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

Tore Christoffersen[1, 2], Nina Emaus[1], Elaine Dennison[3,4], Anne-Sofie Furberg[5,6], Luis Gracia-Marco[7,8], Guri Grimnes[9,10], Ole Andreas Nilsen[1], Dimitris Vlachopoulous[7], Anne Winther[11] Luai A Ahmed, PhD [1,12]

Affiliation

1. Department of Health and Care Sciences, UIT The Arctic University of Norway, Tromsø, Norway

2. Finnmark Hospital Trust, Alta, Norway

3. MRC Lifecourse Epidemiology Unit, Southampton, UK

4. Victoria University, Wellington, New Zealand

5. Department of Community Medicine, UIT the Arctic University of Norway, Tromsø, Norway

6. Department of Microbiology and Infection Control, University Hospital of North Norway, Tromsø, Norway

7. Children's Health and Exercise Research Centre, Sport and Health Sciences, University of Exeter, Exeter, United Kingdom.

8. Growth, Exercise, Nutrition and Development Research Group, University of Zaragoza, Zaragoza, Spain.

9. Division of Internal Medicine, University Hospital of North Norway, Tromsø, Norway

10. Tromsø Endocrine Research Group, Department of Clinical Medicine, UiT The Arctic University of Norway, Tromsø, Norway

11. Division of Neurosciences, Orthopedics and Rehabilitation Services, University Hospital of North Norway, Norway

12. Institute of Public Health, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, UAE

Corresponding author:
Tore Christoffersen,
Department of Health and Care Sciences,
UiT The Arctic University of Norway,
Forskningsparken, Sykehusveien 21
NO-9037 Tromsø
Norway

E-mail: tore.christoffersen@uit.no

Telephone: +47 900 82 718

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

Purpose: Studies suggest that childhood fracture may be an early marker of skeletal fragility. This study compared bone mass in adolescents with and without a history of fracture, and explored the effect of physical activity on the association between childhood fracture and bone strength parameters during adolescence.

Methods: In 2010-2011, we invited school students in two municipalities to the Fit Future study. The present report included 961 girls and boys aged 15-18 years. We measured bone mineral density (BMD) and bone mineral content (BMC) using dual energy X-ray absorptiometry (DXA) at femoral neck (FN), total hip (TH) and total body (TB) and calculated bone mineral apparent density (BMAD, g/cm^3) at FN,TH,TB and arm. All fractures in the cohort from birth to DEXA measurements were retrospectively recorded. We analyzed differences in parameters among participants with and without fractures using independent samples t-test. Through multiple linear regression, we examined the association between childhood fractures and BMD and BMC measurements.

Results: Girls with and without a history of fracture had similar BMC, BMD and BAMD at all sites. Boys with a history of fractures were significantly taller and had lower BMAD-TB compared to peers without fractures. In girls, multiple regression analyses stratified by physical activity intensity (PAi) there was significantly negative associations between fracture and BMD-TH and BMC-FN with coefficients (95% CI) of -0.06 (-0.13, -0.00) and -0.35 (-0.68, -0.02), yet only in participants reporting low PAi. In boys, using similar modeling, there was a negative association between forearm fractures, BMAD-FN, and BMAD-arm in the vigorous active participants.

Conclusion: Our findings indicate a negative association between childhood fractures and bone mass levels in girls reporting low physical activity intensity. In boys, the negative association appears only in vigorous active participants with a history of forearm fractures. Further identification of childhood fractures as a determinant of bone fragility should include detailed quantification of this environmental factor and further examine the observed gender difference.

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, compromising 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. The bone modeling continues until epiphyseal fusion by the end of the second decade of life [8]. The plateau when age-related bone outcomes no longer are 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 pace with linear growth. Indeed, fracture incidence rates peak in early adolescence [2, 4].

Early studies report lower bone mineral content among children and adolescents with fracture [11-14]. Moreover, studies suggest a bone mass tracking during childhood [15]. Together, these findings indicate that fractures in childhood may be associated with low peak bone mass 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 bone mineral content by photon absorptiometry. Later reports, using dual energy x-ray absorptiometry, included only distal forearm fractures [13, 14]. Finally, a more recent cohort study reported fractures (58) in girls only.

