

## REVIEW ARTICLE

# Maternal diet and vitamin D during pregnancy and association with bone health during childhood. Review of the literature

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## ABSTRACT

Deficiencies in maternal diet and low maternal plasma of vitamin D in pregnancy may influence the growth and bone mineral accrual of the offspring during fetal life and childhood. This review summarizes the evidence available from cohort studies that include information of maternal diet and concentrations of vitamin D during pregnancy associated with bone mass of the offspring.

A literature search was conducted through MEDLINE and included studies from 2000 to 2009.

The main associations found in the studies were related to maternal calcium intake and vitamin D concentrations. Several studies reported a high prevalence of maternal vitamin D deficiency (varying from 15% to 66%) associated with increased risk of neonatal vitamin D deficiency [odds ratio (OR) 17.2, 95% CI 8.8-34.3]. A strong positive association between maternal and cord blood serum vitamin D was found in two different studies ( $r = 0.70$  and  $r = 0.755$   $p < 0.001$ ). Mothers who were deficient in vitamin D had offspring with lower whole body bone mineral content (BMC) (mean  $1.04 \text{ kg} \pm 0.16$  vs.  $1.16 \text{ kg} \pm 0.17$ ,  $p = 0.002$ ).

Adequate concentrations of maternal vitamin D are essential for calcium homeostasis and bone health of the newborn. High prevalence of maternal vitamin D insufficiency found in different populations can lead to problems of low BMC or, in severe cases, fetal rickets.

**Key words:** pregnancy diet, vitamin D, bone mass.

## INTRODUCTION

During the last decade there has been growing evidence in epidemiological studies indicating that osteoporosis (OP) and the risk of fractures may begin during intrauterine life due to adverse influences of several factors in early development.<sup>1</sup> Initial studies have shown a relationship between measures of birth weight, infant weight and quantity of bone mass in adulthood. Furthermore, there is evidence that factors such as maternal lifestyle and vitamin D concentrations during pregnancy have a significant impact on newborn bone mineral content (BMC) and further development of fetal bone.<sup>2</sup> It is possible that interventions

targeting the mother's lifestyle during pregnancy may have an impact on the development of stronger bones that, if reinforced during childhood and adolescence, will allow the development of a higher reservoir of mineral content. This may ultimately delay the threshold of fracture.<sup>3</sup>

Skeletal growth is an anabolic process that depends on several factors, some of which are modifiable and others are not. The main non-modifiable factors include genetics, race, gender and hormonal factors. Modifiable factors include those relating to lifestyle of the mother and maternal nutrition during pregnancy. Therefore, newborn bone mass depends on the combination of these factors whose presence is variable in each person.<sup>4</sup>

During pregnancy, the fetus is totally dependent on the mother for acquisition of micronutrients required for bone mineralization. The primary bone-forming minerals are calcium, phosphorus and magnesium (at birth the infant's skeleton contains 98%, 80% and 60%, respectively, of these minerals). Quantitatively, the greatest period of fetal mineral accretion takes place from mid-gestation and is maximal during the third trimester.<sup>5</sup>

Fetal bone mineralization is determined by placental mineral transfer, fetal bone mineral accretion and fetal bone resorption. Because effects on fetal bone are often

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brought through the mother, any disturbance in maternal mineral metabolism (maternal nutritional depletion or diseases) or conditions that affect placental mineral transfer can affect fetal bone mineralization. Therefore, maternal nutritional status and dietary intake of calcium and other minerals during pregnancy could have a significant effect on fetal growth and development.<sup>6</sup>

On the other hand, maternal vitamin D deficiency during pregnancy is a recognized risk factor for rickets and osteomalacia in infancy. There is evidence that low maternal plasma of 25-OHD in pregnancy may influence the growth and bone mineral accrual of the offspring during fetal life, infancy and childhood.<sup>7</sup>

The objective of this review is to summarize the evidence available from cohort studies that include information of maternal diet and concentrations of vitamin D during pregnancy associated with bone health of the child.

