

70th Anniversary Conference on ‘Vitamins in early development and healthy ageing: impact on infectious and chronic disease’

Symposium 2: Vitamins in muscular and skeletal function Does vitamin D during pregnancy impact offspring growth and bone?

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During pregnancy, maternal and fetal Ca demands are met through increased intestinal Ca absorption. Increased Ca absorption may be more dependent on oestrogen's up-regulation of Ca transport genes than on vitamin D status. Numerous studies, however, have found that severe vitamin D deficiency with secondary hyperparathyroidism during pregnancy leads to abnormal Ca homeostasis in the neonate. Some, but not all, studies of maternal vitamin D supplementation during pregnancy find a greater birth weight among infants of mothers with adequate vitamin D status. Observational studies find a higher incidence of small-for-gestational age (SGA) infants among mothers who are vitamin D deficient, but this effect may be modified by genetics. In addition, the effect of vitamin D status on SGA may not be linear, with increased occurrence of SGA at high maternal 25-hydroxyvitamin D (25-OHD) concentrations. Some studies, but not all, also have found that maternal vitamin D status is associated with growth trajectory during the first year of life, although the findings are contradictory. There are recent studies that suggest maternal 25-OHD, or surrogates of vitamin D status, are associated with growth and bone mass later in childhood. These results are not consistent, and blinded randomised trials of vitamin D supplementation during pregnancy with long-term follow-up are needed to determine the benefits, and possible risks, of maternal vitamin D status on offspring growth and bone development. The possibility of adverse outcomes with higher maternal 25-OHD concentrations should be considered and investigated in all ongoing and future studies.

Bone: Growth: Adverse effects

Fetal Ca demands during pregnancy

In order to support fetal bone development, approximately 250 mg Ca/d is transferred to the fetus during the third trimester⁽¹⁾. 1,25-dihydroxyvitamin D (1,25-(OH)₂D) concentrations are increased during pregnancy with concentrations 150–200% of pre-pregnant values during the second and third trimesters. The signal to increase synthesis of the biologically active form of vitamin D, 1,25-(OH)₂D, during pregnancy is not clear since the usual pathway through elevated parathyroid hormone concentrations does not appear to occur. Most of the circulating

1,25-(OH)₂D is thought to be of maternal renal origin, but some may originate in placenta and decidua that have been shown to synthesise 1,25-(OH)₂D⁽²⁾. The increase in 1,25-(OH)₂D concentrations is accompanied by an increase in intestinal Ca absorption, and fractional Ca absorption is approximately 50–60% greater than pre-pregnant levels during the second and third trimesters^(3,4). The increased Ca absorption is thought to be the reason for the hypercalciuria that is observed during pregnancy. Some investigators have suggested that Ca absorption during pregnancy is not dependent on vitamin D, since intestinal Ca transport genes are up regulated by oestrogens, which are increased

Abbreviations: BMC, bone mineral content; CSA, cross-sectional area; 1,25-(OH)₂D, 1,25-dihydroxyvitamin D; 25-OHD, 25-hydroxyvitamin D; SGA, small-for-gestational age; UVB, ultraviolet B.

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during pregnancy⁽⁵⁾. However, severe vitamin D deficiency with secondary hyperparathyroidism during pregnancy has been shown to lead to abnormal neonatal Ca homeostasis.

Effects of maternal vitamin D deficiency on the neonatal Ca

Maternal vitamin D deficiency during pregnancy affects neonatal Ca metabolism. Vitamin D deficiency is associated with secondary hyperparathyroidism and osteomalacia in the mother, and may lead to neonatal hypocalcaemia or tetany^(6,7). In the early 1970s, Purvis *et al.*⁽⁸⁾ noted that the occurrence of neonatal tetany among 112 infants was inversely related to the amount of sunlight exposure the mothers had during the last trimester of pregnancy. The authors speculated that the mothers developed hyperparathyroidism secondary to vitamin D deficiency leading to a transitory neonatal hypoparathyroidism and hypocalcaemia. This finding was reinforced by subsequent studies that reported that infants of mothers with low vitamin D intake during pregnancy had low serum Ca concentrations in cord blood or during the first week of life^(9–11).

