

Intrauterine growth and postnatal skeletal development: findings from the Southampton Women's Survey

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Summary

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We have previously demonstrated associations between fetal growth in late pregnancy and postnatal bone mass. However, the relationships between the intrauterine and early postnatal skeletal growth trajectory remain unknown. We addressed this in a large population-based mother–offspring cohort study. A total of 628 mother–offspring pairs were recruited from the Southampton Women's Survey. Fetal abdominal circumference was measured at 11, 19 and 34 weeks gestation using high-resolution ultrasound with femur length assessed at 19 and 34 weeks. Bone mineral content was measured postnatally in the offspring using dual-energy X-ray absorptiometry at birth and 4 years; postnatal linear growth was assessed at birth, 6, 12, 24, 36 and 48 months. Late pregnancy abdominal circumference growth (19–34 weeks) was strongly ($P < 0.01$) related to bone mass at birth, but less robustly associated with bone mass at 4 years. Early pregnancy growth (11–19 weeks) was more strongly related to bone mass at 4 years than at birth. Postnatal relationships between growth and skeletal indices at 4 years were stronger for the first and second postnatal years, than the period aged 2–4 years. The proportion of children changing their place in the distribution of growth velocities progressively reduced with each year of postnatal life. The late intrauterine growth trajectory is a better predictor of skeletal growth and mineralisation at birth, while the early intrauterine growth trajectory is a more powerful determinant of skeletal status at age 4 years. The perturbations in this trajectory which influence childhood bone mass warrant further research.

Keywords: fetal growth, Southampton Women's Survey, neonatal bone mineralisation, childhood bone mineralisation, childhood growth.

Introduction

We have previously demonstrated that fetal growth in late pregnancy is a determinant of skeletal size and density, assessed by dual-energy X-ray absorptiometry (DXA), in childhood.¹ Other work suggests important relationships between growth trajectories *in utero* and those experienced in the first few years of postnatal life.^{2,3} There are, however, relatively few longitudinal

data relating patterns of intrauterine growth using objective measures such as gestational ultrasound to bone mineral accrual in childhood. The seminal studies by Tanner and colleagues, using linear external measurements during pregnancy, have suggested that fetal growth can be divided into early and late phases.^{2,3} The later phase, when growth velocity is at its peak, accounts for the accrual of 80% of neonatal bone mineral.⁴ Growth during the second half of pregnancy is

thus particularly susceptible to environmental influences, for example nutrition (placental transfer) and maternal constraint, such that heredity only accounts for a small proportion of the variance in birthweight.⁵⁻⁷ These findings are broadly supported by more recent studies using gestational ultrasound scanning.^{8,9} Existing models of pre- and postnatal growth suggest that maternal influences can lead to a temporary reduction of growth velocity in late pregnancy, and that postnatally the infant tends to revert to the original early fetal trajectory if allowed sufficient nutrition^{2,3} in the first 2 years of life. Historically there has been very little objective longitudinal evidence to confirm these clinical models, particularly in relation to skeletal outcomes. At conception the genotype is set, but epigenetic influences occur throughout gestation.¹⁰ We have previously shown that factors such as maternal diet, life style, body build and physical activity¹¹⁻¹⁴ during pregnancy are all associated with offspring bone mineral content (BMC), and appear to exert most effect in late pregnancy. Additionally, in an earlier study,¹ late pregnancy growth in fetal femur length and abdominal circumference (AC) positively predicted measures of bone size and density at 4 years old. We therefore aimed to investigate how offspring growth velocity at periods from early fetal life to 4 years related to their skeletal development utilising an ongoing prospective population-based mother-offspring cohort.

Methods

Participants

The Southampton Women's Survey (SWS) is a unique, prospective cohort study of 12 583 women aged 20-34 years recruited from the general population.¹⁵ Assessments of life style and anthropometry were performed at study entry and then in early (11 weeks) and late (34 weeks) gestation in those women who became pregnant. Maternal height was measured with a stadiometer, weight with calibrated digital scales, and skinfolds (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 optimise consistency. The women were asked to characterise their current walking speed into one of five groups (very slow, stroll at an easy pace, normal speed, fairly brisk or fast). The woman's own birthweight was recorded (by recall, checked by asking her own parents).