The indications of childhood fracture as a marker for reduced bone strength later in life, need confirmation in large population-based studies with both sexes included. Few studies have addressed how the beneficial effect of physical activity on bone mass during childhood [17] may interact in combination with increased risk of fracture associated with vigorous physical activity [18]. With varying physical activity levels between boys and girls [19], there may also be gender differences in this interaction. The complexity of childhood fractures, physical activity levels and bone mass accrual need further studies.

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

Methods

Participants and study design

In 2010/2011, all first year upper secondary school students (n=1117) in one urban and one rural municipality were invited to participate in a population-based health survey, the Tromsø Study, Fit Futures (TFF). The survey is 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 got oral and written information about the study in classrooms and school webpages and 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 and this study included participants 15 -18 years of age (n = 961). Although, not all students continue 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. Furthermore, fractures occurred outside the area was recorded, as follow-up took place at the University Hospital.

A data-collection template containing details on date of injury and localization of fracture and body was used, according to protocols used in the Tromsø Study [20]. The template allowed information on number of fractures if a subsequent fracture was sustained. Criterion for fracture registration included a radiological confirmation of fracture as stated by radiologist. Diagnoses solely stated by clinical findings were excluded. We recorded multiple 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 as one event. A descriptive report of the findings has recently been published [4].

Measurements

During the survey, we measured bone mineral content (BMC), bone area (BA) and bone mineral density (BMD) using dual energy X-ray absorptiometry (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 and 1.17 % for total hip [21]. Furthermore, we calculated bone mineral apparent density (BMAD, g/cm^3) as BMC/projected bone area$^{3/2}$. Anatomical sites measured were femoral neck (FN), total hip (TH), total body (TB) for BMD and BMC. We calculated BMAD for the same sites 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 in the Tromsø Study.

Questionnaires

We collected information on perceived physical activity intensity (PAi) in electronic self-reporting questionnaires using the Health Behavior in Schoolchildren (HBSC) questionnaires [22, 23]. In the present study, we used the question: "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 "not hard at all" (1), "a bit hard" (2), "quite hard" (3), "very hard" (4), and "extremely hard" (5). Answers were recoded into three groups: Low (1-2), moderate (3) and vigorous (5-6), and used as a categorical variable in the analysis. Survey date from the TFF survey and hospital admission date were used to assess difference in time from fracture to bone mass measurements in individual participants.

Statistics

All analyzes were performed sex stratified. Participants were categorized according to status of history of childhood fracture (yes/no) and history of multiple fractures (yes/no). Furthermore, participants with a history of childhood fracture were grouped into a distal forearm fracture group and other fractures group for comparison with previous literature. Continuous baseline characteristics are presented as mean and standard deviation (SD). We tested for differences of means using Independent sample t-test. This was repeated with participants stratified by levels of PAi. We performed simple regression analyses with childhood fracture status as exposure and BMD femoral neck (FN), total hip (TH), total body (TB), BMC (FN, TH, TB) and BMAD FN as outcomes. Furthermore, we performed multiple regression models, adjusted for variables known to affect bone (lean mass, height, PAi and time from fracture to date of measurement) with both a history of childhood fracture and multiple fractures as main exposures. Multiple regression models, using similar covariates, were also performed stratified by levels of PAi. 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.22).

Results

Differences between adolescents with and without fractures.

We registered 253 participants with a history of fracture, 114 girls and 139 boys. Table 1 displays participants' characteristics as measured in *Fit Futures* categorized according to history of childhood fractures to: no fracture, any fracture, forearm or other fracture. In girls, there were no significant differences in neither height, weight, lean mass, BMD, BMC or BMAD between participants with and without history of childhood fractures. Boys with history of childhood forearm fractures were significantly taller compared to peers with other fractures and peers without fractures. Furthermore, boys with forearm fractures had a mean (SD) BMAD-TB at 0.023 (0.001), significantly lower than the boys without fractures (p=0.048) (Table 1).

