



The long-term impact of very preterm birth on adult bone mineral density

Li Feng Xie^a, Nathalie Alos^{a,b}, Anik Cloutier^a, Chanel Béland^a, Josée Dubois^{a,c},
Anne Monique Nuyt^{a,b}, Thuy Mai Luu^{a,b,*}

^a Research Center, Centre Hospitalier Universitaire Sainte-Justine, 3175 Chemin de la Côte-Ste-Catherine, Montreal, Quebec H3T 1C5, Canada

^b Department of Pediatrics, Centre Hospitalier Universitaire Sainte-Justine, 3175 Chemin de la Côte-Ste-Catherine, Montreal, Quebec H3T 1C5, Canada

^c Department of Radiology, Centre Hospitalier Universitaire Sainte-Justine, 3175 Chemin de la Côte-Ste-Catherine, Montreal, Quebec H3T 1C5, Canada



ARTICLE INFO

Keywords:

Prematurity
Bone health
Osteopenia
Bone mineral density

ABSTRACT

Introduction: Preterm infants are at increased risk of osteopenia of prematurity due to insufficient bone mineral accretion. Data on long term effects of prematurity on bone health are conflicting. This study aimed to compare bone mineral density (BMD) in young adults born very preterm and full-term controls and to examine factors associated with long-term bone health.

Methods: This observational cross-sectional study enrolled 101 young adults (18–29 years) born < 29 weeks of gestation and 95 sex- and age-matched full-term controls. Participants underwent dual-energy X-ray absorptiometry to measure areal BMD and body composition. Generalized estimated equations were used to compare groups adjusting for height Z-score, lean body mass and fat mass.

Results: Adults born preterm were shorter and lighter than full-term controls. Areal BMD was reduced at the lumbar spine, the femoral neck and whole body in the preterm versus full-term group, but after adjustment, areal BMD Z-score was only significantly lower at the femoral neck by -0.3 unit (95% confidence interval -0.6 to -0.0). Low BMD (Z-score ≤ -1 standard deviation) at any site was observed in 53% of adults born preterm versus 28% of full-term controls, but this was not statistically significantly different. We did not identify any neonatal factors associated with lower BMD within the preterm group.

Conclusions: Very preterm birth is associated with lower areal BMD at the femoral neck in young adulthood, even after accounting for body size. Whether this will translate into higher risk of osteoporotic fractures later in life remains unknown.

1. Introduction

Nearly one-third of infants born < 1500 g develop bone mineral disease of prematurity, a clinical condition characterized by a significant reduction in bone mineral content without radiological signs. The lower the gestational age (GA), the higher the risk (Sharp, 2007; Nallagonda et al., 2017; Done, 2012). Worldwide, 1 in 10 babies are born preterm before 37 weeks of gestation with 1–2% born very (28 to < 32 weeks' GA) or extremely (< 28 weeks' GA) preterm (Goldenberg et al., 2008). Preterm birth occurs during the third trimester of pregnancy when placental transfer of calcium, magnesium and phosphorus to the foetus is particularly important to foster bone mineralization (Sharp, 2007). However, neonates born preterm are rather exposed to lower amount of minerals from parenteral nutrition

and limited enteral intake. In addition, restricted spontaneous movements *ex utero* reduce mechanical stimulation (Sharp, 2007). Prematurity-related conditions such as pre-eclampsia, sepsis, and lung disease, all known to be associated with high levels of oxidative stress, along with treatments like postnatal steroids or diuretics further contribute to the pathophysiology of metabolic bone disease (Embleton and Wood, 2014; Figueras-Aloy et al., 2014; Bowden et al., 1999; Chan et al., 2008; Viswanathan et al., 2014; Torres-Cuevas et al., 2017). These events can permanently alter programming of bone growth and mineralization (Cooper et al., 2000). Altogether, preterm birth may affect attainment of peak bone mass thus increasing later risk for osteoporosis.

Studies examining the impact of preterm birth on long-term bone health have yielded diverging results. Both Hovi (Hovi et al., 2009) and

Abbreviations: aBMD, areal bone mineral density; BMI, body mass index; CA, corrected age; CI, confidence interval; GA, gestational age; IQR, interquartile range; SD, standard deviation; 25OHD, 25-hydroxy-cholecalciferol

* Corresponding author at: Department of Pediatrics and Research Center, CHU Sainte-Justine, 3175 Chemin de la Côte-Ste-Catherine, Montreal, Quebec, H3T 1C5, Canada.

E-mail address: thuy.mai.luu@umontreal.ca (T.M. Luu).