Prenatal ultrasound scanning

In total, 3156 singleton pregnancies were followed. As this was a population survey, no inclusion criteria were set for the pregnancy study other than singleton pregnancy and ability to provide informed consent. At 11, 19 and 34 weeks gestation, the women underwent high-resolution ultrasound scanning using a Kretz Voluson® 730 (GE Kretz Ultrasound, Zipf, Austria) or Acuson Sequoia® 512 (Siemens, Erlangen, Germany) system, which were cross-calibrated. After establishing correct positioning according to standard anatomical landmarks, measurements of AC (a composite of adiposity and liver size, obtained at all three time points) and femur length (obtained at 19 and 34 weeks) were made on the frozen images using electronic callipers by the two operators (PM and CN), according to internationally accepted and validated methodology.^{16,17} Each measurement was performed in triplicate and the mean value used for analysis.

Neonatal DXA assessment

Mothers registered with specific general practitioner practices were invited to participate in the bone component of the SWS. These practices were selected to avoid the mothers participating in more than one substudy, and were representative of the population of Southampton as a whole. At birth, the babies were weighed on calibrated digital scales (Seca Ltd, Birmingham, UK), and crown-heel length measured using a neonatometer (CMS Ltd, London, UK). The mother was asked to agree to her baby undergoing assessment of bone mass and body composition within 2 weeks of birth, using a Lunar DPX-L instrument with specific paediatric software (paediatric small scan mode, v 4.7c, GE Corporation, Madison, WI, USA). The instrument underwent daily quality assessment, and was calibrated against a water phantom weekly. A total of 1003 neonates underwent DXA assessment. The mothers could either attend as inpatients, or return from home within the 2-week time period. At the visit to the scan room, the baby was pacified and fed if necessary, undressed completely, and then swaddled in a standard towel. It was placed on a waterproof sheet in a standard position on the scanner for measurement of whole body bone area (BA), BMC and body composition, using specific software protocols. The baby was kept in position using rice bags placed over the bottom end of the towel. The short-term and long-term

coefficients of variation (CV) for adult whole body bone mineral density (BMD) for the DXA instrument were 0.8% and 1.4% respectively. It was not possible to scan neonates repeatedly to establish precision values in the study group; however, the ability of DXA to measure bone mass in small subjects has been demonstrated by Abrams *et al*¹⁸ using miniature piglets, where the correlation between DXA-derived BMC and ashed calcium content was 0.90 ($P < 0.001$). The radiation exposure to the baby was estimated as a maximum of 8.9 microsieverts for whole body measurement, which is equivalent to around 3 days' exposure to normal background radiation. All scan results were checked independently by two trained operators and agreement reached as to their acceptability. Thirty-one scans showing unacceptable movement artefact were excluded.

Postnatal growth

Children were assessed at 6 months, 1, 2 and 3 years with a home visit from a research nurse. Information on diet, life style, illness and medication was collected and anthropometric measurements were performed. Height was measured using a Leicester height measure (Seca Ltd) and weight, in underpants only, using calibrated digital scales (Seca Ltd).

Four-year DXA assessment

A subset of 900 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. 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 (Seca Ltd)] and weight [in underpants only, using calibrated digital scales (Seca Ltd)] were measured. AC was not measured at this age as it was not a requirement for the DXA assessment. A whole body DXA scan was obtained, using a Hologic Discovery instrument (Hologic Inc., Bedford, MA, USA) in paediatric scan mode. To encourage compliance, a sheet with appropriate coloured 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 microsieverts for whole body measurement (paediatric scan mode). Thirty-two scans were found to have unacceptable movement artefact,

so were excluded. The manufacturer's CV for the instrument was 0.75% for whole body BMD, and the experimental CV when a spine phantom was repeatedly scanned in the same position 16 times was 0.68%.

Statistical analysis

All women had a reliable date of last menstrual period. All variables were checked for normality. Non-normally distributed variables were transformed logarithmically. The ultrasound-derived measures of fetal size were adjusted for the gestational age at which the measurement was taken and within-group z-scores were subsequently created. Conditional models of change were built using linear regression analysis: AC is used as an example. AC z-score at 11 weeks is the starting point. Conditional change in AC z-score from 11 to 19 weeks is equivalent to the standardised residuals resulting from the linear regression model of AC z-score at 19 weeks on AC z-score at 11 weeks. Accordingly, the conditional change in AC z-score from 19 to 34 weeks is given as the standardised residuals obtained from regressing AC z-score at 34 weeks on both AC z-score at 19 weeks and AC z-score at 11 weeks simultaneously. This process is continued for each subsequent time point, resulting in measures of

