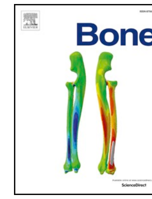
Bone 122 (2019) 150–155

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone



Full Length Article

Femoral stress is prominently associated with fracture risk in children: The Generation R Study

Olja Grgic[a,b,c], Fernando Rivadeneira[a,c,d], Enisa Shevroja[a], Katerina Trajanoska[a,d], Vincent W.V. Jaddoe[c,d], Andre G. Uitterlinden[a,c,d], Thomas J. Beck[e,f], Eppo B. Wolvius[b,c], Carolina Medina-Gomez[a,c,d,*]

[a] *Department of Internal Medicine, Erasmus MC, University Medical Center Rotterdam, Dr Molewaterplein 40, 3015 GD, the Netherlands*

[b] *Department of Maxillofacial Surgery, Special Dental Care and Orthodontics, Erasmus MC, University Medical Center Rotterdam, Dr Molewaterplein 40, 3015 GD, the Netherlands*

[c] *The Generation R Study, Erasmus MC, University Medical Center Rotterdam, Dr Molewaterplein 40, 3015 GD, the Netherlands*

[d] *Department of Epidemiology, Erasmus MC, University Medical Center Rotterdam, Dr Molewaterplein 40, 3015 GD, the Netherlands*

[e] *Beck Radiological Innovations Inc., 922 Rambling Dr., Catonsville, Baltimore, MD 21228, USA*

[f] *Department of Radiology, Johns Hopkins University School of Medicine, 733 N Broadway, Baltimore, MD 21205, USA*

A R T I C L E I N F O

Keywords:
Fracture risk
Femoral stress
Bone mineral density
Paediatric cohort
HSA

A B S T R A C T

Bone modeling is an important process in the growing skeleton. An inadequate bone modeling in response to mechanical loads would lead some children to develop weaker bones than others. The resulting higher stresses in the bones would render them more susceptible to fracture. We aimed to examine the association between femoral stress (FS) derived from structural parameters and BMD in relation to incident fractures in children. Bone stress was evaluated at the medial femoral neck, a skeletal site subject to large forces during normal locomotion. This study comprises 1840 children from the Generation R Study, with whole body and hip DXA scans at a mean age of 6.01 years. Hip structural analysis (HSA) was used to measure femur geometry for the FS calculation. Data on fractures occurring over the following 4 years after the DXA assessment were obtained by questionnaire. Incident fracture was observed in 7.6% of the participating children. Cox-multivariate regression analysis, described as hazard ratios (HR), showed that after adjustment for sex, ethnicity, age, weight and lean mass fraction, there was a significant increase in the risk of incident fracture for every standard deviation (SD) decrease in total body BMD (HR: 1.35, 95% CI 1.05–1.74, *p*-value = 0.021), femoral neck BMD (HR: 1.31, 95% CI 1.09–1.58, p-value = 0.005) and narrow neck BMD (HR: 1.39, 95% CI 1.14–1.68, p-value = 0.001). Whereas, every increment of one SD in femoral stress resulted in 1.33 increased risk of incident fractures (HR: 1.33, 95% CI 1.13–1.57, p-value = 0.001). This association remained (borderline) significant after the adjustment for DXA derived BMD measurements. Our results show that increased bone stress may underlie greater susceptibility to traumatic fractures in children (partially independent of BMD) and underscore the utility of hip DXA scans for the assessment of paediatric bone health and specifically fracture risk.

1. Introduction

Fractures in children represent an important public health issue with increasing high incidence [1–4], and deleterious consequences for health and developmental processes [1,5,6]. Understanding the etiology of childhood fractures is crucial for the development of new preventive strategies aiming at lowering fracture incidence. Fractures in children have been investigated in relation to different risk factors, including age, sex and ethnicity [1,7–13]. In line with the findings in the elderly [14–16], several studies in children [1,17–20] have found that fracture risk is associated with lower levels of bone mineral density (BMD).

However, the strength of the growing skeleton depends not only on the amount of bone material, but also on its distribution – material must

* Corresponding author at: Department of Internal Medicine, Genetic Laboratory, Erasmus University Medical Center Rotterdam, 3015 GD Rotterdam, the Netherlands.

E-mail addresses: f.rivadeneira@erasmusmc.nl (F. Rivadeneira), e.shevroja@erasmusmc.nl (E. Shevroja), k.trajanoska@erasmusmc.nl (K. Trajanoska), v.jaddoe@erasmusmc.nl (V.W.V. Jaddoe), a.g.uitterlinden@erasmusmc.nl (A.G. Uitterlinden), tom@beckradinnovations.com (T.J. Beck), e.wolvius@erasmusmc.nl (E.B. Wolvius), m.medinagomez@erasmusmc.nl (C. Medina-Gomez).

https://doi.org/10.1016/j.bone.2019.02.018
Received 9 August 2018; Received in revised form 11 February 2019; Accepted 18 February 2019
Available online 21 February 2019
8756-3282/

be placed within the bone in a way that it best resists the forces it experiences [21,22]. During skeletal growth, structural geometry of bones is constantly adapting to muscle and gravitational forces exerted during daily activities [23]. Consequently, bone tissue is formed on bone surfaces when strains or local deformations exceed some normative value. Also, bone tissue is removed from the locations where strains fall below some minimum value [24,25]. These changes in bone geometry are primarily influenced by dynamic loads and not by static ones [24]. In line with this, Petit et al. showed that overweight children had wider and stronger femur, which was largely explained by lean mass [26] used as a surrogate for skeletal load.

