Chapter 12
Nutritional Requirements for Fetal and Neonatal Bone Health and Development

Stephanie A. Atkinson and Dilisha Rodrigopulle

Key Points

- Emerging evidence suggests that in pregnancy maternal body composition, diet quality, specific nutrient intake such as vitamin D, calcium and folate, and lifestyle factors such as smoking and exercise may have moderating influences on fetal and child bone development through "developmental programming" mechanisms.
- Specific nutrient needs for fetal skeletal development are currently based on estimates of intrauterine accretion of bone derived from fetal body composition analysis or cross-sectional analysis of preterm infant bone mass at birth but do not account for fetal programming effects.
- Estimates of nutrient needs for skeletal development in premature are higher than for term born infants. For premature infants, delivery of adequate nutrition during early neonatal life to attain intrauterine accretion of bone minerals varies with infant size (appropriate compared to small for gestational age), type of feeding (breast milk compared to formula) and exposure to steroid drugs, but is seldom achieved by term corrected age.
- Future research is required to define maternal nutrition and lifestyle factors in pregnancy and in early infancy in the context of genetic, epigenetic and metabolic factors that will optimize fetal and child skeletal development, achievement of peak bone mass and protect against osteoporosis in later life.

Keywords Developmental origins • Pregnancy nutrition • Fetal bone • Neonatal bone • Infant nutrition • Bone mineral content • Dual energy X-ray absorptiometry

12.1 Introduction

The trajectory for bone mineral deposition through the stages of fetal and infant development is becoming better defined as data emerge on whole-body and regional analysis of bone mineral content (BMC) using dual-energy X-ray absorptiometry (DXA). Previously, knowledge of fetal accretion of nutrients was based on analysis of the chemical composition of fetal and neonatal bodies [1], and more recently for minerals by neutron activation analysis [2]. Accretion of nutrients after birth was derived primarily from metabolic balance studies that yielded retention of mineral. Beginning in the

S.A. Atkinson (✉) • D. Rodrigopulle
Department of Pediatrics, Faculty of Health Sciences, McMaster University,
HSC 3A44, 1280 Main St W, Hamilton, ON, Canada, L8S 4K1
e-mail: satkins@mcmaster.ca

M.F. Holick and J.W. Nieves (eds.), *Nutrition and Bone Health*, Nutrition and Health,
DOI 10.1007/978-1-4939-2001-3_12,

early 1980s, BMC of the radius or humerus using single-photon absorptiometry (SPA) was possible to quantitate in small premature infants. Analysis of whole-body BMC by DXA was facilitated by availability of size-specific software beginning in the 1990s, allowing DXA to be validated as a tool [3, 4] for estimating bone, lean, and fat mass in small infants. All three sources of information—fetal tissue analysis, metabolic balance studies, and estimation of BMC by DXA—have contributed to the determination of recommended intakes of minerals and vitamin D to support healthy bone growth. In addition to nutrients, early skeletal development is dependent on genetics, an appropriate endocrine environment including parathyroid hormone (PTH), 1,25-dihydroxycholecalciferol, growth hormone (GH), insulin and insulin-like growth factors (IGFs), as well as physical activity. The integration of these factors is important to skeletal development per se and also the response of such factors to influences in the environment of the growing fetus and child.

12.2 Determinants of Fetal and Infant Bone

12.2.1 Developmental Programming

Observational studies have demonstrated a strong correlation between parental and offspring BMC and bone mineral density (BMD) [5, 6]. Evidence from twin and family studies suggest that the genetic contribution to BMD is between 60 and 90 % [7]. Some skeletal sites are shown to have a higher degree of heritable contribution than others, with the greatest degree of association being the head [7]. However, it is now acknowledged that environmental exposures during fetal and early life may give rise to epigenetic processes that result in developmental "plasticity or the ability of a single genotype to give rise to several phenotypes" [8].

The concept of "developmental programming" embraces the theory that metabolic events during critical time periods of antenatal and postnatal development have moderating effects on later health. Findings from human epidemiological and animal studies support a role for the interaction of gene variants with exposures during pregnancy such as maternal nutrition and other lifestyle variables to influence the programming of fetal, neonatal, and adult bone outcomes [8–11]. Maternal obesity on entering pregnancy has been linked to bone outcomes in the offspring in some but not all studies. In a multivariable regression analysis of 7,121 children at a mean age of 9.9 years, maternal prepregnancy body mass index (BMI) was positively associated with offspring total bone less head (TBLH) BMC and BMD, and spine BMC and BMD [12]. In contrast, maternal weight and gestational weight gain were inversely related to cord blood concentrations of bone formation markers such as osteocalcin and bone specific alkaline phosphatase [13]. Thus, further investigation is needed into the link between maternal weight and offspring bone health, especially in terms of adiposity hormones such as leptin.

In observational studies, a relationship was documented between maternal intake of dairy foods during pregnancy and a positive impact on bone mass in offspring between 6 and 16 years [14–16]. Not only fetal/infant bone mass but bone size (length) is influenced by maternal diet. In adolescent mothers, consumption of less than 2 dairy servings per day during pregnancy was associated with shorter fetal femur length at 20–34 weeks gestation [17]. Fetal femur and humerus length and infant birth length were significantly greater in adolescent mothers whose calcium intake was >1,050 mg/day, especially when vitamin D status was low (<50 nmol/L) [18]. To date, only one RCT in a small sample ($N=36$) investigated the effect of dairy product supplementation on BMD and bone turn-over in pregnant women in China with habitual low calcium intake [19]. A beneficial effect of milk supplementation during pregnancy was demonstrated for bone mass density at the spine and on suppression of bone resorption [19].

Exposure to individual nutrients may also be important to programming of bone in utero. Given the role of folate in methylation processes, a known mechanism of gene silencing, it is not surprising that folate status of women in pregnancy has been associated with indicators of bone programming in the

offspring. In the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort study [20], maternal dietary intake of folate was significantly associated with BMD and areal BMC of the spine sub-region at 9 years of age. An association of the maternal MTHFR genotype with the same bone measures was also observed at age 9 years [20].

Maternal vitamin D insufficiency in pregnancy impairs placental calcium transport, thus reducing the trajectory of intrauterine bone accrual [21, 22]. This may occur via vitamin D-induced upregulation of placental mRNA expression of PMCA isoforms 1–4, which predict neonatal bone mineral content independent of other key maternal related variables [23]. In observational studies, vitamin D deficiency in women during pregnancy is a risk factor for vitamin D deficiency in the newborn infant [24], reduced intra-uterine long bone growth [25], lower bone mass at birth [26, 27], lower fetal long-bone growth [28], neonatal rickets [29], and significantly lower whole body bone mineral content (BMC), as well as lower lumbar spine BMC at 9 years of age [30]. Fetuses of vitamin D deficient mothers had a pattern of femoral growth that resembled childhood rickets as measured by 3D ultrasound at 19 weeks of gestation [28]. Programming of fetal bone in relation to maternal vitamin D status in pregnancy may also operate via gene methylation since vitamin D plays a regulatory role in the transcription of DNA methyltransferase enzymes.

Maternal dietary intake of calcium during pregnancy was demonstrated to influence fetal bone mineral accretion. For women with low dietary Ca intakes (<600 mg/day), a supplement of 2 g of calcium from before 22 weeks of gestation resulted in higher BMC of the total body in infants born at term [31]. In a prospective study in humans, higher first trimester maternal intakes of protein, calcium, and phosphorus were associated with higher childhood (6 year) bone mass, while higher carbohydrate intake was associated with lower bone mass [32]. The amount of dietary fat may also be important since an animal study found that after 14 weeks, pups of mothers fed a high fat diet had higher trabecular and cortical bone area [33].

