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Different Indices of Fetal Growth Predict Bone Size and Volumetric Density at 4 Years of Age

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ABSTRACT

We have demonstrated previously that higher birth weight is associated with greater peak and later-life bone mineral content and that maternal body build, diet, and lifestyle influence prenatal bone mineral accrual. To examine prenatal influences on bone health further, we related ultrasound measures of fetal growth to childhood bone size and density. We derived *Z*-scores for fetal femur length and abdominal circumference and conditional growth velocity from 19 to 34 weeks' gestation from ultrasound measurements in participants in the Southampton Women's Survey. A total of 380 of the offspring underwent dual-energy X-ray absorptiometry (DXA) at age 4 years [whole body minus head bone area (BA), bone mineral content (BMC), areal bone mineral density (aBMD), and estimated volumetric BMD (vBMD)]. Volumetric bone mineral density was estimated using BMC adjusted for BA, height, and weight. A higher velocity of 19- to 34-week fetal femur growth was strongly associated with greater childhood skeletal size (BA: $r = 0.30$, $p < .0001$) but not with volumetric density (vBMD: $r = 0.03$, $p = .51$). Conversely, a higher velocity of 19- to 34-week fetal abdominal growth was associated with greater childhood volumetric density (vBMD: $r = 0.15$, $p = .004$) but not with skeletal size (BA: $r = 0.06$, $p = .21$). Both fetal measurements were positively associated with BMC and aBMD, indices influenced by both size and density. The velocity of fetal femur length growth from 19 to 34 weeks' gestation predicted childhood skeletal size at age 4 years, whereas the velocity of abdominal growth (a measure of liver volume and adiposity) predicted volumetric density. These results suggest a discordance between influences on skeletal size and volumetric density. © 2010 American Society for Bone and Mineral Research.

KEY WORDS: EPIDEMIOLOGY; OSTEOPOROSIS; PROGRAMMING; DEVELOPMENTAL ORIGINS

Introduction

There are few longitudinal data relating patterns of intrauterine growth to accrual of bone in childhood. The work of Tanner and others has suggested that fetal growth can be divided into early and late phases.[1,2] Eighty percent of neonatal bone mineral is accrued in the later phase, when growth velocity is at its peak. Growth during the second half of pregnancy thus is particularly susceptible to environmental influences, for example, nutrition (placental transfer) and maternal constraint, such that heredity accounts for only a small proportion of the variance in birth weight.[3,4] Established models suggest that maternal influences can lead to a temporary reduction in growth velocity in late pregnancy and that postnatally the infant tends to revert to the original early fetal trajectory if allowed sufficient nutrition[1,2] in the first 2 years of life.

The skeleton develops through fetal, infant, childhood, and young-adult life to a peak bone mass in third to fourth decade. The peak bone mass achieved is a major determinant of osteoporosis risk in later life.[5] Bone mass (a composite measure of bone size and volumetric mineral density) tends to track throughout childhood, and we have demonstrated previously that growth in early life, both in utero and during infancy, predicts adult bone mineral content,[6,7] as well as the risk of hip fracture.[8] It is likely that these findings reflect, in part, the influence of environmental factors acting during intrauterine life. Given that fetal growth in the second half of pregnancy appears

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particularly susceptible to a constrained intrauterine environment, we aimed, in this study, to describe the relationship between velocity of fetal growth from 19 to 34 weeks' gestation and skeletal size and volumetric density measured by dual-energy x-ray absorptiometry (DXA) at 4 years of age.

Methods

Participants

The Southampton Women's Survey is a unique prospective cohort study of 12,583 women aged 20 to 34 years recruited from the general population.[9] Assessments of lifestyle and anthropometry were performed at study entry and then in early (11 weeks) and late (34 weeks) gestation in the women who became pregnant. Maternal height was measured with a stadiometer, weight with calibrated digital scales, and skin folds (biceps, triceps, subscapular, and suprailiac regions) with Harpenden callipers. The research nurses carrying out the measurements underwent regular assessment and retraining during the study to optimize consistency. The women were asked to characterize their current walking speed into one of five groups (very slow, stroll at an easy pace, normal speed, fairly brisk, or fast). The women's own birth weight was recorded (by recall; checked by asking her own parents).