A literature search was conducted through MEDLINE using the following keywords (lifestyle, maternal factors OR maternal vitamin D OR maternal diet during pregnancy) AND (newborn bone mass OR bone in infants). The search period included the years 2000 to 2009. Selection criteria for the studies included (1) published in English; (2) abstract available on-line; (3) referred to original work (instead of literature reviews); (4) studied humans; (5) included only factors during pregnancy and bone health of their offspring in analysis; and (6) cohort-type studies.

For this review, 15 studies were analyzed who met our inclusion criteria and were obtained in full text. Of these studies, nine referred to maternal concentrations of vitamin D and six to maternal diet. The majority of studies (13/15) were published after 2005 and only two were published between 2000 and 2005. Most of the studies originated from the UK and Australia (10/15). The rest of the studies were developed in Iran, Turkey, India, The Netherlands and the U.S. Sample size varied from 87 to 901.

Bone growth as the primary outcome was measured in nine of the studies with dual-energy x-ray absorptiometry (DXA) to estimate bone mineral mass. Six were retrospective studies measuring bone mass of children ages 6 and 9 years old.<sup>8-13</sup> The rest of the studies used different methods like fetal femur length and knee-heel length to estimate bone growth of the offspring.

In most of the studies the mothers were >16 years old and were followed from 17 weeks of gestation until de-

livery. Exclusion criteria were fetal anomalies, multiple pregnancy, maternal disease and intake of medications influencing bone metabolism, etc. All babies were born at term ( $\geq 37$  gestation weeks).

### **Maternal Diet Results**

Table 1 summarizes the six studies that assessed maternal diet associated with bone mass of the offspring. Maternal diet was assessed in all of the six articles by food frequency questionnaires. The main results were the positive associations founded between calcium and dairy intake during pregnancy with higher body bone mineral density (BMD) and bone mineral content (BMC) of the child.

Children of mothers who had a higher intake of dairy products (milk and derivatives) and a high "prudent diet" characterized by increased intake of fruit, vegetables, whole wheat bread, and rice, and low intake of processed foods during pregnancy had higher bone mass (BMC  $r = 0.23$   $p = 0.001$  and BM  $r = 0.15$   $p = 0.02$ ); the association remains positive and significant even after adjustment for some confounding factors.<sup>9</sup> Cole et al. concluded that the percentage of total variance in whole body BMD and BMC explained by maternal "prudent diet" in late pregnancy ranges from 2% to 6%. Another study concluded that a child in the "optimal" levels of dietary exposure (highest tertile of magnesium, potassium, protein and phosphorus intake) had significantly higher adjusted BMD at all sites (femoral neck 5.5%, lumbar spine 12% and total body 6.8%) compared to the remainder of the children.<sup>10</sup>

Calcium intake is one of the most common dietary factors studied. Two different studies determined that greater maternal consumption of calcium and calcium-rich foods, especially milk and derivatives ( $>3$  servings/day) during pregnancy was associated with higher total body BMC in the children at 6 years old ( $\beta$  0.11,  $p < 0.001$ )<sup>8</sup> and had a significant positive effect on fetal femur growth ( $\beta$  0.077  $\pm$  0.024,  $p = 0.001$ ).<sup>14</sup> These associations were statistically significant after adjustment for some confounders such as newborn size, age, gender, infant feeding, maternal energy and protein intake and parity. One more study concluded positive associations between early pregnancy calcium intake and spine BMC and BMD of the offspring (0.28 log mg/day;  $p < 0.02$ ).<sup>15</sup>

Another relevant aspect of the maternal diet is the insufficient intake of some nutrients necessary for bone health, and a low intake of these in women during