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

Girls without fractures, reporting low intensity PA, had significantly lower BMC-FN, BMC-TH and BMAD-FN compared to girls reporting vigorous intensity, with mean (95% CI) differences of -0.34 (-0.51, -0.16) (p<0.001), -2.23 (-3.40, -1.06) (p<0.001) and -0.03 (-0.05, -0.01) (p=0.004), respectively. In the distal forearm fracture group, there were no significant differences between the PAi groups. Girls with other fractures had significantly higher BMC-FN, BMC-TB and BMAD-LN both in the moderate PAi group and the vigorous PAi group, compared with the low PAi group (Figure 1 a).

Boys without fractures, reporting low intensity PA, had significantly lower BMC-FN, BMC-TH and BMAD-LN compared to vigorous active peers with mean (95% CI) differences of -0.72 (-0.98, -0.47) (p<0.001), -4.54 (-6.15, -2.92) (p<0.001) and -0.04 (-0.06, -0.02) (p<0.001), respectively (Figure 1 b). Boys with distal forearm fractures had corresponding differences in mean (95% CI) by -1.18 (-1.98, -0.38) (p=0.01), -8.55 (-13.9, -3.21) (p=0.003) and -0.11 (-0.17, -0.05) (p=0.001) at BMC-FN, BMC-TH and BMAD-LN in the low PAi group compared to the vigorous 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 1 b).

Regression analyzes.

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

In models stratified by PAi, girls reporting low PAi had a significant negative association between fracture during childhood and BMD-TH (β = -0.06, 95% CI -0.13, -0.00) and BMC-FN (β = -0.35, 95% CI -0.68, -0.02]. Similar, in girls with other fractures than forearm, reporting low PAi, there was a significantly negative association between fracture status and BMD-TH and BMC-FN. The trend of a change from negative to positive regression coefficients when going from low to moderate PAi was not significant in any groups (Table 3).

In boys, the model stratified by PAi showed a significant negative association between childhood fracture and BMAD-FN in the low PAi group (β = -0.04, 95% CI -0.08, -0.01). No statistically significant associations were found in the moderate and vigorous PAi group. A history of 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 4).

Multiple childhood fractures in girls were significantly negative associated with BMD-TB (β = -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 (Table 5).

Discussion

This study focus on the differences in bone mass parameters in adolescents with and without a history of fracture during childhood, together with the impact that physical activity may assert on the association between fractures and adolescent bone mass. We could not confirm an association between a history of childhood fractures and bone mass parameters in adolescence when adjusting for lean mass, body height, physical activity intensity and time from fracture to

TFF1 (Table 2). However, when stratifying for PAi, several significant associations appeared. In girls, these associations were consistently negative only among the low PAi group (table 3). In boys on the other side, while fracture was negatively associated with BMAD-FN in the low PAi group, BMAD-arm and BMC-FN were negatively associated with fracture in the vigorous active participants (Table 4). To our knowledge, this gender discrepancy of associations across PAi has not previously been reported.

Previous studies has investigated the relationship between fractures and BMC. Ferrari et al [16] reported significantly lower BMC at ultradistal radius, femoral trochanter and lumbar spine in girls with a mean age of 16.3 years with a history of fracture. The 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, where the 469 girls had a mean age of 16.1 years, we found no differences in bone parameters at any measured sites. In comparison, the girls in TFF were heavier in both the fracture group (61.2 kg vs 56.7 kg) and 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. A notable finding in the present study is the significant difference in BMC-FN, BMC-TH and BMAD-FN according to levels of PAi. This finding may help identifying the lifestyle factors connected to childhood fractures as a marker for osteoporosis.

Other lifestyle factors previously described in the fracture – bone mass relation, includes 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 BMD, body weight and adiposity between the groups. Main findings suggested that also among boys, a distal forearm fracture could be a marker for reduced bone mass accrual. In addition, they found a relation 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 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 mass parameters when reporting moderate and/or vigorous physical activity (Figure 1).

There is strong evidence connected to the beneficial effect of physical activity on bone mass and density during childhood. Children and adolescents reporting to be physically active at ages 8-15 years demonstrate 8-10% more bone mineral content at the hip compared to less active peers [24]. On the other hand, vigorous physical activity increases the risk of fracture, probably because of higher exposure to injuries. In a recent 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 [18].

One 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 mass and architecture [25]. Consequently, vigorous physical activity together with body weight may exert different adaptations 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 [26]. Therefore, the importance of environmental factors such as physical activity are possibly greater in the two latter sites, yet with a larger receptiveness to mechanical adaptation in the hip. In TFF girls, this phenomenon is visualized in the change from nonsignificant 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.