Bone outcomes in the child may also be predicted by fetal growth velocity at specific phases of intrauterine development. Using data from a large ($n = 628$ mother–child pairs) prospective cohort, Harvey et al. [34] demonstrated that early pregnancy abdominal circumference growth defined as 11–19 weeks of gestation, was a stronger determinant of whole body bone area and bone mineral content at 4 years of age while late pregnancy growth defined as 19–34 weeks was more strongly associated with bone mass at birth.

The concept of fetal/neonatal programming of bone status is supported by knowledge of several candidate genes that may explain the genetic basis of adult bone mass such as the vitamin D receptor (VDR) [25], the gene encoding for type 1 collagen and the gene for estrogen receptor [35]. Intrauterine exposure to specific nutritional imbalances may operate via fetal "programming" of candidate endocrine systems that influence skeletal metabolism such as the growth hormone/IGF-1 axis. Cord IGF-1 in term infants was positively associated with whole body bone mineral content of newborn infants but was independent of other proven influences on neonatal bone mass such as maternal body composition and physical activity or birth weight [35].

The genetic variants responsible for BMD variation are beginning to be identified. To date, 66 BMD loci have been identified through candidate gene and genome-wide association studies, confirming the highly polygenic nature of BMD variation [36–38]. These BMD loci have been mostly identified in adult general populations, and their impact on maintenance of BMD post-delivery has yet to be studied.

Other non-dietary factors related to maternal lifestyle such as, smoking, breast feeding and physical activity were identified as determinants of fetal/infant bone status in a population-based cohort study. Infants born at term whose mothers smoked during pregnancy had significantly lower (by 11 %) whole-body BMC than infants of nonsmokers [39]. However, the impact of maternal smoking on bone status of the offspring may not be sustained. In 415 infants in Southern Tasmania who were followed from pregnancy to 16 years of age, maternal smoking was associated with lower bone mass at 8 years but by 16 years there was no effect on bone mass at any site or incidence of fractures [40]. In the latter study, breastfeeding was associated a benefit of 2–3 % higher BMD of the whole body and hip and about a 30 % reduction in fracture risk after adjustment for confounders [40].

Maternal physical exercise is generally promoted during pregnancy and may benefit fetal bone outcomes, although the ideal intensity, duration and type of exercise to achieve a benefit to child bone health are not well prescribed. Maternal thinness as reflected in low triceps skin fold thickness and more frequent and vigorous activity in late pregnancy were also associated with a lower BMC in the infants [39]. Further, analysis by this group reinforced these observations, showing that in a sample of 841 mother–baby pairs lower walking speed in late pregnancy and higher skin fold thickness in mothers during pregnancy were positive predictors of greater neonatal whole body bone and BMC [10]. These maternal predictors of newborn bone mass were independent of placental weight and thus not likely a result of reduced placental delivery of nutrients. However, intrauterine growth restriction leading to small infant size at birth may also be an important marker of ultimate skeletal development, since birth weight is a recognized predictor of bone mass in later life [41, 42].

12.3 Nutrient Needs for Fetal Skeletal Development

Deposition of the key essential minerals for fetal bone development—calcium (Ca), phosphorus (P), and magnesium (Mg)—occurs predominantly in the third trimester of pregnancy, during which approximately 80 % of the mineral of the infant born at term is accrued in the skeleton [43]. A maternal source of vitamin D appears to be important for the transplacental transfer of Ca (and presumably P) to the fetus, and the synthesis of the active metabolite (1,25-dihydroxyvitamin D) that functions in this transport role appears to occur not only in maternal tissues but also in placental tissue and the fetal kidney (reviewed in [21, 44]). After birth, infants are dependent on a normal circulating concentration of 25-hydroxyvitamin D to produce the active metabolite.

12.3.1 Estimates of Intrauterine Accretion of Bone Minerals

Biochemical analysis of body composition of aborted fetuses or infants dying shortly after birth have formed the basis of estimations of accretion of nutrients in the third trimester of pregnancy [1, 43, 45]. From the compositional data, and using weight growth curves of more recent studies, mineral accretion over the period of 24–36 weeks of gestation was estimated to be 90–120 mg/kg fetal body weight/day for Ca, and possibly higher from 36 to 38 weeks of gestation, which is the time of peak fetal accretion of bone mineral [45]. During this intrauterine growth period, P is deposited in amounts of about 60–75 mg/kg/day and Mg is deposited in amounts of about 2.5–3.4 mg/kg/day [45]. The exact amount of maternal vitamin D intake required to optimize fetal bone accretion is unknown. The 25-hydroxyvitamin D accumulates in the fetus and serum concentrations at term birth will reflect maternal vitamin D status, race (African-American being lower than Caucasian), and season of the year [46]. In preterm infants, cord blood concentration of this vitamin D metabolite is variable, with some lower and some higher than the normal reference range (50–215 pmol/L) [47].

12.3.2 Accretion of Bone as a Measure of Calcium Needs During Fetal Life

In vivo intrauterine estimates of fetal bone mineral accretion have not been measured even with DXA technology, due to the small exposure to radiation (of the order of 0.3 mrem per scan). Instead, estimates of BMC at sequential gestational ages have been inferred from cross-sectional measures in preterm infants taken shortly after birth using DXA. For example, in a cross-sectional study of German infants

born at a gestational age of 25–42 weeks, lumbar spine BMC increased 5.5-fold and mid-humerus BMC increased 2.4-fold over the first year of life [48]. In a similar cross-sectional study of US infants [49], accretion of Ca in utero in the third trimester of pregnancy was estimated to be 23.2 ± 35 g (mean ± SD), assuming that bone mineral contains 32.2 % Ca. Reference intrauterine values for BMC in Belgian infants were converted to Ca content of bone and found to compare favorably with the Ca content measured by chemical analysis or with neutron activation analysis [50].

12.3.3 Maternal Nutrition in Pregnancy to Support Nutrient Accretion of Fetal Bone

In pregnancy, maternal vitamin D status is critical to the vitamin D status of the infant at birth and may even program for bone development in childhood. Recommended intakes of vitamin D in pregnancy vary between reports. While the Dietary Reference Intakes from the Institute of Medicine in Washington, DC and Health Canada [51], recommend 600 IU vitamin D day (same amount as for nonpregnant women), the Canadian Pediatric Society recommends 2,000 IU/day [52]. For the prevention of vitamin D deficiency in pregnancy, the American Endocrine Society recommends at least 600 IU/day of vitamin D and states that at least 1,500–2,000 IU/day of vitamin D may be needed to maintain a blood level of 25(OH)D above 30 ng/ml (75 nmol/L) [53]. The latter states that "pregnant women are at high risk for vitamin D deficiency" and that "daily doses of 600 IU vitamin D do not prevent deficiency in pregnant women" [53]. However, claims of "pandemic" or high prevalence of vitamin D deficiency in pregnant and lactating women [52, 53] are not founded on population-based surveys but rather cite literature primarily from Afro-American and Aboriginal groups. The higher recommendations for vitamin D intake in pregnancy are difficult to reconcile based on scientific evidence [54]. In pregnancy, absorption of calcium doubles owing to doubling of the synthesis of the active metabolite 1,25-dihydroxyvitamin D via a non-parathyroid hormone mechanism that upregulates renal 1-alpha-hydroxylase enzyme [21].

