Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study

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Summary

Background Vitamin D insufficiency is common in women of childbearing age and increasing evidence suggests that the risk of osteoporotic fracture in adulthood could be determined partly by environmental factors during intrauterine and early postnatal life. We investigated the effect of maternal vitamin D status during pregnancy on childhood skeletal growth.

Methods In a longitudinal study, we studied 198 children born in 1991–92 in a hospital in Southampton, UK; the body build, nutrition, and vitamin D status of their mothers had been characterised during pregnancy. The children were followed up at age 9 years to relate these maternal characteristics to their body size and bone mass.

Findings 49 (31%) mothers had insufficient and 28 (18%) had deficient circulating concentrations of 25(OH)-vitamin D during late pregnancy. Reduced concentration of 25(OH)-vitamin D in mothers during late pregnancy was associated with reduced whole-body (r=0·21, p=0·0088) and lumbar-spine (r=0·17, p=0·03) bone-mineral content in children at age 9 years. Both the estimated exposure to ultraviolet B radiation during late pregnancy and the maternal use of vitamin D supplements predicted maternal 25(OH)-vitamin D concentration ($p<0·0001$ and p=0·0110, respectively) and childhood bone mass (p=0·0267). Reduced concentration of umbilical-venous calcium also predicted reduced childhood bone mass (p=0·0286).

Interpretation Maternal vitamin D insufficiency is common during pregnancy and is associated with reduced bone-mineral accrual in the offspring during childhood; this association is mediated partly through the concentration of umbilical venous calcium. Vitamin D supplementation of pregnant women, especially during winter months, could lead to longlasting reductions in the risk of osteoporotic fracture in their offspring.

Introduction

In elderly people, vitamin D insufficiency is common[1] and associated with an increased risk of fragility fracture;[2,3] furthermore, calcium and vitamin D supplementation of those at risk of insufficiency seems to reduce their risk of fracture.[4] Vitamin D is also necessary for skeletal growth during infancy and childhood. In a retrospective cohort study, vitamin D supplementation of premature infants during the first year of life was associated with increased whole-body bone mass at age 12 years.[5]

Vitamin D insufficiency is common in otherwise healthy pregnant women[6] and growing evidence shows that the risk of osteoporotic fracture in later life is increased by the action of adverse environmental stimuli during early development, including intrauterine life.[7] Epidemiological studies have shown that weight at birth and in infancy predicts peak bone mass,[7,8] and bone mass in later life.[9,10] Poor intrauterine and childhood growth are associated with an approximate doubling of hip fracture risk six decades later;[11] maternal body build, nutrition, smoking, and physical activity during pregnancy have also been shown to predict the bone mass of their offspring at birth.[12] However, the relation between maternal vitamin D status during pregnancy and postnatal skeletal growth of their children has not yet been directly assessed. We therefore tested the hypothesis that maternal vitamin D insufficiency during pregnancy has persisting effects on childhood bone mass in a UK population-based cohort of otherwise healthy, term-born children.

Methods

Patients and procedures

The study sample was recruited from children born to 596 white women who had participated in a study of maternal nutrition and fetal growth at the Princess Anne Maternity Hospital, Southampton, UK, between 1991 and 1992.[13] The mothers were older than 16 years and registered before 17 weeks' gestation at the antenatal clinic. During early (median 15·1 weeks [IQR 13·9–16·4]) and late (32·6 weeks [32·0–33·4]) pregnancy, the women completed a lifestyle questionnaire and were asked their smoking habits during pregnancy and their weight before pregnancy.[13] We also obtained information about dietary supplement use during pregnancy. The study was approved by the local research ethics committee and informed consent (written and verbal) was obtained from both mothers and children.

During early pregnancy, we measured the women's height (using a stadiometer) and weight (using calibrated electronic scales), and their mid-upper-arm circumference in late pregnancy. Both the expectant

	Maternal values at time of childbirth
Age (years)	27 (4·9)
Height (metres)	1·63 (0·06)
Bodyweight before pregnancy (kg)	59 (54–66)
Mid-upper-arm circumference during late pregnancy (cm)	26·6 (25·1–28·8)
Primiparous pregnancy	105 (53%)
Smoking at time of last menstrual period	61 (31%)
Smoking during pregnancy	39 (20%)
Social class*	
% I, II	59 (30%)
% IIIN, IIIM, IV, V	136 (70%)
25(OH)-vitamin D concentration in late pregnancy (μg/L)	
<11	28 (18%)
11–20	49 (31%)
>20	83 (52%)

Data are mean (SD), median (IQR), or number (%). *I=professional; II=intermediate; IIIN=skilled non-manual; IIIM=skilled manual; IV=partly skilled; V=unskilled.

