body respectively, compared to seldom active peers. Corresponding values for boys were 0.125 g/cm^2, 0.133 g/cm^2 and 0.66 g/cm^2. Measurements of BMC showed the same trends at femoral neck and total hip.

In conclusion, higher levels of PA is associated with increased BMD and BMC levels in adolescents. Frequent participation in physical activity outside school hours seems to be of major importance in both sexes, and boys reporting greater intensity during physical activity revealed stronger associations. These differential relationships according to quantification may have clinical implications with respect to preventive strategies.

4.3 Paper III

The association between birth weight and birth length, and BMD/BMC at different ages is conflicting. Some investigations have shown a significantly positive associations between birth weight and BMD/BMC in children, and strongest with BMC as outcome. However, in adolescents, results are miscellaneous. Furthermore, few studies includes birth length as an exposure. The purpose of this study was to evaluate the influence of birth weight and length on BMD/BMC among the 961 participants the Fit Futures cohort.

We found a positive association between birth weight and BMD-TB and BMC at all sites among girls. Standardized β coefficients [95% CI] were 0.11 [0.01, 0.20] for BMD-TB and 0.15 [0.06, 0.24], 0.18 [0.09, 0.28] and 0.29 [0.20, 0.38] for BMC-FN, TH and TB, respectively. In boys, birth weight was positively associated with BMC at all sites with estimates of 0.10 [0.01, 0.19], 0.12 [0.03, 0.21] and 0.15 [0.07, 0.24] for FN, TH and TB, respectively. Birth length was significantly positive associated with BMC at all sites in both sexes. Multivariable adjustments attenuated the relationships except the association between birth weight and BMC-TB in girls, and birth length and BMC-TB in boys.

We concluded that our findings demonstrate a positive association between birth size and BMC in adolescence. The association debilitates when adjusted for change in size and lifestyle factors. Therefore, upcoming studies in regions with good maternal health should investigate the predictive value of environmental stimuli and modifiable lifestyle factors.

4.4 Paper IV

Suffering a fracture during childhood may be an early marker of a persistent skeletal fragility indicating an increased risk of low bone mineral outcomes throughout life. However, it may also reflect increased levels of vigorous PA, which is considered beneficial for bone mineral accrual. In this study, we investigated the association between a previous history of childhood fracture and adolescent bone mineral parameters both per se and stratified by levels of PA.

We observed that girls with and without previous fractures had similar BMC, aBMD and BMAD at all anatomical sites measured. In boys, we observed corresponding similarity, although boys with a previous forearm fracture were significantly taller compared to peers without fracture and with other sites injured. In multiple regression analyses, stratified by levels of PA intensity, we found a significantly negative association between a previous fracture and aBMD-TH and BMC-FN among girls, yet only in participants reporting low PA levels. In boys, there was a significantly negative association between previous forearm fractures and BMAD-FN/BMAD-arm among the vigorously active participants.
Based on our findings, we concluded that bone mineral outcomes are lower in girls with a history of fracture reporting low PA levels. In boys, the negative association between forearm fracture and BMAD possibly arise from increased exposure to injuries among vigorously active individuals. We suggest future identification of fractures as a marker for bone fragility to include detailed quantification on modes of PA. In addition, the sex discrepancy need further elaboration.

5. Discussion of methodological considerations

Accumulation of bone during childhood is an important basis for lifelong maintenance of bone health and avoidance of the clinical consequence of osteoporosis and fractures in old age. Development of peak bone mass depends on numerous factors. Any interpretation depends on combinations of inherited and acquired determinants, with various influence through fetal life, birth, childhood and puberty according to tissue responsiveness and the timing of exposure. Therefore, observed associations between selected determinants and bone mineral outcomes needs an explanation based on underlying biological mechanisms i.e. we must address to which extent our observations are real. Any deviation from the truth can be a consequence of errors occurring by chance or systematically. Systematic errors or bias appear because of defects in study design, collection of data and through confounders, and is commonly referred to as internal validity. In addition, we need to address the external validity of our data and observations, i.e. to what population(s) are our findings of interest?

5.1 Study design

The cross-sectional design measure presence or absence of disease and risk factors at the same point in time [150]. The main advantages are the possibilities to observe and describe several variables simultaneously, at relatively low costs and time levels [151]. In general, the design is vulnerable to bias with respect to diseases of high mortality and infrequent exposure variables. Although it is well suited for generating hypothesis, the cross-sectional design cannot directly provide evidence on causality [151]. Furthermore, lack of details when collecting historical exposure variables could hamper such a study, compared to prospective design.

Nevertheless, we conducted a cross-sectional study (Fit Futures) where mortality is inapplicable and exposure variables are typical, hence minimizing bias arising from design. Historical exposure data (paper I, III and IV) were collected from comprehensive health registries, and the significant associations we observed may be suitable for testing hypothesis and epidemiologic inference as discussed in section 6.0. [152].

5.2. Random error and precision

Compared to the truth, most estimated associations include some random error resulting in a larger variability of estimates. This noise may affect estimates in both negative and positive direction and is best handled through increased precision; *"Precision in measurement and*

estimation corresponds to the reduction of random error" [153, 154]. The Fit Futures study was performed at UNN, HF in a specialized ward designed for medical research. Dedicated and experienced research technicians, trained in procedures for data collection to reduce inter-observer variability, conducted the study. To prevent and minimize errors, the Fit Futures administration worked out detailed protocols before the study and data quality were monitored throughout the survey. Furthermore, following the central limit theorem, large samples reduce the effect of random error and approach the true estimate of the population. Taken together, the way the study was conducted with a sample size of over 400 individuals of each sex are likely to bring precision and random errors to an acceptable level.

5.3 Systematic errors - Selection bias

Selection bias is defined *as "a systematic error that results from procedures used to select subjects and from factors that influence study participation"* [155] p 96. The threat against internal validity occurs when the association between exposure (e.g. PA, birth weight) and outcome (e.g. BMD, BMC) differ among responders and non-responders [155]. In the Fit Futures study, participants were all students in first-year upper-secondary school. The Norwegian educational system allow all adolescents to enroll at this level, providing complete registration in the given age group. Of the 1301 registered individuals, 70 were missing probably because they dropped out of school before inclusion in the Fit Futures study. In addition, 114 students did not attend school because of persistent disease, or we were not able to contact them. The remaining 1117 students were invited, of which 1038 participated in the survey (92.9%). School dropout may be associated with several life-style exposure variables of interest in our study, and persistent disease may be associated with low bone mineral outcome [156]. Hence, the attending participants could, in theory present over-estimated levels of BMD and BMC compared to the population. On the other hand, analyses on participants lost to follow up in the later Fit Futures 2 survey, demonstrated increased BMI levels in non-attending participants, which could lead to under-estimation of the outcome variable [157]. Corresponding bias between attendants and non-attendants in our participants may reduce the systematical error. Therefore, given the attendance rate of approximately 93%, and the likelihood of marginal influence from non-attendants to introduce one-sided systematical error, we consider selection bias to be of minor consequence to our findings.

5.4 Information bias

Information bias is a common threat to internal validity. It occurs when measurements of exposure variables or outcome variables are systematically inaccurate or erroneous, or if participants reports are incorrect or imprecise [158]. Information bias may lead to misrepresented estimates, and often emerge in the case of inexact definitions of either exposure or response, imprecise procedures in collecting and registering data, or through misclassifications and measurement errors [158-160]. Furthermore, systematical information bias can be non-differential or differential. The former describes error independent of exposure and outcome and is susceptible of blurring the results, more than producing serious faults. In contrast, differential errors occur dependent of variables of interest, may distort the findings in unpredictable directions and represent a serious threat to the internal validity. This hazard must be considered and minimized during the preparation phase of a study [160, 161].

5.4.1 Validity of bone mineral measurements

In papers II-IV, we measured bone mineral outcomes and lean/fat mass by DXA (GE Lunar Prodigy, Lunar Corporation, Madison, WI, USA). Research technicians followed calibrating procedures as described by the manufacturer throughout the Fit Futures study. We did not perform an exclusive precision study prior to the survey, yet the coefficient of variation (CV) of our device has been estimated to 1.2% for total hip and 1.7% for femoral neck [162], which is in accordance with other reports [163]. Overall, DXA is a broadly applied method of measuring BMD at all ages, with several advantages in addition to its good precision. Among these, and important with respect to validity are short scan times, rapid patient set up and effective quality control procedures [129]. DXA measurements limitations relevant for our studies include the 2D projection measurement, discrepancy in measurements dependent of site and errors by heterogeneity in soft tissue. The two former are connected to the incapability of DXA technology to measure true volumetric bone density, hence the estimates presented reflect a combination of bone mass and size. Consequently, large bones are prone to over-estimation in the expressed g/cm^2, and smaller bones conversely under-estimated. To overcome this limitation, the manufacturers' software present BMD measurements related to age, sex and race and thus minimizing the size dependency of BMD measurements during growth. Another possibility in the case of measurements of the femoral neck is the calculation and utilization of estimated volumetric BMD (bone mineral apparent density, BMAD) as performed in paper IV [164, 165]. With respect to soft tissue heterogeneity, again the manufacturers' pediatric software seek to minimize the potential errors in edge detection, by

modifying the thresholds for acquisition between hard and soft tissues. For any further reduction of systematical measurement errors, we performed analyses consistently sex-stratified, which eliminated bone size inaccuracy dependent on sex. Preliminary analyses excluding non-Caucasian participants (4%) suggested that ethnicity had negligible influence to the measurements and finally the analyses were adjusted for anthropometric measurements and/or pubertal status hence reducing the effects of possible measurement errors to a feasible minimum.

5.4.2 Validity of physical activity assessment

PA as defined in the background section of the thesis is responsible for the largest variance in an individual's total daily energy expenditure. In addition to the bodily movement, the energy expenditure incorporate a basal metabolic rate and a thermic effect of food [166]. A major challenge in assessing PA behavior is the great intra- and inter individual variation, dependent on seasons, weeks and days. Over time, a multitude of methods have been developed and made available for evaluating the association between PA and the risk of diseases within the epidemiological context. The methods include both objective measurements (e.g. double-labeled water, direct or indirect calorimetry, heart rate monitors and motion sensors) and subjective assessments (e.g. occupational classification, behavioral observations, diaries, interviews and questionnaires). On the basis of knowledge about bone cell responses, one might consider motion sensors and/or measurements of ground reaction forces, in combination with self- reported questionnaires as the best methodical approach at the present moment [167]. However, large epidemiological studies most often have to rely on questionnaires, where researchers can collect information on PA among many individuals in a cost- and time efficient way and with limited amount of stress for the participants. On the other hand, self- reporting questionnaires, as used in the Fit Futures study, introduce some limitations including possible recall bias, misinterpretation and failure to separate different dimensions of PA, all of which may be a threat to validity and reliability.

For papers II-IV included in the thesis, we used questions from the Health Behaviour in School- Aged Children (HBSC) related to PA behavior. The HBSC is a World Health Organization collaborative cross-national survey collecting common health data through an international standardized questionnaire, allowing quantification of patterns across nations and time [144].

Validation of instruments should be based on correlation with objective, direct measurements as close to the "gold standard" as possible to obtain an acceptable criterion-based validity [168]. The WHO HBSC questionnaires on PA have been the object for validation on several levels. In 2001, the PA questions were validated and test-retest reliability controlled against the Multi-stage Fitness Test (MFT) in 1072 and 954 school students, 13.1 and 15.1 years of age, respectively [145]. The MFT and the WHO HBSC were administered the same day, and a sample of students repeated the questionnaire two weeks later. In contrast to the utilization in our study, the combined responses to the question items were categorized into active or inadequately active, with following assessments on both the initial and the summarized items. The authors reported significantly greater fitness among participants reporting to be active, both in the initial categorization and the summarized groups. Furthermore, these findings were persistent across ages and sex. Among the oldest participants kappa values were 0.70 (85% agreement) in boys and 0.38 (70% agreement) in girls (summarized category), when assessing test-retest reliability. In conclusion, the authors suggested acceptable to good reliability and validity among the oldest school students, although with a decreasing trend in younger adolescents.

A more direct, yet smaller reliability and validity study were performed in 2008 among adolescents aged 13-18 years of age [169]. The WHO HBSC questionnaires were administered twice, 8 -12 days apart for the reliability study, and the questions compared with an objective cardiorespiratory fitness test, VO_{2peak}. In addition, the participants used motion sensors during seven days for calculations of total energy expenditure and PA levels. Intra - class correlation coefficients for reliability was 0.73 for duration and 0.71 for frequency, although with a significant difference between sexes in the latter (girls 0.87, boys 0.59). Spearman correlation coefficients for validity varied from 0.29-0.39 ($p<0.05$), with a modest decrease, yet no longer statistical significant in the duration question, when categorizing the items in "low", "moderate" and "high". The authors concluded that *"the WHO HBSC questionnaire had substantial reliability and were acceptable instrument for measuring cardiorespiratory fitness, especially among girls"* [169] p 1.

In papers II-IV, we interpreted the response "No" to the initial question "Are actively doing sports or physical activity outside school hours?" as low based on the previously classification of PA according to metabolic equivalent < 3 [169]. In preliminary analyses the intensity item were significantly correlated to items of frequency and duration (Pearsons r = 0.38 and Pearsons r = 0.39, $p<0.001$, respectively). Together with the biological rationale described in

the background section and the growing evidence of intensity as the strongest predictor for bone mineral acquisition [170, 171], we found it acceptable to use the perceived intensity as adjustment variables in papers III and IV. This may have made the PA variable susceptible to misclassification in both directions and thus attenuated the validity of our findings. However, as studies indicate that self-reported PA overestimate the true levels [172], our results on bone outcome probably are conservative compared to the real associations [173].

5.4.3 Validity of fracture registration

Overall, fracture registration is prone to misclassification, mainly by erroneous coding or punching at the examination date and events like transferal or re-hospitalizations of the patient [143]. The registration of fractures as outcome have been performed through several methods, e.g. surveillance of medical records, self-reported, combinations of self-reporting and radiographically reviews and computerized register information. In 2001, Joakimsen et al, [143] compared fracture registration methods in the geographical region of interest for our study and demonstrated excellent sensitivity (93% and 97% for hip and wrist, respectively) with no over reporting when using the computerized records from the Department of Radiology. The main exception was registration of vertebral fractures, which seldom led to radiographical examination and, in relation to our study, appear infrequently among children. In papers I and IV, we used the method of computerized linkage between the Fit Futures study and the radiographical archives as described by Joakimsen [143]. However, a possible source of misclassification among the adolescents are individuals born and raised in other regions, suffering a fracture before moving to the present area. Nevertheless, the calculated annual incidence rates as reported in paper I are consistent with other and larger population-based studies across Scandinavia, indicating that the validity of fracture registration is acceptable.

5.4.4 Validity of puberty assessment

Measurements of puberty has over several decades relied on physical examination performed by professional and trained health clinicians, using sexual development criteria described by Tanner and Marshall in 1969 and 1970 [148] [174]. The Tanner staging is still recognized as the closest to gold standard assessment widely available when classifying this biological phenomenon central for a variety of health outcomes [146, 174]. Nevertheless, some authors have described an inverse relationship between validity and feasibility across all methods for measuring puberty characteristics [148]. With respect to feasibility, Tanner staging was not included during the planning of the Fit Futures study. For girls, questions on menarche age

were included and contributed with acceptable accuracy based on the relatively short-term recall period [175]. For boys, we introduced the Pubertal Development Scale (PDS) during the survey. PDS incorporates self-reported secondary sexual characteristics and correlation with Tanner ratings performed by physicians have been estimated to range between 0.61 and 0.67 [176] or adequate for rough estimates of maturation [148, 176-178]. In papers II-IV, both menarche age and PDS were treated as covariates, hence considered sufficiently valid. In paper I, a part of the secondary objectives was to describe fracture patterns by sexual maturation. To accomplish a relevant plot between historical fracture events and maturation stage at the time of the fracture, we used menarche age and one of the items from PDS (pubic hair development) as indicators of puberty onset and subsequent staging [146-148]. Although, puberty onset closely link with age of growth take-off [178] and therefore implies consequences for bone strength as described in the background section, these plots should be handled with caution.

The delayed insertion of PDS led to 23% missing values among boys, compared to 3 % in girls. The latter corresponds to missing data in other lifestyle variables among the girls (2%). This indicate that the missing data in boys had a random distribution, despite the before mentioned vulnerable feasibility in approaching puberty as such sensitiveness is likely to be distributed evenly across sexes. Preliminary sensitivity analyses performed in connection with the initial cohort description supported this presumption [157], although more complex approaches to missing values may have yielded study population estimates nearer to the truth. In summary, we regard potential bias introduced by pubertal status assessment with respect to the bone mineral outcomes as controlled for, assigning acceptable estimates.

5.4.5 Validity of birth registry data

The Medical Birth Registry of Norway (MBRN) contain information about all births in Norway compulsorily reported from all maternity units. The proportion of notified births registered are literally 100% [179], although some variation in notifying specific conditions and diseases are reported [180]. However, the most common variable protocols (e.g. birth weight, birth length) are continuously standardized, and quality secured [179]. A recent study including gestational age and birth weight, variables used as covariate and main exposure respectively in paper III, examined information from MBRN among 786 individuals using local hospital records as reference standard [181]. The conclusion was that validity of gestational age and birth weight in the MBRN was very good. On the other hand, reliability of birth length is discussed in paper III as one limitation. Nevertheless, errors in the birth length

variable is most likely to be random, hence we consider that MBRN all together provide robust data for investigating associations with bone mineral outcomes.

5.4.6 Validity of covariates

Overall, height and weight measurements have high reproducibility and validity [182]. In the Fit Futures study, research technicians performed the collection of anthropometric variables according to study protocols including regulatory calibration of the stadiometer and scale used. Therefore, we consider potential bias in the covariates height, weight and BMI calculated based on these measurements, as negligible. The use of an extensive electronical self-reporting questionnaire make variables prone to recall bias although most errors concerning the questionnaires is likely to be non-differential and probably led to underestimated associations [158]. Nevertheless, variables like smoking habits and alcohol consumption may be susceptible to underreporting as they commonly are connected to negative health effects [183]. Furthermore, these questions are not validated with respect to this specific age group, and even when used only as adjustment variables, interpretation of effect from these variables must be handled with caution.

5.4.7 Confounding and interaction

A main objective within epidemiologic research is to investigate associations between variables as an approach to detect cause and effect. The term causal association has been defined as *"an association between categories of events or characteristics in which an alteration in the frequency or quality of one category is followed by a change in the other category"* [150] p 32. The pathway towards inferring a possible causality in epidemiologic models consists of firstly demonstrating a statistical significant association between the exposure and outcome of interest. Secondly, one must reject bias as the main explanatory reason for the association. Finally, two issues namely confounding and effect modification (interaction) may be responsible that a statistically significant, unbiased relationship between exposure and outcome yet is non-causal [150].

Confounding can be defined as *"distortion of an exposure-outcome association brought about by the association of another factor with both outcome and exposure"* [184]. Recognized procedures to deal with this issue includes randomization, matching through case-control studies, stratification and the statistical approach of multivariate modeling where potential confounders are held constant [150]. In an observational study, it is neither ethically nor logically possible to construct models that generate different groups only according to

exposure. Thus, randomization and matching are ruled out as available strategies. Our strategy in an attempt to reduce the impact of confounding involved both stratification and multivariate adjustments. Based on background knowledge on differences in bone development between girls and boys during growth, we stratified all analyses by sex. In contrast, we did not stratify by age and ethnicity, variables known to influence bone mineral accrual because this yielded small subgroups and a following reduction in statistical power [185]. Because of the findings in paper II, we analyzed associations between fracture and bone mineral outcome stratified by PA levels in paper IV. We included other possible confounders described in the respective papers as adjustment variables. The Fit Futures study include information on a multitude of variables and characteristics, yet limited by the data collected, which implicates that all associations may be hampered by confounders not included in the models and residuals by unmeasured, real confounders. This issue illustrate the general difficulty for an observational to incorporate a complete set of possible confounders, hence contribute with definitive evidence on the causal pathway [150].