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 measurements of physical activity was not available. The self-administered questionnaire may introduce information bias, although reported to be an acceptable instrument [23]. 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 mass levels among inactive girls. In boys, vigorous activity is associated with lower bone mass levels among those suffering 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 mass development is dependent of physical activity and include gender variation.

References

1. 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.
2. 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.
3. Cooper, C., 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.
4. Christoffersen, T., et al., *Fracture incidence rates in Norwegian children, The Tromso Study, Fit Futures.* Arch Osteoporos, 2016. **11**(1): p. 40.
5. Khosla, S., et al., *Incidence of childhood distal forearm fractures over 30 years: a population-based study.* JAMA, 2003. **290**(11): p. 1479-85.
6. Goulding, A., 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.
7. Jones, I.E., et al., *How many children remain fracture-free during growth? a longitudinal study of children and adolescents participating in the Dunedin Multidisciplinary Health and Development Study.* Osteoporos Int, 2002. **13**(12): p. 990-5.
8. Heaney, R.P., et al., *Peak bone mass.* Osteoporos Int, 2000. **11**(12): p. 985-1009.
9. Berger, C., et al., *Peak bone mass from longitudinal data: implications for the prevalence, pathophysiology, and diagnosis of osteoporosis.* J Bone Miner Res, 2010. **25**(9): p. 1948-57.
10. Kirmani, S., et al., *Bone structure at the distal radius during adolescent growth.* J Bone Miner Res, 2009. **24**(6): p. 1033-42.
11. Chan, G.M., et al., *Bone mineral status in childhood accidental fractures.* Am J Dis Child, 1984. **138**(6): p. 569-70.
12. Landin, L. and B.E. Nilsson, *Bone mineral content in children with fractures.* Clin Orthop Relat Res, 1983(178): p. 292-6.
13. Goulding, A., et al., *Bone mineral density in girls with forearm fractures.* J Bone Miner Res, 1998. **13**(1): p. 143-8.
14. Goulding, A., 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.
15. Ferrari, S., et al., *Familial resemblance for bone mineral mass is expressed before puberty.* J Clin Endocrinol Metab, 1998. **83**(2): p. 358-61.
16. Ferrari, S.L., 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.
17. Weaver, C.M., 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.
18. 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.
19. Trost, S.G., et al., *Age and gender differences in objectively measured physical activity in youth.* Med Sci Sports Exerc, 2002. **34**(2): p. 350-5.
20. Ahmed, L.A., et al., *Progressively increasing fracture risk with advancing age after initial incident fragility fracture: the Tromso study.* J Bone Miner Res, 2013. **28**(10): p. 2214-21.
21. Omsland, T.K., et al., *In vivo and in vitro comparison of densitometers in the NOREPOS study.* J Clin Densitom, 2008. **11**(2): p. 276-82.
22. Booth, M.L., 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.

23. Rangul, V., et al., *Reliability and validity of two frequently used self-administered physical activity questionnaires in adolescents.* BMC Med Res Methodol, 2008. **8**: p. 47.
24. Bailey, D.A., 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.
25. Klein-Nulend, J., et al., *Mechanosensation and transduction in osteocytes.* Bone, 2013. **54**(2): p. 182-90.
26. Pocock, N.A., et al., *Genetic determinants of bone mass in adults. A twin study.* J Clin Invest, 1987. **80**(3): p. 706-10.

Abbreviations:

PBM: Peak bone mass

BMD: Bone mineral density

BMC: Bone mineral content

BMAD: Bone mineral apparent density

TFF: the Tromsø Study, Fit Future

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 Vlachopoulous, 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.

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)*#*	*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)*
BMD-FN	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	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	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	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	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	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	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-TH	0.193 (0.022)	0.192 (0.024)	*0.188 (0.018)*	*0.194 (0.025)*	0.186 (0.024)	0.186 (0.022)	*0.182 (0.022)*	*0.188 (0.022)*
BMAD-TB	0.024 (0.001)	0.024 (0.001)	*0.024 (0.001)*	*0.024 (0.002)*	0.024 (0.001)	0.024 (0.002)	*0.023(0.001)**	*0.024 (0.002)*
BMAD-arm	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)*

*P<0.05 compared to No fracture group.
#p<0.05 compared to Other fracture group.
BMD: Bone Mineral Density (g/cm^2), BMC: Bone Mineral Content (g), BMAD: Bone Mineral Apparent Density (g/cm^3), PAi: Physical Activity intensity, 95% CI: 95% Confidence Interval, FN: Femoral Neck, TH: Total Hip, TB: Total Body, Fx: Fracture.

