The influence of birth weight and length on bone mass in adolescence. The Tromsø Study, Fit Futures.

Tore Christoffersen MSc [a, b], Luai A Ahmed PhD [a, c], Anne Kjersti Daltveit PhD [d, e], Elaine M Dennison PhD [f, g], Elin K Evensen MSc [h], Anne-Sofie Furberg PhD [i, j], Luis Gracia-Marco PhD [k, l], Guri Grimnes PhD [m, n], Ole-Andreas Nilsen MSc [a], Berit Schei PhD [o, p], Grethe S Tell PhD [q, r], Dimitris Vlachopoulos MSc [k], Anne Winther PhD [s], Nina Emaus PhD [a]

Affiliation

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

b. Finnmark Hospital Trust, Alta, Norway

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

d. Department of Public Health and Primary Health Care, University of Bergen, Bergen, Norway

e. Medical Birth Registry of Norway, Division of Epidemiology, Norwegian Institute of Public Health, Bergen, Norway.

f. MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, United Kingdom

g. School of Biological Sciences, Victoria University of Wellington, New Zealand

h. Clinical Research Department, University Hospital of North Norway, Tromsø, Norway

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

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

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

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

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

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

o. Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Trondheim, Norway

p. Department of Obstetrics and Gynecology, St. Olavs Hospital Trondheim University Hospital, Trondheim, Norway

q. Domain for Health Data and Digitalization, Norwegian Institute of Public Health, Bergen, Norway

r. Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

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

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

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Abbreviations:

PBM: Peak bone mass

BMD: Bone mineral density

BMC: Bone mineral content

FF1: the Fit Future Study

MBRN: the Medical Birth Registry of Norway

DXA: Dual-energy X-ray absorptiometry

CV: Coefficient of variation

FN: Femoral neck

TH: Total hip

TB: Total body

GA: Gestational age

PA: Physical activity

PAi: Physical activity intensity

HBSC: Health Behavior in School Children

STD: Standard deviation scores (z-scores)

SD: Standard deviation

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The influence of birth weight and length on bone mass in adolescence. The Tromsø Study, Fit Futures.

Purpose: The influence of birth weight and length on bone mass later in life is unclear, especially in adolescence. This study evaluated the impact of birth weight and length on bone mass among adolescents.

Methods: We included 961 participants from the population-based Fit Future study (2010-2011). Dual-energy X-ray absorptiometry (DXA) was used to measure bone mineral density (BMD) and bone mineral content (BMC) at femoral neck (FN), total hip (TH) and total body (TB). Bone mass measures were linked with birth weight and length ascertained from the Medical Birth Registry of Norway. Linear regression models were used to investigate the influence of birth parameters on bone mass.

Results: Birth weight was positively associated with 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. Corresponding analyses using birth length as exposure gave significantly positive associations with BMC at all sites in both sexes. The significant positive association between birth weight and BMC-TB in girls, and birth length and BMC-TB in boys remained after multivariable adjustment.

Conclusions: We found a positive association between birth size and BMC in adolescence. However, this association was attenuated after adjustment for weight, height and physical activity during adolescence.

Osteoporotic fractures are a major health issue worldwide [1, 2]. Traditional public health policies have aimed at reducing risk factors associated with bone mass losses during adulthood to prevent osteoporotic fractures in later life [3]. An alternative strategy for prevention of osteoporotic fractures is to focus on optimizing peak bone mass (PBM) [4]. PBM is the result of numerous factors that influence the development of the skeleton. Genetic [5, 6] as well as several environmental and lifestyle factors contribute with varying impact. Evidence suggests that optimization of PBM in early-life may reduce later risk of osteoporosis [7, 8].

Several studies have shown an effect of various early-life exposures, resulting in changed risk of various diseases later in life [9-12]. Prematurity and uteroplacental insufficiency, both with low birth weight as proxy and with subsequent rapid growth, have been shown to be independently associated with low bone mass [13].

The association of birth weight with bone mass at different ages is conflicting; some studies have shown positive associations between birth weight and bone mineral density (BMD) in pre-pubertal individuals [14, 15]. Similarly, positive associations have been observed between birth weight and bone mineral content (BMC) in young adults, postmenopausal women and elderly [16, 17]. However, inverse associations between birth weight and bone mass have also been reported in pre-pubertal children [11] and young adults [18]. A recent meta-analysis concludes that the association between birth weight on BMD and BMC are positive in children and stronger with BMC as outcome, while there is lack of evidence concerning adolescents [19].