If the adaptive process is like other biological phenomena, one should expect some heterogeneity, where some individuals build stronger bones than others when subjected to similar mechanical stimuli. A convenient location for studying this adaptation is the inferior medial cortex of the femoral neck. This site exhibits a relatively thick cortex because it concentrates the ground reaction and muscle forces from normal locomotion. Those who may show an inadequate bone modeling should deposit less bone in the medial cortex of the femoral neck, what would translate in higher load stresses [23]. Recently, a derivation of the femoral stress (FS), computed using a single plane engineering model incorporating loading information and femur geometry – extracted from DXA images – using the hip structural analysis (HSA) software method, was described [23,25,27]. This comprehensive biomechanical assessment comprises both axial and bending forces acting on the femur [23].

The aim of this study was to examine prospectively the association between femoral structural parameters summarized in the FS, as assessed by HSA, and incident fracture risk. We studied incident fracture over a period of 4 years after DXA assessment in children, with an average age of 6 years, taking part in a large population-based pregnancy cohort in Rotterdam, The Netherlands.

2. Methods

2.1. Study population

This study was embedded in The Generation R, a multiethnic, prospective, prenatal cohort established at the Erasmus University Medical Center, Rotterdam. A total of 9778 pregnant women with a fixed delivery date (April 2002–January 2006) were enrolled. Details about cohort design and data collection have been previously described [28]. All measurements used in the current research (except fracture history) were registered in the second phase of the study at a mean age of 6.01 (± 0.45) years. This study followed the guidelines of the Helsinki Declaration and it was approved by the ethics committee (The Medical Ethics Committee of the Erasmus Medical Centre- MEC-2012-165). Written informed consent was signed by both parents and the measurements were performed only in children who were willing to participate.

2.1.1. Participant characteristics

Child's date of birth and sex were extracted from the hospital registries and medical records. Age of the child was calculated at the date of the DXA scan. Trained personnel at the Erasmus research center measured height and weight of children, using standardized procedures. Child's ethnic background was assessed from a questionnaire based on country of birth of the child's parents (classification of Statistics Netherlands) [29]. Further, ethnic background of the children was narrowed to three main ethnical groups (European, Asian and African) as described elsewhere [25]. Level of physical activity (PA) in children was assessed through questionnaires as sport participation (yes/no) and number of hours per day spent playing outside (dichotomized to less/ > 2 h) [30]. Indicators of socioeconomic status (household income and maternal education level) were assessed using questionnaires administrated to the parents. Household income was classified in 3 categories (net income < 2000, from 2000 to 3200, > 3200 euros per month), while maternal education level was assessed based on the Dutch Standard Classification of Education [31,32].

2.1.2. DXA measurements

Participants underwent DXA scanning at a mean age of 6.01 (± 0.45) years using a GE–Lunar iDXA device (GE Healthcare Lunar, Madison, WI, USA) following standard manufacturer's protocols and analyzed using enCORE software (V. 13.60). The coefficient of variation was determined to be 0.23% [33]. Daily quality assurance was performed using a phantom. Before scanning, all participants had to take off heavy clothes and shoes and to remove metal accessorizes. They were placed in a supine position, with their arms alongside the body, flat hands and the palms down on the scanner. The feet of the participants were positioned with toes placed together to form an inverted V shape, procuring internal rotation of the hips and strapped to avoid movement. Total body scans were available in 6508 children, while only 3976 children underwent total hip scans. Furthermore, all scans underwent stringent quality control and were excluded from further analysis when device errors, incorrect positioning or movement during scanning occurred (62 total body and 107 hip scans). Lean mass (LM) was obtained from total body DXA scans and lean mass fraction (LMF) was calculated (LMF = LM/weight). Femoral neck (FN) BMD was assessed from total hip scans. Total body less head (TBLH) BMD was used to assess bone density rather than total body BMD following the recommendations for the measurements in children (International Society for Clinical Densitometry for the measurement in children) [34].

2.1.3. Hip structural analysis and femoral stress

The HSA software developed by Beck et al. [35] was used to derive structural parameters from the hip DXA scans to compute FS. FS was calculated in the narrowest point of the femoral neck cross-section (where narrow neck (NN) BMD was also determined) on its medial surface using a single plane mechanical model, as described in detail elsewhere [23]. FS comprises both bending and axial forces acting on femur in a one-legged stance configuration: the force exerted on the great trochanter by the hip abductor muscle, the joint force applied on the femur by the pelvis and the reaction force at the knee [23]. The distribution of forces in the one-legged stance configuration, which was used to assess biomechanical loading of the hip, has been shown to closely resemble the average distribution of stress during the walking cycle [36].

The general formula for FS calculation is described below:

$$\mathrm{FS} = \frac{M_s * Y_{Medial}}{I} + \frac{P_s}{A}$$

(M_s – bending moment (N-m) on the neck cross-section using measured femoral neck length (m) and body weight (N), P_s – axial load on the neck cross-section using body weight (N), I – the cross-sectional moment of inertia at the NN (m^4), A – cross-sectional area of the NN (m^2), Y_{medial} – the perpendicular distance between the medial surface and the neutral axis (m)). Detailed derivation of the formulas to calculate the FS can be found in the Supplementary Note 1.

2.1.4. Fractures

Fracture history was assessed in the third phase of the study at a mean age of 9.85 (± 0.34) years using questionnaires administrated to the parents. It inquired fractures occurring since birth. In the present study, BMD parameters and femoral stress were studied in relation to incident fractures, occurring after the age of the DXA scan. However, fractures occurring since birth were also included in the sensitivity analysis, as if there is an inadequate bone modeling response, it might probably be present since birth.