Table 1. Characteristics of mothers

| Maternal characteristics ($n = 628$) | Median [IQR] |
|--|------------------|
| Age at child's birth (years) | 30.8 [27.9–33.6] |
| Triceps skinfold 34 weeks (mm) | 20.8 [16.9–25.9] |
| Body mass index pre-pregnancy (kg/m^2) | 24.2 [22.2–27.2] |
| | Mean (SD) |
| Height (cm) | 163.9 (6.6) |
| | n (%) |
| Walking speed at 34 weeks | |
| Very slow | 95 (15.3) |
| Stroll at an easy pace | 337 (54.2) |
| Normal speed | 157 (25.2) |
| Fairly brisk | 32 (5.1) |
| Fast | 1 (0.2) |
| Parity | |
| 0 | 298 (47.5) |
| 1+ | 330 (52.5) |
| Smoking before pregnancy | |
| No | 496 (79.0) |
| Yes | 132 (21.0) |
| Smoking in late pregnancy | |
| No | 557 (89.5) |
| Yes | 65 (10.5) |

conditional growth which are mutually uncorrelated. AC measurements were available at all time points up to and including 3 years of age; length assessment comprised femur length at 19 and 34 weeks gestation, crown–heel length at birth, 6 and 12 months, and height at 2–4 years.

Correlation and linear regression methods were used to explore the relationship between the growth measurements and bone size and density at birth and 4 years, using STATA V11.0 (Statacorp, College Station, TX, USA). At birth, whole body BA, BMC and areal BMD (aBMD) were used as the primary skeletal outcomes. At 4 years, the same DXA indices were used but for the whole body minus head site.

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

Results

There were 628 children (330 boys) with complete pregnancy ultrasound, postnatal growth and 4-year

DXA data. The characteristics of the mothers and children are shown in Tables 1 and 2.

Compared with mothers of children born to the SWS during the same time frame, but who did not have DXA scans at 4 years, the mothers of children who did have DXA assessments were, on average, slightly older at the birth of their child (mean age 31.2 years vs. 30.6 years, $P = 0.007$), better educated (24.8% with higher degree vs. 20.6%, $P = 0.002$) and smoked less (8.5% smoked before pregnancy vs. 17.4%, $P < 0.001$).

Relationships between intrauterine growth and postnatal skeletal development

In the subset of children who had undergone DXA assessment at birth, we observed that conditional AC growth in early pregnancy strongly and statistically significantly predicted bone mineral measures at 4 years; these associations appeared less marked for bone mineral measures at birth. In contrast, conditional AC growth in late gestation appeared to be more

Table 2. Characteristics of children

| | Boys ($n = 330$) Mean (SD) | Girls ($n = 298$) Mean (SD) | P |
|---------------------------------|---------------------------------|----------------------------------|--------|
| 11 weeks: Mean AC (cm) | 5.6 (0.7) | 5.6 (0.7) | 0.97 |
| 19 weeks: Mean AC (cm) | 14.6 (0.8) | 14.4 (0.9) | 0.11 |
| 34 weeks: Mean AC (cm) | 30.8 (1.4) | 30.7 (1.4) | 0.53 |
| Birth: Mean AC (cm) | 31.8 (1.8) | 31.9 (1.9) | 0.86 |
| 1 year: Mean AC (cm) | 50.0 (3.0) | 49.4 (3.4) | 0.17 |
| 2 years: Mean AC (cm) | 49.3 (2.8) | 49.1 (3.1) | 0.52 |
| 3 years: Mean AC (cm) | 51.7 (3.0) | 51.2 (2.9) | 0.23 |
| 19-week scan: Femur length (cm) | 3.1 (0.2) | 3.1 (0.2) | 0.69 |
| 34-week scan: Femur length (cm) | 6.5 (0.3) | 6.6 (0.3) | 0.02 |
| Birth: Crown–heel length (cm) | 50.5 (2.0) | 50.1 (1.8) | 0.04 |
| 1 year: Crown–heel length (cm) | 76.3 (2.3) | 75.2 (2.6) | <0.001 |
| 2 years: Height (cm) | 87.2 (2.8) | 86.5 (3.1) | 0.02 |
| 3 years: Height (cm) | 96.4 (3.2) | 96.1 (3.7) | 0.39 |
| 4 years: Height (cm) | 104.3 (3.6) | 104.3 (4.3) | 0.95 |
| Birthweight (g) | 3576 (475) | 3507 (463) | 0.07 |
| Gestational age (weeks) | 40.0 (1.2) | 40.3 (1.2) | 0.009 |
| Four-year DXA | | | |
| WB BA (cm ²) | 748.4 (44.0) | 768.9 (51.1) | <0.001 |
| WB BMC (g) | 371.1 (42.2) | 378.8 (48.3) | 0.04 |
| WB aBMD (g/cm ²) | 0.50 (0.03) | 0.49 (0.04) | 0.23 |

AC, abdominal circumference; DXA, dual-energy X-ray absorptiometry; WB, whole body; BA, bone area; BMC, bone mineral content; aBMD, areal bone mineral density.