Effect modification, or interaction refers to cases where the exposure impact on the outcome is dependent on the impact if other variables. This effect is distinctly different from confounding (and selection and measurement error) as it does not display a bias but a real impact that may be of considerable interest and therefore should not be removed or controlled, yet accounted for [186]. Throughout the papers II-IV, we checked for potential effect modifiers by adding the product statement of outcome variables and stratum of interest to the multivariate model. In the case of non-significance, interaction terms are removed from the models. However, in paper III the interaction terms are presented despite non-significance, because of the importance for correct interpretation of results and according to the suggested rationale from Lucas et al [149].

5.5 Generalizability (external validity)

If findings in an observational study are not valid for the attending individuals, evaluation of validity for other individuals are pointless. In the previous section, we have discussed the level of internal validity and argued that errors are within an acceptable range with respect to the presented associations. The next step is to address the ability, or to which extent these findings are generalizable to a larger population. The external validity may be connected to whether the sample are representative for another population, or if the association per se are applicable among others [150, 184].

The Fit Futures sample is a convenient sample, including all first-year upper secondary school students as mentioned in the methods section. Such participant inclusion with absence of self-selection and randomization will comprise high generalizability to other groups with similar distribution of characteristic. Compared to national descriptive data, the prevalence of overweight and obesity is higher in the region of interest in our study [187, 188]. In addition, the adolescents in our sample report slightly higher PA levels compared to participants in another national epidemiological study [157, 189]. Both exposures may be associated with altered BMD levels, hence questioning to what extent our sample is representative at a national level. Nevertheless, external validity does not solely depend on statistical generalization. Valid universal statements can also be indicated if the sample, including its characteristics distinguish competing hypothesis in an appropriate manner [153], as discussed in the previous validity section.

The cohort in the initial Tromsø Study comes from whole birth cohorts and additional randomly selected individuals and assessed as fairly representative for Caucasians at a national level [135]. We assume analog traits for younger inhabitants of the same region. Summarized and added with the concordance to literature as discussed in the respective papers, we claim acceptable generalizability to Norwegian adolescents and fair validity for Caucasian individuals at the same age resident in Western communities.

6.0 Discussion of main findings

Determination of a causal relationship is necessary when assessing adequate preventive strategies and treatment options in health. In epidemiological research, where experimental research and designs are unfeasible, this exercise is not straight forward, nor is it completely objective [150, 159]. Thus, epidemiological evidence as obtained throughout this thesis is generally not sufficient for claiming direct causality. However, following a long evolution from early Greek philosophers to modern epidemiology, scientific criteria have developed to guide inference about cause and effect. In 1965, Austin Bradford Hill proposed the most cited criteria and combined with John Stuart Mill's description of inquiry methods in groups, [150, 190] the aims of this thesis are discussed in the light of the term "Mill's cannons" [150, 191] wherever it is applicable. These contemporary conventions for judging causality based on observations in a population include temporal sequencing, strength of association, consistency, dose-response relationship and biological plausibility.

6.1 Fracture incidence rates

To investigate determinants of adolescent bone mineral accrual, which is the main objective of this thesis, we had to identify the most common problem connected to bone in childhood, namely childhood fractures (paper I). The findings support national and international literature, stating that approximately 25 % of children experience one or more fractures before adulthood and that childhood fractures are more common in boys than in girls. Furthermore, we identified forearm as the most common fracture site and a possible vulnerability dependent of maturation in both sexes. The validity of our findings is discussed in the previous section and the descriptive nature of the present findings makes any causality approach irrelevant. Nevertheless, some aspects are important both per se and in the line of arguments with respect to the associations between fractures and bone mineral outcomes presented in paper IV.

Population-based studies in other Scandinavian countries [119, 192, 193] including the landmark study of Landin and its' follow-up, have demonstrated decreasing incidence rates in the respective regions after 1980. The reports from 1999 and 2010 by Tiderius [193] and Mäyränpää [192] respectively, are remarkable similar to our findings, indicating that our result is a snapshot of the same overall secular trend in Scandinavia. Interestingly, in our study the male/female ratio (55% boys) were more balanced compared to other pediatric reports [117, 119, 192, 193], where this ratio also has been stable over time. A possible explanation for observed distribution according to sex in our data can be the relatively equal

PA levels reported by the participants, as presented in paper II, IV and a previous cohort description paper [157].

Another notable aspect with respect to biological relevance is the description of fracture incidence based on sexual maturation. In the discussion section of paper I, we have underlined the novelty of this approach because it contrasts traditional evaluations where incidence rates are plotted against chronological age, hence indirectly illustrates bone vulnerability with respect to puberty. Although the reason for this vulnerability may arise from several occasions, biologically through cortical thinning during growth as well as socially through increased risk-seeking behavior and novelty-seeking activities connected to hormonal changes in puberty, the identification of a relationship between fracture and puberty may be used in interpreting causality in subsequent hypothesis.

6.2. Associations between different dimensions of PA and BMD/BMC in adolescents.

In paper II, we observed that adolescents with higher levels of PA, both with respect to frequency and perceived intensity had consistently higher BMD and BMC values, with a dose-response relationship. The associations between PA levels and BMD and BMC were strong and meaningful with respect to statistical significance, and most likely clinically important based on estimates suggesting a 50% fracture risk reduction connected to 10% increase in peak bone mass [194]. We observed BMD and BMC levels at femoral neck and total hip 10-14% higher among highly active participants compared to less active peers, and even higher compared to inactive adolescents. The observed associations included covariates, both anthropometric- and lifestyle factors, known to predict bone mineral outcomes. In combination with the observed dose-response relationship, these strong associations indicate a greater likelihood of a causal relationship between PA and bone mineral accrual, although limitations in the PA data previously mentioned could hamper both conventions.

The mechanostat theory is responsible for a possible biological explanation of the observed associations [195]. Outlined in the background of this thesis, bone adapt their strength as a response to exerted mechanical loading, favoring dynamic, novel and high shear stress, mainly through the mechanosensation by osteocytes. Hence, hard or vigorous PA levels are likely to produce sufficient loading, explaining the strong associations observed in our data. The latter supports studies evaluating the association between BMD and objectively measured PA intensities using accelerometers [196]. Our regression coefficient at femoral neck of 0.105 in boys reporting themselves to be physically active at very hard levels corresponds to

regression coefficients of 0.096 for the same site in boys measured to perform exercise above 4.2 gravitational forces. A systematic review by Bielemann et al [197] indicated that the positive associations between PA and bone mineral outcome were present, yet weaker among girls, explained by a greater participation in peak strain activities among males. This aspect may be accountable for the minor discrepancy in effect estimates between sexes in our cohort as well. Nevertheless, in girls the effect estimates are only slightly weaker compared to boys, probably highlighting the equalization of participation in PA in Norwegian youths mentioned in the fracture incidence rates section of the discussion.

Another aspect that may strengthen the results lies within the evaluation of the additive factors of bone strength in contrast to bone mineral accrual alone. Daly and Bass [198] demonstrated no association between PA and BMD, yet a significant association between lifetime PA and femur strength measured as mid-femur total and cortical area by quantitative computed tomography. Thus, although the associations in our study are consistently positive across PA dimensions, measured anatomical sites, and sexes, they may still be underestimated with respect to three-dimensional expressions more comprehensively connected to bone strength [199].

A temporal sequence between exposure and outcome must be present to interpret an association as causal, i.e. the levels of PA must be stable and precede bone mineral outcomes with sufficient time for bone to adapt to mechanical loading. In a cross-sectional design, this temporality is impossible to control. Nevertheless, the habitual behavior of PA and the assessment of tracking have been the objective of several investigations [200-204]. The initial findings showed low to moderate tracking from childhood through adolescence to adulthood. On the other hand, these early studies may have been hampered by low validity, especially in self-reported instruments utilized on very young subjects, e.g. younger than 10 years [204], hence probably underestimating the tracking effect. Findings from Kristensen et al. (2008) [204] demonstrated moderately, but significant tracking over 6 years with stability of coefficients of around 0.50 independent of sex, with stability and predictability highly sensitive to variation and measurement errors, in objective measurements. The authors concluded that PA behavior initiated during childhood continue to later age. This indicates that most participants in our cohort, giving a positive response to the question *"Are you actively doing sports outside school hours?"* have established habitual PA levels over time, hence allowing sufficient time for biological adaptations.

6.3. Investigation of the association between birth weight/birth length, and BMD/BMC at the ages 15-18 years.

The Barker hypothesis suggests that environmental factors during intrauterine life stimulate fetal tissues to altered structure and function throughout life [205]. However, with respect to bone mineral outcomes in adolescents, such in utero programming with birth weight and length as proxy is unclear. A meta-analysis revealed eight studies proposing a significant positive association between birth weight and adolescent BMC and four studies, including one statistically significant study indicating inverse associations [206]. Our present findings (paper III) of a weak but significantly positive association between birth weight/length and BMC in both sexes, attenuated by anthropometric and lifestyle adjustments indicate a substantial contribution from lifestyle factors on bone mineral outcome during growth. We can discuss our results by taking into account four levels of studies each proposing rationale for adapting the Barker hypothesis to bone mineral development [207]. Dennison et al (2001) [50], suggested that undernutrition in utero may modify the genetic influences on adult bone size and density by alterations in the vitamin D receptor gene. Subsequent epidemiological studies have replicated these findings and taken together they make up the population-based evidence for claiming developmental origins of osteoporosis risk. The second level includes physiological studies that support a hypothesis claiming intrauterine stressors as responsible for alterations in growth plate sensitivity, mainly through variations in circulating growth hormone and cortisol [208-210]. Thirdly, mother/offspring studies have demonstrated that maternal health influences the founding of skeletal growth trajectories at an early point [211-213]. Finally, the intrauterine environment makes premises for childhood growth, which again links to later hip fracture risk, suggesting that children growing at a rate faster than the capacity to mineralize are susceptible of high fracture risk as adults [62].

With respect to the three former groups of studies, it might be plausible to derive that our results, which indicated no significant association in adjusted models, are consequences of appropriate nutrition in utero, overall low levels of stress during pregnancy and generally good health among the maternal population. If so, the near optimization of adaptive responses during the period of high developmental plasticity lead to greater impact from environmental stimuli after birth. Indeed, the rates of low birth weight cases (4%) in our cohort were small in a global context and even small compared to European reports [214], which indicate adequate premises for maternal and fetal health. The final aspect, childhood growth is not accounted directly for in paper III, as no measurements were available from between birth and DXA

scanning. However, this issue is statistically considered following the suggestion from Lucas et al [149] on modeling. Lucas et al state: *"If the fetal origins hypothesis holds, the early model should have a significant and negative coefficient (negative relation of early size to later adverse outcome), this should be possibly more negative in the combined model; and when an interaction between early and late size is found, it should be a negative one"* [149]p 4. Keeping in mind that higher BMD/BMC is positive in our case; the latter is not the result of our analyses, flagging the importance of postnatal growth in our cohort. This is in line with a previous Danish report [215] concluding that the association between birth weight and BMC at ages 16-19 years may be mediated by change in size after birth more than fetal programming. In contrast, a report from southern Brazil using the same statistical approach as ours [216] identified independent effects of both birth weight and postnatal growth on bone mineral outcomes. However, mean birth weight of 10% below our cohort for both sexes, higher rates of low birth weights, and other cohort characteristics may explain the dispersion between intrauterine and postnatal contribution to bone mineral outcomes among Brazilian youths.

6.4. Association between childhood fractures and BMD/BMC at the ages 15-18 years, stratified by levels of PA.

In paper IV, we could not initially confirm previously reported relationships between childhood fracture and adolescent bone mineral outcomes i.e. we could not support the hypothesis that childhood fracture is an early marker of persistent skeletal fragility. However, the absence of statistically significant associations changed when we stratified for PA intensity reported by the participants. In girls, we observed a consistently negative association, statistically significant between exposure and BMD-TH/BMC-FN, yet only in participants reporting themselves to exert low levels of PA intensity. Outlined in the background section and discussed in section 6.2, the mechanostat theory most likely explains these observations on a biological mechanism level. Primarily, bone morphology is genetically determined yet mechanical loading provide higher ability to counteract fracture due to increased bone mineral parameters and presumably better material properties, geometry and tissue quality [83]. Moreover, responsiveness to mechanical loading is evidently greater during growth [70-77] due to large proportion of active bone cells and the highly active modeling going on [83]. Deterioration to utilize this potential may impede optimal bone mineral accrual, leading to both increased susceptibility to fracture during growth and diminished bone mineral levels later in life. On the other hand, our findings in

girls indicate that attending moderate to vigorous PA intensities compensate for a potential risk in a way that a history of previous fracture does not predict later bone mineral outcome.

With respect to a dose-response relationship in the association between fracture and bone mineral outcomes, it is inappropriate to quantify a weaker or stronger exposure to childhood fracture. The initial non-significant associations, before stratification on PA level, differed when we defined multiple childhood fractures as the main exposure variable, yet again only in girls. In the dose-response aspect, our findings of a significantly negative association between multiple childhood fractures and BMD may support previous studies suggesting a link between early fractures and risk of osteoporosis [127]. In a prospective study, Ferrari et al [127] reported significantly lower BMC at radius, femoral trochanter and lumbar spine among 42 girls with fractures compared to 83 non-fracture peers, together with lower BMC gain during follow up. Although the design might be more suitable for causal interpretation, the link appear inconsistently because of our indications of diversity across PA levels. Indeed, we report significantly different BMC-FN, BMC-TH and BMAD-FN in girls according to the reported levels of PA intensity, which may indicate that vigorous PA is a key to decrease risk of bone disease, regardless of childhood fracture history.

In boys without fractures, our findings of significantly lower bone mineral outcomes in participants exerting low PA intensity is in accordance to results from paper II. This trend was the same in the group of boys with previous forearm fractures and in boys with previous fractures at other anatomical sites. As reported among the girls, we could not confirm any overall association between any type of fracture and bone mineral outcome. Interestingly, when stratifying by levels of PA intensity, we found a significantly negative association between a history of fracture and BMC-FN/BMAD-arm yet only in the boys with forearm fracture reporting themselves to be vigorously active. The negative association between forearm fracture and BMAD-arm can be explained by different mechanosensation responses dependent on weight bearing, i.e. adaptations in non-weight bearing sites like the forearm are low compared to the hip and spine. However, this cannot explain the negative association between forearm fractures and BMC-FN among the highly active boys. One might speculate that this finding reflects the issue of cortical thinning during peak growth velocity, not yet compensated for by the highly active modeling processes, even though adjusting for covariates should have minimized the importance of such effects.

In contrast to the findings among girls, in boys we observed no associations between multiple childhood fractures and bone mineral parameters. The inconsistency across sex both with

respect to multiple childhood fractures as exposure and when stratified by PA intensity weaken the line of argument of an overall causal link between childhood fractures and bone mineral accrual. This claim is supportive to a study by Clark et al (2008) [217], which aimed to confirm variables that predict fracture risk and which of the variables, were independent of bone mass. The authors concluded that the evident bone mass – PA association could not compensate for fracture risk, because of the greater risk of fracture merely due to increased exposure to injuries when exerting vigorous PA. Indeed, they discuss that suffering a fracture during childhood may on the contrary be an indication of high levels of PA, consequently yielding a higher PBM because of mechanical loading with reduced risk of osteoporosis later as the final outcome [217]. Such reasoning might be transferable to our results in explaining the complexity of fracture, PA and bone mineral development.

7.0 Conclusions

In summary, our studies demonstrate that factors from early life throughout childhood and early adolescence influence bone mineral accrual with varied importance on the path towards PBM. A life-style factor such as PA seem highly important in a population were intrauterine health is considered adequate. Furthermore, the beneficial effects of vigorous PA is likely to play a crucial role in optimization of bone mineral development, despite the increased risk of suffering a fracture attending such levels:

- We found fracture incidence rates in accordance with present numbers across the Scandinavian countries and correspondent with estimated secular trends although with a more balanced ratio between boys and girls. The findings of a vulnerability dependent of maturation support the hypothesis of size-dependent alteration in bone strength during peak growth velocity.
- Our results support the growing evidence of PA during growth as a crucial determinant for establishing good bone health, which again is likely to have consequences for timing of when the inevitable bone loss reaches critical levels. More studies are needed to quantify the role of different PA dimensions on both bone mineral parameters and the extended term “bone strength”.
- We found a crude association between birth size parameters and bone mineral outcomes in adolescence, yet attenuated by lifestyle factors and size development, supporting that fetal tissues respond to environmental stimuli in utero but in the case of few critical impacts, life-style factors probably contribute with greater effects.
- We could not confirm that childhood fracture are early markers of persistent skeletal fragility based on the findings that this association is inconsistently across levels of PA and sex. This discrepancy need further investigation, both with respect to sex difference and PA measurements.

8.0 Implications for public health and future research

8.1 Implications for public health

- PA during growth should be emphasized as an important factor in the prevention of osteoporosis due to the high potential of bone mineral accrual. It is important that habitual PA established during childhood be carried forward throughout the vulnerable years of adolescence into adulthood.
- Recommendations and guidelines from Norwegian health authorities, stating that 60 minutes moderate to vigorous daily PA in childhood is sufficient to preserve good health, is likely to be adequate for a satisfactory peak bone mass development. Higher PA levels may additionally enhance bone benefits.
- As there is growing concern about increased sedentary life-style among Norwegian children, knowledge about and interventions to promote PA as beneficial for bone should be incorporated in settings where children spend most of their time e.g. schools and sports organizations.
- In order to obtain an optimal PBM, daily weight-bearing moderate to vigorous PA should be recommended to children and adolescents.
- Girls suffering one or more fractures during childhood, and simultaneously display a sedentary life-style should be identified for follow up.

8.2 Implications for future research

The findings presented disclose several relevant aspects for forthcoming studies to follow up:

In further identification of early determinants, we would like to investigate the association between birth parameters and fractures during childhood. As mentioned, birth weight as a proxy for intrauterine environment constitute a basis of bone development, and we found a crude association between birth size parameters and bone mineral outcome. We would like to test the hypothesis that birth weight/length is associated with fractures during childhood and especially the relationship between birth size parameters and fractures during early childhood versus fractures in the period of puberty.

The second wave of the Fit Future study was carried out in 2012/2013 and allow follow up on a multitude of the variables presented. It would have been interesting to investigate the deterministic value of our exposure variables on the repeated measurements collected when the participants are closer to the timing of PBM. Furthermore, several aspect concerning the

PA variable are interesting to explore, e.g. rates of attendance carried through, sex difference in withdrawal from PA outside school hours and changes in dimensions and types; and their potential consequences for bone development.

In addition, the planning and execution of Fit Futures 3 will allow several interesting aspects connected to the development and consolidation of bone mass parameters in a longitudinal perspective. In combination with a completed fracture registration throughout adolescence, the Fit Futures follow up allow testing of various hypothesis possible, including addressing determinants for a final PBM and predictors for bone mass development after achieving this peak.