To our knowledge, only a few studies have investigated the association of birth length with later bone mass [14, 20]. Birth length has been reported to significantly contribute to BMD at all measured sites at age 8 [14]. Furthermore, a one standard deviation unit increase in birth length has been identified as significantly increasing the risk of experiencing a pre-pubertal fracture [20]. Whether similar associations might be found in an adolescent population has yet to be investigated. Both length and weight increase during growth, dependent of lifestyle factors and with different timing in boys and girls, with dramatic spurts in adolescence. Hence, the element of size dependency of bone mass is important when interpreting results in age groups that are still growing [4] and when assessing the predictive value of birth parameters on bone mass.

The aim of this study was therefore to investigate the influence of birth weight and birth length on BMD and BMC in an adolescent cohort, stratified by sex and controlling for weight, height and physical activity during adolescence.

Methods

Study population and design: The Tromsø Study, Fit Futures

In 2010-2011, an expansion of the Tromsø Study, the Fit Futures (FF1), invited all first year upper secondary school students in Tromsø and more rural neighboring municipalities to a health survey among adolescents. The invited cohort comprised 1117 adolescents and 1038 (508 girls and 530 boys) attended the survey (93%). The cohort characteristics have been described in detail previously [21, 22]. The present investigation includes participants aged 15-18 years of age (n = 961). All participants gave written informed consent. In addition, participants younger than 16 years had to bring written consent from a parent or guardian. Examinations were performed in a well-established research unit at the University Hospital of North Norway by trained and dedicated research technicians. Data from the FF1 cohort were linked to the Medical Birth Registry of Norway (MBRN), a compulsory registry of all births in Norway [23]. The registry is run and managed by The Norwegian Institute of Public

Health, and includes information on maternal health, pregnancy, delivery and the newborn. Complete data were obtained in 765 participants (360 girls and 405 boys). 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).

Measurements

Bone mass parameters were measured by dual-energy X-ray absorptiometry (DXA; GE Lunar prodigy, Lunar Corporation, Madison, Wisconsin, USA), using 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 [24]. The outcomes in this study were BMD and BMC measured as g/cm^2 and g, respectively, at femoral neck (FN), total hip (TH) and total body (TB). 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. Birth length (cm), birth weight (g) and gestational age (GA) in weeks were collected from the MBRN.

Questionnaires

Information on perceived intensity of physical activity (PA) was collected in electronic self-reporting questionnaires at the study site by using the Health Behavior in Schoolchildren (HBSC) questionnaires [25]. The following questions were used in the present study: "If you are actively doing sports or physical activity outside school, how hard do you find the sports you are doing?" The individual answers were initially categorized into "not hard at all" (1), "a bit hard" (2), "quite hard" (3), "very hard" (4), and "extremely hard" (5), The answers were recoded into three groups: Not hard (1-2), quite hard (3-4) and hard (5-6) and used as a categorical variable in the analysis.

Statistics

Continuous baseline characteristics (mean and standard deviation) were analyzed by independent samples t-test for differences of means. Bivariate correlation coefficients of bone mass parameters with birth weight, birth length, age, weight and height at FF screening and PA were assessed with Pearson's r. Likewise, between GA and birth length and weight. Further analyses were stratified by sex. Exposure and outcome variables were converted to standard deviation (STD) scores (z-scores) based on the distribution of the samples. Residual analyses were performed to check for normal distribution, linearity, homogeneity of variance and outliers. No assumptions were considered violated. Simple linear regressions were performed with birth weight and birth length as exposure variables, while BMD and BMC at FN, TH and TB were the outcomes. Multiple linear regression with four different models were performed, in accordance with the proposal from Lucas et al [26]. All models were adjusted for age due to the relatively large age range in the cohort. Furthermore, gestational age in weeks were included in all models as a continuous variable to control whether potential effects of birth weight and length was attributable to preterm birth or intrauterine growth restriction. In addition, as intensity of physical activity previously has shown to be significantly positive associated to bone mass parameter in the cohort [22], all models were adjusted to check that potential effects were independent of adolescent levels of physical activity. Model 1 was used to relate size at birth to the outcome. Model 2 added weight and height respectively, at adolescence to model 1 to control for change in size, i.e. centile crossing. Model 3 added the interaction term between early and later weight and height to model 2. For completeness, model 4 had adolescence weight and length as exposure to help interpreting separate importance of birth parameters and adolescent anthropometrics. All regression analyses included measures of multicollinearity and no variance inflation factor above 10 was found. Values of $p < 0.05$ were considered statistical significant. All statistical analyses were run at the Statistical Package of Social Science (SPSS v.22).

Results

Descriptives

At birth, boys were heavier and longer than girls ($p<0.001$ for both comparisons). There was no significant sex difference in gestational age (Table 1). In adolescence, boys were taller and heavier than the girls. BMD measurements were 3.2%, 4.9% and 3.2% higher in boys than in girls for FN, TH and TB, respectively. Corresponding values for BMC were 20.9%, 24.5% and 16.7% (Table 1).