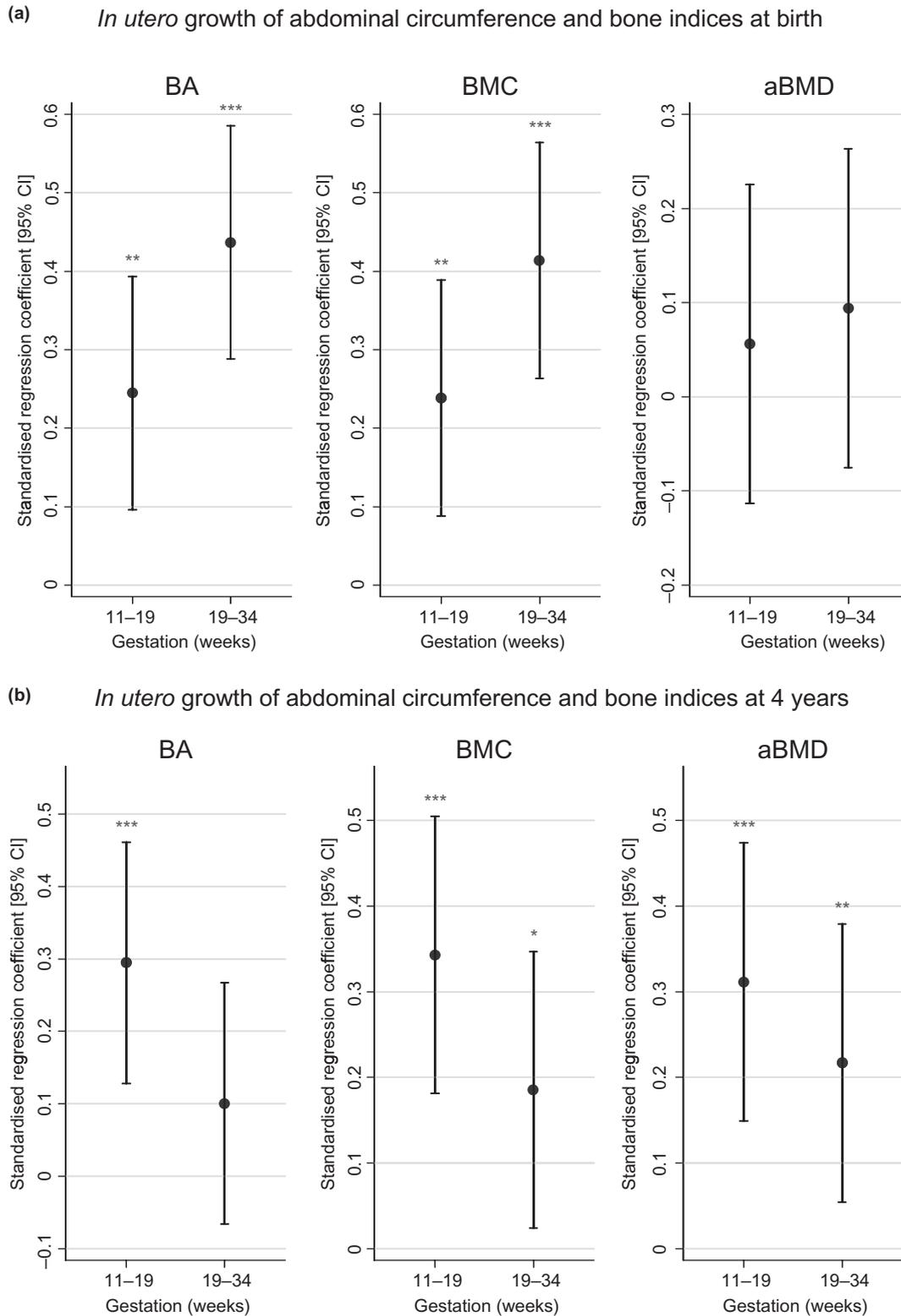


Figure 1. (a) Plot of standardised regression coefficients for whole body minus head bone area (BA), bone mineral content (BMC) and areal bone mineral density (aBMD) at birth on conditional growth in abdominal circumference 11–19 weeks (early) and 19–34 weeks (late). Growth variables are all independent. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. (b) Plot of standardised regression coefficients for whole body BA, BMC and aBMD at 4 years on conditional growth in abdominal circumference 11–19 weeks (early) and 19–34 weeks (late). Growth variables are all independent. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