To date, evidence to support higher intakes of vitamin D in pregnancy have relied on a single randomized clinical trial in which 494 women were randomized in early pregnancy to vitamin D supplements of 400, 2,000 or 4,000 IU per day and 350 women were followed to term birth [55]. For the groups receiving 2,000–4,000 IU/day, >80 % of subjects achieved a serum 25OHD of >80 nmol/L and both maternal and cord blood 25OHD was significantly higher than for the group randomized to 400 IU/day vitamin D [55]. No adverse effects were reported for hypercalcemia or hypocalcemia, hypercalciuria or parathyroid hormone level [55]. However, the higher vitamin D status was not reported to benefit clinical outcomes of infant growth (including birth weight which was similar across vitamin D supplement groups) or bone size or bone mass; nor was there any association of vitamin D status with outcomes of pregnancy comorbidities [56]. These findings support data from a previous study in 125 Gambian women who all achieved serum vitamin D in pregnancy >50 nmol/L [57]. No differences in birth weight, infant length, whole body, or radius bone measures by DXA at 1 year of age were observed between groups whose mothers had vitamin D status during pregnancy above or below 80 nmol/L [57]. Thus, the need to achieve vitamin D status in pregnancy over 80 nmol/L in order to optimize bone size and mass outcomes in the offspring does not seem warranted based on existing evidence. In addition, there is no evidence that increasing the vitamin D content of breast milk by super dosing the mother produces sufficient transfer of vitamin D to the infant to maintain a normal vitamin D status unless the mother consumes >6,400 IU/day for >6 months [58]. At maternal intakes of 2,000 IU vitamin D/day for 3 months during lactation, milk vitamin D rose only moderately (from 40 to 70 IU/L) and no effect was observed on vitamin D status of the nursing infant [58]. Thus, recommendations for vitamin D intakes beyond the 600 IU/day in pregnant and lactating women do not appear warranted. A prudent approach is to follow current guidelines of directly supplementing the infant with 400 IU/day of vitamin D [51] rather than super dosing the mother.

Table 12.1 Comparison of nutrient recommendations by various groups for mineral and vitamin D intakes of premature infants

	Preterm infants—US [59]	Preterm infants—Europe [60]	Preterm infants—Tsang et al. [61]
Calcium, mg/day	115–220	120–140	160–220
Phosphorus, mg/day	75–140	65–90	78–118
Vitamin D, IU/day	200–400	800–1,000	400

12.4 Nutrient Needs for Skeletal Development in Premature Infants

Recommendations for nutrient intakes for premature infants vary among international sources. A comparison of current recommendations for the bone nutrients—calcium, phosphorus, and vitamin D—for premature infants by the American Academy of Pediatrics in the United States [59], the European Society for Pediatric Gastroenterology, Hepatology and Nutrition [60], and a global consensus [61] is shown in Table 12.1. The recommendations are provided as a range of values reflecting the fact that not all preterm infants are the same and nutrient needs will vary depending of stage of prematurity, size at birth (small versus appropriate for gestational age), and rate of growth.

For vitamin D, the European recommendation is more than twice that of the North American sources. The rationale for this discrepancy is not clear in their report [60]. Premature infants are at risk of poor vitamin D status due to low nutrient stores at birth, low content of vitamin D in human milk and prolonged hospitalization, which prevents endogenous production of vitamin D [47]. For preterm infants or very low birth weight preterm infants, there are three randomized trials supporting the position that 400 IU per day is sufficient supplemental vitamin D for both short term [about 3 months [47]], and long term (9–11 years) normal bone health [62, 63]. After discharge from hospital, premature infants should receive vitamin D supplements as recommended for term infants.

Premature infants fed premature formula or expressed breast milk fortified with human milk fortifiers that have vitamin D added require a vitamin D supplement until they are being fed at least 300–400 ml/day, depending on the product being used. This volume of formula or fortified expressed breast milk is the amount that would supply 400 IU/day of vitamin D. There are few situations where calcium supplementation of infants is indicated. Preterm infants have higher calcium requirements than term infants and preterm formulas and human milk fortifiers are accordingly fortified with added calcium. There is no evidence to indicate, once term corrected age is reached, that higher amounts of calcium need be provided as a supplement.

12.5 Nutrient Needs for Skeletal Development in Term-Born Infants

The most recent nutrient-based recommendations for mineral and vitamin D intakes are those of the Food and Nutrition Board, Institute of Medicine (IOM) [51, 64], which are intended for use by Americans and Canadians (Table 12.2). For infants, the recommended intakes are intended for term-born, healthy, breast-fed infants who are considered the model for normal infant growth.

For vitamin D, setting an AI could not be based on the content of human milk as it contains only marginal amounts of vitamin D. An AI for vitamin D of 400 IU/day was set for infants from 0 to 12 months, based on this intake being associated with maintenance of serum 25-hydroxyvitamin D above 30 nmol/L and likely closer to 50 nmol/L, which represent a vitamin D status that is above that usually associated with clinical rickets in infants. The revised AI for vitamin D of 400 IU/day for infants now set by the Institute of Medicine was previously established by the Canadian Pediatric

Table 12.2 Dietary Reference Intakes for minerals calcium, phosphorus, magnesium, and fluoride for infants [51, 64]

Nutrient	0–6 months	7–12 months
Calcium		
Al (mg/day)	200	260
UL	ND	ND
Phosphorus		
Al (mg/day)	100	275
UL	ND	ND
Magnesium		
Al (mg/day)	30	75
UL	ND	ND
Fluoride		
Al (mg/day)	0.01	0.5
UL (mg/day)	0.7	0.9

AI Adequate Intake, *ND* not determinable due to lack of data of adverse effects in infants, *RDA* Recommended Dietary Allowance, *UL* upper limit

Society [52] and the American Academy of Pediatrics [65]. For breast-fed infants to meet the AI of 400 IU of vitamin D/day they must be provided with a vitamin D supplement. For formula-fed infants, intake of nearly 1,000 ml/day is required to achieve the AI for vitamin D since infant formulas in North America are regulated to contain 400 IU/L of liquid formula.

The DRIs for calcium, phosphorus and magnesium for infants were based on the content of human milk to derive an estimated average intake (AI) for age 0–6 months and with the addition of intake from complementary foods for age 7–12 months. For calcium, the values reflect those provided in the revised DRI report for Calcium and Vitamin D [51]. The AI value of 200 mg/day for breast-fed infants from 0 to 6 months was substantiated by considering that average calcium absorption in infants is around 60 % thus yielding retention of calcium of 120 mg/day, a value about 20 % higher than the estimated accretion of calcium for an infant of about 100 mg/day. For infants 6–12 months of age, recent data on calcium intakes from solid foods for formula fed infants was used to add to the intake from breast milk to yield an AI of 260 mg/day. For fluoride, intake from human milk was the reference for the first 6 months only. After 6 months, the AI for fluoride was set at 0.05 mg/kg/day and adjusted to a reference weight for age, based on the well-documented evidence of the benefit of fluoride intake for the prevention of dental caries (Table 12.2).

12.6 Infants at Risk of Bone Abnormalities due to Nutritional Deficiency/Excess

Sub-optimal bone mineralization still exists in certain infant groups despite widespread recommendations of supplementation with vitamin D. In a survey of rickets by the Canadian Pediatric Society [29], 104 documented of infants with rickets (at a mean age of 1.4 years, range 2 weeks–6.3 years) were identified and associated with vitamin D deficiency. The primary cause was attributed to 94 % of the cases of rickets having been or currently being breast fed, most with no vitamin D supplements. Another causative factor may have exposure to maternal subclinical vitamin D deficiency in utero. As demonstrated in this Canadian surveillance of rickets [29], subclinical maternal vitamin D deficiency was likely since 79 % of mothers did not drink milk during pregnancy and only 12.5 % had taken a supplement with vitamin D. Another key risk factor identified was dark skin colour since 33 % of

infants were Afro-American, 24 % were First Nations or Inuit, 14 % were middle Eastern with only 10 % Caucasian and living in the north (the Territories and Nunavut), Thus, a key issue is not that 400 IU/day vitamin D is not adequate for pregnant women or infants but rather that compliance with taking that recommended amount of vitamin D was almost non-existent [29]. Clearly, the lack of compliance with current recommendations for breast-fed infants to receive 400 IU vitamin D/day from birth is a key issue that needs to be addressed through improved education by health professionals.