Correlations

In bivariate analyses, birth parameters were significantly correlated with BMD/BMC at all sites, except for birth weight and BMD-FN. Weight, height and PA in adolescence were significantly correlated with all bone mass measurements. Weight at FF1 demonstrated the highest coefficients with BMD- TB and BMC-TB, whilst height at FF1 demonstrated highest coefficients with BMC-FN and BMC-TH (Supplementary Table 1). Furthermore, GA was significantly correlated with birth weight and birth length with $r = 0.55$ and 0.54, respectively (data not shown).

Simple linear regression

In simple linear regression, birth weight in girls was positively associated with BMD-TB z-scores (STD [95% CI]) of 0.11 [0.01, 0.20] and BMC at all sites, 0.15 [0.06, 0.24], 0.18 [0.09. 0.28] and 0.29 [0.20, 0.38] for FN, TH, and TB respectively. In boys, birth weight was significantly positively associated with BMC, 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 (Figure 1).

Birth length was positively associated with BMC at all sites in both sexes (Figure 2). Analyses in girls displayed coefficients of 0.14 [0.05, 0.24], 0.19 [0.10, 0.29] and 0.26 [0.16, 0.35] for FN, TH and TB, respectively, whilst the corresponding values for boys were 0.12 [0.03, 0.21], 0.14 [0.05, 0.23] and 0.17 [0.08, 0.26].

Multiple linear regression

In model 1, the positive association between birth weight and BMC-TB among the girls was maintained when adjusting for birth length, GA, PA and age (Table 2). Correspondingly, for boys, the multiple regression model attenuated the associations between birth weight and BMC at all sites to become non-significant (Table 3).

Furthermore, model 1 showed no significant association between birth length and BMD or BMC in girls (Table 2). Boys maintained a significant positive association with 0.20 [0.03, 0.36] STD (95%CI) increase in BMC-TB per unit increase in birth length (Table 3).

Models 2 and 3, combining early and late weight and length and checking for interactions, attenuated all associations to become non-significant in both sexes. No significant interaction terms were found in model 3.

In the final model, weight in adolescent girls and boys were significantly positive associated with both BMD and BMC at all sites (Table 2 and Table 3). Height in adolescence was significantly positive associated with BMC at all sites in both sexes (Table 2 and Table 3)

Discussion

This study focuses on the predictive value of birth weight and length on BMD and BMC measured in adolescents aged 15 to 18 years of age. In girls, there were significantly positive associations between birth weight and BMD-TB and BMC at all sites in crude models. Likewise, birth length was significantly positively associated with BMC at all sites. However, in multivariable regression models, birth anthropometric and lifestyle factors attenuated these findings, and only the association between birth weight and BMC-TB remained significant. In addition, when adjusting for change in size from birth and adolescence, and possible interactions i.e. the magnitude of change in size, all associations were attenuated. In boys, there were corresponding findings. Adjustment for birth anthropometrics, age and physical activity attenuated all this relationships, except for the association between birth length and BMC-TB and likewise further modeling removed significant findings. To our knowledge, this study is the first that focus on both birth weight and length predictions of bone health in this particular age group and in both sexes.

Both in girls and boys, there were significant positive associations between birth weight and BMC at all sites in crude models. In the recent systematic review and meta-analysis by Martìnez-Mesa et al. [19], seven studies that evaluated adolescents and young adults were included. All of these had birth weight as an exposure. Out of 26 independent analyses, eight presented positive associations with bone mass measurements. Four analyses indicated inverse associations, although only one was significantly negative. The age range in these studies varied from 17-24, hence in the upper range and above the age in our cohort. Although the systematic review conclude that birth weight positively influence bone health later in life, the authors were not able to demonstrate evidence of such during adolescence.

In 2008, Jensen et al [27] reported the findings from a longitudinal cohort examined by DXA at the age of 16-19 years of age. They found a positive association between birth weight and whole body BMC, lumbar spine BMC and lumbar spine BMD. However, when adjusting for height and weight at the time of DXA measurements, all associations became nonsignificant. Interestingly, fetal growth velocity in the study of Jensen et al. were positively associated with only whole body BMC, whilst weight at 1 years showed stronger positive associations with whole body BMC and lumbar spine BMC, compared with associations with birth weight.