Table 1: **Anthropometric and lifestyle characteristics of mothers in follow-up study**

mothers and their partners were asked to contact their own parents to ascertain their own birthweight; fathers were also asked for their height. During late pregnancy (mean 34 weeks [SD 2]), a serum sample was taken from the mothers and samples were stored at −40ºC before measurement of serum 25(OH)-vitamin D by radioimmunoassay (IDS Diagnostics Ltd, Boldon, Tyne & Wear, UK; intra-assay and interassay coefficient of variation [CV]<10%) and the procedure met the requirements of the UK National External Quality Assurance Scheme (NEQAS). This assay measures both vitamin D_2 and D_3. We examined pregnancies that were singleton and term; gestational age was calculated from the date of the last menstrual period and confirmed by ultrasonography of fetal size at the initial visit.

After delivery, two trained fieldworkers recorded neonatal anthropometric measures (birthweight, mid-upper-arm circumference, crown-heel length, and crown-rump length). After clamping of the umbilical cord and before placental delivery, umbilical venous blood samples were taken. Serum samples were stored at −40ºC before calcium, albumin, phosphorus, alkaline phosphatase, and creatinine concentrations were measured, in the Southampton University Hospitals NHS Trust Department of Chemical Pathology, which also subscribes to NEQAS. Measurements were made with a standard Beckman CX-7 analyser (Beckman Coulter Inc, Fullerton, CA, USA); all alkaline phosphatase isoforms are detected by the assay used. The weight of the placenta was measured after the removal of any obvious clots, cutting of the umbilical cord flush with its insertion into the placenta, and stripping of both the fetal and maternal membranes.

We estimated the concentration of ionised calcium in cord blood by adjusting for albumin concentration with the following formula: corrected calcium=calcium (mmol/L)+0·01×(38–albumin). In the absence of agreed healthy ranges for 25(OH)-vitamin D during pregnancy, we used adult thresholds to divide the mothers into: vitamin D replete (>20 μg/L), insufficient (11–20 μg/L), and deficient (<11 μg/L).[14] Estimated exposure to ultraviolet B radiation (UV-B) was derived from the hours of sunshine per month of pregnancy recorded at a local meteorological station (Leckford, Hampshire, UK). We adjusted the total hours of monthly sunshine for seasonal variation in UV-B radiation (Wh/m^2) using the SoDa-IS web service for professionals in solar energy and radiation. The estimated cumulative UV-B exposure in late pregnancy was derived from the 7th month of gestation (187–217 days), because this period was concurrent with the time of the late pregnancy maternal venous sample.

About 9 years later, we invited women and children from the initial cohort who still lived in the local area to attend follow-up. With an interviewer-administered questionnaire, socioeconomic status, diet and exercise of both mother and child (including daily milk intake,[15] sports participation, and outdoor walking) were recorded. The children's heights and weights were measured with a stadiometer and calibrated electronic scales. Additionally, all children underwent measurements of whole-body and lumbar-spine bone-mineral content (BMC), bone area, and areal bone-mineral density (BMD) by DXA (dual energy x-ray absorptiometry; Lunar DPX-L instrument using specific paediatric software; version 4.7c, GE Corporation, Madison, WI, USA). The instrument was calibrated every day and all scans were done with the children wearing light clothing. The position of regional markers on the whole-body and lumbar-spine DXA images were adjusted according to the manufacturer's guidelines. The short-term and long-term coefficients of variation of the instrument were 0·8% and 1·4%, respectively.

For **SoDa-IS** see http://www.soda-is.com/index.html.