Table 2. The association between history of childhood fracture and bone mass parameters during adolescence in girls and boys. The Tromsø Study Fit Future.

	BMD Beta coefficients [95% CI]			**BMC** Beta coefficients [95% CI]			**BMAD** Beta coefficients [95% CI]	
	Femoral Neck	Total Hip	Total Body	Femoral Neck	Total Hip	Total Body	Femoral Neck	Arm
Girls								
All Fractures	-0.01 [-0.05, 0.04]	-0.01 [-0.05, 0.03]	-0.01 [-0.03, 0.02]	-0.19 [-0.40, 0.03]	-0.77 [-2.17, 0.64]	-79.3 [-192, 34.1]	0.01 [-0.02, 0.04]	0.00 [-0.00, 0.00]
Forearm fractures	0.01 [-0.09, 0.12]	0.00 [-0.10, 0.10]	0.00 [-0.06, 0.06]	-0.19 [-0.60, 0.33]	-0.15 [-3.47, 3.17]	-113 [-373, 146]	0.02 [-0.05, 0.09]	-0.00 [-0.01, 0.00]
Other fractures	-0.01 [-0.05, 0.04]	-0.01 [-0.06, 0.04]	-0.01 [-0.04, 0.02]	-0.18 [-0.42, 0.06]	-0.85 [-2.41, 0.70]	-73.2 [-197, 51.5]	0.01 [-0.02, 0.04]	0.00 [-0.00, 0.00]
Boys								
All Fractures	-0.02 [-0.06, 0.02]	-0.01 [-0.05, 0.03]	-0.02 [-0.04, 0.01]	-0.08 [-0.32, 0.16]	-0.05 [-1.59, 1.48]	-33.9 [-133, 65.5]	-0.01 [-0.04, 0.01]	0.00 [-0.00, 0.00]
Forearm fractures	-0.04 [-0.11, 0.04]	-0.03 [-0.11, 0.05]	-0.03 [-0.07, 0.02]	-0.29 [-0.75, 0.17]	-1.24 [-4.22, 1.75]	-91.5 [-288, 105]	-0.01 [-0.06, 0.04]	0.00 [-0.00, 0.01]
Other fractures	-0.01 [-0.06, 0.01]	-0.01 [-0.05, 0.04]	-0.01 [-0.04, 0.02]	-0.01 [-0.29, 0.27]	0.34 [-1.42, 2.10]	-12.9 [-126, 100]	-0.01 [-0.04, 0.02]	-0.00 [-0.00, 0.00]