Prenatal ultrasound scanning

A total of 3159 singleton pregnancies were followed. Since this was a population survey, no inclusion criteria were set for the pregnancy study other than singleton pregnancy, ability to provide informed consent, and willingness and ability to comply with study visits. Thus the cohort included a small number of mothers taking medications for chronic disorders. At 19 and 34 weeks' gestation, the women underwent high-resolution ultrasound scanning using a Kretz Voluson 730 system (GE Kretz Ultrasound, Zipf, Austria) or an Acuson Sequoia 512 system (Siemens, Malvern, PA, USA), which were cross-calibrated. After establishing correct positioning according to standard anatomic landmarks, measurements of femur length (a measure of skeletal size) and abdominal circumference (a composite of adiposity and liver size) were made on the frozen images using electronic callipers by the two operators (PM and CN) according to internationally accepted and validated methodology.[10,11] Each measurement was performed in triplicate, and the mean value was used for analysis. The coefficient of variation (CV) for triplicate measurements of femur length was 0.6% at 19 weeks and 0.4% at 34 weeks.

Four-year DXA assessment

A subset of participants was recruited sequentially from the SWS cohort. The mother (or father/guardian) and child were invited to visit the Osteoporosis Centre at Southampton General Hospital for assessment of bone mass by dual-energy X-ray absorptiometry (DXA). At this visit, written informed consent for the DXA scan was obtained from the mother or father/guardian. The child's height (using a Leicester height measurer) and weight [in underpants only, using calibrated digital scales (Seca, Ltd., Birmingham, UK)] were measured. A whole-body DXA scan was obtained using a Hologic Discovery instrument (Hologic Inc., Bedford, MA, USA) in pediatric scan mode. To encourage compliance, a sheet with appropriately colored cartoons was laid on the couch first; to help reduce movement artefact, the children were shown a suitable DVD cartoon. The total radiation dose for the scans was 4.7 μSv for whole-body measurement (pediatric scan mode). The manufacturer's CV for the instrument was 0.75% for whole-body bone mineral density, and the experimental CV when a spine phantom was scanned repeatedly in the same position 16 times was 0.68%.

Statistical analysis

All variables were checked for normality. Nonnormally distributed variables were transformed logarithmically. In women with a reliable date of last menstrual period, Royston models were fitted to fetal measurements of femur length and abdominal circumference at 19 and 34 weeks to create *Z*-scores for size and conditional growth.[12] Correlation and linear regression methods were used to explore the relationship between the fetal ultrasound measurements and bone size and density at 4 years using Stata Version 10.0 (Statacorp, College Station, Texas, USA). Whole body minus head bone area (BA), bone mineral content (BMC), and areal mineral density (aBMD) were used as the primary skeletal outcomes. To explore the size-corrected measures of bone mass and thus estimate volumetric bone mineral density (vBMD), we used three methods: (1) linear regression to adjust BMC for BA, (2) linear regression to adjust BMC for BA, height, and weight, and (3) a mathematical estimate[13] termed *bone mineral apparent density* ($\text{BMAD} = \text{BMC}/\text{BA} \times \sqrt{\text{BA}}$). The second method was used as the primary estimate of volumetric bone mineral density (vBMD) because it was felt to control for body size most effectively, and the first and third methods were used as checks to confirm or refute consistency of associations. Relationships between vBMD and childhood body composition were explored using whole body minus head percentage lean and percentage fat mass. Finally, we tested for difference in correlation coefficients for any associations that were compared.

The study had full approval from the Southampton and Southwest Hampshire Local Research Ethics Committee, and all participants gave written informed consent.

Results

Characteristics of the cohort

After exclusion of 13 children who had excessive movement artefact on the DXA scan, there were 380 mother-child pairs, among which 197 of the offspring were male. All were term deliveries (37 weeks' gestation or greater) and had complete DXA and pregnancy scan data. The mean (SD) age of the mothers at the initial interview was 28.7 (3.7) years and at delivery was 30.6 (3.7) years; 44% were in their first pregnancy, and 22% were smokers at the initial interview. Thirty-nine percent of the women who had smoked before conception had given up by late pregnancy, such that 9% were still smoking at this time point. The proportion consuming more than 10 units of alcohol each week decreased from 26% before pregnancy to 0.27% in late pregnancy. Ninety-six percent of the mothers were of

Table 1. Anthropometric and DXA Measures Among 197 Male and 183 Female Offspring at 4 Years of Age