| | BA | | BMC | | aBMD | |
|-------------------------|----------|----------|----------|----------|----------|----------|
| | <i>b</i> | <i>P</i> | <i>b</i> | <i>P</i> | <i>b</i> | <i>P</i> |
| Δ AC z-score | | | | | | |
| 11–19 weeks | 0.17 | 0.008 | 0.23 | <0.001 | 0.23 | <0.001 |
| 19–34 weeks | 0.05 | 0.418 | 0.15 | 0.017 | 0.21 | 0.001 |
| 0–1 year | 0.20 | 0.003 | 0.26 | <0.001 | 0.26 | <0.001 |
| 1–2 years | 0.21 | 0.001 | 0.26 | <0.001 | 0.25 | <0.001 |
| 2–3 years | 0.11 | 0.090 | 0.13 | 0.029 | 0.12 | 0.043 |
| <i>R</i> ² | 0.19 | | 0.27 | | 0.26 | |
| Δ Length z-score | | | | | | |
| 19–34 weeks | 0.28 | <0.001 | 0.26 | <0.001 | 0.19 | <0.001 |
| 0–1 year | 0.44 | <0.001 | 0.44 | <0.001 | 0.33 | <0.001 |
| 1–2 years | 0.32 | <0.001 | 0.40 | <0.001 | 0.39 | <0.001 |
| 2–3 years | 0.23 | <0.001 | 0.33 | <0.001 | 0.35 | <0.001 |
| 3–4 years | 0.14 | <0.001 | 0.15 | <0.001 | 0.14 | 0.001 |
| <i>R</i> ² | 0.48 | | 0.56 | | 0.44 | |

Table 3. Conditional growth in abdominal circumference (AC) from 11 weeks to 3 years and bone indices at 4 years old and conditional growth in length from 19 weeks to 4 years and bone indices at 4 years

Length measured as femur length (19–34 weeks) and crown–heel length birth to 1 year and height 2–4 years.

The table shows standardised regression coefficient (SD change in bone outcome per SD change in conditional growth) from multiple regression analyses with maternal height, parity, late pregnancy triceps, walking speed and smoking as confounders.

BA, bone area; BMC, bone mineral content; aBMD, areal bone mineral density.

strongly related to bone mineral measures at birth than at 4 years of age (Figure 1). However, on formal statistical testing, the differences in regression coefficients for early and late growth with bone outcomes at birth or 4 years did not attain statistical significance.

Patterns of fetal and infant growth as determinants of bone indices at 4 years

Table 3 summarises the conditional analyses of growth from early gestation to the end of the fourth year of postnatal life as determinants of bone indices at 4 years, for both AC and length. It clearly demonstrates significant influences of these growth measures at each time interval over this period, but considerable heterogeneity in effect size for each stage. Figure 2 demonstrates these associations for BMC. Thus, growth at all time intervals (except 19–34 week AC growth for BA) predicted positively and statistically significantly whole body minus head BA, BMC and aBMD, but not estimated vBMD (estimated volumetric BMD) at 4 years. As in the subset with both neonatal and 4-year DXA, in this larger group AC growth in early pregnancy was more strongly associated with bone outcomes at 4 years than was that in late pregnancy. The pattern of postnatal growth was similar for both AC and length,

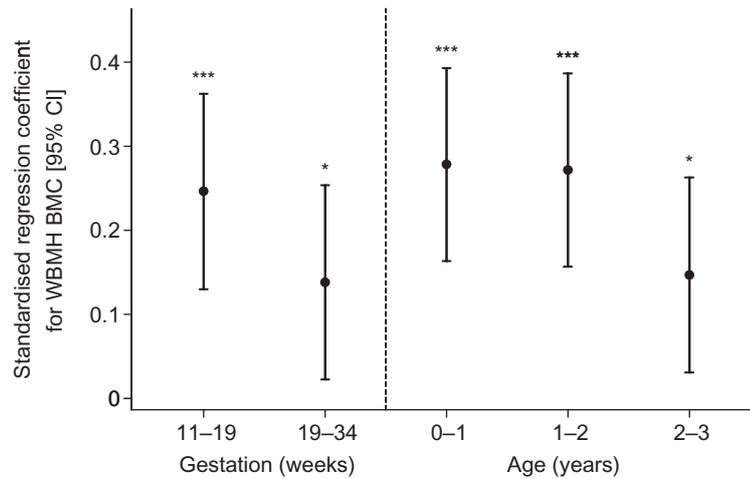
and for BA, BMC and aBMD, with weaker relationships for estimated vBMD. Thus, the associations between growth and bone indices at 4 years were stronger for growth at 0–1 year and 1–2 years than at 2–3 years and 3–4 years.

