Placental size at 19 weeks predicts offspring bone mass at birth: Findings from the Southampton Women's Survey

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ABSTRACT

Objectives: In this study we investigate the relationships between placental size and neonatal bone mass and body composition, in a population-based cohort.

Study design: 914 mother–neonate pairs were included. Placental dimensions were measured via ultrasound at 19 weeks gestation. Dual X-ray absorptiometry (DXA) was performed on the neonates within the first two weeks of life.

Results: We observed positive relationships between placental volume at 19 weeks, and neonatal bone area (BA; $r = 0.26$, $p < 0.001$), bone mineral content (BMC; $r = 0.25$, $p < 0.001$) and bone mineral density (BMD; $r = 0.10$, $p = 0.001$). Thus placental volume accounted for 6.25% and 1.2% of the variation in neonatal BMC and BMD respectively at birth. These associations remained after adjustment for maternal factors previously shown to be associated with neonatal bone mineral accrual (maternal height, smoking, walking speed in late pregnancy, serum 25(OH) vitamin D and triceps skinfold thickness).

Conclusions: We found that placental volume at 19 weeks gestation was positively associated with neonatal bone size and mineral content. These relationships appeared independent of those maternal factors known to be associated with neonatal bone mass, consistent with notion that such maternal influences might act through modulation of aspects of placental function, e.g. utero-placental blood flow or maternal nutrient concentrations, rather than placental size itself. Low placental volume early in pregnancy may be a marker of a reduced postnatal skeletal size and increased risk of later fracture.

1. Introduction

Osteoporosis is a major cause of morbidity and mortality through its association with age-related fractures. Bone size and density appear to track throughout childhood to peak in early adulthood, and this peak bone mass has been shown to be a major determinant of osteoporosis risk in later life [1]. We have previously demonstrated that growth in utero and early childhood predict adult bone mineral content (BMC) [2,3] and risk of hip fracture in later life [4]. Maternal factors such as smoking, body build, physical activity, diet [5] and circulating 25(OH) vitamin D status [6] during pregnancy are associated with offspring bone mineral accrual. During the period of a normal human pregnancy the fetus accumulates approximately 30 g of calcium [7]. This fetal demand is met through placental calcium transport, which results in a higher calcium concentration in fetal than maternal blood [8]. We have previously demonstrated that the expression of a placental calcium transporter (PMCA3) gene predicts neonatal bone mineral content [9], but it remains unclear whether the maternal influences described act on fetal bone development via placental size or function.

In this study we investigate the relationships between placental dimensions, measured by ultrasound scanning, and offspring body composition, bone size and density assessed by dual x-ray absorptiometry (DXA) at birth, using a longitudinal population-based mother-offspring cohort, the Southampton Women's Survey (SWS).

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2. Methods

2.1. Participants

Details of the SWS have been published previously [10]. In brief, 12,583 non-pregnant women aged 20–34 years were recruited via their general practitioners. Assessments of lifestyle, diet (by validated food frequency questionnaire) 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 social class was also measured via questionnaire. Maternal height was measured pre-pregnancy with a stadiometer (Seca, Birmingham, UK), weight with calibrated digital scales (Seca, Birmingham, UK) and skin folds (biceps, triceps, subscapular and supra-iliac) with Harpenden callipers (Baty International, Sussex, UK). Serum 25(OH) Vitamin D was measured in late pregnancy (Diasorin Liaison RIA, Minnesota, USA). Women were asked to characterise their walking speed into one of five categories (very slow, stroll at an easy pace, normal speed, fairly brisk or fast) as a marker of overall physical activity. The women's own birth weight was recorded (by recall, checked, where possible, by asking her to consult her own parents).

2.2. Prenatal ultrasound scanning

3159 singleton pregnancies were followed. At 19 weeks gestation, the women underwent high-resolution ultrasound scanning using an Acuson Sequoia 512 system (Siemens, Malvern, PA, USA) with a 5–8 MHz curvelinear transducer. After establishing correct positioning according to standard anatomical landmarks, measurements of placental section perimeter, length of attachment to the uterine wall and cross-sectional area were made on the frozen two-dimensional images using electronic callipers by an experienced sonographer (either PM or CN) – (Fig. 1). The sonographer measured the placenta in two planes, initially along the longest edge of attachment to the uterine wall (length) and then at 90° to this, so that the image plane bisected the longitudinal axis (breadth). Each measurement was performed in triplicate and the mean value used for analysis. Placental volume was later calculated using the two-dimensional ultrasound measurements. To estimate the volume of the placenta we assumed that it was an ellipsoid. The two measured section perimeters and two areas were expressed as functions of the three ellipsoid radii. Estimates of the radii, obtained by least squares, were then combined to estimate the volume. This method demonstrated good correlation with placental volume measured by 3D ultrasound (Kretz Voluson 730 ($r = 0.64$, $p < 0.0001$)) in a sub-set of 28 pregnancies at mean 19.9 (0.4) weeks gestation.