Consequently, they concluded that the association between early-life size and BMC might be influenced more by postnatal growth than fetal programming. Our findings are in line with the study of Jensen et al. Although they applied a proposal from Prentice et al [28] for correction of size-related artefacts in their statistical analyses, whilst we used models as suggested by Lucas et al [26], both detected no significant associations after adjustments. Some further differences in methodology should still be highlighted. The mean age in their cohort was 0.7 years and 1 year older in boys and girls respectively. These differences could be crucial with respect to the impact of peak growth velocity on bone development. There is also a major difference in subjects included in the studies. The Danish study included 119 versus 765 in ours. Furthermore, as bone mass acquisition varies in girls and boys during adolescence [21], our analyses were performed sex stratified in contrast to the study of Jensen et al.

Sex stratification was not an issue in the study of Saito et al. [29]. They recruited 86 female participants among first-year university students for assessment of birth weight and growth as predictors of bone mass. In accordance with the Danish study [27], they found positive associations between birth weight and lumbar spine BMC. In addition, birth weight was associated with total hip BMC in a model adjusted for physical activity and current weight. The previous study contrasts our findings of no significant associations in birth weight and BMC in models controlling for both early life effects, centile size crossing (Model 2) and interactions. Saito el al [29] also reported correlation coefficients between size and bone mass during growth. Interestingly, in total hip BMC, all of these were statistically significant, but birth weight presented the weakest coefficients. However, this was also the case for birth length correlations with bone mass. Again, age may complicate the comparison of results. Saito et al. [29] did their analyses on women from 18 to 21 years of age. At this time in life, peak bone mass probably is reached [30], except in the spine, and the participants could be compared with adult subjects.

A main purpose in the present study was to investigate associations between birth length and BMD/BMC. In girls and boys birth length and BMC were significantly positive associated in crude models. Interestingly, a study by Eide et al. [31] aimed to examine the contribution of birth length and birth weight on adult length and weight. They suggested that birth length perhaps is a better predictor of adult height and weight than birth weight. Furthermore, their findings pointed to that length and weight at birth contributed independently to adult stature. In respect to adult height, these effects were additive and therefor indicate that birth weight and birth length influence stature, and therefore bone mass, through different pathways. In our study, we observed a significantly positive association between birth weight and BMC-TB in girls, adjusted for birth length, gestational age, physical activity and age. This was not found in boys. In contrast, birth length was positively associated with BMC-TB among boys using the same model. However, as further modeling attenuated these effects, one might argue that postnatal growth and later size is likely to be more relevant to predict bone mass in adolescence. A possible explanation for the observed sex-difference is the peak growth velocity in adolescence [32]. A higher peak velocity and longer lasting growth spurt in boys could contribute to the indication of discrepancy in multivariate analyses.

The rationale for an environmental modification during early life, strong enough to alter risk of osteoporosis is based on several groups of studies [33]. Detailed analyses at a population study level have suggested that malnutrition in utero may modify genetic influence on adult mineral density [34]. Physiological studies have strengthened the theory that stress during intrauterine life alter growth hormone and cortisol sensitivity, leading to reduced peak skeletal size and accelerated bone loss later [35]. Furthermore, studies of maternal health have shown relations to neonatal bone mass [36] and finally there is evidence that link childhood growth with later risk of hip fracture [37]. In our cohort the mean birth weight (standard deviation) was 3453 (576) g and 3601 (590) g in girls and boys, respectively. The frequency of low birthweight incidences (4%, data not shown), is low compared with global reports [38] and even when compared within industrialized countries in Europe. Thus, one might speculate that our cohort indicate relatively stronger environmental modifications based on adequate nutrition in utero, low levels of stress and good maternal health. When these predictive adaptive response are optimized during the phase of high developmental plasticity [39], it is plausible that the actual environment after birth might have a higher impact in further skeletal development in such a population.

The main strengths of this study are the large sample size and population-based design in Fit Future, including the high attendance rate at bone mass screening. Both sexes are represented and the study included participants from both urban and rural regions. The MBRN secure robust registry data on birth parameters, minimizing the risk of recall bias in retrospective data collection. Furthermore, the use of dedicated research technicians at the research unit at the University Hospital of North Norway is likely to reduce measurement errors. Some limitations are notable. It has been claimed that birth weight measurements are more reliable than length measurements [40] and that birth length measurements show less variability when compared with birth weight measurements. Thus, it has been discussed whether this variable should be treated as a discrete variable, even when measured and reported as cm [31]. However, for healthy newborns, any measurement error is probably random with respect to final height and hence bone mineral content. Finally, nutrition can affect bone mass mineral during growth. This variable was not available in this study.

In conclusions, our results demonstrate a positive association between birth weight and length, and BMC in adolescence. However, these associations were attenuated when adjusted for growth determining later size and physical activity. With respect to optimizing the genetic peak bone mass, further studies should consider the impact of environmental stimuli and lifestyle factors during growth. Especially in regions where maternal health is good and malnutrition is rare.