<https://doi.org/10.1016/j.bonr.2018.100189>

Received 15 August 2018; Received in revised form 5 December 2018; Accepted 11 December 2018

Available online 12 December 2018

2352-1872/ © 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Balasuriya (Balasuriya et al., 2017) showed that young adults born preterm with birth weight < 1500 g had lower areal bone mineral density (aBMD) relative to term controls, which concurred with findings from Fewtrell who compared participants born preterm to population norms (Fewtrell et al., 2009). In contrast, others did not find any difference (Weiler et al., 2002; Erlandson et al., 2011; Dalziel et al., 2006; Breukhoven et al., 2011). Furthermore, very few studies have specifically examined perinatal factors that could be associated with aBMD in young adults born preterm.

We aimed to assess aBMD in young adults aged 18–29 years born at < 29 weeks in comparison to controls born full-term. We further sought to investigate perinatal factors associated with bone health. We postulated that in this group of adults born very preterm, lower aBMD would be observed in relation to term controls. In addition, indicators of neonatal illness would be linked to reduced aBMD among the very preterm group.

2. Methods

2.1. Study design and participants

This research is part of a larger observational cross-sectional study aiming to comprehensively assess several body systems in young adults born very preterm. Approval from our Research Ethics Board was obtained. All participants provided informed written consent.

Participants were traced and recruited from a list of 485 patients born below 29 weeks' gestational age between 1987 and 1996 at Centre Hospitalier Universitaire Sainte-Justine, Montreal, Canada, who had survived to 18 months corrected age. Currently pregnant women and individuals with severe neurosensory impairment precluding test completion were excluded. The 83 recruited participants were comparable to the 402 non-participants in terms of GA, birth weight, small for gestational age, sex, oxygen use at 36 weeks' GA, severe brain injury, severe retinopathy of prematurity and duration of neonatal hospitalization. We further recruited 18 additional participants born at or below 29 weeks in the province of Quebec through targeted advertisement to individuals born preterm. Among the 101 young adults born preterm, 95 were matched on age (± 3 years old) and sex to a control born full-term selected from friends or siblings (Fig. 1 – Supplemental material).

2.2. Neonatal and general health data

Neonatal characteristics were extracted from medical charts. Birth weight of infants born preterm was converted to percentile using Hadlock growth curve (Hadlock et al., 1991). For full-term controls, we used Kramer's Canadian reference for birth weight for GA (Kramer et al., 2001). Small for gestational age was defined as a birth weight below the 10th percentile. Subsequent weight measures were converted to Z-scores using the Clinical Actual Age Percentile and Z-score Calculator based on Fenton Growth chart if post-menstrual age was equal or < 50 weeks (Fenton and Kim, 2013) or World Health Organization Growth Charts if post-menstrual age was > 50 weeks (World Health Organization, 2006).

Participants completed questionnaires on past medical history, current medication use, smoking, and level of physical activity to estimate cardiorespiratory fitness (Trivel et al., 2004). An intake of dietary habits over the past year was used to obtain average daily intake of calcium, vitamin D, and proteins (Shatenstein et al., 2005; Shatenstein et al., 2010). More specifically, we inquired about long bone and spine fractures. Because we were interested in significant fracture history likely to be associated with fragile bones (Shepherd et al., 2015), we excluded sites such as fingers, toes, clavicles, skull and ribs. Parents reported on their estimated height through a mailed questionnaire to calculate participant potential height (average of both parental heights plus 13 cm for men and minus 13 cm for women). We considered that the participant had reached potential height if current

height was within the genetic target ± 8 cm (Tanner et al., 1970).

Finally, serum total 25-hydroxy-cholecalciferol (25OHD) assay and C reactive protein (CRP) were measured in all participants given their role in the development of chronic bone diseases.

2.3. Dual-energy X-ray absorptiometry and anthropometry

Dual-energy X-ray absorptiometry (DXA scan, Lunar Prodigy; GE Medical System) was used to determine lean body mass, body fat percentage, body fat in Z-score, bone mineral content (BMC) and aBMD at the lumbar spine (L2-L4), the femoral neck and for whole body. The precision of our method for the Prodigy Lunar GE machine was validated using a spine phantom; in vivo precision for lumbar spine BMD ranged from 0.003 to 0.01 g/cm². The Lunar Prodigy system provided BMD Z-scores for the corresponding age and gender from the built-in reference population. For the purpose of our study, low aBMD was defined as a Z-score ≤ -1.0 SD given that we were interested in minor dysfunction prior to the onset of pathological diseases. In addition, we estimated volumetric density (BMD_{vol}) at the lumbar spine to account for bone size using the following Kroger formula: $aBMD \times [4/(\pi \times \text{width of measurement area in lumbar spine})]$ (Kroger et al., 1995).