2.3. Neonatal DXA assessment

Mothers registered with specific general 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 sub-study, and were representative of the population Southampton as a whole. At birth, the babies were weighed on calibrated digital scales (Seca, UK). The mother was asked to give written informed consent for her

baby to undergo assessment of bone mass and body composition within 2 weeks of birth, using a DXA scanner with specific paediatric software (Lunar DPX-L paediatric small scan mode v 4.7c, GE Corporation, Madison, Wisconsin, USA). The instrument underwent daily quality assessment and was calibrated against a water phantom weekly.

At the visit to the scan room, the baby was pacified and fed if necessary, undressed completely, and then swaddled in a standard towel. Measurement of whole body bone area (BA), bone mineral content (BMC), areal bone mineral density (aBMD) and body composition were performed (total and proportionate fat and lean). The short-term and long-term coefficients of variation (CV) for adult whole body BMD for the DXA instrument were 0.8% and 1.4% respectively. The radiation exposure to the baby was estimated as a maximum of 8.9 microsieverts for whole body measurement, which is equivalent to 3 days' exposure to normal background radiation. All DXA scans were reviewed and those with movement artefact (41 scans) were excluded from the study.

2.4. Statistical analysis

Gestational age was determined using an algorithm combining last menstrual period and early ultrasound data. All variables were checked for normality. Neonatal total fat mass, proportionate lean mass and proportionate fat mass were not normally distributed and were transformed using a Fisher–Yates transformation (standard deviate units). Unpaired t-tests were used to compare unstandardized neonatal characteristics by sex. A Mann–Whitney U test was used if assumptions of normality were not met.

Pearson correlation and linear regression were used to relate placental measurements to neonatal body composition and bone size and density. We then explored whether previously identified maternal determinants of neonatal bone mass might be mediated via placental measurements using multivariate linear regression. Stata V11.1 (StataCorp LP, College Station, TX) was used for all analyses. Bone outcomes included whole body BA, BMC and aBMD. To adjust for body size we used size corrected BMC (BMC adjusted for BA, and the baby's length and weight (scBMC)). DXA measurements were associated with the square of offspring age at the scan, consistent with the known tendency of infants to lose weight transiently over the first week of postnatal life. Thus, all neonatal outcomes were adjusted for gestational age, sex and the square of the age at DXA; birth weight was adjusted for gestational age. The ultrasound-derived placental measures were also adjusted for gestational age at which the measurement was taken using the method of Royston and subsequently standardized to z-scores [11].

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

3. Results

3.1. Characteristics of the mothers and neonates

Of the 3159 participants, 914 had complete 19 week ultrasound and neonatal DXA data, and delivered after 37 weeks gestation. Baseline characteristics of the women are shown in Table 1(a). The median (IQR) age of the mothers at the birth of their babies was 31.1 (28.0–33.8) years. Their mean (SD) height was 163.4 (6.3) cm and median (IQR) BMI pre-pregnancy was 24.2 (22.0–27.5) kg/m^2.

The baseline characteristics of the 914 (474 male) neonates are shown in Table 1(b). The boys tended to be heavier at birth, with higher BA, BMC and aBMD. All outcome measures were therefore adjusted for infant's sex.

Compared with mothers of children born to the SWS cohort during the same time frame but who did not have placental measurements at 19 weeks or a neonatal DXA scan, the mothers in this study were more highly educated (24.5% versus 21.2% achieving a higher degree, $p = 0.10$) and were less likely to smoke in pregnancy, although this did not achieve statistical significance (17.6% vs. 21.7%, $p = 0.06$). There were no differences in maternal age at child's birth, maternal height, BMI or smoking before pregnancy between the two groups.