REFERENCES

1. Graff-Iversen, S., S. Skurtveit, A. Nybo, et al., *[Trends when it comes to occupational physical activity among Norwegians aged 40-42 years during the period 1974-94].* Tidsskr Nor Laegeforen, 2001. **121**(22): p. 2584-8.
2. *Public Health Report*. 2014 [cited 2017 June 14th]; Available from: https://www.fhi.no/en/op/public-health-report-2014/.
3. Omsland, T.K., K. Holvik, H.E. Meyer, et al., *Hip fractures in Norway 1999-2008: time trends in total incidence and second hip fracture rates: a NOREPOS study.* Eur J Epidemiol, 2012. **27**(10): p. 807-14.
4. Lofthus, C.M., F. Frihagen, H.E. Meyer, et al., *Epidemiology of distal forearm fractures in Oslo, Norway.* Osteoporos Int, 2008. **19**(6): p. 781-6.
5. *Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis.* Am J Med, 1993. **94**(6): p. 646-50.
6. Nih Consensus Development Panel on Osteoporosis Prevention, D. and Therapy, *Osteoporosis prevention, diagnosis, and therapy.* JAMA, 2001. **285**(6): p. 785-95.
7. Johnell, O. and J. Kanis, *Epidemiology of osteoporotic fractures.* Osteoporos Int, 2005. **16 Suppl 2**: p. S3-7.
8. Cummings, S.R. and L.J. Melton, *Epidemiology and outcomes of osteoporotic fractures.* Lancet, 2002. **359**(9319): p. 1761-7.
9. Johnell, O. and J.A. Kanis, *An estimate of the worldwide prevalence, mortality and disability associated with hip fracture.* Osteoporos Int, 2004. **15**(11): p. 897-902.
10. Hershkovitz, A., I. Polatov, Y. Beloosesky, et al., *Factors affecting mortality of frail hip-fractured elderly patients.* Arch Gerontol Geriatr, 2010. **51**(2): p. 113-6.
11. Bliuc, D., N.D. Nguyen, V.E. Milch, et al., *Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women.* JAMA, 2009. **301**(5): p. 513-21.
12. Omsland, T.K., N. Emaus, G.S. Tell, et al., *Mortality following the first hip fracture in Norwegian women and men (1999-2008). A NOREPOS study.* Bone, 2014. **63**: p. 81-6.
13. Center, J.R., T.V. Nguyen, D. Schneider, et al., *Mortality after all major types of osteoporotic fracture in men and women: an observational study.* Lancet, 1999. **353**(9156): p. 878-82.
14. Melton, L.J., 3rd, *Adverse outcomes of osteoporotic fractures in the general population.* J Bone Miner Res, 2003. **18**(6): p. 1139-41.
15. Ray, N.F., J.K. Chan, M. Thamer, et al., *Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: report from the National Osteoporosis Foundation.* J Bone Miner Res, 1997. **12**(1): p. 24-35.
16. Ettinger, B., D.M. Black, M.C. Nevitt, et al., *Contribution of vertebral deformities to chronic back pain and disability. The Study of Osteoporotic Fractures Research Group.* J Bone Miner Res, 1992. **7**(4): p. 449-56.
17. Burge, R., B. Dawson-Hughes, D.H. Solomon, et al., *Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025.* J Bone Miner Res, 2007. **22**(3): p. 465-75.
18. Burge, R.T., D. Worley, A. Johansen, et al., *The cost of osteoporotic fractures in the UK: projections for 2000–2020.* Journal of Medical Economics, 2001. **4**(1-4): p. 51-62.
19. Johnell, O., *The socioeconomic burden of fractures: today and in the 21st century.* Am J Med, 1997. **103**(2A): p. 20S-25S; discussion 25S-26S.
20. Hektoen, L.F., *Kostnader ved hoftebrudd hos eldre (Costs of hip fractures in elderly)*. 2014, Høgskolen i Oslo og Akershus.
21. Cooper, C., G. Campion, and L.J. Melton, 3rd, *Hip fractures in the elderly: a world-wide projection.* Osteoporos Int, 1992. **2**(6): p. 285-9.

22. *Fractured neck of femur. Prevention and management. Summary and recommendations of a report of the Royal College of Physicians.* J R Coll Physicians Lond, 1989. **23**(1): p. 8-12.
23. Johnell, O., B. Gullberg, E. Allander, et al., *The apparent incidence of hip fracture in Europe: a study of national register sources.* Osteoporos Int, 1992. **2**(6): p. 298-302.
24. Elffors, I., E. Allander, J.A. Kanis, et al., *The variable incidence of hip fracture in southern Europe: the MEDOS Study.* Osteoporos Int, 1994. **4**(5): p. 253-63.
25. Kannus, P., J. Parkkari, H. Sievanen, et al., *Epidemiology of hip fractures.* Bone, 1996. **18**(1 Suppl): p. 57S-63S.
26. Lau, E.M. and C. Cooper, *The epidemiology of osteoporosis. The oriental perspective in a world context.* Clin Orthop Relat Res, 1996(323): p. 65-74.
27. Yan, L., B. Zhou, A. Prentice, et al., *Epidemiological study of hip fracture in Shenyang, People's Republic of China.* Bone, 1999. **24**(2): p. 151-5.
28. Omsland, T.K. and J.H. Magnus, *Forecasting the burden of future postmenopausal hip fractures.* Osteoporos Int, 2014. **25**(10): p. 2493-6.
29. Orians, G.H., H.C. Heller, D.E. Sadava, et al., *Life : the science of biology*, in *Life : the science of biology*, W.K. Purves, Editor. 1998, Sinauer Associates: Sunderland, Mass. p. 973-992.
30. Clarke, B., *Normal bone anatomy and physiology.* Clin J Am Soc Nephrol, 2008. **3 Suppl 3**: p. S131-9.
31. Mirzaali, M.J., J.J. Schwiedrzik, S. Thaiwichai, et al., *Mechanical properties of cortical bone and their relationships with age, gender, composition and microindentation properties in the elderly.* Bone, 2016. **93**: p. 196-211.
32. Eswaran, S.K., A. Gupta, M.F. Adams, et al., *Cortical and trabecular load sharing in the human vertebral body.* J Bone Miner Res, 2006. **21**(2): p. 307-14.
33. Keaveny, T.M., E.F. Wachtel, X.E. Guo, et al., *Mechanical behavior of damaged trabecular bone.* J Biomech, 1994. **27**(11): p. 1309-18.
34. de Gorter, D.J.J. and P. ten Dijke, *Signal transduction cascades controlling osteoblast differentiation*, in *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*, C.J. Rosen, et al., Editors. 2013, Wiley: Hoboken. p. 15-21.
35. Logan, C.Y. and R. Nusse, *The Wnt signaling pathway in development and disease.* Annu Rev Cell Dev Biol, 2004. **20**: p. 781-810.
36. Ross, F.P., *Osteoclast biology and bone resorption*, in *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*, C.J. Rosen, et al., Editors. 2013, Wiley: Hoboken. p. 25-31.
37. Bonewald, L.F., *Osteocytes*, in *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*, C.J. Rosen, et al., Editors. 2013, Wiley: Hoboken. p. 34-39.
38. Petrtyl, M., J. Hert, and P. Fiala, *Spatial organization of the haversian bone in man.* J Biomech, 1996. **29**(2): p. 161-9.
39. Parfitt, A.M., *Osteonal and hemi-osteonal remodeling: the spatial and temporal framework for signal traffic in adult human bone.* J Cell Biochem, 1994. **55**(3): p. 273-86.
40. Hadjidakis, D.J. and Androulakis, II, *Bone remodeling.* Ann N Y Acad Sci, 2006. **1092**: p. 385-96.
41. Yang, T., M. Grover, K.S. Joeng, et al., *Human fetal and neonatal bone development*, in *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*, C.J. Rosen, et al., Editors. 2013, Wiley: Hoboken. p. 121-124.
42. Yang, Y., *Skeletal Morphogenesis and Embryonic Development*, in *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*, C.J. Rosen, Editor. 2013, Wiley: Hoboken. p. 3-10.
43. Tao Yang, M.G., Kyu Sang Joeng, Brendan Lee, *Human Fetal and Neonatal Bone Development*, in *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*, C.J. Rosen, Editor. 2013, Wiley: Hoboken. p. 121-126.
44. Salle, B.L., F. Rauch, R. Travers, et al., *Human fetal bone development: histomorphometric evaluation of the proximal femoral metaphysis.* Bone, 2002. **30**(6): p. 823-8.

45. Neer, R., M. Berman, L. Fisher, et al., *Multicompartmental analysis of calcium kinetics in normal adult males.* J Clin Invest, 1967. **46**(8): p. 1364-79.
46. Kovacs, C.S. and H.M. Kronenberg, *Maternal-fetal calcium and bone metabolism during pregnancy, puerperium, and lactation.* Endocr Rev, 1997. **18**(6): p. 832-72.
47. Salle, B.L., F.H. Glorieux, and E.E. Delvin, *Perinatal vitamin D metabolism.* Biol Neonate, 1988. **54**(4): p. 181-7.
48. Dennison, E.M., H.E. Syddall, S. Rodriguez, et al., *Polymorphism in the growth hormone gene, weight in infancy, and adult bone mass.* J Clin Endocrinol Metab, 2004. **89**(10): p. 4898-903.
49. Mehta, G., H.I. Roach, S. Langley-Evans, et al., *Intrauterine exposure to a maternal low protein diet reduces adult bone mass and alters growth plate morphology in rats.* Calcif Tissue Int, 2002. **71**(6): p. 493-8.
50. Dennison, E.M., N.K. Arden, R.W. Keen, et al., *Birthweight, vitamin D receptor genotype and the programming of osteoporosis.* Paediatr Perinat Epidemiol, 2001. **15**(3): p. 211-9.
51. Bodnar, L.M., H.N. Simhan, R.W. Powers, et al., *High prevalence of vitamin D insufficiency in black and white pregnant women residing in the northern United States and their neonates.* J Nutr, 2007. **137**(2): p. 447-52.
52. Wang, Q. and E. Seeman, *Skeletal growth and peak bone strength*, in *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*, C.J. Rosen, et al., Editors. 2013, Wiley: Hoboken. p. 127 -131.
53. Clark, E.M., A.R. Ness, and J.H. Tobias, *Gender differences in the ratio between humerus width and length are established prior to puberty.* Osteoporos Int, 2007. **18**(4): p. 463-70.
54. Hogler, W., C.J. Blimkie, C.T. Cowell, et al., *A comparison of bone geometry and cortical density at the mid-femur between prepuberty and young adulthood using magnetic resonance imaging.* Bone, 2003. **33**(5): p. 771-8.
55. Manolagas, S.C., M. Almeida, and R.L. Jilka, *Gonadal Steroids*, in *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*, C.J. Rosen, et al., Editors. 2013, Wiley: Hoboken. p. 195-208.
56. Bonjour, J.P., G. Theintz, F. Law, et al., *Peak bone mass.* Osteoporos Int, 1994. **4 Suppl 1**: p. 7-13.
57. Davies, J.H., B.A. Evans, and J.W. Gregory, *Bone mass acquisition in healthy children.* Arch Dis Child, 2005. **90**(4): p. 373-8.
58. Heaney, R.P., S. Abrams, B. Dawson-Hughes, et al., *Peak bone mass.* Osteoporos Int, 2000. **11**(12): p. 985-1009.
59. Hui, S.L., C.W. Slemenda, and C.C. Johnston, Jr., *The contribution of bone loss to postmenopausal osteoporosis.* Osteoporos Int, 1990. **1**(1): p. 30-4.
60. Barker, D.J., *The fetal and infant origins of disease.* Eur J Clin Invest, 1995. **25**(7): p. 457-63.
61. Lucas, A., *Programming by Early Nutrition in Man*. 2007, Chichester, UK: Chichester, UK: John Wiley & Sons, Ltd. 38-55.
62. Cooper, C., S. Westlake, N. Harvey, et al., *Developmental origins of osteoporotic fracture.* Adv Exp Med Biol, 2009. **639**: p. 217-36.
63. Cooper, C., S. Westlake, N. Harvey, et al., *Review: developmental origins of osteoporotic fracture.* Osteoporos Int, 2006. **17**(3): p. 337-47.
64. Eide, M.G., N. Oyen, R. Skjaerven, et al., *Size at birth and gestational age as predictors of adult height and weight.* Epidemiology, 2005. **16**(2): p. 175-81.
65. Weaver, C.M., C.M. Gordon, K.F. Janz, et al., *The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations.* Osteoporos Int, 2016. **27**(4): p. 1281-386.
66. Caspersen, C.J., K.E. Powell, and G.M. Christenson, *Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research.* Public Health Rep, 1985. **100**(2): p. 126-31.
67. Forwood, M.R. and C.H. Turner, *Skeletal adaptations to mechanical usage: results from tibial loading studies in rats.* Bone, 1995. **17**(4 Suppl): p. 197S-205S.

68. Turner, C.H., M.R. Forwood, J.Y. Rho, et al., *Mechanical loading thresholds for lamellar and woven bone formation.* J Bone Miner Res, 1994. **9**(1): p. 87-97.
69. Turner, C.H. and A.G. Robling, *Designing exercise regimens to increase bone strength.* Exerc Sport Sci Rev, 2003. **31**(1): p. 45-50.
70. Forwood, M.R. and D.B. Burr, *Physical activity and bone mass: exercises in futility?* Bone Miner, 1993. **21**(2): p. 89-112.
71. Heinonen, A., H. Sievanen, P. Kannus, et al., *High-impact exercise and bones of growing girls: a 9-month controlled trial.* Osteoporos Int, 2000. **11**(12): p. 1010-7.
72. Jarvinen, T.L., I. Pajamaki, H. Sievanen, et al., *Femoral neck response to exercise and subsequent deconditioning in young and adult rats.* J Bone Miner Res, 2003. **18**(7): p. 1292-9.
73. Kannus, P., H. Haapasalo, M. Sankelo, et al., *Effect of starting age of physical activity on bone mass in the dominant arm of tennis and squash players.* Ann Intern Med, 1995. **123**(1): p. 27-31.
74. Kontulainen, S., H. Sievanen, P. Kannus, et al., *Effect of long-term impact-loading on mass, size, and estimated strength of humerus and radius of female racquet-sports players: a peripheral quantitative computed tomography study between young and old starters and controls.* J Bone Miner Res, 2002. **17**(12): p. 2281-9.
75. Parfitt, A.M., *The two faces of growth: benefits and risks to bone integrity.* Osteoporos Int, 1994. **4**(6): p. 382-98.
76. Rubin, C.T., S.D. Bain, and K.J. McLeod, *Suppression of the osteogenic response in the aging skeleton.* Calcif Tissue Int, 1992. **50**(4): p. 306-13.
77. Turner, C.H., Y. Takano, and I. Owan, *Aging changes mechanical loading thresholds for bone formation in rats.* J Bone Miner Res, 1995. **10**(10): p. 1544-9.
78. Hert, J., M. Liskova, and J. Landa, *Reaction of bone to mechanical stimuli. 1. Continuous and intermittent loading of tibia in rabbit.* Folia Morphol (Praha), 1971. **19**(3): p. 290-300.
79. Hert, J., M. Liskova, and B. Landrgot, *Influence of the long-term, continuous bending on the bone. An experimental study on the tibia of the rabbit.* Folia Morphol (Praha), 1969. **17**(4): p. 389-99.
80. Rubin, C.T. and L.E. Lanyon, *Regulation of bone formation by applied dynamic loads.* J Bone Joint Surg Am, 1984. **66**(3): p. 397-402.
81. Turner, C.H., I. Owan, and Y. Takano, *Mechanotransduction in bone: role of strain rate.* Am J Physiol, 1995. **269**(3 Pt 1): p. E438-42.
82. Rubin, C.T. and L.E. Lanyon, *Regulation of bone mass by mechanical strain magnitude.* Calcif Tissue Int, 1985. **37**(4): p. 411-7.
83. Forwood, M.R., *Growing a healthy skeleton: The importance of mechanical loading*, in *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*, C.J. Rosen, et al., Editors. 2013, Wiley: Hoboken. p. 149-153.
84. Robling, A.G., D.B. Burr, and C.H. Turner, *Partitioning a daily mechanical stimulus into discrete loading bouts improves the osteogenic response to loading.* J Bone Miner Res, 2000. **15**(8): p. 1596-602.
85. Gustavsson, A., T. Olsson, and P. Nordstrom, *Rapid loss of bone mineral density of the femoral neck after cessation of ice hockey training: a 6-year longitudinal study in males.* J Bone Miner Res, 2003. **18**(11): p. 1964-9.
86. Karlsson, M.K., C. Linden, C. Karlsson, et al., *Exercise during growth and bone mineral density and fractures in old age.* Lancet, 2000. **355**(9202): p. 469-70.
87. Nordstrom, A., T. Olsson, and P. Nordstrom, *Bone gained from physical activity and lost through detraining: a longitudinal study in young males.* Osteoporos Int, 2005. **16**(7): p. 835-41.
88. Fuchs, R.K., J.J. Bauer, and C.M. Snow, *Jumping improves hip and lumbar spine bone mass in prepubescent children: a randomized controlled trial.* J Bone Miner Res, 2001. **16**(1): p. 148-56.

89. Gunter, K., A.D. Baxter-Jones, R.L. Mirwald, et al., *Impact exercise increases BMC during growth: an 8-year longitudinal study.* J Bone Miner Res, 2008. **23**(7): p. 986-93.
90. Gunter, K., A.D. Baxter-Jones, R.L. Mirwald, et al., *Jump starting skeletal health: a 4-year longitudinal study assessing the effects of jumping on skeletal development in pre and circum pubertal children.* Bone, 2008. **42**(4): p. 710-8.
91. Bass, S.L., L. Saxon, R.M. Daly, et al., *The effect of mechanical loading on the size and shape of bone in pre-, peri-, and postpubertal girls: a study in tennis players.* J Bone Miner Res, 2002. **17**(12): p. 2274-80.
92. Reid, I.R., *Fat and bone.* Arch Biochem Biophys, 2010. **503**(1): p. 20-7.
93. Lee, S.H., S.S. Desai, G. Shetty, et al., *Bone mineral density of proximal femur and spine in Korean children between 2 and 18 years of age.* J Bone Miner Metab, 2007. **25**(6): p. 423-30.
94. De Laet, C., J.A. Kanis, A. Oden, et al., *Body mass index as a predictor of fracture risk: a meta-analysis.* Osteoporos Int, 2005. **16**(11): p. 1330-8.
95. Kanis, J.A., F. Borgstrom, C. De Laet, et al., *Assessment of fracture risk.* Osteoporos Int, 2005. **16**(6): p. 581-9.
96. Travison, T.G., A.B. Araujo, G.R. Esche, et al., *The relationship between body composition and bone mineral content: threshold effects in a racially and ethnically diverse group of men.* Osteoporos Int, 2008. **19**(1): p. 29-38.
97. Zhu, K., M. Hunter, A. James, et al., *Associations between body mass index, lean and fat body mass and bone mineral density in middle-aged Australians: The Busselton Healthy Ageing Study.* Bone, 2015. **74**: p. 146-52.
98. Ackerman, A., J.C. Thornton, J. Wang, et al., *Sex difference in the effect of puberty on the relationship between fat mass and bone mass in 926 healthy subjects, 6 to 18 years old.* Obesity (Silver Spring), 2006. **14**(5): p. 819-25.
99. Arabi, A., H. Tamim, M. Nabulsi, et al., *Sex differences in the effect of body-composition variables on bone mass in healthy children and adolescents.* Am J Clin Nutr, 2004. **80**(5): p. 1428-35.
100. Ausili, E., D. Rigante, E. Salvaggio, et al., *Determinants of bone mineral density, bone mineral content, and body composition in a cohort of healthy children: influence of sex, age, puberty, and physical activity.* Rheumatol Int, 2012. **32**(9): p. 2737-43.
101. Pietrobelli, A., M.S. Faith, J. Wang, et al., *Association of lean tissue and fat mass with bone mineral content in children and adolescents.* Obes Res, 2002. **10**(1): p. 56-60.
102. Favus, M.J. and D. Goltzman, *Regulation of calcium and magnesium*, in *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*, C.J. Rosen, et al., Editors. 2013, Wiley: Hoboken. p. 173-177.
103. Matkovic, V. and R.P. Heaney, *Calcium balance during human growth: evidence for threshold behavior.* Am J Clin Nutr, 1992. **55**(5): p. 992-6.
104. Goulding, A., A.M. Grant, and S.M. Williams, *Bone and body composition of children and adolescents with repeated forearm fractures.* J Bone Miner Res, 2005. **20**(12): p. 2090-6.
105. Manias, K., D. McCabe, and N. Bishop, *Fractures and recurrent fractures in children; varying effects of environmental factors as well as bone size and mass.* Bone, 2006. **39**(3): p. 652-7.
106. Oberg, J., R. Jorde, B. Almas, et al., *Vitamin D deficiency and lifestyle risk factors in a Norwegian adolescent population.* Scand J Public Health, 2014. **42**(7): p. 593-602.
107. Jones, G., C. Blizzard, M.D. Riley, et al., *Vitamin D levels in prepubertal children in Southern Tasmania: prevalence and determinants.* Eur J Clin Nutr, 1999. **53**(10): p. 824-9.
108. Jones, G., T. Dwyer, K.L. Hynes, et al., *Vitamin D insufficiency in adolescent males in Southern Tasmania: prevalence, determinants, and relationship to bone turnover markers.* Osteoporos Int, 2005. **16**(6): p. 636-41.
109. Looker, A.C., B. Dawson-Hughes, M.S. Calvo, et al., *Serum 25-hydroxyvitamin D status of adolescents and adults in two seasonal subpopulations from NHANES III.* Bone, 2002. **30**(5): p. 771-7.