Physical examination was limited to height and weight measurement in triplicate. Height in Z-score was obtained using World Health Organization growth standards (World Health Organization, 2006). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

2.4. Statistical analysis

Descriptive statistics were summarized as means and 95% confidence intervals (CI), medians and interquartile range (IQR) or proportions. Given the matched study design, between-group comparisons for the 95 pairs were performed with dependent Student's *t*-test for continuous variables and McNemar test for categorical variables. Within pair comparisons of aBMD Z-scores with adjustment for adult height Z-score, lean body mass, and fat mass were done with generalized estimating equations. To examine factors associated with low aBMD in young adults born preterm ($n = 101$), independent *t*-test, Chi-square or Mann-Whitney *U* test were used. Given the exploratory nature of the latter analyses, we did not correct for multiple testing. All analyses were carried with IBM SPSS 24 (North Castle, NY, USA).

3. Results

3.1. Neonatal characteristics

Table 1 displays neonatal characteristics of our study population. Mean GA and birth weight were 27.1 weeks and 957 g for the preterm group; 44% were male. Almost half of preterm infants were exposed to antenatal steroids, a similar proportion had received surfactant, and 28% received postnatal steroids. Parenteral nutrition was given for a median of 17 days (interquartile range (IQR): 28, 40). Median length of hospitalization was 83 days (IQR: 66, 108).

3.2. Adult characteristics

Participants were assessed at a mean age of 23 years. Young adults born preterm, as a group, had significantly lower weight, height, and lean body mass than controls (Table 1). Of note, only 83% of preterm participants reached mid-parental height, as compared to 98% of controls. Estimated cardiorespiratory fitness and smoking were reportedly similar between the two groups. Inhaled steroids were used by 7% and 8% individuals born preterm and full-term, respectively. A subgroup of participants ($n = 34$ pairs) had complete dietary data and were comparable to others in terms of age, sex, weight and height. There was no difference in daily calcium and protein intake between participants

Table 1
Neonatal characteristics and current health for the 95 matched pairs.

	Very preterm N = 95	Term N = 95
Neonatal characteristics		
Male sex, n (%)	42 (44)	42 (44)
Gestational age, weeks	27.1 (26.9, 27.4)	39.5 (39.3, 39.8)
Birth weight, g	957 (912, 1002)	3391 (3307, 3472)
Small for gestational age, n (%)	6 (6)	6 (6)
Antenatal steroids, n (%)	41 (44)	0
Surfactant, n (%)	43 (45)	0
Postnatal steroids, n (%)	27 (28)	0
Bronchopulmonary dysplasia, n (%)	35 (37)	0
Necrotizing enterocolitis, n (%)	5 (5)	0
Weight Z-score at discharge	-2.1 (-2.3, -1.8)	NA
Weight at discharge < 10th percentile, n (%)	67/83 (81)	NA
Current health		
Age, year	23.2 (22.8, 23.7)	23.2 (22.8, 23.7)
Weight, kg		
Male	67 (63, 71)*	77 (73, 82)
Female	58 (55, 58)*	65 (61, 68)
Height, cm		
Male	172 (170, 175)*	178 (175, 180)
Female	160 (158, 162)*	166 (164, 167)
Height, Z-score		
Male	-0.6 (-0.9, -0.2)*	0.2 (-0.1, 0.5)
Female	-0.5 (-0.7, -0.2)*	0.4 (0.2, 0.6)
Body mass index, kg/m ²		
Male	22 (21, 24)*	24 (23, 26)
Female	23 (22, 24)	24 (22, 25)
% body fat, Z-scores		
Male	0.7 (-0.2, 1.4)	1.0 (0.1, 1.6)
Female	0.8 (0.6, 1.3)	0.8 (0.5, 1.3)
Lean body mass, kg		
Male	51 (48, 54)*	57 (54, 59)
Female	35 (35, 37)*	39 (38, 41)
Reached potential height, n (%)		
Male	23 (77)*	25 (100)
Female	30 (88)	32 (97)
Smoking, n (%)	22 (23)	17 (18)
Estimated VO _{2max} #, mL/kg/min	43 (41, 48)	46 (45, 51)
25-hydroxyvitamine D, nmol/L	61.5 (55.9, 67.1)	59.6 (54.2, 64.9)

Data expressed as mean (95% confidence interval) unless specified otherwise. #Maximal O₂ consumption (VO_{2max}) estimated using Huet Physical Activity Questionnaire.

NA: Not applicable.

* Means between very preterm and term significantly different at < 0.05.

born preterm and term. Measured serum 25OHD level and the proportion of adults with level below 50 nmol/L was similar between the two groups (preterm: 40%, term: 37%). CRP level was also similar between groups (preterm 2.5 ± 3.3 mg/L, term 2.6 ± 5.7 mg/L).

