

The association between childhood fractures and adolescence bone outcomes: a population based study, The Tromsø Study, Fit Futures.

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Purpose: Childhood fracture may be an early marker of skeletal fragility, or increased levels of physical activity (PA), which are beneficial for bone mineral accrual. This study investigated the association between a previous history of childhood fracture and adolescent bone mineral outcomes by various PA levels.

Methods: We recruited 469 girls and 492 boys aged 15-18 years to this study. We assessed PA levels by questionnaire and measured areal bone mineral density (aBMD) and bone mineral content (BMC) using dual-energy X-ray absorptiometry (DXA) at arm, femoral neck (FN), total hip (TH) and total body (TB) and calculated bone mineral apparent density (BMAD, g/cm^3). Fractures from birth to time of DXA measurements were retrospectively recorded. We analyzed differences among participants with and without fractures using independent samples t-test. Multiple linear regression was used to examine the association between fractures and aBMD and BMC measurements according to adolescent PA.

Results: Girls with and without a previous history of fracture had similar BMC, aBMD and BMAD at all sites. In multiple regression analyses stratified by physical activity intensity (PAi) there was a significant negative association between fracture and aBMD-TH and BMC-FN yet only in girls reporting low PAi. There was a significant negative association between forearm fractures, BMAD-FN, and BMAD-arm among vigorously active boys.

Conclusion: Our findings indicate a negative association between childhood fractures and aBMD/BMC in adolescent girls reporting low PAi. In boys, such an association appears only in vigorously active participants with a history of forearm fractures.

Keywords: Fracture, Child, Physical activity, bone mineral density, DXA

Introduction

Fractures are common during childhood and constitute 10 – 25 % of pediatric injuries. Epidemiological studies have found that 27 – 40 % of girls and 42 – 50% of boys suffer at least one fracture during childhood, corresponding to annual incidence rates of 103-165/10,000 girls and 162–257/10,000 boys [1-4]. A majority of childhood fractures involves the upper extremities, and the most common anatomic location is the distal forearm, comprising 25 – 35 % of all childhood fractures [3, 5]. Furthermore, a fracture during growth is associated with higher risk of sustaining subsequent fractures [6, 7].

During growth, the human skeleton undergoes continuous bone deposition and resorption, with a net increase in bone size. Bone modeling continues until epiphyseal fusion by the end of the second decade of life [8]. The plateau when age-related bone outcomes are no longer positive is often referred to as peak bone mass (PBM) [9]. During the rapid changes in late childhood and early adolescence, the skeleton is particularly vulnerable through cortical thinning, low volumetric bone mineral density and increased cortical porosity [10]. I.e., mineralization do not keep pace with linear growth. Indeed, fracture incidence rates peak in early adolescence [2, 4]. Early studies report lower bone mineral content (BMC) among children and adolescents with fracture [11-14]. Moreover, studies suggest areal bone mineral density (aBMD) and BMC track during childhood [15]. Together, these findings indicate that fractures in childhood may be associated with low PBM and that fractures suffered during childhood may be a marker for persistent bone fragility [16]. However, the earliest case-control studies [11, 12] comprised relatively few participants (17 and 90, respectively) and measured BMC by photon absorptiometry. Later reports, using dual energy x-ray absorptiometry (DXA), included only distal forearm fractures [13, 14]. Finally, a more recent cohort study reported 58 fractures in girls only [16].

Few studies have addressed how the beneficial effect of physical activity (PA) on bone mass during childhood [17-19] may be counteracted by increased risk of fracture associated with vigorous PA [20]. With varying PA levels between boys and girls [21-23], there may also be sex differences in this interaction. The indications of childhood fracture as a marker for reduced bone strength later in life, requires confirmation in large population-based studies including both sexes and interrelationships between childhood fractures, PA levels and bone mineral accrual need further studies.

Therefore, the aim of this study was (1) to compare bone mineral parameters in adolescents with and without childhood fractures and (2) to explore the possible effect modification of physical activity on the association between childhood fractures and bone mineral parameters during adolescence.

Methods

Participants and study design

In 2010/2011, all first year upper secondary school students (n=1117) in two municipalities were invited to participate in a population-based health survey, the Tromsø Study, Fit Futures (TFF). The survey was a collaboration between UiT the Arctic University of Norway, The University Hospital of North Norway and the National Public Health Institute. Participants were recruited through a close collaboration between the schools and the research unit at the University Hospital of North Norway. Students received oral and written information about the study in classrooms and school webpages, and participants signed a declaration at the study site. In addition, individuals younger than 16 years brought written permission from their guardians. One thousand and thirty-eight (93%) adolescents attended the health survey in 2010/2011 and this study included participants 15 -18 years of age (n = 961). Although not every students continues directly to upper-secondary school, we consider this convenient

sample to be representative of the normal population. Dedicated and experienced research nurses, following standardized protocols for all examinations, ran the survey at the hospital research unit. The study was approved by The Norwegian Data Protection Authority (reference number 2009/1282) and by The Regional Committee of Medical and Health Research Ethics (reference number 2011/1702/REKnord).