Cockburn *et al.*⁽¹²⁾ reported higher maternal, cord and infant 25-hydroxyvitamin D (25-OHD) concentrations among 506 women who attended a clinic where supplemental vitamin D (10 µg (400 IU)/d from the 12th week of gestation) was provided compared with 633 women who attended a clinic where vitamin D was not provided. They also found the incidence of neonatal hypocalcaemia to be less with vitamin D supplementation, although this was modified by the infant's feeding: the incidence of hypocalcaemia with maternal vitamin D supplementation was 3.1 and 6.5% among breast-fed and formula-fed infants compared with 5.5 and 16.5% among breast-fed and formula-fed infants of mothers who did not receive vitamin D supplements. These observational studies were followed by several randomised trials of vitamin D supplementation during pregnancy^(12–18).

Several randomised trials of vitamin D supplementation (25 µg (1000 IU)/d) during pregnancy found that infants of mothers receiving vitamin D had higher serum Ca concentrations within the first week of life than infants of mothers receiving placebo^(12–17) (Fig. 1). It should be noted, however, that these studies were completed in populations at increased risk for vitamin D deficiency. The studies show the importance of maternal vitamin D status on neonatal Ca homeostasis.

Effects of maternal vitamin D deficiency on fetal growth and neonatal bone development

Maternal vitamin D deficiency during pregnancy may lead to impaired fetal growth and bone development. The majority of the reported studies were completed in populations at high risk of vitamin D deficiency (e.g., Asians from the Indian subcontinent living in Great Britain). Some investigators^(13,16), but not all^(15,19), have reported lower birth weights among infants born to mothers with low v. adequate vitamin D status. A trial conducted in London of vitamin D supplementation (25 µg (1000 IU)/d during

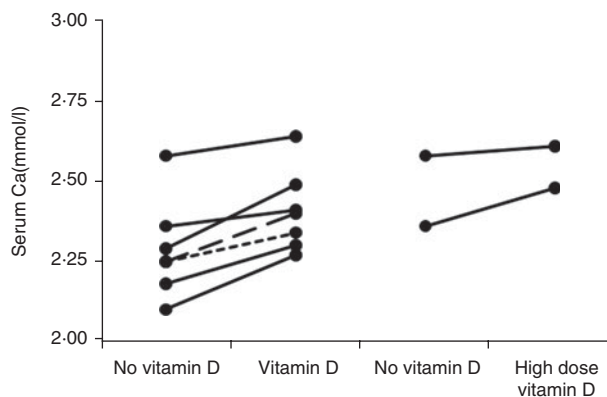


Fig. 1. Serum Ca concentrations in neonates of mothers with and without vitamin D supplementation during pregnancy. Lines connect means from the same supplementation trial. Populations were at high risk of vitamin D deficiency and supplemented groups received 25 µg (1000 IU) vitamin D/d during the third trimester unless noted otherwise. Dashed line is an observational study that provided 12.5–37.5 µg (500–1500 IU)/d among mothers in the vitamin D group. The dotted line is a trial that provided 10 µg (400 IU) vitamin D/d during the second and third trimesters. Data from references^(12–17).

third trimester) among pregnant Asian women found a trend for a higher percentage of infants randomised to the placebo group being small-for-gestational age (SGA) compared with infants in the supplemented group (29 v. 15%); however, this difference in percent SGA was not statistically significant⁽¹⁷⁾.

Results from community-based studies that were not limited to women at high risk of vitamin D deficiency are conflicting with regard to the effect of maternal vitamin D on birth weight and length. A recent community-based longitudinal study (multi-ethnic cohort of 3730 women) in the Netherlands reported a higher SGA risk and lower birth weight in women with 25-OHD concentrations <30 nmol/l during early pregnancy (median 13 weeks gestation)⁽²⁰⁾, supporting findings from studies among high risk women. A nested case-control study of seventy seven mothers who had their serum 25-OHD concentrations determined at 22 weeks gestation reported a significant association with both low (<37.5 nmol/l) and high (>75 nmol/l) maternal 25-OHD concentrations and the incidence of SGA⁽²¹⁾ (Fig. 2). This relationship remained significant when significant covariates were included in the analyses. This study also found an association between the vitamin D receptor genotype and SGA risk, and both maternal vitamin D status and vitamin D receptor genotype were independent risk factors for SGA. Morley *et al.*⁽²²⁾ also found an association of the vitamin D receptor FokI genotype and birth size: infants with the FF or Ff polymorphism had lower mean birth weight if their mother was vitamin D deficient compared with infants with the ff polymorphism. The FokI polymorphism did not influence birth size if the mother had adequate vitamin D status. Both the Avon Longitudinal Study of Parents and Children (ALSPAC) and the Southampton Women's Study include data on serum 25-OHD concentrations during pregnancy (see more detailed description later). Neither of these