3.2. Placental ultrasound measurements at 19 weeks and neonatal body composition

Table 2 summarises the relationships between placental measurements and offspring body composition and bone size and
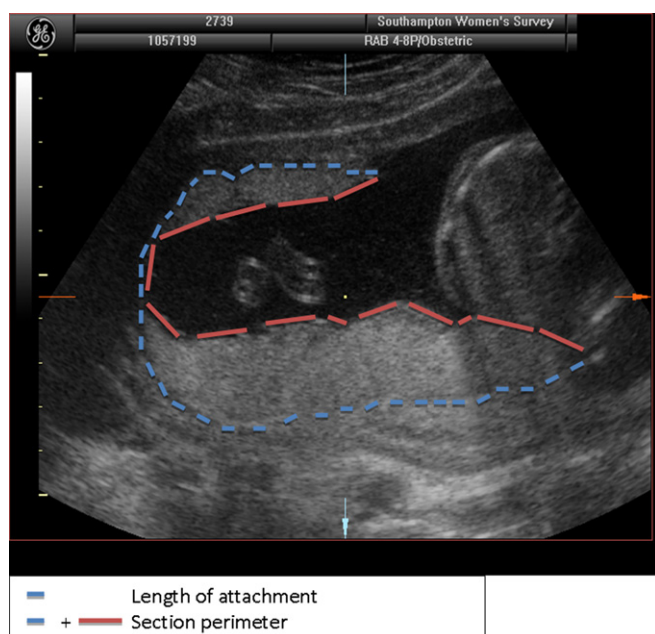

Fig. 1. A 19 week ultrasound scan showing placental size measurements in the longitudinal plane.

Table 1
Characteristics of mothers and neonates.

A) Maternal characteristics $n = 914$	
Age at child's birth (yr)	31.1 (28.0–33.8)
Height (cm)	163.4 (6.3)
BMI pre-pregnancy (kg/m^2)	24.2 (22.0–27.5)
Triceps skinfold at 34 weeks (mm)	20.6 (16.7–25.6)
Parity	
0	480 (52.5%)
1 or more	434 (47.5%)
Smoking before pregnancy	
No	665 (72.8%)
Yes	249 (27.2%)
Smoking at 34 weeks	
No	760 (86.6%)
Yes	118 (13.4%)
Walking speed at 34 weeks	
Very slow	139 (16.2%)
Stroll	433 (50.5%)
Normal speed	230 (26.5%)
Fairly brisk	52 (6.1%)
Fast	3 (0.4%)
Serum 25(OH) Vitamin D at 34 weeks (nmol/l)	63.9 (44.0–87.0)
Placental circumference[a] at 19 weeks (cm)	29.5 (27.2–32.2)
Placental circumference[b] at 19 weeks (cm)	29.2 (26.7–38.9)
Placental length of attachment[a] at 19 weeks (cm)	15.6 (14.1–17.4)
Placental length of attachment[b] at 19 weeks (cm)	15.6 (14.0–22.4
Placental cross-sectional area[a] at 19 weeks (cm^2)	24.4 (21.0–28.5)
Placental cross-sectional[b] at 19 weeks (cm^2)	24.3 (20.6–28.9)
Placental volume at 19 weeks (cm^3)	230.1 (192.7–277.9)

B) Neonatal characteristics	Boys $n = 474$	Girls $n = 440$	p Diff
Birth weight (kg)	3.59 (0.5)	3.49 (0.5)	0.002
Gestational age (weeks)	40.1 (1.2)	40.3 (1.2)	0.01
Gestational age at time of scan (weeks)	19.6 (0.6)	19.6 (0.5)	0.7
Birth crown-heel length (cm)	50.5 (1.9)	49.7 (1.9)	<0.001
Age at DXA (days)	6.4 (2–11)	6.5 (2–12)	0.69
Whole body bone area (cm^2)	121.4 (25.3)	118.0 (24.9)	0.001
Whole body BMC (g)	65.0 (15.6)	61.3 (15.1)	<0.001
Whole body aBMD (g/cm^2)	0.5 (0.03)	0.5 (0.3)	<0.001
Size corrected BMC (g)	62.4 (2.9)	61.8 (2.9)	0.003
Total lean mass (g)	3026.6 (358.8)	2884.9 (323.7)	<0.001
Total fat mass (g)	507.7 (382.4–655.6)	533.3 (403.5–694.6)	0.01
%Lean mass (%)	84.2 (81.2–87.3)	83.0 (79.6–85.6)	<0.001
%Fat mass (%)	13.9 (11–16.9)	15.3 (12.7–18.5)	<0.001

Data are mean (SD), median (IQR) or number (%).
[a] Measured along the longest edge of attachment to the uterine wall (length).
[b] Placenta measured perpendicular to the longest edge of attachment to the uterine wall (breadth).

density. We observed strong positive relationships between each of placental section perimeter, length of attachment to the uterine wall and cross-sectional area at 19 weeks and neonatal BA and BMC (all $p < 0.001$). However, there was some disparity in the relationship between neonatal aBMD and these placental measurements depending on the plane of placental measurement; a positive association was seen between placental measurements and aBMD when the placenta was measured along its breadth (p

Table 2
Relationship between placental size and neonatal bone mass and body composition.