Clinical assessment

The University Hospital of North Norway is a secondary care university hospital, also serving as a primary care center for the city of Tromsø and surrounding region. The hospital provide free of charge and easy access pediatric services for all municipalities included in the TFF study. Records from the radiology department were retrospectively reviewed for all participants in the TFF cohort, and any fracture from birth to their examination date at the research unit were registered. We also recorded fractures among participants temporarily staying in other regions or abroad, as follow-up took place at the University Hospital.

We used a data-collection template containing details on date of injury and localization of fracture and body side, according to protocols used in the Tromsø Study [24]. The template allowed information on number of fractures if a subsequent fracture was sustained. Inclusion criterion for fracture registration was a radiological confirmation of fracture as stated by radiologist. Diagnoses solely stated by clinical findings or debated in records were excluded. In the case of multiple fractures, we recorded every fracture as one event with the following exceptions: fractures of skull, toes or fingers, simultaneous fractures of radius and ulna on one forearm, tibia and fibula on one leg and multiple vertebral fractures were recorded as one event. A descriptive report of the findings has recently been published [4]. Participants were categorized according to status of childhood fracture (yes/no) and multiple fractures (yes/no). Furthermore, participants with childhood fracture were grouped into a distal forearm fracture

group and other fractures group for comparison with previous literature. Survey date from the TFF survey and hospital admission date were used to assess difference in time from fracture to bone mass measurements.

Measurements

During the survey, we measured BMC, bone area (BA), aBMD and lean mass (LM) using DXA (GE Lunar Prodigy, Lunar Corporation, Madison, Wisconsin, USA) and analyzed the data with Encore pediatric software. The same device was used throughout the entire study. The densitometer coefficient of variation (CV) has been estimated at 1.72 % for femoral neck (FN) and 1.17 % for total hip (TH) [25]. Furthermore, we calculated bone mineral apparent density (BMAD, g/cm^3) as $\text{BMC}/\text{projected bone area}^{3/2}$. Anatomical sites measured were FN, TH, total body (TB) for aBMD and BMC. We calculated BMAD for the FN and arm for comparison with previous literature.

Height and weight were measured to the nearest 0.1 cm and 0.1 kg on the Jenix DS 102 Stadiometer (Dong Sahn Jenix, Seoul, Korea) according to standardized procedures.

Questionnaires

We collected information on perceived physical activity intensity (PAi) in electronic self-reporting questionnaires using the Health Behavior in Schoolchildren (HBSC) questionnaires [26, 27]. In the present study, we used the questions: “Are you actively doing sports or physical activity outside school hours?” and “If you are actively doing sports or physical activity outside school, how hard do you find the sports you are doing?” The answers were initially categorized into “yes” or “no” for the former and “not hard at all” (1), “a bit hard” (2), “quite hard” (3), “very hard” (4), and “extremely hard” (5) for the latter. Answers were recoded into three groups: Low (no or 1-2), moderate (3) and vigorous (5-6), and used as a categorical variable in the analysis. Pubertal status was collected through the same electronic self-reporting questionnaire.

Girls were asked: “If you have started menstruating, how old were you when you had your first menstruation?” Answers were used as a continuous adjustment variable in analyses and categorized into “early” (<12.5 years), “intermediate” (12.5 – 13.9 years), or late (>14 years) for descriptive purposes. Boys were asked according to Pubertal Development Scale (PDS) [28]. Secondary sexual characteristics like growth spurt, pubic hair growth, changes in voice and facial hair were rated on a scale from 1 (have not begun) to 4 (complete). The summarized score were divided by 4 and categorized as “have not begun (<2), “barely started” (2-2.9), “underway” (3-3.9) or “complete” (4).

Statistics

All analyses were performed stratified by sex. Continuous baseline characteristics are presented as mean and standard deviation (SD). We tested for differences of means using Independent sample t-test among participants with and without fractures and between fracture groups. This was repeated with participants stratified by levels of PAi. We did simple regression analyses with childhood fracture status as exposure and aBMD (FN, TH, TB), BMC (FN, TH, TB) and BMAD (FN, arm) as outcomes. Moreover, we built multiple regression models, adjusted for variables known to affect bone (LM, height, pubertal status, PAi and time from fracture to date of measurement) [18, 19, 29, 30] with both childhood fracture and multiple fractures as main exposures. Multiple regression models, using the same covariates, were also performed stratified by levels of PAi. Overall, variables had less than 3% missing, except for PDS score in boys (23%). Because introduction of PDS questions appeared late in the survey, we assumed these data as missing at random, and performed complete case analyses. We used residual analyses to check the normal distribution, linearity, homogeneity of variance and outliers. No assumptions were considered violated. Values of $p < 0.05$ were considered statistically

significant. All statistical analyses were performed using the Statistical Package of Social Science (SPSS v.24).

Results

Differences between adolescents with and without fractures.

We registered 253 participants with a previous fracture, 114 girls and 139 boys. Table 1 displays participants' characteristics categorized according to previous childhood fractures: no fracture, any fracture, forearm or other fracture. In girls, there were no significant differences in neither height, weight, lean mass, aBMD, BMC nor BMAD between any of the groups. Boys with previous childhood forearm fractures were significantly taller compared to peers with other fractures ($p = 0.007$) and peers without fractures ($p = 0.004$).