3.3. Bone mineral density in young adulthood

BMC, aBMD and aBMD z-scores were significantly lower in the preterm group for all measures taken (Table 2). Given the correlation between aBMD z-scores at all sites and height Z-score (Pearson's r between 0.26 and 0.39), lean body mass ($r = 0.25-0.36$), and fat mass ($r = 0.22-0.42$), we adjusted for these three variables; only the difference in aBMD in Z-score at the femoral neck remained significant. We further adjusted aBMD for levels of serum vitamin D and cardiorespiratory fitness, but discerned no additional change in our results (not shown). Moreover, there was no between-group difference in estimated

BMD_{vol} at the lumbar spine. We observed a larger proportion of preterm participants versus full-term controls with low aBMD, but this was only statistically significantly different at the femoral neck once adjusting for body size ($P = 0.028$). When examining number of participants with a Z-score < -2.5 SD, 4 were born preterm and 1 full-term. Finally, past history of long bone and vertebral fractures was similar between the preterm and term groups (preterm: 20%, term: 20%). In addition, fractures were not reportedly more frequent in individuals with low aBMD (preterm: 20%, term: 27%) than in those with normal aBMD (preterm: 20%, term: 18%).

3.4. Characteristics of preterm participants with lower aBMD

We carried out a subgroup analysis for the preterm group ($n = 101$), comparing those with aBMD ≤ -1 SD in any of the three regions in young adulthood ($n = 51$) to those with normal aBMD i.e. a Z-score higher than -1 SD ($n = 50$). As shown in Table 3, we did not identify any neonatal factors associated with lower aBMD.

4. Discussion

Young adults born very preterm had reduced aBMD. This was mostly accounted for by lower adult weight and height in comparison to full-term controls, except at the level of the femoral neck. Our study is unique as it examined a cohort of young adults born at earlier GA (≤ 29 weeks) than what has been previously reported (Hovi et al., 2009; Balasuriya et al., 2017; Fewtrell et al., 2009; Breukhoven et al., 2011; Buttazzoni et al., 2016). In addition, we matched participants by age and sex, using siblings and friends, thus reducing differences in environmental factors such as smoking (correlation of 86% among pairs), physical activity ($r = 0.70$), and vitamin D levels ($r = 0.38$). This facilitated isolation of the effects of very preterm birth. Finally, the collection of complete neonatal history also allowed us to explore indicators of long-term bone health though current study could not identify any specific risk factors.

Our findings confirmed previous research from Hovi et al. and Balasuriya et al. showing lower peak bone mass in young adults born preterm and with birth weights < 1500 g (Hovi et al., 2009; Balasuriya et al., 2017). In the Helsinki Study of Very Low Birth Weight Adults, Hovi et al. examined 144 individuals born between 24 and 36 weeks' GA (mean GA of 29 weeks) and 139 controls born full-term (Hovi et al., 2009). They observed a reduction of 0.51 unit in Z-score at the level of the lumbar spine, 0.56 unit at the femoral neck, and 0.33 unit for whole body in young adults born preterm, which is comparable to our unadjusted results. This difference remained statistically significant only at the lumbar spine and femoral neck after they adjusted for sex, adult height and BMI. Similarly, Balasuriya et al. studied 52 very-low-birth-weight young adults with mean GA of 29 weeks and 75 full-term controls (Balasuriya et al., 2017). Mean difference in aBMD Z-score, adjusted for adult weight and height, was statistically significantly lower at the level of the femoral neck and whole body, but not the lumbar spine. Overall, findings suggest lower than average aBMD Z-scores in young adults born preterm at a time when bone mass accrual should be at its peak. These results may be partly explained by lower adult weight and height in individuals born preterm. Indeed, BMD assessed by DXA scan measures areal density and is thus influenced by bone size. As a result, DXA scan underestimates aBMD in lighter and shorter individuals (Compston et al., 1995). In a young population such as ours, in addition to aBMD, clinicians also need to consider past medical history of fractures to predict future risk of recurrent fractures (Shepherd et al., 2015). Consistent with previous work (Balasuriya et al., 2017), there was no difference between young adults born preterm versus full-term in their previous history of fractures. Unlike Balasuriya et al., we did not distinguish between high- and low-impact injuries. Nevertheless, participants were seen at a relatively young age for osteoporotic fractures, which incidence usually starts rising beyond

Table 2
Bone health in young adults born preterm versus term.