2.2. Statistical analyses

Association between incident fracture and standardized TBLH-BMD, FN-BMD, NN-BMD or FS of the participants was evaluated in a Cox regression model adjusted for sex, ethnicity, age, weight and LMF. Also, association between incident fracture and BMD parameters was evaluated in models additionally adjusted for height (as recommended by the ISCD guidelines) [37]. The association between incident fracture and FS was evaluated in the models additionally adjusted for the site-specific BMD parameters (TBLH-, FN- and NN-BMD) to assess effect independence. The same analyses were conducted for the BMD parameters/FS and fractures occurring since birth in a logistic regression model and using already described adjustment(s). Furthermore, sensitivity analyses were conducted as follows: 1) Analysis adjusting for a previous fracture (prior to the age of DXA); 2) Analysis excluding children who sustained multiple fractures after the age of DXA (*N* = 1829); 3) Analysis adjusting for number of hours per day spent playing outside and sport participation; 4) Analysis adjusting for socio-economic status (maternal education level and net household income). To avoid loss of power due to missing data for socio-economic (4.7–8.3%) or physical activity variables (5.0–16.0%), multiple imputation based on the Markov Chain Monte Carlo method was performed. Five imputed datasets were created and pooled effect estimates calculated. The associations between fractures and bone variables are described as hazard ratios (HRs) and 95% confidence intervals (CI) for Cox regression models. Pearson correlations between the FS and the different BMD parameters were also calculated. Statistical significance threshold was set at p-value ≤ 0.025 after Bonferroni correction for multiple-testing (p-value ≤ 0.05/k; k = 2, based on two main hypotheses: bone mineral density against bone geometry in prediction of incident fractures in children). The variation inflation factor (VIF) was estimated for all the models to assess potential multicollinearity. SPSS Statistics version 21 (IBM Corp, New York, USA) was used in all the analysis.

2.2.1. Non-response analysis

To assess a probable selection bias in our analyses, baseline characteristics (i.e. sex, ethnicity, age, weight, height, LMF and TBLH-BMD) of the 1840 children included in our study were compared to: 1) 2729 children who did not have data available for FN-BMD, NN-BMD and/or FS; 2) 1691 children who did not have fracture data available, 3) 1264 children who were lost in follow-up.

3. Results

Of 1840 children (945 girls and 895 boys) with valid total body and hip DXA scans at a mean age of 6.01 (± 0.45) years, 139 (7.6%) sustained at least one fracture over the following 4 years (Table 1). As previously reported [13], out of 139 reported fractures, 57% were localized in arm or wrist, 12% in leg or ankle, 30% were of other localizations, while 1% did not have information on localization. Only 11 children (7.9%) reported more than one fracture during the follow-up period. In our study, children of European background were the majority (1614, 87.7%), followed by children of African (136, 7.4%) and Asian (90, 4.9%) background. Information about the total number of fractures (occurring since birth) together with their localization and severity in the Generation R Study has been described elsewhere [13]. Non-response analyses showed that Generation R participants not included in our study were on average older, heavier, taller, had higher TBLH-BMD and lower LMF, also the study population comprised a higher proportion of children of European background as compared to those not included in this study (Supplementary Table 1).

In our study population, there were no significant differences in the percentages of boys (7.2%) and girls (7.9%) who sustained a fracture during follow-up (p-value = 0.52). Although the percentage of children from European background who fractured (8.0%) was almost two times higher than the percentage of children from Asian (4.4%) or African (4.4%) background, no significant differences in the proportions were detectable (p-value = 0.06), probably due to the low number of non-European children included (Table 1). Weight, height or LMF of children, at the DXA date, did not differ significantly between the children that fractured during follow-up and those who did not. However, children who did not sustain a fracture had significantly higher BMD at all skeletal sites (TBLH-BMDmean_difference = 0.01 g/cm^2, 95% CI 0.002–0.02, p-value = 0.011; FN-BMD mean_difference = 0.02 g/cm^2, 95% CI 0.01–0.04, p-value = 0.003; NN-BMDmean_difference = 0.02 g/cm^2, 95% CI 0.01–0.02, p-value = 0.001) and significantly lower FS (FSmean_difference = 0.003 MPa, 95% CI 0.001–0.006, p-value = 0.018) **(**Table 1**)**.

Further adjustment for sex, ethnicity, age, weight and LMF, resulted in ~1.3 increase risk of incident fracture per SD decrease in TBLH-BMD (HR: 1.35, 95% CI 1.05–1.74, p-value = 0.021, VIF < 3.4); FN-BMD (HR: 1.31, 95% CI 1.09–1.58, p-value = 0.005, VIF < 2.4) and NN-BMD (HR: 1.39, 95% CI 1.14–1.68, p-value = 0.001, VIF < 2.4) **(**Table 2**)**. Additional adjustment for height resulted in negligible changes in effect size estimates (data not shown). Also, every SD

Table 1
Descriptive characteristics of the study sample; N – sample size, SD – standard deviation, LMF – lean mass fraction, TBLH-BMD – total body less head bone mineral density, FN-BMD – femoral neck BMD, NN-BMD – narrow neck BMD, FS – femoral stress, N/A – not applicable.