110. Rockell, J.E., C.M. Skeaff, S.M. Williams, et al., *Serum 25-hydroxyvitamin D concentrations of New Zealanders aged 15 years and older.* Osteoporos Int, 2006. **17**(9): p. 1382-9.
111. Winzenberg, T., S. Powell, K.A. Shaw, et al., *Effects of vitamin D supplementation on bone density in healthy children: systematic review and meta-analysis.* BMJ, 2011. **342**: p. c7254.
112. Winzenberg, T.M., S. Powell, K.A. Shaw, et al., *Vitamin D supplementation for improving bone mineral density in children.* Cochrane Database Syst Rev, 2010(10): p. CD006944.
113. Yoon, V., N. Maalouf, and K. Sakhaee, *The effects of smoking on bone metabolism.* Osteoporosis Int, 2012. **23**(8): p. 2081-2092.
114. Perez-lopez, F., P. Chedraui, and J. Cuadros-lopez, *Bone Mass Gain During Puberty and Adolescence: Deconstructing Gender Characteristics.* Current Medicinal Chemistry, 2010. **17**(5): p. 453-466.
115. Dorn, L., S.J. Beal, H. Kalkwarf, et al., *Longitudinal Impact of Substance Use and Depressive Symptoms on Bone Accrual Among Girls Aged 11-19 Years.* J. Adolesc. Health, 2013. **52**(4): p. 393-399.
116. Berg, K.M., H.V. Kunins, J.L. Jackson, et al., *Association Between Alcohol Consumption and Both Osteoporotic Fracture and Bone Density.* The American Journal of Medicine, 2008. **121**(5): p. 406-418.
117. Cooper, C., E.M. Dennison, H.G. Leufkens, et al., *Epidemiology of childhood fractures in Britain: a study using the general practice research database.* J Bone Miner Res, 2004. **19**(12): p. 1976-81.
118. Kopjar, B. and T.M. Wickizer, *Fractures among children: incidence and impact on daily activities.* Inj Prev, 1998. **4**(3): p. 194-7.
119. Landin, L.A., *Fracture patterns in children. Analysis of 8,682 fractures with special reference to incidence, etiology and secular changes in a Swedish urban population 1950-1979.* Acta Orthop Scand Suppl, 1983. **202**: p. 1-109.
120. Bailey, D.A., H.A. McKay, R.L. Mirwald, et al., *A six-year longitudinal study of the relationship of physical activity to bone mineral accrual in growing children: the university of Saskatchewan bone mineral accrual study.* J Bone Miner Res, 1999. **14**(10): p. 1672-9.
121. Bass, S., P.D. Delmas, G. Pearce, et al., *The differing tempo of growth in bone size, mass, and density in girls is region-specific.* J Clin Invest, 1999. **104**(6): p. 795-804.
122. Wang, Q., X.F. Wang, S. Iuliano-Burns, et al., *Rapid growth produces transient cortical weakness: a risk factor for metaphyseal fractures during puberty.* J Bone Miner Res, 2010. **25**(7): p. 1521-6.
123. Khosla, S., L.J. Melton, 3rd, M.B. Dekutoski, et al., *Incidence of childhood distal forearm fractures over 30 years: a population-based study.* JAMA, 2003. **290**(11): p. 1479-85.
124. Goulding, A., I.E. Jones, R.W. Taylor, et al., *More broken bones: a 4-year double cohort study of young girls with and without distal forearm fractures.* J Bone Miner Res, 2000. **15**(10): p. 2011-8.
125. Goulding, A., I.E. Jones, R.W. Taylor, et al., *Bone mineral density and body composition in boys with distal forearm fractures: a dual-energy x-ray absorptiometry study.* J Pediatr, 2001. **139**(4): p. 509-15.
126. Jones, I.E., R.W. Taylor, S.M. Williams, et al., *Four-year gain in bone mineral in girls with and without past forearm fractures: a DXA study. Dual energy X-ray absorptiometry.* J Bone Miner Res, 2002. **17**(6): p. 1065-72.
127. Ferrari, S.L., T. Chevalley, J.P. Bonjour, et al., *Childhood fractures are associated with decreased bone mass gain during puberty: an early marker of persistent bone fragility?* J Bone Miner Res, 2006. **21**(4): p. 501-7.
128. Ma, D. and G. Jones, *Television, computer, and video viewing; physical activity; and upper limb fracture risk in children: a population-based case control study.* J Bone Miner Res, 2003. **18**(11): p. 1970-7.

129. Blake, G., J.E. Adams, and N. Bishop, *DXA in Adults and Children*, in *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*, C.J. Rosen, et al., Editors. 2013, Wiley: Hoboken. p. 251-263.
130. Ammann, P. and R. Rizzoli, *Bone strength and its determinants.* Osteoporos Int, 2003. **14 Suppl 3**: p. S13-8.
131. Johnell, O., J.A. Kanis, A. Oden, et al., *Predictive value of BMD for hip and other fractures.* J Bone Miner Res, 2005. **20**(7): p. 1185-94.
132. Marshall, D., O. Johnell, and H. Wedel, *Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures.* BMJ, 1996. **312**(7041): p. 1254-9.
133. Hough, S., *Fast and slow bone losers. Relevance to the management of osteoporosis.* Drugs Aging, 1998. **12 Suppl 1**: p. 1-7.
134. Warden, S.J., S.M. Mantila Roosa, M.E. Kersh, et al., *Physical activity when young provides lifelong benefits to cortical bone size and strength in men.* Proc Natl Acad Sci U S A, 2014. **111**(14): p. 5337-42.
135. Jacobsen, B.K., A.E. Eggen, E.B. Mathiesen, et al., *Cohort profile: the Tromso Study.* Int J Epidemiol, 2012. **41**(4): p. 961-7.
136. *The Tromsø Study*. 2017 [cited 2017 June 12th]; Available from: https://uit.no/forskning/forskningsgrupper/gruppe?p_document_id=367276.
137. *Declaration of Helsinki*. 2013 [cited 2017 May 8th]; Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.
138. *Health Research Act*. 2008 [cited 2017 May 21th]; Available from: https://lovdata.no/dokument/NL/lov/2008-06-20-44?q=helseforskning.
139. *Patients' Rights Act*. 2015 [cited 2017 May 21th]; Available from: https://lovdata.no/dokument/NL/lov/1999-07-02-63?q=pasientrettighetsloven.
140. *Lunar enCore, supplement til pediatrisk referansedata*. 2010, GE Healthcare.
141. *Medical Birth Registry of Norway*. 2016 [cited 2017 May 23th]; Available from: https://www.fhi.no/en/hn/health-registries/medical-birth-registry-of-norway/medical-birth-registry-of-norway/.
142. Joakimsen, R.M., V. Fonnebo, J.H. Magnus, et al., *The Tromso Study: physical activity and the incidence of fractures in a middle-aged population.* J Bone Miner Res, 1998. **13**(7): p. 1149-57.
143. Joakimsen, R.M., V. Fonnebo, A.J. Sogaard, et al., *The Tromso study: registration of fractures, how good are self-reports, a computerized radiographic register and a discharge register?* Osteoporos Int, 2001. **12**(12): p. 1001-5.
144. *Health behaviour in shool-aged children, WHO collaborative cross-national survey*. 2017 [cited 2017 January 23th]; Available from: http://www.hbsc.org/.
145. Booth, M.L., A.D. Okely, T. Chey, et al., *The reliability and validity of the physical activity questions in the WHO health behaviour in schoolchildren (HBSC) survey: a population study.* Br J Sports Med, 2001. **35**(4): p. 263-7.
146. Duke, P.M., I.F. Litt, and R.T. Gross, *Adolescents' self-assessment of sexual maturation.* Pediatrics, 1980. **66**(6): p. 918-20.
147. Gluckman, P.D. and M.A. Hanson, *Changing times: the evolution of puberty.* Mol Cell Endocrinol, 2006. **254-255**: p. 26-31.
148. Coleman, L. and J. Coleman, *The measurement of puberty: a review.* J Adolesc, 2002. **25**(5): p. 535-50.
149. Lucas, A., M.S. Fewtrell, and T.J. Cole, *Fetal origins of adult disease-the hypothesis revisited.* BMJ, 1999. **319**(7204): p. 245-9.
150. Dishman, R.K., G.W. Heath, and R.A. Washburn, *Concepts and Methods in Physical Activity Epidemiology*, in *Physical activity epidemiology*, R.K. Dishman, G.W. Heath, and R.A. Washburn, Editors. 2004, Human Kinetics: Champaign, Ill. p. 17-36.

151. Veierød, M.B. and D.S. Thelle, *Tverrsnittsstudier*, in *Epidemiologiske og kliniske forskningsmetoder*, M.B. Veierød, et al., Editors. 2007. p. 235-258.
152. Jacobsen, G., *[Analytical epidemiology--case-control and cohort studies].* Tidsskr Nor Laegeforen, 2002. **122**(27): p. 2636-40.
153. Rothman, K.J. and S. Greenland, *Precision and Validity in Epidemiologic Studies*, in *Modern epidemiology*, K.J. Rothman and S. Greenland, Editors. 1998, Lippincott-Raven: Philadelphia. p. 115-134.
154. Laake, P., M. Thoresen, and M.B. Veierød, *Målefeilsproblemer*, in *Epidemiologiske og kliniske forskningsmetoder*, M.B. Veierød, et al., Editors. 2007, Gyldendal akademisk: Oslo. p. 128-167.
155. Rothman, K.J., *Epidemiology : an introduction*. 2002, Oxford: Oxford University Press.
156. Dorn, L.D., S.J. Beal, H.J. Kalkwarf, et al., *Longitudinal impact of substance use and depressive symptoms on bone accrual among girls aged 11-19 years.* J Adolesc Health, 2013. **52**(4): p. 393-9.
157. Winther, A., E. Dennison, L.A. Ahmed, et al., *The Tromso Study: Fit Futures: a study of Norwegian adolescents' lifestyle and bone health.* Arch Osteoporos, 2014. **9**: p. 185.
158. Hjartåker, A. and E. Lund, *Kohortstudier*, in *Epidemiologiske og kliniske forskningsmetoder*, M.B. Veierød, et al., Editors. 2007, Gyldendal akademisk: Oslo. p. 185 - 209.
159. Last, J.M. and A. International Epidemiological, *A Dictionary of epidemiology*. 4th ed. ed. 2001, Oxford: Oxford University Press.
160. Szklo, M. and F.J. Nieto, *Epidemiology : beyond the basics*. 2000, Gaithersburg: Aspen.
161. Gerstman, B.B., *Epidemiology kept simple : an introduction to traditional and modern epidemiology*. 2nd ed. ed. 2003, Hoboken, N.J: Wiley.
162. Omsland, T.K., N. Emaus, C.G. Gjesdal, et al., *In vivo and in vitro comparison of densitometers in the NOREPOS study.* J Clin Densitom, 2008. **11**(2): p. 276-82.
163. Shepherd, J.A., Y. Lu, K. Wilson, et al., *Cross-calibration and minimum precision standards for dual-energy X-ray absorptiometry: the 2005 ISCD Official Positions.* J Clin Densitom, 2006. **9**(1): p. 31-6.
164. Katzman, D.K., L.K. Bachrach, D.R. Carter, et al., *Clinical and anthropometric correlates of bone mineral acquisition in healthy adolescent girls.* J Clin Endocrinol Metab, 1991. **73**(6): p. 1332-9.
165. Lu, P.W., C.T. Cowell, L.L.-J. SA, et al., *Volumetric bone mineral density in normal subjects, aged 5-27 years.* J Clin Endocrinol Metab, 1996. **81**(4): p. 1586-90.
166. Dishman, R.K., G.W. Heath, and R.A. Washburn, *Measurement and surveillance of physical activity and fitness*, in *Physical activity epidemiology*, R.K. Dishman, G.W. Heath, and R.A. Washburn, Editors. 2004, Human Kinetics: Champaign, Ill. p. 37-70.
167. Khan, K., *Physical activity and bone health*. 2001, Champaign, IL: Human kinetics.
168. Lee, I.-M., *Epidemiologic Methods in Physical Activity Studies*. 2009, Oxford: Oxford University Press. 352.
169. Rangul, V., T.L. Holmen, N. Kurtze, et al., *Reliability and validity of two frequently used self-administered physical activity questionnaires in adolescents.* BMC Med Res Methodol, 2008. **8**: p. 47.
170. Gracia-Marco, L., L.A. Moreno, F.B. Ortega, et al., *Levels of physical activity that predict optimal bone mass in adolescents: the HELENA study.* Am J Prev Med, 2011. **40**(6): p. 599-607.
171. Heidemann, M., C. Molgaard, S. Husby, et al., *The intensity of physical activity influences bone mineral accrual in childhood: the childhood health, activity and motor performance school (the CHAMPS) study, Denmark.* BMC Pediatr, 2013. **13**: p. 32.
172. Watkinson, C., E.M. van Sluijs, S. Sutton, et al., *Overestimation of physical activity level is associated with lower BMI: a cross-sectional analysis.* Int J Behav Nutr Phys Act, 2010. **7**: p. 68.

173. Celis-Morales, C.A., F. Perez-Bravo, L. Ibanez, et al., *Objective vs. self-reported physical activity and sedentary time: effects of measurement method on relationships with risk biomarkers.* PLoS One, 2012. **7**(5): p. e36345.
174. Dorn, L.D. and E.J. Susman, *The Audio Computer-Assisted Self-Interview method for self-report of puberty: is it ready for prime time?* J Adolesc Health, 2011. **48**(4): p. 323-4.
175. Koo, M.M. and T.E. Rohan, *Accuracy of short-term recall of age at menarche.* Ann Hum Biol, 1997. **24**(1): p. 61-4.
176. Brooks-Gunn, J., M.P. Warren, J. Rosso, et al., *Validity of self-report measures of girls' pubertal status.* Child Dev, 1987. **58**(3): p. 829-41.
177. Petersen, A.C., L. Crockett, M. Richards, et al., *A self-report measure of pubertal status: Reliability, validity, and initial norms.* J Youth Adolesc, 1988. **17**(2): p. 117-33.
178. Limony, Y., S. Koziel, and M. Friger, *Age of onset of a normally timed pubertal growth spurt affects the final height of children.* Pediatr Res, 2015. **78**(3): p. 351-5.
179. Irgens, L.M., *[Medical birth registry--an essential resource in perinatal medical research].* Tidsskr Nor Laegeforen, 2002. **122**(26): p. 2546-9.
180. Lie, R.T., A.J. Wilcox, and R. Skjaerven, *A population-based study of the risk of recurrence of birth defects.* N Engl J Med, 1994. **331**(1): p. 1-4.
181. Moth, F.N., T.R. Sebastian, J. Horn, et al., *Validity of a selection of pregnancy complications in the Medical Birth Registry of Norway.* Acta Obstet Gynecol Scand, 2016. **95**(5): p. 519-27.
182. Willett, W.C., *Nutritional epidemiology*. 2011. 580-597.
183. Klesges, R.C., M. Debon, and J.W. Ray, *Are self-reports of smoking rate biased? Evidence from the Second National Health and Nutrition Examination Survey.* J Clin Epidemiol, 1995. **48**(10): p. 1225-33.
184. Elwood, M., *Critical Appraisal of Epidemiology Studies and Clinical Trails*. Vol. 3rd ed. 2007, New York: Oxford University Press.
185. Bhopal, R.S., *Concepts of Epidemiology: Integrating the ideas, theories, principles and methods of epidemiology* 2nd ed. 2008, New York: Oxford University Press.
186. Pearce, N. and P. Boffetta, *General issues of study design and analysis in the use of biomarkers in cancer epidemiology.* IARC Sci Publ, 1997(142): p. 47-57.
187. Groholt, E.K., H. Stigum, and R. Nordhagen, *Overweight and obesity among adolescents in Norway: cultural and socio-economic differences.* J Public Health (Oxf), 2008. **30**(3): p. 258-65.
188. Hovengen, R., A. Biehl, and K. Glavin, *Barns vekst i Norge 2008-2012. Høyde, vekt og livvidde blant 3. klassinger*. 2014, Folkehelseinsituttet.
189. Logstein, B., A. Blekesaune, and R. Almas, *Physical activity among Norwegian adolescents--a multilevel analysis of how place of residence is associated with health behaviour: the Young-HUNT study.* Int J Equity Health, 2013. **12**: p. 56.
190. Hill, A.B., *The Environment and Disease: Association or Causation?* Proc R Soc Med, 1965. **58**: p. 295-300.
191. Susser, M., *What is a cause and how do we know one? A grammar for pragmatic epidemiology.* Am J Epidemiol, 1991. **133**(7): p. 635-48.
192. Mayranpaa, M.K., O. Makitie, and P.E. Kallio, *Decreasing incidence and changing pattern of childhood fractures: A population-based study.* J Bone Miner Res, 2010. **25**(12): p. 2752-9.
193. Tiderius, C.J., L. Landin, and H. Duppe, *Decreasing incidence of fractures in children: an epidemiological analysis of 1,673 fractures in Malmo, Sweden, 1993-1994.* Acta Orthop Scand, 1999. **70**(6): p. 622-6.
194. Rizzoli, R., M.L. Bianchi, M. Garabedian, et al., *Maximizing bone mineral mass gain during growth for the prevention of fractures in the adolescents and the elderly.* Bone, 2010. **46**(2): p. 294-305.
195. Frost, H.M., *Bone's mechanostat: a 2003 update.* Anat Rec A Discov Mol Cell Evol Biol, 2003. **275**(2): p. 1081-101.