In some situations, the recommendation of 400 IU vitamin D per day may not be adequate in the following subgroups of infants: infants born to mothers with sub-clinical or overt vitamin D deficiency due to inadequate placental transfer of vitamin D in utero to build the infant body stores of 25OH-D [29]; infants with liver or renal disease or malabsorption syndromes [66–68]; obese infants due to possible sequestration of vitamin D metabolites in the excess adipose [69]; or those with intermediate or dark skin, who avoid exposure to sun or who cover the majority of their skin outside the home [70]. Such infants may require greater than 400 IU vitamin D per day but intake should not be in excess of the Upper Level (UL) set by the DRI of 1,000 IU/day for infants to 6 months and 1,500 IU/day for infants 6–12 months [51]. For infants living in northern communities (above 40° north), especially those with intermediate or dark skin colour, the Canadian Pediatric Society Nutrition Committee supports the recommendation to supplement term infants with 400 IU/day of vitamin D, but further recommends that infants living in the far north be supplemented with 800 IU/day of vitamin D [52]. However, this recommendation is not based on clinical trial evidence. Rather, risk of vitamin D deficiency has been implied from observational studies in regional communities such as in the Winnipeg area in Aboriginal populations [71].

12.7 Bone Mineral Content in Term and Preterm Infants

Term infants: In term infants, accretion of bone mass in the whole body measured by DXA over the first year of life follows the pattern shown in Fig. 12.1. Longitudinal measures of whole-body bone mineral content (WBBMC) in term-born infants demonstrated that BMC increases by 2.5–3.6-fold over the first year of life [72, 73]. Based on reports of DXA measures of body composition in term infants, Koo [74] estimated that BMC increased by 400 % during infancy while body weight increased by 330 %. However, body weight appears to be the strongest determinant of BMC in growing healthy infants [50, 75]. The independent influence of diet—such as vitamin D or mineral intake or dietary practice of breast feeding compared to formula feeding—on bone mineral accretion in infancy has been addressed in a few studies.

Whole-body BMC in breast-fed term infants has consistently been observed to be lower than in formula-fed infants [73, 75]. In one study [73], a significantly lower BMC was observed at 3 and 6 months of age in breast-fed infants (average milk Ca and P of 300 and 150 mg/L) compared to those fed formula containing moderate amounts of Ca and P (510 and 390 mg/L) but not low Ca and P (430 and 220 mg/L). However, from 6 to 12 months of age, the previously breast-fed infants were fed formula with moderate or high (1,350 mg Ca and 900 mg P/L) mineral content now demonstrated a greater rate of accretion of BMC (81 ± 161 mg/6 months) than the infants fed formula in the first 6 months (73 ± 15 and 71 ± 15 mg/6 months). As a result, by 12 months of age there were no differences in whole-body BMC between feeding groups. If infants were breast-fed beyond 6 months, a lower whole-body BMC than formula-fed infants was maintained to 12 months of age, but such differences were not apparent by 2 years of age [75]. A lower intake of protein and macrominerals from exclusive feeding with breast milk compared to standard infant formulas is the likely explanation for observed variations in growth patterns in early life [75]. Taken together, the available studies indicate that slower accretion of bone mass in early life may represent the biological norm and is not predictive

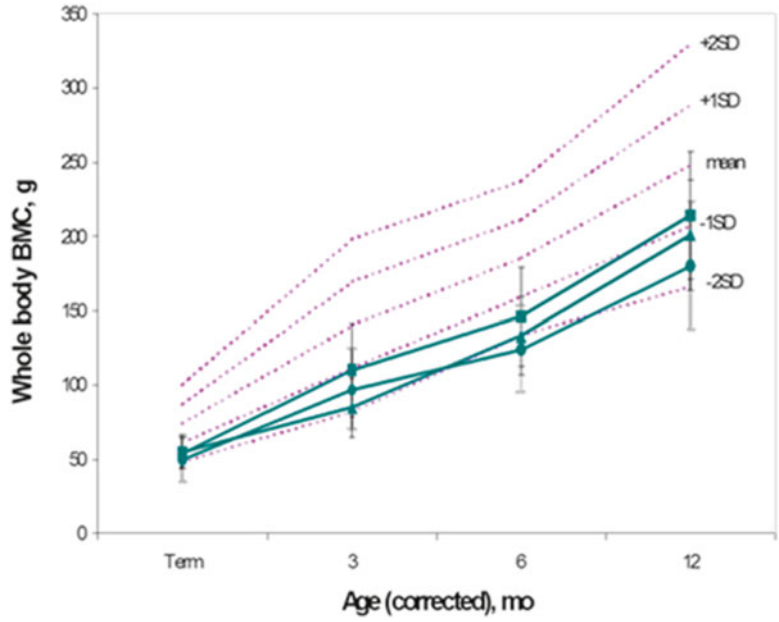

Fig. 12.1 Pattern of whole-body bone mineral content (WBBMC) accretion by DXA in Canadian term born infants fed standard term formula from birth to 1 year is shown in hatched lines (mean ± 2 SD). The *solid green lines* indicate the pattern of change in WBBMC in preterm infants of different birth weight categories and feeding regimens after hospital discharge: *filled circle* Low birth weight (birth weight = 1,154 g, $N = 24$) and breast fed to 6 months and then some term formula to 12 months; *filled square* Low birth weight (birth weight = 1,029 g, $N = 22$) and fed term formula to 12 months; *filled triangle* very low birth weight (birth weight = 866 g, $N = 18$) and fed term formula (Data provided by S Atkinson)

of lower ultimate bone mass in early childhood. It remains to be determined whether differences in patterns of skeletal accretion of bone mineral in fetal and early life influences subsequent metabolic programming of growth and final adult bone mass.

Preterm infants: In utero, the fetus experiences the greatest deposition of calcium and phosphorus into bone during the third trimester of pregnancy, peaking between 32 and 34 weeks of gestation [1, 43]. Thus, preterm infants are born with lower bone mass compared to term born infants. The short-term impact of early nutrition (while in hospital) on whole-body measures of BMC at term-adjusted age have been evaluated in relation to feeding of fortified mother's milk compared to preterm formulas. In some studies in infants less than 1,500 g birth weight and gestational age less than 32 weeks, no differences in whole-body BMC were observed at or near term age between those fed fortified mother's milk or preterm formula in hospital [76, 77]. But the mean BMC of the preterm infants was lower than −1 SD from the mean value for the term infants [76, 77]. In preterm infants of larger birth weight (<1,750 g), feeding of preterm formula compared to fortified human milk for 3 weeks resulted in higher whole-body BMC at 37 weeks gestational age [78]. However, BMC related to bone area or to body weight were similar between the feeding groups and represented about a −2 z-score compared to term-born reference infants [78]. Taken together, the reported studies provide evidence that bone mineral deposition equivalent to that which occurs in utero in the third trimester of pregnancy is not achieved by term age in infants born prematurely, despite the many advances in the delivery of nutrients in early life in this population.

Some of the observed differences in BMC at term age between reported studies may relate to differences in birth size, particularly if the population studied included infants of extremely LBW or small for gestational age [79]. As published previously [80], mean values for whole-body BMC at term-corrected age for preterm infants of varying birth weight and in-hospital feeding regimens fall below

(<−1.5 SD) that of term reference infants (see values at term age in Fig. 12.1). Mean absolute BMC for preterm infants who were appropriate for gestational age (AGA) at term-corrected age was 16–30 % lower, and for those who were small for gestational age (SGA) was 36 % lower than BMC in term-born infants [80]. Since most preterm infants are smaller in both weight and length at term-corrected age than term-born infants, BMC values were expressed as a function of weight or length. Compared to a whole-body BMC for body weight of 20 ± 2 g/kg for term infants, SGA infants (17 ± 3 g/kg) and AGA infants (17 ± 2 g/kg) had lower bone mass at term-corrected age [80]. Expressed as a function of length, BMC g/cm was 1.5 ± 0.2, 1.0 ± 0.3, and 1.1 ± 0.2 for the term, preterm SGA, and preterm AGA infants, respectively [80]. Thus, even with correction for body size, the premature infants did not attain a bone mass comparable to term infants at birth.