Characteristic	Boys ($n = 197$)	Girls (n = 183)	p
Gestational age, weeks (mean, SD)	40.0 (1.2)	40.2 (1.2)	.064
Age at DXA, years (median, IQR)[a]	4.11 (4.08–4.16)	4.11 (4.08–4.15)	.718
Birthweight, g (mean, SD)	3604 (459)	3503 (438)	.031
Height, cm (mean, SD)	104.3 (3.5)	104.1 (4.3)	.680
Weight, kg (median, IQR)[a]	17.7 (16.7–19.2)	17.5 (16.2–18.9)	.250
WB BA, cm^2 (mean, SD)	750.4 (45.2)	767.6 (53.7)	.0008
WB BMC, g (mean, SD)	372.8 (42.7)	377.9 (50.0)	.283
WB aBMD, g/cm^2 (mean, SD)	0.496 (0.034)	0.491 (0.038)	.186
WB vBMD, units (mean, SD)	374.9 (16.0)	371.8 (18.5)	.089
FL 19 weeks, mm (mean, SD)	30.8 (1.9)	30.6 (1.9)	.426
FL 34 weeks, mm (mean, SD)	65.1 (2.8)	65.5 (2.7)	.167
AC 19 weeks, mm (mean, SD)	146.6 (8.1)	144.1 (8.7)	.004
AC 34 weeks, mm (mean, SD)	308.0 (14.6)	307.9 (14.5)	.985
ΔFL 19–34 weeks, mm (mean, SD)	34.3 (2.6)	34.9 (2.5)	.037
ΔAC 19–34 weeks, mm (mean, SD)	161.3 (13.2)	163.7 (14.4)	.101

WB = whole body minus head; BA = bone area; BMC = bone mineral content; aBMD = areal bone mineral density; vBMD = estimated volumetric bone mineral density; FL = femur length; AC = abdominal circumference.
[a]Wilcoxon rank-sum test.

Caucasian ethnicity. The characteristics of the children are shown in Table 1.

Compared with mothers of children born to the SWS cohort during the same time frame but who did not have DXA scans at 4 years, the mothers in this study tended to be slightly (mean) older (30.6 versus 29.8 years), taller (164.1 versus 162.7 cm), more highly educated (27.9% versus 18.7% with higher degrees), and less likely to smoke before (21.6% versus 30%) and during (8.8% versus 18.4%) pregnancy (all $p < .05$). There was no difference in BMI between the two groups.

Pregnancy ultrasound measurements and height and weight at 4 years

Absolute femur length and abdominal circumference at 19 weeks' gestation were both positively associated ($p < .01$) with height at 4 years (Table 2). However, the association with childhood weight was statistically significant only for abdominal circumference. At 34 weeks' gestation, fetal femur length and abdominal circumference predicted childhood weight similarly ($p = .67$ for difference in correlation coefficients), but the associations between the ultrasound measurements and 4-year height were stronger ($p = .0002$ for difference between compared correlation coefficients) for femur length ($r = 0.36$, $p < .001$) than for abdominal circumference ($r = 0.15$, $p = .003$). The conditional change in femur length from 19 to 34 weeks' gestation was strongly correlated with height at 4 years ($r = 0.32$, $p < .001$) in contrast ($p = .0001$ for difference between compared correlation coefficients) to the conditional change in abdominal circumference from 19 to 34 weeks' gestation, which showed no relationship ($r = 0.06$, $p = .28$). Both conditional ultrasound measures had similar associations with weight at 4 years. Table 2 summarizes these findings.

Pregnancy ultrasound measurement and bone size and density at 4 years

Absolute femur length and abdominal circumference at 19 and 34 weeks' gestation predicted bone size and density differently.

Table 2. Relationships of Absolute and Conditional Femur Length and Abdominal Circumference at 19 and 34 Weeks' Gestation With Whole Body Minus Head Bone Size and Density and Height and Weight at 4 Years

	DXA measurement at 4 years					
	BA	BMC	aBMD	vBMD	Height	Weight
Femur length						
19 weeks	0.14^{**}	0.13^{*}	0.09	−0.003	0.17^{**}	0.09
34 weeks	0.33^{***}	0.31^{***}	0.23^{***}	0.03	0.36^{***}	0.23^{***}
Δ19–34 weeks	0.30^{***}	0.29^{***}	0.21^{***}	0.03	0.32^{***}	0.22^{***}
Abdominal circumference						
19 weeks	0.11^{*}	0.13^{*}	0.12^{*}	−0.04	0.18^{*}	0.19^{*}
34 weeks	0.12^{*}	0.21^{***}	0.25^{***}	0.11^{*}	0.15^{**}	0.27^{***}
Δ19–34 weeks	0.06	0.15^{**}	0.20^{***}	0.15^{**}	0.06	0.18^{***}

Table shows Pearson correlation coefficients: $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$.
BA = bone area; BMC = bone mineral content; aBMD = areal bone mineral density; vBMD = estimated volumetric bone mineral density.