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Table 1: Characteristics and bone mineral density and bone mineral content levels at different anatomical sites. The Tromsø Study, Fit Futures

	Girls N	Mean (SD)	Boys n	Mean (SD)	p
Age FF1	469	16.6 (0.41)	492	16.6 (0.41)	0.237
Height FF1 (cm)	467	164.9 (6.5)	492	176.9 (6.7)	<0.001
Weight FF1 (kg)	467	60.9 (11.5)	492	70.2 (14.4)	<0.001
Birth weight (g)	443	3454.8 (576.7)	470	3601.0 (590.0)	<0.001
Birth length (cm)	419	49.4 (2.3)	454	50.2 (2.3)	<0.001
GA (weeks)	393	39.7 (1.8)	429	39.6 (2.1)	0.226
BMD_{FN} (g/cm^2)	459	1.066 (0.123)	485	1.100 (0.151)	<0.001
BMD_{TH} (g/cm^2)	458	1.060 (0.123)	483	1.112 (0.147)	<0.001
BMD_{TB} (g/cm^2)	466	1.142 (0.077)	490	1.178 (0,095)	<0.001
BMC_{FN} (g)	459	4.916 (0.702)	485	5.947 (1.003)	<0.001
BMC_{TH} (g)	458	32.03 (4.80)	483	39.79 (6.63)	<0.001
BMC_{TB} (g)	466	2524.7 (391.4)	490	2947.2 (475.2)	<0.001
PAi	469		492		0.938
Not hard	151	32.2%	175	35.6%	
Quite hard	210	44.8%	189	38.4%	
Hard	108	23.0%	128	26.0%	

GA: Gestational Age, BMD: Bone Mineral Density, BMC: Bone Mineral Content, FN: Femoral Neck, TH: Total Hip, TB: Total Body, FF1: Fit Futures 1, PAi: Physical Activity intensity.

Table 2: Associations between birth weight/length and bone mineral density and bone mineral content in girls 15-18 years. The Tromsø Study, Fit Futures (n = 360)

	BMD (standardized β coefficient [95% CI])			BMC (standardized β coefficient [95% CI])		
	Femoral neck	Total hip	Total body	Femoral neck	Total hip	Total body
BW	0.04 [-0.06, 0.13]	0.05 [-0.04, 0.14]	**0.11 [0.01, 0.20]**	**0.15 [0.06, 0.24]**	***0.18 [0.09, 0.28]***	***0.29 [0.20, 0.38]***
Model 1	-0.01 [-0.18, 0.18]	0.03 [-0.16, 0.21]	0.14 [-0.05, 0.33]	0.12 [-0.06, 0.30]	0.09 [-0.09, 0,27]	***0.30 [0.12, 0.48]***
Model 2	-0.13 [-0.30, 0.04]	-0.10 [-0.28, 0.07]	-0.05 [-0.21, 0.11]	-0.06 [-0.21, 0.10]	-0.09 [-0.24, 0.06]	0.05 [-0.07, 0.17]
Model 3	-0.13 [-0.31, 0.04]	-0.11 [-0.28, 0.07]	-0.05 [-0.21, 0.11]	-0.06 [-0.21, 0.10]	-0.09 [-0.24, 0.06]	0.05 [-0.07, 0.17]
Model 4	***0.42 [0.31, 0.54]***	***0.46 [0.34, 0.58]***	***0.66 [0.56, 0.77]***	***0.58 [0.48, 0.69]***	***0.57 [0.47, 0.67]***	***0.82 [0.74, 0.90]***
BL	0.07 [-0.03, 0.16]	0.06 [-0.04, 0.16]	0.08 [-0.02, 0.18]	**0.14 [0.05, 0.24]**	***0.19 [0.10, 0.29]***	***0.26 [0.16, 0.35]***
Model 1	0.08 [-0.09, 0.26]	0.05 [-0.12, 0.23]	0.03 [-0.15, 0.20]	0.09 [-0.09, 0.23]	0.16 [-0.01, 0.33]	0.12 [-0.05, 0.30]
Model 2	0.03 [-0.14, 0.20]	0.05 [-0.12, 0.22]	-0.01 [-0.17, 0.14]	-0.03 [-0.18, 0.12]	0.02 [-0.12, 0.17]	-0.04 [-0.16, 0.08]
Model 3	0.06 [-0.13, 0.25]	0.05 [-0.15, 0.24]	0.02 [-0.16, 0.19]	-0.02 [-0.19, 0.15]	0.01 [-0.16, 0.17]	-0.01 [-0.13, 0,13]
Model 4	0.04 [-0.09, 0.18]	-0.08 [-0.21, 0.06]	-0.04 [-0.16, 0.09]	***0.23 [0.11, 0.35]***	***0.31 [0.19, 0,43]***	**0.34 [0.25, 0.43]**