	BA (cm^2)	BMC (g)	aBMD (g/cm^2)	BA adjusted for crown-heel length (cm^2)	Size corrected BMC (g/cm^2)	Total lean (g)	Total fat (z)	%Lean (z)	%Fat (z)
	r	r	r	r	r	r	r	r	r
Placental measurements at 19 weeks									
Section perimeter[a] (z)	0.15***	0.13***	0.04	0.07*	−0.03	0.14***	0.12***	−0.10***	0.09**
Length of attachment[a] (z)	0.12***	0.11***	0.04	0.06	−0.03	0.11**	0.09**	−0.08*	0.07*
Cross-sectional area[a] (z)	0.18***	0.17***	0.05	0.09*	−0.01	0.18***	0.18***	−0.15***	0.15***
Section perimeter[b] (z)	0.20***	0.19***	0.11**	0.14***	0.006	0.16***	0.16***	−0.14***	0.14***
Length of attachment[b] (z)	0.16***	0.16***	0.09**	0.13***	0.008	0.10**	0.13***	−0.13***	0.13***
Cross-sectional area[b] (z)	0.22***	0.21***	0.11***	0.14***	0.02	0.18***	0.19***	−0.18***	0.17***
Volume (z)	0.26***	0.25***	0.11**	0.16***	−0.001	0.23***	0.23***	−0.20***	0.19***

Table shows Pearson's correlation coefficients (r) from univariate regression analyses.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
[a] Measured along the longest edge of attachment to the uterine wall (length).
[b] Measured perpendicular to the longest edge of attachment to the uterine wall (breadth).

all < 0.01), but no association was seen when the placenta measured along its longest axis (length).

Placental volume correlated positively with neonatal BA, BMC and aBMD (p all < 0.01) and neonatal BA adjusted for crown-heel length ($r = 0.15$, $p < 0.001$). Thus, for every 1 SD increase in placental volume, BA increased by 6.2 cm², BMC increased by 3.6 g, aBMD increased by 0.0029 g/cm² and BA adjusted for crown-heel length increased by 2.9 cm² (Fig. 2). No significant association was observed between placental size and neonatal size corrected BMC (all $p > 0.36$).

Placental volume at 19 weeks was positively associated with neonatal total lean mass ($r = 0.23$, $p < 0.0001$) and fat mass ($r = 0.23$, $p < 0.0001$). There was a different pattern with proportionate body composition. Thus, placental volume was positively related to percent fat ($r = 0.19$, $p < 0.0001$) but negatively to percent lean ($r = -0.20$, $p < 0.0001$), indicating that as placental volume increased, total neonatal size increased, but with an increase in percentage fat and a reduction in percentage lean within the overall size envelope (Fig. 3).

We performed a sensitivity analysis by removing extreme values (excluding those participants with placental volume > 500 mm³, total lean mass < 2200 g, percent lean < 70 and percent fat > 30) and the strongly significant relationships remained with little or no change in r value (Pearson correlation coefficient for association with placental volume: total lean mass, $r = 0.2$, $p < 0.00001$; total fat mass, $r = 0.23$, $p < 0.00001$; percent lean, $r = -0.17$, $p < 0.00001$; percent fat, $r = 0.18$, $p < 0.00001$).

All associations remained after adjustment for maternal factors previously shown to affect neonatal bone mineral accrual (parity, smoking, walking speed, maternal serum 25(OH) vitamin D and maternal triceps skinfold thickness in pregnancy). In addition, the relationship between placental size and offspring bone mass was adjusted for maternal height, as maternal body build tends to be collinear with placental size, and although this attenuated some results, the relationships remained statistically significant (Table 3).

Relationships between placental and DXA measurements were similar in boys and girls, with all placental measurement/sex interactions on bone outcomes failing to achieve statistical significance ($p > 0.05$).

We calculated the ratio of placental volume: birth weight as a marker of placental "efficiency". This was positively associated with neonatal BA and BMC ($p < 0.01$), however after adjustment for maternal factors known to affect neonatal bone mineral accrual, significant associations were no longer seen.