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

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

	BMD Beta coefficients [95% CI]			**BMC** Beta coefficients [95% CI]			**BMAD** Beta coefficients [95% CI]	
	Femoral Neck	Total Hip	Total Body	Femoral Neck	Total Hip	Total Body	Femoral Neck	Arm
All Fractures								
PAi								
Low	-0.05 [-0.12, 0.02]	**-0.06 [-0.13,-0.00]**	-0.02 [-0.06, 0.02]	**-0.35 [-0.68, -0.02]**	-1.95 [-3.97, 0.08]	-121 [-308, 65.5]	-0.01 [-0.06, 0.03]	0.00 [-0.00, 0.01]
Moderate	0.05 [-0.02, 0.13]	0.05 [-0.03, 0.13]	0.01 [-0.03, 0.06]	0.05 [-0.35, 0.44]	0.97 [-1.84, 3.79]	-49.7 [-262, 163]	0.04 [-0.01, 0.09]	0.00 [-0.00, 0.01]
Vigorous	0.00 [-0.09, 0.09]	0.00 [-0.09, 0.09]	-0.00 [-0.05, 0.05]	-0.21 [-0.66, 0.25]	-1.13 [-3.97, 1.71]	-47.7 [-239, 144]	0.01 [-0.04, 0.07]	-0.00 [-0.01, 0.00]
Forearm fractures								
PAi								
Low	0.03 [-0.12, 0.19]	-0.01 [-0.15, 0.13]	-0.02 [-0.11, 0.07]	-0.17 [-0.96, 0.61]	-0.26 [-5.08, 4.55]	-300 [-724, 123]	0.03 [-0.08, 0.13]	-0.00 [-0.01, 0.00]
Moderate	0.03 [-0.15, 0.21]	0.02 [-0.17, 0.21]	-0.02 [-0.13, 0.09]	0.01 [-0.90, 0.93]	1.11 [-5.47, 7.69]	-179 [-669, 310]	0.04 [-0.08, 0.16]	-0.00 [-0.01, 0.01]
Vigorous	-0.01 [-0.24, 0.23]	0.01 [-0.22, 0.24]	0.05 [-0.07, 0.17]	-0.39 [-1.16, 0.81]	-1.01 [-8.45, 6.43]	199 [-299, 698]	-0.00 [-0.16, 0.15]	0.00 [-0.01, 0.02]
Other fractures								
PAi								
Low	-0.07 [-0.14, 0.01]	**-0.07 [-0.14,-0.00]**	-0.03 [-0.07, 0.02]	**-0.38 [-0.75, -0.02]**	-2.25 [-4.53, 0.03]	-89.7 [-295, 115]	-0.02 [-0.07, 0.03]	0.00 [-0.00, 0.01]
Moderate	0.06 [-0.02, 0.15]	0.06 [-0.03, 0.15]	0.02 [-0.03, 0.08]	0.07 [-0.37, 0.51]	1.10 [-2.03, 4.23]	-33.2 [-275, 209]	0.05 [-0.01, 0.10]	0.00 [-0.00, 0.01]
Vigorous	0.00 [-0.10, 0.10]	-0.01 [-0.11, 0.10]	-0.01 [-0.07, 0.04]	-0.12 [-0.64, 0.40]	-0.79 [-4.03, 2.45]	-76.4 [-294, 141]	0.01 [-0.05, 0.08]	-0.00 [-0.01, 0.00]