Further investigation revealed that growth from 0 to 6 months accounted for much of the influence of growth from birth to 1 year. Thus, the regression coefficient for BMC at 4 years on AC growth 0–6 months was 0.26 ($P < 0.001$) and for 6–12 months was 0.14 ($P = 0.022$); the corresponding results for conditional growth in length were 0.39 ($P < 0.001$) and 0.23 ($P < 0.001$). Figure 3 shows the proportion of subjects who stayed in the same third of the AC or length growth distribution at each time interval. These data demonstrate a progressive increase in the proportion of subjects who stay in the same third of the distribution with each successive postnatal time interval.

Correlation between rates of growth in fetal and postnatal life

Non-mutually adjusted conditional growth variables were generated to explore whether growth in early pregnancy (11–19 weeks) was related to that at 2–3 or

(a) Abdominal circumference growth and WBMH BMC at 4 years



(b) Linear growth and WBMH BMC at 4 years

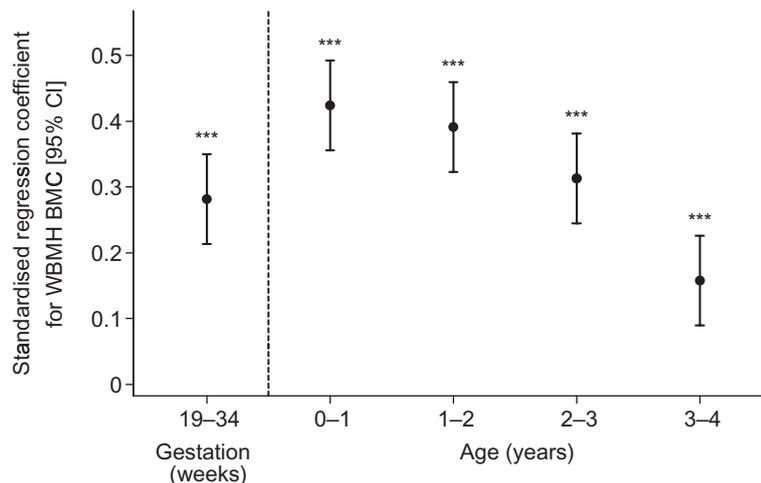


Figure 2. Plot of standardised regression coefficients for whole body minus head (WBMH) bone mineral content (BMC) at 4 years on conditional growth at each time point. Growth variables are all independent. (a) Abdominal circumference. (b) Length (uses: femur length at 19 and 34 weeks, crown-rump length at birth and 1 year, height at 2, 3 and 4 years). * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

3–4 years, when the children appeared to be settling onto a more sustained trajectory. The correlation between conditional change in AC 11–19 weeks and 2–3 years was very low ($r = -0.10$, $P = 0.126$); that between absolute femur length at 19 weeks (equivalent to growth from 0 to 19 weeks) and conditional change in crown-heel length from 3 to 4 years also demonstrated little association ($r = 0.03$, $P = 0.581$). Exploring changes around birth, conditional growth in femur length from 19 to 34 weeks was statistically significantly associated with conditional growth in crown-heel length from birth to 6 months ($r = 0.16$, $P = 0.002$)

but not 6 months to 1 year ($r = 0.002$, $P = 0.972$). The pattern with AC was contrasting, revealing stronger relationships between conditional AC growth 19–34 weeks and conditional AC growth 6 months to 1 year ($r = 0.19$, $P = 0.004$) than conditional AC growth from birth to 6 months ($r = 0.11$, $P = 0.093$).

Maternal determinants of offspring growth

We have previously demonstrated that maternal factors such as height, parity, and fat stores (triceps skinfold thickness), smoking and walking speed in late preg-