BW: Birth Weight, BL: Birth Length, BMD: Bone Mineral Density, BMC: Bone Mineral Content, CI: Confidence Interval.
All models are adjusted for Gestational age, Physical Activity intensity and age at BMD and BMC screening.
Model 1: Adjusted for BL or BW.
Model 2: Adjusted for Model 1 + Adolescence Height (AH) or Adolescence Weight (AW).
Model 3: Model 2 + interaction terms (BW·AW, BL·AH).
Model 4: Adjusted for AW or AL
No significant interaction terms in model 3
P<0.05 in bold, P<0.001 in italic bold.

Table 3: Association between birth weight/length and bone mineral density and bone mineral content in boys 15-18 years. The Tromsø Study, Fit Futures (n = 405)

	BMD (standardized β coefficient [95% CI])			BMC (standardized β coefficient [95% CI])		
	Femoral neck	Total hip	Total body	Femoral neck	Total hip	Total body
BW	0.04 [-0.05, 0.14]	0.05 [-0.04, 0.14]	0.04 [-0.05, 0.13]	**0.10 [0.01, 0.19]**	**0.12 [0.03, 0.21]**	**0.15 [0.07, 0.24]**
Model 1	-0.08 [-0.09, 0.24]	0.09 [-0.25, 0.06]	-0.04 [-0.20, 0.12]	-0.03 [-0.18, 0.13]	-0.01 [-0.17, 0.14]	0.02 [-0.14, 0.18]
Model 2	-0.13 [-0.27, 0.18]	-0.14 [-0.28, 0.09]	-0.11 [-0.24, 0.03]	-0.08 [-0.21, 0.06]	-0.07 [-0.20, 0.05]	-0.06 [-0.16, 0.04]
Model 3	-0.12 [-0.27, 0.03]	-0.13 [-0.28, 0.02]	-0.12 [-0.25, 0.01]	-0.08 [-0.22, 0.05]	-0.07 [-0.20, 0.07]	-0.05 [-0.15, 0.05]
Model 4	***0.35 [0.26, 0.43]***	***0.34 [0.26, 0.43]***	***0.47 [0.39, 0.55]***	***0.36 [0.28, 0.44]***	***0.39 [0.31, 0.47]***	***0.57 [0.51, 0.62]***
BL	0.06 [-0.03, 0.15]	0.07 [-0.02, 0.17]	0.05 [-0.04, 0.14]	**0.12 [0.03, 0.21]**	**0.14 [0.05, 0.23]**	***0.17 [0.08, 0.26]***
Model 1	0.08 [-0.09, 0.24]	0.09 [-0.07, 0.25]	0.07 [-0.09, 0.24]	0.12 [-0.04, 0.28]	0.12 [-0.04, 0.28]	**0.20 [0.03, 0.36]**
Model 2	-0.03 [-0.19, 0.12]	0.03 [-0.13, 0.18]	-0.04 [-0.18, 0.10]	-0.04 [-0.18, 0.10]	-0.05 [-0.19, 0.09]	-0.03 [-0.13, 0.08]
Model 3	-0.01 [-0.19, 0.16]	0.04 [-0.14, 0.22]	0.00 [-0.16, 0.16]	-0.03 [-0.19, 0.14]	-0.05 [-0.21, 0.11]	-0.03 [-0.15, 0.09]
Model 4	0.11 [-0.01, 0.24	-0.01 [-0.01, 0.07]	-0.01 [-0.04, 0.03]	***0.30 [0.19, 0.41]***	***0.29 [0.18, 0.40]***	***0.42 [0.34, 0.50]***

BW: Birth Weight, BL: Birth Length, BMD: Bone Mineral Density, BMC: Bone Mineral Content, CI: Confidence Interval.
All models are adjusted for Gestational age, Physical Activity intensity and age at bone parameters screening.
Model 1: Early model, adjusted for BL/BW.
Model 2: Combined model, adjusted for Model 1 + Adolescence Height (AH) /Adolescence Weight (AW).
Model 3: Interaction model: Model 2 + (BW·AW, BL·AL).
Model 4: Late model: exposure: AW/AL
No significant interaction terms in model 3
P<0.05 in bold, P<0.001 in italic bold.