**Table 1.** Maternal diet associated with bone mass of offspring

Author, country (year)	Study design	n	Outcome in children	Results
Ganpule A et al. <sup>8</sup> Pune, India (2006)	Retrospective cohort	698	Total body and total spine BMC and BMD were measured using DXA in the children at 6 years old	Both parents DXA measurements were positively correlated with the equivalent measurement in the children. (mother $r = 0.36$ and father $r = 0.38$ , $p < 0.001$ ) Children of mothers who had a higher frequency of calcium-rich food intake during pregnancy had higher total BMC ( $\beta = 0.11$ , $p < 0.001$ )
Cole Z et al. <sup>9</sup> Southampton, UK (2009)	Retrospective cohort	198	Measurements of bone mass using DXA at 9 years of age	A high "prudent diet" in late pregnancy, characterized by elevated intake of fruit, vegetables, whole wheat bread and rice, and low intake of processed foods, was associated with greater whole body and lumbar spine BMC ( $r = 0.23$ $p = 0.001$ ) and BMD ( $r = 0.15$ $p = 0.02$ ) in the offspring after adjustment for confounding factors
Godfrey K et al. <sup>15</sup> Southampton, UK (2001)	Prospective cohort	145	Neonatal BMC and BMD using DXA in infants born at term	Positive associations between early pregnancy calcium intake and spine BMC and BMD ( $0.28$ log mg/day $p < 0.02$ ) Maternal intakes of protein, carbohydrate, fat, and green vegetables explained no variance in whole body BMC or BMD
Jones G et al. <sup>10</sup> Tasmania, Australia (2000)	Retrospective cohort	173	BMC and BMD were measured using DXA at the lumbar spine and femoral neck at 8 yr of age	After adjustment for confounders, total body BMD was positively associated with magnesium ( $r^2 = 0.27$ $p = 0.006$ ), phosphorus ( $r^2 = 0.25$ $p = 0.054$ ), potassium ( $r^2 = 0.25$ $p = 0.021$ ) and protein ( $r^2 = 0.25$ $p = 0.046$ ) intake A child at the "optimal" level of dietary exposures had significantly higher adjusted BMD at all sites (femoral neck 5.5%, lumbar spine 12% and total body 6.8%)
Chang S et al. <sup>14</sup> Baltimore, MD, U.S. (2003)	Prospective cohort	350	Fetal femur length <i>in utero</i>	Dairy intake had a significant positive effect on fetal femur growth after adjustment for gestational age, biparietal diameter, maternal age, height, and pre-pregnancy body mass index ( $\beta = 0.077 \pm 0.024$ , $p < 0.001$ ) Fetal femur length was significantly lower in the lowest dairy-intake group ( $< 2$ servings/day) than in the highest dairy-intake group ( $> 3$ servings/day), and a dose-response relation was suggested in the intermediate dairy-intake group ( $2-3$ servings/day; $p = 0.089$ )
Tobias JH et al. <sup>11</sup> Avon, South West England (2005)	Retrospective cohort	445	Total body BMC and BMD by DXA carried out at 9 years of age	Maternal magnesium intake was related to total body BMC ( $\beta = 4.9$ , $7.4-23.1$ ; g) and BMD ( $\beta = 4.9$ , $2.5-7.3$ ; g/cm <sup>2</sup> $p < 0.001$ ) Maternal potassium intake was related to spinal BMC ( $\beta = 1.8$ , $0.8-2.9$ ; g) and BMD ( $\beta = 10.5$ , $4.9-16.0$ ; g/cm <sup>2</sup> , $p < 0.001$ ) A significant association was also observed between maternal folate intake and spinal BMC adjusted for bone area ( $\beta = 0.55$ , $0.16-0.94$ ; g; $p = 0.006$ )

BMD, bone mineral density; BMC, bone mineral content; DXA, dual-emission X-ray absorptiometry

pregnancy may have a negative effect on fetal skeletal mineralization. Two different studies found that total body BMD of the children were positively associated

with maternal intake of magnesium ( $\beta = 4.9$ ,  $2.5-7.3$ ; g/cm<sup>2</sup>  $\times 10^3$   $p < 0.001$  and  $r^2 = 0.27$   $p = 0.006$ ),<sup>10,11</sup> and maternal intake of potassium ( $\beta = 10.5$ ,  $4.9-16.0$ ; g/cm<sup>2</sup>  $\times 10^3$