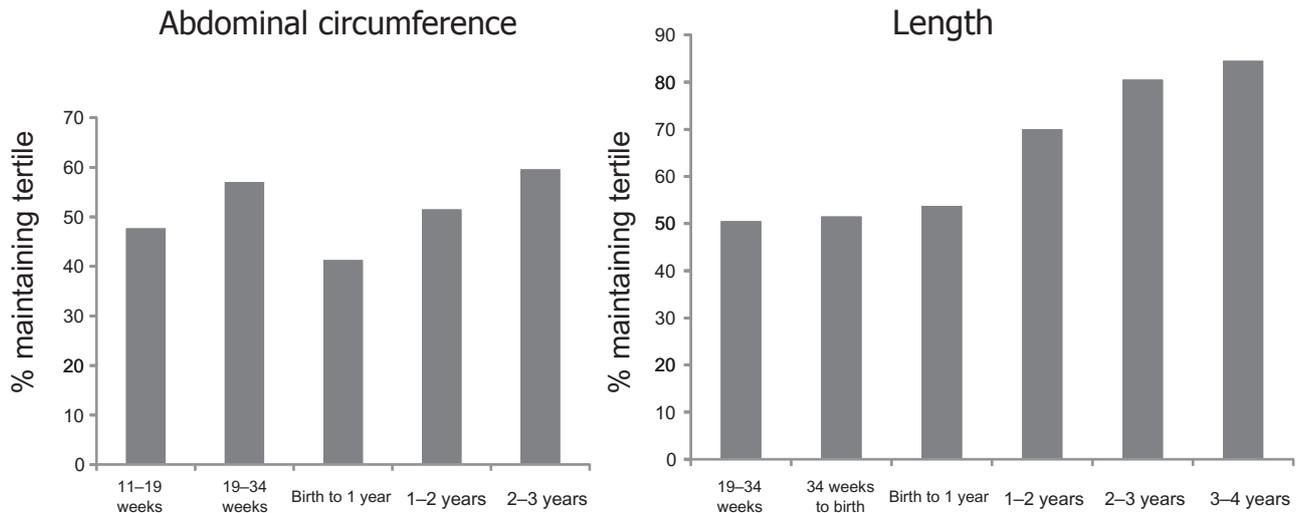


Figure 3. Proportion of subjects who stay within original third of size/distribution for each growth period. Left panel: abdominal circumference; Right panel: length (femur length at 19 and 34 weeks, crown–rump length at birth and 1 year, height at 2, 3 and 4 years).

nancy all predict offspring bone mass at birth.¹² However, when these variables were added into the regression models including growth and bone indices at birth or 4 years, the observed relationships did not change appreciably.

Discussion

To the best of our knowledge, this is the first study to measure fetal and postnatal growth prospectively in relation to objectively measured bone size and density. Our results are consistent with there being at least two general phases of fetal growth, and with late intrauterine growth strongly predicting DXA-derived bone indices at birth and, in contrast, early pregnancy growth more strongly predicting DXA indices at 4 years. These two phases were defined by the available measurement times, and thus may represent a summary of a more complicated multiphase trajectory. The postnatal growth measurements are consistent with the notion that, after the temporary disturbance of growth patterns in late gestation, there is a time of readjustment over the first 2 years of postnatal life, with subsequent settling to a more stable trajectory. These observations suggest that a failure to adequately adjust the growth trajectory in postnatal life after a late pregnancy insult will have an adverse influence on skeletal development.

We studied a large, well established cohort, with detailed characterisation of mothers before and during

pregnancy; we also used DXA, a well validated technique for measuring bone mineralisation in 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 following internationally agreed guidelines^{16,17} and repeatability was good. Additionally, we were only able to measure two time intervals during pregnancy, and therefore may have missed a growth pattern which comprised more than two phases. Furthermore, the differences between regression coefficients for early and late growth and offspring bone outcomes did not achieve statistical significance. Measurement of BMC in young children is hampered by their tendency to move and also by their low absolute BMC. However, we used specific paediatric 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.¹⁸ The study cohort was a subset of the SWS: mothers whose children underwent DXA scanning were on average taller, more educated and smoked less than mothers of children who did not undergo DXA. However, our results are based on internal comparisons, so will not have been biased by these differences. Additionally, there is no reason to suppose that the relationships between fetal growth and childhood bone mass would be different in these two groups.

Finally, although in our earlier paper we found associations between fetal growth and estimated volumetric BMD, in this current subset, these relationships were attenuated, consistent with a stronger relationship between fetal growth and postnatal bone size than with volumetric density. However, the use of DXA does not allow measurement of true volumetric bone density, thus making it difficult to be certain about differential determinants of skeletal size and volumetric density.