Differences between adolescents with and without childhood fractures according to levels of PAi.

Figure 1a shows that girls without fractures, reporting vigorous PAi, had significantly higher BMC-FN, BMC-TH and BMAD-FN compared to girls reporting low PAi, with mean (95% CI) differences of 0.34 (0.16, 0.51), 2.23 (1.06, 3.40) and 0.03 (0.01, 0.05), respectively.

Girls with other fractures had significantly higher BMC-FN, BMC-TH and BMAD-FN in both the moderate and vigorous PAi group compared to the low PAi group. Mean (95% CI) differences between the moderate and low PAi group were 0.47 (0.04, 0.09), 3.02 (0.28, 5.77), and 0.06 (0.02, 0.10), respectively. The vigorous PAi group had mean (95%CI) differences of 0.40 (0.04, 0.76), 2.64 (0.28, 5.00) and 0.06 (0.02, 0.09), respectively, higher compared with the low PAi group.

In the distal forearm fracture group, there were no significant differences between the PAi groups.

Figure 1b shows that boys without fractures, reporting vigorous PAi, had significantly higher BMC-FN, BMC-TH and BMAD-FN compared to low PAi peers with mean (95% CI) differences of 0.72 (0.47, 0.98), 4.54 (2.92, 6.15) and 0.04 (0.02, 0.06), respectively. Boys with distal forearm fractures had corresponding differences in mean (95% CI) by 1.18 (0.38, 1.98), 8.55 (3.21, 13.9) and 0.11 (0.05, 0.17) at BMC-FN, BMC-TH and BMAD-FN between the vigorous and low PAi group. Among boys with other fractures, there were significant differences between the low and moderate PAi groups and between the low and vigorous PAi groups (Figure 1b).

Simple and multivariate regression analysis and models stratified by PAi.

Using simple regression analyses, there were no significant associations between fracture during childhood and bone parameters during adolescence neither in girls nor in boys (data not shown). Likewise, shown in Table 2, multiple regression models adjusted for LM, body height, pubertal status, PAi and time from fracture to TFF measurement, showed no significant associations between fracture during childhood and aBMD, BMC and BMAD at any sites in both sexes.

In models stratified by PAi (Table 3), there was a significant negative association between fracture and adolescent aBMD-TH ($\beta = -0.06$, 95% CI -0.13, -0.00) and BMC-FN ($\beta = -0.35$, 95% CI -0.67, -0.02) among girls reporting low PAi. Similarly, in low PAi girls with other fractures, there was a significant negative association between fracture during childhood and adolescent aBMD-TH and BMC-FN.

In models stratified by PAi (Table 4) boys reporting low PAi had a significant negative association between fracture during childhood and adolescent BMAD-FN ($\beta = -0.04$, 95% CI -0.08, -0.01). No statistically significant associations were found in the moderate and vigorous PAi group. A distal forearm fracture during childhood was significantly negatively associated

with BMC-FN and BMAD-arm in the vigorous PAi boys and significantly positive associated with BMAD-arm in moderate PAi boys.

Table 5 shows that multiple childhood fractures in girls were significantly negative associated with adolescent aBMD-TH ($\beta = -0.05$, 95% CI -0.10, -0.00) and aBMD-TB ($\beta = -0.03$, 95% CI -0.06, -0.00). Although all other regression coefficients were negative in girls and positive in boys, neither were statistically significant.

Discussion

Analyses of data from 469 girls and 492 boys could not confirm any overall association between previous childhood fractures (n=253) and bone mineral parameters during adolescence. However, our findings differed when stratifying for PAi in adolescence. In girls, the associations were consistently negative in those who reported low PAi and statistically significant for aBMD-TH and BMC-FN (Table 3). In boys, while fracture during childhood was negatively associated with BMAD-FN during adolescence in the low PAi group, the associations between BMAD-arm and BMC-FN with childhood fracture were negatively associated in the vigorous active participants (Table 4). To our knowledge, this gender discrepancy of associations across PAi has not previously been reported.

Previous studies have investigated the relationship between concurrent fractures and BMC. Ferrari et al [16] reported significantly lower BMC at ultradistal radius, femoral trochanter and lumbar spine among 42 girls with fracture compared to 83 non-fracture subjects (mean age of 16.3 years). These findings, together with indications of decreased BMC gain through 8.5-year follow-up, suggested fractures as a marker of subsequent increased osteoporosis risk. In the present study, we did not find differences in bone parameters at any measured sites in the 469 girls (mean age = 16.1 years). In comparison, the girls in TFF were heavier in the fracture group (61.2 kg vs 56.7 kg) as well as in the no-fracture group (60.8 kg vs 57.2 kg) compared to the

girls in the study by Ferrari et al [16]. Furthermore, the comparable measurement (BMC-FN) indicated lower bone mass parameters with 4.55 g and 4.69 g (fracture/no fracture) in the latter compared to 4.92 g and 4.91 g (fracture/no fracture) among TFF girls. In our study, the bone mineral measurements were consistently similar in the fracture and no fracture group across anatomical sites (Table 1). A possible explanation may be within the two-dimensional properties of DXA-measurements, where contribution of bone geometry to fracture risk will not be fully recognized. Hence, assessment of bone mineral parameters by DXA solely, may not identify individuals susceptible for persistent bone fragility. Nevertheless, previous studies have used the discrepancy between DXA measurements in fracture versus no fracture groups as a marker of increased vulnerability with respect to bone health [13, 14, 16].