Statistical analysis

Data were double entered and analysed by use of Stata version 7.0. Bodyweight, skin-fold thickness, body-mass index, and fat mass, as measured by DXA, were

	Male (n=104)	Female (n=94)	p
During childhood			
Age (years)	8·9 (0·3)	8·8 (0·3)	0·38
Height (metres)	1·32 (0·06)	1·30 (0·06)	0·021
Weight (kg)	28·4 (26·2–32·0)	28·3 (25·2–32·3)	0·57
Whole-body BMC (kg)	1·2 (0·18)	1·1 (0·16)	0·0031
Lean mass (kg)	22·5 (2·8)	20·3 (2·3)	<0·0001
Fat mass (kg)	4·9 (3·7–6·9)	7·2 (5·1–9·3)	0·0001
At birth			
Gestational age (weeks)	40·0 (39·0–40·9)	40·4 (39·1–41·1)	0·27
Birthweight (kg)	3·48 (0·44)	3·37 (0·44)	0·083
Placental weight (kg)	0·53 (0·13)	0·55 (0·12)	0·47
Crown heel length (cm)	50·6 (1·9)	49·8 (1·7)	0·0019

Data are mean (SD) or median (IQR) for variables that are not normally distributed.

Table 2: **Anthropometric characteristics of children in follow-up study**

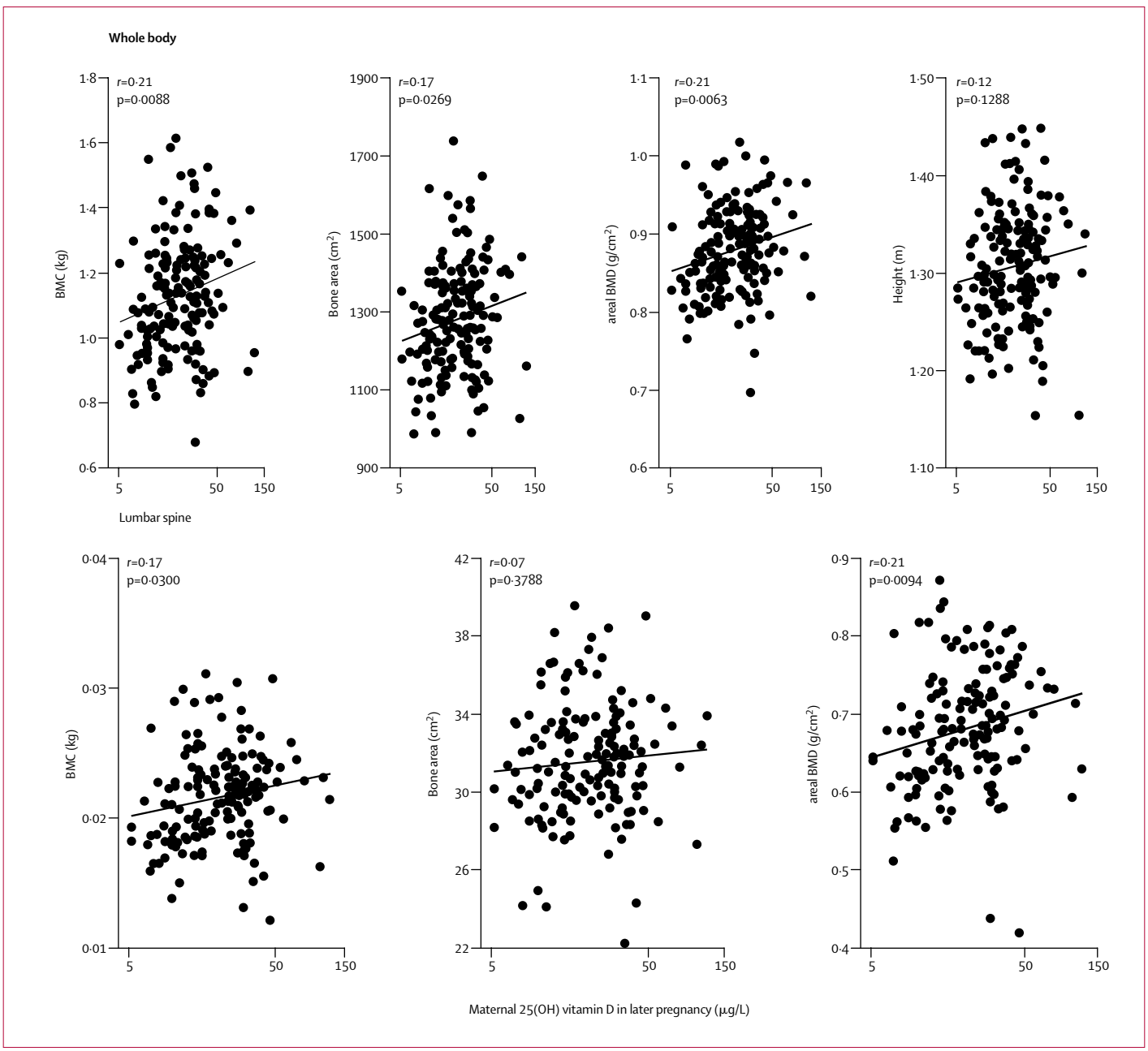

Figure 1: **Maternal 25(OH)-vitamin D concentration in late pregnancy and childhood bone mass at age 9 years**
r=Pearson correlation coefficients after adjustment for gestational and chronological age. Linear regression lines are shown.