	N pairs	Very preterm	Term	Unadjusted mean difference (95% CI)	Adjusted mean difference (95% CI)#
Lumbar spine					
BMC, g	95	49.9 (47.6, 52.1)	54.6 (52.3, 56.8)	-4.7 (-7.2, -2.1)*	-3.2 (-6.0, -0.4)*
Bone area, cm ²	95	43.6 (41.5, 45.8)	44.7 (43.2, 46.2)	-1.1 (-3.3, 1.1)	-1.1 (-3.5, 1.3)
aBMD, g/cm ²	95	1.16 (1.13, 1.18)	1.21 (1.19, 1.24)	-0.06 (-0.09, -0.03)*	-0.03 (-0.06, 0.00)
aBMD Z-score	95	-0.6 (-0.8, -0.4)	-0.2 (-0.4, 0.0)	-0.4 (-0.7, -0.2)*	-0.2 (-0.4, 0.1)
BMD _{vol} , g/cm ³	95	0.36 (0.35, 0.37)	0.37 (0.35, 0.38)	0 (-0.02, 0.01)	-
Femoral neck					
BMC, g	87	4.5 (4.3, 4.8)	5.2 (5.0, 5.4)	-0.7 (-0.9, -0.5)*	-0.2 (-0.4, -0.1)*
Bone area, cm ²	87	4.5 (4.4, 4.7)	4.8 (4.6, 4.9)	-0.2 (-0.4, -0.1)	0.0 (-0.4, 0.1)
aBMD, g/cm ²	87	1.00 (0.97, 1.03)	1.09 (1.06, 1.12)	-0.09 (-0.13, -0.05)*	-0.05 (-0.08, -0.01)*
aBMD Z-score	87	-0.5 (-0.7, -0.3)	0.1 (0.0, 0.3)	-0.6 (-0.9, -0.4)*	-0.3 (-0.6, -0.0)*
Whole body					
BMC, g	94	2476 (2375, 2577)	2788 (2689, 2887)	-311 (-422, -199)*	-27 (-113, 58)
aBMD, g/cm ²	94	1.14 (1.13, 1.16)	1.19 (1.17, 1.21)	-0.05 (-0.07, -0.02)*	-0.01 (-0.03, 0.01)
aBMD Z-score	94	-0.3 (-0.5, 0.0)	0.3 (0.1, 0.5)	-0.6 (-0.8, -0.3)*	-0.2 (-0.4, 0.1)
aBMD Z-score ≤ -1, n (%)					
Lumbar spine	95	36 (38)	24 (25)		
Femoral neck	87	32 (34)**	14 (16)		
Whole body	94	23 (25)	10 (11)		
Any of the 3 regions	95	50 (53)	27 (28)		

BMC, bone mineral content; aBMD, areal bone mineral density; BMD_{vol}, volumetric BMD; CI, confidence interval.

height Z-score, fat mass and lean mass in g.

* Mean difference between very preterm and term (reference) significantly different from 0 at $p < 0.05$.

** Proportion between very preterm and term significantly different at $p < 0.05$ after adjusting for height Z-score, fat and lean mass.

Table 3
Neonatal factors associated with low aBMD in young adults born preterm.

Neonatal characteristics	Adults with low aBMD N = 51	Adults with normal aBMD N = 50
Male sex, n (%)	26 (51)	19 (38)
Gestational age, weeks	26.9 (26.5, 27.3)	27.2 (26.8, 27.6)
Birth weight, g	949 (847, 1037)	981 (817, 976)
Antenatal steroids, n (%)	22 (48)	18 (36)
Surfactant, n (%)	26 (46)	17 (36)
Postnatal steroids, n (%)	16 (33)	13 (26)
Bronchopulmonary dysplasia, n (%)	22 (45)	16 (32)
Necrotizing enterocolitis, n (%)	1 (2)	4 (8)
Late-onset sepsis, n (%)	5 (10)	10 (20)
Days of oxygen, median	62 [16,94]	49 [13,71]
Days of parenteral nutrition, median (IQR)	26 [19,37]	28 [17, 42]
Days of hospitalization, median (IQR)	89 [66,117]	77 [60,102]
Weight at discharge, Z-score	-2.1 (-2.5, -1.7)	-1.8(-2.6, -1.6)

Data expressed as mean (95% confidence interval) unless specified otherwise.

65 years (Cooper and Melton, 1992). Whether rates of fractures will increase at a higher rate in individuals born preterm as they get older remains to be determined. The reduction in aBMD observed in our young adult cohort is still concerning given inevitable upcoming age-related bone loss. Our findings are especially important for maximizing peak BMD in this high-risk population through lifestyle approaches to promote bone health from infancy throughout adulthood.