$p < 0.001$ ;<sup>11</sup> and  $r^2 = 0.25$   $p = 0.021$ ).<sup>10</sup> On the other hand, a positive association between phosphorus ( $r^2 = 0.25$   $p = 0.054$ ), protein ( $r^2 = 0.25$   $p = 0.046$ ) and folate ( $\beta = 0.55$ ,  $0.16$ – $0.94$  g;  $p = 0.006$ ) maternal intake and BMD of the children were found after adjustment for confounders.<sup>10,11</sup>

### Maternal Vitamin D Results

Table 2 summarizes the nine studies of maternal vitamin D associated with bone mass of the offspring. In eight of these, maternal vitamin D samples were taken between 23 and 36 weeks of pregnancy, and only in one study the samples were taken at delivery. In most of the studies, the serum was assayed for 25-hydroxyvitamin D3, calcium, phosphorus and parathyroid hormone.

Adequate vitamin D concentrations during pregnancy are necessary to ensure appropriate maternal response to the calcium demands of the fetus and neonatal for bone development. As shown in Table 2, the prevalence of vitamin D deficiency in maternal samples varied from 15% to 66%. Otherwise, a significant correlation was observed between maternal and cord blood serum vitamin D ( $r = 0.70$  and  $r = 0.755$ ,  $p < 0.001$ ).<sup>16,17</sup> One of the studies observed that maternal vitamin D deficiency increased the risk of neonatal vitamin D deficiency (OR 17.2, 95% CI 8.8–34.3).<sup>18</sup>

Morley et al. observed that babies of mothers in the low 25-(OH)D group ( $< 28$  nmol/liter) had a  $-2.7$  mm smaller knee-heel length than babies of mothers with higher vi-

**Table 2.** Maternal vitamin D associated with bone mass of the offspring

Author, country (year)	n	Study design	Measurements in the mother and the children	Results
Maghbooli Z et al. <sup>16</sup> Tehran, Iran (2007)	552	Prospective cohort	Maternal and cord blood samples were taken at delivery. Serum was assayed for 25-(OH)D3, calcium, phosphorus and parathyroid hormone	Prevalence of vitamin D deficiency in maternal samples was 66.8%, and in the cord blood was 93.3% ( $< 35$ nmol/L) Positive correlation between maternal and cord blood serum concentrations of vitamin D ( $r = 0.706$ , $p = 0.0001$ ) Vitamin D concentrations in cord blood were lower in newborns of mothers with vitamin D deficiency ( $15.6 \pm 7.2$ vs. $20.2 \pm 14.9$ , $p = 0.009$ ) Positive correlation between maternal alkaline phosphatase and birth weight ( $r = 0.14$ , $p = 0.02$ )
Morley R et al. <sup>19</sup> Melbourne, Australia (2006)	374	Prospective cohort	Maternal vitamin D at 28–32 weeks gestation and knee-heel length at birth of the offspring	25-(OH)D concentration was less than 28 nmol/liter in 7.2% of the women at 28–32 weeks Knee-heel length was 4.3 mm lower (95% CI $-7.3$ , $-1.3$ ) in infants of mothers with low 25-(OH)D After adjustment for gestation length, the difference was reduced to $-2.7$ (95% CI $-5.4$ , $-0.1$ )
Prentice A et al. <sup>7</sup> Cambridge, UK (2009)	123	Prospective cohort	Maternal blood sample was collected at 20 and 36 weeks gestation. Infant birth weight and bone mineral accretion by DXA	20% and 16% of the mothers had 25-OHD $< 80$ nmol/L at 20 and 36 week of pregnancy, respectively No significant relationship or trends in the data were observed between maternal 25-(OH)D concentration and birth weight, length, head circumference, BMC and BMD of the midshaft radius and whole body
Javaid K et al. <sup>12</sup> Southampton, UK (2006)	198	Retrospective cohort	Vitamin D status of the mother during late pregnancy. Whole body and lumbar-spine BMC and BMD by DXA at 9 years old.	31% of mothers were regarded as vitamin D insufficient ( $11$ – $20$ $\mu\text{g/L}$ ), and 18% as deficient ( $< 11$ $\mu\text{g/L}$ ) in late pregnancy Mothers with lower serum concentrations of 25-(OH)D had children with reduce whole-body BMC and BMD at 9 years ( $r = 0.21$ and $r = 0.12$ , $p = 0.03$ ) Deficient vitamin D mothers had offspring whose whole body BMC was significantly lower than those born to mothers who were vitamin D replete (mean $1.04 \text{ kg} \pm 0.16$ vs. $1.16 \text{ kg} \pm 0.17$ , $p = 0.002$ )