positively skewed and therefore were log-transformed to normality for the analysis. A non-parametric Kruskal-Wallis test was used to compare results between groups if non-normality or variance heterogeneity suggested a *t* test was inappropriate. SDs for continuous anthropometric and bone-mineral variables were generated internally. Despite the narrow age range of the sample studied (1·6 years), we recorded a strong association between age at scanning and whole-body BMC (r=0·21, p=0·004); hence, when appropriate, results were adjusted for the age of the child at the time of the scan. Whole-body and lumbar-spine BMC measurements were analysed unadjusted, and were partly corrected for size by use of bone area to calculate areal BMD. We calculated volumetric lumbar-spine BMD using the method of Prentice.[16] Infant and childhood height gain were determined by the residuals from linear regression models of height at every successive timepoint, conditional on the height measured at the previous timepoints.

Role of the funding source
The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
596 infants were included in the original cohort; 461 were still resident in the local area and were invited to attend. 270 mothers responded and 215 agreed to participate in the bone densitometry component of the follow-up survey. Of these participants, 160 had vitamin D measurements in late pregnancy and their children had both whole-body and lumbar-spine measurements recorded. Women who took part in the follow-up study had similar characteristics in most aspects to those in the remainder of the initial cohort. However, participants were slightly older than non-participants in the original cohort (mean 27·1 years *vs* 26·1 years, p=0·014) and were less likely to have smoked at the time of the last menstrual period (61 [31%] *vs* 143 [40%], p=0·039) and during pregnancy (39 [20%] *vs* 107 [30%], p=0·011). Maternal social class and body build did not differ significantly between these groups. Compared with the infants in the remainder of the initial cohort, those who participated in the follow-up study were of similar birth size and gestation, and had similar umbilical-vein mineral measurements.

Table 1 shows anthropometric and lifestyle characteristics during pregnancy of the 198 mothers. At the time of birth, the mothers in the study had a mean age of 27 (SD 4·9) years; 53% were primiparous, 31% reported smoking at the time of their last menstrual period, and 20% smoking during pregnancy. Of the mothers, 31% were regarded as vitamin D insufficient and 18% as vitamin D deficient in late pregnancy. Table 2 shows the anthropometric characteristics of the children participating in the follow-up. Their mean age was 8·9 years, and boys were significantly taller and heavier than girls. However, boys had a lower fat mass than girls, a difference that led to the similar bodyweights.

Mothers with lower serum concentrations of 25(OH)-vitamin D during late pregnancy had children with reduced whole-body BMC, bone area, and areal BMD at age 9 years (figure 1). Mothers who were deficient in vitamin D (ie, <11 μg/L) had offspring whose whole-body BMC was significantly lower than those born to mothers who were vitamin D replete (mean 1·04 kg [SD 0·16] *vs* 1·16 kg [0·17], p=0·002). Children born to mothers with insufficient concentrations of vitamin D (ie, 11–20 μg/L) showed a smaller deficit in whole-body BMC than the children of deficient mothers (1·14 kg [0·17] *vs* 1·16 kg [0·17], p=0·56). Maternal vitamin D status was also significantly associated with lumbar-spine BMC and areal BMD, but not with bone area at 9 years of age. The relations were no longer significant (p=0·14) for estimates of volumetric (or corrected for height, weight, and area) lumbar-spine BMD. Neither childhood height nor lean mass were associated with maternal vitamin D status during late pregnancy.