Interestingly, in all three studies on young adults born preterm (Hovi et al., 2009; Balasuriya et al., 2017; Fewtrell, 2011), decreased aBMD at the femoral neck remained significant even after accounting for weight and height, thus suggesting other pathological pathways linking preterm birth and lower aBMD in adulthood. Other variables such as physical activity and timing of gross motor milestones could also be determinants of aBMD at the femoral neck (Mori et al., 2014; Pocock et al., 1986; Ireland et al., 2016; Ireland et al., 2017). Indeed, in the Avon Longitudinal Study of Parents and Children, infants with impaired gross motor skills at 18 months had lower hip BMD and

strength at 17 years of age (Ireland et al., 2016). Given that preterm birth is associated with motor delays (Synnes et al., 2017), lower habitual loading of the lower limbs, which is determined by early-life motor competence, could result in subsequent decreased in femoral aBMD. Unfortunately, we did not collect data on gross motor development.

Earlier studies which did not find any effect of preterm birth on adult bone health recruited individuals of higher gestational ages (Dalziel et al., 2006; Breukhoven et al., 2011). Buttazoni et al. did observe that adults born preterm (mean GA 32 weeks) and small-for-gestational-age had reduced bone mass, but not those with birth weight appropriate for GA (Buttazoni et al., 2016). Hovi et al. found that for each additional gestational week, BMD Z-score at the lumbar spine increased by 0.19 units (Hovi et al., 2009). Given that maximal fetal bone accretion occurs in the last trimester of pregnancy, infants born at earlier GA are at increased risk of neonatal illness which may result in poor nutrition, increased inflammation, and exposure to medications that hinder bone mineralization. All these factors may contribute to osteopenia of prematurity (Sharp, 2007; Nallagonda et al., 2017; Done, 2012). However, we could not find any association between neonatal factors and adult bone health.

Study limitations must be acknowledged. First, despite efforts in recruitment, there may be selection bias as our cohort was a small sample set of the historical population. Young adults with severe neurodevelopmental issues were excluded due to challenges in completing the research protocol. Therefore, we might have underestimated the true difference in aBMD between young adults born very preterm and full-term. Second, we could not explore the relationship between current aBMD and neonatal diagnosis of osteopenia of prematurity because the latter was not systematically documented in the charts. Third, we did not have sufficient data to explore the impact of childhood growth on current aBMD. Fourthly, history of fracture was documented but the frequency and the cause of the fracture were not requested in the questionnaire. This information could have facilitated our understanding of the impact of lower BMD on bone health. Our study has important clinical implications for current generations of young adults born prematurely. However, nutritional interventions in neonatal intensive care units and post-discharge have changed in the past 20 years,

and more research has been done to improve parenteral solutions (Bridges et al., 2015; Fewtrell et al., 2011) and breast milk fortification (Fewtrell, 2011; Schanler et al., 1999; Wood et al., 2013). In addition, parent-administered exercise interventions in the NICU have been developed to promote bone mineralization (Moyer-Mileur et al., 2000; Moyer-Mileur et al., 2008). Therefore, it is possible that newer cohorts of very preterm children will be at lower risk of later bone health complications.

5. Conclusions

Young adults born very preterm display reduced aBMD compared to those born full-term especially at the femoral neck. Currently, the International Society for Clinical Densitometry recommendations do not specifically list prematurity as an indication for aBMD screening with DXA. Close monitoring for osteoporotic fractures will be important to guide clinical practice for very preterm populations.

Conflict of interest

None.

Transparency document

The [Transparency document](#) associated with this article can be found, in online version.

Acknowledgements

We would like to thank Valérie Orlando, research assistant, H el ene Gagnon and Guylaine Aub e, research nurses, Danielle Buch, medical editor, Thierry Ducruet, biostatistician, and most importantly, all participants in this study and their parents.

Funding

This work was supported by the Canadian Institutes of Health Research (CIHR 133572) and Fondation du CHU Sainte-Justine. Thuy Mai Luu is supported by a salary award from the Fonds de Recherche en Sant e du Qu ebec. None of these organizations were involved in the study design, data collection and analysis, and manuscript writing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bonr.2018.100189>.