The impact of mineral fortification of mother's milk or specialized formulas for preterm infants in early life during hospitalization on accretion of bone mineral measured by bone densitometry has been inconsistent. In a systematic review [81], the effectiveness of multicomponent fortification of human milk on the promotion of growth and bone mineralization in preterm infants was evaluated. Ten trials ($N = 596$ infants) were included in the analysis, which represented random or quasi-random allocation to supplementation of human milk with multiple nutrients or no supplementation within a nursery setting. Unfortunately, only half of the reported trials measured BMC, and there was inconsistency in the use of radial or whole-body measures of bone. The main results of the review showed that BMC was increased by nutrient fortification of formula. However, in four of five studies in which BMC was measured, there were no statistical differences between control and treatment groups. A meta-analysis of BMC measures from the 5 studies (in which one study contributed 59 of 79 infants) showed a positive effect on BMC of fortification of mother's milk with a human milk fortifier (weighted mean difference [WMD] 8.3 mg/cm, 95 % confidence interval (CI) 3.8–12.8 mg/cm) [81]. Plasma alkaline phosphatase, a marker of bone turnover, was not different between treatment groups.

Physical activity, in particular weight-bearing exercise, positively influences bone mass accretion even in preterm infants in early neonatal life as measured using SPA [82] or DXA [83]. Using quantitative ultrasound of the tibia early (about 2 weeks postnatal), intervention with brief daily passive range of motion exercise reduced the usually observed postnatal decline in tibial speed of sound (SOS) measures [84]. The interactive effects of diet and physical activity on accretion of bone mass is just beginning to be addressed in young children [85], but in preterm infants they remain to be elucidated.

The expected time for "catch-up" growth and bone accretion and the nutrients needed to support skeletal development in preterm infants are not well defined. Longitudinal measures of whole-body BMC from term date to 1 year corrected age demonstrated that prematurely born infants [86, 87] experience an increase in BMC of 3.6–4-fold from term corrected age to 12 months, similar to that of term-born infants [80]. However, the velocity of accretion of BMC and capacity for catch-up bone mineral accretion (that which crosses centile or standard deviation lines) in the whole body of preterm infants appears to vary with birth size and nutritional management over the first year of life (Fig. 12.1). By 12 months corrected age, "catch-up" in BMC to above −1 SD was achieved only in infants of mean birth weight over 1,000 g who were AGA (Fig. 12.1). Those infants who were SGA or of ELBW had whole-body BMC at 12 months corrected age between −2 and −1 SD compared to term-born reference infants (Fig. 12.1). Breast-fed premature infants who received more than 60 % of milk intake as breast milk, had lower WBBMC at 3 and 6 months corrected age when compared to formula-fed term infants but by 12 months corrected age their BMC was similar to the formula–fed preterm infants, albeit still below the mean value for term born formula-fed infants (Fig. 12.2).

Catch-up in bone accretion in preterm infants following discharge from hospital was proposed as a benefit of feeding nutrient-fortified formulas. In two randomized trials of a dietary intervention to 3 months corrected age, nutrient-enriched formula that included supplemental dietary protein, Ca, and P after hospital discharge had a positive immediate benefit to BMC when the intervention was

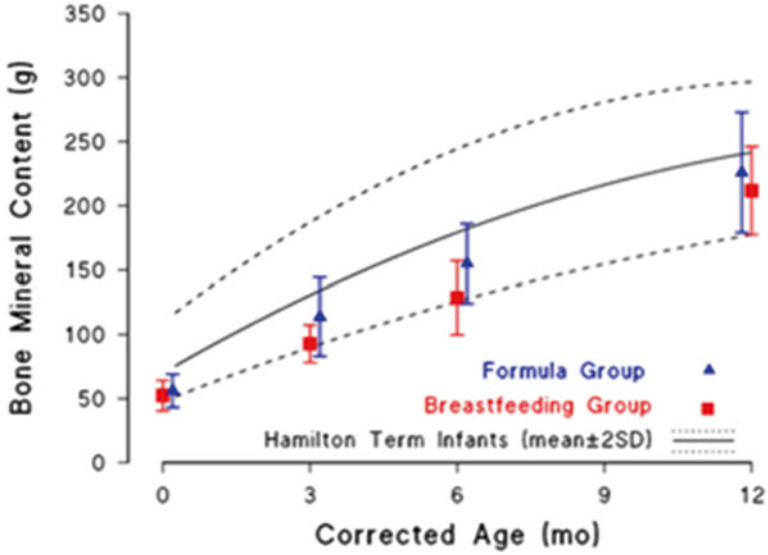

Fig. 12.2 Whole-body bone mineral content by DXA in prematurely born infants fed primarily mother's breast milk or standard term formula. The Breastfeeding Group of preterm infants was fed fortified human milk in hospital and received >60 % of feeding as mother's milk after hospital discharge ($N = 27$, birth weight = 1,187 ± 232 g, gestational age at birth = 29 ± 3 weeks). The Formula Group of premature infants was fed standard term infant formula (FF) from hospital discharge to 1 year corrected age ($N = 26$, birth weight = 1,068 ± 328 g, gestational age at birth = 29 ± 3 weeks). *NOTE*: At 3 and 6 months of age, BMC for the Formula Group was significantly greater than Breastfeeding Group ($p < 0.05$) but not at 12 months corrected age (Data provided by SA Atkinson, McMaster University)

continued to 3 months [88] or 9 months [89] corrected age. However, such a positive effect of early nutrition on BMC is not always sustained [87, 90]. A randomized trial in small-for-gestational age premature infants in response to nutrient-fortified formula feeding to 1 year corrected age, demonstrated that the nutrient enriched formula did not support significantly greater bone mass accretion (Fig. 12.3). Both feeding intervention groups achieved some "catch-up" in BMC as referenced to term infants although neither reached the mean value for term infants by 12 months corrected age (Fig. 12.3). Thus, the whole-body BMC attained in the preterm infants does not catch up to that of term infants at 1 year of age, regardless of receiving protein and mineral intakes that are greater than those fed to term born infants in the first year of life.

Does early nutrition of preterm infants influence bone health in childhood and adolescence? Early "catch-up" of bone mass may not be important for preterm infants if final bone growth and attainment of peak bone mass is not compromised [91]. This question has recently been addressed through observational studies of former preterm infants at various stages of childhood or adolescence. At 8–12 years of age, whole-body BMC in prematurely born infants was significantly lower than for children of similar age born at term [62]. However, the preterm infants were also shorter and lighter, so that their BMC was appropriate for body mass when compared with children born at term. Neither diet in early life (breast milk compared to formula) nor current calcium intake or weight-bearing physical activity was significant determinants of BMC at this peripubertal age [62]. Measures of bone mass of the radius and lumbar spine in 70 preterm infants followed at 9–11 years of age were also lower and height shorter than in term infants; and neonatal diet interventions of Ca, P, or vitamin D were not associated with BMC in childhood [62]. Preliminary evidence suggests that catch-up does not occur during the pubertal growth spurt. Further follow-up of the Fewtrell et al. cohort ($N = 202$) in young adulthood (~20 years), found the former preterm infants to be significantly shorter and with lower