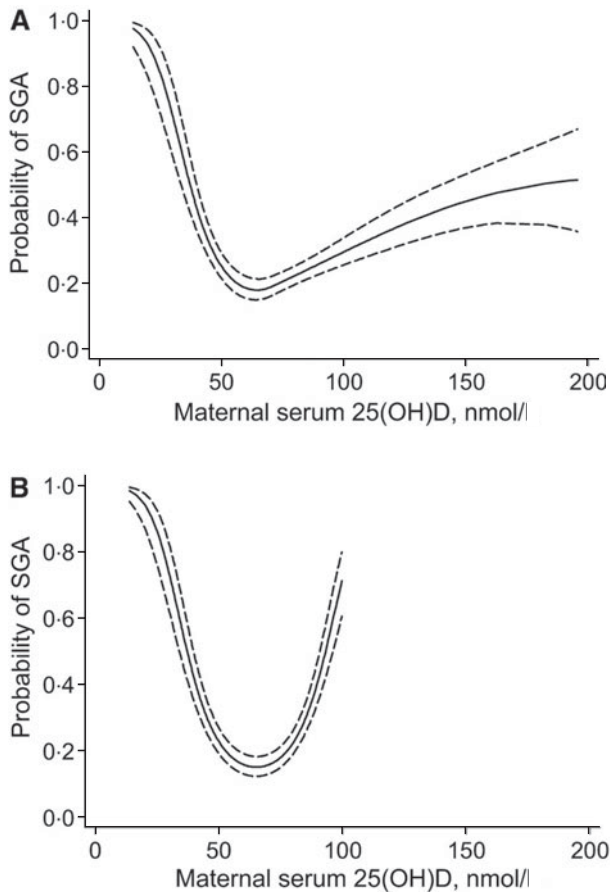


Fig. 2. Unadjusted association between the probability of small-for-gestational age (SGA) births and serum 25-hydroxyvitamin D (25-OHD) concentrations among white women (A; n 273) and white women with a 25-OHD \leq 100 nmol/l (B; n 217) at <22 week. The point estimates were derived from logistic regression models with serum 25-OHD concentrations specified as a quadratic spline with knot at 70 nmol/l (P = 0.006; A) or quadratic term (P < 0.0001; B). The solid line represents the point estimate and the dotted lines represent the 95% confidence bands. Taken from⁽²¹⁾.

studies found associations between maternal 25-OHD concentrations and birth weight or length^(23–25).

Fetal or congenital rickets of the newborn is rare. There are, however, case reports of congenital rickets in newborn infants of mothers with severe nutritional osteomalacia associated with vitamin D or Ca deficiency^(26–28). A case-control study by Reif *et al.*⁽²⁹⁾ reported an association between craniotabes, or delayed ossification of the cranial vertex, and maternal and neonatal 25-OHD concentrations. However, these findings have not been replicated in other observational studies or trials^(10,17). Although Brooke *et al.*⁽¹⁷⁾ did not find an association between craniotabes and vitamin D status, they found that infants of mothers' who received placebo (n 67) had larger fontanelles than infants of mothers supplemented with vitamin D (n 59) that is consistent with impaired skull ossification. A study of 256 breast-fed infants conducted in China also found possible evidence of a relationship between maternal vitamin D deficiency and impaired fetal bone ossification⁽³⁰⁾. The presence of wrist ossification centres in neonates was

associated with cord serum 25-OHD concentrations: a higher rate of ossification centres in neonates of mothers with adequate vitamin D status (14%) was observed compared with neonates of mothers with low vitamin D status (4%)⁽³⁰⁾.

There are few studies on the association between maternal vitamin D status and infant bone mineralisation^(10,20,31–33). One of the original studies investigating this relationship measured forearm bone mineral content (BMC) using single-photon absorptiometry in infants of forty-five Asian and twelve Caucasian women and found that neonatal BMC did not differ by history of vitamin D supplementation during pregnancy and was not correlated with cord serum 25-OHD concentrations⁽¹⁰⁾. Weiler *et al.*⁽³³⁾ conducted a similar study among fifty Canadian infants and found that birth weight and length were both greater in infants with lower cord 25-OHD (with infant 25-OHD defined as inadequate at level <27.5 nmol/l) concentrations compared with adequate cord 25-OHD concentrations (defined as 25-OHD >27.5 nmol/l), findings opposite to those reported by others^(17,20,23,24). Total body BMC was similar between these two groups of infants, but when expressed as BMC per kilogram body weight, infants with low cord 25-OHD concentrations had lower BMC than infants with higher cord concentrations.