Associations generally were stronger at 34 weeks than at 19 weeks' gestation (see Table 2). There were strong statistically significant correlations between conditional change in femur length from 19 to 34 weeks' gestation and indices of skeletal size but not volumetric density (BA: $r = 0.30$, $p < .0001$; vBMD: $r = 0.03$, $p = .51$; $p = .0002$ for difference between compared correlation coefficients). Conversely, conditional change in abdominal circumference was positively associated with indices of vBMD, but there was no association with bone size (BA: $r = 0.06$, $p = .21$; vBMD: $r = 0.15$, $p = .004$), although the difference in correlation coefficients here did not reach statistical significance ($p = .24$). Similar results were observed with all methods of estimation of vBMD. Thus the Pearson correlation coefficients for the associations between 19 to 34 weeks' gestation conditional abdominal circumference growth and vBMD measured by BMC for BA; BMC for BA, height, and weight; and BMAD were $r = 0.15$, $p = .004$; $r = 0.20$, $p = .0001$; and $r = 0.21$, $p = .0001$, respectively; femur length change was not statistically significantly associated with any measure of vBMD. Both fetal measurements were positively associated with BMC and aBMD, indices influenced by both size and density. Thus the correlation coefficients with femur length conditional growth were BMC: $r = 0.29$, $p < .0001$, and aBMD: $r = 0.21$, $p < .0001$, and with abdominal circumference conditional growth were BMC: $r = 0.15$, $p = .003$, and aBMD: $r = 0.20$, $p = .0001$. These are summarized in Fig. 1. The difference in aBMD (the bone parameter used most commonly in clinical practice) between children who had been in highest versus lowest quintiles of abdominal circumference growth from 19 to 34 weeks' gestation was 0.56 SD.

Nineteen-week absolute versus 19- to 34-week change in femur length and abdominal circumference

Absolute femur length at 34 weeks' gestation was a more powerful predictor of bone size (BA, BMC, and aBMD; $p = .0001$, .0002, and .004, respectively, for difference between compared correlation coefficients) at 4 years than was absolute femur length at 19 weeks' gestation (see Table 2). This pattern was explained by the strong relationship between conditional change in femur length from 19 to 34 weeks' gestation and 4-year bone size. When combined in a bivariate regression model, 19-week absolute femur length and 19- to 34-week conditional change in femur length were found to exert independent effects; the interaction terms with all measures of bone mineral at 4 years were not statistically significant (p values for interaction between 19-week absolute femur length and 19- to 34-week conditional change in femur length are BA: $p = .092$; BMC: $p = .179$; aBMD: $p = .324$; and vBMD: $p = .675$). Neither change nor absolute femur length at 19 weeks gestation were associated with vBMD.

The pattern with abdominal circumference was a little different (see Table 2). Thus 19-week absolute abdominal circumference weakly predicted BA at 4 years ($p = .036$), whereas the relationship between conditional change in abdominal circumference and BA was not statistically significant. There was no association between 19-week abdominal circumference and vBMD at 4 years ($p = .45$), but conditional change in abdominal circumference strongly predicted this outcome ($p = .004$).