References

- Balasureya, C.N.D., Evensen, K.A.I., Mosti, M.P., et al., 2017. Peak bone mass and bone microarchitecture in adults born with low birth weight preterm or at term: a cohort study. *J. Clin. Endocrinol. Metab.* 102 (7), 2491–2500. [28453635](#).
- Bowden, L.S., Jones, C.J., Ryan, S.W., 1999. Bone mineralisation in ex-preterm infants aged 8 years. *Eur. J. Pediatr.* 158 (8), 658–661. [10445346](#).
- Breukhoven, P.E., Leunissen, R.W., de Kort, S.W., Willemsen, R.H., Hokken-Koelega, A.C., 2011. Preterm birth does not affect bone mineral density in young adults. *Eur. J. Endocrinol.* 164 (1), 133–138. [21030495](#).
- Bridges, K.M., Pereira-da-Silva, L., Tou, J.C., Ziegler, J., Brunetti, L., 2015. Bone metabolism in very preterm infants receiving total parenteral nutrition: do intravenous fat emulsions have an impact? *Nutr. Rev.* 73 (12), 823–836.
- Buttazzoni, C., Rosengren, B., Tveit, M., Landin, L., Nilsson, J.A., Karlsson, M., 2016. Preterm children born small for gestational age are at risk for low adult bone mass. *Calcif. Tissue Int.* 98 (2), 105–113. [26472429](#).
- Chan, G.M., Armstrong, C., Moyer-Mileur, L., Hoff, C., 2008. Growth and bone mineralization in children born prematurely. *J. Perinatol.* 28 (9), 619–623. [18548083](#).
- Compston, J., Cooper, C., Kanis, J., 1995. Bone densitometry in clinical practice. *BMJ: Br. Med. J.* 310 (6993), 1507.
- Cooper, C., Melton 3rd, L.J., 1992. Epidemiology of osteoporosis. *Trends Endocrinol. Metab.* 3 (6), 224–229. [18407104](#).
- Cooper, C., Walker-Bone, K., Arden, N., Dennison, E., 2000. Novel insights into the pathogenesis