**Table 2.** Maternal vitamin D associated with bone mass of the offspring

Author, country (year)	n	Study design	Measurements in the mother and the children	Results
Gale C et al. <sup>13</sup> Southampton, UK (2008)	178	Retrospective cohort	Serum measurement of 25-(OH)D during late pregnancy and DXA of the child at 9 years old	50.4% of the women had 25-(OH)D >50 nmol/L, 28.3% had concentrations between 27.5-50 nmol/L and 21.2% had concentrations <27.5 nmol/L Children whose mothers had higher 25-(OH)D (>75 nmol/L) concentrations had a significantly larger head circumference at age 9 years than those whose mothers had lower concentrations (<30 nmol/L), (mean 53.6 ± 1.43 vs. 52.6 ± 1.59, $p = 0.012$ )
Dijkstra SH et al. <sup>21</sup> Rotterdam, Netherlands (2007)	87	Prospective cohort	Maternal vitamin D was collected at the end of the third trimester and umbilical cord blood at birth was taken to obtain vitamin D concentrations.	63.3% of the newborn infants of mothers with dark skin had vitamin D deficiency, compared with the control group that was 15.8% Vitamin D values in pregnant women and their newborn infants showed a positive correlation ( $r = 0.88$ , $p < 0.001$ ) Newborn infants of mothers at risk of vitamin D deficiency showed higher mean alkaline phosphatase concentrations than controls, which suggests increased bone turnover: 161 (124-213) vs. 177 (156-217) U/l ( $p = 0.050$ )
Mahon P et al. <sup>20</sup> Southampton, UK (2010)	424	Prospective cohort	Maternal blood sample at 34 weeks was taken to measure 25-(OH)D. Fetal femur length and distal metaphyseal cross-sectional area.	63.4% of the women were sufficient/borderline (>50 nmol/L), 30.7% were insufficient (25 to 50 nmol/L) and 5.9 % were deficient (<25 nmol/L) of vitamin D Lower maternal 25-(OH)D concentration was not related to fetal length but was positively associated with greater femoral metaphyseal cross-sectional area and higher femoral splaying index ( $r = -0.10$ 95% CI -0.20 to 0.00 and $r = -0.11$ 95% CI -0.21 to -0.01), respectively
Akcakus M et al. <sup>17</sup> Turkey (2006)	100	Prospective cohort	Serum Ca, P, alkaline phosphatase and 25-(OH)D levels were measured of the mothers at birth in winter and their neonate. Whole body BMD and BMC by DXA at birth.	25-(OH)D levels of the neonates and the mothers were highly correlated ( $r = 0.755$ , $p < 0.05$ ) 93% of the neonates and 82% of their mothers had 25-(OH)D levels <10 µg/L Whole body BMC and whole body BMD were positively correlated with birthweight ( $r = 0.910$ , $p < 0.05$ ) and gestational age ( $r = 0.70$ , $p < 0.05$ ) but not with serum 25-(OH)D
Bowyer L et al. <sup>18</sup> Australia (2009)	901	Prospective cohort	Serum 25-OHD, PTH, calcium, albumin, phosphate and alkaline phosphatase were measured in women at 23-32 weeks gestation and on the cord blood at delivery.	Vitamin D deficiency (<25nmol/L) was found in 15% of the women and in 11% of the neonates Maternal vitamin D deficiency increased the risk of neonatal vitamin D deficiency (OR 17.2, 95% CI 8.8-34.3) and birth weight was lower among infants of deficient against sufficient mothers: (3245 g ± 545 vs. 3453 g ± 555, $p < 0.001$ ).