N = 1840	Fracture (139) Mean (SD)	No_Fracture (1701) Mean (SD)	p-Value ΔFracture
Sex[§]			
Females (*N* = 945, 51.4%)	75 (7.94%)	870 (92.06%)	0.52
Males (*N* = 895, 48.6%)	64 (7.15%)	831 (92.85%)	
Ethnicity[§]			
European (*N* = 1614, 87.7%)	129 (7.99%)	1485 (92.01%)	0.06
Asian (*N* = 90, 4.9%)	4 (4.44%)	86 (95.56%)	
African (*N* = 136, 7.4%)	6 (4.41%)	130 (95.59%)	
Age (years)	5.94 (0.31)	6.02 (0.46)	**0.007**
Weight (kg)	22.22 (3.52)	22.63 (3.63)	0.20
Height (m)	1.18 (0.05)	1.19 (0.06)	0.38
LMF (%)	72.57 (4.80)	72.16 (4.83)	0.34
TBLH-BMD (g/cm^2)	0.532 (0.05)	0.543 (0.05)	**0.011**
FN-BMD (g/cm^2)	0.678 (0.09)	0.701 (0.09)	**0.003**
NN-BMD (g/cm^2)	0.358 (0.05)	0.374 (0.05)	**0.001**
FS (MPa)	0.094 (0.02)	0.090 (0.02)	**0.018**

[§] = Count (percentage), significant p-values (p-value ≤ 0.05) are presented in bold.

Table 2
Association between bone mineral density (BMD) parameters and FS measured in 1840 children at 6.01 (± 0.45) years of age and incident fracture risk in the following 4 years. Table presents hazard ratios (HRs) with 95% confidence intervals (CI) and *p*-values for incident fractures per standard deviation (SD) decrease in BMD and SD increase in FS calculated by Cox regression model corrected for sex, ethnicity, age, weight and LMF; Z – standardized values, TBLH-BMD – total body less head bone mineral density (g/cm^2), FN-BMD – femoral neck bone mineral density (g/cm^2), NN-BMD – narrow neck bone mineral density (g/cm^2), FS – femoral stress (MPa), LMF- lean mass fraction, N/A – not applicable.

Variables	HR FS (95% CI)	p-Value	HR BMD (95% CI)	p-Value
Z_TBLH-BMD	N/A	N/A	1.35 (1.05–1.74)	**0.021**
Z_FN-BMD	N/A	N/A	1.31 (1.09–1.58)	**0.005**
Z_NN-BMD	N/A	N/A	1.39 (1.14–1.68)	**0.001**
Z_FS	1.33 (1.13–1.57)	**0.001**	N/A	N/A
Z_FS (+TBLH-BMD)	1.28 (1.08–1.53)	**0.006**	1.22 (0.94–1.58)	0.15
Z_FS (+FN-BMD)	1.23 (1.00–1.52)	0.05	1.14 (0.91–1.44)	0.25
Z_FS (+NN-BMD)	1.18 (0.94–1.47)	0.15	1.23 (0.96–1.58)	0.11

Significant p-values (p-value ≤0.025) are presented in bold.

increment in FS was associated with 1.33 increase risk of incident fracture (HR: 1.33, 95% CI 1.13–1.57, p-value = 0.001, VIF < 2.10) (Table 2). Additional adjustment for DXA derived BMD measurements resulted in a small attenuation of this association, specifically, HR: 1.28 (95% CI 1.08–1.53, p-value = 0.006, VIF < 3.6) when adjusting for TBLH-BMD and HR: 1.23 (95% CI 1.00–1.52, p-value = 0.05, VIF < 2.6) when adjusting for FN-BMD. In contrast, inclusion of FS as covariate in the survival models, reduced fracture risk per TBLH-BMD- and FN-BMD-SD decrease for 10% and 13% respectively. Adjustment for HSA-derived NN-BMD caused an 11% decrease in the risk of fracture per SD increment in FS (HR: 1.18, 95% CI 0.94–1.47, p-value = 0.15, VIF < 2.7) and per SD decrease in NN-BMD rendering both associations non-significant (Table 2). The analysis including fractures occurring since birth supported the same conclusions (Supplementary Table 2). All the Cox models satisfied proportional hazard assumption. The FS was not significantly correlated with TB-BMD (ρ = −0.01, p-value = 0.68), while it was moderately correlated with FN-BMD (ρ = −0.46) and NN-BMD (ρ = −0.49) (p-value < 0.0001).

Results remained practically unchanged even after adjusting for previous fracture, socio-economic status (maternal educational level and household income) or PA (Supplementary Tables 3, 4 and 5). Likewise, no relevant changes in estimates were found after exclusion of 11 children who sustained more than one fracture during the follow-up.

4. Discussion

The present study examined the association between site specific BMD and FS in 1840 children aged 6.01 years and incident fracture over the following 4 years. Every SD decrease in TBLH-BMD was associated with 1.35 higher risk of fracture after correcting for sex, ethnicity, age, weight and LMF. These results were mirrored by BMD measured at femoral and narrow neck, where every SD decrease in FN- and NN-BMD was associated with 1.31 and 1.39 increase in risk of fractures respectively. Furthermore, every SD increment in FS translated to a 1.33 increased risk of incident fracture. Interestingly, when site-specific BMD was included in the model, the association of BMD and incident fracture became non-significant (p-value > 0.1). Conversely, association between femoral stress and incident fractures remained (borderline) significant after correction for both TBLH- and FN-BMD. Our results show that FS predicts the risk of incident fracture in children partially independent from DXA derived BMD (TBLH- and FN-BMD). These results suggest that in the absence of 3D imaging techniques at the femur, the implementation of structural analysis techniques to evaluate DXA images (i.e., HSA analysis and FS derivation) provide additional insight to the assessment of bone health in the paediatric population. Moreover, FS captures fracture propensity in children at a systemic level, possibly reflecting biomechanical characteristics of the developing skeleton.