Adjustment for childhood height did not significantly weaken the relation between maternal vitamin D status in late pregnancy and whole-body BMC. Maternal vitamin D status during late pregnancy was not associated with birthweight (p=0·24), birth length (p=0·07), placental weight (p=0·43), abdominal circumference

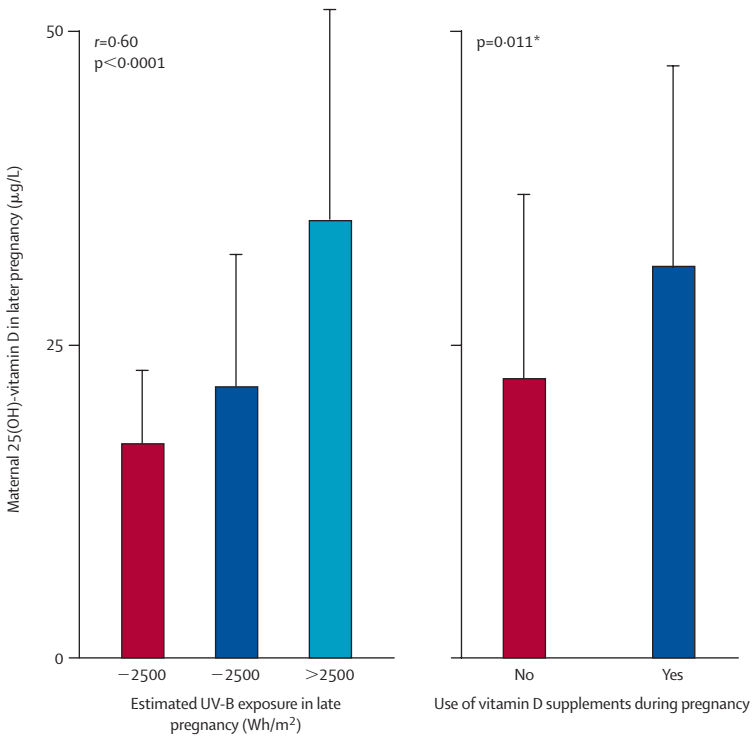

Figure 2: **Estimated UV-B radiation exposure and use of vitamin D supplements in late pregnancy as determinants of maternal 25(OH)-vitamin D concentration**
Date are mean values (error bars are SDs). *r*=Spearman correlation coefficient. **t* test significance.

	Relation to whole-body BMC*			
	Unadjusted		Adjusted†	
	R^2	p	R^2	p
Umbilical-venous constituent				
Calcium (mmol/L)	4·7%	0·0084	3·4%	0·025
Albumin (mmol/L)	2·6%	0·049	0·8%	0·27
Phosphate (mmol/L)	0%	0·83	0·1%	0·71
Alkaline phosphatase (IU/L)	0·1%	0·75	0·3%	0·53
Creatinine (mmol/L)	2·0%	0·086	1·8%	0·10

*Adjusted for children's age. †Adjusted for gestational age. R^2=proportion of variation in whole-body BMC, which is accounted for by every umbilical-venous measurement derived from multiple-regression model.