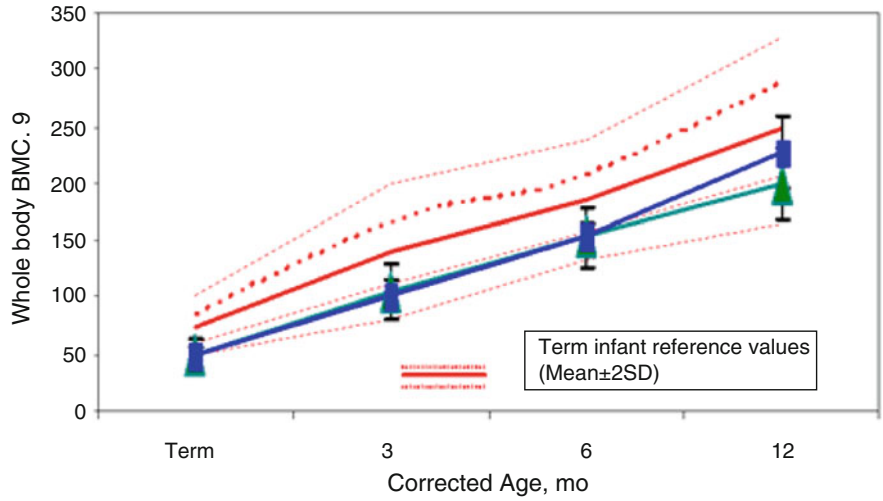

Fig. 12.3 Whole-body bone mineral content (WBBMC) in small-for-gestational age preterm infants randomized from hospital discharge and fed to 1 year corrected age on enriched post-discharge formula (EPDF) ($n=22$, birth weight = 1,410 ± 422 g, gestational age = 33.5 ± 3 weeks) indicated by ■; or standard term formula (SF) ($n=28$, birth weight = 1,411 ± 461 g, gestational age = 33.4 ± 3 weeks) indicated by ▲. Data for SGA preterm infants are plotted against reference data for term infants who were fed standard infant formula. Absolute means and velocity of WBBMC were not different between SF and EPDF groups. (Data provided by SA Atkinson, McMaster University)

lumbar spine BMD compared to reference data [91]. This observation was particularly apparent in those former preterm infants who were born small-for-gestational age [91]. In a study in Canada, former preterm infants ($n=26$) studied at 16–19 years were also found to be shorter and with lower BMC in the whole body, hip, and lumbar spine, although the BMC was appropriate for body size compared to 23 adolescents who were born at term [92]. In the latter study, early life variables such as the amount of human milk fed and duration of time until regain of birth weight was achieved were inversely associated with BMC at adolescence [92].

Birth size and neonatal exposure to steroid therapy may also impact later skeletal development. Extremely low birth weight infants (birth weight = 839 ± 189, $N=47$) who received dexamethasone therapy in early life to low birth weight infants (birth weight = 1,167 ± 215 g, $N=36$) had significantly whole body BMC Z-scores and lower BMD at the lumbar spine at 6–8 years of age compared to term born infants (birth weight 3,470 ± 391 g, $N=36$) [93]. Explanation for the significant delay in bone mass accretion for the extremely low birth weight infants may be multifactorial including lung disease that was treated with steroid therapy in early life, their earlier gestational age, and possibly greater exposure to inhaled steroids in childhood. Delayed early growth may also have contributed to the later delay in bone accretion in childhood [93].

12.8 Conclusion

In summary, evidence is emerging on the significance of exposures during pregnancy including maternal diet and lifestyle factors as well as early nutrition, physical activity and growth patterns in the infant, to achievement of peak bone mass by the end of the second decade and long-term programming of skeletal health. Once such knowledge is confirmed, recommendations for nutrient requirements and lifestyle practices can be better defined in order to optimize skeletal mineralization, achievement of peak bone mass and reduced risk of osteoporosis in later life.

Acknowledgments The contributions of collaborators, research assistants, and graduate students to the research cited in this chapter from the author's laboratory are gratefully acknowledged.

References

1. Widdowson EM, Dickerson JWT. Chemical composition of the body as a whole. In: Comar CL, Bronne F, editors. Mineral metabolism: an advanced treastise. Part A, vol. 2. New York, NY: Academic; 1964. p. 1–247.
2. Ellis KJ, Shypailo RH, Schanler RJ, et al. Body composition analysis of the neonate: new reference data. Am J Hum Biol. 1993;3:323–30.
3. Brunton JA, Weiler HA, Atkinson SA. Improvement in the accuracy of dual energy X-ray absorptiometry for whole body and regional analysis of body composition. Validation using piglets and methodological considerations in infants. Pediatr Res. 1997;41:1–7.
4. Koo WWK, Walters J, Bush AJ. Technical considerations of dual-energy X-ray absorptiometery-based bone mineral measurements for pediatric studies. J Bone Miner Res. 1995;10:1998–2004.
5. Harvey NC, Javaid MK, Poole JR, et al. Paternal skeletal size predicts intrauterine bone mineral accrual. J Clin Endocrinol Metab. 2008;93(5):1676–81.
6. Yang TL, Zhao LJ, Liu YJ, Liu JF, Recker RR, Deng HW. Genetic and environmental correlations of bone mineral density at different skeletal sites in females and males. Calcif Tissue Int. 2006;78(4):212–7.
7. Tse KY, Macias BR, Meyer RS, Hargens AR. Heritability of bone density: regional and gender differences in monozygotic twins. J Orthop Res. 2009;27(2):150–4.
8. Holroyd C, Harvey N, Dennison E, Cooper C. Epigenetic influences in the developmental origins of osteoporosis. Osteoporos Int. 2012;23(2):401–10.
9. Cooper C, Westlake S, Harvey N, Javaid K, Dennison E, Hanson M. Review: developmental origins of osteoporotic fracture. Osteroporos Int. 2006;17(3):337–47.
10. Harvey NC, Javaid MK, Arden NK, et al. Maternal predictors of neonatal bone size and geometry: the Southampton women's survey. J Dev Orig Health Dis. 2010;1(1):35–41.
11. Devlin MJ, Bouxsein ML. Influence of pre- and peri-natal nutrition on skeletal acquisition and maintenance. Bone. 2012;50(2):444–51.
12. Macdonald-Wallis C, Tobias JH, Smith GD, Lawlor DA. Relation of maternal prepregnancy body mass index with offspring bone mass in childhood: is there evidence for an intrauterine effect? Am J Clin Nutr. 2010;92(4):872–80.
13. Hogler W, Schmid A, Raber G, et al. Perinatal bone turnover in term human neonates and the influence of maternal smoking. Pediatr Res. 2003;53(5):817–22.
14. Ganpule A, Yajnik CS, Fall CH, et al. Bone mass in Indian children – relationships to maternal nutritional status and diet during pregnancy: the Pune maternal nutrition study. J Clin Endocrinol Metab. 2006;91(8):2994–3001.
15. Yin J, Dwyer T, Riley M, Cochrane J, Jones G. The association between maternal diet during pregnancy and bone mass of the children at age 16. Eur J Clin Nutr. 2010;64(2):131–7.
16. Cole ZA, Gale CR, Javaid MK, Robinson SM, Law C, Boucher BJ, Crozier SR, Godfrey KM, Dennison EM, Cooper C. Maternal dietary patterns during pregnancy and childhood bone mass: a longitudinal study. J Bone Miner Res. 2009;24(4):663–8.
17. Chang S-C, O'Brien KO, Nathanson MS, Caulfield LE, Mancini J, Witter FR. Fetal femur length is influenced by maternal dairy intake in pregnant African American adolescents. Am J Clin Nutr. 2003;77(5):1248–54.
18. Young BE, McNanley TJ, Cooper EM, McIntyre AW, Witter F, Harris ZL, O'Brien KO. Maternal vitamin D status and calcium intake interact to affect fetal skeletal growth in utero in pregnant adolescents. Am J Clin Nutr. 2012;95(5):1103–12.
19. Liu Z, Qiu L, Chen YM, Su YX. Effect of milk and calcium supplementation on bone density and bone turnover in pregnant Chinese women: a randomized controlled trail. Arch Gynecol Obstet. 2011;283:205–11.
20. Steer CD, Tobias JH. Insights into the programming of bone development from the Avon Longitudinal study of parents and children (ALSPAC). Am J Clin Nutr. 2011;94(6 Suppl):1861S–4.
21. Kovacs CS. Vitamin D, in pregnancy and lactation: maternal, fetal, and neonatal outcomes from human and animal studies. Am J Clin Nutr. 2008;88:520S–8.
22. O'Brien KO, Donangelo CM, Ritchie LD, Gildengorin G, Abrams S, King JC. Serum 1,25-dihydroxyvitamin D and calcium intake affect rates of bone calcium deposition during pregnancy and the early postpartum period. Am J Clin Nutr. 2012;96(1):64–72.
23. Martin R, Harvey NC, Crozier SR, Poole JR, Javaid MK, Dennison EM, et al. Placental calcium transporter (PMCA3) gene expression predicts intrauterine bone mineral accrual. Bone. 2007;40(5):1203–8.