3.3. Maternal characteristics and placental size

Several maternal factors were positively correlated with placental volume at 19 weeks (Table 4). Placental volume was positively associated with maternal height ($r = 0.09$, $p = 0.007$), body fat pre-pregnancy ($r = 0.11$, $p = 0.001$) and age at child's birth ($r = 0.07$, $p = 0.03$). Smoking, 25(OH) vitamin D status, parity, social class and walking speed pre-pregnancy were not statistically significantly associated with placental volume.

4. Discussion

To our knowledge, this is the first study to relate ultrasound measurements of mid-pregnancy placental size to postnatal infant bone mass and body composition measured by DXA. Placental section perimeter, length of attachment and volume were positively associated with offspring intrauterine bone mineral accrual. An association between mid-pregnancy placental size and neonatal body composition was also observed; thus greater placental volume was associated with greater birth weight, higher percentage fat and lower percentage lean. These relationships appeared independent of maternal height and other factors (parity, smoking, walking speed, maternal serum 25(OH) vitamin D and maternal triceps skinfold thickness in pregnancy) known to influence neonatal bone mass, consistent with the notion that these maternal factors may act through modulation of aspects of placental function, such as utero-placental blood flow or maternal nutrient concentrations, rather than size alone.

This was a large prospective study, with detailed characterization of the mothers and babies, using a validated measure of bone mineral. However, several limitations should be considered in the interpretation of our results. First, intrauterine ultrasound measurements are prone to reproducibility error; however the scans were performed by two experienced sonnographers following standard guidelines. Second, although the use of DXA is well established in adults, there are limitations to its use in neonates due to their tendency to move and their low absolute BMC. Specific paediatric software was used to minimise loss of edge detection, and movement artefact was modest and uniform across the cohort. Babies with excessive movement were excluded from the analysis. It was not possible to perform repeat DXA assessments on the neonates to determine values for the coefficient of variation of DXA in children. However, DXA measurements of bone mass have been shown to correlate well with whole body calcium
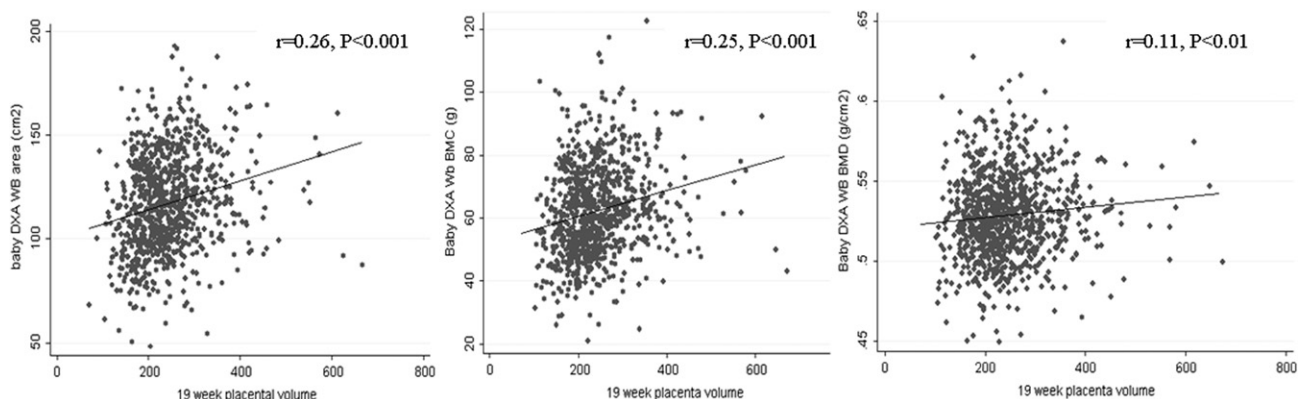

Fig. 2. Association between placental volume at 19 weeks and neonatal bone mass Scatter-plots illustrating the relationship between placental volume, measured by ultrasound at 19 weeks, and neonatal bone mass measured by dual x-ray absorptiometry (DXA). Placental volume correlated positively with neonatal BA, BMC and aBMD (p all < 0.01). For every 1 SD increase in placental volume, BA increased by 6.2 cm², BMC increased by 3.6 g, aBMD increased by 0.0029 g/cm² and BA adjusted for crown-heel length increased by 2.9 cm². Placental volume adjusted for gestational age. BA, BMC, BMD adjusted for sex, gestational age and square of age at scan. WB: whole body