196. Deere, K., A. Sayers, J. Rittweger, et al., *Habitual levels of high, but not moderate or low, impact activity are positively related to hip BMD and geometry: results from a population-based study of adolescents.* J Bone Miner Res, 2012. **27**(9): p. 1887-95.
197. Bielemann, R.M., J. Martinez-Mesa, and D.P. Gigante, *Physical activity during life course and bone mass: a systematic review of methods and findings from cohort studies with young adults.* BMC Musculoskelet Disord, 2013. **14**: p. 77.
198. Daly, R.M. and S.L. Bass, *Lifetime sport and leisure activity participation is associated with greater bone size, quality and strength in older men.* Osteoporos Int, 2006. **17**(8): p. 1258-67.
199. Robling, A.G., F.M. Hinant, D.B. Burr, et al., *Improved bone structure and strength after long-term mechanical loading is greatest if loading is separated into short bouts.* J Bone Miner Res, 2002. **17**(8): p. 1545-54.
200. Janz, K.F., T.L. Burns, S.M. Levy, et al., *Tracking of activity and sedentary behaviors in childhood: the Iowa Bone Development Study.* Am J Prev Med, 2005. **29**(3): p. 171-8.
201. Malina, R.M., *Physical activity and fitness: pathways from childhood to adulthood.* Am J Hum Biol, 2001. **13**(2): p. 162-72.
202. Raitakari, O.T., K.V. Porkka, S. Taimela, et al., *Effects of persistent physical activity and inactivity on coronary risk factors in children and young adults. The Cardiovascular Risk in Young Finns Study.* Am J Epidemiol, 1994. **140**(3): p. 195-205.
203. Sallis, J.F., C.C. Berry, S.L. Broyles, et al., *Variability and tracking of physical activity over 2 yr in young children.* Med Sci Sports Exerc, 1995. **27**(7): p. 1042-9.
204. Kristensen, P.L., N.C. Moller, L. Korsholm, et al., *Tracking of objectively measured physical activity from childhood to adolescence: the European youth heart study.* Scand J Med Sci Sports, 2008. **18**(2): p. 171-8.
205. Barker, D.J., *In utero programming of chronic disease.* Clin Sci (Lond), 1998. **95**(2): p. 115-28.
206. Martinez-Mesa, J., M.C. Restrepo-Mendez, D.A. Gonzalez, et al., *Life-course evidence of birth weight effects on bone mass: systematic review and meta-analysis.* Osteoporos Int, 2013. **24**(1): p. 7-18.
207. Cooper, C., N. Harvey, Z. Cole, et al., *Developmental origins of osteoporosis: the role of maternal nutrition.* Adv Exp Med Biol, 2009. **646**: p. 31-9.
208. Antoniades, L., A.J. MacGregor, T. Andrew, et al., *Association of birth weight with osteoporosis and osteoarthritis in adult twins.* Rheumatology (Oxford), 2003. **42**(6): p. 791-6.
209. Fall, C., P. Hindmarsh, E. Dennison, et al., *Programming of growth hormone secretion and bone mineral density in elderly men: a hypothesis.* J Clin Endocrinol Metab, 1998. **83**(1): p. 135-9.
210. Dennison, E., P. Hindmarsh, C. Fall, et al., *Profiles of endogenous circulating cortisol and bone mineral density in healthy elderly men.* J Clin Endocrinol Metab, 1999. **84**(9): p. 3058-63.
211. Godfrey, K., K. Walker-Bone, S. Robinson, et al., *Neonatal bone mass: influence of parental birthweight, maternal smoking, body composition, and activity during pregnancy.* J Bone Miner Res, 2001. **16**(9): p. 1694-703.
212. Javaid, M.K., S.R. Crozier, N.C. Harvey, et al., *Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study.* Lancet, 2006. **367**(9504): p. 36-43.
213. Zamora, S.A., R. Rizzoli, D.C. Belli, et al., *Vitamin D supplementation during infancy is associated with higher bone mineral mass in prepubertal girls.* J Clin Endocrinol Metab, 1999. **84**(12): p. 4541-4.
214. World Health Organization. *Low birthweight -country, regional and global estimates*. 2004 [cited 2016 9 dec]; Available from: http://apps.who.int/iris/bitstream/10665/43184/1/9280638327.pdf.
215. Jensen, R.B., S. Vielwerth, J. Frystyk, et al., *Fetal growth velocity, size in early life and adolescence, and prediction of bone mass: association to the GH-IGF axis.* J Bone Miner Res, 2008. **23**(3): p. 439-46.
216. Schlussel, M.M., J.A. de Castro, G. Kac, et al., *Birth weight and bone mass in young adults from Brazil.* Bone, 2010. **46**(4): p. 957-63.

217. Clark, E.M., A.R. Ness, and J.H. Tobias, *Vigorous physical activity increases fracture risk in children irrespective of bone mass: a prospective study of the independent risk factors for fractures in healthy children.* J Bone Miner Res, 2008. **23**(7): p. 1012-22.

Appendix A

Ethical Approval 2013/1466/REK nord

Norwegian Data Protection Authority, Extended License Fit Futures

Norwegian Social Science Data Service, Extended License Fit Futures

Norwegian Versions

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord			08.10.2013	2013/1466/REK nord
			Deres dato:	**Deres referanse:**
			27.08.2013	

Vår referanse må oppgis ved alle henvendelser

Nina Emaus
MH bygget

2013/1466 Fødselsvekt og bruddrisiko hos unge

Forskningsansvarlig: Universitetet i Tromsø
Prosjektleder: Nina Emaus

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK nord) i møtet 26.09.2013. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikklovens § 4.

Prosjektleders prosjektomtale
Norge har høyeste rapporterte forekomst av underarm og hoftebrudd. Det en sterk sammenheng mellom beinmasse og bruddrisiko. God skjeletthelse etableres i vekstfasen til beintettheten når "peak bone mass" i 20-30 årene. Dette prosjektet undersøker sammenhengen mellom fødselsvekt, brudd i barneår (0-19 år) og beinmasse målt mellom 16-19 år. Hypotesen er at høy fødselsvekt er assosiert med lavere bruddrisiko og høyere beinmasse ved 16-19 år, mens "obesity" har en negativ effekt. Datagrunnlaget hentes fra ungdomsundersøken Fit Futures (FF). Til FF1 i 2010-2011 møtte 508 jenter og 530 gutter i alderen 16-17 år (oppmøte >90 %). Til FF2 2012-2013 møtte ca. 800 av av disse til en oppfølgende undersøkelse. Beinmasse er målt i hofter og helkropp med DEXA, GE Lunar Progidy. Livsstilsinformasjon er samlet inn og høyde og vekt er målt. Vi vil koble data fra FF med data på fra nasjonalt nasjonalt fødselsregister og registere ikke-vertebrale brudd i kohorten gjennom UNNs røntgenarkiv.

Vurdering

Åshild Bjørnerem ble vurdert som inhabil og fratrådte under behandlingen av denne saken. Johan Svartberg har deltatt i behandlingen pr. e-post og komiteen anser seg med dette som vedtaksdyktig.

Kobling av data – avgitt samtykke i Fit Futures studien
Det søkes om å koble data fra Medisinsk fødselsregister, Fit Futures og pasientjournal. Det er tidligere avgitt samtykke i forbindelse med deltakelse i Fit Futures.

Vurdering
Komiteen har vurdert formålet med studien og hvilke opplysninger som skal innhentes mot det avgitte samtykket i Fit Futures og finner samtykket dekkende for den omsøkte studien.

Vedtak
Med hjemmel i helseforskningsloven § 10 og forskningsetikkloven § 4 godkjennes prosjektet og det gis tillatelse til følgende kobling av data:
Medisinsk fødselsregister (MMFR) - Barnets vekt ved fødsel, barnets høyde ved fødsel og i hvilken graviditetsuke barnet er født.
Fit Futures, Tromsøundersøkelsen - Beinmassemålinger i hofter og helkropp (DEXA lunar progidy), målinger av kroppssammensetning (skjelett, muskler og fett også målt ved DEXA lunar progidy, høyde, vekt, røyking, snus, alkohol, fysisk aktivitet og kostholdsinformasjon.
Pasientjournaler ved Universitetssykehuset i Nord Norge, Røntgenarkivet - Brudd, hvilken type og når (brudddato).

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK nord på eget skjema senest 30.06.2019, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK nord dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningslovens § 28 flg. Klagen sendes til REK nord. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

May Britt Rossvoll
sekretariatsleder

Kopi til: postmottak@iho.uit.no

Datatilsynet

Universitetssykehuset i Nord-Norge
Avdeling for mikrobiologi og smittevern
V/ Furberg
9037 TROMSØ

Deres referanse	Vår referanse (bes oppgitt ved svar)	Dato
	07/00886-7 /CGN	27. juli 2010

Vedrørende søknad om utvidelse av konsesjon

Datatilsynet viser til Deres søknad av 27.04.2010 om utvidelse av konsesjon til å behandle helseopplysninger i forbindelse med Tromsøundersøkelsen I-VI.

Konsesjon til å behandle opplysninger i forbindelse med Tromsøundersøkelsen I-VI, ble forlenget i vedtak av 05.05.2010. Konsesjonen har varighet til 31.12.2011.

Søknaden om utvidelse omfatter en somatisk helseundersøkelse blant totalt ca 1100 elever på første trinn på videregående skole i Tromsø region 2010-2011, kalt *Fit futures*. Data fra Fit futures skal legges til å databasesystemet EUTRO (Epidemiologiske undersøkelser i Tromsø) ved Universitetet i Tromsø.

Metodene som skal benyttes i undersøkelsen, er spørreskjema og intervju med elevene, kliniske undersøkelser, laboratorieanalyser og kobling av registerdata.

Deltakelse i denne undersøkelsen skal baseres på samtykke. Deltakerne i studien er ungdommer på 15 og 16 år. I følge søknaden, skal det innhentes selvstendige samtykker fra de registrerte som har fylt 16 år, og fra de under 16 år skal det i tillegg innhentes samtykke fra deres foreldre.

Datatilsynet har vurdert søknaden og gir dem med hjemmel i helseregisterlovens § 5, jf. personopplysningslovens § 33, jf. § 34, utvidelse av konsesjon til å behandle helseopplysninger i forbindelse med helseundersøkelsen *Fit futures*. Utvidelsen er i samsvar med det omsøkte.

Utvidelsen medfører for øvrig ingen endringer i den opprinnelige konsesjonen med etterfølgende utvidelser.

Postadresse:	Kontoradresse:	Telefon:	Telefaks:	Org.nr:	Hjemmeside:
Postboks 8177 Dep 0034 OSLO	Tollbugt 3	22 39 69 00	22 42 23 50	974 761 467	www.datatilsynet.no

Dette vedtak kan påklages til Personvernnemnda i medhold av forvaltningslovens kapittel IV. Eventuell klage må sendes til Datatilsynet senest tre uker etter mottaket av dette brev.

Med hilsen

Monica Fornes
seniorrådgiver

Camilla Nervik
rådgiver

Kopi: NSD, Harald Hårfagresgate 29, 5007 Bergen

Norsk samfunnsvitenskapelig datatjeneste AS
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Datatilsynet
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0034 OSLO

Dato: 27.04.2010 Vår ref: 16896 LT/LR Deres dato: 28.08.2007 Deres ref: 07/00886-2 /CAO

SØKNAD OM UTVIDELSE OG ENDRING AV KONSESJON FOR TROMSØUNDERSØKELSEN I-VI

Vi viser til konsesjon gitt av Datatilsynet, for opprettelse av personregister i forbindelse med forskningsprosjekt:

16896: *Tromsøundersøkelsen I-VI*
Daglig ansvarlig: *Inger Njølstad*

Personvernombudet har mottatt endringsmelding fra prosjektledelsen 12.04.2010 med søknad om utvidelse og endring av konsesjonen, se vedlegg.

Personvernombudet ber om at Datatilsynet prioriterer behandlingen. Grunnen til vi ber om dette er at prosjektledelsen er blitt vesentlig forsinket i forhold til opprinnelig tidsplan. Ved melding om endring i oktober 2009 ble søknad sendt Regional komité for medisinsk og helsefaglig forskningsetikk da de trodde at det var de som skulle behandle søknaden. Det er imidlertid siden blitt avklart at det er Datatilsynet som må gi utvidet konsesjon for prosjektet, jf. brev fra Helsedepartementet datert 02.11.2009 om samtykkebaserte helseregistre som slår fast at slike registre fortsatt må ha konsesjon fra Datatilsynet.

Endringen og utvidelsen omfatter en somatisk helseundersøkelse blant totalt ca. 1100 elever på første trinn i videregående skole i Tromsø region i 2010-2011, kalt *Fit futures*. Innenfor *Fit futures* inngår flere delprosjekter. Dette er en ny ungdomsundersøkelse der de faktiske undersøkelsene i store trekk representerer en gjentakelse av elementer i den sjette Tromsøundersøkelsen. Det vises til vedlagte, meget godt beskrevne, protokoll datert 12.04.2010 som gir en fullstendig oversikt over *Fit futures*. Protokollen gir en redegjørelse for ansvarsforhold, tema og målsetninger herunder beskrivelse av delprosjektene, metoder for datainnsamling, praktisk gjennomføring herunder etterundersøkelser og longitudinelle oppfølgninger samt lagring av data og datautlevering. Protokollen inneholder videre en redegjørelse for de etiske vurderinger ved gjennomføringen av prosjektet.

I forkant av *Fit futures* skal det gjennomføres en pilotstudie som i innhold er lik, men som kun omfatter 15-20 elever fra en klasse på 1. trinn i videregående skole i Tromsø. Denne skal gjennomføres før sommeren.

Personvernombudets kommentarer

Personvernombudet finner søknaden meget godt gjennomarbeidet. Det er etter ombudets vurdering gjort en omfattende refleksjon og gjennomgang av alle sider ved gjennomføring av *Fit futures*.

Prosjektledelsen har lagt opp til at ungdommer på 16 år og eldre kan samtykke på selvstendig grunnlag mens for ungdom under 16 år vil det i tillegg til ungdommens eget samtykke også innhentes skriftlig samtykke fra foreldre/foresatte.

Personvernombudet finner at informasjonsskrivet tilfredsstiller de krav som må stilles til at registreringen som foretas er basert på et frivillig, uttrykkelig og informert samtykke.

Hovedregelen når det innhentes sensitive personopplysninger fra mindreårige er at foresatte skal samtykke. Det er imidlertid personvernombudets vurdering at ungdom over 16 år på selvstendig grunnlag, i dette prosjektet, kan avgjøre om de vil gi sitt samtykke til å deltakelse.

Personvernombudet viser til at ungdom over 16 år har selvbestemmelse på en rekke områder, som valg av videregående skole og til helsehjelp. Videre skal ungdom i henhold til barneloven gradvis få muligheten til å treffe selvstendige valg om forhold som berører dem selv. Denne undersøkelsen berører forhold som er viktige for disse ungdommenes helse og levekår, og det er derfor relevant og nødvendig å innhente opplysningene fra ungdommene selv. Personvernombudet vurderer at behandlingen for ungdom på 16 år og eldre kan finne sted med hjemmel i personopplysningsloven §§ 8 første ledd og 9 a. Alle opplysningene som innhentes for denne undersøkelsen innhentes etter informert samtykke fra de forespurte. For ungdom under 16 år hvor det innhentes skriftlig samtykke fra foreldre/foresatte og ungdommen, finner personvernombudet at behandlingen kan finne sted med hjemmel i personopplysningsloven §§ 8 første ledd og 9 a.

Universitetet i Tromsø ved Tromsøundersøkelsen har inngått avtaler om samarbeid med Universitetssykehuset Nord-Norge og Nasjonalt folkehelseinstitutt angående den praktiske gjennomføringen av *Fit futures*. Så snart undersøkelsen er gjennomført ved Universitetssykehuset Nord-Norge, vil alle data i *Fit futures* bli lagt til databasesystemet EUTRO (Epidemiologiske Undersøkelser i Tromsø) ved Universitetet i Tromsø, som er behandlingsansvarlig institusjon. Når det gjelder samarbeidende forskere og forskergrupper i *Fit futures*, vil det bli inngått egne samarbeidsavtaler som omfatter ansvarsfordeling, ansvarsstruktur, hvem som initierer prosjektet, bruk av data og eventuelt eierskap. Liste over godkjente forskningsprosjekter og ansvarlige for prosjektene vil være tilgjengelig på Tromsøundersøkelsen sin nettside. Prosjektledelsen understreker at all tilgang til data for analyse vil forutsette utlevering av data i avidentifisert form.

Personvernombudet finner personvernet for den enkelte deltaker godt ivaretatt gjennom prosedyrene som er valgt for håndtering av datamaterialet i studien. Institutt for samfunnsmedisin i Tromsø har utstrakt erfaring med gjennomføring av store befolkningsstudier og håndtering av store mengder sensitive person- og

helseopplysninger. Det vises her til protokollen side 11 samt til tidligere oversendt søknad i forbindelse med søknad om konsesjon for Tromsøundersøkelsen I-VI (vår ref. 16896 /GT 04.06.2007).

Til orientering kan også nevnes at prosjektledelsen i høst sendte prosjektet for vurdering til Nord-Norge REK NORD, se vedlegg. Prosjektledelsen har imidlertid i ettertid orientert leder ved Nord-Norge REK NORD om at utvidelsen og endringen må gis tillatelse av Datatilsynet.

I forhold til lagring og utlevering vil dette være lik som for Tromsøundersøkelsen I-VI.

Når det gjelder prosjektperiode vises det til oversendt søknad om forlengelse av konsesjonen 16.03.2010. Her er det søkt om forlengelse av konsesjonen frem til forskrift for samtykkebaserte helseundersøkelser.

Personvernombudets anbefaling
Personvernombudet for forskning anbefaler at prosjektet gis utvidet konsesjon i henhold til helseregisterloven § 5, jf. personopplysningsloven § 33.

Vennlig hilsen

Bjørn Henrichsen

Lis Tenold

Kontaktperson: Lis Tenold tlf. 55 58 33 77/ 55 58 21 17

Kopi: Ansvarlig Tromsøundersøkelsen I-VI, Inger Njølstad

Appendix B

Pamphlet of information, The Fit Futures

Consent of participation, The Fit Futures

Norwegian Versions

PERSONVERN OG SIKKERHET

Alle medarbeidere som jobber med undersøkelsen, har taushetsplikt. Opplysningene som samles inn, vil bare bli brukt til godkjente forskningsformål, som beskrevet over.

Opplysningene og prøvene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver. Koden oppbevares separat ved Universitetet i Tromsø, og kun noen få autoriserte personer har tilgang. Den enkelte forsker får ikke tilgang til opplysninger som gjør det mulig å identifisere enkeltpersoner. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

I noen tilfeller kan det være aktuelt å gjøre analyser av blodprøver eller genetiske analyser ved forskningsinstitusjoner i utlandet. Hvis dette gjøres, vil våre utenlandske samarbeidspartnere ikke få opplysninger som kan knytte prøvene opp mot deg som person.

Tromsøundersøkelsen gjennomfører Fit futures i samarbeid med Universitetssykehuset Nord-Norge og Nasjonalt folkehelseinstitutt. Data som samles inn på sykehuset, overføres til Universitetet i Tromsø når datainnsamlingen er avsluttet. Ingen av opplysningene som framkommer i undersøkelsen, lagres i journalsystemet på sykehuset. Databehandlingsansvarlig er Universitetet i Tromsø. Tromsøundersøkelsen administrerer utlevering av data til forskningsprosjekter. Hvem som er ansvarlig for forskningsprosjektene, finner du her http://www.tromsoundersokelsen.no. Fit futures er godkjent av Datatilsynet og Regional komité for medisinsk og helsefaglig forskningsetikk, Nord-Norge. Deltakere er forsikret gjennom Norsk Pasientskadeerstatningsordning.