Childhood fractures have already been reported as associated with reduced BMD [17–20,38]. In a previous prospective study examining the association between childhood fractures and DXA-derived parameters of bone [1], a 12% increase in risk of fractures was reported per SD decrease in TBLH-BMD. Our results confirm the inverse association between TBLH-BMD and incident fractures, but we find a three times higher risk per TBLH-BMD SD than that reported earlier by Clark et al. [1]. The discrepancies in the results could be due to the difference of age at the DXA assessment (9 years) or the shorter follow-up (2 years) of their study. Nevertheless, we consider that the adjustment for weight (in our study) could play a major role in the reported discrepancies. By this adjustment we are accounting for the fact that heavier children would develop stronger bones, and considering bone characteristics in fracture prediction independently of body size. Already in Clark et al., when evaluating the association of bone area and bone mineral content with fracture, the inclusion of weight in the association models led to a greater inverse association between these variables and fracture risk. Unfortunately, the same analyses are not reported for BMD [1].

The same study evaluated the association between incident fracture risk and humeral geometric and biomechanical properties in 1317 children, finding no evidence for an influence of these parameters on fracture risk. However, these properties were assessed on whole body DXA scans, which provide much lower resolution for measuring site-specific skeletal properties as compared to the proximal femur scans used in our study. Also, they did not focus particularly on the association between fracture risk and stresses developed in the bone. Our study reports a strong association between FS and risk of incident fracture in children. The correlation between femoral stress and risk of fracture has also been reported in an adult population [23].

To our knowledge, this is the first study attempting to determine whether femurs among children suffering incident fractures are geometrically weaker. The FS gathers bone mechanical properties from DXA data that is not evident when expressed as BMD. In contrast to HSA strength parameters (e.g. cross-sectional moment of inertia which measures directly the ability of bone to resist bending), the FS comprises both bending and axial forces of the femoral neck, and therefore, provides a more comprehensive description of the distribution of stress in the proximal femur. Although the stress is derived from measurements assessed at the femoral neck, our results indicate that it is able to capture differences in fracture susceptibility at other sites, i.e. most of the fractures in children are located in the arm or wrist [13]. This suggests that the inadequate bone modeling, if present, may be systemic. Since the skeletal forces are predominantly muscle generated [39], our models were adjusted for LMF and PA (sensitivity analysis) to account for differences in skeletal loads among children [23]. In children, total, leg or appendicular lean mass have a very high correlation, and therefore, the use of any of these parameters for correction in the models did not essentially modify the effect estimates. The fact that the association of stress with fracture was evident even after adjustment for LMF, sport participation and number of hours per day spent playing outside, may support the hypothesis that the FS can be capturing aspects of inadequate bone modeling in response to skeletal loads. However, the assessments of PA in our study are crude (questionnaire-based) and may not fully represent the magnitude, frequency and duration the bones are exposed to loading; therefore, we cannot fully discard that PA patterns are influencing our findings.

The Generation R Study is well-suited to investigate the determinants of paediatric bone health as participants have a narrow age range, live in the same geographical area and are followed up within one research center using the same DXA device. However, our study has also some limitations. The proximal femur scanning is currently not recommended by ISCD for the assessment of paediatric bone health [40]. However, the ISCD recognizes that data used for this recommendation was of limited size and only fair quality [40]. As this study comprises healthy children, we are restricted by the amount of radiation exposure permitted to perform repeated measurements within a short time frame. Therefore, it was not possible to determine the coefficient of variation for this measurement. However, it can be high especially in growing children. Despite the possible drawbacks when using paediatric hip DXA scans, the measurements derived from them have been highlighted as important for understanding the influence of mechanical loading on the hip development and bone health in general during childhood [41]. Our findings, together with the findings of Medina-Gomez et al. [25], conducted in a well powered setting, underscore the utility of hip DXA scans in the field of paediatric bone health. During the follow-up of our study, some participants could have entered puberty, a period of pronounced hormonal changes, growth and increase in bone accrual in children [42]. For instance, it is known that during the pubertal growth spurt and early adolescence, fracture incidence in children shows a steep rise [2,43]. Also, prior to the occurrence of puberty, during the mid-childhood growth spurt, secretion of adrenal androgens might affect body composition [44]. Both of these events could potentially influence the process of bone accrual and thus our results. Hence, due to the critical changes occurring during puberty and narrow age range of the Generation R Study, our findings may not be generalizable to children outside the studied age range. In addition, information on fractures was collected from questionnaires, in only 39.2% of the participants, and not radiographically confirmed, which could have resulted in some degree of recall bias. Furthermore, FS is derived from HSA measurements. Even though HSA is a well-established methodology for the measurement of structural geometry of the proximal femur, it remains a two-dimensional assessment of a 3D structure. Some of the underlying assumptions about trabecular/cortical bone proportions and degree of mineralization differ between children and adults, potentially leading to less precise measurements [45]. However, even if measurement errors were introduced, we would expect them to be systematically distributed across the whole sample having low implications in the differences reported here. LMF was used as a proxy of muscle force. Although lean mass was shown to be highly correlated with pQCT assessed muscle cross-sectional area, this was reported in children of a narrow age range (9–12 years) and should be further investigated [26]. Despite sensitivity analysis and number of included confounders, residual confounding cannot be discarded. For instance, hip DXA scans were performed only in approximately half of the participants and differences in baseline characteristics between the evaluated children and these with missing data were found. Also, 1264 children were lost to follow-up for unknown reasons, and thus, selection bias cannot be ruled out in our study.