- of osteoporosis: the role of intrauterine programming. *Rheumatology* 39 (12), 1312–1315.
- Dalziel, S.R., Fenwick, S., Cundy, T., et al., 2006. Peak bone mass after exposure to antenatal betamethasone and prematurity: follow-up of a randomized controlled trial. *J. Bone Miner. Res.* 21 (8), 1175–1186.
- Done, S.L., 2012. Fetal and neonatal bone health: update on bone growth and manifestations in health and disease. *Pediatr. Radiol.* 42 (Suppl. 1), S158–S176. [22395728](#).
- Embleton, N., Wood, C.L., 2014. Growth, bone health, and later outcomes in infants born preterm. *J. Pediatr.* 90 (6), 529–532. [25128223](#).
- Erlandson, M.C., Sherar, L.B., Baxter-Jones, A.D., et al., 2011. Preterm birth and adolescent bone mineral content. *Am. J. Perinatol.* 28 (02), 157–163.
- Fenton, T.R., Kim, J.H., 2013. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr.* 13, 59. [23601190](#).
- Fewtrell, M.S., 2011. Does early nutrition program later bone health in preterm infants? *Am. J. Clin. Nutr.* 94 (6 Suppl), 1870S–1873S. [21543543](#).
- Fewtrell, M.S., Williams, J.E., Singhal, A., Murgatroyd, P.R., Fuller, N., Lucas, A., 2009. Early diet and peak bone mass: 20 year follow-up of a randomized trial of early diet in infants born preterm. *Bone* 45 (1), 142–149. [19306955](#).
- Fewtrell, M.S., Edmonds, C.J., Isaacs, E., Bishop, N.J., Lucas, A., 2011. Aluminium exposure from parenteral nutrition in preterm infants and later health outcomes during childhood and adolescence. *Proc. Nutr. Soc.* 70 (3), 299–304. [21781356](#).
- Figueroa-Aloy, J., Alvarez-Dominguez, E., Perez-Fernandez, J.M., Moretones-Sunol, G., Vidal-Sicart, S., Botet-Mussons, F., 2014. Metabolic bone disease and bone mineral density in very preterm infants. *J. Pediatr.* 164 (3), 499–504. [24331689](#).
- Goldenberg, R.L., Culhane, J.F., Iams, J.D., Romero, R., 2008. Epidemiology and causes of preterm birth. *Lancet* 371 (9606), 75–84. [18177778](#).
- Hadlock, F.P., Harrist, R.B., Martinez-Poyer, J., 1991. In utero analysis of fetal growth: a sonographic weight standard. *Radiology* 181 (1), 129–133. [1887021](#).
- Hovi, P., Andersson, S., Jarvenpaa, A.L., et al., 2009. Decreased bone mineral density in adults born with very low birth weight: a cohort study. *PLoS Med.* 6 (8), e1000135. [19707270](#).
- Ireland, A., Sayers, A., Deere, K.C., Emond, A., Tobias, J.H., 2016. Motor competence in early childhood is positively associated with bone strength in late adolescence. *J. Bone Miner. Res. Off. J. Am. Soc. Bone Miner. Res.* 31 (5), 1089–1098. [26713753](#).
- Ireland, A., Muthuri, S., Rittweger, J., et al., 2017. Later age at onset of independent walking is associated with lower bone strength at fracture-prone sites in older men. *J. Bone Miner. Res. Off. J. Am. Soc. Bone Miner. Res.* 32 (6), 1209–1217. [28181695](#).
- Kramer, M.S., Platt, R.W., Wen, S.W., et al., 2001. A new and improved population-based Canadian reference for birth weight for gestational age. *Pediatrics* 108 (2), E35. [11483845](#).
- Kroger, H., Vainio, P., Nieminen, J., Kotaniemi, A., 1995. Comparison of different models for interpreting bone mineral density measurements using DXA and MRI technology. *Bone* 17 (2), 157–159. [8554924](#).
- Mori, T., Ishii, S., Greendale, G.A., et al., 2014. Physical activity as determinant of femoral neck strength relative to load in adult women: findings from the hip strength across the menopause transition study. *Osteoporos Int.* 25 (1), 265–272. [23812598](#).
- Moyer-Mileur, L.J., Brunstetter, V., McNaught, T.P., Gill, G., Chan, G.M., 2000. Daily physical activity program increases bone mineralization and growth in preterm very low birth weight infants. *Pediatrics* 106 (5), 1088–1092. [11061779](#).
- Moyer-Mileur, L.J., Ball, S.D., Brunstetter, V.L., Chan, G.M., 2008. Maternal-administered physical activity enhances bone mineral acquisition in premature very low birth weight infants. *J. Perinatol.* 28 (6), 432–437. [18337741](#).
- Nallagonda, S., Nallagonda, M., Deorukhkar, A., 2017. Metabolic bone disease of prematurity—an overview. *Paediatr. Child Health* 27 (1), 14–17.
- Pocock, N.A., Eisman, J.A., Yeates, M.G., Sambrook, P.N., Eberl, S., 1986. Physical fitness is a major determinant of femoral neck and lumbar spine bone mineral density. *J. Clin. Invest.* 78 (3), 618–621. [3745429](#).
- Schanler, R.J., Shulman, R.J., Lau, C., 1999. Feeding strategies for premature infants: beneficial outcomes of feeding fortified human milk versus preterm formula. *Pediatrics* 103 (6 Pt 1), 1150–1157. [10353922](#).
- Sharp, M., 2007. Bone disease of prematurity. *Early Hum. Dev.* 83 (10), 653–658. [17881164](#).
- Shatenstein, B., Amre, D., Jabbour, M., Feguery, H., 2010. Examining the relative validity of an adult food frequency questionnaire in children and adolescents. *J. Pediatr. Gastroenterol. Nutr.* 51 (5), 645–652. [20871415](#).
- Shatenstein, B., Nadon, S., Godin, C., Ferland, G., 2005. Development and validation of a food frequency questionnaire. *Can. J. Diet. Pract. Res.* 66 (2), 67–75.
- Shepherd, J.A., Schousboe, J.T., Broy, S.B., Engelke, K., Leslie, W.D., 2015. Executive summary of the 2015 ISCD position development conference on advanced measures from DXA and QCT: fracture prediction beyond BMD. *J. Clin. Densitom.* 18 (3), 274–286. [26277847](#).
- Synnes, A., Luu, T.M., Moddemann, D., et al., 2017. Determinants of developmental outcomes in a very preterm Canadian cohort. *Arch. Dis. Child. Fetal Neonatal Ed.* 102, F235–f4.
- Tanner, J.M., Goldstein, H., Whitehouse, R.H., 1970. Standards for children's height at ages 2–9 years allowing for heights of parents. *Arch. Dis. Child.* 45 (244), 755–762. [5491878](#).
- Torres-Cuevas, I., Parra-Llorca, A., Sanchez-Illana, A., et al., 2017. Oxygen and oxidative stress in the perinatal period. *Redox Biol.* 12, 674–681. [28395175](#).
- Trivel, D., Calmels, P., Leger, L., et al., 2004. Validity and reliability of the Huet questionnaire to assess maximal oxygen uptake. *Can. J. Appl. Physiol.* 29 (5), 623–638. [15509875](#).
- Viswanathan, S., Khasawneh, W., McNelis, K., et al., 2014. Metabolic bone disease: a continued challenge in extremely low birth weight infants. *JPEN J. Parenter. Enteral Nutr.* 38 (8), 982–990. [23963689](#).
- Weiler, H., Yuen, C., Seshia, M., 2002. Growth and bone mineralization of young adults weighing less than 1500 g at birth. *Early Hum. Dev.* 67 (1), 101–112.
- World Health Organization, 2006. WHO Child Growth Standards: Length/height-for-age, Weight-for-age, Weight-for-length, Weight-for-height and Body Mass Index-for-age: Methods and Development. World Health Organization, Geneva. <http://www.who.int/iris/handle/10665/43413>.
- Wood, C.L., Wood, A.M., Harker, C., Embleton, N.D., 2013. Bone mineral density and osteoporosis after preterm birth: the role of early life factors and nutrition. *Int. J. Endocrinol.* 2013, 902513. [23662104](#).