Models adjusted for lean mass (g), body height (cm) 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 mass parameters during adolescence in boys, stratified by level of physical activity intensity (PAi). The Tromsø Study Fit Future.

	BMD Beta coefficients [95% CI]			BMC Beta coefficients [95% CI]			BMAD Beta coefficients [95% CI]	
	Femoral Neck	Total Hip	Total Body	Femoral Neck	Total Hip	Total Body	Femoral Neck	Arm
All Fractures								
PAi								
Low	-0.04 [-0.10, 0.02]	-0.01 [-0.07, 0.05]	-0.02 [-0.06, 0.01]	-0.13 [-0.47, 0.21]	0.16 [-2.01, 2.37]	-76.6 [-231, 77.9]	**-0.04 [-0.08, -0.01]**	0.00 [-0.00, 0.00]
Moderate	-0.00 [-0.09, 0.08]	-0.03 [-0.11, 0.05]	0.00 [-0.05, 0.05]	-0.01 [-0.53, 0.52]	-1.44 [-4.67, 1.80]	25.8 [-179, 230]	0.00 [-0.05, 0.06]	0.00 [-0.00, 0.00]
Vigorous	-0.01 [-0.09, 0.07]	-0.02 [-0.10, 0.07]	-0.02 [-0.06, 0.02]	-0.17 [-0.65, 0.31]	0.31 [-2.79, 3.40]	-40.5 [-215, 134]	0.01 [-0.04, 0.06]	0.00 [-0.00, 0.00]
Forearm fractures								
PAi								
Low	-0.03 [-0.14, 0.09]	-0.00 [-0.11, 0.11]	-0.00 [-0.07, 0.07]	-0.06 [-0.73, 0.60]	0.42 [-3.95, 4.78]	0.69 [-313, 315]	-0.04 [-0.11, 0.03]	0.01 [-0.00, 0.01]
Moderate	-0.01 [-0.18, 0.16]	-0.02 [-0.18, 0.15]	-0.02 [-0.12, 0.08]	-0.14 [-1.20, 0.93]	-2.55 [-9.17, 4.07]	-240 [-665, 185]	-0.03 [-0.16, 0.10]	**0.01 [0.00, 0.02]**
Vigorous	-0.10 [-0.25, 0.04]	-0.12 [-0.28, 0.04]	-0.09 [-0.17, 0.01]	**-0.96 [-1.83, -0.09]**	-4.20 [-9.98, 1.58]	-218 [-553, 116]	-0.00 [-0.09, 0.09]	**-0.01 [-0.02, -0.00]**
Other fractures								
PAi								
Low	-0.01 [-0.10, 0.03]	-0.01 [-0.07, 0.06]	-0.03 [-0.07, 0.01]	-0.13 [-0.52, 0.25]	0.20 [-2.29, 2.69]	-93.9 [-266, 78.5]	-0.04 [-0.08, 0.00]	-0.00 [-0.01, 0.00]
Moderate	-0.00 [-0.10, 0.09]	-0.04 [-0.13, 0.06]	0.01 [-0.05, 0.06]	0.02 [-0.60, 0.64]	-1.33 [-5.17, 2.51]	91.6 [-144, 328]	0.01 [-0.05, 0.07]	-0.00 [-0.01, 0.00]
Vigorous	0.03 [-0.07, 0.12]	0.02 [-0.08, 0.12]	0.01 [-0.05, 0.06]	0.12 [-0.45, 0.69]	1.94 [-1.72, 5.59]	29.8 [-179, 239]	0.02 [-0.04, 0.07]	0.00 [-0.00, 0.01]