5. Conclusions

This is the first prospective study showing that the HSA-derived femoral stress, which integrates the stress distribution of the femur in relation to the ground, joint and muscle forces acting on the femur, actually constitutes the biomechanical assessment that captures fracture propensity in children partially independent from DXA derived BMD. In assessment of paediatric bone health, DXA derived measurements are not providing complete picture and should be accompanied with biomechanical bone parameters. The femoral stress suggests differential bone modeling adaptations to mechanical stimuli in the developing bones of children; which are plausibly controlled by genetic, environmental, and hormonal interactions subject to interventions guided to identify and prevent fracture susceptibility. We believe that our findings demonstrate the utility of hip DXA scans in the field of paediatric bone health and fracture risk assessment.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2019.02.018.

Declarations of interest

We want to draw the attention of the Editor that one of the co-authors - Thomas J. Beck is the owner of the company Beck Radiological Innovations. Besides this, we are not aware of other conflicts of interest associated with the publication.

Acknowledgements

We gratefully acknowledge the contribution of children and parents, general practitioners, hospitals, midwives and pharmacies in Rotterdam who participate in the Generation R Study. We would also like to thank Stanislav Grgic for helping in the generation of the graphical aids included in this manuscript.

Funding sources

The general design of Generation R Study is made possible by financial support from The Erasmus Medical Center, Rotterdam, The Erasmus University Rotterdam, The Netherlands Organization for Health Research and Development (ZonMw), The Netherlands Organisation for Scientific Research (NWO), The Ministry of Health, Welfare and Sport. Co-authors of this manuscript are supported by additional grants from The Netherlands Organization for Health (ZonMw 907.00303, ZonMw 916.10159, ZonMw VIDI 016.136.361 to V.W.V.J., and ZonMw VIDI 016.136.367 to F.R. and C.M-G).