tamin D concentrations. They speculated that moderately severe maternal vitamin D deficiency would result in reduced fetal circulation in 25-(OH)D and 1,25-(OH)<sub>2</sub>D concentrations and may lead to reduced osteoblastic activity, affecting long bone growth.<sup>19</sup> Mahon et al. also observed that low maternal 25-(OH)D concentrations have a slight association with greater femur metaphyseal

cross-sectional area and femur splaying index at 19 and 34 weeks gestation, using high-resolution 3D ultrasound ( $r = -0.10$  95% CI -0.20 to 0.00 and  $r = -0.11$  95% CI -0.21 to -0.01  $p < 0.001$ , respectively).<sup>20</sup>

One study reported that mothers deficient in vitamin D during late pregnancy had offspring whose whole-body BMC was significantly lower than those born to mothers



who were vitamin D replete (mean  $1.04 \text{ kg} \pm 0.16$  vs.  $1.16 \text{ kg} \pm 0.17$ ,  $p = 0.002$ ). This association between mothers with lower serum concentrations of 25-(OH)D and bone mineral accrual in their children persisted up to the age of 9 years old.<sup>12</sup>

Another important result was the association between vitamin D and other serum markers like parathyroid hormone, calcium, phosphorus and alkaline phosphatase. Dijkstra et al. found that newborn infants of mothers at risk of vitamin D deficiency showed higher mean alkaline phosphatase concentrations than controls, which suggested increase of bone turnover.<sup>21</sup>

## DISCUSSION

Calcium and vitamin D are two of the most important nutrients in the development of the skeletal system. Maternal diet and maternal concentrations of vitamin D are related to bone mineralization of the newborn and the child. Most of the studies were published after 2005, which point to a recent growing trend of investigations on the issue.

It is known that bone mass is determined by genetics 60-80% of the time;<sup>22</sup> however, diet should be considered an important modifiable factor to promote bone accretion as well as many other benefits that a proper diet can provide to a mother and her newborn. The studies reviewed showed that maternal diet in pregnancy had a small but consistent contribution toward bone mass in childhood.

Some studies determined that higher intakes of calcium and dairy products during pregnancy lead to improved bone accretion and growth. These studies, however, have found no hard data on the increase in BMD or BMC in infants whose mothers had calcium-rich dietary intake vs. calcium-deficient diets.<sup>9,14,15</sup>

The associations of bone outcome in children with estimated maternal calcium intakes were weaker compared to those with milk and milk product intakes. This is the case of the study that concluded that mothers in the lowest dairy-intake group (<2 servings/day) had lower fetal femur length than mothers in the highest dairy-intake group (>3 servings/day); however, the relationship between the growth of the fetal femur and its degree of mineralization is unknown.<sup>14</sup>

Some calcium-rich foods were also high in protein. Although the association with calcium-rich foods was independent of protein intake, protein quality may be an

important factor. Any causal association between calcium-rich foods and bone mass could reflect postnatal, rather than intrauterine, effects related to breast milk quality or postnatal diet.<sup>23</sup> Other nutrients such as protein, phosphorus, magnesium, potassium and some vitamins are also involved in growth and development of bone mass and must be present in adequate amounts. For this reason, several studies focused on the relationship between these nutrients and bone development.<sup>10,11</sup> There is, however, insufficient evidence to date on the role of these various nutrients in bone development of the newborn. Future studies are needed to address the mechanisms and long-term effects of nutrient intake during pregnancy on neonatal bone mass.

Evidence based on literature concerning the association between maternal vitamin D and newborn bone mass has increased in the last decade. Vitamin D concentrations are determined by serum concentrations of 25-(OH)D. In children and adolescents, vitamin D concentrations are considered: normal 25-(OH)D  $\geq 20 \text{ ng/ml}$  (50 nmol/L), insufficient 25-(OH)D between 15 and 20 ng/ml (37.5 to 50 nmol/L) and deficient 25-(OH)D  $\leq 15 \text{ ng/ml}$  (37.5 nmol/L).<sup>24,25</sup> Based on general information about vitamin D deficiency, it has been concluded that vitamin D insufficiency is a global phenomenon, with an estimated 1 billion people worldwide having suboptimal levels of 25-(OH)D.<sup>26</sup> There is evidence that 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.<sup>27</sup>

Positive associations have been reported between maternal and cord blood serum vitamin D. Also, insufficient vitamin D in the mother is associated with smaller knee-heel length and less whole body BMC in the offspring. The association between mothers with lower serum concentrations of 25-(OH)D and bone mineral accrual in their children persisted at 9 years of age.