Interestingly, the negative association between girls with fractures reporting low PAi and BMD-TH and BMC FN was not found in boys (Table 3 and 4). Pre-puberty and early puberty are considered the most advantageous periods for adaptive responses to mechanical loading [31-33]. Because of the later chronological timing of puberty among males, their pre-pubertal development of the skeleton lasts longer. Indeed, in our cohort 6.7% of boys report completed puberty, contrasted by 39.9% in girls. Thus, in girls the earlier deceleration of periosteal apposition combined with insufficient mechanical loading in the low PAi group may be responsible for the association between fracture and BMD/BMC in our study.

Although there is strong evidence connected to the beneficial effect of physical activity on aBMD and BMC [18], we observed negative associations between fractures and BMC-FN/BMAD-arm in vigorous active boys. Other studies have shown that children and adolescents reporting themselves to be physically active at ages 8-15 years demonstrate 8-10% more BMC at the hip compared to less active peers [32]. On the other hand, vigorous PA increases the risk of fracture, probably because of higher exposure to injuries. In a recent prospective study, children attended daily vigorous physical activity had a doubled risk of fracture compared with

children being vigorously active less than four times per week [20]. However, in the present study the notable finding of a significant difference in BMC-FN, BMC-TH and BMAD-FN according to levels of PAi, may indicate that PAi is a key to prevent the negative consequences of childhood fractures on bone outcomes and subsequent risk of bone diseases [18].

Another possible explanation of our findings may be within site-specific responses to mechanical loading. Osteocytes are responsible for the sensation and subsequent response to loading. In turn this provide adequate bone mineral accrual and architecture [34]. Consequently, vigorous PA together with body weight may exert different effects to the cortical components in weight bearing sites as the hip compared to the forearm. At the same time, it is suggested that the genetic contribution to bone mass is higher in the spine compared to proximal femur and distal forearm [35]. Therefore, the importance of environmental factors, such as physical activity, are possibly greater in the two latter sites, yet with a larger effect of mechanical loading in the hip merely because of weight bearing. In TFF girls, this phenomenon is visualized in the change from non-significant coefficients in multiple regression analyses (Table 2) to significantly negative associations for BMD-TH and BMC-FN (Table 3), when stratifying for PAi levels. Interestingly, this was not the case among the boys. One might speculate that the significantly negative associations between forearm fractures and BMC-FN/BMAD-arm are connected to the notable finding that boys with forearm fractures were significantly taller than others.

Other lifestyle factors previously described in the fracture – bone mass relation were previously described in a case- control study from Goulding et al in 2001 [14]. The study recruited 100 boys with distal forearm fractures and 100 fracture- free controls with a purpose of determining differences in aBMD, body weight and adiposity between the groups. The main findings suggested that a distal forearm fracture could be a marker for reduced bone mass accrual. In addition, the authors found a relationship between high BMI/high adiposity and fracture risk.

Although not directly comparable to our findings because of the mean 12.0 years of age versus our 16.1 years of age, some resemblance is noted. The study from Goulding et al. found significantly lower activity scores among overweight boys. Furthermore, high BMI and adiposity each both increased fracture risk. This link between fracture, body composition and activity in boys is supported in the present study through a more direct connection between activity and bone mass status. In our study, boys without fractures, boys with distal forearm fractures and boys with other fractures all had higher bone mineral parameters when reporting moderate and/or vigorous physical activity (Figure 1).

The strengths of this study are the population-based approach with high attendance rate in both sexes, including adolescents from rural and urban schools. Furthermore, free health care services in public hospitals and the possibility to review journal notes from radiologists, increase the likelihood for capturing virtually every fracture in the cohort. There are some limitations to the study. First, objective longitudinal measurements of physical activity were not available and the self-administered questionnaire may introduce information bias. In addition, the HBSC-questionnaire measured against Total Energy Expenditure show low correlation, although reported to be an acceptable instrument when measured against more stable measurements of fitness [26, 27]. Moreover, physical activity tracks acceptably from childhood to adolescence, with reported stability coefficients of 0.5 for both sexes [36]. Secondly, the study is prone to non-participation bias because of school dropouts, susceptible to present an unhealthy lifestyle. However, we consider the high attendance rate to minimize this issue. Finally, comprehensive information on fracture trauma mechanisms and energy could nuance the present findings. Furthermore, children and adolescents within organized sports may receive treatment outside the local hospital, leading to missing fracture registration. However, we consider fractures treated outside the primary health care rare because of the free of cost service provided by public hospitals.