References

[1] E.M. Clark, A.R. Ness, N.J. Bishop, J.H. Tobias, Association between bone mass and fractures in children: a prospective cohort study, J Bone Min. Res. 21 (2009) 1489–1495, https://doi.org/10.1359/jbmr.060601.Association.
[2] S. Khosla, J.L.I. Melton, M.B. Dekutoski, S.J. Achenbach, A.L. Oberg, B.L. Riggs, Incidence of childhood distal forearm fractures over 30 years: a population based study, JAMA. 290 (2003) 1479–1485, https://doi.org/10.1001/jama.290.11.1479.
[3] D. Jerrhag, M. Englund, I. Petersson, V. Lempesis, L. Landin, M.K. Karlsson, B.E. Rosengren, Increasing wrist fracture rates in children may have major implications for future adult fracture burden: a registry study involving 2.8 million patient years based on the Skåne region of Sweden, 1999–2010, Acta Orthop. 87 (2016) 296–300, https://doi.org/10.3109/17453674.2016.1152855.
[4] J.C.Y. Lee, K.T.S. Tung, T.M.H. Li, F.K.W. Ho, P. Ip, W.H.S. Wong, C.B. Chow, Fall-related attendance and associated hospitalisation of children and adolescents in Hong Kong: a 12-year retrospective study, BMJ Open 7 (2017), https://doi.org/10.1136/bmjopen-2016-013724.
[5] M. Fuchs, A. Losch, E. Noak, K. Stürmer, Long-term results after conservative treatment of pediatric femoral shaft fractures, Orthopade. 32 (2003) 1136–1142, https://doi.org/10.1007/s00132-003-0502-6.
[6] P.S. Yuan, M.E. Pring, T.P. Gaynor, S.J. Mubarak, P.O. Newton, Compartment syndrome following intramedullary fixation of pediatric forearm fractures, J. Pediatr. Orthop. 24 (2004) 370–375.
[7] K. Thandrayen, S.A. Norris, J.M. Pettifor, Fracture rates in urban South African children of different ethnic origins: The Birth to Twenty Cohort, Osteoporos. Int. 20 (2009) 47–52, https://doi.org/10.1007/s00198-008-0627-x.
[8] T.A.L. Wren, J.A. Shepherd, H.J. Kalkwarf, B.S. Zemel, J.M. Lappe, S. Oberfield, F.J. Dorey, K.K. Winer, V. Gilsanz, Racial disparity in fracture risk between white and nonwhite children in the United States, J. Pediatr. 161 (2012) 1035–1040, https://doi.org/10.1016/j.jpeds.2012.07.054.
[9] R.J. Moon, N.C. Harvey, E.M. Curtis, F. de Vries, T. van Staa, C. Cooper, Ethnic and geographic variations in the epidemiology of childhood fractures in the United Kingdom, Bone. 85 (2016) 9–14, https://doi.org/10.1016/j.bone.2016.01.015.
[10] C. Cooper, E.M. Dennison, H.G. Leufkens, N. Bishop, T.P. van Staa, Epidemiology of childhood fractures in Britain: a study using the general practice research database, J. Bone Miner. Res. 19 (2004) 1976–1981, https://doi.org/10.1359/jbmr.040902.
[11] L. Rennie, C.M. Court-Brown, J.Y.Q. Mok, T.F. Beattie, The epidemiology of fractures in children, Injury. 38 (2007) 913–922, https://doi.org/10.1016/j.injury.2007.01.036.
[12] T. Christoffersen, L.A. Ahmed, A. Winther, O.A. Nilsen, A.S. Furberg, G. Grimnes, E. Dennison, J.R. Center, J.A. Eisman, N. Emaus, Fracture incidence rates in Norwegian children, The Tromsø Study, Fit Futures, Arch. Osteoporos. 11 (2016) 1–8, https://doi.org/10.1007/s11657-016-0294-z.
[13] O. Grgic, K. Chung, E. Shevroja, K. Trajanoska, A.G. Uitterlinden, E.B. Wolvius, F. Rivadeneira, C. Medina-Gomez, Fractures in school age children in relation to sex and ethnic background: The Generation R Study, Bone. 121 (2019), https://doi.org/10.1016/j.bone.2019.01.019.
[14] D. Chalhoub, P.M. Cawthon, K.E. Ensrud, M.L. Stefanick, D.M. Kado, R. Boudreau, S. Greenspan, A.B. Newman, J. Zmuda, E.S. Orwoll, J.A. Cauley, Risk of nonspine fractures in older adults with sarcopenia, low bone mass, or both, J. Am. Geriatr. Soc. 63 (2015) 1733–1740, https://doi.org/10.1111/jgs.13605.
[15] N.C. Wright, E.R. Hooker, C.M. Nielson, K.E. Ensrud, S.L. Harrison, E.S. Orwoll, E. Barrett-Connor, for T.O.F. in M. (MrOS) S.R. Group, The epidemiology of wrist fractures in older men: the Osteoporotic Fractures in Men (MrOS) study, Osteoporos. Int. 29 (2018) 859–870, https://doi.org/10.1007/s00198-017-4349-9.
[16] M.L. Gourlay, V.S. Ritter, J.P. Fine, R.A. Overman, J.T. Schousboe, P.M. Cawthon, E.S. Orwoll, T.V. Nguyen, N.E. Lane, S.R. Cummings, D.M. Kado, J.A. Lapidus, S.J. Diem, K.E. Ensrud, for the O.F. in M. (MrOS) S. Group, Comparison of fracture risk assessment tools in older men without prior hip or spine fracture: the MrOS study, Arch. Osteoporos. 12 (2017) 91, , https://doi.org/10.1007/s11657-017-0389-1.
[17] M. Deqiong, J. Graeme, The association between bone mineral density, metacarpal morphometry, and upper limb fractures in children: a population-based case-control study, J. Clin. Endocrinol. Metab. 88 (2003) 1486–1491, https://doi.org/10.1210/jc.2002-021682.
[18] A. Goulding, R. Cannan, S.M. Williams, E.J. Gold, R.W. Taylor, Bone mineral density in girls with forearm fractures, J. Bone Miner. Res. 13 (1998) 143–148, https://doi.org/10.1359/jbmr.1998.13.1.143.
[19] J. Schalamon, G. Singer, G. Schwantzer, Quantitative ultrasound assessment in children with fractures, J. Bone Miner. Res. 19 (2004) 1276–1279, https://doi.org/10.1359/JBMR.040401.
[20] E. Clark, J. Tobias, A. Ness, Association between bone density and fractures in children: a systematic review and meta-analysis, Pediatrics. 117 (2006) e291–e297, https://doi.org/10.1542/peds.2005-1404.
[21] P.A.Æ.R. Rizzoli, Bone strength and its determinants, Oste. 14 (2003) 13–18, https://doi.org/10.1007/s00198-002-1345-4.
[22] P. Ammann, R. Rizzoli, J. M., J. B., Bone density and shape as determinants of bone strength in IGF-I and/or pamidronate-treated ovariectomized rats, Osteoporos. Int. 6 (1996) 219–227, https://doi.org/10.1007/BF01622738.

[23] C.J. Hamilton, S.A. Jamal, T.J. Beck, A.S. Khaled, J.D. Adachi, J.P. Brown, K.S. Davison, Heterogeneity in skeletal load adaptation points to a role for modeling in the pathogenesis of osteoporotic fracture, J. Clin. Densitom. 17 (2014) 170–176, https://doi.org/10.1016/j.jocd.2013.02.003.

[24] H.M. Frost, Bone's Mechanostat: a 2003 Update, Anat. Rec. Part A. 275A (2003) 1081–1101, https://doi.org/10.1002/ar.a.10119.

[25] C. Medina-Gomez, D.H. Heppe, J.-L. Yin, K. Trajanoska, A.G. Uitterlinden, T.J. Beck, V.W. Jaddoe, F. Rivadeneira, Bone mass and strength in school age children exhibit sexual dimorphism related to differences in lean mass: the Generation R Study, J. Bone Miner. Res. 31 (2016) 1099–1106, https://doi.org/10.1002/jbmr.2755.

[26] M.A. Petit, T.J. Beck, J. Shults, B.S. Zemel, B.J. Foster, M.B. Leonard, Proximal femur bone geometry is appropriately adapted to lean mass in overweight children and adolescents, Bone. 36 (2005) 568–576, https://doi.org/10.1016/j.bone.2004.12.003.

[27] T. Beck, C. Ruff, K. Warden, W. Scott, G. Rao, Predicting femoral neck strength from bone mineral data. A structural approach, Investig. Radiol. 25 (1990) 6–18.

[28] M. Kooijman, C.J. Kruithof, C.M. van Duijn, L. Duijts, O.H. Franco, M. Ijzendoorn, J. Jongste, The Generation R Study: design and cohort update 2017, Eur. J. Epidemiol. 31 (2016) 1243–1264, https://doi.org/10.1007/s10654-010-9516-7.