FRIVILLIG DELTAKELSE

Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i undersøkelsen, og dette vil ikke få noen konsekvenser for deg. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte Tromsøundersøkelsen, Institutt for samfunnsmedisin, Universitetet i Tromsø, 9037 Tromsø, telefon 77644816, e-post: tromsous@uit.no.

RETT TIL INNSYN OG SLETTING AV PRØVER OG OPPLYSNINGER OM DEG

Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har også rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

ENERGI

VIL DU DELTA?

Hvis du er fylt 16 år, gir du selv ditt samtykke til å delta. Du kan da signere vedlagte skjema (hvitt ark) og ta det med til undersøkelsen. Det er også mulig å undertegne skjemaet når du kommer til Forskningsposten.

Hvis du ikke er fylt 16 år, må du be dine foreldre/foresatte om lov til å delta. Da må både du og dine foreldre/foresatte signere vedlagte skjema (hvitt ark) som du tar med deg til undersøkelsen.

ANSVARLIGE FOR GJENNOMFØRING AV FIT FUTURES UNDERSØKELSEN

Fit futures ledes av en styringsgruppe, og følgende forskere er ansvarlige for gjennomføringen:

Anne-Sofie Furberg
prosjektleder, lege, Universitetssykehuset Nord-Norge
e-post: anne-sofie.furberg@unn.no, telefon 77 75 58 24

Christopher Sivert Nielsen
psykolog, Nasjonalt folkehelseinstitutt
e-post: Christopher.Sivert.Nielsen@fhi.no, telefon 21 07 82 77

Guri Grimnes
lege, Universitetssykehuset Nord-Norge og Universitetet i Tromsø
e-post: guri.grimnes@unn.no, telefon 77 66 94 83

SPØRSMÅL?

Dersom du/dere har spørsmål om undersøkelsen, kontakt Forskningsposten UNN på telefon 77 62 69 09 eller prosjektadministrator for Fit futures på telefon 930 03 925.

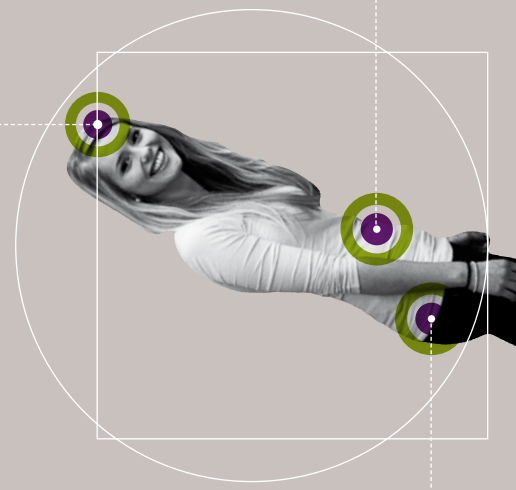
www.fitfutures.no

UNN · VI BRYR OSS · SAMMEN TAR VI ANSVAR

UNIVERSITETET I TROMSØ

folkehelseinstituttet

FAST FOOD

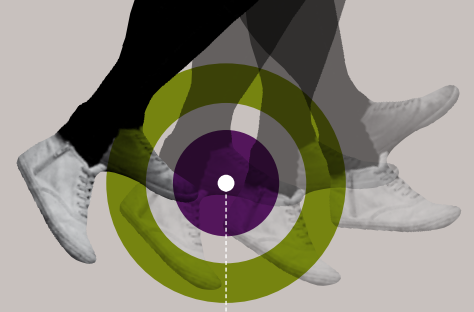


SOSIALT NETTVERK

FitFutures
EN DEL AV TROMSØUNDERSØKELSEN

DIN HELSE DIN FREMTID

INVITASJON TIL Å DELTA I HELSEUNDERSØKELSE BLANT UNGDOM



HVA ER FIT FUTURES?

Fit futures er et forskningsprosjekt der vi undersøker ungdommers fysiske helse og livsstil.

HVORFOR ER DETTE VIKTIG?

Voksnes helse undersøkes i mange studier, men man har mindre kunnskap om helse blant ungdom. Selv om få ungdommer har alvorlige sykdommer, legges mye av grunnlaget for fremtidig helse i ungdomsårene. Denne undersøkelsen kan bidra til at vi får økt kunnskap om hvordan man kan forebygge sykdom og om hvordan diagnoser kan stilles på et tidligere tidspunkt.

HVA FORSKES DET PÅ?

Hovedområdene det forskes på er:

- Eksem og kviser
- Infeksjoner
- Fysisk aktivitet og overvekt
- D-vitamin
- Jernmangel
- Genmodifisert mat
- Miljøgifter
- Smerte
- Beintetthet
- Diabetes
- Øresus
- Medisinbruk
- Frafall fra skole
- Tannhelse

Informasjonen fra undersøkelsen vil også bli brukt til forskning om de store folkehelseproblemene generelt, slik som hjerte-karsykdommer, lungesykdommer, kreft, nedsatt fruktbarhet og smerte. Det vil også bli forsket på arbeidsførhet i skole og yrke i forhold til sykdom, helse og livsstil. En del av prosjektene vil studere samspillet mellom arv, miljø og sykdom og helse; til slike prosjekter vil det bli hentet ut genetisk arvestoff fra blodprøvene. I framtiden kan data bli brukt i forskningsprosjekter som i dag ikke er planlagt. For alle slike nye prosjekter kreves det at prosjektet er godkjent av Regional komité for medisinsk og helsefaglig forskningsetikk. En oversikt over godkjente prosjekter finner du her (www.tromsoundersokelsen.no). Nettsiden holdes løpende oppdatert. Her kan du også lese om våre forskningsresultater.

HVEM KAN DELTA?

Alle ungdommer på VG1 blir invitert til å delta. Hvis du er 16 år eller mer, kan du selv bestemme om du vil delta. Er du under 16 år, må du ha samtykke fra dine foreldre eller foresatte.

AKTIVITET

SLIK FOREGÅR UNDERSØKELSEN

Undersøkelsen gjennomføres i skoletiden. Selve undersøkelsen tar 2-3 timer, og du må påregne å være borte fra skolen en halv dag. Skolen anser dette som gyldig skolefravær. Du blir undersøkt på Forskningsposten, Universitetssykehuset Nord-Norge, av erfarne forskningssykepleiere og tannleger/tannhelsesekretærer. Undersøkelsen består av følgende deler:

- *Spørreskjema* der vi spør om livsstil, trivsel, sykdommer og helseplager gjennom livet, og familieforhold.
- *Intervju* der vi spør om hvilke medisiner du bruker, om du har noen sykdom i dag og litt om sosialt nettverk. Kvinner spørres også om menstruasjon og graviditet.
- *Generell helseundersøkelse* der vi måler høyde, vekt, livvidde og hoftevidde, blodtrykk og puls, samt tar blodprøve, en hårprøve fra nakken, og en bakterieprøve fra nesebor og hals med en fuktet vattpinne.
- Måling av *smerteølsomhet* der vi måler følsomhet for trykk, kulde og varme. Smerten kommer gradvis, og du kan selv avbryte når som helst.
- *Kroppsscan* (DEXA) der vi måler beintetthet og forholdet mellom fett- og muskelvev. Dette skjer ved at du ligger rolig i ca. 10 minutter mens kroppen scannes.
- *Tannundersøkelse* som blir din årlige undersøkelse ved den offentlige tannhelsetjenesten og omfatter klinisk undersøkelse, tannrøntgen, kliniske foto og avtrykk for studiemodeller.

Etter undersøkelsen vil du få utlevert en liten *aktivitetsmåler* som er festet i et smalt strikkbelte til å ha under klærne. Denne måler hvor mye du beveger deg i løpet av dagen. Apparatet leveres på skolen etter en ukes bruk. Da vil det samtidig tas ny bakterieprøve fra nesebor og hals.

Noen deltakere vil bli forespurt om å undersøkes en gang til. Det vil da være aktuelt å gjenta noen av undersøkelsene og gjøre enkelte utvidede undersøkelser.

HVA SKJER MED DE BIOLOGISKE PRØVENE?

Med blodprøven gjøres analyser av bl.a. hormonnivåer, fettstoffer, blodsukker, vitaminer, miljøgifter og markører på betennelse og sykdommer. Det blir også hentet ut arvestoff (DNA og RNA) for genetiske analyser. Bakterieprøvene brukes til å måle forekomst av gule stafylokokker. Hårprøven analyseres for å se på nivå av kvikksølv. Prøvene lagres i Forskningsbiobanken for Tromsøundersøkelsen ved Universitetet i Tromsø. Hvis du sier ja til å delta, gir du også samtykke til at de biologiske prøvene og analyseresultatene inngår i biobanken.

INFORMASJON FRA ANDRE KILDER OG BRUK AV DATA I FRAMTIDEN

TEKNOLOGI

Opplysninger og prøver som du gir, blir oppbevart på ubestemt tid til bruk i forskning omkring helse og sykdom som omtalt i denne brosjyren. Det kan også hende at vi tar kontakt med deg igjen for å spørre om du vil være med på en ny undersøkelse. For spesielle forskningsprosjekter kan det være aktuelt å sammenstille informasjon fra Fit futures med nasjonale helseregistre som Reseptregisteret, Medisinsk fødselsregistrer, Kreftregisteret, Norsk pasientregister, Dødsårsaksregisteret og andre nasjonale registre over sykdommer som det forskes på i Tromsøundersøkelsen. I tillegg kan det være aktuelt å innhente helseopplysninger fra spesialist- og primærhelsetjenesten, for eksempel informasjon om beinbrudd og høyde- og vektdata fra helsestasjon, til bruk i forskning på sykdommer og helseproblemer som det forskes på i Tromsøundersøkelsen. Det kan også bli innehentet data fra registre i Statistisk sentralbyrå slik som miljø, befolkning, utdanning, inntekt, offentlige ytelser, arbeidsdeltakelse og andre forhold som kan ha betydning for helsa. For å undersøke om sykdommer går i arv, kan opplysninger om deg sammenstilles med opplysninger om dine slektninger, dersom disse har deltatt i deler av Tromsøundersøkelsen. Dette blir gjort ved å innhente opplysinger om slektskap fra Familieregisteret. Fra skolen vil vi innhente dine opplysninger om studieprogram, klasse, kjønn, antall fraværsdager, om du fullfører skoleåret og om karakterer i fagene norsk, matematikk og engelsk.

Sammenstillinger av informasjon krever noen ganger nytt samtykke og/eller annen type godkjenning slik som dispensasjon fra taushetsplikten eller godkjenning av offentlige instanser, for eksempel Regional komité for medisinsk og helsefaglig forskningsetikk, Datatilsynet eller NAV.

MULIGE ULEMPER OG FORDELER

Deltakelse innebærer at du må bruke noe tid. Deler av undersøkelsen kan også innebære ubehag. Dette gjelder særlig blodprøven. Dersom du vet at du har problemer med å ta blodprøve, kan du kontakte Forskningsposten på telefon 77 62 69 09 eller snakke med sykepleier når du kommer til undersøkelsen for å finne en løsning på dette.

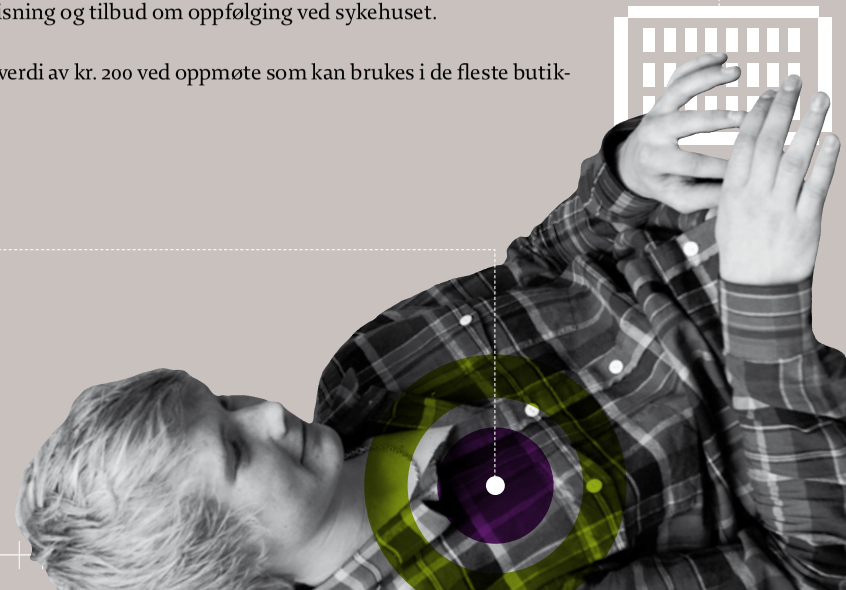
Dersom resultatet av prøvene dine viser at det er nødvendig med oppfølging av tannlege, lege eller henvisning til spesialist, vil du bli orientert om det. Ved behov for henvisning til spesialist, vil vi sørge for henvisning og tilbud om oppfølging ved sykehuset.

Deltakere får et gavekort til en verdi av kr. 200 ved oppmøte som kan brukes i de fleste butikker i Tromsø.

SMERTE

MILJØGIFTER

RØYK OG SNUS



FitFutures
EN DEL AV TROMSØUNDERSØKELSEN

VIL DU DELTA?

Samtykke til å delta i studien Fit futures

Jeg er villig til å delta i studien

____

(DITT FULLE NAVN I BLOKKBOKSTAVER)

Sted ____________________ Dato ____________________

____

(DIN SIGNATUR)

VIL DU DELTA OG ER UNDER 16 ÅR?

Foreldre/foresatte sitt samtykke til deltakelse i Fit futures

Jeg samtykker herved i at mitt/vårt barn kan delta i undersøkelsen

____

(BARNETS FULLE NAVN I BLOKKBOKSTAVER)

Sted ____________________ Dato ____________________

____

(SIGNATUR FORELDER/FORESATT 1)

____

(SIGNATUR FORELDER/FORESATT 2)

Appendix C

Birth Registry Form 1967-1998, The Medical Birth Registry of Norway

Fracture Register Template

Norwegian Versions

STATENS HELSETILSYN
Postboks 8128 Dep.
0032 OSLO

Medisinsk registrering av fødsel

Sendes 9. dag etter fødselen til fylkeslegen (stadsfysikus) i det fylket der moren er bosatt.

Merk: Det skal fylles ut blankett for hvert barn (foster). Dør barnet etter fødselen, skal det også fylles ut legeerklæring om dødsfall, og/eller dødsfallet meldes til skifteretten (lensmannen).

Barnet

Barnet var 1 ☐ Levende født 2 ☐ Dødfødt foster | Født dag, mnd., år | Klokkeslett | Personnr. | Skriv ikke her

1 ☐ Enkel 2 ☐ Tvilling 3 ☐ Trilling 4 ☐ Firling | Kjønn 1 ☐ Gutt 2 ☐ Pike

Etternavn, alle fornavn (bare for levendefødte)

Fødested. Navn og adresse på sykehuset/fødehjemmet | Kommune

Faren

Etternavn, alle fornavn | Født dag, mnd., år | Bostedskommune

Moren

Etternavn, alle fornavn. Pikenavn | Født dag, mnd., år

Bosted. Adresse | Kommune

Ekteskapelig status 1 ☐ Ugift 6 ☐ Samboende 2 ☐ Gift 3 ☐ Enke 4 ☐ Separert 5 ☐ Skilt | Ekteskapsår (gifte)

Antall tidligere fødte (før denne fødselen) | Levende fødte | Av disse i live | Dødfødte

Er moren i slekt med faren? 1 ☐ Nei 2 ☐ Ja. Hvilket slektskapsforhold:

Morens helse før svangerskapet

1 ☐ Normal 2 ☐ Sykdom (spesifiser):

Siste menstruasjons første blødningsdag

Morens helse under svangerskapet

1 ☐ Normal 2 ☐ Komplikasjoner (spesifiser):

Ble fødselen provosert

1 ☐ Nei 2 ☐ Ja

Inngrep under fødselen

1 ☐ Nei 2 ☐ Ja (spesifiser):

Inngrepet utført av 1 ☐ Lege 2 ☐ Jordmor

Komplikasjoner i forbindelse med fødselen

1 ☐ Nei 2 ☐ Ja (spesifiser):

Fostervann, placenta og navlesnor

1 ☐ Normalt 2 ☐ Patologisk (spesifiser):

Barnets tilstand

Bare for levende fødte. Tegn på asfyksi? 1 ☐ Nei 2 ☐ Ja | Apgarscore etter 1 min. | etter 5 min.

For levende fødte og dødfødte. Tegn på medfødt anomali, på skade eller sykdom? 1 ☐ Nei 2 ☐ Ja. Hvilke:

Lengde (i cm) | Hode-omkr. (i cm) | Vekt (i g) | For døde innen 24 timer Livet varte i | Timer | Min

For dødfødte. Døden inntrådte 1 ☐ Før fødselen 2 ☐ Under fødselen
Dødsårsak:

Seksjon? 1 ☐ Nei 2 ☐ Ja

Alvorlige arvelige lidelser i slekten

1 ☐ Nei 2 ☐ Ja Sykdommens art og hos hvilke slektninger:

Sted (sykehusets stempel) | Dato | Jordmor | Lege

50 000. 5.96. SEM GRAFISK

PERSONNR	NAVN	FØDSELSDATO		LOKALNO	USDAG	

SIKKERBR	BRUDD#	BRUDDLOK	SIDE	TRENERGI	IS	*Comments*

BRUDDLOK	BRUDD#	TRENERGI	SIKKERBR	IS	SIDE
Albu flere	1	Usikker	Ja	Ukjent	DEX
Annet	2	Lav	Nei	Nei	SIN
Ansikts fx	3	Sportsuhell		Ja	
Bekken fx	4	Hoy			
Bruddlok	5	Patol			
Cervicalcol	6				
Clavicula fx	7				
Coccyx fx	8				
Femur collum	9				
Femur distal	10				
Femur skaft					
Femur troch.					
Fibula dist.					
Fibula prox					
Fibula skaft					
Finger fx					
Fotrots fx					
Hode/ skalle fx					
Humerus dist					
Humerus prox					
Humerus skaft					
Håndrots fx					
Kjeveben fx					
Kne flere					
Lumbal col					
Metacarp fx					
Metatars fx					
Radius dist.					
Radius prox					
Radius skaft					
Ribben					
Sacrum fx					
Skulderblad fx					
Sternum fx					
Thoracal col					
Tib/ Fib dist					
Tib/ Fib prox					
Tib/Fib skaft					
Tibia dist					
Tibia prox					
Tibia skaft					
Tå fx					
Ulna dist					
Ulna prox					
Ulna skaft					
Ulna/ Rad dist					
Ulna/ Rad prox					

Ulna/ Rad skaft	

Lokalisasjonskoder

RGAM	Underarm
RGBM	Overarm
RGCLAV	Clavicula
RGCOST	Ribben
RGCR	Legg
RGCS	Sacrum og coccyx
RGCU	Albue
RGCX	Hofte
RGFA	Ansikt
RGFE	Lårben
RGHS	Skulder
RGGE	Kne
RGKC	Hode
RGKV	Bihuler
RGMA	Hånd
RGMADIG	Fingre
RGMD	Kjeve
RGMAAR	Håndledd
RGNA	Nese
RGOR	Øyenhule
RGPE	Bekken
RGPEAR	Iliosaccralledd
RGPECX	Bekken og hofter
RGPS	Hælbein/ Mellomfot
RGPSAR	Ankel
RGPSDIG	Tær
RGSC	Skulderblad
RGSTER	Sternum

Appendix D

Interview guide, The Fit Futures

Printout of Electronic Questionnaire, The Fit Futures

Norwegian Versions

Fit futures

- en del av Tromsøundersøkelsen

Intervju og Spørreskjema

Versjon: 12.04.2010

Intervju

Skriftlig samtykke:

☐ Ja ☐ Nei

Hvis nei, avbrytes undersøkelsen.