In conclusion, our findings indicate an association between childhood fractures and reduced bone mineral levels among girls reporting low physical activity intensity. In boys, the negative association appears only in vigorously active participants with a previous history of forearm fractures, possibly through an increased exposure to injuries. Further identification of fractures as an early marker for bone fragility should consider detailed quantification on dimensions, timing and doses of physical activity as the variation of bone mineral development is dependent of physical activity and include gender variation.

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Abbreviations:

PBM: Peak bone mass

aBMD: areal bone mineral density
BMC: Bone mineral content
BMAD: Bone mineral apparent density
TFF: the Tromsø Study, Fit Futures
DXA: Dual-energy X-ray absorptiometry
CV: Coefficient of variation
FN: Femoral neck
TH: Total hip
TB: Total body
PA: Physical activity
PAi: Physical activity intensity
HBSC: Health Behavior in School Children
SD: Standard deviation

Acknowledgement: We are grateful to the study participants, the staff at the Clinical Research Unit at University Hospital of North Norway (UNN HF) and the *Fit Futures* administration for conducting the study. We thank Robert Kechter at Finnmark Hospital Trust and Carsten Rolland at School of Sport Sciences UiT The Arctic University of Norway for office and administration contribution. We also thank The Norwegian Osteoporosis Association for supporting paediatric software and the Northern Norway Regional Health Authorities for funding this work.

Funding Sources: North Norwegian Health Authorities (SFP1160-14) funded this study. The funders had no role in the study design, data collection, analysis or interpretation, or in the decision to submit this manuscript for publication.

Conflict of interest: Tore Christoffersen, Nina Emaus, Elaine M Dennison, Anne-Sofie Furberg, Luis Gracia-Marco, Guri Grimnes, Ole-Andreas Nilsen, Dimitris Vlachopoulos, Anne Winther and Luai A Ahmed have no conflict of interest to disclose.

Authors' contribution: Study design: TC, AW, LAA and NE. Study conduct: A-SF, GG and NE. Data collection: TC, A-SF, GG, NE, OAN and AW. Data analysis: TC, LAA, and NE. Data interpretation: TC, LAA, ED and NE. Drafting manuscript: TC, LAA and NE. Revising manuscript content: TC, LAA, ED, A-SF, LGM, GG, O-AN, DV, AW, and NE. Approving final version of manuscript TC, LAA, ED, A-SF, LGM, GG, O-AN, DV, AW, and NE. TC, LAA and NE take responsibility for the integrity of the data analysis.

Figure Caption

Figure 1. Bone mineral content (BMC) at Femoral neck and Total hip, and Bone mineral apparent density (BMAD) at Femoral neck across different levels of Physical activity intensity by childhood fracture status in adolescent a) girls and b) boys. The Tromsø Study, Fit Futures.

Figure footnote

* = difference between Low and Vigorous physical activity intensity, # = difference between Low and Moderate physical activity intensity.

Mini abstract

Childhood fracture may predict persistent skeletal fragility, but it may also reflect high physical activity which is beneficial to bone development. We observe a difference in the relationship between previous fracture and bone outcome across physical activity level and sex. Further elaboration on this variation is needed.

Table 1. Characteristics of participants with and without a history of fractures. The Tromsø Study, Fit Futures.

	Girls				Boys			
	No Fracture (n=355)	All fractures (n = 114)	Forearm Fx (n=25)	Other Fx (n=89)	No Fracture (n=353)	All fractures (n = 139)	Forearm Fx (n=34)	Other Fx (n=105)
Age (years)	16.1 (0.4)	16.1 (0.4)	16.1 (0.3)	16.1 (0.4)	16.1 (0.4)	16.1 (0.5)	16.1 (0.6)	16.1 (0.4)
Height (cm)	164.6 (6.2)	165.7 (7.2)	165.6 (6.2)	165.8 (7.4)	176.8 (6.6)	177.2 (7.1)	180.2 (6.7) ^{a,b}	176.2 (6.9)
Weight (kg)	60.8 (11.1)	61.2 (12.4)	61.0 (10.1)	61.4 (12.9)	70.2 (14.7)	70.1 (13.5)	69.3 (13.4)	70.3 (13.6)
Lean mass (kg)	38.4 (4.4)	38.8 (5.1)	38.5 (4.4)	38.9 (5.2)	53.6 (6.8)	54.0 (7.3)	54.8 (7.5)	53.6 (7.2)
PAi (n)								
<i>Low</i>	163 (45.9%)	52 (45.6%)	11 (44.0%)	41 (46.1%)	167 (47.4%)	64 (46.0%)	15 (44.1%)	49 (46.7%)
<i>Moderate</i>	95 (26.8%)	34 (29.8%)	9 (36.0%)	25 (28.1%)	93 (26.3%)	34 (24.5%)	7 (20.6%)	27 (25.7%)
<i>Vigorous</i>	97 (27.3%)	28 (24.6%)	5 (20.0%)	23 (25.8%)	93 (26.3%)	41 (29.5%)	12 (35.3%)	29 (27.6%)
Pubertal Status (n)								
<i>Early/Completed</i>	147 (42.1%)	40 (35.7%)			22 (7.9%)	11 (10.8%)		
<i>Intermediate/Underway</i>	129 (37.0%)	43 (38.4%)			205 (73.7%)	80 (78.4%)		
<i>Late/Barley started</i>	73 (20.9%)	29 (25.9%)			51 (18.4%)	11 (10.8%)		
BMD-FN (g/cm ²)	1.067 (0.120)	1.068 (0.132)	1.069(0.119)	1.067 (0.135)	1.100 (0.148)	1.101 (0.157)	1.089 (0.156)	1.105 (0.158)
BMD-TH (g/cm ²)	1.061 (0.120)	1.056 (0.132)	1.040(0.106)	1.061 (0.138)	1.112 (0.149)	1.114 (0.143)	1.096 (0.144)	1.119 (0.142)
BMD-TB (g/cm ²)	1.141 (0.075)	1.137 (0.083)	1.140(0.073)	1.137 (0.085)	1.179 (0.094)	1.176 (0.099)	1.162 (0.093)	1.180 (0.100)
BMC-FN (g)	4.92 (0.68)	4.91 (0.77)	4.88 (0.75)	4.92 (0.78)	5.94 (0.99)	5.96 (1.03)	5.95 (1.06)	5.97 (1.02)
BMC-TH (g)	32.05 (4.72)	31.99 (5.08)	31.84 (4.80)	31.99 (5.15)	39.74 (6.62)	39.89 (6.65)	39.86 (7.12)	39.90 (6.52)