[29] M. Alders, Classification of the population with a foreign background in the Netherlands, Meas. Mismeasure Popul. Stat. Use Ethn. Racial Categ. Multicult. Soc. Centre d'Etudes et de Recherches Internationales (CERI) and the Institut National d'Etudes D emographiques (INED), Paris, 2001, pp. 1–14.

[30] A.I. WIjtzes, S.H. Bouthoorn, W. Jansen, O.H. Franco, A. Hofman, W.V.V. Jaddoe, H. Raat, Sedentary behaviors, physical activity behaviors, and body fat in 6-year-old children: the Generation R Study, Int. J. Behav. Nutr. Phys. Act. 11 (2014) 1–10, https://doi.org/10.1186/s12966-014-0096-x.

[31] CBS, Standaard Onderwijsindeling 2014 (/15) (2014) 2006.

[32] R. Schaart, M.B. Moens, S. Westerman, The Dutch Standard Classification of Education, Statistics Netherlands, Voorburg/Heerlen, 2008.

[33] D.H. Heppe, C. Medina-Gomez, A. Hofman, O.H. Franco, F. Rivadeneira, W.V.V. Jaddoe, Maternal first-trimester diet and childhood bone mass: the Generation R Study, Am. J. Clin. Nutr. 98 (2013) 224–232, https://doi.org/10.3945/ajcn.112.051052.

[34] E.M. Lewiecki, C.M. Gordon, S. Baim, N. Binkley, J.P. Bilezikian, D.L. Kendler, D.B. Hans, S. Silverman, N.J. Bishop, M.B. Leonard, M.L. Bianchi, H.J. Kalkwarf, C.B. Langman, H. Plotkin, F. Rauch, B.S. Zemel, Special report on the 2007 adult and pediatric Position Development Conferences of the International Society for Clinical Densitometry, Osteoporos. Int. 19 (2008) 1369–1378, https://doi.org/10.1007/s00198-008-0689-9.

[35] T.J. Beck, Extending DXA beyond bone mineral density: understanding hip structure analysis, Curr. Osteoporos. Rep. 5 (2007) 49–55. https://doi.org/10.1007/s11914-007-0002-4.

[36] H. Debevec, D. Pedersen, A. Iglič, M. Daniel, One-legged stance as a representative static body position for calculation of hip contact stress distribution in clinical studies, Hum. Kinet. 26 (2010) 522–525.

[37] E.M. Lewiecki, N. Binkley, S.L. Morgan, C.R. Shuhart, B.M. Camargos, J.J. Carey, C.M. Gordon, L.G. Jankowski, J.K. Lee, W.D. Leslie, Best practices for dual-energy X-ray absorptiometry measurement and reporting: International Society for Clinical Densitometry Guidance, J. Clin. Densitom. 19 (2016) 127–140, https://doi.org/10.1016/j.jocd.2016.03.003.

[38] E.M. Clark, The epidemiology of fractures in otherwise healthy children, Curr. Osteoporos. Rep. 12 (2014) 272–278, https://doi.org/10.1007/s11914-014-0227-y.

[39] F. Rauch, E. Schoenau, The developing bone: slave or master of its cells and molecules, Pediatr. Res. 50 (2001) 309–314, https://doi.org/10.1203/00006450-200109000-00003.

[40] C.M. Gordon, L.K. Bachrach, T.O. Carpenter, N. Crabtree, G. El-Hajj Fuleihan, S. Kutilek, R.S. Lorenc, L.L. Tosi, K.A. Ward, L.M. Ward, H.J. Kalkwarf, Dual energy X-ray absorptiometry interpretation and reporting in children and adolescents: the 2007 ISCD pediatric official positions, J. Clin. Densitom. 11 (2008) 43–58, https://doi.org/10.1016/j.jocd.2007.12.005.

[41] J.M. Eichenberger Gilmore, C.A. Pauley, T.L. Burns, J.C. Torner, E.M. Letuchy, K.F. Janz, M.C. Willing, S.M. Levy, A hip analysis protocol for pediatric bone densitometry: The Iowa Bone Development Study, J. Clin. Densitom. 13 (2010) 361–369, https://doi.org/10.1016/J.JOCD.2010.06.003.

[42] G. Saggese, G.I. Baroncelli, S. Bertelloni, Puberty and bone development, Best Pract. Res. Endocrinol. Metab. 16 (2002) 53–64, https://doi.org/10.1053/beem.2002.0180.

[43] L.A. Landin, Fracture patterns in children. Analysis of 8682 fractures with special reference to incidence, etiology and secular changes in a Swedish urban population 1950–1979, Acta Orthop. Scand. (Suppl. 202) (1983) 1–109, https://doi.org/10.3109/17453678309155630.

[44] J.M. Tanner, N. Cameron, Investigation of the mid-growth spurt in height, weight and limb circumferences in single-year velocity data from the London, 1966-67 growth survey, Ann. Hum. Biol. 7 (1980) 565–577, https://doi.org/10.1080/03014468000004681.

[45] M.R. Forwood, D.A. Bailey, T.J. Beck, R.L. Mirwald, A.D.G. Baxter-Jones, K. Uusi-Rasi, Sexual dimorphism of the femoral neck during the adolescent growth spurt: a structural analysis, Bone. 35 (2004) 973–981, https://doi.org/10.1016/J.BONE.2004.06.005.