Table 3: **Umbilical-vein blood chemistry and whole-body BMC at age 9 years**

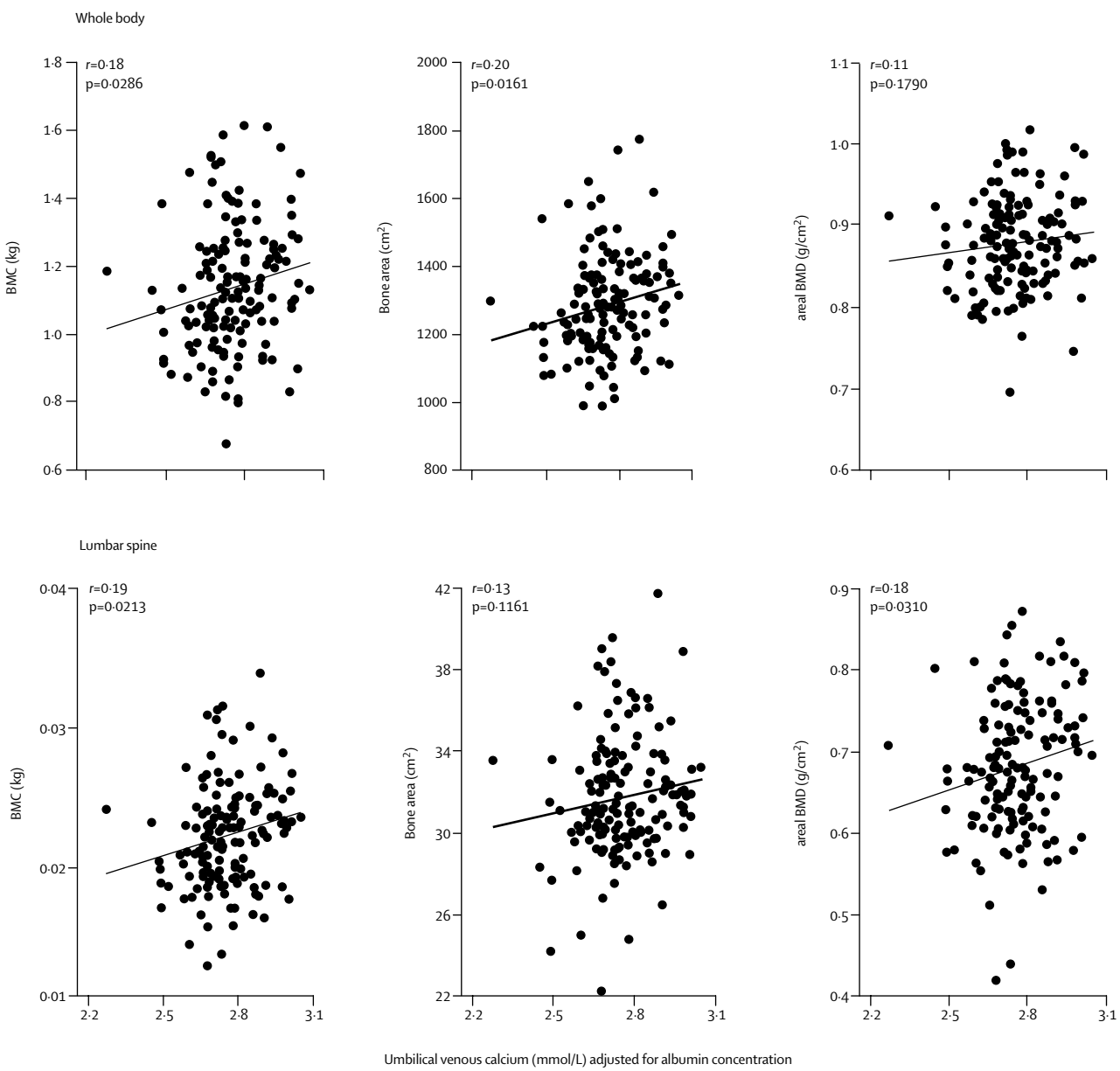

***Figure 3*: Umbilical-venous calcium concentration and children's bone mass at age 9 years**
r=Pearson correlation coefficients after adjustment for gestational and chronological age. Linear regression lines are shown.

(p=0·10), or head circumference (p=0·51). Finally, we were also able to assess the conditional effects of maternal vitamin D status on linear growth at birth, 9 months, and 9 years. This conditional model confirmed a significant effect of maternal 25(OH)-vitamin D at 9 months (p=0·02), but no additional explanatory effect on height at 9 years (p=0·13).

We could identify only two predictors of maternal concentrations of 25(OH)-vitamin D in late pregnancy: estimated UV-B exposure and the use of vitamin D supplements (figure 2). Estimated UV-B exposure during late pregnancy (total hours of sunshine in the 7th month of pregnancy adjusted for seasonal variation) had a greater effect on BMD than bone area at both the whole-body and lumbar-spine sites. Estimated UV-B exposure during late pregnancy significantly correlated with whole-body BMC (*r*=0·15, p=0·040) and areal BMD (*r*=0·17, p=0·020); we recorded even stronger

associations for lumbar-spine BMC (r=0·18, p=0·012) and BMD (*r*=0·22, p=0·002). As expected, maternal serum amounts of 25(OH)-vitamin D varied by season (median in winter 14·1 μg/L, spring 14·2 μg/L, summer 30·5 μg/L, and autumn 20·8 μg/L; p<0·0001). Although season of birth was not significantly associated with childhood bone mass (p=0·41), the offspring of mothers whose third trimester was during the summer had a 0·5 SD higher childhood whole-body BMC than those born to mothers whose third trimester was during the winter (p=0·008).