Foreldresamtykke (for de som er under 16 år)

☐ Ja ☐ Nei

Dersom de har glemt å ta med dette ber man om lov til å tas kontakt med foreldre for å innhente samtykke per telefon. To teknikere signerer på at dette er gjort.
Dersom det mangler samtykke for de under 16 år, avbrytes undersøkelsen.

Dagens dato registreres automatisk. Genererer:

[Alder i hele år]

Føler du deg frisk i dag?

☐ Ja ☐ Nei

Hvis nei:

Hva er det som feiler deg?

☐ Feber ☐ Forkjølet ☐ Hodepine ☐ Magesmerter ☐ Andre smerter
☐ Kvalme ☐ Annet
Tekstfelt for annet: _____

Har du noen form for infeksjon?

☐ Ja ☐ Nei

Hvis ja:
Beskriv: _____

Har du noen form for kroniske eller vedvarende sykdommer?
Hvor gammel var du da du fikk denne sykdommen første gang?

Diagnose 1: [ICD10 kode] Alder sykdom 1:
Diagnose 2: [ICD10 kode] Alder sykdom 2:
Diagnose 3: [ICD10 kode] Alder sykdom 3:
Diagnose 4: [ICD10 kode] Alder sykdom 4:
Diagnose 5: [ICD10 kode] Alder sykdom 5:

Tekstfelt for annet: _____

Tar du noen form for medisiner fast?

☐ Ja ☐ Nei

Hvis ja:
Medisin 1: [ATC kode]
Medisin 2: [ATC kode]
Medisin 3: [ATC kode]
Medisin 4: [ATC kode]
Medisin 5: [ATC kode]

Har du tatt noen form for smertestillende medisiner i løpet av de siste 24 timene, for eksempel Paracet, Ibux, Parlagin forte?

☐ Ja ☐ Nei

Hvis ja:
Medisin 1: [ATC kode] [Timer siden] [Antall tabletter]
Medisin 2: [ATC kode] [Timer siden] [Antall tabletter]
Medisin 3: [ATC kode] [Timer siden] [Antall tabletter]

Har du tatt noen form for antibiotika i løpet av de siste 24 timene, for eksempel Penicillin, mot infeksjon eller kviser?

☐ Ja ☐ Nei

Hvis ja:
Medisin 1: [ATC kode]
Medisin 2: [ATC kode]
Medisin 3: [ATC kode]

Når spiste du sist?

[ ] klokkeslett – omkodes automatisk til timer siden siste måltid

Sosialt nettverkskartlegging (se redegjørelse i protokoll)

[Løpenummer venn 1]
[Løpenummer venn 2]
[Løpenummer venn 3]
[Løpenummer venn 4]
[Løpenummer venn 5]

Jenter

Har du fått menstruasjon?

☐ Ja ☐ Nei

Hvis ja (har fått menstruasjon):

Hvor regelmessig er menstruasjonene dine?

☐ Alltid regelmessig ☐ Oftest regelmessig ☐ Uregelmessig

Hvor mange dager er det mellom start av hver menstruasjon?

[Antall dager]

Hvilken dag startet siste menstruasjon? ***Dato registreres, genererer:***

[Dager siden siste menstruasjon]

Bruker du noen form for hormonell prevensjon, for eksempel p-piller?

(følges eventuelt opp med spørsmål om type prevensjon om dette ikke sies spontant)

☐ Nei ☐ P-piller ☐ P-sprøyte ☐ Annet

Er det noen mulighet for at du kan være gravid nå?
□ Ja □ Nei

Hvis ja:
Er det greit for deg at vi tar en gravitest?
□ Ja □ Nei
(resultat av prøven formidles ikke til foreldre)

Hvis ja:
Resultat av gravitest:
□ Negativ □ Positiv □ Ikke utført

Klarert for DEXA (genereres automatisk)
□ Ja □ Nei

Følgende personer er ikke klarert:
Kvinner som sier det er mulighet for at de er gravide som ikke vil gjøre gravitest
Kvinner som har positiv gravitest.

Alle: ved innsamling av aktigraf

Hvor mange timer totalt var du utendørs i dagslys i løpet av de siste 7 dagene?
[ ] [ ] timer

FF - Generelt spørreskjema - Uke 1

Vi ønsker å vite mer om livsstil og helse.

Bruk den tiden du trenger til å svare så presist du kan.

Alle svarene dine blir behandlet med taushetsplikt.

Bruk "neste >>" og "<< tilbake" - knappene i skjema for å bla deg fremover og bakover.

Lykke til og tusen takk for hjelpen!

DEG OG DIN FAMILIE

1) Er du:

- ○ Jente
- ○ Gutt

2) Hvem bor du sammen med nå? (sett ett eller flere kryss)

- [ ] Mor
- [ ] Far
- [ ] 1-2 søsken
- [ ] 3 eller flere søsken
- [ ] Mors nye mann/samboer
- [ ] Fars nye kone/samboer
- [ ] Fosterforeldre
- [ ] Adoptivforeldre
- [ ] Besteforeldre
- [ ] Venner
- [ ] Alene/på hybel
- [ ] Institusjon
- [ ] Annet

3) Hvor lenge er det siden du flyttet hjemmefra?

- ( ) Mindre enn 6 måneder
- ( ) 6 - 11 måneder
- ( ) 1 - 2 år
- ( ) Mer enn 2 år

4) Er moren din i arbeid? (sett ett eller flere kryss)

- [ ] Ja, heltid
- [ ] Ja, deltid
- [ ] Arbeidsledig
- [ ] Uførerygdet
- [ ] Hjemmeværende
- [ ] Går på skole, kurs, e.l.
- [ ] Pensjonist
- [ ] Mor er død
- [ ] Vet ikke
- [ ] Annet

5) Er faren din i arbeid? (sett ett eller flere kryss)

- [ ] Ja, heltid
- [ ] Ja, deltid
- [ ] Arbeidsledig
- [ ] Uførerygdet
- [ ] Hjemmeværende
- [ ] Går på skole, kurs, e.l.
- [ ] Pensjonist
- [ ] Far er død
- [ ] Vet ikke
- [ ] Annet

6) Hva er den høyeste fullførte utdanningen til dine foreldre? (sett kryss for alle utdanningene du vet om for mor og far)

	Grunnskole	Yrkesfaglig videregående, yrkesskole	Allmennfaglig videregående skole eller gymnas	Høyskole eller universitet, mindre enn 4 år	Høyskole eller universitet, 4 år eller mer	Vet ikke
Mors utdanning	○	○	○	○	○	○
Fars utdanning	○	○	○	○	○	○

7) Hva regner du deg selv som: (kryss av for ett eller flere alternativ)

- ☐ Norsk
- ☐ Samisk
- ☐ Kvensk/Finsk
- ☐ Annet, spesifiser her

8) I hvilken kommune bodde du da du var 5-6 år (førskolealder/1.klasse)?

Velg kommune ▼

9) Er du født i Norge?

- ○ Ja
- ○ Nei, spesifiser hvilket land

10) Er din biologiske mor født i Norge?

- ○ Ja
- ○ Nei, spesifiser hvilket land

11) Er din biologiske far født i Norge?

- ○ Ja
- ○ Nei, spesifiser hvilket land

12) Har du noen gang oppholdt deg 4 uker eller mer sammenhengende i Australia, USA, Argentina eller Sør-Afrika?

- Ja
- Nei

Hvis det har vært flere opphold, oppgi varighet av siste opphold.

13) Hvor lenge varte oppholdet?

- Mindre enn 2 måneder
- 2-6 måneder
- Mer enn 6 måneder

Hvis det har vært flere opphold, oppgi når du hadde siste opphold.

14) Når var oppholdet? (Oppgi årstall når oppholdet sluttet - 4 siffer)

VENNER OG SKOLE

15) Har du vurdert å avbryte eller ta pause fra den videregående opplæringen du er i gang med?

- Ja
- Nei

16) Hvor sannsynlig er det at du fullfører den utdanningen du er i gang med?

- Liten - kommer til å slutte
- God - kommer sannsynligvis til å fullføre
- Stor - Kommer helt sikkert til å fullføre
- Vet ikke

17) Hvor mange tekstmeldinger (SMS/MMS) sendte du med mobiltelefon i går?

- Ingen
- 1-5 meldinger
- 6-10 meldinger
- 11-20 meldinger
- 21-50 meldinger
- Mer enn 50 meldinger

18) Nedenfor er det noen spørsmål om hvordan du synes du selv er. Kryss av for det som passer best for deg.

	Stemmer svært godt	Stemmer nokså godt	Stemmer nokså dårlig	Stemmer svært dårlig
Jeg synes det er ganske vanskelig å få venner				
Jeg har mange venner				
Andre ungdommer har vanskelig for å like meg				
Jeg er populær blant jevnaldrende				
Jeg føler at jevnaldrende godtar meg				

19) Hvilke avgangskarakterer fikk du fra ungdomsskolen? (sett ett kryss for hvert fag)

	1	2	3	4	5	6	Husker ikke
Norsk skriftlig							
Matematikk							
Engelsk							

HELSE

20) Hvordan vurderer du din egen helse sånn i alminnelighet?

- Meget god
- God
- Verken god eller dårlig
- Dårlig
- Meget dårlig

21) Hvor ofte har du i løpet av de siste 4 ukene brukt følgende medisiner?

	Ikke brukt siste 4 uker	Sjeldnere enn hver uke	Hver uke, men ikke daglig	Daglig
Smertestillende på resept (f. eks. Paralgin forte, Pinex forte)	○	○	○	○
Smertestillende uten resept (f. eks. Paracet, Pinex, Ibux)	○	○	○	○
Sovemidler	○	○	○	○
Medisin mot depresjon	○	○	○	○
Medisiner mot ADHD	○	○	○	○
Beroligende medisiner	○	○	○	○

22) Har du diabetes?

○ Ja ○ Nei

23) Har din biologiske mor diabetes?

○ Ja ○ Nei ○ Vet ikke

24) Har din biologiske far diabetes?

○ Ja ○ Nei ○ Vet ikke

25) Bruker mor insulin? (Penn eller pumpe)

○ Ja ○ Nei ○ Vet ikke

26) Hvor gammel var mor da hun fikk diabetes?

○ < 20 år ○ 20 - 40 år ○ > 40 år

27) Bruker far insulin? (Penn eller pumpe)

○ Ja ○ Nei ○ Vet ikke

28) Hvor gammel var far da han fikk diabetes?

○ < 20 år ○ 20 - 40 år ○ > 40 år

PSYKISKE VANSKER

29) Har du gått i behandling hos psykolog, psykiater eller PP-tjenesten det siste året?

○ Ja ○ Nei

30) Under finner du en liste over ulike problemer. Har du opplevd noe av dette den siste uken (til og med i dag)?

	Ikke plaget	Litt plaget	Ganske mye	Veldig mye
Plutselig frykt uten grunn	○	○	○	○
Føler deg redd eller engstelig	○	○	○	○
Matthet eller svimmelhet	○	○	○	○
Føler deg anspent eller oppjaget	○	○	○	○
Lett for å klandre deg selv	○	○	○	○
Søvnproblemer	○	○	○	○
Nedtrykt, tungsindig	○	○	○	○
Følelse av å være unyttig, lite verdt	○	○	○	○
Følelse av at alt er et slit	○	○	○	○
Følelse av håpløshet med hensyn til framtida	○	○	○	○

31) De følgende spørsmålene handler om hva du følte og gjorde de siste to ukene.

	Riktig	Noen ganger riktig	Ikke riktig
Jeg var lei meg eller ulykkelig	○	○	○
Jeg følte meg så trøtt at jeg bare ble sittende uten å gjøre noen ting	○	○	○
Jeg var veldig rastløs	○	○	○
Jeg var ikke glad for noe	○	○	○
Jeg følte meg lite verdt	○	○	○
Jeg gråt mye	○	○	○
Jeg hatet meg selv	○	○	○
Jeg tenkte at jeg aldri kunne bli så god som andre ungdommer	○	○	○
Jeg følte meg ensom	○	○	○
Jeg tenkte at ingen egentlig var glad i meg	○	○	○
Jeg følte meg som et dårlig menneske	○	○	○
Jeg gjorde alt galt	○	○	○
Jeg syntes det var vanskelig å tenke klart eller å konsentrere meg	○	○	○

PUBERTET

Her har vi noen spørsmål om kroppslige forandringer som skjer gjennom ungdomstiden:

32) Har du fått menstruasjon?

- Ja
- Nei

Hvor gammel var du da du fikk menstruasjon første gang?

33) År

Velg...

34) Måneder

Velg...

35) Har du fått eller begynt å få kjønnshår?

- Ja
- Nei

36) Har du fått eller begynt å få bryster?

- Ja
- Nei

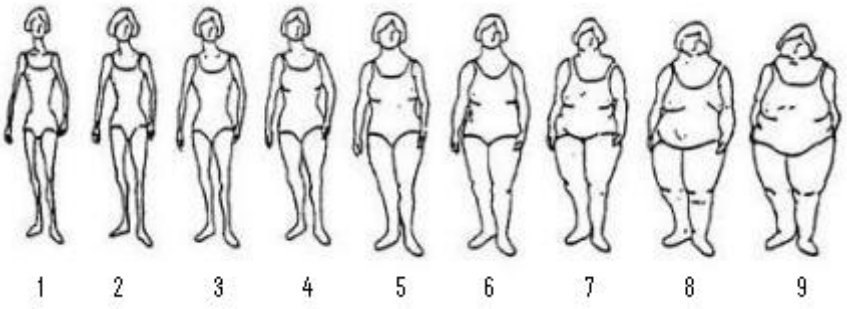
37) Har du fått eller begynt å få kjønnshår?

- Ja
- Nei

38) Hvor gammel var du da du begynte å få kjønnshår?

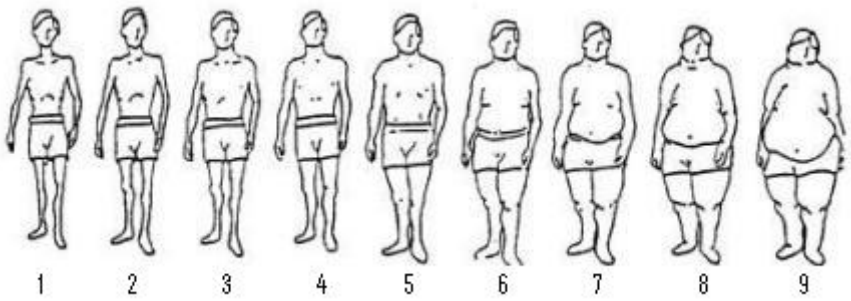
Velg...

KROPP OG VEKT



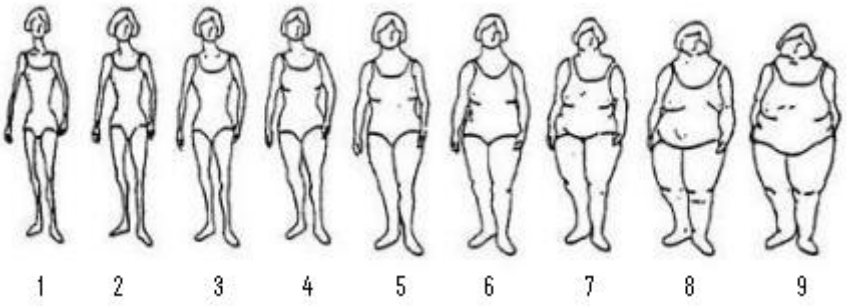
39) Hvilken av disse kroppsfasongene likner mest på kroppen til moren din?

1 2 3 4 5 6 7 8 9



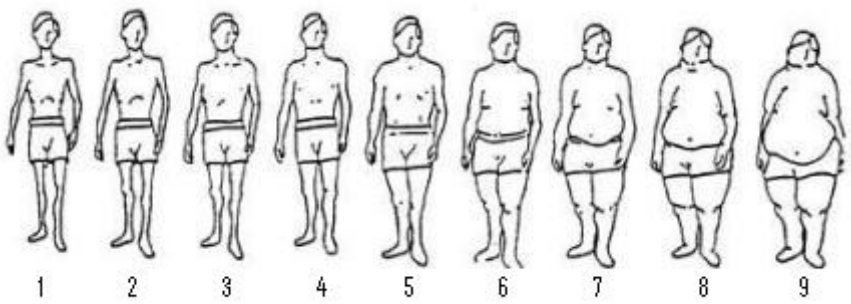
40) Hvilken av disse kroppsfasongene likner mest på kroppen til faren din?

1 2 3 4 5 6 7 8 9



41) Hvilken av disse kroppsfasongene likner mest på din kropp slik du er i dag?

○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9



42) Hvilken av disse kroppsfasongene likner mest på din kropp slik du er i dag?

○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9

RØYK, SNUS OG ALKOHOL

43) Røyker du?

○ Nei, aldri ○ Av og til ○ Daglig

44) Bruker du snus eller skrå?

○ Nei, aldri ○ Av og til ○ Daglig

45) Hvor mange sigaretter røyker du vanligvis i løpet av en uke?

○ 1 eller færre

○ 2-3

○ 4-6

○ 7-10

○ Mer enn 10

46) Hvor mange sigaretter røyker du vanligvis per dag?

- 1
- 2-3
- 4-6
- 7-10
- Mer enn 10

47) Hvor mange priser snus/skrå bruker du vanligvis i løpet av en uke?

- 1 eller færre
- 2-3
- 4-6
- 7-10
- Mer enn 10

48) Hvor mange priser snus/skrå bruker du per dag?

- 1
- 2-3
- 4-6
- 7-10
- Mer enn 10

49) Hvor ofte drikker du alkohol?

- Aldri
- 1 gang per måned eller sjeldnere
- 2-4 ganger per måned
- 2-3 ganger per uke
- 4 eller flere ganger per uke

50) Hvor mange enheter alkohol (en øl, ett glass vin eller en drink) tar du vanligvis når du drikker?

- 1-2
- 3-4
- 5-6
- 7-9
- 10 eller flere

51) Hvor ofte drikker du 6 eller flere enheter alkohol ved en anledning?

- Aldri
- Sjeldnere enn 1 gang per måned
- 1 gang per måned
- 1 gang per uke
- Daglig eller nesten daglig

FYSISK AKTIVITET

52) Hvilken beskrivelse passer best når det gjelder din fysiske aktivitet på fritiden det siste året?

- Sitter ved PC/TV, leser eller annen stillesittende aktivitet.
- Går, sykler eller beveger deg på annen måte minst 4 timer i uken (her skal du også regne med tur til/fra skolen, shopping, søndagsturer med mer).
- Driver med idrett/trening, tyngre utearbeid, snømåking eller liknende minst 4 timer i uka.
- Trener hardt eller driver konkurranseidrett regelmessig og flere ganger i uka.

53) Hvordan kommer du deg vanligvis til og fra skolen i sommerhalvåret?

- Med bil, motorsykkel/moped
- Med buss
- Med sykkel
- Går

54) Hvor lang tid bruker du vanligvis til og fra skolen (en vei) i sommerhalvåret?

- Mindre enn 5 minutter
- 6 til 15 minutter
- 16 til 30 minutter
- 1/2 til 1 time
- Mer enn 1 time

55) Hvordan kommer du deg vanligvis til og fra skolen i vinterhalvåret?