Total lean mass

Total fat mass
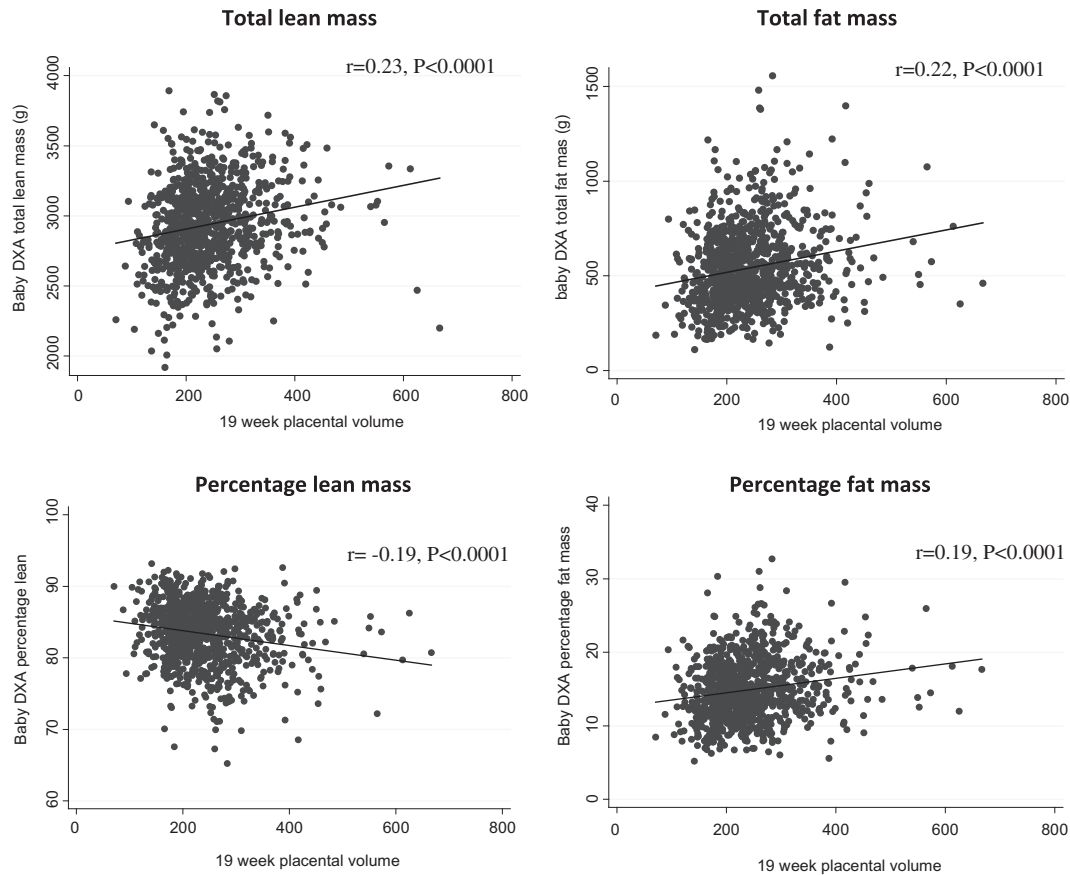

Percentage lean mass

Percentage fat mass

Fig. 3. Association between placental volume at 19 weeks and neonatal fat and lean mass Scatter-plots illustrating the relationship between placental volume, measured by ultrasound at 19 weeks, and neonatal bone mass measured by dual x-ray absorptiometry (DXA). Placental volume at 19 weeks was positively associated with neonatal total lean mass ($r = 0.23$, $p < 0.0001$) and fat mass ($r = 0.23$, $p < 0.0001$). There was a different pattern with proportionate body composition. Thus, placental volume was positively related to percent fat ($r = 0.19$, $p < 0.0001$) but negatively to percent lean ($r = -0.20$, $p < 0.0001$). Volume adjusted for gestational age. Lean mass and fat mass adjusted for sex, gestational age and square of age at scan

content in studies of small animals such as piglets [12]. We have reported on a sub-set of the original SWS births. On average the mothers included in this study were better educated and were slightly less likely to smoke in pregnancy compared with SWS mothers of babies who were not assessed by ultrasound at 19 weeks nor had neonatal DXA measurements. However, as the observations we report are based on internal comparisons, there is no reason to suppose that this would have biased the results. The use of DXA does not allow for true measurement of volumetric bone density, making it difficult to distinguish relationships with bone size from those with bone density. Finally, as this was an observational study it is not possible to be sure about the direction of associations between placental size and offspring bone mass, and whether they represent causal relationships; the lack of detailed physiological data also meant that we were unable to positively delineate effects of placental size and placental function.