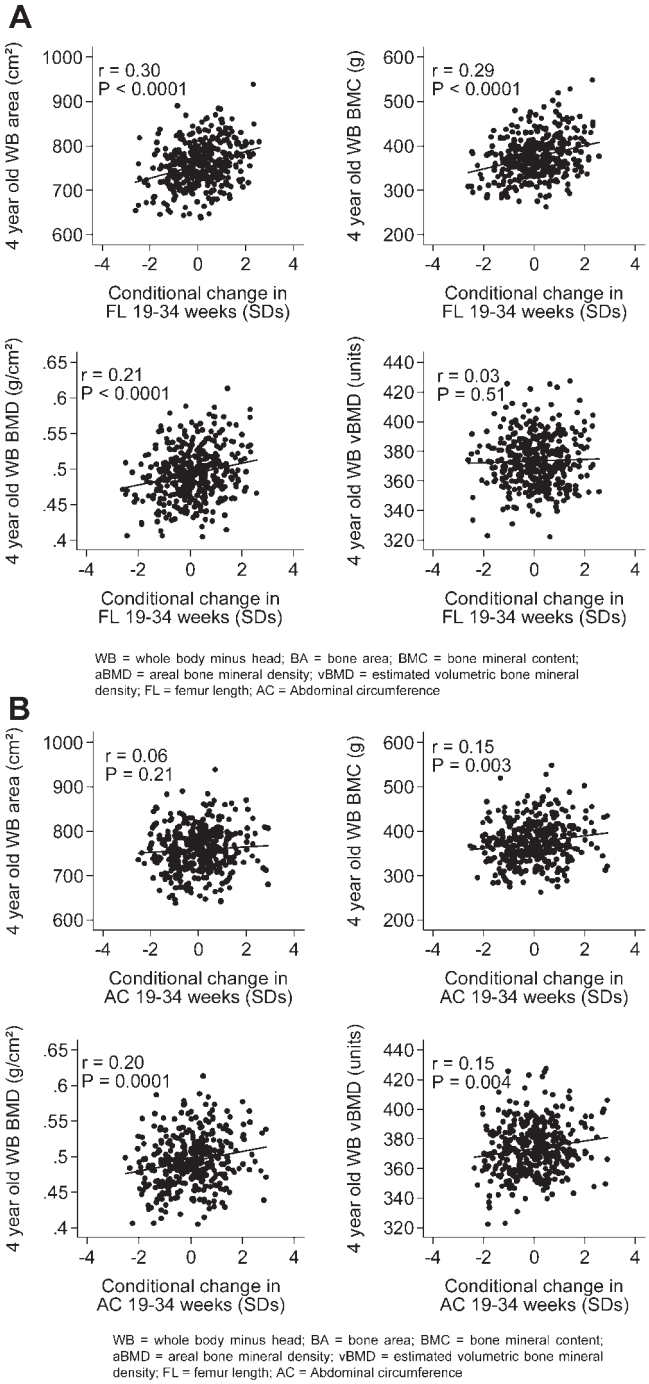

Fig. 1. (*A*) Conditional change in fetal femur length from 19 to 34 weeks' gestation and childhood bone size and density at 4 years of age. (*B*) Conditional change in fetal abdominal circumference from 19 to 34 weeks' gestation and childhood bone size and density at 4 years of age.

Conditional change in abdominal circumference was similarly associated with BMC and aBMD ($p = .61$ and .23, respectively, for difference in compared r values) for the 19-week measurement, and the interaction terms for all these relationships did not attain statistical significance (p values for the interaction between 19-week absolute abdominal circumference and 19- to 34-week

conditional growth in abdominal circumference: BA: $p = .878$; BMC: $p = .755$; aBMD: $p = .763$; and vBMD: $p = .847$).

Volumetric BMD and childhood body composition

There was no statistically significant relationship between conditional abdominal circumference growth from 19 to 34 weeks' gestation and percentage fat at 4 years. All three estimates of vBMD were negatively related to 4-year percentage body fat. Thus the Pearson correlation coefficients for percentage fat with BMC for BA; BMC for BA, height, and weight; and BMAD were $r = -0.33$, $p < .0001$; $r = -0.17$, $p = .0008$; and $r = -0.15$, $p = .0037$ respectively. Opposite relationships were observed for percentage lean mass ($r = 0.31$, $p < .0001$; $r = 0.17$, $p = .0009$; and $r = 0.14$, $p = .0054$, respectively).

Maternal lifestyle and diet

We found previously that maternal anthropometric and lifestyle factors are associated with neonatal bone mineral content. Inclusion of maternal height, parity, smoking, walking speed, and triceps skinfold thickness in late pregnancy in multivariate models did not significantly alter the relationships between intrauterine growth and bone size and density at 4 years.