Mahon *et al.*⁽³²⁾ measured femur length and cross-sectional area (CSA) of the distal femur at 19 and 34 weeks of gestation using three-dimensional fetal ultrasound in 395 women participating in the Southampton Women's Survey. They found that the maternal serum 25-OHD concentrations at 34 weeks gestation were inversely correlated to the distal CSA and a femur splaying index (CSA/femur length), with no linear relationship to femur length. These results suggest that infants of mother's with low vitamin D status have larger distal femur CSA than infants of mother's with higher vitamin D concentrations. The authors speculated based on the increased splaying index that fetal bone changes with low maternal 25-OHD concentrations were similar to what is observed in rickets. Viljakainen *et al.*⁽³¹⁾ measured 25-OHD concentrations in ninety-eight Finnish mothers during their first trimester and postpartum period, as well as newborn bone parameters by peripheral quantitative computed tomography⁽³¹⁾. They found that mothers with mean 25-OHD concentrations below 43 nmol/l had newborn infants with lower tibia bone mass and smaller CSA in the midshaft of the tibia than infants of mothers with mean 25-OHD concentrations greater than 43 nmol/l. In summary, some studies, but not all, find maternal vitamin D status during pregnancy to be associated with fetal growth; this effect may be modified by genetic factors. Results from studies suggest a relationship between maternal vitamin D status and fetal or neonatal bone.

Effects of maternal vitamin D deficiency on growth and bone later in life

Longitudinal studies on the influence of maternal vitamin D status during pregnancy on growth later in life are varied. The study by Brooke *et al.*, which did not find

differences in birth weight or length in a vitamin D supplementation trial (25 µg (1000 IU)/d) among pregnant Asian Indians in Great Britain, reported greater weight and length during the first year of life among infants of vitamin D supplemented mothers⁽¹⁹⁾. Weight was greater at 3, 6, 9 and 12 months of age, while length was greater at 9 and 12 months in infants of mothers who received the vitamin D supplement compared with infants of mothers without vitamin D supplements. The recent study of the Netherlands Amsterdam Born Children and their Development cohort found the opposite results in 2715 infants whose mothers had 25-OHD concentrations determined early in pregnancy: mean infant birth weight was lower in mothers who were vitamin D deficient, but these infants showed accelerated growth in both weight and length during the first year of life⁽²⁰⁾ (Fig. 3). At 12 months of age, there was a length difference in infants whose mothers had serum 25-OHD concentrations <30 nmol/l (standard deviation score (SDS) = +0.12) compared with infants whose mothers had concentrations >50 nmol/l (SDS = -0.13). Whether this is a result of accelerated growth among the deficient group, or decelerated growth among the high-vitamin D group, or a combination of both, was not discussed. These differences in height and weight persisted even after controlling for potential covariates (gestational age, season, infant sex, maternal height, parity, maternal age, smoking, pre-pregnancy BMI, educational level and duration of exclusive breastfeeding).

Two studies from England, the Avon Longitudinal Study of Parents and Children and the Southampton Women's Survey, were briefly mentioned earlier. Both of these studies followed cohorts of mothers and their children and obtained growth and bone measures up to 9 years of age. They also obtained measures of maternal vitamin D status, either serum 25-OHD concentrations or surrogates of ultraviolet B (UVB) exposure. These studies are described in greater detail below and are summarised in Table 1.