24. Zeghoud F, Vervel C, Guillozo H, Walrant-Debray O, Boutignon H, Garabédian M. Subclinical vitamin D deficiency in neonates: definition and response to vitamin D supplements. Am J Clin Nutr. 1997;65:771–8.
25. Morley R, Carlin JB, Pasco JA, Wark JD, Ponsonby AL. Maternal 25-hydroxyvitamin D concentration and offspring birth size: effect modification by infant VDR genotype. Eur J Clin Nutr. 2009;63(6):802–4.
26. Weiler H, Fitzpatirck-Wong S, Veitch R, et al. Vitamin D deficiency and whole-body and femur bone mass relative to weight in healthy newborns. CMAJ. 2005;172:757–61.
27. Viljakainen HT, Saarnio E, Hytinantti T, Miettinen M, Surcel H, Mäkitie O, Andersson S, Laitinen K, Lamberg-Allardt C. Maternal vitamin D status determines bone variables in the newborn. J Clin Endo Metab. 2010;95(4):1749–57.
28. Mahon P, Harvey N, Crozier S, Inskip H, Robinson S, Arden N, Swaminathan R, Cooper C, Godfrey K. Low maternal vitamin D status and fetal bone development: cohort study. J Bone Mineral Res. 2010;25(1):14–9.
29. Ward LM, Gaboury I, Ladhani M, Zlotkin S. Vitamin D-deficiency rickets among children in Canada. CMAJ. 2007;177:161–6.
30. Javaid MK, Crozier SR, Harvey NC, Gale CR, Dennison EM, Arden K, Princess Anne Hospital Study Group, et al. Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study. Lancet. 2006;367:36–43.
31. Koo WW, Walters JC, Esterlitz J, Levine RJ, Bush AJ, Sibai B. Maternal calcium supplementation and fetal bone mineralization. Obstet Gynecol. 1999;94(4):577–82.
32. Heppe DH, Medina-Gomez C, Hofman A, Franco OH, Rivadeneira F, Jaddoe VW. Maternal first-trimester diet and childhood bone mass: the generation R study. Am J Clin Nutr. 2013;98(1):224–32.
33. Devlin MJ, Grasemann C, Cloutier AM, et al. Maternal perinatal diet induces developmental programming of bone architecture. J Endocrinol. 2013;217(1):69–81.
34. Harvey NC, Mahon PA, Kim M, Cole ZA, Robinson SM, et al. Intrauterine growth and postnatal development: findings form the Southampton Women's Survey. Paediatr Perinat Epidemiol. 2011;26:34–44.
35. Lanham SA, Roberts C, Cooper C, Oreffo RO. Intrauterine programming of bone. Part 1: alteration of the osteogenic environment. Osteoporos Int. 2008;19(2):147–56.
36. Hsu YH, Kiel DP. Clinical review: genome-wide association studies of skeletal phenotypes: what we have learned and where we are headed. J Clin Endocrinol Metab. 2012;97:E1958–77.
37. Richards JB, Zheng HF, Spector TD. Genetics of osteoporosis from genome-wide association studies: advances and challenges. Nat Rev Genet. 2012;13:576–88.
38. Estrada K, Styrkarsdottir U, Evangelou E, Hsu YH, et al. Genome-wide meta-analysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture. Nat Genet. 2012;44(5):491–501.
39. Godfrey K, Walker-Bone K, Robinson S, et al. Neonatal bone mass: influence of parental birth weight, maternal smoking, body composition and activity during pregnancy. J Bone Miner Res. 2001;16(9):1694–703.
40. Jones G, Hynes KL, Dwyer T. The association between breastfeeding, maternal smoking in utero, and birth weight with bone mass and fractures in adolescents: a16-year longitudinal study. Osteoporos Int. 2013;24(5):1605–11.
41. Jones G, Dwyer T. Birth weight, birth length, and bone density in prepubertal children: evidence for an association that may be mediated by genetic factors. Calcif Tissue Int. 2000;67:304–8.
42. Gale CR, Martyn CN, Kellingray S, Eastell R, Cooper C. Intrauterine programming of adult body composition. J Clin Endocrinol Metab. 2001;86:247–52.
43. Widdowson EM, Southgate DA, Hey E. Fetal growth and body composition. In: Linblad BS, editor. Perinatal nutrition. New York, NY: Academic; 1988. p. 3–14.
44. Salle BL, Delvin EE, Lapillone A, Bishop NJ, Glorieux FH. Perinatal metabolism of vitamin D. Am J Clin Nutr. 2000;71:1317S–22.
45. Ziegler EE, Am O'D, Nelson SE, Fomon SJ. Body composition of the reference fetus. Growth. 1976;40:329–41.
46. Hollis BW, Pittard WB. Evaluation of the total fetomaternal vitamin D relationships at term: evidence for racial differences. J Clin Endocrinol Metab. 1984;59:652–7.
47. Backstrom MC, Maki R, Kuusela AL, et al. Randomised controlled trial of vitamin D supplementation on bone density and biochemical indices in preterm infants. Arch Dis Child Fetal Neonatal Ed. 1999;80:F161–6.
48. Pohlandt F, Mathers N. Bone mineral content of appropriate and light for gestational age preterm and term newborn infants. Acta Paediatr Scand. 1989;78:835–9.
49. Koo WWK, Walters J, Bush AJ, Chesney RW, Carlson SE. Dual energy X-ray absorptiometry studies of bone mineral status in newborn infants. J Bone Miner Res. 1996;11:997–1002.
50. Rigo J, Nyamugabo K, Picaud JC, et al. Reference values of body composition obtained by dual energy X-ray absorptiometery in preterm and term neonates. J Pediatr Gastroenterol Nutr. 1998;25:184–90.
51. Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy Press. 2011 Available at http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx

52. Canadian Paediatric Society, Position statement [Principal author: J. Godel]. Vitamin D supplementation: recommendations for Canadian mothers and infants. Paediatr Child Health 2007; 12(7):583–9. Available at: http://www.cps.ca/en/documents/position/vitamin-d
53. American Endocrine Society. Guidelines for the evaluation, treatment and prevention of vitamin D deficiency. 2011. Available at: https://www.endocrine.org/~/media/endosociety/Files/Publications/Clinical%20Practice%20Guidelines/FINAL-Standalone-Vitamin-D-Guideline.pdf
54. Rosen CJ, Abrams SA, Aloia JF, et al. IOM committee members respond to Endocrine Society vitamin D guideline. J Clin Endocrinol Metab. 2012;97(4):1146–52.
55. Hollis BW, Johnson D, Hulsey TC, Ebeling M, Wagner CL. Vitamin D supplementation during pregnancy: double blind, randomized clinical trial of safety and effectiveness. J Bone Miner Res. 2011;10:2341–57.
56. Wagner CL, McNeil RB, Johnson DD, Hulsey TC, Ebeling M, Robinson C, Hamilton SA, Hollis BW. Health characteristics and outcomes of two randomized vitamin D supplementation trials during pregnancy: a combined analysis. J Steroid Biochem Mol Biol. 2013;136:313–20.
57. Prentice A, Jarjou LM, Goldberg GR, Bennett J, Cole TJ, Schoenmakers I. Maternal plasma 25-hydroxyvitamin D concentration and birth weight, growth and bone mineral accretion of Gambian infants. Acta Paediatr. 2009;98:1360–2.
58. Basile LA, Taylor SN, Wagner CL, Horst RL, Hollis BW. The effect of high-dose vitamin D supplementation on serum vitamin D levels and milk calcium concentration in lactating women and their infants. Breastfeed Med. 2006;1(1):27–35.
59. Abrams SA, Committee on Nutrition, AAP. Calcium and vitamin D requirements of enterally fed preterm infants. Pediatrics. 2013;131(5):e1676–83.
60. Agostini C, Buonocore G, Carnielli VP, European Society for Pediatric Gastroenterology, Committee on Nutrition (ESPGHAN), et al. Enteral nutrient supply for preterm infants: commentary from the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2010;50:85–91.
61. Atkinson SA, Tsang RC. Calcium, magnesium, phosphorus and vitamin D. In: Uauy R, Tsang RC, Zlotkin S, editors. Nutrition of the preterm infant. Scientific basis and practical guidelines. Cincinnati, OH: Digital Educational Publishing; 2005.
62. Fewtrell MS, Prentice A, Jones SC, et al. Bone mineralization and turnover in preterm infants at 8–12 years of age: the effect of early diet. J Bone Miner Res. 1999;14:810–20.
63. Backstrom MC, Maki R, Kuusela AL, et al. The long-term effect of early mineral, vitamin D, and breast milk intake on bone mineral status in 9- to 11-year-old children born prematurely. J Pediatr Gastroenterol Nutr. 1999;29:575–82.
64. Institute of Medicine, Food and Nutrition Board. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, DC: National Academy Press; 1997.
65. Wagner CL, Greer FR. American Academy of Pediatrics Section on Breastfeeding: American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children and adolescents. Pediatrics. 2008;122:1142–52.
66. Högler W, Baumann U, Kelly D. Growth and bone health in chronic liver disease and following liver transplantation in children. Pediatr Endocrinol Rev. 2010;7(3):266–74.
67. Lee GH, Benner D, Regidor DL, Kalantar-Zadeh K. Impact of kidney bone disease and its management on survival of patients on dialysis. J Ren Nutr. 2007;17(1):38–44.
68. Pappa HM, Grand RJ, Gordon CM. Report on the vitamin D status of adult and pediatric patients with inflammatory bowel disease and its significance for bone health and disease. Inflamm Bowel Dis. 2006;12(12):1162–74.
69. Alemzadeh R, Kichler J, Babar G, Calhoun M. Hypovitaminosis D in obese children and adolescents: relationship with adiposity, insulin sensitivity, ethnicity, and season. Metabolism. 2008;57(2):183–91.
70. Taha SA, Dost SM, Sedrani SH. 25-Hydroxyvitamin D and total calcium: extraordinarily low plasma concentrations in Saudi mothers and their neonates. Pediatr Res. 1984;18(8):739–41.
71. Weiler HA, Leslie WD, Krahn J, Steiman PW, Metge CJ. Canadian Aboriginal women have a higher prevalence of vitamin D deficiency than non-Aboriginal women despite similar dietary vitamin D intakes. J Nutr. 2007;137:461–5.
72. Koo WWK, Bush AJ, Walters J, Carlson SE. Postnatal development of bone mineral status during infancy. J Am Coll Nutr. 1998;17:65–70.
73. Specker BL, Beck A, Kalkwarf H, Ho M. Randomized trial of varying mineral intake on total body bone mineral accretion during the first year of life. Pediatrics. 1999;99:e12.
74. Koo WWK. Body composition measurements in infants. In: Yasumura S, editor. 5th International symposium on In Vivo body composition studies, Ann N Y Acad Sci, vol. 904. New York, NY: Academy of Science; 2000. p. 383–92.
75. Lapillonne A, Braillon P, Claris O, Chatelain PG, Delmas PD, Salle BL. Body composition in appropriate and in small for gestational infants. Acta Pediatr. 1997;86:196–200.
76. Butte NF, Wong WW, Hopkinson JM, Smith EO, Ellis KJ. Infant feeding mode affects early growth and body composition. Pediatrics. 2000;106(6):1355–66.

77. Wauben I, Atkinson SA, Grad TL, Shah JK, Paes B. Moderate nutrient supplementation to mother's milk for preterm infants supports adequate bone mass and short-term growth. A randomized controlled trial. Am J Clin Nutr. 1998;67:465–72.
78. Lapillone AA, Glorieux FH, Salle B, et al. Mineral balance and whole body bone mineral content in very-low-birth-weight infants. Acta Pediatr Suppl. 1994;405:117–22.
79. Faerk J, Petersen S, Peitersen B, Fleischer MK. Diet and bone mineral content at term in premature infants. Pediatr Res. 2000;47:148–56.
80. Atkinson SA, Randall-Simpson J. Factors influencing body composition of premature infants at term-adjusted age. In: Yasumura S, editor. 5th International symposium on In Vivo body composition studies, Ann N Y Acad Sci, vol. 904. New York, NY: Academy of Science; 2000. p. 393–400.
81. Kuschel CA, Harding JE. Multicomponent fortified human milk to promote growth in preterm infants (Cochrane Review). In: The Cochrane Library, Issue 2, 1999. Update Software, Oxford.
82. Moyer-Mileur L, Leutkemeler M, Boomer L, Chan GM. Effect of physical activity on bone mineralization in premature infants. J Pediatr. 1995;125:620–3.
83. Moyer-Milleur L, Brunstetter V, McNaught TP, Gill G, Chan GM. Daily physical activity program increases bone mineralization and growth in preterm very low birth weight infants. Pediatrics. 2000;106:1082–92.
84. Nemet D, Dolfin T, Litmanovitz I, Shainkin-Kestenbaum R, Lis M, Eliakim A. Evidence for exercise-induced bone formation in premature infants. Int J Sports Med. 2002;23:1–4.
85. Specker B, Binkley T. Randomized trial of physical activity and calcium supplementation on bone mineral content in 3- to 5-year-old children. J Bone Miner Res. 2003;18:885–92.
86. Wauben IPM, Atkinson SA, Shah JK, Paes B. Growth and body composition of preterm infants: influence of nutrient fortification of mother's milk in hospital and breast feeding post-hospital discharge. Acta Paediatr. 1998;87:780–5.
87. Brunton JA, Saigal S Atkinson S. Nutrient intake similar to recommended values does not result in catch-up growth by 12 mo of age in very low birth weight infant (VLBW) with bronchopulmonary dysplasia (BPD). Am J Clin Nutr 1997; 55(i), Abstr. 102.
88. Brunton JA, Saigal S, Atkinson SA. Growth and body composition in infants with bronchopulmonary dysplasia up to 3 months corrected age: a randomized trial of a high-energy nutrient-enriched formula fed after hospital discharge. J Pediatr. 1998;133:340–5.
89. Bishop NJ, King FJ, Lucas A. Increased bone mineral content of preterm babies fed with a nutrient enriched formula after discharge from hospital. Arch Dis Child. 1993;68:573–8.
90. Rubinacci A, Sirtori P, Moro G, Galli L, Minoli I, Tessari L. Is there an impact of birth weight and early life nutrition on bone mineral content in preterm born infants and children? Acta Pediatr. 1993;82:711–3.
91. Fewtrell M. Does early nutrition program later bone health in preterm infants? Am J Clin Nutr. 2011;94(6):1970S–3.
92. Weiler HA, Yuen CK, Seshia MM. Growth and bone mineralization of young adults weighing less than 1500 g birth weight. J Ear Hum Dev. 2002;67:101–12.
93. Wang D, VanderMeulen J, Atkinson SA. Early life factors predict abnormal growth and bone accretion at prepuberty in former premature infants with/without neonatal dexamethasone exposure. Pediatr Res. 2007;61(1):111–6.