Table 3
Relationship between placental size and neonatal bone mass and body composition, adjusting for potentially confounding maternal influences.

	BA (cm^2)	BMC (g)	aBMD (g/cm^2)	BA adjusted for crown-heel length (cm^2)	Size corrected BMC (g/cm^2)	Total lean (g)	Total fat (z)	%Lean (z)	%Fat (z)
	r	r	r	r	r	r	r	r	r
Section perimeter[a] (z)	0.15 ***	0.13 ***	0.03	0.07*	−0.05	0.14 ***	0.14 ***	−0.12 ***	0.12 **
Length of attachment[a] (z)	0.15 ***	0.13 ***	0.04	0.08*	−0.04	0.11 **	0.12 **	−0.10**	0.09**
Cross-sectional area[a] (z)	0.15 ***	0.14 ***	0.03	0.08 *	−0.01	0.15 ***	0.16 ***	−0.14 ***	0.14 ***
Section perimeter[b] (z)	0.22 ***	0.22 ***	0.12***	0.15***	0.02	0.19 ***	0.20 ***	−0.17***	0.17 ***
Length of attachement[b] (z)	0.20 ***	0.20 ***	0.12***	0.13***	0.03	0.16 ***	0.18 ***	−0.16 ***	0.16 ***
Cross-sectional area[b] (z)	0.18 ***	0.18 ***	0.10 **	0.10**	0.04	0.18 ***	0.16 ***	−0.15 ***	0.14 ***
Volume (z)	0.24 ***	0.23 ***	0.10 **	0.14***	0.003	0.22 ***	0.23 ***	−0.20 ***	0.19 ***

Table shows Pearson's correlation coefficients (r) from multiple regression analyses taking account of maternal height, smoking in pregnancy, walking speed in late pregnancy, triceps skinfold thickness in late pregnancy and serum 25(OH) Vitamin D in late pregnancy as confounders.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
[a] Measured along the longest edge of attachment to the uterine wall (length).
[b] Measured perpendicular to the longest edge of attachment to the uterine wall (breadth).

Table 4
Relationship between maternal characteristics and placental volume.

	Placental volume adjusted for gestation (z)			
	β (95% CI)	p	Mutually adjusted β (95% CI)	p
Age (SD)	0.07 (0.008–0.13)	**0.03**	0.01 (−0.008–0.12)	0.09
Height (SD)	0.09 (0.02–0.15)	**0.01**	0.08 (0.01–0.14)	**0.02**
Parity, 2 groups	0.12 (−0.01–0.24)	0.07	0.10 (−0.03–0.23)	0.14
Walking speed pre-pregnancy (5 groups)	−0.003 (−0.09–0.08)	0.95	−0.03 (−0.12–0.06)	0.50
Body fat pre-pregnancy (SD)	0.11 (0.05–0.17)	**0.001**	0.09 (0.03–0.16)	**0.004**
Smoking in pregnancy (Yes/No)	0.11 (−0.07–0.29)	0.23	0.12 (−0.06–0.30)	0.19
Social class (6 groups)	0.01 (−0.02–0.05)	0.45	0.03 (−0.03–0.09)	0.29

Table shows regression coefficient (95% confidence interval) and mutually adjusted regression coefficient from univariate and multiple regression analyses respectively. Bold type denotes $p < 0.05$.

Several studies have investigated the association between birth weight and placental size at various points in gestation. Placental volume measured by 3D ultrasound scanning in the first trimester was positively associated with birth weight in one study of 199 women [13]. Likewise, placental volume derived from ultrasound measurements in mid-pregnancy and by direct measurement at birth have been shown to correlate positively with birth weight [14–17]. The rate of placental growth appears to be an important determinant of birth weight, with the rate between 17 and 20 weeks gestation being a predictor of fetal abdominal and head circumference, femoral length and biparietal diameter; weaker associations are observed for placental growth earlier in pregnancy (at 14–17 weeks) [18].