The Avon Longitudinal Study of Parents and Children is a longitudinal study of approximately 14 000 children who are being followed from early pregnancy; analyses of growth and bone data up to 9 years of age on 6995 of these children have been reported^(25,34). Some of the mothers (*n* 355) had 25-OHD concentrations measured in the third trimester of pregnancy⁽²⁵⁾. Sayers and Tobias estimated UVB exposure of the mothers during the third trimester from local meteorological records and these UVB estimates were found to correlate with the mothers' third trimester 25-OHD concentrations⁽²⁵⁾. They found a positive association between estimated UVB exposure and birth length, and both weight and height at 9 years of age. Estimated maternal UVB exposure during the third trimester also was associated with the child's total body lean mass, BMC and bone area at 9 years of age. However, when they examined the relationship between maternal 25-OHD concentrations and these growth and bone outcomes in 355 mother-child pairs, there was no evidence of an association with any of the outcomes. In addition, these investigators previously reported no relationship between maternal vitamin D intake during the last trimester of pregnancy and total body BMC at 9 years of age among

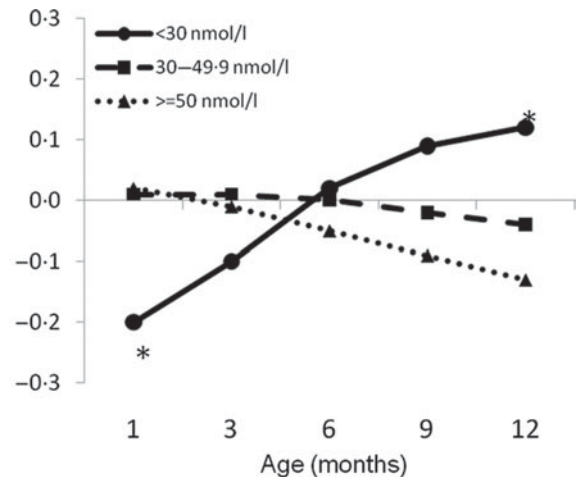


Fig. 3. The Netherlands Amsterdam Born Children and their Development cohort (*n* 2715) reported accelerated linear growth during the first year of life in infants whose mothers were deficient in vitamin D early in pregnancy. Differences in height and weight persisted even after controlling for potential covariates (gestational age, season, infant sex, maternal height, parity, maternal age, smoking, pre-pregnancy BMI, educational level, and duration of exclusive breastfeeding). Data from⁽²⁰⁾.

the offspring, although they did find an associations between maternal Mg and K intakes and total body BMC⁽³⁴⁾. The authors speculated that UVB was a more important determinant of maternal 25-OHD concentrations than maternal vitamin D intake. Mg content is high in vegetables, and vegetables may be consumed more often during summer months than winter months. It is possible that the association between BMC at 9 years of age and maternal UVB exposure during pregnancy is confounded by seasonal differences in Mg and K intakes, or other factors that might vary by season. In addition, the authors noted that based on these findings and previous observations that tall individuals are at increased risk of hip fracture, high UVB exposure, and thus high vitamin D concentrations, during pregnancy may increase the child's later risk for hip fracture since these offspring are taller.

The Southampton Women's Study enrolled 596 women during pregnancy and measured serum 25-OHD concentrations in 160 of these women during the last trimester⁽²⁴⁾. They found no association between maternal 25-OHD and birth weight, birth length or childhood height and lean mass (9 years of age). They did, however, report an association between maternal 25-OHD and length at 9 months of age, but a later study by this same group that included 440 mother-child pairs reported no relationship between maternal 25-OHD concentrations and length or weight at 9 months of age⁽²³⁾. Maternal 25-OHD concentrations during the third trimester were associated with the child's total body BMC and bone area at 9 years of age and the relationship with total body BMC remained significant when height was included in the analysis. It was not clear whether other potential covariates that could influence bone, such as lean and fat mass, were included in the analysis. The authors did note that the child's activity

Table 1. Summary of studies investigating effect of maternal vitamin D status during pregnancy on growth and bone later in life