Figure 1. Crude associations between birth weight and bone mineral density/bone mineral content. The Tromsø Study, Fit Futures

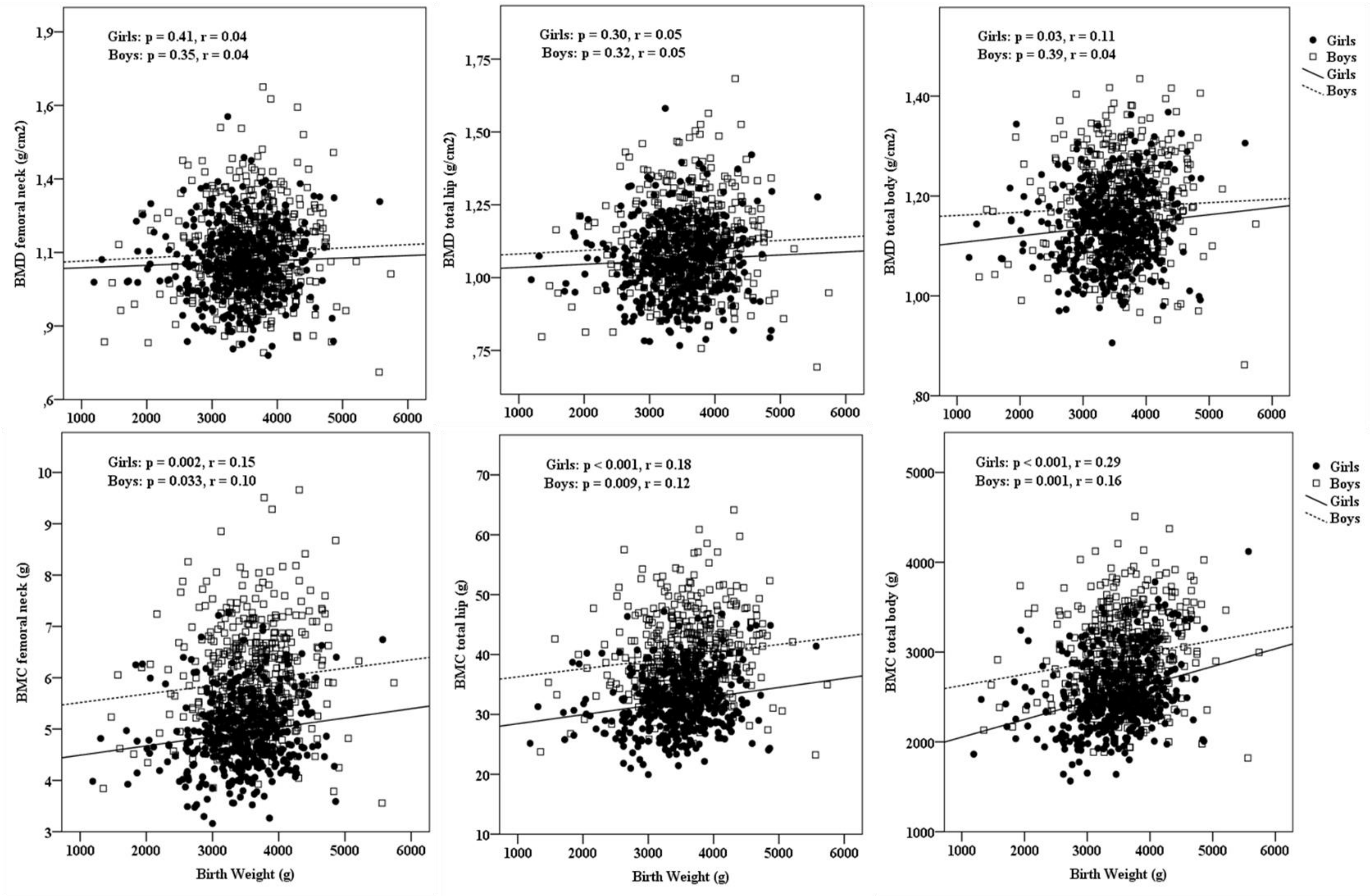
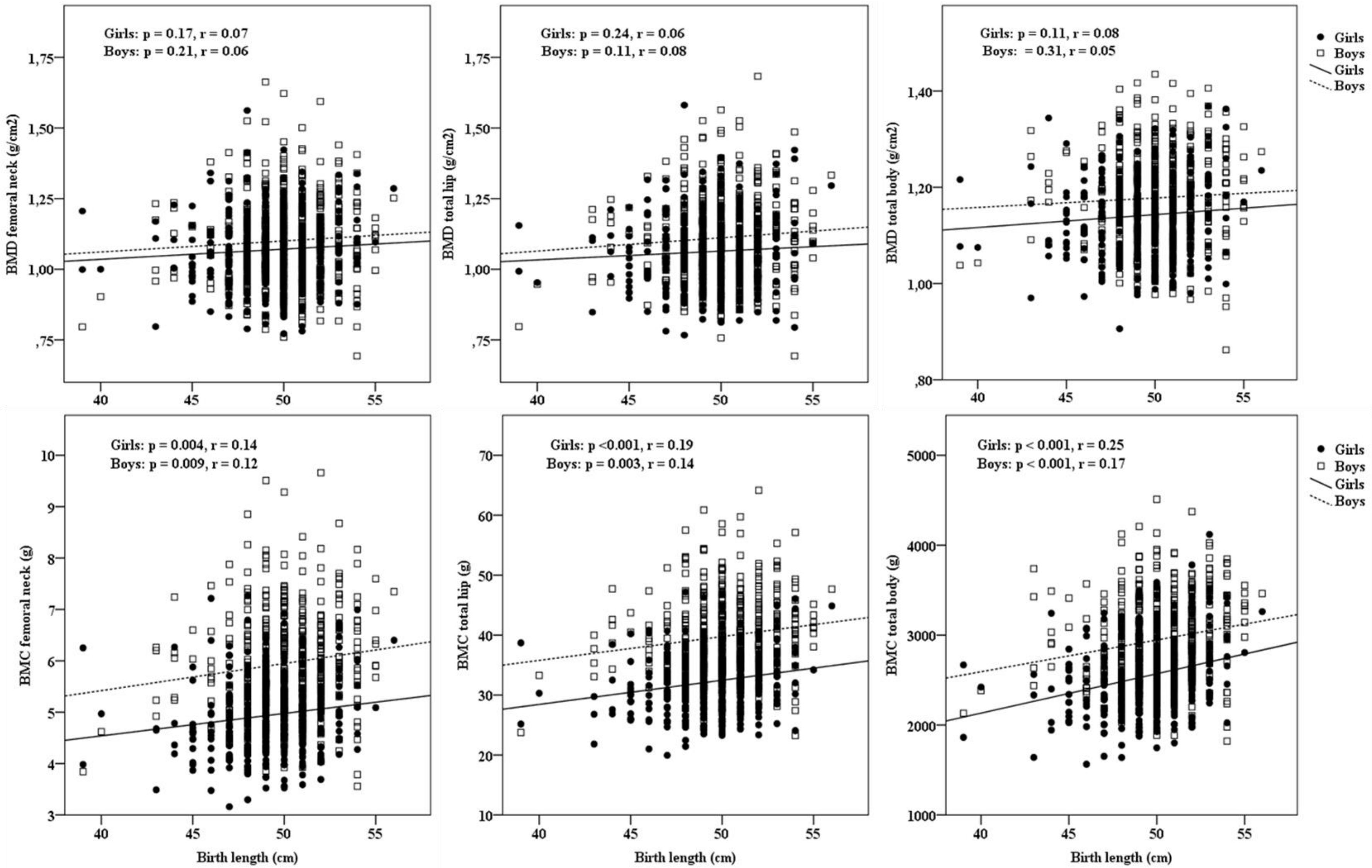