117 (59%) mothers reported supplement use of any type during pregnancy; however, only 30 (15%) took supplements containing vitamin D. As expected, women who used vitamin D supplements had higher median concentrations of 25(OH)-vitamin D than those who did not (29·3 μg/L [IQR 20·4–40·0] *vs* 19·6 μg/L [12·4–30·8]; p=0·011; figure 2). The lowest 25(OH)-vitamin D concentration in these supplement users was 13·6 μg/L, whereas 40 (24%) non-users had amounts lower than this value. The children of women who took vitamin D supplements had significantly greater whole-body BMC (0·42 SD, p=0·0267) and bone areas (0·45 SD, p=0·024) than non-users, but not areal BMD (0·28 SD, p=0·16); we recorded similar effects at the lumbar spine: BMC (0·38 SD, p=0·055), bone area (0·23 SD, p=0·24), and areal BMD (0·41, p=0·040). The associations between childhood bone mass and use of vitamin D supplements did not change greatly after adjustment for socioeconomic status. In a separate analysis, the relation between maternal 25(OH)-vitamin D concentration in late pregnancy and childhood bone mass was similar in mothers who did and in those who did not use supplements. We saw a weak association between 25(OH)-vitamin D concentration and mid-upper-arm circumference in late pregnancy (*r*=0·17, p=0·036), although this relation was no longer significant after adjustment for supplementation status (*r*=0·15, p=0·062).

We recorded no significant association between childhood whole-body BMC and umbilical venous concentrations of phosphorus, alkaline phosphatase, or creatinine. By contrast, both unadjusted (umbilical venous) concentrations of calcium (*r*=0·22, p=0·0084) and albumin (*r*=0·16, p=0·049) correlated with whole-body BMC in the children at 9 years (table 3). After adjustment for gestational age, current chronological age, and umbilical-venous albumin concentration, the concentration of cord calcium remained a significant predictor of childhood whole-body BMC (figure 3). None of the maternal anthropometric and lifestyle characteristics recorded during pregnancy (smoking, nutritional indices, or physical activity) predicted umbilical-venous calcium concentration. We analysed the type and duration of postnatal feeding during the first 3 months of life, which again did not affect the bone mass of the children at age 9 years.

The association between maternal vitamin D status in late pregnancy and umbilical-venous calcium concentration was not significant (*r*=0·09, p=0·34), but in a bivariate model of whole-body BMC at age 9 years, the effect of maternal vitamin D status was dominant, whereas the association with umbilical-venous calcium did not remain significant. For lumbar-spine BMC, both variables were significant independent predictors (maternal 25(OH)-vitamin D, p=0·014; umbilical-venous calcium, p=0·041).

Milk intake and physical activity in the children at age 9 years were not significant determinants of childhood whole-body BMC or areal BMD. As determinants of childhood bone mass, no interaction was seen between maternal vitamin D status, umbilical-venous calcium concentration, and childhood diet or exercise.

Discussion

Our results suggest that maternal vitamin D insufficiency (or deficiency) during late pregnancy is associated with a deficit in bone-mineral accrual in their children that persists to age 9 years. The deficit manifests as a reduction in both bone size and BMC without effects on childhood height or lean mass. The study also shows that the estimated concentration of ionised calcium of umbilical-venous blood is correlated with whole-body BMC of the child at age 9 years; this association can be partly explained by maternal vitamin D status.

Several longitudinal studies attest to the tracking of bone mass throughout childhood and adolescence, and mathematical models suggest that modification of peak bone mass will have biologically relevant effects on skeletal fragility in old age.[17,18] Peak bone mass is partly inherited, but currently identified genetic markers only explain a small proportion of the variation in individual bone mass and fracture risk. We and other researchers have previously shown that weight at birth and, more strongly, weight at 1 year predict bone mass in later life.[8,9] These relations are independent of known genetic and adult environmental determinants of bone mass.[19,20] Postnatal feeding patterns have been linked with infant weight and bone mass in childhood,[10] but none of the follow-up studies of infants born at term has found significant associations between the type of infant feeding and bone mass in later adult life. Mathematical analyses of growth after birth suggest that the transition between fetal and childhood phases occurs at about age 1 year, and that infant growth rates are strongly affected by the trajectory of intrauterine growth.[21] These findings suggest that effects that determine the fetal phase of growth could have long-term implications for the risk of osteoporosis. Our study provides direct evidence that the intrauterine environment, as indicated by maternal vitamin D status during pregnancy, is significantly correlated with bone-mineral accrual at age 9 years.

The mechanisms underlying the long-term effect of the intrauterine environment are not known, but include the

fetal programming of endocrine systems that affect skeletal metabolism. Programming refers to the mechanism whereby environmental effects during critical periods of early development lead to persistent changes in structure and function.[22] Increasing evidence suggests that these effects are mediated by epigenetic mechanisms, such as the methylation status of imprinted genes that regulate fetal and placental growth, as well as specific transport systems.[23] Our results show that maternal vitamin D status during pregnancy and placental calcium transfer, as indicated by concentrations of umbilical-venous calcium, are significantly correlated with bone-mineral accrual in offspring by age 9 years.