Study	Number	Predictor	Growth in first year	At 9 years of age:			
				Weight and height	Total body BMC	Total body bone area	Lean mass
Brooke <i>et al.</i> ⁽¹⁷⁾	59 Vitamin D 67 Placebo	Treatment group	Accelerated. Infants of mothers not receiving vitamin D (deficient): Length: = at birth, ↓ at 1 year Weight: = at birth, ↓ at 1 year	ND	ND	ND	ND
Leffelaar <i>et al.</i> , Netherlands Amsterdam Born Children and their Development ⁽²⁰⁾	2715	Maternal 25-OHD (first trimester)	Accelerated. Infants of deficient mothers: Length: ↓ at birth, ↑ at 1 year Weight: = at birth and 1 year, ↑ at 9 months	ND	ND	ND	ND
Avon Longitudinal Study of Parents and Children							
Sayers and Tobias ⁽²⁵⁾	6995	Estimated maternal UVB exposure	ND	↑UVB → ↑height and ↑weight	↑UVB → ↑BMC	↑UVB → ↑BA	↑UVB → ↑lean mass
Sayers and Tobias ⁽²⁵⁾	355	Maternal 25-OHD (third trimester)	ND	Not significant	Not significant	Not significant	Not significant
Tobias and Tobias ⁽³⁴⁾	4451	Maternal vitamin D intake	ND	Not significant	Not significant	Not significant	Not significant
Southampton Womens Survey							
Javaid <i>et al.</i> ⁽²⁴⁾	160	Maternal 25-OHD	Accelerated. No difference in birth weight or length; length ↑ at 1 year (no differences in weight)	Weight – not mentioned Height – not significant	↑25-OHD → ↑BMC	↑25-OHD → ↑BA	Not significant
Gale <i>et al.</i> ⁽²³⁾	440	Maternal 25-OHD	No differences in length or weight at birth or 9 months.	Not significant (n 178)	ND	ND	ND

BMC = bone mineral content; BA = bone area; 25-OHD = 25-hydroxyvitamin D; UVB = ultraviolet B radiation; ND = not done.