Figure 2. Crude associations between birth length and bone mineral density/bone mineral content. The Tromsø Study, Fit Futures



Supplementary Table 1. Bivariate correlations with bone mineral density and bone mineral content, The Tromsø Study, Fit Futures.

	BMD (g/cm^2) Pearson's r (n)			BMC (g) Pearson's r (n)		
	Femoral Neck	Total Hip	Total Body	Femoral Neck	Total Hip	Total Body
Birth weight (g)	0.06 (896)	**0.07** (893)	**0.09** (908)	***0.17*** (896)	***0.19*** (893)	***0.24*** (908)
Birth length (cm)	**0.08** (857)	**0.10** (854)	**0.09** (868)	***0.20*** (857)	***0.22*** (854)	***0.26*** (868)
Age (year)	**0.09** (913)	0.05 (941)	**0.09** (956)	0.06 (944)	0.02 (941)	0.05 *(956)*
Weight FF1 (kg)	***0.39*** (944)	***0.39*** (941)	***0.57*** (956)	***0.56*** (944)	***0.59*** (941)	***0.76*** (956)
Height FF1 (cm)	***0.25*** (944)	***0.24*** (941)	***0.33*** (956)	***0.60*** (944)	***0.63*** (941)	***0.65*** (956)
PA (no/yes)	***0.21*** (934)	***0.22*** (931)	***0.16*** (946)	***0.17*** (934)	***0.15*** (931)	**0.10** (946)

BMD: bone mineral density. BMC: bone mineral content. FF1: Fit Futures screening time. PA: Physical activity.
P<0.05 in bold, P<0.001 in italic bold.