- Med bil, motorsykkel/moped
- Med buss
- Med sykkel
- Går

56) Hvor lang tid bruker du vanligvis til og fra skolen (en vei) i vinterhalvåret?

- Mindre enn 5 minutter
- 6 til 15 minutter
- 16 til 30 minutter
- 1/2 til 1 time
- Mer enn 1 time

57) Driver du med idrett eller fysisk aktivitet (f.eks. skateboard, fotball, dans, løping) utenom skoletid?

- Ja
- Nei

58) Hvor mange dager i uken driver du med idrett/fysisk aktivitet utenom skoletid?

- Aldri
- Sjeldnere enn 1 dag i uka
- 1 dag i uka
- 2-3 dager i uka
- 4-6 dager i uka
- Omtrent hver dag

59) Omtrent hvor mange timer per uke bruker du til sammen på idrett/fysisk aktivitet utenom skoletid?

- Ingen
- Omtrent 1/2 time
- Omtrent 1 - 1 1/2 time
- Omtrent 2 - 3 timer
- Omtrent 4 - 6 timer
- 7 timer eller mer

60) Hvor slitsom er vanligvis idretten/aktiviteten du driver med utenom skoletid?

- Ikke anstrengende
- Litt anstrengende
- Ganske anstrengende
- Meget anstrengende
- Svært anstrengende

Utenom skoletid: Hvor mange timer per dag ser du på PC, TV, DVD og liknende?

61) Hverdager, antall timer per dag:

- Ingen
- Omtrent 1/2 time
- Omtrent 1 - 1 1/2 time
- Omtrent 2 - 3 timer
- Omtrent 4 - 6 timer
- Omtrent 7 - 9 timer
- 10 timer eller mer

62) Fridager (helg, helligdager, ferie), antall timer per dag:

- Ingen
- Omtrent 1/2 time
- Omtrent 1 - 1 1/2 time
- Omtrent 2 - 3 timer
- Omtrent 4 - 6 timer
- Omtrent 7 - 9 timer
- 10 timer eller mer

Svar på en skala fra 1 til 5, der 1 tilsvarer svært sjelden eller aldri og 5 tilsvarer svært ofte.

63) I hvilken grad har andre oppmuntret deg til å være fysisk aktiv

	1	2	3	4	5
Foreldre/foresatte					
Søsken					
Venner					
Trenere					
Gymlærere					
Nabolaget					

Svar på en skala fra 1 til 5, der 1 tilsvarer helt enig og 5 tilsvarer helt uenig.

64) Hvordan passer disse utsagnene for deg?

	1	2	3	4	5
Det er morsommere å drive med trening eller fysisk aktivitet enn å gjøre andre ting...	○	○	○	○	○
Jeg skulle ønske jeg kunne drive mer med trening eller fysisk aktivitet enn det jeg har anledning til å gjøre...	○	○	○	○	○
Jeg føler at jeg er bedre enn de fleste på min alder i idrett/fysisk aktivitet...	○	○	○	○	○
Jeg føler at jeg lett kan holde følge med de andre på min alder når vi driver med idrett/fysisk aktivitet...	○	○	○	○	○

Svar på en skala fra 1 til 5, der 1 tilsvarer helt enig og 5 tilsvarer helt uenig.

65) Hvordan passer disse utsagnene for deg?

	1	2	3	4	5
Jeg liker ikke å trene mens noen står å ser på...	○	○	○	○	○
Tilgang til egen garderobe hadde gjort det lettere å trene...	○	○	○	○	○
Jeg blir ubehagelig andpusten, svett eller får vondt i kroppen ved trening...	○	○	○	○	○
Gymtimene er organisert slik at jeg ikke henger med...	○	○	○	○	○
Jeg har ingen å trene sammen med...	○	○	○	○	○
Jeg mangler utstyr for å drive med den aktiviteten jeg har lyst til...	○	○	○	○	○
Jeg har for mange andre oppgaver som gjør at jeg ikke får tid til å trene (f.eks lekser, hjemmeoppgaver)...	○	○	○	○	○
Det mangler egnede haller eller gode uteområder for å drive fysisk aktivitet der jeg bor...	○	○	○	○	○

MATVANER OG KOSTHOLD

66) Hvor ofte pleier du å spise følgende i løpet av en uke?

	Hver dag	4-6 dager i uka	1-3 dager i uka	Sjelden eller aldri
Frokost	○	○	○	○
Middag	○	○	○	○

67) Hvor ofte spiser du matpakke hjemmefra på skolen?

- ○ Hver dag
- ○ 3-4 ganger per uke
- ○ 1-2 ganger per uke
- ○ Sjelden eller aldri

68) Hvor ofte spiser du vanligvis disse matvarene?

	Sjelden/ aldri	1-3 ganger per måned	1-3 ganger per uke	4-6 ganger per uke	Hver dag
Ost (alle typer)	○	○	○	○	○
Fet fisk (f.eks. laks, ørret, makrell, sild)	○	○	○	○	○
Mager fisk (f.eks. torsk, sei, hyse)	○	○	○	○	○
Pizza, hamburger eller pølser	○	○	○	○	○
Hermetisert mat (fra metallbokser)	○	○	○	○	○
Godteri (f.eks. sjokolade, drops)	○	○	○	○	○
Snacks og søtsaker (f.eks. potetgull, kake, kjeks, bolle)	○	○	○	○	○
Sukkerfri tyggegummi	○	○	○	○	○

69) Hvor ofte spiser du vanligvis

	Sjelden/ aldri	1-3 ganger per mnd	1-3 ganger per uke	4-6 ganger per uke	1-2 ganger per dag	3-4 ganger per dag	5 eller flere ganger per dag
Frukt	○	○	○	○	○	○	○
Grønnsaker	○	○	○	○	○	○	○

70) Hvor mange ganger i året spiser du vanligvis disse matvarene?

	0	1-3	4-5	6-9	10 eller flere
Mølje med fiskelever	○	○	○	○	○
Måsegg	○	○	○	○	○
Reinsdyrkjøtt	○	○	○	○	○
Selvplukket sopp	○	○	○	○	○

71) Hvor mye drikker du vanligvis av følgende?

	Sjelden/ aldri	1-6 glass per uke	1 glass per dag	2-3 glass per dag	4 glass eller mer per dag
Helmelk, kefir, yoghurt	○	○	○	○	○
Lettmelk, cultura, lettyoghurt	○	○	○	○	○
Skummet melk (sur/søt)	○	○	○	○	○
Ekstra lett melk	○	○	○	○	○
Juice	○	○	○	○	○
Saft med sukker	○	○	○	○	○
Lettsaft, kunstig søtet	○	○	○	○	○
Brus med sukker (1/2 liters flaske = 2 glass)	○	○	○	○	○
Lettbrus, kunstig søtet (1/2 liters flaske = 2 glass)	○	○	○	○	○
Vann	○	○	○	○	○

72) Bruker du følgende kosttilskudd?

	Ja, daglig	Iblant	Nei
Tran, trankapsler, fiskeoljekapsler	○	○	○
Vitamin- og/eller mineraltilskudd	○	○	○

SØVN OG SØVNVANER

73) Når pleier du å legge deg for å sove på ukedagene?

Velg...

74) Når pleier du å legge deg for å sove i helgen?

Velg...

75) Hvor lenge pleier du å ligge våken før du får sove på ukedagene?

Velg...

76) Hvor lenge pleier du å ligge våken før du får sove i helgen?

Velg...

77) Når pleier du å våkne på ukedagene (endelig oppvåkning)?

Velg...

78) Når pleier du å våkne i helgen (endelig oppvåkning)?

Velg...

79) Hvor mange timer sover du vanligvis pr. natt?

Velg...

80) Hvor mange timer søvn trenger du pr. natt for å føle deg uthvilt?

Velg...

81) Synes du at du får tilstrekkelig med søvn?

- Ja, absolutt tilstrekkelig
- Ja, stort sett tilstrekkelig
- Nei, noe utilstrekkelig
- Nei, klart utilstrekkelig
- Nei, langt fra tilstrekkelig

HUD

Her har vi noen spørsmål om vanlige hudplager/hudsykdommer.

82) Har du hatt kløende utslett i løpet av de siste 12 månedene?

Ja Nei Vet ikke

83) Har dette utslettet sittet på noen av de følgende stedene: rundt hals, ører eller øyne, i albuebøyene (på innsiden), under baken, bak knærne eller foran på anklene?

Ja Nei

84) Hvor gammel var du første gang du fikk denne typen utslett?

Velg...

Hvor mye plaget er du av dette utslettet i dag?
Svar på en skala fra 0-10, der 0 tilsvarer ingen plager og 10 tilsvarer verst tenkelige plager.

0 1 2 3 4 5 6 7 8 9 10

86) Har du hatt håndeksem flere ganger?

○ Ja ○ Nei ○ Vet ikke

Hvor mye plaget er du av håndeksem i dag?
Svar på en skala fra 0-10, der 0 tilsvarer ingen plager og 10 tilsvarer verst tenkelige plager.

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

88) Har du noen gang vært plaget av kviser?

○ Ja ○ Nei ○ Vet ikke

Hvor mye plaget er du av kviser i dag?
Svar på en skala fra 0-10, der 0 tilsvarer ingen plager og 10 tilsvarer verst tenkelige plager.

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

90) Har du noen gang oppsøkt lege på grunn av kviser?

○ Ja ○ Nei

91) Har du fått noen av disse behandlingene av lege?

	Ja	Nei	Vet ikke
Lokalbehandling (f.eks. kremer eller oppløsninger)	○	○	○
Antibiotika tabletter (f.eks. Tetracyclin)	○	○	○
Roaccutan tabletter	○	○	○

92) Har du eller har du noen gang hatt psoriasis?

- Ja
- Nei
- Vet ikke

Hvor mye plaget er du av psoriasis i dag?
Svar på en skala fra 0-10, der 0 tilsvarer ingen plager og 10 tilsvarer verst tenkelige plager.

- 0
- 1
- 2
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- 6
- 7
- 8
- 9
- 10

Verkebyller er svært store kviser som er ømme/smertefulle og som ofte gir arr.

94) Har du noen gang hatt verkebyller under armene/armhulene?

- Ja
- Nei
- Vet ikke

95) Har du noen gang oppsøkt lege pga verkebyllene?

- Ja
- Nei

96) Har du noen gang hatt verkebyller i lyskene/nært skrittet?

- Ja
- Nei
- Vet ikke

97) Har du noen gang oppsøkt lege på grunn av verkebyllene?

- Ja
- Nei

98) Har en lege noen gang sagt at du har...

	Ja	Nei	Vet ikke
høysnue eller neseallergi?			
astma?			
barneeksem eller atopisk eksem?			

SMERTER

99) Har du langvarige eller stadig tilbakevendende smerter som har vart i 3 måneder eller mer?

- Ja
- Nei

100) Hvor lenge har du hatt disse smertene? (Dersom du har flere typer smerte, svar for den som har vart lengst)

- 3 - 6 måneder
- 6 - 12 måneder
- 1-2 år
- 3-6 år
- Mer enn 6 år

101) Hvor ofte har du vanligvis disse smertene?

- Hele tiden, uten opphør
- Hver dag, men ikke hele tiden
- Hver uke, men ikke hver dag
- Sjeldnere enn hver uke

Hvor er det vondt?
(kryss av på alle aktuelle steder)

	Venstre side	Høyre side
Skulder	☐	☐
Arm/albue	☐	☐
Hånd	☐	☐
Hofte	☐	☐
Lår/kne/legg	☐	☐
Ankel/fot	☐	☐

	Midten
Hode/ansikt	☐
Kjeve/kjeveledd	☐
Nakke	☐
Øvre del av ryggen	☐
Korsryggen	☐
Bryst	☐
Mage	☐
Underliv/kjønnsorganer	☐

104) Hva mener du er årsaken til smertene? (flere svar mulig)

- [ ] PC-bruk, dataspill og lignende
- [ ] Idrettsskade
- [ ] Ulykke/skade
- [ ] Kirurgisk inngrep/operasjon
- [ ] Migrene/hodepine
- [ ] Medfødt sykdom
- [ ] Tannproblemer
- [ ] Whiplash
- [ ] Prolaps (skiveutglidning i ryggen)
- [ ] Annet ryggproblem
- [ ] Nerveskade
- [ ] Mage- eller tarmsykdom
- [ ] Annet, spesifiser her
- [ ] Vet ikke

Hvis du har langvarige smerter flere steder i kroppen, gjelder de 4 neste spørsmålene smerten som plager deg mest.

Hvor sterke vil du si at smertene vanligvis er?
Svar på en skala fra 0-10, der 0 tilsvarer ingen smerte og 10 tilsvarer verst tenkelig smerte.

Dersom du har flere typer smerte, svar den som plager deg mest.

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Hvor sterke er smertene når de er på sitt sterkeste?
Svar på en skala fra 0-10, der 0 tilsvarer ingen smerte og 10 tilsvarer verst tenkelig smerte.

Dersom du har flere typer smerte, svar den som plager deg mest.

0 1 2 3 4 5 6 7 8 9 10

I hvor stor grad påvirker smertene søvnen din?
Svar på en skala fra 0-10, der 0 tilsvarer ingen smerte og 10 tilsvarer verst tenkelig smerte.

Dersom du har flere typer smerte, svar den som plager deg mest.

0 1 2 3 4 5 6 7 8 9 10

I hvor stor grad hindrer smertene deg i å utføre vanlige aktiviteter hjemme og på skolen?
Svar på en skala fra 0-10, der 0 tilsvarer ingen smerte og 10 tilsvarer verst tenkelig smerte.

Dersom du har flere typer smerte, svar den som plager deg mest.

0 1 2 3 4 5 6 7 8 9 10

MAGE- OG TARMPROBLEMER

109) I løpet av de siste 2 månedene: Hvor ofte har du hatt smerte eller ubehag i magen?

- Aldri
- 1-3 ganger i måneden
- En gang i uka
- Flere ganger i uka
- Hver dag

110) Hvor lenge har du vært plaget av smerte eller ubehag i magen?

- Mindre enn 1 måned
- 2 måneder
- 3 måneder
- 4-11 måneder
- Ett år eller mer

111) I hvilken del av magen er det du har hatt smerte eller ubehag? (kryss av for alt som passer)

- [ ] Over navlen
- [ ] Rundt navlen
- [ ] Nedenfor navlen

112) Når du har smerter eller ubehag i magen, hvor lenge varer det vanligvis?

- ○ Mindre enn 1 time
- ○ 1-2 timer
- ○ 3-4 timer
- ○ Mesteparten av dagen
- ○ Hele døgnet

Når du har smerte eller ubehag i magen, hvor sterke smerter har du vanligvis?
Svar på en skala fra 0-10, der 0 tilsvarer ingen smerte og 10 tilsvarer verst tenkelig smerte.

Dersom du har flere typer smerte, svar den som plager deg mest.

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

114) Når du har smerter eller ubehag i magen, hvor ofte blir det bedre etter at du har hatt avføring?

- ○ Sjelden eller aldri
- ○ En del ganger
- ○ For det meste/hver gang

115) Når du har smerter eller ubehag i magen, hvor ofte skjer det i forbindelse med at du..

	Sjelden eller aldri	En del ganger	For det meste
har fastere eller mer klumpete avføring enn vanlig?	○	○	○
har løsere eller mer vannaktig avføring enn vanlig?	○	○	○
hadde avføring oftere enn vanlig?	○	○	○
hadde avføring sjeldnere enn vanlig?	○	○	○

HODEPINE

116) Har du vært plaget av hodepine det siste året?

○ Ja ○ Nei

117) Hva slags hodepine er du plaget av? (Du kan sette flere kryss)

☐ Migrene ☐ Annen hodepine ☐ Vet ikke

118) Omtrent hvor mange dager per måned har du hodepine?

○ Mindre enn 1 dag
○ 1-6 dager
○ 7-14 dager
○ Mer enn 14 dager

119) Er hodepinen vanligvis:

	Ja	Nei
Bankende/dunkende smerte	○	○
Pressende smerte	○	○
Ensidig smerte (høyre eller venstre)	○	○

120) Hvor lenge varer hodepinen vanligvis?

- Mindre enn 4 timer
- 4 timer - 1 døgn
- 1-3 døgn
- Mer enn 3 døgn

121) Før eller under hodepinen, kan du da ha forbigående:

	Ja	Nei
Synsforstyrrelse? (takkede linjer, flimring, tåkesyn, lysglimt)		
Nummenhet i halve ansiktet eller i hånden?		
Forverring ved moderat fysisk aktivitet?		
Kvalme og/eller oppkast?		

122) Hvor ofte pusser du vanligvis tennene dine? (sett ett kryss)

- Sjeldnere enn 1 gang per uke
- 1 gang per uke
- 2-3 ganger per uke
- 4-6 ganger per uke
- 1 gang daglig
- 2 eller flere ganger daglig

Hvor smertefullt, jevnt over, synes du det er å gå til tannlegen?
Svar på en skala fra 0-10, der 0 tilsvarer ingen smerte og 10 tilsvarer verst tenkelig smerte.

0 1 2 3 4 5 6 7 8 9 10

Nedenfor er det fire spørsmål om hvordan du opplever det er å gå til tannlege. Les hvert spørsmål og velg det svaralternativet som du synes passer best for deg.

124) Dersom du skulle gå til tannlegen i morgen, hva ville du føle?

- Jeg ville se frem til det som en ganske hyggelig opplevelse
- Det ville være det samme for meg, ikke bety noe
- Det ville gjøre meg litt urolig
- Jeg ville bli redd for at det skulle bli ubehagelig og vondt
- Jeg ville bli svært redd med tanke på hva tannlegen kanskje skulle gjøre

125) Når du venter på tannlegens venteværelse, hvordan føler du deg da?

- Avslappet
- Litt urolig
- Anspent, nervøs
- Redd, engstelig
- Så redd at jeg av og til begynner å svette eller nesten føler meg syk

126) Når du sitter i tannlegestolen og venter på at tannlegen skal begynne behandlingen, hvordan føler du deg da?

- Avslappet
- Litt urolig
- Anspent, nervøs
- Redd, engstelig
- Så redd at jeg av og til begynner å svette eller nesten føler meg syk

Tenk at du sitter i tannlegestolen og skal få tennene renset og pusset. Mens du sitter og venter på at tannlege skal finne frem instrumentene som brukes til å skrape og pusse med,

127) hvordan føler du deg da?

- Avslappet
- Litt urolig
- Anspent, nervøs
- Redd, engstelig
- Så redd at jeg av og til begynner å svette eller nesten føler meg syk

128) Har du øresus?

- Aldri
- Sjelden
- Ofte

129) Hvor ofte har du øresus?

- Hele tiden, uten opphør
- Hver dag, men ikke hele tiden
- Hver uke, men ikke hver dag
- Sjeldnere enn hver uke

130) Hvor lenge varer vanligvis periodene med øresus?

- Mindre enn 10 minutter
- 10 minutter - 1 time
- Mer enn 1 time

131) Når får du vanligvis øresus?

- [ ] Etter sterke lyder
- [ ] Når det er stille
- [ ] Vet aldri når

Noen bryr seg ikke om lyden, for andre oppleves det svært plagsomt å ha øresus. Angi hvor plaget du er av øresusen.
Svar på en skala fra 0 til 10, der 0 tilsvarer ingen plager og 10 tilsvarer verst tenkelige plager.

- 0
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10

133) På hvilket øre har du vanligvis øresus?

- Bare høyre
- Bare venstre
- Begge, men mest høyre
- Begge, men mest venstre
- Like mye på begge

134) Omtrent hvor gammel var du når du begynte å ha øresus ofte?

Velg... ▼