The mechanisms by which maternal vitamin D status during pregnancy affects bone mass in the child remain unknown. It has been postulated that maternal vitamin D insufficiency during pregnancy leads to an impairment of placental calcium transport, perhaps mediated by parathyroid hormone-related peptide (PTHrP) and thereby reduces the trajectory of intrauterine and subsequent childhood bone mineral accrual.<sup>12</sup>

It is generally accepted that maternal vitamin D status during pregnancy reflects the maternal and neonatal calcium homeostasis. Due to the strong relationship between concentrations of vitamin D with PTH, calcium, phosphorus and albumin, it is important to measure these markers to determine if the association between maternal vitamin D with bone growth is independent of the biological markers.

Another source of variation in vitamin D concentrations is measure of sun exposure because skin exposure to UV-B is thought to be the major determinant in healthy vitamin D status. Also, it is important to report data on pigmentation and clothing habits and their possible association with vitamin D deficiency.<sup>28</sup>

Further studies are needed to provide more conclusive evidence of the long-term consequences of fetal and neonatal vitamin D deficiency and bone development. The lack of evidence so far has led to contradictory recommendations in vitamin D supplementation during pregnancy in many countries. The test of these findings would be through a randomized controlled trial of vitamin D supplementation in early pregnancy.<sup>29</sup>

Our study found some limitations in the reviewed studies. Some of the studies measured the outcome in pediatric age rather than measuring bone mass in the newborn.<sup>8-13</sup> This situation could weaken the associations and the conclusions because there are many environmental factors during life that are related to the status of bone. Despite adjustment for confounders, we cannot exclude the possibility of residual environmental confounding and causality cannot be assumed from these observational data.

Maternal intake was assessed only at entry into prenatal care, assuming that this level of intake remained somewhat consistent across gestation; this could increase the random error and diminish the strength of observed associations. On the other hand, many of the dietary nutrients are collinear and single nutrients may potentiate or attenuate the effects of others, a reason why it is better to evaluate the complete diet rather than single nutrients.

The use of DXA to measure bone mass in pediatric age has been validated and widely used; however, DXA has technical limitations when used in children. This is because the reduced amounts of bone mineral lead to increased proportional precision error and variability between the proportion of fat and lean tissue could lead to accuracy errors in estimation of BMC by as much as 20%.<sup>30</sup> Also in infants, variations in positioning may lead to error in

estimating bone area, making BMD data less robust.<sup>31</sup>

Other environmental factors in pregnancy that need to be considered are assessments of maternal lifestyle, body composition, and biochemical markers of the bone turnover in cord blood. All of these will help in obtaining more accurate estimates of the dietary bone mass associations. The assessment of maternal serum 25-hydroxyvitamin D and umbilical venous calcium concentrations would be helpful in evaluating intrapregnancy mechanisms for the association between maternal milk intake and childhood bone mass.<sup>32</sup>

Maternal diet and vitamin D concentrations are essential in growth and bone mineral accrual of the offspring during fetal life. Several studies have found a high prevalence of maternal vitamin D insufficiency during pregnancy associated with an increased risk of neonatal vitamin D deficiency and presence of lower bone mineral content in the offspring. Women with naturally dark skin, inadequate exposure to sunlight and living at higher latitudes have the highest risk for vitamin D deficiency.

Further information is urgently required to better characterize the optimal intrauterine environment for future skeletal health. More studies are needed to provide conclusive evidence of the long-term benefits of an adequate maternal diet as well as vitamin D concentrations on fetal bone development.

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