The fetus accumulates about 30 g of calcium from the mother in utero, and 80% of this transfer occurs in the last trimester of pregnancy.[24] The maternal capacity to supply the fetus with calcium is dependent on many factors, including maternal calcium intake and vitamin D status; intestinal calcium absorption; maternal bone turnover; maternal renal function; and the capacity for placental calcium transfer.[25] The mechanisms by which maternal vitamin D status during pregnancy affects bone mass in the child remain unknown. We postulate that maternal vitamin D insufficiency during pregnancy leads to an impairment of placental calcium transport, perhaps mediated by parathyroid-hormone-related peptide (PTHrP)[26] and thereby reduces the trajectory of intrauterine and subsequent childhood bone-mineral accrual. Animal models are consistent with this hypothesis.[27–29] The findings are also consistent with observations in human beings, showing that umbilical-venous alkaline phosphatase concentrations in premature infants are associated with reduced childhood bone mass.[30] Some short-term supplementation studies of vitamin D during pregnancy have been undertaken.[31]

Although supplementation with vitamin D seems to lead to improvements in circulating calcium and vitamin D concentrations in newborn babies, no consistent effect on either fetal weight or length has been shown. This finding accords with our own, which could not show a measurable effect of maternal vitamin D status in late pregnancy on neonatal size. Notably, our vitamin D assay could not distinguish between the D_2 and D_3 molecular forms; the most appropriate means of supplementation therefore needs further research.

Our study had several weaknesses. First, a minority of the original cohort was traced. However, we showed that the study participants did not differ from non-responders with respect to maternal body build or lifestyle; furthermore, it is difficult to see how differences in response rate would have spuriously revealed an association between maternal vitamin D status, umbilical-venous calcium concentration, and childhood bone mass.

Second, we could only measure total serum concentrations of 25(OH)-vitamin D; pregnancy is associated with a concomitant increase in vitamin-D-binding protein, as well as 1,25$(OH)_2$-vitamin D concentration.[24] Third, no widely accepted methods are available for the correction of circulating concentrations of total calcium for protein binding in the neonatal period.[32] We therefore used a method analogous to that used in adults, which depended on adjustment for umbilical-venous albumin concentration.

Fourth, our study relied on DXA to measure bone mass. Although validated in adults, DXA use in children raises unique technical considerations. The reduced absolute amounts of bone mineral led to increased percentage precision errors. A study in piglets showed coefficients of variation up to 2·4% for whole-body BMC and 1·8% for BMD;[33] these values are greater than those reported in adults. Furthermore, the variability between the proportion of intra-osseous marrow fat and that in lean tissue could lead to an inaccuracy in the estimation of BMC by as much as 20%.[34] Again, it is difficult to see how the use of DXA would have greatly affected the relation between umbilical-venous calcium and whole-body BMC. We corrected bone-mineral measurements for bone size using the separate mathematical algorithms.[16] These adjustments greatly weakened the relation between concentration of umbilical-cord serum calcium and bone mass at age 9 years, suggesting that the determinants of bone size differ from those of volumetric bone-mineral density.

In summary, our study shows that the vitamin D status of mothers in late pregnancy predicts the bone mass of their offspring measured by DXA some 9 years later. Vitamin D insufficiency was a frequent finding in this cohort of white women. However, vitamin D supplementation of such mothers, especially when the last trimester of pregnancy occurs during the winter months, could lead to an enhanced peak bone-mineral accrual and a reduced risk of fragility fracture in offspring during later life. The potential for such a supplementation programme warrants investigation in a randomised controlled trial.

Contributors

M K Javaid, C R Gale, K M Godfrey, and C Cooper designed the study, secured funding, managed data collection, supervised analysis, and wrote the report. S R Crozier analysed the data; B J Boucher did the vitamin D assays. N C Harvey, E M Dennison, and N K Arden contributed to study design and to the written report. Other members of the Princess Anne Hospital Study Group contributed to administration of the study. C Cooper is the guarantor of the study. The Princess Anne Hospital Study Group are: F O'Callaghan, P Taylor, K Noonan, C N Martyn, and C M Law.

Conflict of interest statement

We declare that we have no conflict of interest.

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