The size, weight and shape of the placenta are all subject to wide variations [19], and growth along one axis may be controlled differently from that along the other axis [20]. Growth of the placenta may be polarised from the time of implantation, and it has been suggested that growth along the major axis (maximal diameter or placental length) is aligned with the rosto-caudal axis of the embryo, whereas tissue along the minor axis (breadth) may be more important for transfer of nutrient to the fetus and may be more sensitive to the mother's nutrition [20]. Thus, the human fetus may attempt to compensate for under-nutrition by expansion of the placenta along its minor axis. Pre-eclampsia, which is associated with reduced placental size, is an example of this. Placentas from pregnancies complicated by pre-eclampsia have increased thickness due to a reduction in breadth, with no significant association with length [21]. In our study, length of attachment to the uterine wall, section perimeter and cross-sectional area measured along both axis, were equally associated with offspring BA and BMC. These placental measurements, when taken transversely along the minor axis, were also associated with neonatal aBMD; in contrast, no association with aBMD was seen when the placenta was measured along its longest axis (length). This may suggest that growth along the minor axis may be more important for nutrient transfer and capacity for mineralisation.

Nutrient transport is one of the many functions of the placenta. Up to 30 g of calcium crosses to the fetus in a successful pregnancy; in the third trimester calcium transport quadruples to around 140 mg/kg per day to sustain adequate mineralisation of the fetal skeleton [7]. Placental calcium transport occurs in the synctiotrophoblast [22]; calcium crosses the placenta bound to calcium transport proteins including calbindin-D9K and calnexin before being actively extruded from the basal plasma membrane of the trophoblast layer to the fetal circulation via a number of pumps and exchangers, such as Na^+/Ca^{2+} exchanger and plasma membrane Ca^{2+}-ATPase. This last group of transport proteins includes four individual isoforms (PMCA 1–4) [22]. It has previously been demonstrated in animal models that a 2–3 fold increase in PMCA gene expression is associated with a 72-fold increase in calcium transport across the placenta in late gestation [23].

Maternal 25 (OH) vitamin D concentration appears to influence offspring bone mineral accrual though effects on the concentration of umbilical venous calcium [6], and it is possible that regulation of placental transport may be important in the relationships between placenta and offspring bone mass. Indeed we have previously shown that expression of PMCA 3 was positively related to neonatal whole body BMC [9], and several studies have demonstrated the importance of nutrient transport across the placenta, even after adjustment for overall size. Maternal vitamin D concentration may exert its effects on offspring bone mass through PMCA 3 expression [9], however mechanistic confirmation is required to determine whether the effects are due to altered presentation of nutrient to the placenta (substrate dependent) or a direct action on transport processes. It is difficult to distinguish between the two potential mechanisms, and our results would be consistent with either, rather than an effect purely on placental size per se.

The strongest associations detected in our study were between placental size and neonatal skeletal size. Placental volume predicted neonatal BA and BMC more strongly than aBMD and scBMC. This finding is consistent with previous studies showing that skeletal size, rather than volumetric density is influenced by early life factors. Density tends to be more dependent on environmental influences later in the life course, such as loading and nutrition [2,24]. However, in adult studies, bone size and BMC perform well as predictors for fracture risk suggesting that the overall size of the skeletal envelope will have longer term implications.

Thus, recent work has suggested that peak bone mass is a critically important determinant of osteoporosis in later life [1] and we have previously demonstrated that early growth predict adult bone mass [2,3] and risk of hip fracture in later life [4]. We have found that for every 1 SD increase in placental volume, neonatal BMC increases by 3.6 g. Placental volume accounted for 6.25% of the variation in BMC and 1.2% in the variation of BMD at birth. Although these associations appear modest, they are potentially biologically significant: the difference in mean BMC or BMD for those individuals who were in the top compared with bottom quartile of placental volume at 19 weeks was 0.7 SD and 0.3 SD respectively. If these differences were to be sustained into adulthood, they might equate to a 15% difference in risk of fracture [25]. This figure is similar to the 13% increased risk of vertebral fractures in women who smoke [a risk factor incorporated into the standard international method of risk stratification (FRAX™) [26]] compared to women who do not. Therefore our findings may well be relevant in terms of later bone health.

5. Conclusions

In conclusion, we have demonstrated that placental size measured in mid-pregnancy by ultrasound predicts neonatal bone mass and body composition, independently of maternal factors known to influence neonatal bone mass (parity, smoking, walking

speed, maternal serum 25(OH) vitamin D and maternal triceps skinfold thickness in pregnancy). These findings would be consistent with these factors acting through modulation of aspects of placental function, such as utero-placental blood flow or maternal nutrient concentrations, rather than placental size; this observation requires positive demonstration in further studies. Low placental volume early in pregnancy may be a marker of a smaller postnatal skeletal size and potentially increased risk of fracture in older age.

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Conflict of interest

All authors report no conflict of interest.

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