Discussion

In our study, measures of intrauterine growth were strongly associated with childhood bone size and estimated volumetric density at 4 years of age. There was evidence of size/density discordance such that change in femur length from 19 to 34 weeks' gestation was associated with childhood skeletal size at 4 years of age, whereas change in fetal abdominal circumference predicted estimated volumetric density. These findings suggest that intrauterine growth may differentially influence postnatal skeletal size and volumetric density and that tracking of skeletal development has its origins in the prenatal period. Additionally, our findings are consistent with previous data suggesting that factors that influence late intrauterine growth may have persisting effects on postnatal skeletal development and thus challenge the notion that perturbations in late gestation growth are fully compensated by postnatal catch-up or catch-down. While many other factors also affect skeletal growth, these early influences therefore are likely to be of relevance to later bone health, suggesting that osteoporosis prevention should be considered at all stages of the lifecourse.

We studied a large, well-established cohort with detailed characterization of mothers before and during pregnancy; we also used DXA, a well-validated technique, for measuring bone indices in the neonates. However, there are several limitations to our study: Intrauterine ultrasound measurements are prone to a certain amount of error, but we used two experienced operators, and repeatability was good. Owing to the limitations of fetal ultrasound, we were unable to measure liver volume, fat content, and subcutaneous fat thickness separately. It is possible that extramedullary hematopoiesis may have contributed to liver size, but hepatic hematopoiesis decreases from midgestation onward to low levels by the third trimester of pregnancy[14]; splenic hematopoiesis does not seem to occur from midgestation.[15] Thus it is unlikely that extramedullary hematopoiesis would have influenced the associations seen. Measurement of bone mineral in young children is hampered by their tendency to move and also by their low absolute BMC. However, we used specific pediatric software, and movement artefact was modest and uniform across the cohort; those few children with excessive movement were excluded from the analysis. DXA measures of bone mass have been shown to correlate well with whole-body calcium content in ashing studies of piglets.[16] The study cohort was a subset of the SWS cohort. Mothers whose children underwent DXA scanning were, on average, taller, more educated, and smoked less than mothers of children who were did not undergo DXA. However, our results are based on internal comparisons and so will not have been biased by these differences. Additionally, there is no reason to suppose that the relationship between fetal growth and childhood bone mass would be different in these two groups. Finally, the use of DXA does not allow measurement of true vBMD, thus making it difficult to be certain about differential determinants of skeletal size and volumetric density. However, the associations were consistent across three different estimates of volumetric density, which supports the conclusions made.

Our previous work has demonstrated positive associations between birth size and whole-body BMC at peak bone mass and in later life.[6,7,17] Maternal physical activity, lifestyle, and anthropometric factors predicted skeletal size but not density in the offspring at birth.[18] Prospective postnatal observation of childhood bone development has demonstrated tracking,[19,20] that is, the tendency for an individual to stay in the same position relative to peers over the growth period in the distribution of bone mineral. Factors such as physical activity[21,22] and calcium intake[23,24] have been shown to transiently influence bone mineral accrual postnatally, but given the associations between adult bone mineral and birth weight, it is likely that the trajectory of skeletal development is set at an early stage of development. With the observed strong correlations between pregnancy ultrasound measurements and bone size and density at 4 years, our study demonstrates that this phenomenon is likely to have its origin during intrauterine life.

Existing data suggest that tracking is strong for skeletal size rather than for volumetric density.[6,7] In this study, however, we found that change in fetal abdominal circumference from 19 to 34 weeks' gestation was positively associated with estimated vBMD at 4 years. Ultrasound measurement of fetal abdominal circumference is representative of liver volume and subcutaneous fat stores, although the technique currently does not allow the contribution of each to be evaluated separately. Liver and adipose tissue secrete insulin-like growth factor 1 (IGF-1) and leptin, respectively, both of which are known to influence osteoblast function and thus offer potential explanations for fetal influences on skeletal development.

IGF-1 is produced mainly by the fetal liver, and concentrations rise with increasing duration of pregnancy.[25–27] Levels have been shown to correlate strongly with birth weight after adjustment for gestational age[26,27] and experimental manipulations that reduce liver growth decrease IGF-1 levels[28]; IGF-1 has a positive effect on osteoblast function.[29] However, results from an earlier mother-offspring cohort in Southampton[26]

demonstrated that umbilical cord concentrations of IGF-1 were positively associated with whole-body BA and BMC in the neonate but not with estimated vBMD. Thus cord IGF-1 appeared to correlate better with skeletal size than volumetric density in this previous work.