There are very few existing data relating to fetal growth using objective ultrasound and DXA measurements. Clinical observation suggests that the increase in fetal weight reaches a maximum velocity at around 34 weeks, when it begins to slow, probably because of physical constraint, partly as a result of maternal pelvic size.² Thus, a child genetically predisposed to be large, as a result of a large father, but carried by a small mother, can be delivered. This is consistent with animal studies of cross-breeding shire horses and Shetland ponies: when the mother is the shire horse, the baby is larger than when the mother is the Shetland pony.¹⁹ Both foals became of similar size after a few months, midway between the size of their parents. We have previously demonstrated persisting positive relationships between fetal growth in late pregnancy (femur length and AC) and postnatal bone size and density at 4 years old.¹ This earlier study compared the influence of these two different intrauterine growth parameters on postnatal skeletal indices, and did not examine the relative contribution of growth in early and late pregnancy, as it was not possible to acquire femur length measurements at 11 weeks. Thus, the results of the current analysis confirm positive relationships between late pregnancy AC growth and 4-year BMC and aBMD, but additionally indicate that this association is weaker than that between 4-year bone indices and AC growth measured in early pregnancy (11–19 weeks).

Much of the work on human growth and development has been carried out by Tanner, using external linear measurements rather than ultrasound, and no inclusion of bone indices as outcomes. These early studies have comprehensively mapped the possible growth patterns *in utero* and childhood, suggesting a relatively early postnatal reversion to the initial intrauterine trajectory.^{2,3} These sorts of data have informed the development of standard child linear-growth charts and our data are consistent with the pattern of growth so documented, with stronger asso-

ciations for the non-size-corrected variables. Karlberg developed mathematical models to describe phases of growth, labelling them 'Infancy', 'Childhood' and 'Puberty'. These models, based on analysis of a birth cohort, but without measurements of intrauterine growth or postnatal bone mass, suggested a rapid slowing of growth velocity in the first 6 months of postnatal life (infancy component) and a more slowly decelerating childhood component commencing at about 6 months, with increased adjustment of the distribution in year 2 and subsequent settling to a more sustained trajectory.^{20,21} This model, which the authors suggest matches the understanding of the endocrine determinants of growth, gives a similar overall pattern to that which we found in our study. Karlberg made the assumption that the infancy phase was a continuation of the growth trajectory in late pregnancy. Indeed, our results for femur length are consistent with this notion. However, the relationships we observed for AC suggest a stronger relationship between late pregnancy growth and that from 6 to 12 months postnatally, rather than in the first 6 months of life. This may reflect differences in the trajectories of longitudinal growth and accumulation of body fat/liver size, both of which contribute to AC.

We explored the correlations between non-mutually adjusted conditional measures of growth in early pregnancy and late infancy/early childhood, to test the idea that the child eventually reverts to the early pregnancy growth trajectory. Although the growth in AC from 11 to 19 weeks predicted bone indices at 4 years more strongly than did growth in AC from 19 to 34 weeks, we found that the correlation between AC growth 11–19 weeks and 2–3 years was very weak; these data, and similar results for length, suggest that the child settles on a longer-term postnatal trajectory, but that its similarity to that experienced in early gestation is limited.

Epidemiological studies suggest that growth in early life, both *in utero* and during infancy, predicts adult BMC,^{22,23} as well as the risk of hip fracture.²⁴ Our results demonstrated a 0.56 standard deviation difference in aBMD between highest and lowest quintiles of conditional AC growth from 19 to 34 weeks. If this difference were to persist into adult life, it could account for up to a 50% difference in relative risk of fracture, as a 1 standard deviation difference in adult aBMD equates to up to a two-fold fracture risk difference,^{25,26} suggesting that these differences will be clinically relevant. Our results clearly demonstrate that tracking of skeletal

growth has its origins *in utero*, but that there is potential for change in later pregnancy and infancy. We have previously shown that maternal parity, life style, body build and physical activity influence offspring bone mass.^{11,12} Inclusion of these variables in our regression models did not alter the relationships found, and it is likely that these factors act on bone mass via an effect on fetal growth. As the eventual childhood trajectory appears to be different from that experienced in early gestation, it is possible that such environmental factors might have a permanent influence on the future development of the child, either through modulation of physiological systems or epigenetic mechanisms.¹⁰ Further work will be needed to explore these interactions more fully, possibly to elucidate findings on which to base novel public health strategies aimed at optimising childhood skeletal development.

In conclusion, we have demonstrated objectively, with validated methodology, in a large prospective population cohort, that if fetal growth is dichotomised into early (11–19 weeks gestation) and late (19–34 weeks gestation) phases, growth velocity in the late phase appears to predict bone mass at birth more strongly than does growth in the early phase. In contrast, bone mass at 4 years appears to be predicted more strongly by growth in early than in late pregnancy. Our results are consistent with a reordering of individuals within the growth distribution during late pregnancy and in the early years of postnatal life serving to bring the individual to a more stable trajectory by 4 years old, but which is different to that experienced in early gestation. Further exploration of the environmental characteristics which might modify gene expression in these developmentally plastic periods should increase our understanding of possible interventions to optimise growth.

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