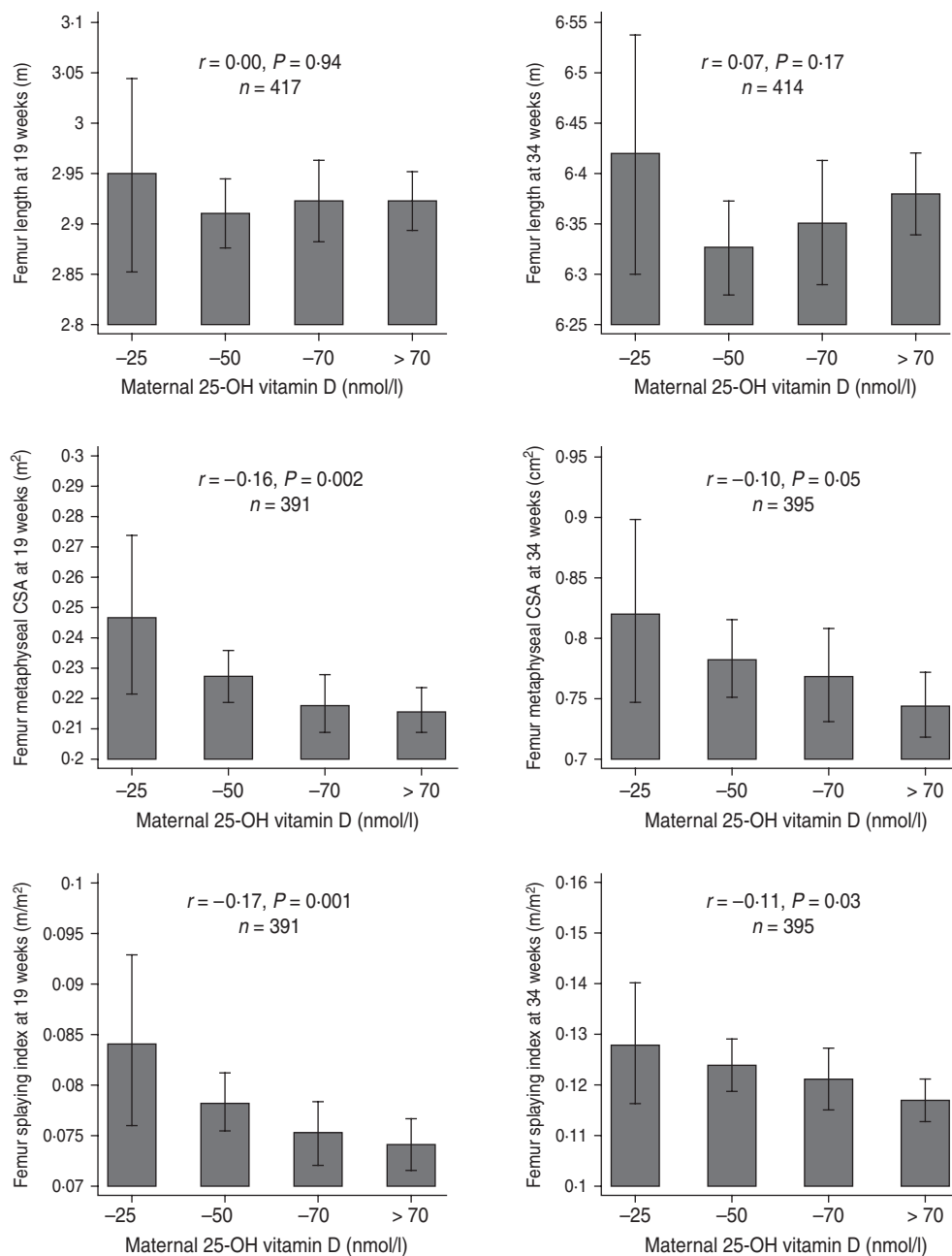


Fig. 4. Mean femur length, geometric mean distal femoral metaphyseal cross-sectional area (CSA), and geometric mean femoral splaying index according to maternal 25-OHD concentrations in 424 mother-offspring pairs at 34 weeks' gestation. Error bars indicate 95% CI. Taken from⁽³²⁾.

level and Ca intake were insignificant predictors of the child's BMC at 9 years.

In summary, some studies, but not all, have found an association between maternal vitamin D status and growth trajectories during the first year of life. In addition, the studies that have found associations are not consistent. Two observational studies reported accelerated growth during the first year of life among infants of vitamin D deficient mothers, while one supplementation trial among women at risk of vitamin D deficiency found decelerated growth among infants of mother's who received placebo. Results on the influence of maternal 25-OHD or surrogates

of vitamin D status, and growth and bone mass later in childhood also are not consistent.

Potential risks of high maternal vitamin D

There are several reports indicating that the relationship between mortality and serum 25-OHD concentrations is not linear, but is elevated at both low and high concentrations that have been described as a U-shaped curve⁽³⁵⁾. Similar non-linear relationships have been reported for pregnancy outcomes and maternal 25-OHD concentrations.

As described earlier, Bodnar *et al.*⁽²¹⁾ found this type of relationship between SGA probability and maternal serum 25-OHD concentrations, with increased probabilities occurring at about 70 nmol/l. Potential adverse effects of high maternal 25-OHD concentrations on growth later in life also have been recently documented. Leffelaar *et al.*⁽²⁰⁾ reported that length at 1 year of age was greater in infants of mothers with low vitamin D during pregnancy (<30 nmol/l; standardised Z score of +0.12) compared with infants of mothers with high vitamin D (>50 nmol/l; standardised Z score of -0.13). These results also could be interpreted as a decreased linear growth among the infants of mothers with high serum 25-OHD concentrations during pregnancy.

With regard to bone outcomes, Mahon *et al.*⁽³²⁾ reported what appeared to be a U-shaped relationship between fetal femur length at 34 weeks and maternal 25-OHD concentrations, although they reported no significant association when analysed using linear regression analysis (Fig. 4)⁽³²⁾. Preliminary results from the Southampton Women's Study that were presented in abstract form showed a non-linear relationship between total body BMC in 211 children aged 9 years whose mothers had 25-OHD concentrations determined during pregnancy⁽³⁶⁾. This study found lower total body BMC of the child at maternal 25-OHD concentrations <35 nmol/l (1.06 kg) during the third trimester compared with 25-OHD concentrations <35 nmol/l (about 1.06 kg v. 1.18 kg, respectively), but total BMC appeared to decrease at the higher levels of 25-OHD (about 1.10 kg at 25-OHD >77 nmol/l). Since it was analysed by linear correlation it was not possible to determine whether this was a significant non-linear relationship. These results indicate that low bone mass may be observed in offspring of mothers with high 25-OHD concentrations, as well as low 25-OHD concentrations.

In addition to potential adverse effects of high maternal serum 25-OHD concentrations on growth and bone of their offspring, Gale *et al.*⁽²³⁾ also found increased risk of reported pneumonia and diarrhoea in offspring at 9 months of age, and visible eczema and asthma in children at 9 years of age. These results remained significant ($P < 0.05$) after controlling for potential confounders.

Conclusion

Several areas of research have recently suggested a role of maternal vitamin D during pregnancy on growth and bone mass of the offspring later in life. The majority of these results are based on observational studies and require confirmation with results from well-designed randomised vitamin D supplementation trials during pregnancy. The possibility of adverse outcomes with higher maternal 25-OHD concentrations should be considered and investigated in all ongoing and future studies.

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