In contrast, in this previous cohort, estimated vBMD was positively associated with concentrations of leptin in the umbilical vein at delivery.[30] Leptin is a peptide hormone involved in the regulation of fat metabolism and appetite through hypothalamic mechanisms.[31] Circulating leptin in the fetus is produced mainly from its own fat stores[32] and the placenta,[33] and concentrations in the umbilical cord have been shown to correlate positively with birth size and adiposity.[34–38] Recent work in animals has suggested that the primary effect of leptin on bone formation is via hypothalamic action on the sympathetic nervous system.[39] How this relates to mechanisms in humans is as yet unclear. Leptin may push mesenchymal stem cells toward differentiation to osteoblasts rather than adipocytes,[40,41] and leptin receptors have been found on osteoblasts, chondrocytes, and bone marrow stromal cells.[42] Thus fetal leptin concentrations might play a persisting role in the trajectory of accrual of vBMD and potentially account for the relationship we observed between abdominal circumference and vBMD. Against this notion is the finding that conditional change in abdominal circumference from 19 to 34 weeks' gestation did not predict percentage fat mass at 4 years. However, this is not incompatible with 19- to 34-week abdominal circumference acting through adiposity in utero and resulting in a persisting effect on the trajectory of skeletal development in postnatal life. There are many further influences on fat deposition in infancy and childhood, such as nutrition, physical activity, and catch-up/catch-down growth, which would reduce any association between adiposity in fetal and postnatal life. Additionally, bone is the minority of body composition measured by DXA, with lean and fat the majority, so any strong relationship with percentage lean must be mirrored in percentage fat. It is therefore difficult to make a definite conclusion about whether the positive relationship between percentage muscle and vBMD or the negative relationship between vBMD and percentage fat is the primary driver of the observed postnatal associations. Ultimately, there are very few data in this novel area of research, and therefore, the exact nature of what is measured by abdominal circumference in utero must remain subject to speculation.

Studies suggest that fetal growth slows in late pregnancy, constrained by placental nutrient flow and maternal pelvic size.[2] Hence the local environment is of critical importance to growth in late pregnancy. There is evidence, however, that postnatally the infant tends to revert to the trajectory followed in the first half of fetal development[1,2] and that this original trajectory is subsequently followed. Thus 19- to 34-week femur length gives us a measure of linear skeletal growth in the second half of pregnancy. In contrast to previous work, our results are more consistent with growth velocity in late rather than early pregnancy being a significant determinant of childhood skeletal size. Additionally, this notion is supported by the absolute measurements at 34 weeks' gestation being stronger predictors of bone size and density at 4 years than those at 19 weeks. Our current results suggest that growth in late pregnancy may not just influence birth size, with subsequent normalization, but may have a persisting effect on skeletal development. Clearly, further work is required to elucidate these relationships in more detail.

Our results demonstrated a 0.56 SD difference in aBMD between highest and lowest quintiles of conditional abdominal circumference growth from 19 to 34 weeks' gestation. If this difference were to persist into adult life, it could account for up to a 50% difference in relative risk of fracture because a 1 SD difference in adult aBMD equates to up to a twofold fracture risk difference.[8,43] Thus, although the variation in bone mass explained by these measures of fetal growth seems modest initially, it is likely to be significant clinically. We have demonstrated previously that maternal lifestyle, body build, physical activity, and vitamin D status influence offspring bone mass.[18,44] Our current study relates fetal growth to 4-year bone size and density. The next step is to explore the relationships between these two sets of data to better understand mechanistically the critical influences on skeletal development early in life. Ultimately, increased characterization of these processes may lead to novel public health interventions aimed at optimizing bone size and density from the very beginning of the lifecourse.

In conclusion, we found that the velocity of growth in femur length from 19 to 34 weeks' gestation predicted childhood skeletal size at 4 years, whereas the velocity of growth in fetal abdominal circumference (a measure of liver volume and fetal adiposity) predicted volumetric density. These results suggest a possible discordance between influences on volumetric density and bone size and that the intrauterine environment in the second half of pregnancy may have persisting influences on skeletal development in postnatal life. These data may facilitate further investigation of the determinants of skeletal development in utero and their relationship with longer-term bone health in postnatal life.

Disclosures

The SWS Study Group includes P Taylor, LJ Greenaway, M Hanson, DJP Barker, and CM Law. All the authors state that they have no conflicts of interest.

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