BMC-TB (g)	2519.6 (373.2)	2540.9(444.9)	2566.0(438.8)	2533.5(446.3)	2945.0(467.8)	2953.0 (495.2)	2952.7(503.1)	2953.1(495.1)
BMAD-FN (g/cm ³)	0.745 (0.076)	0.751 (0.075)	0.744 (0.066)	0.752 (0.078)	0.725 (0.081)	0.722 (0.087)	0.719 (0.087)	0.722 (0.087)
BMAD-arm (g/cm ³)	0.065 (0.006)	0.065 (0.007)	0.064 (0.005)	0.065 (0.007)	0.064 (0.007)	0.063 (0.006)	0.064 (0.009)	0.063 (0.005)

^aP<0.05 compared to No fracture group.

^bp<0.05 compared to Other fracture group.

BMD: Bone Mineral Density (g/cm²), BMC: Bone Mineral Content (g), BMAD: Bone Mineral Apparent Density (g/cm³), FN: Femoral Neck, TH: Total Hip, TB: Total Body, Fx: Fracture. PAi: Physical Activity intensity. Pubertal status in girls: Menarche age. Categories are early (<12.5), intermediate (12.5-13.9) and late (>14). Pubertal status in boys: Puberty Development Scale. Categories are have not begun (< 2), barely started (2-2.9), underway (3-3.9) and completed (4). Continuous variables are presented in mean (SD).

Table 2. The association between history of childhood fracture and bone mineral parameters during adolescence in girls (n =469) and boys (n= 492). The Tromsø Study Fit Futures.

	BMD			BMC			BMAD	
	Beta coefficients			Beta coefficients			Beta coefficients	
	[95% CI]			[95% CI]			[95% CI]	
	Femoral Neck	Total Hip	Total Body	Femoral Neck	Total Hip	Total Body	Femoral Neck	Arm
Girls								
All Fractures (n=114)	-0.01 [-0.05, 0.04]	-0.01 [-0.05, 0.03]	-0.01 [-0.03, 0.02]	-0.18 [-0.39, 0.04]	-0.75 [-2.16, 0.66]	-76.5 [-189, 36.1]	0.01 [-0.02, 0.04]	0.00 [-0.00, 0.00]
Forearm fractures (n= 25)	0.01 [-0.10, 0.10]	-0.01 [-0.11, 0.09]	-0.01 [-0.06, 0.05]	-0.26 [-0.77, 0.25]	-0.43 [-3.75, 2.89]	-135 [-391, 122]	0.01 [-0.05, 0.08]	-0.00 [-0.01, 0.00]
Other fractures (n = 89)	-0.01 [-0.05, 0.04]	-0.01 [-0.06, 0.04]	-0.01 [-0.03, 0.02]	-0.15 [-0.39, 0.09]	-0.77 [-2.33, 0.79]	-65.4 [-189, 58.6]	0.01 [-0.02, 0.05]	0.00 [-0.00, 0.00]
Boys								
All Fractures (n = 139)	-0.02 [-0.06, 0.03]	-0.00 [-0.05, 0.05]	-0.01 [-0.04, 0.02]	-0.08 [-0.35, 0.20]	0.24 [-1.53, 2.02]	-13.8 [-124, 96.7]	-0.01 [-0.04, 0.02]	-0.00 [-0.00, 0.00]
Forearm fractures (n=34)	-0.00 [-0.11, 0.10]	0.02 [-0.09, 0.12]	-0.01 [-0.07, 0.05]	-0.17 [-0.79, 0.46]	-0.00 [-4.12, 4.12]	16.0 [-242, 274]	-0.00 [-0.07, 0.07]	-0.00 [-0.01, 0.00]
Other fractures (n=105)	-0.02 [-0.07, 0.03]	-0.01 [-0.06, 0.05]	-0.01 [-0.04, 0.02]	-0.07 [-0.38, 0.24]	0.24 [-1.73, 2.21]	-24.7 [-147, 97.6]	-0.02 [-0.05, 0.02]	-0.00 [-0.00, 0.00]

Models adjusted for lean mass (g), body height (cm), pubertal status, physical activity intensity and time from fracture to TFF measurement (years).