Models adjusted for lean mass (g), body height (cm) 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 and bone mass parameters during adolescence in girls and boys. The Tromsø Study Fit Future.

	BMD Beta coefficients [95% CI]			**BMC** Beta coefficients [95% CI]			**BMAD** Beta coefficients [95% CI]	
	Femoral Neck	Total Hip	Total Body	Femoral Neck	Total Hip	Total Body	Femoral Neck	Arm
Girls								
Fractures	-0.02 [-0.07, 0.03]	-0.05 [-0.10, 0.00]	**-0.03 [-0.06, -0.00]**	-0.19 [-0.44, 0.05]	-1.50 [-3.07, 0.08]	-113 [-239, 14.1]	-0.02 [-0.05, 0.01]	-0.00 [-0.00, 0.00]
Boys								
Fractures	0.04 [-0.01, 0.09]	0.04 [-0.01, 0.09]	0.02 [-0.00, 0.05]	0.08 [-0.20, 0.36]	1.61 [-0.19, 3.40]	82.7 [-31.2, 197]	0.02 [-0.01, 0.05]	0.00 [-0.00, 0.00]

Models adjusted for lean mass (g), body height (cm), 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.

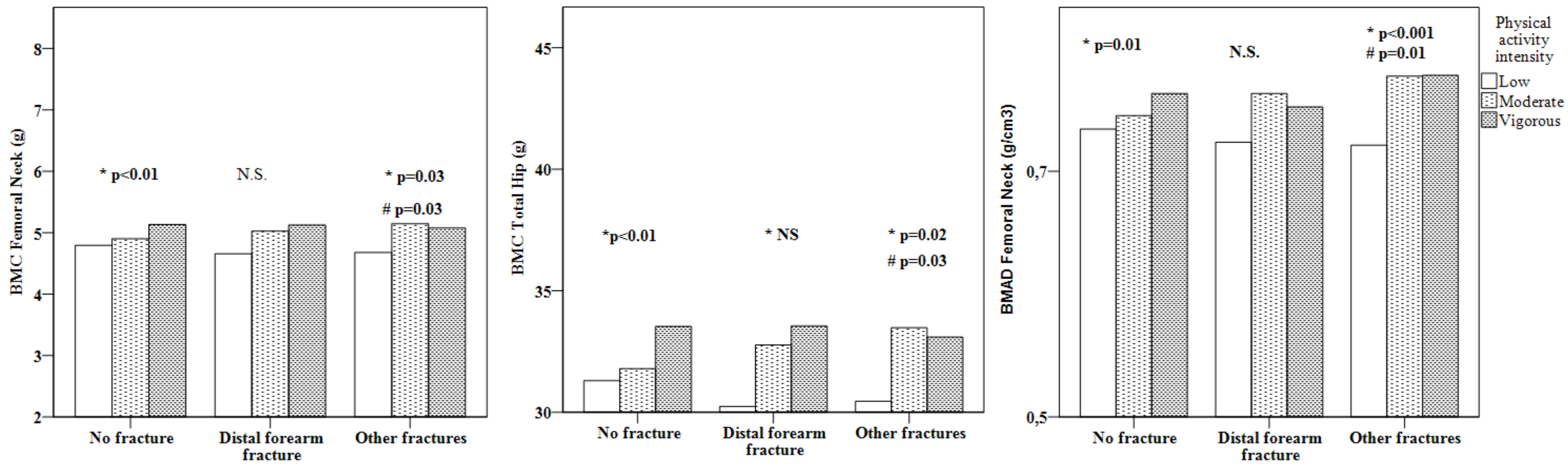
Figure Capiton

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

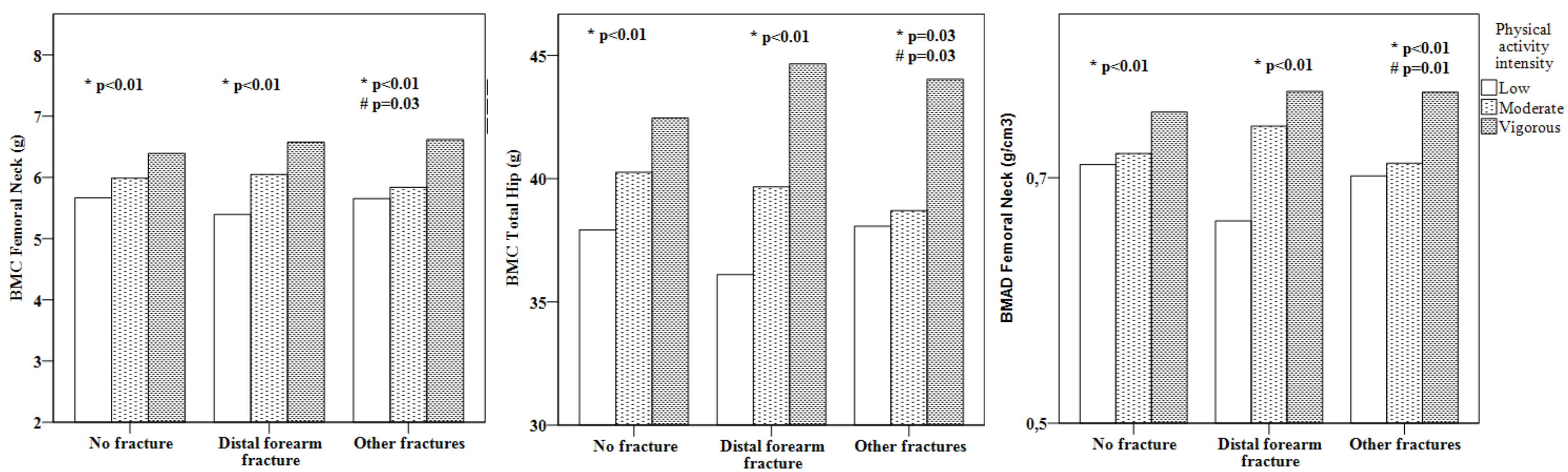
Figure footnote

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

a)


BMC Femoral Neck (g)
* p<0.01
N.S.
* p=0.03
# p=0.03
No fracture
Distal forearm fracture
Other fractures
BMC Total Hip (g)
*p<0.01
* NS
* p=0.02
# p=0.03
BMAD Femoral Neck (g/cm3)
* p=0.01
N.S.
* p<0.001
# p=0.01
Physical activity intensity
Low
Moderate
Vigorous

b)


BMC Femoral Neck (g)
* p<0.01
* p<0.01
* p<0.01
# p=0.03
No fracture
Distal forearm fracture
Other fractures
BMC Total Hip (g)
* p<0.01
* p<0.01
* p=0.03
# p=0.03
BMAD Femoral Neck (g/cm3)
* p<0.01
* p<0.01
* p<0.01
# p=0.01
Physical activity intensity
Low
Moderate
Vigorous