Table 3. The association between history of childhood fracture and bone mineral parameters during adolescence in girls, stratified by level of physical activity intensity (PAi). The Tromsø Study Fit Futures.

	BMD			BMC			BMAD	
	Beta coefficients			Beta coefficients			Beta coefficients	
	[95% CI]			[95% CI]			[95% CI]	
	Femoral Neck	Total Hip	Total Body	Femoral Neck	Total Hip	Total Body	Femoral Neck	Arm
All Fractures								
PAi								
<i>Low (n= 52)</i>	-0.05 [-0.11, 0.02]	-0.06 [-0.13,-0.00]	-0.02 [-0.06, 0.01]	-0.35 [-0.67, -0.02]	-1.94 [-3.98, 0.10]	-122 [-307, 63.3]	-0.01 [-0.06, 0.03]	0.00 [-0.00, 0.01]
<i>Moderate (n= 34)</i>	0.05 [-0.02, 0.13]	0.05 [-0.03, 0.13]	0.02 [-0.03, 0.06]	0.05 [-0.34, 0.44]	1.04 [-1.75, 3.84]	-48.3 [-262, 165]	0.04 [-0.01, 0.09]	0.00 [-0.00, 0.01]
<i>Vigorous (n= 28)</i>	-0.01 [-0.10, 0.09]	0.00 [-0.09, 0.09]	0.01 [-0.04, 0.05]	-0.17 [-0.63, 0.28]	-0.97 [-3.85, 1.92]	-10.2 [-194, 174]	0.02 [-0.04, 0.08]	-0.00 [-0.01, 0.00]
Forearm fractures								
PAi								
<i>Low (n= 11)</i>	0.02 [-0.13, 0.18]	-0.02 [-0.16, 0.13]	-0.03 [-0.12, 0.06]	-0.24 [-1.02, 0.54]	-0.41 [-5.25, 4.43]	-339 [-758, 80.8]	0.02 [-0.09, 0.12]	-0.01 [-0.01, 0.00]
<i>Moderate (n=9)</i>	0.04 [-0.15, 0.22]	0.02 [-0.16, 0.21]	-0.02 [-0.12, 0.09]	0.03 [-0.87, 0.93]	1.17 [-5.36, 7.71]	-175 [-666, 317]	0.04 [-0.08, 0.17]	-0.00 [-0.01, 0.01]
<i>Vigorous (n=5)</i>	-0.01 [-0.25, 0.23]	0.01 [-0.23, 0.24]	0.05 [-0.07, 0.16]	-0.42 [-1.60, 0.75]	-1.18 [-8.57, 6.22]	168 [-292, 628]	-0.01 [-0.16, 0.15]	0.01 [-0.01, 0.02]
Other fractures								
PAi								
<i>Low (n=41)</i>	-0.06 [-0.14, 0.01]	-0.07 [-0.14,-0.00]	-0.02 [-0.07, 0.02]	-0.35 [-0.72, -0.01]	-2.19 [-4.48, 0.10]	-78.5 [-283, 126]	-0.02 [-0.07, 0.03]	0.00 [-0.00, 0.01]
<i>Moderate(n= 25)</i>	0.07 [-0.02, 0.15]	0.06 [-0.03, 0.15]	0.02 [-0.03, 0.08]	0.08 [-0.35, 0.51]	1.19 [-1.92, 4.30]	-32.3 [-275, 210]	0.05 [-0.01, 0.10]	0.00 [-0.00, 0.01]
<i>Vigorous(n= 23)</i>	0.00 [-0.10, 0.11]	0.01 [-0.10, 0.11]	0.01 [-0.05, 0.05]	-0.05 [-0.58, 0.47]	-0.45 [-3.75, 2.85]	-13.1 [-220, 195]	0.02 [-0.05, 0.09]	-0.00 [-0.01, 0.00]

Models adjusted for lean mass (g), body height (cm), menarche age and time from fracture to TFF measurement (years). BMD: Bone Mineral Density, BMC: Bone Mineral Content, BMAD: Bone Mineral Apparent Density, PAi: Physical Activity intensity, 95% CI: 95% Confidence Interval.

Bold: p <0.05

Table 4. The association between history of childhood fracture and bone mineral parameters during adolescence in boys, stratified by level of physical activity intensity (PAi). The Tromsø Study Fit Futures.

	BMD			BMC			BMAD	
	Beta coefficients			Beta coefficients			Beta coefficients	
	[95% CI]			[95% CI]			[95% CI]	
	Femoral Neck	Total Hip	Total Body	Femoral Neck	Total Hip	Total Body	Femoral Neck	Arm
All Fractures								
PAi								
<i>Low (n=64)</i>	-0.04 [-0.10, 0.02]	-0.01 [-0.07, 0.05]	-0.03 [-0.06, 0.01]	-0.13 [-0.48, 0.21]	0.15 [-2.08, 2.37]	-80.5 [-236, 74.8]	-0.04 [-0.08, -0.01]	-0.00 [-0.00, 0.00]
<i>Moderate (n=34)</i>	-0.01 [-0.09, 0.08]	-0.03 [-0.11, 0.05]	0.01 [-0.05, 0.05]	-0.01 [-0.54, 0.52]	-1.53 [-4.79, 1.73]	20.7 [-186, 227]	0.00 [-0.05, 0.05]	0.00 [-0.01, 0.00]
<i>Vigorous (n=41)</i>	-0.01 [-0.09, 0.07]	-0.01 [-0.10, 0.07]	-0.02 [-0.06, 0.03]	-0.17 [-0.66, 0.32]	0.33 [-2.82, 3.47]	-52.2 [-230, 125]	0.01 [-0.03, 0.06]	-0.00 [-0.01, 0.00]
Forearm fractures								
PAi								
<i>Low (n= 15)</i>	-0.02 [-0.14, 0.10]	0.00 [-0.11, 0.12]	0.01 [-0.07, 0.08]	-0.05 [-0.72, 0.62]	0.48 [-3.93, 4.88]	10.9 [-306, 327]	-0.04 [-0.11, 0.04]	0.00 [-0.00, 0.01]
<i>Moderate (n=7)</i>	0.00 [-0.17, 0.17]	-0.01 [-0.19, 0.16]	-0.01 [-0.11, 0.10]	-0.09 [-1.20, 1.02]	-2.94 [-9.84, 3.96]	-254 [-698, 189]	-0.01 [-0.15, 0.12]	0.01 [0.01, 0.02]
<i>Vigorous (n=12)</i>	-0.10 [-0.25, 0.05]	-0.12 [-0.28, 0.04]	-0.09 [-0.17, 0.01]	-0.98 [-1.87, -0.09]	-4.62 [-10.5, 1.24]	-226 [-568, 116]	0.00 [-0.08, 0.09]	-0.01 [-0.02, -0.00]
Other fractures								
PAi								
<i>Low (n= 49)</i>	-0.04 [-0.11, 0.03]	-0.01 [-0.07, 0.06]	-0.03 [-0.08, 0.01]	-0.14 [-0.52, 0.25]	0.22 [-2.31, 2.75]	-101 [-276, 73.2]	-0.04 [-0.09, 0.00]	-0.00 [-0.01, 0.00]
<i>Moderate(n= 27)</i>	-0.01 [-0.10, 0.09]	-0.04 [-0.13, 0.06]	0.00 [-0.05, 0.06]	0.01 [-0.89, 0.53]	-1.18 [-5.04, 2.68]	93.0 [-145, 331]	0.01 [-0.05, 0.07]	-0.00 [-0.01, 0.00]
<i>Vigorous (n=29)</i>	0.04 [-0.06, 0.13]	0.03 [-0.07, 0.13]	0.01 [-0.05, 0.06]	0.15 [-0.44, 0.73]	2.21 [-1.53, 5.95]	17.2 [-197, 232]	0.02 [-0.04, 0.08]	0.00 [-0.00, 0.01]

Models adjusted for lean mass (g), body height (cm), PDS-score and time from fracture to TFF measurement (years). BMD: Bone Mineral Density, BMC: Bone Mineral Content, BMAD: Bone Mineral Apparent Density, PAi: Physical Activity intensity, 95% CI: 95% Confidence Interval.

Bold: p < 0.05

Table 5. The association between history of multiple childhood fracture (n=68) and bone mineral parameters during adolescence in girls and boys. The Tromsø Study Fit Futures.

	BMD			BMC			BMAD	
	Beta coefficients			Beta coefficients			Beta coefficients	
	[95% CI]			[95% CI]			[95% CI]	
	Femoral Neck	Total Hip	Total Body	Femoral Neck	Total Hip	Total Body	Femoral Neck	Arm
Girls								
Fractures (n = 32)	-0.02 [-0.07, 0.03]	-0.05 [-0.10, -0.00]	-0.03 [-0.06, -0.00]	-0.17 [-0.41, 0.07]	-1.50 [-3.07, 0.11]	-92.5 [-219, 34.0]	-0.02 [-0.05, 0.01]	-0.00 [-0.00, 0.00]
Boys								
Fractures (n= 34)	0.04 [-0.01, 0.09]	0.04 [-0.01, 0.09]	0.02 [-0.00, 0.05]	0.07 [-0.20, 0.35]	1.60 [-0.17, 3.37]	82.2 [-32.1, 196]	0.02 [-0.01, 0.05]	0.00 [-0.00, 0.00]

Models adjusted for lean mass (g), body height (cm), pubertal status, physical activity intensity, and time from fracture to TFF measurement (years). BMD: Bone Mineral Density, BMC: Bone Mineral Content, BMAD: Bone Mineral Apparent Density, PAi: Physical Activity intensity, 95% CI: 95% Confidence Interval.

